TOXICOLOGICAL PROFILE FOR DICHLORVOS

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

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UPDATE STATEMENT

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

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FOREWORD

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

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

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

Each profile includes the following:

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

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

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

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on April 29, 1996 (61 FR 18744). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.

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

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

PEER REVIEW

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

1. Dr. U. John Bell, Saf-Risk, 411 Bath Club Boulevard, S., St. Petersburg, FL;

2. Dr. Robert Coppock, R.W. Coppock and Associates, Vegreville, Alberta, Canada;

3. Dr. Rudy Richardson, Professor and Director of Toxicology, University of Michigan Toxicology Program, Neurotoxicology Research Laboratory, Ann Arbor, MI.; and

4. Dr. Josef Seifert, Department of Environmental Biochemistry, University of Hawaii, Honolulu, HI.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about dichlorvos and the effects of exposure. The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup. Dichlorvos has been found in at least 3 of the 1,430 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with dichlorvos may increase. This is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact. If you are exposed to dichlorvos, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS DICHLORVOS?

Dichlorvos is a synthetic organic chemical used as an insecticide. Dichlorvos does not occur naturally in the environment, but is manufactured by industry. Dichlorvos is sold under many trade names including Vapona®, Atgard®, Nuvan®, and Task®. Dichlorvos may also be called DDVP, which is an abbreviation for its full chemical name. Pure dichlorvos is a dense colorless liquid that evaporates easily into the air and dissolves slightly in water. Dichlorvos has a sweetish smell and readily reacts with water. The dichlorvos used in pest control is

diluted with other liquids and used as a spray. It can also be incorporated into plastic that slowly releases the chemical. The dichlorvos present at hazardous waste sites will most likely be in a liquid solution or as solid plastic pellets or strips.

Dichlorvos is manufactured by a reaction between two other chemicals called chloral and trimethyl phosphite. It is also manufactured by heating a chemical called trichlorfon. In 1984, about 1 million pounds of dichlorvos was manufactured in the United States. The main uses of dichlorvos are for insect control in food storage areas, greenhouses, and barns, and for parasite control in livestock. Dichlorvos is generally not used on outdoor crops. It is sometimes used for insect control in workplaces and the home. Veterinarians also use it to control parasites in pets. Dichlorvos was the active ingredient in "No-Pest Strips," but is no longer used for this purpose. You will find further information on the physical properties and uses of dichlorvos in Chapters 3 and 4 of this profile.

1.2 WHAT HAPPENS TO DICHLORVOS WHEN IT ENTERS THE ENVIRONMENT?

Dichlorvos enters the air, water, and soil during its manufacture and use. Wastes containing dichlorvos that are generated during its manufacture and use are sometimes disposed of in landfills. It can enter the environment from these landfills. Dichlorvos also enters the environment from accidental spills during transport and leaks from storage containers.

Dichlorvos evaporates easily into the air, which is why it is usually used in enclosed areas. Once in the air, it can react with water vapor and be broken down. The higher the temperature and the humidity, the more rapidly dichlorvos is broken down. Experiments in greenhouses and food storage areas show that 90% of the applied dichlorvos disappeared in 3-6 hours. The products of this breakdown are two chemicals called dimethyl phosphate and dichloroacetaldehyde. These chemicals are less harmful than dichlorvos and are not believed to cause health effects in people.

If dichlorvos is spilled into a lake or river, it will dissolve in the water. Some dichlorvos will then evaporate into the air, but most of it will be broken down when it reacts with the water.

The less acid the water is, the more rapidly dichlorvos is broken down. Bacteria and other microorganisms (microscopic plants and animals) in lakes and rivers can also break down dichlorvos. In an experiment where dichlorvos was applied to a pond, 50% of the chemical was broken down in 24-36 hours.

Dichlorvos does not seem to bind to soil. This means it can move through soil fairly rapidly. The breakdown in soil is less rapid than in air or water. Dichlorvos breakdown is most rapid in moist soils with low acidity. In a laboratory experiment with soil that contained 200 parts of dichlorvos per million parts of soil (200 ppm), 37% of the dichlorvos remained in the soil after 3 days. Dichlorvos remains for longer periods in dry, acidic soil. Certain bacteria and other microorganisms in the soil can also break down dichlorvos.

Dichlorvos is not stored, accumulated, or concentrated by plants, fish, animals, or people.

You will find further information about what happens to dichlorvos in the environment in Chapter 5 of this profile.

1.3 HOW MIGHT I BE EXPOSED TO DICHLORVOS?

The general population is not likely to be exposed to dichlorvos. It has not been found in drinking water in the United States and only very rarely in outdoor air. Dichlorvos has occasionally been found on raw foods (fruits, vegetables, grains), but washing and processing destroys the residue. Maximum limits (ranging from 0.02 to 2 ppm) have been established by the U.S. EPA. Dichlorvos has not been found in prepared foods.

People living near hazardous waste sites containing dichlorvos or near its manufacturing, processing, or storage facilities, could potentially be exposed. Because of the chemical properties, the most likely way a person would be exposed is by breathing in air contaminated with dichlorvos. Another possible route of exposure is skin contact with soil contaminated with dichlorvos.

You are most likely to be exposed to dichlorvos if you are involved in manufacturing or using it. Chemical plant workers, transport workers, and pesticide applicators are the major occupational groups that might be exposed. People in these groups are mainly exposed by breathing air containing dichlorvos, but significant exposure through the skin can occur as well. An estimated 24,000 workers in the United States are exposed to dichlorvos because of their occupations. Measured air levels in factories and workplaces have ranged from 0.005 to 0.08 ppm dichlorvos.

You might also be exposed to dichlorvos in the home after pesticide application. You are most likely to be exposed by breathing air containing dichlorvos, but skin contact with contaminated surfaces, or eating food that has been left out during dichlorvos application can also result in exposure. Measured levels of dichlorvos in room air immediately after pesticide applications have ranged from 0.08 to 2.7 ppm. It has been recommended that people should not reenter a room or house treated with dichlorvos until after a lo-hour ventilation period.

You will find further information on the potential for exposure to dichlorvos in Chapter 5.

1.4 HOW CAN DICHLORVOS ENTER AND LEAVE MY BODY?

Dichlorvos can enter your body through your lungs if it is in the air you breathe. It can also enter your body through your stomach if it is in your drinking water or food. It can also enter through your skin. Dichlorvos is taken into your body very rapidly by any of these routes (lungs, stomach, or skin). How much dichlorvos enters your body depends on how long you are exposed and the amount to which you are exposed.

Once dichlorvos enters your body, it goes into your bloodstream and is carried to all the organs in your body. There are enzymes in your liver and blood that rapidly break it down. These breakdown products are less harmful than dichlorvos. Most of these breakdown products quickly leave the body in the urine. Some of these products are broken down further and leave your body in your breath. Dichlorvos and its breakdown products are not stored in your body.

You will find further information on how dichlorvos enters and leaves your body in Chapter 2.

1.5 HOW CAN DICHLORVOS AFFECT MY HEALTH?

Dichlorvos is a member of a group of chemicals called organophosphorus compounds. Some of these chemicals are extremely harmful to insects and are widely used as insecticides. At higher doses than those used to kill insects, these chemicals can also be harmful to people. Dichlorvos can chemically react with an important enzyme in your brain and nerves called acetylcholinesterase and stop them from working properly. When this happens, signals sent between your nerve cells and to your muscles are disrupted. To understand the harmful effects of dichlorvos that might occur at levels of exposure that people are likely to experience, scientific studies have been done with people and laboratory animals. To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

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

We do not know how much dichlorvos is necessary to cause harmful effects in people. This is because few people have been exposed to enough dichlorvos to cause symptoms of poisoning. From the results of animal testing, we can estimate that if a person breathed in air containing more than 1 ppm dichlorvos for more than one hour, harmful effects might result. Accidentally drinking as little as 1 ounce or 30 milliliters (mL) of a pesticide containing 5% dichlorvos could also cause harmful effects. Spilling an ounce of the same strength dichlorvos solution on your skin and failing to wash it off promptly could also be harmful.

1. PUBLIC HEALTH STATEMENT

If you have been poisoned by dichlorvos, you will suddenly feel nauseated, anxious, and restless. You may also have teary eyes and heavy sweating. If this happens, you should seek medical attention immediately. Emergency rooms have drugs that stop the harmful effects of dichlorvos. Further symptoms can include loss of bladder control, muscle tremors, and labored breathing. Severe poisoning (5 ounces or more of a 5% dichlorvos solution) can result in coma, inability to breathe, and death.

Most people who have survived poisoning by dichlorvos make a complete recovery, although this can sometimes take several months. Dichlorvos poisoning does not appear to cause permanent damage to the nerves (a condition called “delayed neuropathy”).

A few studies have been done on people who have been exposed to dichlorvos in the air in their workplaces. When dichlorvos is used properly, air levels of 0.01-0.03 ppm are achieved. This level kills most insects within one hour. In tests done with volunteers, exposure at about 20 times this level (0.23 ppm) for 2 hours a day for 4 days had no harmful effects. In a study in rats exposed to air with very high levels of dichlorvos (up to 34 ppm), all the animals died within 3 days. The rats showed similar signs of effects on the nervous system as in people that have been poisoned with dichlorvos. In general, harmful effects have not been seen in animals exposed to air levels of dichlorvos below 0.5 ppm. In a 2-year study in rats, breathing air every day with low-to-moderately high levels (0.006-0.6 ppm) of dichlorvos had no effect on how long the rats lived or on their general health.

In at least one case, a person who drank a pesticide containing dichlorvos died. The doctors who treated this patient were unable to tell exactly how much dichlorvos she had taken. Volunteers who ate 0.03 milligrams dichlorvos per kilogram body weight (0.03 mg/kg) for 21 days showed no harmful effects. In studies where animals (rats and mice) have been force-fed dichlorvos, about half the animals died when given approximately 100 mg/kg. Before the animals died, they showed signs of harmful effects to their nervous systems similar to those seen in human poisoning cases.

1. PUBLIC HEALTH STATEMENT

Two pesticide workers died after spilling concentrated dichlorvos on their skin and failing to wash it off promptly. It is not known exactly how much dichlorvos they absorbed through their skin. Experiments in animals show that dichlorvos can be just as harmful when it is applied to the skin as when it is breathed in or swallowed. Monkeys that had dichlorvos put on their skin (50 mg each day) died after 10 doses.

It is not known if exposure to dichlorvos can affect fertility or development of the fetus in people. Experiments done in animals that were fed or breathed in dichlorvos did not show any effect on fertility or health of the offspring.

There is no evidence that exposure to dichlorvos increases the risk of cancer in people. Rats that breathed in air containing dichlorvos for 2 years had the same rate of cancer as rats that did not breathe in dichlorvos. However, a 2-year study in rats and mice force-fed dichlorvos showed an increase in certain forms of cancer. Rats had increased rates of cancer in the pancreas and also had more cases of leukemia than rats that had not been treated with dichlorvos. Female mice had a higher rate of a form of stomach cancer.

The U.S. Department of Health and Human Services (DHHS) has determined that dichlorvos may reasonably be anticipated to be a carcinogen (a substance that can cause cancer). The International Agency for Research on Cancer (IARC) has determined that dichlorvos is possibly carcinogenic to humans. The U.S. EPA has determined that dichlorvos is a probable human carcinogen.

The U.S. EPA has calculated that a lifetime of drinking water containing 0.1 micrograms of dichlorvos per liter μg/L) would cause one extra case of cancer in every million people exposed to this level. Dichlorvos has not been found in drinking water in the United States.

You will find further information on how dichlorvos may affect your health in Chapter 2.

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

Two blood tests exist that can determine whether you have been exposed to significant levels of dichlorvos. These tests can be performed by any hospital or clinical laboratory. These tests measure the activity of two enzymes (called serum cholinesterase and erythrocyte [red blood cell] acetylcholinesterase) that are affected by dichlorvos. Dichlorvos affects these enzymes at lower levels of exposure than necessary to produce harmful effects. This means that if these enzymes have been affected, you will not necessarily have effects on your health. Many other insecticides also affect these enzymes. To determine whether you have been specifically exposed to dichlorvos, a laboratory test must measure the breakdown products in your urine. Tests of this type are not routinely done in hospital laboratories and your doctor will have to send a sample to a specialized laboratory.

You will find further information on how you can be tested for exposure to dichlorvos in Chapter 2.

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

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

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals, then they are adjusted to help

protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for dichlorvos include the following:

- The U.S. OSHA has set a permissible exposure limit (PEL) of 1 mg/m^3 (0.11 ppm) of dichlorvos for workplace air over a l0-hour workday.

- The U.S. EPA requires reporting of any discharge of dichlorvos to the environment that exceeds 10 pounds. The EPA has also designated dichlorvos as a hazardous substance and specific regulations regarding its disposal are in effect.

- The U.S. EPA has established maximum permissible levels of dichlorvos in various food products ranging from 0.02 to 2 parts per million (ppm). Samples from the food supply are regularly tested for dichlorvos.

Further information on federal and state regulations and recommendations concerning dichlorvos is found in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: (404) 639-6000
Fax: (404) 639-63 15 or 6324

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22 16 1
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of dichlorvos. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of dichlorvos are indicated in Table 2-2 and Figure 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

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

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

asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

All of the studies discussed in this section were conducted in exposure chambers into which air containing dichlorvos was introduced. Thus, some exposure may also have occurred by the oral and/or dermal route, since dichlorvos vapor came into contact with chamber surfaces and the bodies of the subjects. In some studies, food may have been in the chambers during the exposure.

Air concentrations of dichlorvos in all of the studies discussed below were expressed in units of either μg/L or mg/m^3. Since inhalation exposure to dichlorvos is more likely to be to the vapor phase than to aerosols, air concentrations are also presented as the equivalent parts per million (ppm). All concentrations in the inhalation exposure sections of the Levels of Significant Exposure (LSE) table (Table 2-l) and figure (Figure 2-l) are expressed as ppm, as are those for the Minimal Risk Levels derived for this profile (Section 2.5). The conversion calculation is described in the footnote to Table 2-l and in Appendix A.

Effective insecticidal air concentrations for dichlorvos are in the range of 0.15-0.25 mg/m^3 (0.017-0.028 ppm) (Hayes 1982). Insects are particularly sensitive to dichlorvos because of a lack of organophosphate metabolizing enzymes compared to mammals. Their open gas-exchange system (a network of tubules penetrating the body) also allows high concentrations of dichlorvos to reach target tissues in the nervous system.

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to dichlorvos.

Deaths have been reported in animals after acute-duration inhalation exposure to dichlorvos. In an early toxicity study (Durham et al. 1957), male and female Sherman rats were exposed to an

atmosphere derived from air bubbled through dichlorvos before entering the chamber. The air was essentially saturated with dichiorvos. Dichlorvos concentrations in the incoming air were measured in one trial: 8 separate determinations averaged 306 mg dichlorvos/m^3 (34 ppm) (range = 230-341 mg/m^3 or 25-38 ppm). The time until death depended on how long the chamber had been pre-equilibrated with the atmosphere containing dichlorvos. The time to death was shorter (as little as 4.5 hours) in chambers pre-equilibrated for the longest times. Rats were exposed until death occurred, which took from 6.9 to 61.9 hours on average. Clinical signs reported before death included slow, labored respiration, sialorrhea, and paleness in the extremities.

In an experiment designed to investigate the toxicity of dichlorvos after spraying in an enclosed area, Sherman rats and Rhesus monkeys were placed in a chamber whose walls and ceilings had been sprayed with a xylene emulsion containing 2.5% dichlorvos by weight and applied to give 1.08 g/m^2 of surface (Durham et al. 1957). The initial dichlorvos concentration in the air of the chamber was about 6 mg/m^3 (0.66 ppm); it fell to about 1 mg/m^3 (0.11 ppm) after 3 days and then to 0.1 mg/m^3 (0.01 ppm) for the rest of the 2-week exposure. No deaths occurred during this experiment. Dichlorvos was determined in this study by a total phosphate method. This method also detects the breakdown products of dichlorvos, so these concentrations may be overestimated.

No deaths were reported in male Swiss CF-1 mice exposed for 16 hours to atmospheres containing 30 or 55 mg dichlorvos/m^3 (3.3 or 6.1 ppm) (Dean and Thorpe 1972) or in male Sprague-Dawley rats exposed for 3, 7, or 14 days at levels up to 56 mg dichlorvos/m^3 (6.3 ppm) (Schmidt et al. 1979). No deaths were reported in pregnant CF-1 mice exposed to 4 mg dichlorvos/m^3 (0.44 ppm) for 7 hours a day for 10 days (gestation days 6-15) or in pregnant New Zealand rabbits exposed to the same concentration for 7 hours a day for 13 days (gestation days 6-18) (Schwetz et al. 1979).

Deaths were reported in rabbits from inhalation exposure to dichlorvos in an intermediate-duration study (Thorpe et al. 1972). In this experiment, groups of 20 pregnant Dutch rabbits were exposed to dichlorvos for 23 hours a day at concentrations of 0, 0.25, 1.25, or 6.25 mg/m^3 (0, 0.03, 0.14, or 0.69 ppm, respectively) for the 28 days of gestation. Sixteen of the 20 rabbits died at the 6.25 mg/m^3 concentration. Nine of these deaths may have been related to an unintentional increase to a level of 8 mg/m^3 (0.88 ppm) for one day during the experiment. Before death, the animals were anorexic, lethargic, showed tremors and torticollis, and had nasal discharges and diarrhea; these are all signs of dichlorvos neurotoxicity. Some animals in a state of advanced toxicosis were killed. An additional

group of 20 pregnant rabbits was exposed to 4 mg/m^3 (0.44 ppm) over the 8-day gestational period. Six of these rabbits died during the study, and clinical signs were similar to those observed in the 6.25 mg/m^3 (0.69 ppm) treatment group. Five of these animals died following an increase in dichlorvos concentration due to a filter failure. The maximum concentration due to system failure was not given. None of the rabbits exposed at levels of 0.25 or 1.25 mg/m^3 (0.03 or 0.14 ppm) died over the 28 days of exposure.

No deaths were reported in pregnant Carworth E rats exposed to atmospheres containing 0, 0.25, 1.25, or 6.25 mg/m^3 (0, 0.03, 0.14, and 0.69 ppm, respectively) over their 20-day gestation period (Thorpe et al. 1972), in male CF-1 mice exposed to 2.1 or 5.8 mg/m^3 (0.23 and 0.64 ppm, respectively) for 4 weeks (Dean and Thorpe 1972), or in 20-kg Yorkshire-Landrace pigs exposed for a 24-day period to concentrations of 0.092-0.114 mg/m^3 (0.01-0.013 ppm) (Loeffler et al. 1976).

In the only chronic-duration inhalation study available (Blair et al. 1976), groups of 50 Carworth E rats of each sex were exposed 23 hours a day to atmospheres containing dichlorvos at levels of 0, 0.05, 0.5, or 5 mg/m^3 (0, 0.006, 0.06, or 0.6 ppm, respectively) for 2 years. Survival was slightly increased in the rats exposed to the higher levels of dichlorvos, compared with controls. Clinical signs of intoxication were not observed in the 0.05 and 0.5 mg/m^3 groups. Rats in the 5 mg/m^3 group had necrosis of the tips of their tails, which was not seen in the control or other treated groups. However, because more than half of both sexes of the control rats died in this study, conclusions on the lethality of dichlorvos after chronic inhalation exposure cannot be drawn.

All reliable LOAELs for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

No studies regarding systemic effects in humans after inhalation exposure to dichlorvos were located. No studies regarding gastrointestinal, renal, musculoskeletal, endocrine, dermal, or ocular effects in animals after inhalation exposure to dichlorvos were located. Most of the systemic effects observed after inhalation exposure to dichlorvos are the result of the neurotoxicity of this chemical.

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

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Neurological						
1	Human	20 or 10 hr		0.08 M			Blair et al. 1975
2	Rat (Sprague-Dawley)	3-14 d		0.20[b] M		0.48 M (62% inhibition of erythrocyte AChE)	Schmidt et al. 1979
	Reproductive						
3	Mouse (CF-1)	16 hr		6.1 M			Dean and Thorpe 1972
	Developmental						
4	Mouse (CF-1)	10 d Gd 6-15 7 hr/d		0.44			Schwetz et al. 1979
5	Rabbit (New Zealand)	13 d Gd 6-18 7 hr/d		0.44			Schwetz et al. 1979
	INTERMEDIATE EXPOSURE						
	Death						
6	Rabbit (Dutch)	Gd 1-28 23 hr/d				0.44 F (6 of 20 dams died)	Thorpe et al. 1972
	Neurological						
7	Rat (Carworth E)	Gd 1-20 23 hr/d		0.03[c] F	0.14 F (erythrocyte and brain AChE inhibition 29% and 28% respectively)	0.69 F (erythrocyte and brain AChE inhibition 88% and 83% respectively)	Thorpe et al. 1972
8	Rabbit (Dutch)	Gd 1-28 23 hr/d		0.03 F		0.14 F (68% and 56% inhibition of erythocyte AChE and brain AChE respectively in dams)	Thorpe et al. 1972

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

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
9	Pig (Yorkshire Landrace)	24 d 23 hr/d		0.013			Loeffler et al. 1976
	Reproductive						
10	Rat (Carworth E)	20 d Gd 1-20 23 hr/d		0.69 F			Thorpe et al. 1972
11	Mouse (CF-1)	4 wk 23 hr/d		0.64			Dean and Thorpe 1972
12	Rabbit (Dutch)	28 d Gd 1-28 23 hr/d		0.44 F			Thorpe et al. 1972
	Developmental						
13	Rat (Carworth E)	20 d Gd 1-20 23 hr/d		0.69			Thorpe et al. 1972
14	Rabbit (Dutch)	28 d Gd 1-28 23 hr/d		0.44			Thorpe et al. 1972
	CHRONIC EXPOSURE						
	Systemic						
15	Rat (Carworth E)	2 yr 23 hr/d	Hemato	0.6			Blair et al. 1976
			Hepatic	0.06	0.6 M (increased SGOT and SGPT levels)		
			Bd Wt	0.06		0.6 M (greater than 20% reduction in body weight)	
			Metabolic	0.06	0.6 M (decreased serum chloride)		

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

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Neurological							
16	Rat (Carworth E)	2 yr 23 hr/d		0.006[d]	0.06 F (31% inhibition of erythrocyte AChE)	0.6 (79-81% inhibition of brain AChE, 95-96% inhibition of erythrocyte AChE)	Blair et al. 1976

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

[b]Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.002 ppm. Concentration divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive an intermediate-duration inhalation MRL of 0.0003 ppm. Concentration divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[d]Used to derive a chronic-duration inhalation MRL of 0.00006 ppm. Concentration divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Note: Dichlorvos air levels reported as µg/L were converted to the equivalent parts per million dichlorvos by the following equation:

(µg dichlorvos/L x (24.45 L/mole) x (220.98 g dichlorvos/mole) = µg/g = parts per million where 24.45 is the volume of 1 mole of vapor at 25 degrees Centigrade 760 mm Hg and 220.98 is the molecular weight of dichlorvos in grams/mole.

AChE = acetylcholinesterase; Bd Wt = body weight; d = day(s); F = female; Gd = gestational day; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; SGOT = serum glutamic oxaloacetate transaminase; SGPT = serum glutamic pyruvic transaminase; wk = week(s).

Figure 2-1. Levels of Significant Exposure to Dichlorvos - Inhalation

Acute (≤14 days)

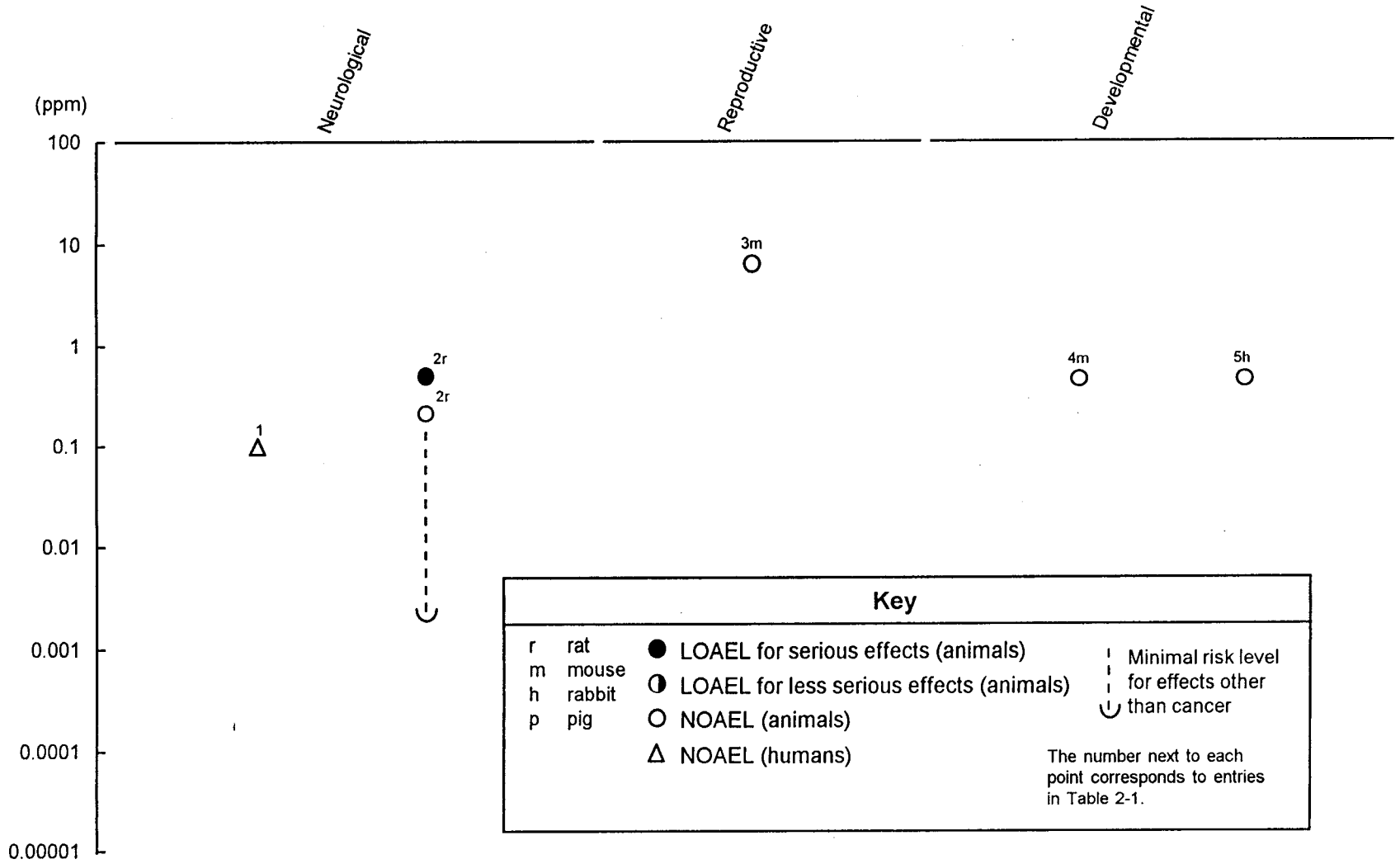


Figure 2-1. Levels of Significant Exposure to Dichlorvos - Inhalation (cont.)

Intermediate (15-364 days)

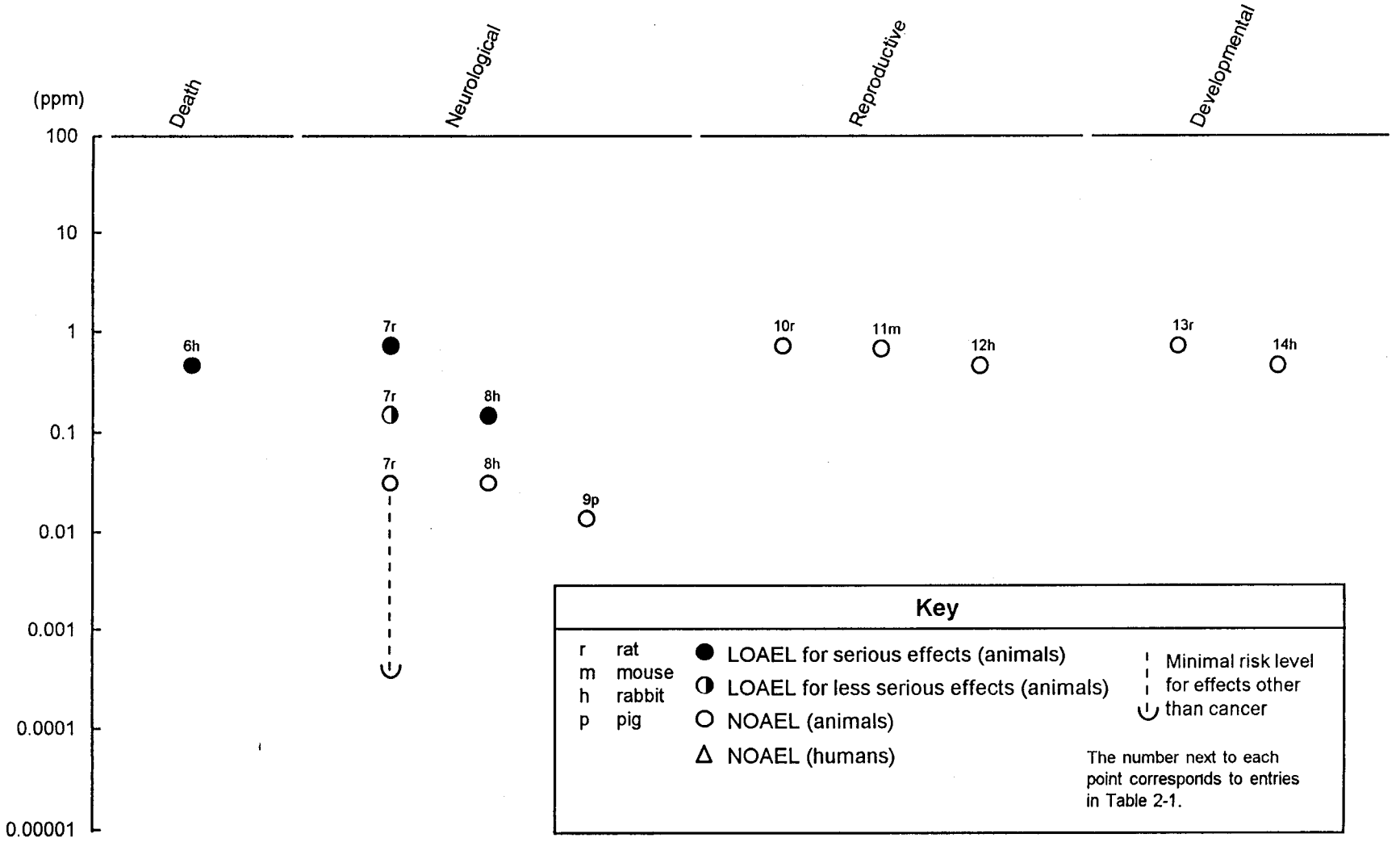
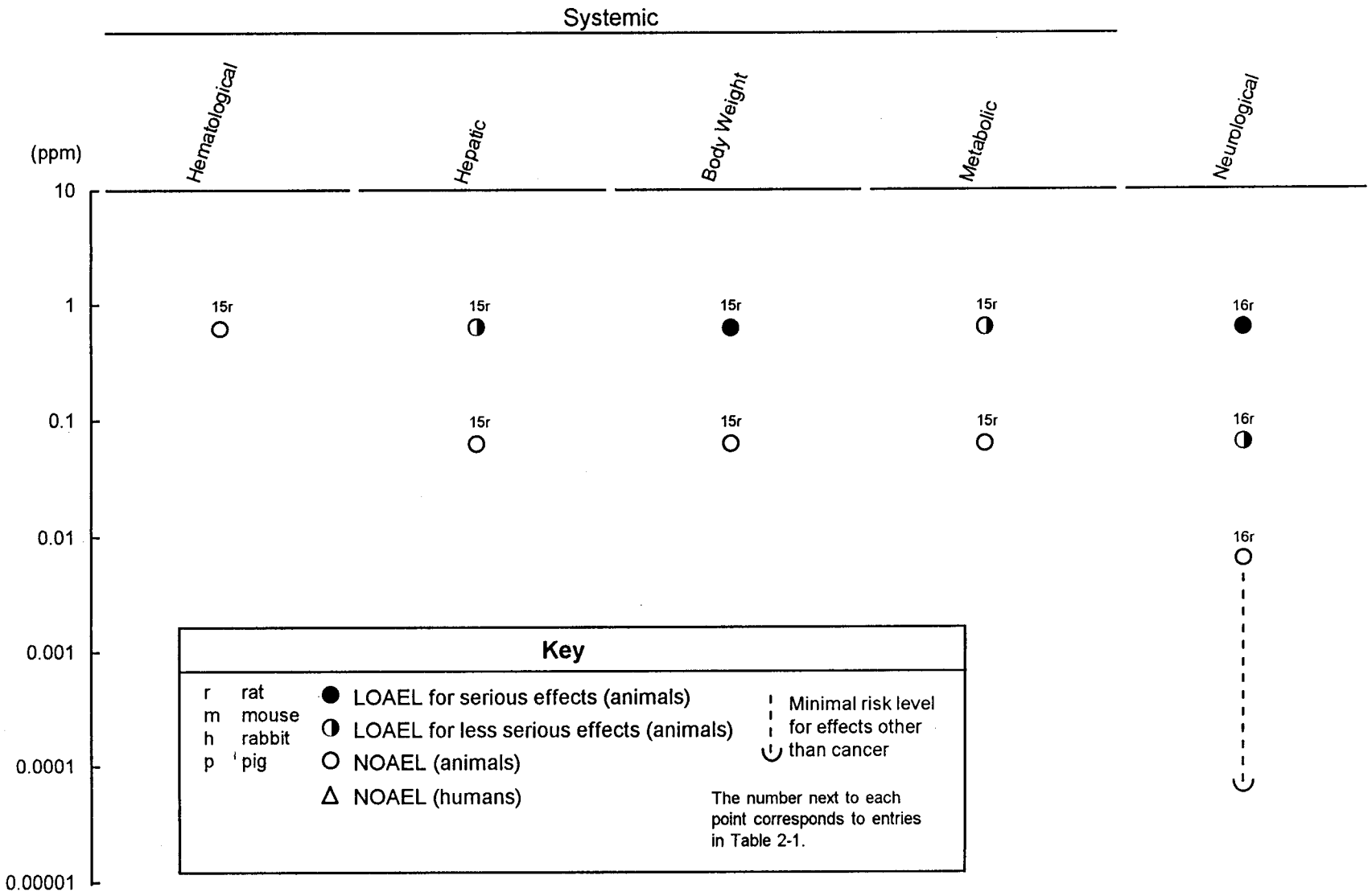


Figure 2-1. Levels of Significant Exposure to Dichlorvos - Inhalation (cont.)

Chronic (≥365 days)



The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. Prior to death, slow, labored respiration was seen in Sherman rats exposed to dichlorvos in chambers where the incoming air contained 306 mg/m^3 (34 ppm) on average (Durham et al. 1957). These signs were seen within two hours of exposure in chambers pre-equilibrated with dichlorvos.

Cardiovascular Effects. Paleness of the extremities, suggesting inadequate perfusion, was seen in Sherman rats within 2 hours of exposure in chambers until death occurred (4.5-61.9 hours). The incoming air contained, on average, 306 mg/m^3 (34 ppm), with a range of 230-341 mg/m^3 (25-38 ppm) (Durham et al. 1957).

Hematological Effects. Hematological parameters (hemoglobin concentration, erythrocyte numbers, total and differential leucocyte numbers, prothrombin time, and kaolin-cephalin coagulation time) for rats exposed to atmospheres containing up to 5 mg dichlorvos/m^3 (0.6 ppm) for 2 years were not significantly different from controls (Blair et al. 1976).

Hepatic Effects. Increased serum levels of serum glutamic oxaloacetic transaminase (SGOT, now identified as aspartate aminotransferase [AST]) and serum glutamic pyruvic transaminase (SGPT, now identified as alanine aminotransferase [ALT]), possibly indicating hepatic damage, were observed in male Carworth E rats exposed to 5 mg dichlorvos/m^3 (0.6 ppm) in a 2-year inhalation study (Blair et al. 1976). No changes in SGOT or SGPT were reported in rats of either sex exposed to 0.06 ppm dichlorvos.

Body Weight Effects. The body weight of male Cat-worth E rats exposed to atmospheres containing 5 mg dichlorvos/m^3 (0.6 ppm) for 2 years was consistently 20% or more below the body weight of control rats from the tenth week of treatment (Blair et al. 1976). Body weights of female rats exposed under the same conditions were not significantly different from controls.

Metabolic Effects. Decreased serum chloride was reported in male Carworth E rats exposed to 5 mg/m^3 dichlorvos (0.6 ppm) in a 2-year inhalation study (Blair et al. 1976). The magnitude of this

decrease was not reported. No changes in serum chloride were reported in rats of either sex exposed to 0.06 ppm dichlorvos.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to dichlorvos were located. However, total and differential leucocyte numbers were unchanged compared to controls in Carworth E rats exposed to atmospheres containing up to 5 mg/m^3 (0.6 ppm) for 2 years (Blair et al. 1976).

2.2.1.4 Neurological Effects

Dichlorvos exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase. This enzyme is present at cholinergic synapses throughout the central and peripheral nervous systems, and is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased firing of the postsynaptic neuron or increased neuroeffector activity. The consequences of increased cholinergic activity in the parasympathetic autonomic nervous system (muscarinic receptors) can include increased salivation, lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, frequent micturition, and incontinence. The effects of increased neuroeffector activity on skeletal muscles (nicotinic receptors) can include muscle fasciculations, cramps, muscle weakness, and depolarization-type paralysis. Effects on cholinergic synapses in the central nervous system (predominantly muscarinic) can result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma. These classical symptoms of organophosphate neurotoxicity increase in severity and rapidity of onset in a dose-dependent manner (Ecobichon 1991).

Acetylcholinesterase is also present in erythrocytes where it is known as erythrocyte acetylcholin esterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor ek al. 1993). In *in vitro* assays, erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to dichlorvos and many other organophosphorus compounds with insecticide activity (Hayes 1982). Measurement of erythrocyte acetylcholinesterase is used as a surrogate of the inhibition of neural acetylcholinesterase. A cholinesterase capable of hydrolyzing acetylcholine is also produced by the liver and circulates in the blood. This enzyme, called serum cholinesterase, is also inhibited by

dichlorvos and is often used as a marker for exposure. The endogenous substrate of this enzyme is unknown. Usually, this enzyme is inhibited by dichlorvos at lower levels of exposure than required to inhibit neural or erythrocyte acetylcholinesterase (Hayes 1982).

Male volunteers exposed to atmospheres containing 0.25 or 0.7 mg/m^3 (0.03 or 0.08 ppm) showed no signs of neurological toxicity (Blair et al. 1975). One volunteer was exposed to 0.25 mg/m^3 for 10 hours and another was exposed to 0.7 mg/m^3 for 20 hours. Blood samples were not assayed for erythrocyte acetylcholinesterase, which would have suggested whether neural acetylcholinesterase was affected by the exposure to dichlorvos. Another group of seven male volunteers was exposed to dichlorvos-containing atmospheres in a simulated aircraft cabin to learn safe levels for aircraft insect control (Witter et al. 1961). In this study, the volunteers were exposed to dichlorvos on 4 consecutive days for either one or 2 hours. The average dichlorvos concentration was 0.49 mg/m^3 (range, 0.26-0.88 mg/m^3) (0.055 ppm, range 0.029-0.097 ppm) in the first experiment and 2.1 mg/m^3 (range, 0.9-3.5 mg/m^3) (0.23 ppm, range 0.10-0.38 ppm) in a second experiment with the same group. General physical examinations were performed and blood samples drawn three times before the beginning of the experiment to establish baseline rates of serum cholinesterase and erythrocyte acetylcholinesterase activity. Other samples were taken daily before exposure, thus enzyme activity was determined 24 hours after exposure. In the first experiment, no changes were observed in serum cholinesterase or erythrocyte acetylcholinesterase in any of the men whether they had been exposed for one or 2 hours a day to 0.49 mg/m3 over the 4-day exposure period. Serum cholinesterase was slightly inhibited (about 20%) in 2 of 3 volunteers exposed for 2 hours a day for 4 consecutive days at 2.1 mg/m^3. No changes were seen in erythrocyte acetylcholinesterase in any of the men exposed to 2.1 mg/m^3 for either one or 2 hours a day over the 4-day period.

In the same study , groups of 2 rhesus monkeys (one of each sex) were exposed to atmospheres containing 0.48, 2.3, 2.6, or 12.9 mg/m^3 (0.053, 0.25, 0.29, or 1.43 ppm, respectively) for 2 hours a day on 4 consecutive days (Witter et al. 1961). The blood sampling procedures were the same as those used on the humans in this study. At the 0.48 and 2.3 mg/m^3 level, the monkeys were exposed with the humans. Exposure for 2 hours a day on 4 consecutive days at 0.48 mg/m^3 did not affect serum cholinesterase or erythrocyte acetylcholinesterase. Similar exposure at 2.3 and 2.6 mg/m^3 did not affect erythrocyte acetylcholinesterase, but caused about a 30% inhibition of serum cholinesterase. Exposure at 12.9 mg/m^3 (1.43 ppm) had visible effects on both cholinesterases and produced miosis, a clinical sign of organophosphate neurotoxicity. The monkeys exposed at this level showed substantial

inhibition of both cholinesterases from the first day of exposure. Activity fell throughout the 4-day exposure period; after the last day of exposure, serum cholinesterase was inhibited about 40-50% in both monkeys, and erythrocyte acetylcholinesterase fell about 40% in one monkey and 67% in the other. Pronounced miosis was also noted in both monkeys at the end of each 2-hour exposure period, but was not observed 24 hours later. No other clinical signs were noted. Serum cholinesterase and erythrocyte acetylcholinesterase determinations after exposure was terminated suggested that 40-50 days were required for a return to pre-exposure levels.

Rhesus monkeys housed in a chamber whose walls and ceiling had been sprayed with a xylene emulsion of dichlorvos were observed for two weeks (Durham et al. 1957). The original concentration in the chamber was approximately 6 mg/m^3 (0.66 ppm) and decreased to about 1 mg/m^3 (0.11 ppm) after 3 days and was about 0.1 mg/m^3 (0.01 ppm) for the remainder of the 2-week exposure. Blood samples were taken before exposure, after 1 week, after 2 weeks, and after exposure ceased, until serum cholinesterase and erythrocyte acetylcholinesterase had returned to pre-exposure values. Signs of neurological toxicity were not observed. By the end of the first week, both serum cholinesterase and erythrocyte acetylcholinesterase had fallen from their pre-exposure levels. Inspection of a graph in this report shows that levels of both blood cholinesterases fell about 50-60% during the first week of the study. Serum cholinesterase recovered partially in the third week, but erythrocyte acetylcholinesterase did not. After exposure was ended, the activities of both enzymes returned to pretreatment values in about five weeks.

Ten Sherman rats of each sex housed in the same chamber as the monkeys were also monitored in this experiment (Durham et al. 1957). No clinical signs of neurological toxicity were observed in the rats over the 2-week exposure period. There was a slight decrease in serum cholinesterase and erythrocyte acetylcholinesterase at the end of the first week (about 10% for each enzyme). At the end of 2 weeks, no difference was observed between exposed rats and controls. Bronchial and erythrocyte acetylcholinesterase were measured in male Sprague-Dawley rats exposed to atmospheres ranging from 0 to 56.64 mg/m^3 (0-6.26 ppm) over a 3-day period (Schmidt et al. 1979). A dose-dependent reduction in both bronchial and erythrocyte acetylcholinesterase was observed. Bronchial tissue acetylcholinesterase measured in homogenates from treated rats at 0.83 and 1.82 mg/m^3 (0.09 and 0.20 ppm, respectively) was lower than in control rats; bronchial tissue acetylcholinesterase was inhibited by 50% at 1.82 mg/m^3, a dose that did not affect erythrocyte acetylcholinesterase. Erythrocyte acetylcholin-esterase was inhibited by 62% at 4.32 mg/m^3 (0.48 ppm) and was more than 80% inhibited at

8.2 mg/m^3 (0.91 ppm) after 3 days exposure. The authors reported that "similar" results were found in animals exposed for 7- and l4-day periods, but the data were not presented. Because clinical signs or pulmonary function parameters were not reported in this study, the toxicological significance of this level of bronchial enzyme inhibition in the male Sprague-Dawley rats cannot be assessed.

Several studies in animals have addressed neurological effects after intermediate-duration inhalation exposure to dichlorvos. In a study of pregnant Carworth E rats exposed over their gestation period (20 days), some dams exposed to atmospheres containing 6.25 mg/m^3 (0.69 ppm) were less active than controls (Thorpe et al. 1972). Exposure at 0.25 mg/m^3 (0.03 ppm) did not affect erythrocyte or brain acetylcholinesterase. Exposure at 1.25 mg/m^3 (0.14 ppm) resulted in a 29% inhibition of erythrocyte and a 28% inhibition of brain acetylcholinesterase, while exposure at 6.25 mg/m^3 resulted in 88% inhibition of erythrocyte acetylcholinesterase and an 83% inhibition of brain acetylcholinesterase. In the same exposure atmosphere, pregnant Dutch rabbits showed inhibition of 14 and 10% in erythrocyte and brain acetylcholinesterase, respectively, at an exposure of 0.25 mg/m^3 (0.03 ppm) over a period of 28 days (Thorpe et al. 1972). At exposures of 1.25 mg/m^3 (0.14 ppm) erythrocyte acetylcholinesterase was inhibited 68% and brain acetylcholinesterase was inhibited 56% compared to controls. Exposure of Yorkshire pigs for 24 days to atmospheres containing 0.09-0.11 mg/m^3 (0.010-0.012 ppm) had no effect on serum cholinesterase or erythrocyte acetylcholinesterase (Loeffler et al. 1976).

In a 2-year chronic inhalation study with dichlorvos (Blair et al. 1976), 50 Carworth E rats of each sex were exposed to atmospheres containing 0, 0.05, 0.5, or 5 mg/m^3 (0, 0.006, 0.06, or 0.6 ppm). No clinical signs of neurological toxicity were seen in any of the groups. Acetylcholinesterase activity was measured in brain and erythrocytes, as was serum cholinesterase, at the end of this study. In male animals exposed to 0.05 mg/m^3 (0.006 ppm), no significant differences with control animals were seen for any of the cholinesterases. Female animals at this exposure level had a statistically significant decrease of 12% in erythrocyte acetylcholinesterase. At 0.5 mg/m^3 (0.06 ppm), brain cholinesterase was 10% lower compared to controls in both male and female rats. Females at this exposure level also showed erythrocyte acetylcholinesterase inhibition of 31%, while the males were unaffected. At 5 mg/m^3 (0.6 ppm), brain acetylcholinesterase was inhibited by 79% and 81% in male and female rats, respectively. Erythrocyte acetylcholinesterase inhibition at this dose was 96% in the male rats and 95% in the female rats.

No studies were located in humans or animals describing organophosphate-induced delayed neuropathy (OPIDN) after inhalation exposure to dichlorvos. This is a syndrome observed in humans and some animal models after recovery from the acute cholinergic effects of certain organophosphorus compounds, for example tri-o-cresyl phosphate (Coppock 1995; Johnson 1981). The characteristic signs are disturbances of gait, and a “dying-back” type degeneration of motor fibers. Studies on the relationship between dichlorvos and OPIDN for parenteral routes of exposure are discussed in Section 2.5.

All reliable NOAELs and LOAELs for neurological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive toxicity in humans after inhalation exposure to dichlorvos.

In a reproductive toxicity study involving male CF-1 mice, groups of 16 mice were exposed to atmospheres containing dichlorvos at 0, 30, or 55 mg/m^3 for 16 hours (0, 3.3, or 6.1 ppm) (Dean and Thorpe 1972). Following dosing, each male mouse was caged with 3 randomly selected females for 7 days; this procedure was repeated weekly for a total of 8 weeks. Thirteen days after the presumed mating (which occurred by the middle of the week), the female mice were sacrificed and the uteri removed for examination. There were no differences between control and treated mice in the number of early fetal deaths, late fetal deaths, or live fetuses found in the pregnant females. The percentages of pregnancies for females mated to males exposed to 30 or 55 mg/m^3 (3.3 or 6.1 ppm) for 16 hours ranged from 67 to 88% and 63-92%, respectively; for controls, the percentages ranged from 73 to 88%. Under these exposure conditions, dichlorvos did not appear to affect the fertility of male CF-1 mice.

In another experiment in this study, similar results were obtained for male mice exposed for 4 weeks to atmospheres containing 2.1 or 5.8 mg/m3 (0.23 or 0.64, respectively) dichlorvos for 23 hours a day (Dean and Thorpe 1972).

Maternal toxicity was reported in Dutch rabbits exposed throughout gestation to atmospheres containing dichlorvos at 4 or 6.25 mg/m^3 (0.44 or 0.69 ppm). Sixteen of 20 dams died at the higher dose; when the concentration was reduced to 4 mg/m^3, 6 of 20 dams died (Thorpe et al. 1972). Exposure spikes occurred at both exposure concentrations and may have contributed to the observed toxicity. Maternal toxicity was not observed in Carworth E strain rats exposed to atmospheres containing 0, 0.25, 1.25, and 6.25 ug/L dichlorvos (0, 0.03, 0.14, and 0.69 ppm) through day 20 of pregnancy (Thorpe et al. 1972).

The NOAELs for reproductive effects are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.6 Developmental Effects

No studies were located regarding developmental toxicity in humans after inhalation exposure to dichlorvos.

Several animal studies examining developmental toxicity during continuous inhalation exposure to dichlorvos are available. A study in which pregnant mice and rabbits were exposed to dichlorvos only during the organogenesis period of gestation showed no significant effect on development (Schwetz et al. 1979). In this study, pregnant CF-1 mice were exposed to 4 mg/m^3 (0.44 ppm) dichlorvos for 7 hours a day during gestation days 6-15. At sacrifice on day 18, no significant effects were seen on the mean number of fetuses per litter, the incidence or distribution of resorptions, or on fetal body measurements. Twenty control litters and 15 litters from treated animals were examined in this study. There was no difference between the litters from controls and dichlorvos-treated dams. Pregnant New Zealand rabbits exposed to 4 mg/m^3 (0.44 ppm) for 7 hours a day during gestation days 6-18 also showed no evidence of developmental toxicity (Schwetz et al. 1979). Mean number of fetuses per litter, incidence or distribution of resorptions and fetal body measurements were similar in 14 control litters and 19 treated litters.

Groups of 15 pregnant Cat-worth E rats were exposed to atmospheres containing 0, 0.25, 1.25, or 6.25 mg/m^3 (0, 0.03, 0.14, or 0.69 ppm) throughout their 20-day gestation period (Thorpe et al. 1972). At the end of 20 days, the rats were sacrificed and the uteri removed for examination. The number of live fetuses, late fetal deaths, and resorption sites were noted, and live fetuses were weighed and examined for external malformations. Approximately half the fetuses in each litter were processed for

alizarin-stained preparations of the skeleton, and the other half were fixed in Bouin's fluid and examined for structural abnormalities of the viscera by transverse sections. Exposure of dams to all three concentrations of dichlorvos did not affect the number of fetal resorptions, late fetal deaths, litter size, or mean weight per fetus. One fetus in the litter of dams in the 0.25 mg/m^3 group had skeletal defects and gastroschisis. Because no other fetuses from dams exposed to the same or higher concentrations had these defects, the authors concluded that they were not exposure-related. Brain and erythrocyte acetylcholinesterase activities were inhibited 83 and 88%, respectively, in dams in the high-exposure (6.25 mg/m^3) group, suggesting that acetylcholinesterase inhibition is not associated with teratogenicity. Measurement of acetylcholinesterase activities in the pups was not performed.

In a parallel experiment conducted on groups of 20 pregnant Dutch rabbits (Thorpe et al. 1972), similar results were seen. Dams exposed to dichlorvos at 6.25 mg/m^3 (0.69 ppm), as in the previously described rat study, had high mortality (16 of 20 died). Consequently, the doses used in this experiment were 0, 0.25, 1.25, 2, and 4 mg/m^3 (0, 0.03, 0.14, 0.22, and 0.44 ppm) over the 28-day rabbit gestational period. Six of the 20 rabbits exposed to 4 mg/m^3 died. In both the 4 and 6.25 mg/m^3 exposure groups, spiking of the exposure concentration occurred. Sizes of litters, fetal resorptions, and late fetal deaths were unaffected by inhalation exposure to dichlorvos. Mean fetal weights were significantly depressed (23.1 ± 0.98 g for controls and 20.2 ± 0.98 g for the 4 mg/m^3 exposure group), but the authors ascribed this to maternal toxicity. Clinical signs were similar to signs for dams exposed to 6.25 mg/m^3; 6 dams out of 20 in this group died during the study. Three fetuses from groups that had not been exposed to dichlorvos had gastroschisis. Two dead fetuses from one litter in the 4 group had cleft palates, but this may also be a result of maternal toxicity rather than a developmental effect.

The NOAELS for developmental toxicity are recorded in Table 2-l and plotted, in Figure 2-l.

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to dichlorvos.

In a 2-year carcinogenicity study of dichlorvos by inhalation exposure (Blair et al. 1976). groups of 50 Carworth E rats of each sex were exposed to atmospheres containing dichlorvos at 0, 0.05, 0.5, or 5 mg/m^3 (0, 0.006, 0.06, or 0.6 ppm) for 23 hours a day. Necropsies were carried out on animals that died or were sacrificed because of ill health during the study. At the end of the study, the surviving rats were sacrificed, and blood samples taken, necropsies performed, and major organs weighed. Major viscera, macroscopic tumors, and blocks of tongue, nasal cavity, trachea, skeletal muscle, eye, and lachrymal gland were fixed in formalin and processed for paraffin section. Respiratory tissue from a small number (not stated) of control and high-dose animals was examined by electron microscope. Only 11 of the unexposed male controls and 25 of the unexposed female controls survived to the end of the study. Survival was highest in the rats exposed to the highest concentration of dichlorvos (32 of 50 males and 34 of 50 females). Microscopical examination revealed a wide range of lesions in all groups; the authors stated that these are commonly seen in old rats of this strain. There was a high incidence in control and treated groups of chronic nephrosis, focal myocardial fibrosis, degenerative artery disease, lymphoid hyperplasia of the spleen, and testicular atrophy. Common tumors in all groups were adenomas of the anterior pituitary gland, parafollicular cell adenomas and carcinomas of the thyroid gland, adrenal pheochromocytomas, and mammary fibroadenomas in the females. Examination of the lungs (presumably the tissue receiving the highest dose) revealed minor changes in all groups. Peribronchial and perivascular lymphoid aggregates, mild degrees of bronchiolitis, and focal alveolar thickening were noted. Electron microscopic examination of bronchi, bronchioli, and alveoli of a small number of control and high-dose group animals showed no differences between the groups. None of the lesions in the study was associated with dichlorvos exposure.

The high mortality of the control animals in this study makes interpretation of the carcinogenicity data problematic. The possibility also exists that exposure by the oral and dermal routes occurred since the animals received whole-body exposure to dichlorvos vapor in cages rather than nose-only exposure. However, no significant increase in neoplastic or non-neoplastic lesions was found in the nasal and respiratory tract tissues that presumably received the highest dose of dichlorvos.

2.2.2 Oral Exposure

2.2.2.1 Death

Two deaths in humans have been associated with oral exposure to dichlorvos (Hayes 1982). In one case, a young woman who drank an undetermined amount of dichlorvos died despite prompt medical treatment. In another case, a 19-month-old girl who ate part of a cake-like bait that contained dichlorvos died after 4 days (Hayes 1982). The actual bait she consumed was not recovered for analysis, but because similar baits were found to contain both dichlorvos and malathion, it is possible that an interaction with malathion may have occurred. Malathion had much lower acute toxicity than dichlorvos when measured in an LD 50 (lethal dose, 50% kill) study in male Sherman rats; the LD_{50} for malathion was 1,375 mg/kg, while that for dichlorvos was 80 mg/kg (Durham et al. 1957). Severe cerebral edema was considered the cause of death.

A number of oral exposure LD_{50} studies have been done with dichlorvos in rats and mice. Based on reported LD_{50} values, dichlorvos is considered to be of moderate to high acute toxicity (WHO 1989). In the most extensive study of this type, dichlorvos was one of 5 chemicals used in a study designed to investigate how well an experimentally derived LD50 value would predict the level that would result in 1% lethality (LD_l value) for CD-l mice (Haley et al. 1975). The LD50 for male mice in this study was calculated to be 139 mg/kg, and the LD50 for females was 133 mg/kg. In a subsequent study at lower doses, the LD_l for the male mice was 84 mgkg (predicted LD_1 was 81 mg/kg). In the female mice, the LD_1 was 95 mg/kg (predicted LD_1 was 106 mg/kg). The authors further estimated an $LD_{0.1}$ of 70 mg/kg for male mice and 82 mg/kg for female mice. An LD_{50} of 110 mg/kg was reported in male ICR mice (Takahashi et al. 1987). Dichlorvos administered by gavage in water at a dose of 150 mg/kg to male Swiss mice caused 100% lethality within 9 minutes (Mohammad et al. 1989).

In Sherman rats, oral LD_{50} values of 80 mg/kg in males and 56 mg/kg in females were reported (Durham et al. 1957). The LD_{50} for female Wistar rats was reported to be 58.8 mg/kg (Gajewski and Katkiewicz 1981) and in male Fischer 344 rats 97.5 mg/kg (Ikeda et al. 1990). Crossbred pigs weighing 12-27 kg treated with dichlorvos in gelatin capsules were reported to have an LD_{50} of 157 mg/kg (Stanton et al. 1979).

Other studies have reported deaths in animals after acute-duration oral exposure to dichlorvos. Three of 12 greyhound dogs receiving 22 mg/kg in a gelatin capsule died (Snow and Watson 1973). Two of the dogs died within 20 minutes of dosing; cyanosis was severe and progressive, and sounds of gas passage in the respiratory tract ceased in spite of continued respiratory effort. This was followed soon afterwards by respiratory arrest and then cardiac arrest. Another dog dosed at 22 mg/kg was comatose for a long period, had repeated convulsive episodes, and died 15.5 minutes after dosing. In castrated male (surgery at 10 days of age) and female crossbred pigs treated with dichlorvos in gelatin capsules, deaths occurred 15-30 minutes after dosing (Stanton et al. 1979) in a single pig dosed with 560 mg/kg, in 7 of 8 at 320 mg/kg, in 5 of 8 at 150 mg/kg, and in 2 of 8 at 100 mg/kg. Clinical signs observed in these animals included hypoactivity, vomiting, ataxia, muscle fasciculations, uncoordinated movements, frothy salivation, and defecation. One white Leghorn hen treated on 2 consecutive days with 7.1 mg/kg in gelatin capsules also died after the second treatment (Francis et al. 1985). Clinical signs were staggering gait, salivation and convulsions. Birds are generally more susceptible to organophosphorus compounds due to lack of detoxification pathways.

Intermediate-duration exposure to dichlorvos has also caused death in experimental animals. In a dose-finding study where Osborne-Mendel rats (5 of each sex) were exposed to dichlorvos-containing feed at dosages of 0-360 mg/kg/day for a 6-week period, all rats consuming 2180 mg/kg/day died (NCI 1977). Exposure to 90 mg/kg/day did not cause any deaths. In a dose-finding study for a 2-year carcinogenicity experiment, Fischer 344 rats (10 of each sex) were treated by corn oil gavage 5 days a week for 13 weeks over a dosage range of 0-64 mg/kg/day (NTP 1989). All rats receiving 32 and 64 mg/kg died before the end of the study. Some animals that died were trembling and inactive immediately before death. Of the male rats receiving 64 mg/kg, 90% died by the first week of the study, while 90% of the male rats receiving 32 mg/kg died in the seventh week of the study. One of the 10 male rats receiving 16 mg/kg died, but the authors stated that this was gavage-related. Male rats at dosages of 2, 4, and 8 mg/kg survived for 13 weeks. All female rats receiving 32 or 64 mg/kg died in the first week. Four of 10 females receiving 16 mg/kg died by the seventh week. All female rats receiving 2, 4, and 8 mg/kg survived for 13 weeks.

In similar intermediate-duration studies in mice, groups of 5 $B6C3F_1$ mice were exposed by feed to dosages ranging from 0 to 1,080 mg/kg/day for 6 weeks (NCI 1977). Four of 5 females died at the 720 mg/kg/day dose; all mice consuming 1,080 mg/kg/day died. No deaths were reported in mice consuming 360 mg/kg/day or less. In another study (NTP 1989), groups of 10 $B6C3F_1$ mice of each

sex were dosed by corn oil gavage at levels ranging from 0 to 160 mg/kg for 5 days a week for 13 weeks. All 10 male mice and 9 of 10 female mice who received 160 mg/kg died. Eight of the male mice died in the first week, as did 3 female mice. Five of 10 male mice died after receiving 80 mg/kg.

In a chronic-duration study (2 years) where Osborne-Mendel rats of both sexes were exposed through feed to doses of 0, 13.5, and 29.3 mg/kg/day, survival was higher in the treated groups than in the matched control animals (NCI 1977); 76% of the high-dose and 64% of the low-dose males survived, as did 84% of the high-dose and 80% of the low-dose females. The authors stated the rats were in poor condition in both In a similar study using Fischer 344 rats (NTP 1989), no significant differences were observed in survival among groups of either sex treated by corn oil gavage at doses of 0, 4, or 8 mg/kg for 5 days a week for 103 weeks. In a 2-year study of $B6C3F_1$ mice, no significant differences in survival were noted between groups of either sex exposed through feed to doses of 0, 57.2, or 114.3 mg/kg/day (NCI 1977). In another 2-year study in $B6C3F_1$ mice (NTP 1989), no significant differences in survival were noted among groups treated by corn oil gavage at doses of 0, 10, or 20 mg/kg for 5 days a week in male mice or at 0, 20, or 40 mg/kg for 5 days a week in female mice.

No deaths were reported in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day dichlorvos by capsule in corn oil for 52 weeks (AMVAC Chemical Corp. 1990).

All reliable LD_{50} values and LOAELs for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies regarding systemic effects in humans after oral exposure to dichlorvos were located. No studies regarding musculoskeletal or metabolic effects in animals after oral exposure to dichlorvos were located. Most of the systemic effects of dichlorvos after oral exposure are secondary to the neurotoxicity of this chemical.

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

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sherman)	once (GO)				80 M (LD_{50}) 56 F (LD_{50})	Durham et al. 1957
2	Rat (Wistar)	once (GO)				58.8 F (LD_{50})	Gajewski and Katkiewicz 1981
3	Rat (Fischer- 344)	once (GO)				97.5 M (LD_{50})	Ikeda et al. 1990
4	Mouse (CD-1)	once (GO)				139 M (LD_{50}) 133 F (LD_{50})	Haley et al. 1975
5	Mouse (ICR)	once (G)				110 M (LD_{50})	Takahashi et al. 1987
6	Dog (greyhound)	once (C)				22 (3 of 12 died)	Snow and Watson 1973
7	Pig (Hybrid)	once (C)				157 (LD_{50})	Stanton et al. 1979
8	Chicken (white leghorn)	2 d 1 x/d (C)				7.1 F (1 of 1 died)	Francis et al. 1985

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

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
9	Dog (greyhound)	once (C)	Hemato		11 (transient increase in hematocrit > 10%)		Snow and Watson 1973
			Musc/skel		11 (increase in serum creatine phosphokinase)		
			Hepatic		11 (increase in SGOT)		
	Immunological/Lymphoreticular						
10	Mouse (C57BL/6N)	1 x or 4 x (GO)		40M	120M (reduced IgM response, 11% decrease in relative spleen weight)		Casale et al. 1983
	Neurological						
11	Rat (Fischer- 344)	10 d 5 x/wk (GO)		16			NTP 1989
12	Rat (Albino)	once (NS)				40 M (83% inhibition of brain AChE 15 min after administration)	Pachecka et al. 1977
13	Rat (Sprague-Dawley)	once (GO)				40 M (brain AChE inhibited 70%)	Teichert et al. 1976
14	Rat (Sprague-Dawley)	14 d 1 x/d (GO)			4[b] M (brain AChE inhibited 45%)		Teichert et al. 1976
15	Mouse (C57BL/6N)	1x or 4 x (GO)			40M (30 and 31% reductions in brain and erythrocyte AChE respectively)	120 M (75% reduction in brain AChE 1 hour after dosing, tremor)	Casale et al. 1983

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

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference
16	Mouse (B6C3F1)	11 d 5 x/wk (GO)		40				NTP 1989
17	Dog (greyhound)	once (C)				11	(ataxia, fasciculations, 75% decrease in erythrocyte AChE)	Snow and Watson 1973
18	Pig (NS)	once (C)				18	(ataxia, fasciculations)	Stanton et al. 1979
	Reproductive							
19	Mouse (CF-1)	10 d Gd 6-15 1 x/d (GO)		60				Schwetz et al. 1979
	Developmental							
20	Mouse (CF-1)	10 d Gd 6-15 1 x/d (GO)		60				Schwetz et al. 1979
21	Rabbit (New Zealand)	13 d Gd 6-18 1 x/d (GO)		5				Schwetz et al. 1979

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

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Death						
22	Rat (Osborne-Mendel)	6 wk (F)				180 (10 of 10 died)	NCI 1977
23	Rat (Fischer- 344)	13 wk 5 d/wk (GO)				16 F (4 of 10 died in the 7th week)	NTP 1989
24	Mouse (B6C3F1)	6 wk (F)				720 F (4 of 5 died)	NCI 1977
25	Mouse (B6C3F1)	13 wk 5 d/wk (GO)				80 M (5 of 10 died) 160 F (9 of 10 died)	NTP 1989
	Neurological						
26	Human	21 d 3 x/d (F)		0.033[c] M			Boyer et al. 1977
27	Rat (Sherman)	90 d (F)		3.5 F	14.2 F (30% inhibition of erythrocyte AChE)	35.7 F (80% inhibition of erythrocyte AChE)	Durham et al. 1957
28	Rat (Fischer- 344)	32 d 5 x/wk (GO)		8 M 16 F	16M (22% inhibition of erythrocyte AChE on day 24)		NTP 1989
29	Mouse (B6C3F1)	25 or 33 d 5 x/wk (GO)		40			NTP 1989

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

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
30	Chicken (white leghorn)	35-90 d 1 x/d (C)		4.4 F		6.1 F (staggering gait after 35 days)	Francis et al. 1985
	CHRONIC EXPOSURE						
	Systemic						
31	Rat (Fischer- 344)	103 wk 5 d/wk (GO)	Cardio	8			NTP 1989
			Gastro	8			
			Musc/skel	8			
			Hepatic	8 F	4 M (cytoplasmic vacuolization in liver cells)		
			Renal	8			
			Endocr		4 (cytoplasmic vacuolization in adrenal cortical cells)		
			Dermal	8			
			Bd Wt	8			

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

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
32	Mouse (B6C3F1)	103 wk 5 d/wk (GO)	Resp	20 M 40 F			NTP 1989
			Cardio	20 M 40 F			
			Hemato	20 M 40 F			
			Musc/skel	20 M 40 F			
			Hepatic	20 M 40 F			
			Renal	20 M 40 F			
			Endocr	20 M 40 F			
			Dermal	20 M 40 F			
			Bd Wt	20 M 40 F			

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
33	Dog (Beagle)	52 wk 1 x/d (C)	Resp	3.0			AMVAC Chemical Corp. 1990
			Cardio	3.0			
			Gastro	3.0			
			Hemato	3.0			
			Musc/skel	3.0			
			Hepatic	3.0			
			Renal	3.0			
			Endocr	3.0			
			Dermal	3.0			
			Ocular	3.0			
			Bd Wt	3.0			
			Metab	3.0			
	Immunological/Lymphoreticular						
34	Dog (Beagle)	52 wk 1 x/d (C)		3.0			AMVAC Chemical Corp. 1990
	Neurological						
35	Rat (Fischer- 344)	103 wk 5 d/wk (GO)			4 (mild diarrhea)		NTP 1989
36	Mouse (B6C3F1)	103 wk 5 d/wk (GO)		20 M 40 F			NTP 1989

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

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
37	Dog (Beagle)	52 wk 1 x/d (C)		0.05 d	1.0 M (22% inhibition of brain AChE, 53% inhibition of erythrocyte AChE) 1.0 F (45% inhibition of erythrocyte AChE)	3.0 M (47% inhibition of brain AChE, 85% inhibition of erythrocyte AChE) 3.0 F (81% inhibition of erythrocyte AChE)	AMVAC Chemical Corp. 1990
Reproductive							
38	Rat (Fischer- 344)	103 wk 5 d/wk (GO)		8			NTP 1989
39	Mouse (B6C3F1)	103 wk 5 d/wk (GO)		20 M 40 F			NTP 1989
40	Dog (Beagle)	52 wk 1 x/d (C)		3.0			AMVAC Chemical Corp. 1990

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

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Cancer						
41	Mouse (B6C3F1)	103 wk 5 d/wk (GO)				40 F CEL: (forestomach squamous cell papillomas and carcinomas)	NTP 1989

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an acute-duration minimal risk level (MRL) of 0.004 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for human variability and 10 for extrapolation from animals to humans)

[c]Used to derive an intermediate-duration MRL of 0.003 mg/kg/day; dose divided by an uncertainty factor of 10 for human variability.

[d]Used to derive a chronic-duration MRL of 0.0005 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for human variability and 10 for extrapolation from animals to humans).

AChE = acetylcholinesterase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cander effect level; d = day(s); F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; SGO = serum glutamic oxaloacetic transaminase; (W) = water; wk = week(s); x = times.

Figure 2-2. Levels of Significant Exposure to Dichlorvos - Oral

Acute (≤14 days)

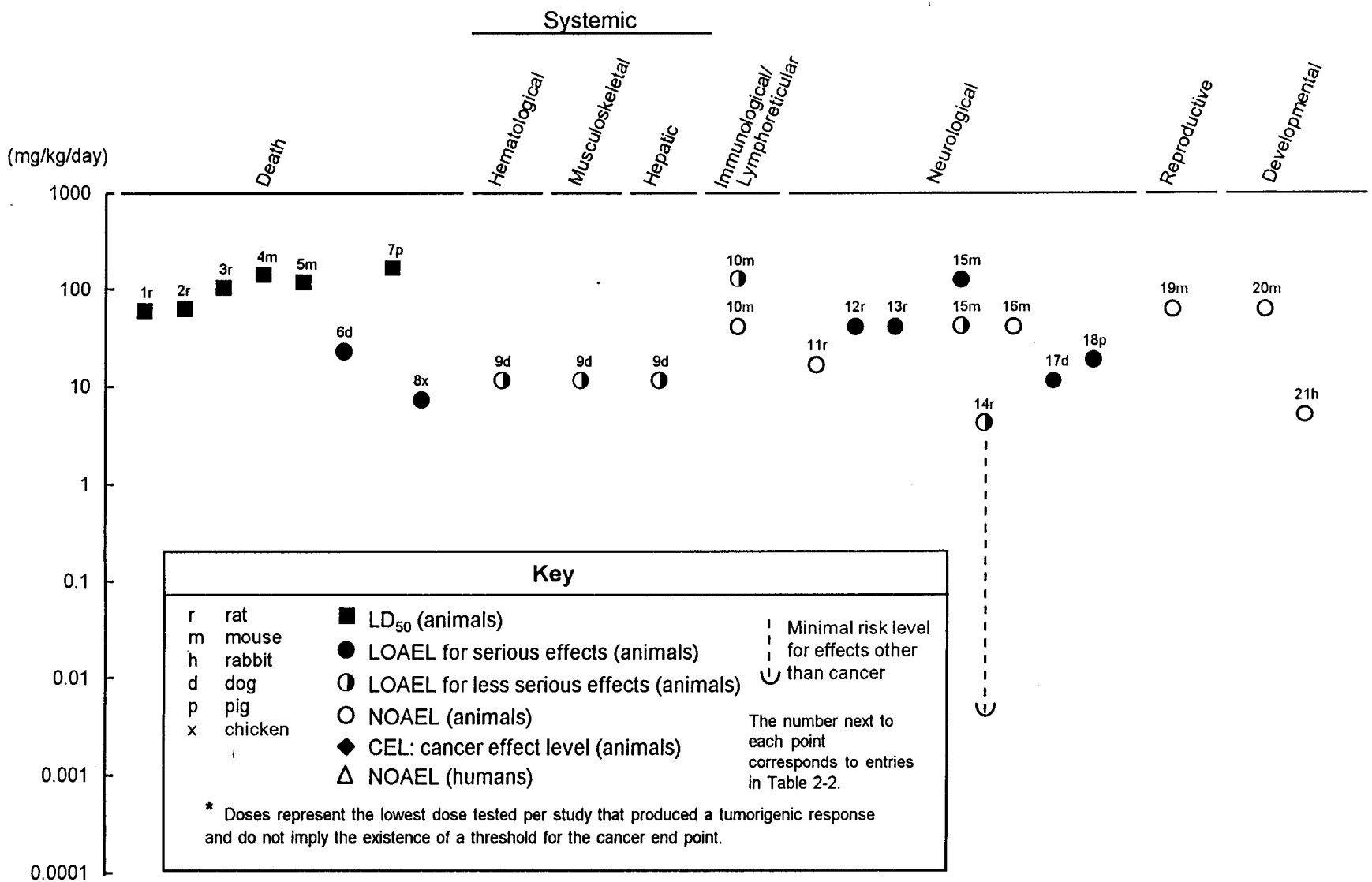


Figure 2-2. Levels of Significant Exposure to Dichlorvos - Oral (cont.)

Intermediate (15-364 days)

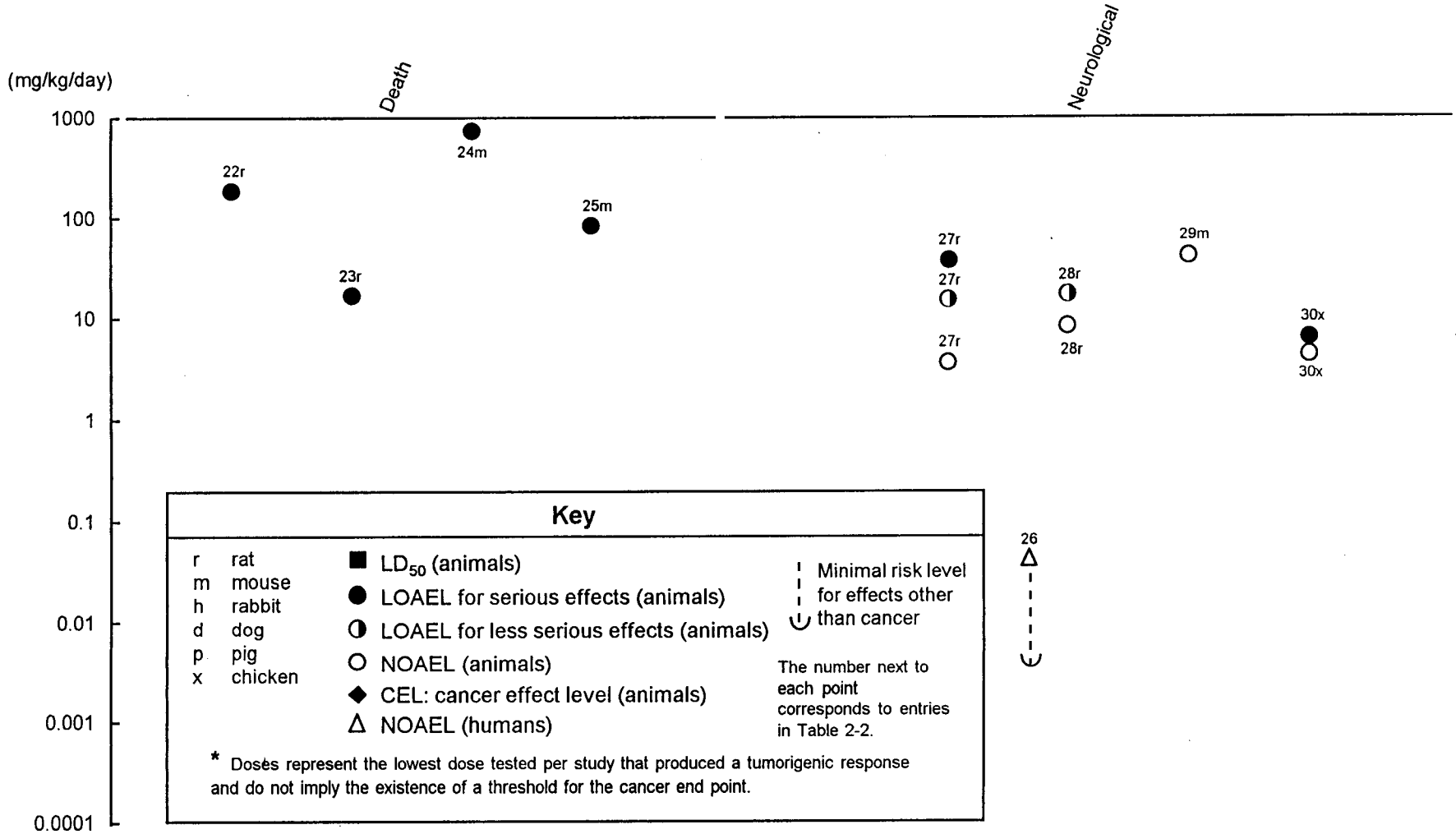
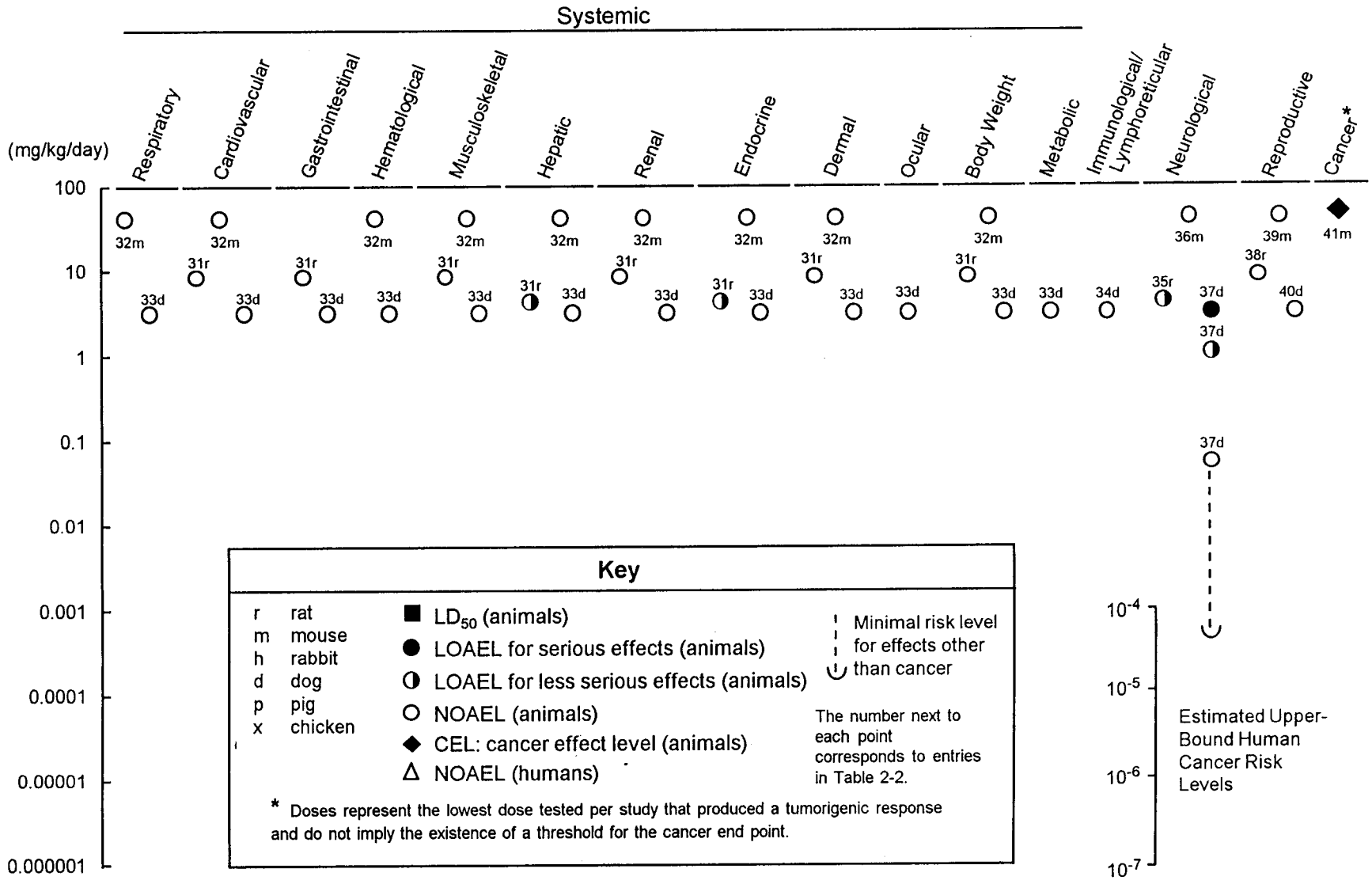


Figure 2-2. Levels of Significant Exposure to Dichlorvos - Oral (cont.)

Chronic (≥365 days)



Respiratory Effects. No gross or histological evidence of treatment-related damage to the lungs, mainstream bronchi, or trachea was observed in B6C3F, mice treated by oral gavage with dichlorvos at 20 mg/kg/day (males) or 40 mg/kg/day (females) for 5 days a week for 2 years (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

Cardiovascular Effects. No gross or histological evidence of treatment-related damage to the heart was seen in Fischer 344 rats treated with up to 8 mg/kg/day dichlorvos for 5 days a week for 2 years. Similar results were seen in B6C3Fl mice treated in the same study with dichlorvos at 20 mg/kg/day (males) or 40 mg/kg/day (females) for 5 days a week (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

Gastrointestinal Effects. Diarrhea, sometimes bloody, and vomiting were observed in greyhound dogs exposed orally to dichlorvos in gelatin capsules at a single dose of 11 mg/kg (Snow and Watson 1973). Vomiting and defecation were also reported in crossbred pigs dosed at 18 mg/kg in gelatin capsules (Stanton et al. 1979). Excessive salivation and defecation were observed before death in male Swiss mice receiving 150 mg dichlorvos emulsion/kg by water gavage (Mohammad et al. 1989). Diarrhea was reported in Osborne-Mendel rats receiving 90 mg dichlorvos kg/day over a 3-week period (NCI 1977). This diarrhea was so severe that the dichlorvos dose was reduced to 29 mg/kg/day for the remainder of this 2-year study. Similar signs were seen in B6C3F, mice receiving 360 mg/kg/day dichlorvos in the same study (NCI 1977), and dosages were reduced to 114 mg/kg/day in these mice. Mild diarrhea was reported throughout a 2-year study in male rats receiving 4 or 8 mg/kg/day dichlorvos (NTP 1989). Diarrhea and vomiting may reflect a local irritant action of dichlorvos on the gastrointestinal tract; however, these signs may also be caused by muscarinic cholinergic stimulation (Ecobichon 1991).

No gross or histological evidence of treatment-related damage to gastrointestinal tissues (cecum, colon, duodenum, esophagus, ileum, jejunum, rectum and stomach) was found in Fischer 344 rats treated with up to 8 mg/kg/day dichlorvos by gavage 5 days a week for 2 years (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990). Significantly increased neoplastic lesions were found in the forestomach of female mice treated in the NTP study at doses of 20 and 40 mg/kg/day (see Section 2.2.2.8).

Hematological Effects. A 10% increase in hematocrit was seen in greyhound dogs exposed to a single dose of 11 mg/kg and showing moderate to severe signs of toxicity (Snow and Watson 1973). Total plasma proteins increased in all but one dog that received 22 mg/kg. Diarrhea was also observed, thus the increase in hematocrit and total plasma proteins may have been caused by dehydration. In dogs dosed with 11 or 22 mg/kg, a slight leukocytosis was observed in animals showing moderate to severe signs of toxicity (Snow and Watson 1973).

No gross or histological evidence of treatment-related damage to bone marrow or spleen was observed in $B6C3F_1$ mice treated with up to 40 mg/kg/day dichlorvos by gavage for 5 days a week for 2 years (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990). Significantly increased neoplastic lesions (leukemia) were observed in Fischer 344 male rats in the NTP study at doses of 4 and 8 mg/kg/day (See Section 2.2.2.8)

Musculoskeletal Effects. A l0-fold increase in serum creatine phosphokinase, suggestive of muscle damage, was observed in a greyhound dog treated once with 11 mg/kg dichlorvos in capsules (Snow and Watson 1973). No gross or histological evidence of treatment-related damage to skeletal muscle was observed in Fischer 344 rats treated with up to 8 mg/kg/day dichlorvos by gavage 5 days a week for 2 years, $B6C3F_1$ mice treated with up to 40 mg/kg/day dichlorvos by gavage for 5 days a week for 2 years (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

Hepatic Effects. A 2-fold increase in SGFT, indicating liver damage, was observed in a greyhound dog treated once with 11 mg/kg dichlorvos in capsules (Snow and Watson 1973). Cytoplasmic vacuolization of liver cells was noted in male Fischer 344 rats receiving 4 or 8 mg/kg/day dichlorvos by gavage for 5 days a week for 2 years (NTP 1989). The authors stated that these changes were minor in extent but have been associated with lipid accumulation in cells. No gross or histological evidence of treatment-related damage was observed in livers from female rats or in $B6C3F_1$ mice receiving 20 mg/kg/day (males) or 40 mg/kg/day (females) for 2 years in the same study (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

Renal Effects. No gross or histological evidence of treatment-related damage to the kidneys was observed in Fischer 344 rats or B6C3Ft mice treated with dichlorvos by gavage 5 days a week for 2 years at doses of 8 mg/kg/day (rats), 20 mg/kg/day (male mice) or 40 mg/kg/day (female mice) (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

Endocrine Effects. Cytoplasmic vacuolization of adrenal cortical cells was noted in male Fischer 344 rats receiving 4 or 8 mg/kg/day dichlorvos by gavage for 5 days a week for 2 years (NTP 1989). The authors stated that these changes were minor in extent but have been associated with lipid accumulation in cells. Significant neoplastic lesions of the pancreas (adenomas) were also observed in the male rats (see Section 2.2.2.8). No increase in lesions was observed for male or female rats in the parathyroid, pituitary, thyroid or thymus glands. No treatment-related lesions were observed for any endocrine tissue in $B6C3F_I$ mice treated for 2 years at 20 mg/kg/day (males) or 40 mg/kg/day (females) (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

Dermal Effects. No gross or histological evidence of treatment-related damage to the skin was observed in Fischer 344 rats or $B6C3F_1$, mice treated with dichlorvos by gavage 5 days a week for 2 years at doses of 8 mg/kg/day (rats), 20 mg/kg/day (male mice), or 40 mg/kg/day (female mice) (NTP 1989) or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

Ocular Effects. The effect of dichlorvos on pupillary response to light has been studied in Beagles (Wagstaff and Winston 1980). The dogs received 0, 13.5, 27, or 40.5 mg/kg in a PVC-resin formulation. Dichlorvos did not affect the resting pupil and no miosis was observed. However, in response to a strobe light flash, dogs receiving 27 or 40.5 mg/kg had a greater contraction and a slower recdvery to baseline pupillary diameter. No histopathological evidence of ocular damage related to dichlorvos treatment was found in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

Body Weight Effects. No effects on body weight were observed in Fischer 344 rats or $B6C3F_1$, mice treated with dichlorvos by gavage 5 days a week for 2 years at doses of 8 mg/kg/day (rats),

20 mg/kg/day (male mice) or 40 mg/kg/day (female mice) (NTP 1989), or in Beagle dogs (groups of 4 of each sex) receiving up to 3 mg/kg/day by capsule for 52 weeks (AMVAC Chemical Corp. 1990).

2.2.2.3 Immunological and Lymphoreticular Effects

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

Immunosuppression after oral exposure to dichlorvos has been reported (Desi et al. 1978). A doserelated suppression of the humoral immune response induced by *Salmonella typhimurium* was observed in rabbits administered 0.3-2.5 mg/kg dichlorvos 5 days a week for 6 weeks (Desi et al. 1978). A single oral dose of 120 mg/kg dichlorvos in male C57B l/6 mice inoculated with sheep erythrocytes 2 days earlier suppressed the primary IgM response observed 48 hours later (Casale et al. 1983). A decrease in relative spleen weight was also noted in this study. Severe signs of dichlorvos neurotoxicity were noted, and the authors stated that the immunosuppression observed in this study may have been mediated indirectly by toxic chemical stress.

In Beagle dogs treated with dichlorvos at up to 3 mg/kg/day for 52 weeks (AMVAC Chemical Corp. 1990) no histopathologic treatment-related changes were seen in the mesenteric lymph node, spleen, sternum with bone marrow, and thymus. Leukocyte and reticulocyte counts were also unchanged compared to control, as was the leukocyte differential count.

2.2.2.4 Neurological Effects

Dichlorvos exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase. This enzyme is present at cholinergic synapses throughout the central and peripheral nervous systems, and is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synaptic cleft, resulting in increased depolarization of the post-synaptic membrane. The consequences of this increased cholinergic activity in the parasympathetic autonomic nervous system can include lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, increased salivation, and increased urinary frequency and incontinence. Effects on motor nerve fibers in the skeletal muscles can include muscle fasciculations, cramps, muscle weakness, and paralysis. Effects on cholinergic synapses in the

central nervous system result in drowsiness, fatigue, mental confusion, headache, convulsions. and coma. These classical symptoms of organophosphate neurotoxicity increase in severity and rapidity of onset in a dose-dependent manner (Ecobichon 1991).

This same enzyme is present in erythrocytes where it is known as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor et al. 1993). Erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to dichlorvos and other organophosphorus compounds (Hayes 1982); measurement of erythrocyte acetylcholin-esterase is used as a surrogate of the inhibition of neural acetylcholinesterase.

Neurological effects have been seen in many studies in animals after acute oral exposure to dichlorvos. Male Fischer 344 rats exposed to dichlorvos by olive oil gavage during an LD_{50} study had signs of excessive cholinergic stimulation including salivation, tremors, lacrimation, fasciculations, irregular respiration, and prostration (Ikeda et al. 1990). The authors did not report the dose at which these signs appeared; the LD_{50} calculated from the study was 97.5 mg/kg. In 2 other studies, in which clinical signs were not reported, single oral doses of 40 mg/kg dichlorvos in male rats resulted in a 70% inhibition of brain acetylcholinesterase after one hour (Teichert et al. 1976) and an 83% inhibition after 15 minutes (Pachecka et al. 1977). Brain acetylcholinesterase activity was inhibited 45% in rats receiving 4 mg/kg/day dichlorvos for 14 consecutive days (Teichert et al. 1976). Dichlorvos given to Fischer 344 rats by corn oil gavage 5 days a week over a l0-day period did not affect erythrocyte acetylcholinesterase at doses of up to 16 mg/kg/day (NTP 1989).

Whole-body tremor in male Swiss mice was evident within 3.6 minutes after a single dose of 150 mg/kg dichlorvos by gavage (Mohammad et al. 1989). Tremor was reported in male C57BL/6N mice receiving a single dose of 120 mg/kg dichlorvos by gavage (Casale et al. 1983). This clinical sign was accompanied by a 75% reduction in brain acetylcholinesterase activity one hour after dosing. In mice receiving 40 mg/kg on days 1, 3, 5, and 7, and sacrificed on day 8, significant reductions in acetylcholinesterase were observed in brain (30%) and erythrocytes (31%). Erythrocyte acetylcholin-esterase was not affected by administration of dichlorvos by gavage for 5 days a week over an 11-day period at doses up to 40 mg/kg in B6C3FI mice (NTP 1989).

In greyhound dogs receiving 11 or 22 mg/kg in a single dose, signs of neurological toxicity appeared within 7-15 minutes of dosing (Snow and Watson 1973). Restlessness was seen initially, followed by

increased salivation. muscle fasciculations, involuntary urination, diarrhea, sometimes bloody, and tenesmus. There was no apparent difference in severity of clinical signs between dogs given 11 or 22 mg/kg. Erythrocyte acetylcholinesterase was determined in 11 dogs, and the values ranged from 69 to 97% inhibition. The dog with 97% inhibition of erythrocyte acetylcholinesterase (dosed at 11 mg/kg) had severe clinical signs of intoxication but survived. Crossbred pigs receiving single doses from 18 to 560 mg/kg had clinical signs of neurological toxicity including hypoactivity, vomiting, ataxia, muscle fasciculations, uncoordinated movements, frothy salivation, and defecation (Stanton et al. 1979).

In an intermediate-duration 21-day study in which volunteers were given dichlorvos orally, no signs of neurological toxicity were seen at doses of 0.033 mg/kg/day (Boyer et al. 1977). Twenty-four male volunteers had their serum cholinesterase and erythrocyte acetylcholinesterase determined twice a week for 3 weeks to establish their baseline levels. They were then given 0.9 mg dichlorvos 3 times a day for 21 days in either a pre-meal capsule or a 3-ounce container of gelatin. Serum cholinesterase and erythrocyte acetylcholinesterase were measured twice a week during the exposure period. Once a week, each volunteer had his vital signs measured, and was examined for tremor, pupillary response to light, and skin moisture. Following.the end of the study, serum cholinesterase and erythrocyte acetyl-cholinesterase were measured weekly for the next seven weeks. No clinical signs of neurological toxicity were observed in any of the volunteers. Erythrocyte acetylcholinesterase was not inhibited at 0.033 mg/kg/day in either the gelatin or capsule formulation. Serum cholinesterase was inhibited, on average, 38% in the group given the pre-meal capsule and 28% in the gelatin group. Measurements after the dosing period showed that the half-life for regeneration of serum cholinesterase was 13.7 days.

In a 90-day study in female Sherman rats, groups of 10 animals were exposed to doses ranging from 0 to 69.9 mg/kg/day in their feed (Durham et al. 1957). Two animals from each group were bled on days 3, 11, 60, and 90, and serum cholinesterase and erythrocyte acetylcholinesterase were determined. Clinical signs of neurological toxicity were not noted in any dosage group. Cholinesterase data was presented graphically so the percentage inhibition of the cholinesterases can only be estimated. For serum cholinesterase, doses of 0.4 and 1.5 mg/kg/day appeared to have no effect. Doses of 3.5 and 14.2 mg/kg/day appeared to produce 25-40% inhibition of enzyme activity compared to control values by the third day of feeding; activity remained depressed up to 60 days, and rose to near control values by the end of the experiment at 90 days. Serum cholinesterase in rats consuming

35.7 and 69.9 mg/kg/day fell by 50% after 3 days and remained at this level throughout the experiment. Erythrocyte acetylcholinesterase was unaffected at doses up to 3.5 mg/kg/day. Acetylcholinesterase activity was inhibited by 30% after 3 days at 14.2 mg/kg/day and remained depressed until the end of the experiment. At 35.7 and 69.9 mg/kg/day, erythrocyte acetylcholinesterase was inhibited about 50% after 3 days and 80% after 10 days. There appeared to be some recovery to about 50% of control by the end of the experiment. Female Fischer 344 rats treated with dichlorvos by oral gavage 5 days a week for up to 32 days had no significant changes in erythrocyte acetylcholinesterase activity at doses up to 16 mg/kg/day (NTP 1989). Male rats at the same dosage levels had a 22% decrease in erythrocyte acetylcholinesterase at day 24 at 16 mg/kg/day.

In a similar study with $B6C3F_1$ mice, gavage doses of dichlorvos 5 days a week up to 40 mg/kg/day did not affect erythrocyte acetylcholinesterase after 32 days of treatment (NTP 1989).

Staggering gait was observed in a white Leghorn chicken receiving 6.1 mg/kg/day dichlorvos by oral gavage after 35 days (Francis et al. 1985). In 5 hens treated in this study with doses ranging from 3.1 to 4.4 mg/kg/day, no adverse neurological effects were observed.

Mild diarrhea was reported in Fischer 344 rats receiving dichlorvos at 4 and 8 mg/kg/day, 5 days a week for 103 weeks (NIT 1989). There were no adverse neurological effects reported in a similar study in male B6C3FI mice receiving up to 20 mg/kg/day or females receiving up to 40 mg/kg/day (NTP 1989). No gross or histopathological changes were observed in brain or sciatic nerve in any of the rats or mice at the end of this study (NTP 1989).

Inhibition of erythrocyte and brain acetylcholinesterase, but no neurological signs, were reported in Beagles receiving 0.05, 1.0, or 3 mg/kg/day dichlorvos in capsules for 52 weeks (AMVAC Chemical Corp. 1990). No changes were noted at 0.05 mgkglday, but erythrocyte acetylcholinesterase was inhibited 45-53% in dogs receiving 1 mg/kg/day and 81-85% in dogs receiving 3 mg/kg/day. Brain acetylcholinesterase was inhibited 22% in male dogs receiving 1 mg/kg/day and 47% and 29%, respectively, in male and female dogs receiving 3 mg/kg/day. No treatment-related changes were seen upon histopathology review of the following neural tissues: brain with brainstem, cervical, thoracic or lumbar spinal cord, optic nerve, and sciatic nerve.

No studies were located in humans or animals describing OPIDN after oral exposure to dichlorvos. This is a syndrome observed in humans and some animal models after recovery from the acute effects of certain organophosphorus compounds (for example tri-o-cresyl phosphate) (Coppock et al. 1995; Johnson 1981). The characteristic signs are disturbances of gait, an axonalpathy or "dying-back" type degeneration of motor fibers. Studies on the relationship between dichlorvos and OPIDN during parenteral routes of exposure are discussed in Section 2.5.

All reliable NOAELs and LOAELs for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive toxicity in humans after oral exposure to dichlorvos. Maternal toxicity was not reported in CF-1 mice treated by gavage with 60 mg/kg/day dichlorvos during gestation days 6-15 or in New Zealand rabbits treated by gavage with 5 mg/kg/day (Schwetz et al. 1979). Microscopic examination of male reproductive tissues (prostate, testes, epididymis) and female reproductive tissues (ovaries, uterus) revealed no changes attributable to oral dichlorvos exposure during 2-year studies in Fischer 344/N rats treated at 4 or 8 mg/kg/day for 5 days a week or $B6C3F_1$ mice (males treated at 10 or 20 mg/kg/day, females at 20 or 40 mg/kg/day) (NTP 1989). Similar results were obtained in Beagle dogs receiving dichlorvos by capsule for 52 weeks at up to 3 mg/kg/day (AMVAC Chemical Corp. 1990). Male reproductive tissues examined were the testes, prostate, and epididymides; female tissues examined were the cervix, ovaries, uterus, and vagina.

2.2.2.6 Developmental Effects

No studies were located regarding developmental toxicity in humans after oral exposure to dichlorvos.

No adverse developmental effects were observed in CF-1 mice treated by gavage with 60 mg/kg/day dichlorvos during gestation days 6-15 (Schwetz et al. 1979). There was no significant effect on implantations, mean number of fetuses per litter, incidence or distribution of resorptions, or on fetal body measurements. Similar results were observed in New Zealand rabbits treated by gavage with 5 mg/kg/day over gestation days 6-18 (Schwetz et al. 1979).

Pregnant crossbred sows given PVC-resin formulations of dichlorvos in the diet at a daily dose of 0, 5, or 25 mg/kg during the last 30 days of pregnancy had 100% live births and birth weights similar to control animals (Stanton et al. 1979). There are a number of reports on dichlorvos treatment of pregnant sows causing a dose-related increase in percentage of live births, mean birth weights and weaning weights. The mechanism of action for this phenomenon has not been established (Gallo and Lawryk 1991).

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to dichlorvos.

In a carcinogenicity study in Osborne-Mendel rats, groups of 50 animals of each sex were originally dosed through feed at levels of 45 and 90 mg/kg/day. Ten animals of each sex were used as controls and were pooled with 50 other control rats of each sex from studies conducted concurrently on 5 other compounds (NCI 1977). During the initial 3 weeks of dosage, acute signs of toxicity were observed, including tremor and diarrhea in the 90-mg/kg/day group. Therefore, the dosages were then lowered to 30% of the original. The time-weighted average (TWA) doses over the 80-week period of dosing were 13.5 and 29.3 mg/kg/day. After the go-week dosing period, the animals were observed for a further 30 weeks until sacrifice. Gross necropsy was done on all animals that died during the study and at termination. Microscopic examination was done on sections of brain, pituitary, adrenal, thyroid, parathyroid, trachea, esophagus, thymus, salivary gland, lymph nodes, heart, lung, spleen, liver, kidney, stomach, pancreas, small intestine, large intestine, urinary bladder, prostate or uterus, testis or ovary, mammary gland, skin, and bone, including marrow. Adverse clinical signs (hematuria, rough coats, epistaxis) were noted in control and dosed animals gradually increasing during the second year of the study. The authors stated that at the end of the study, the rats (i.e., both treated and control) were in generally poor condition. The matched control groups had significantly lower survival than the treated groups at the end of the study, mainly due to deaths during the 30-week observation period after treatment (NCI 1977). At the end of the study, only 2 of 10 male rats and 5 of 10 female rats survived in the matched control groups. For this reason, these control rats were pooled with control

rats from concurrent studies for comparison with the treated groups. Of the male rats, 76% of the high-dose and 64% of the low-dose group survived to the end of the study, as did 84% of the highdose and 80% of the low-dose females.

Many inflammatory, degenerative, and proliferative lesions commonly seen in aged rats occurred with approximately equal frequency in treated and the pooled control rats (NCI 1977). Several nonneoplastic lesions occurred more frequently in the treated rats than in the controls. These included aggregates of alveolar macrophages in the lungs, interstitial fibrosis of the myocardium, and focal follicular cell hyperplasia in the male rats. Benign endocrine neoplasms occurred frequently in both test and control rats. There was a high incidence of benign mammary neoplasms in both control and treated rats. Because of the low survival of the matched control rats, control animals from other concurrent studies were pooled for statistical analysis. The authors stated that on the basis of variability of both the incidence and type of spontaneous lesions, and the lack of significant proportions of tumors in the dosed groups compared to the controls, no statistical significance could be attached to the incidence of tumors seen in the dichlorvos-treated rats in this study. Because of the poor survival of control animals in this study, the results are difficult to interpret. Dichlorvos was subsequently re-tested by the National Toxicology Program (NTP 1989).

In another carcinogenicity study in rats, groups of 50 Fischer 344 rats of each sex were dosed with dichlorvos in corn oil by oral gavage at levels of 0, 4, or 8 mg dichlorvos for 5 days a week for 103 weeks (NTP 1989). Necropsy and histopathologic examinations were performed on all animals at the end of the study or at the time of death. Histopathology was done on the following tissues: adrenal gland, brain, cecum, colon, duodenum, esophagus, femur including marrow, heart, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mammary glands, mandibular and mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, prostate/testes/epididymis or ovaries/uterus, rectum, salivary glands, sciatic nerve, skin, spleen, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. No significant differences in survival were noted between any groups. Survival rates were: 31 of 50-for male and female controls; 25 of 50 males and 26 of 50 females in the low-dose group; and 24 of 50 males and 26 of 50 females in the high-dose group.

Statistically significant increases in neoplasms compared to control animals were observed in the pancreas and hematopoietic system in male rats and in the mammary gland in female rats in this study

(NTP 1989). Adenoma of the exocrine pancreas exhibited a significant positive trend, and the incidences were greater in treated as compared to control groups (16 of 50 in vehicle control, 25 of 49 in the low-dose group and 30 of 50 in the high-dose group). When horizontal sections of the pancreas were examined, additional adenomas were observed. When the data from both methods were combined, the incidences of pancreatic adenoma were 25 of 50 in the controls, 30 of 49 in the low-dose group, and 33 of 50 in the high-dose group. The incidence for the treated groups was statistically significant compared to the vehicle controls.

A significant positive trend (i.e., not dose related) for mononuclear cell leukemia was also observed in the male rats. This neoplasm was found in 11 of 50 controls, 20 of 50 in the low-dose group, and 21 of 50 in the high-dose group. A significant positive trend also occurred for mammary gland tumors in female rats. Fibroadenoma, adenoma, or carcinoma occurred in 9 of 50 control rats, 19 of 50 in the low-dose group, and 17 of 50 in the high-dose group. Peer review panels characterized these results as “some evidence” of carcinogenic activity in male rats and “equivocal evidence” in female rats.

Dichlorvos has also been tested for carcinogenicity in two long-term studies on $B6C3F_1$ mice (NCI 1977; NTP 1989). Using the same protocol as the NCI (1977) study described above for Osbome-Mendel rats, groups of 50 male and 50 female $B6C3F_1$ rats were fed dichlorvos in the diet at doses of 57 or 114 mg/kg/day for 80 weeks followed by a 14-week observation period before sacrifice (NCI 1977). These doses were converted from the originally reported dichlorvos-in-feed doses (318 and 635 ppm) by conversion factors for average mouse daily feed consumption (EPA 1988). Groups of 10 male and 10 female mice served as matched controls. The same tissues were examined histologically as in the Osborne-Mendel rat study described above. Two squamous-cell carcinomas of the esophagus (in one low-dose male and one high-dose female) and one papilloma of the esophagus in a high-dose female were seen. The authors stated that these were historically very rare lesions in this strain of mice. Focal hyperplasia of the esophageal epithelium was also seen in three low-dose males. However, no statistically significant differences in neoplastic lesions were seen due to treatment.

Dichlorvos was also tested for carcinogenicity in male and female B6C3Fl mice by a protocol similar to that used on the Fischer 344 rats described above (NTP 1989). Because of higher toxicity in male mice during the dose-finding study, groups of 50 male mice were dosed by corn oil gavage at 0, 10, or 20 mg/kg for 5 days a week, while the female groups were dosed at 0, 20, or 40 mg/kg for 5 days a

week. Necropsy and histopathologic examinations were performed on all animals at the end of the study (102 weeks) or at the time of death. The same tissues were examined as in the Fischer 344 rat study described above.

The only neoplasms that occurred with a significant positive trend in treated compared to control mice were squamous cell papilloma and carcinomas of the forestomach. The overall incidences of this lesion in male mice were 1 of 50 in the controls, 1 of 50 in the low-dose group, and 5 of 50 in the high-dose group. In the females, overall incidences were 5 of 49 in the control group, 6 of 49 in the low-dose group and 18 of 50 in the high-dose group. Incidence was near the historical incidence of 1% in male controls, but was higher in the female controls (10% compared to 1%). Peer review panels characterized the level of carcinogenic activity as “some evidence” in male mice and “clear evidence” in female mice.

2.2.3 Dermal Exposure

2.2.3.1 Death

Two workers in Costa Rica died after splashing a concentrated formulation of dichlorvos on their bare arms and failing to wash it off promptly (Hayes 1982). Information on the concentration of dichlorvos in the concentrate was not available.

Three cynomolgus monkeys were given daily dermal doses of dichlorvos in xylene on a shaved area between the shoulder blades (Durham et al. 1957). A monkey receiving 100 mg/kg/day died after 4 days. A monkey given 50 mg/kgl/day died after 8 doses over 10 days and a monkey given 75 mg/kg/day died after 10 doses over 12 days. Clinical signs occurred within 10-20 minutes after dosing. Signs in their order of appearance were nervousness, gritting of teeth, incoordination, muscle fasciculations, excessive salivation, labored breathing, miosis, and flaccidity.

In an LD_{50} study in Sherman rats where dichlorvos in xylene was applied to an area of clipped skin between the shoulder blades (Durham et al. 1957), the dermal LD_{50} was 107 mg/kg for male rats and 75 mg/kg for females. All rats killed by a single dermal dose died within 20 minutes of dosage, except a male dosed at 110 mg/kg that survived for 40 minutes and another male dosed at 125 mg/kg that survived for 17 days. The symptoms of poisoning observed were bulging eyes, lacrimation,

sialorrhea, muscle fasciculations, and tremors. Some animals had convulsions just before death. Rats that survived appeared to make a full recovery. In another LD_{50}, study where dichlorvos was applied to female Wistar rats in ethanol-water on depilated skin, an LD_{50} of 70.4 mg dichlorvos was found (Gajewski and Katkiewicz 1981). Two white Leghorn chickens dosed daily on the ventral wing surface at the humerus with 14.4 and 15.7 mg/kg in an emulsion containing xylene and 2% Triton X-100 died after 2 and 3 doses, respectively (Francis et al. 1985). Five of 9 hens in this study receiving 0.54-3.8 mg/kg/day dichlorvos died between 30 and 45 days after the beginning of dosing. The lowest dose resulting in death was 1.7 mg/kg/day after 36 days.

All reliable LOAELs for death are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies regarding systemic effects in humans after dermal exposure were located except for dermal effects. No studies regarding systemic effects in animals were located except for respiratory, dermal and ocular effects.

The LOAELs for systemic effects are recorded in Table 2-3.

Respiratory Effects. Labored breathing was observed in 3 cynomolgus monkeys receiving daily dermal doses of 50, 75, or 100 mg/kg/day (Durham et al. 1957). The authors stated that these and other cholinergic signs occurred within 10-20 minutes of dosing.

Dermal Effects. A 52-year-old male truck driver who had been hauling pesticide containers presented with dermatitis of his neck, anterior chest, dorsal hands, and forearms (Mathias 1983). On the previous day, several containers spilled in his truck, and he apparently had direct dermal contact with a pesticide containing 5% dichlorvos, 15% petroleum distillates, and 80% trichloroethane. A faint papular dermatitis was present over the dorsal arms, hands, and V of the neck. .Vertical erythematous, slightly scaling streaks were present over the lateral and posterior neck, a pattern suggesting that liquid droplets had produced the dermatitis. The dermatitis was treated with 1% hydrocortisone ointment. Follow-up examination six weeks later showed persistent vertical, mildly erythematous streaks over the posterior and lateral neck; the arms and anterior chest had cleared.

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

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious	Serious		
ACUTE EXPOSURE							
Death							
Monkey (Cyno-molgus)	12 d 5 d/wk 1 x/d (NS)				50 mg/kg/d	(death after 8 doses over 10 days)	Durham et al. 1957
Rat (Sherman)	once				107 M mg/kg 75 mg/kg F	(LD_{50}) (LD_{50})	Durham et al. 1957
Rat (Wistar)	once				70.4 F mg/kg	(LD_{50})	Gajewski and Katkiewicz 1981
Chicken (white leghorn)	2-3 d 1 x/d				14.4 mg/kg/d	(1 of 1 died in 2 days)	Francis et al. 1985
Systemic							
Monkey (Cyno-molgus)	4-12 d 5 d/wk 1 x/d (NS)	Resp			50 mg/kg/d	(labored breathing)	Durham et al. 1957
Neurological							
Monkey (Cyno-molgus)	4-12 d 5 d/wk 1 x/d (NS)				50 mg/kg/d	(muscle fasciculations, erythrocyte AChE activity decreased by 80%)	Durham et al. 1957

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

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
INTERMEDIATE EXPOSURE						
Death						
Chicken (white leghorn)	28-90 d 1 x/d				1.7 F (death after 36 days) mg/kg/d	Francis et al. 1985
Neurological						
Chicken (white leghorn)	28-90 d 1 x/d		0.71 F		1.8 F (staggering gait) mg/kg/d	Francis et al. 1985

AChE = acetylcholinesterase; d = day(s); F = female; LOAEL = lowest-observable-adverse-effect level; M = male; LD_{50} = lethal dose, 50% kill; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Negative patch test results suggested that the dermatitis resulted from a primary irritant effect of dichlorvos on the skin. Dermatitis resolved completely approximately 10 weeks after onset. The persistence of dermatitis 2 months after exposure is very unusual, and the author suggested that this may be related to some unique local toxic effect of dichlorvos, but did not speculate further.
As part of a study on the ability of dichlorvos to cause sensitization in a guinea pig maximization test (Ueda et al. 1994), the threshold irritation concentration of dichlorvos on guinea pig skin was reported to be 1%. No further details were given.

Ocular Effects. Miosis was observed in cynomolgus monkeys receiving daily dermal doses of 50, 75, or 100 mg/kg/day (Durham et al. 1957). It was not reported whether this resolved before the next daily dose. This sign is related to the cholinergic overstimulation caused by dichlorvos.

2.2.3.3 Immunological and Lymphoreticular Effects

Six of 59 males and 9 of 48 females in an occupational study of flower growers showed positive reactions on patch testing to dichlorvos for an overall rate of 14%. Twelve of 18 subjects who had positive skin patch test reactions to triforine (1,4-bis [2,2,2-trichlor- 1-formamidoethyl] piperazine) also showed positive reactions to dichlorvos (Ueda et al. 1994). These subjects may have also been occupationally exposed to dichlorvos.

In a guinea pig maximization test conducted in this study, induction with dichlorvos by intradermal injection and topical application and subsequent challenge with topical dichlorvos solutions showed sensitization (Ueda et al. 1994). Cross-reactivity with dichlorvos was demonstrated in animals induced with triforine.

2.2.3.4 Neurological Effects

Dichlorvos exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase. This enzyme is present at cholinergic synapses throughout the central and peripheral nervous systems and is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased firing of the postsynaptic neuron or increased contractions in muscle. The consequences of this increased cholinergic

activity in the parasympathetic autonomic nervous system can include lacrimation, perspiration. miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, increased salivation, and increased urinary frequency and incontinence. Effects on motor nerve fibers in the skeletal muscles can include muscle fasciculations, cramps, muscle weakness and flaccidity. Effects on cholinergic synapses in the central nervous system result in drowsiness, fatigue, mental confusion, headache, convulsions and coma (Ecobichon 1991).

This same enzyme is present in erythrocytes where it is known as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor et al. 1993). Erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to dichlorvos and other organophosphorus compounds; measurement of erythrocyte acetylcholinesterase is used as an indicator of inhibition of neural acetylcholinesterase (Hayes 1982).

A truck driver who had direct skin contact with a pesticide solution containing dichlorvos developed dermatitis and also complained of headache, mild rhinorrhea, a burning sensation on his tongue and a bitter taste in his mouth the day after exposure occurred (Mathias 1983). He was exposed to a solution containing 5% dichlorvos, 15% petroleum distillates, and 80% trichloroethane. Initial blood cholinesterase determination (specific enzyme not specified) were in the low-normal range and had risen to the high-normal range two weeks later.

Three cynomolgus monkeys were exposed to dichlorvos dissolved in xylene by daily derrnal doses on a shaved area between the shoulder blades (Durham et al. 1957); cholinergic signs appeared within 10-20 minutes of dosage. Signs of toxicity in order of appearance were: nervousness, incoordination, muscle fasciculations, excessive salivation, labored breathing, miosis, and inability to move. The authors stated that at a given dose, the cholinergic signs tended to become more severe with subsequent doses. Serum cholinesterase and erythrocyte acetylcholinesterase were measured in one monkey that received 75 mg/kg/day. After 2 doses, erythrocyte acetylcholinesterase had declined about 67%, while serum cholinesterase was unchanged. When these values were measured shortly after the next day’s dosage, the serum cholinesterase had fallen about 33%, while erythrocyte acetyl-cholinesterase remained inhibited about 67%. The serum cholinesterase recovered after 2 days without dosing, but the erythrocyte acetylcholinesterase did not. After 5 doses, the erythrocyte acetyl-cholinesterase had fallen by 90% and stayed there until death occurred after 12 days, during which 10 doses were administered.

Signs of neurological toxicity were also observed in Sherman rats dermally exposed to dichlorvos during an LD_{50} experiment (Durham et al. 1957). Rats that survived exhibited bulging eyes, excessive lacrimation, and generalized muscle fasciculation and tremors. Surviving rats appeared to completely recover after 24 hours.

In a study involving daily dermal administration of dichlorvos in white Leghorn chickens, 3 hens receiving 2.8-3.8 mg/kg/day exhibited a staggering gait after 14 days of treatment (Francis et al. 1985). Three hens receiving doses between 0.54 and 0.71 mg/kg/day showed no signs of abnormal gait over 90 days of dosing.

In a study designed to determine the optimal configuration of skin patches for delivery of dichlorvos as a potential therapy for Alzheimer's disease (Moriearty et al. 1993), dichlorvos was dissolved in mineral oil or olive oil and applied in 10-mg doses (34 $mg/cm^2/kg$). Groups of three male Sprague-Dawley rats received patches of different materials taped in place on the shaved intracapsular area. At one and 7 days after administration, rats were sacrificed and brain acetylcholinesterase, serum cholinesterase and erythrocyte acetylcholinesterase were measured. Brain acetylcholinesterase inhibition after 24 hours ranged from 47.5% in the olive oil patches to 67.4% in the mineral oil patches. Brain acetylcholinesterase inhibition persisted for seven days. An experiment delivering 4 different doses of dichlorvos over a l0-fold range showed a linear log-dose relationship for inhibition of brain acetylcholinesterase. Erythrocyte acetylcholinesterase was not reported, although the authors said it was "similar" to the inhibition seen in brain. Serum cholinesterase inhibition peaked on the first day (approximately 60%), and returned to normal by the seventh day. No clinical signs of toxicity were reported.

No studies were located in humans or animals describing OPIDN after dermal exposure to dichlorvos. This is a syndrome observed in humans and some animal models after recovery from the acute effects of certain organophosphorus compounds, for example tri-o-cresyl phosphate (Coppock et al. 1995; Johnson 1981). The characteristic signs are disturbances of gait, a "dying-back" type degeneration of motor fibers. Studies on the relationship between dichlorvos and OPIDN during parenteral routes of exposure are discussed in Section 2.5.

The LOAELs for neurological effects are recorded in Table 2-3.

No studies were located regarding the following effects in humans or animals after dermal exposure to dichlorvos:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies regarding cancer in humans or animals after dermal exposure to dichlorvos were located.

2.3 TOXICOKINETICS

Dichlorvos is a small, lipid-soluble molecule that can be absorbed by passive diffusion through the lungs, gastrointestinal tract, or skin. Little information is available on how rapidly dichlorvos is absorbed during inhalation exposure, but it appears to be rapidly absorbed by the oral and dermal routes of exposure. Because of the difficulty in assaying dichlorvos in biological tissues, this rapid rate of absorption is inferred from the time to onset of clinical signs and/or cholinesterase inhibition. This is due to the rapid degradation of dichlorvos by tissue esterases, particularly in the liver and the serum. The half-life of dichlorvos in human blood in vitro is about 10 minutes (Blair et al. 1975). Distribution is also difficult to study because of rapid metabolism, but there does not appear to be preferential distribution to particular tissues. Dichlorvos does not appear to be stored or concentrated in any tissue. The products of the esterase-catalyzed degradation of dichlorvos are dimethyl phosphate and dichloroacetaldehyde. Dimethyl phosphate is excreted in the urine, while dichloroacetaldehyde can be reduced to dichloroethanol or dehalogenated to glyoxal, which enters 2-carbon metabolism. Dichloroethanol is either conjugated to glucuronic acid and excreted in the urine or dehalogenated and further metabolized. There is also evidence that dichlorvos can be demethylated in a glutathione-dependent reaction. The target for the toxicity of dichlorvos is neural acetylcholinesterase in the central and peripheral nervous systems. Dichlorvos chemically reacts with this enzyme’s active site

and inhibits enzyme activity. None of the metabolites of dichlorvos inhibit neural acetylcholinesterase activity. Reported kinetic parameters for dichlorvos are listed in Table 2-4.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Indirect evidence for absorption of dichlorvos following inhalation in humans was obtained by measuring dichloroethanol, a specific dichlorvos metabolite, in the urine of a male volunteer (Hutson and Hoadley 1972b). This individual was exposed at the extremely high level of 38 mg/m3 (4.2 ppm) for 105 minutes. The first urine sample obtained after exposure ended was analyzed by gas-liquid chromatography and 0.42 μg dichloroethanol/mL urine was detected (Hutson and Hoadley 1972b). The dichlorvos metabolite dimethyl phosphate was found in the urine of 3 of 13 male volunteer pesticide applicators who applied dichlorvos during an 8hour workday (Das et al. 1983). During the application, they wore goggles, caps, respirators, coats, gloves, and shoes. Each applicator sprayed 4 homes using 10-14 aerosol cans (230-330 g dichlorvos) and 18-22 pints of 0.5% emulsion spray (40-50 g dichlorvos). A range of 0.32-l .39 μg of dimethyl phosphate was measured in the urine of 3 workers. No effect was seen in clinical parameters or plasma cholinesterase activities. Dichlorvos was not detected (detection limit was 1 μg/g) in the blood of 2 male volunteers immediately after exposure to air concentrations of 0.25 mg/m^3 (0.03 ppm) for 10 hours or to 0.7 mg/m^3 (0.08 ppm) for 20 hours (Blair et al. 1975). Low-level exposure and breakdown by esterases may account for nondetection of dichlorvos.

In Sherman rats exposed to air saturated with dichlorvos (approximately 33 ppm), clinical signs of cholinergic stimulation were observed within 2 hours, showing that absorption had taken place (Durham et al. 1957). Intact dichlorvos was detected in rats after inhalation only at very high atmospheric levels. Thus, 0.07 and 0.08 μg/g could only be detected in the kidney of 2 of 3 male rats exposed for 4 hours to 10 mg/m^3 (1.1 ppm) (Blair et al. 1975). Similarly, dichlorvos was detected in all the tissues tested in the male mice and in blood, fat, and lungs of 3 female mice exposed for 4 hours to 90 mg/m^3 (10 ppm) (Blair et al. 1975). Neither dichlorvos nor desmethyl dichlorvos was detected in tissues of 3 young pigs (20 kg; 1 female, 2 males) that were exposed to 1-^{14}C-vinylldichlorvos (0.092 mg/m^3 for the female, and 0.114 mg/m^3 for the males) for 23 hours a day for

Table 2-4. Kinetic Parameters for Dichlorvos

Parameter	Value	Tissue (species)	Description	Reference
Absorption rate	3.8 mg/min/cm^2	skin (rabbit)	Percutaneous absorption rate for dichlorvos	Shellenberger et al. 1965
K_m	7.1 mM	serum (human)	K_m for degradation of dichlorvos	Traverso et al. 1989
K_m	4.0 mM	serum (human)	K_m for degradation of dichlorvos	Reiner er al. 1980
V_{max}	143 nmol/min/mL	serum (human)	V_{max} for degradation of dichlorvos	Traverso et al. 1989
$t_{1/2}$	8.1 min	whole blood (human male)	half-life for degradation of dichlorvos	Blair et al. 1975
$t_{1/2}$	11.2 min	whole blood (human female)	half-life for degradation of dichlorvos	Blair et al. 1975
$t_{1/2}$	18.0 min	serum (human)	half-life for degradation of dichlorvos	Blair et al. 1975
$t_{1/2}$	2.0 min	whole blood (rabbit male)	half-life for degradation of dichlorvos	Blair et al. 1975
$t_{1/2}$	3.6 min	whole blood (rabbit female)	half-life for degradation of dichlorvos	Blair et al. 1975
$t_{1/2}$	19.9 min	whole blood (rat male)	half-life for degradation of dichlorvos	Blair et al. 1975
k_i	$1.4x10^3$ M^{-1} min^{-1}	brain AChE (rat)	rate constant for inhibition of brain AChE	Maxwell 1992
IC_{50}	0.95 µm	brain AChE (human)	50% inhibition concentration for brain AChE	Lotti and Johnson 1978
IC_{50}	10 µm	brain NTE (human)	50% inhibition concentration for brain NTE	Lotti and Johnson 1978

AChE = acetylcholinesterase; IC = inhibitory concentration; NTE = neurotoxic esterase

24 days (detection limit 3 ng/g) (Loeffler et al. 1976). Total radioactivity expressed as ppm dichlorvos equivalent in tissues ranged from 0.2 to 0.4 ppm in brain and subcutaneous fat to 2.4-2.6 ppm in liver.

2.3.1.2 Oral Exposure

When 5 mg [vinyl-^{14}C]dichlorvos was ingested in orange juice by a male volunteer, 27% of the dose was recovered from expired air as ^{14}CO, (Hutson and Hoadley 1972b). Dichlorvos was detected (0.18 mg/L) in the blood of fetuses 5 minutes after oral administration of 6 mg/kg dichlorvos in sunflower oil to 5 pregnant rabbits on the day of delivery (Maslinska et al. 1979). A total of 38.2% of the [l-^{14}C-vinyl]dichlorvos (40 mg/kg in PVC pellets) was absorbed in 9 young male Yorkshire pigs (Potter et al. 1973a), the remainder was recovered in the pellets. In another experiment, where [l-^{14}C-vinylldichlorvos was mixed with feed, absorption of dichlorvos was demonstrated by the recovery of 4% of the radioactivity in the urine, 5% in the feces, and 6.6% in the expired air (Potter et al. 1973b). Small amounts (ppb) of organosoluble [^{32}P] (presumably dichlorvos or desmethyl dichlorvos) was detected in the milk of a lactating cow after the oral administration of 1 mg/kg/day [^{32}P]dichlorvos for 7 days followed by a dose of 20 mg/kg on day 8 in gelatin capsules (Casida et al. 1962). Dichlorvos was effectively absorbed in 6 male and 6 female rats following the oral administration of 3.6 mg/kg [methyl-^{14}C]dichlorvos in arachis oil as indicated by the recovery of 64.6% of the dose in urine (Hutson and Hoadley 1972a). Identical recovery was obtained in 6 male and 6 female mice given 22 mg/kg [methyl-^{14}C]dichlorvos (Hutson and Hoadley 1972a). When [vinyl-^{14}C]dichlorvos was administered orally to 2 male Syrian hamsters at a dose of 3.7 mg/kg and to a female at a dose of 1.5 mg/kg, it was rapidly absorbed and 11.9-21.8% of the dose was recovered in the urine.

Evidence for rapid absorption of dichlorvos by the oral route includes death of Swiss mice within 9 minutes after a single gavage dose of 150 mg/kg (Mohammad et al. 1989) and in crossbred swine within 15-30 minutes receiving 100-560 mg/kg in an LD_{50} study (Stanton et al. 1979). Signs of cholinergic toxicity (vomiting, diarrhea) were observed in greyhound dogs within 7-15 minutes of receiving 11 mg/kg dichlorvos by gelatin capsule (Snow and Watson 1973).

2.3.1.3 Dermal Exposure

Dichlorvos appears to be rapidly absorbed by dermal exposure, although absorption by this route has not been well characterized. Monkeys exposed dermally to dichlorvos in xylene solution at doses of

50, 75, or 100 mg/kg exhibited signs of neurotoxicity within 15-20 minutes of administration, indicating rapid absorption (Durham et al. 1957). Similar results were seen in Sherman rats during an LD_{50}, study (LD_{50}s were 107 mg/kg for males and 75 mg/kg for females). In this study, all rats that died did so within 20 minutes (Durham et al. 1957).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Inhalation exposure of rats and mice to a concentration of 90 mg/m^3 (10 ppm) dichlorvos in air for 4 hours produced mild signs of toxicity such as lethargy and pupil constriction (Blair et al. 1975). Dichlorvos concentrations were very low or undetectable in blood (<0.2 mg/kg), liver, testes, lung, and brain (<0.1 mg/kg) of rats. In contrast, kidneys and fat contained concentrations as high as 2.4 and 0.4 mg/kg tissue, respectively. In rats, dichlorvos seemed to have been trapped in the trachea as indicated by its higher concentration in the trachea compared to lungs. When rats were exposed for 4 hours to 10 mg/m^3 (1.1 ppm) in air, only the kidneys of the male animals contained detectable or measurable concentrations (0.08 mg/kg). The results in mice were different from rats, the mice having higher concentrations of dichlorvos in fat, lung, and testes, but much lower concentrations in the kidneys. No residues (<0.00l mg/kg) of dichlorvos were detected in blood, liver, kidney, renal fat, or lung tissues of rats exposed to 0.5 or 0.05 mg/m^3 (0.06 or 0.006 ppm) for 14 days. On the other hand, exposure of male rats to 50 mg/m^3 (6 ppm) resulted in detectable dichlorvos (1.7 mg/kg) in the kidneys after 2 and 4 hours exposure time. On removal of rats from exposure, the concentration of dichlorvos in the kidneys decreased rapidly with an estimated half-life of 13.5 minutes. Dichlorvos disappeared from the blood within 15 minutes after exposure (Blair et al. 1975).

Neither dichlorvos nor its metabolite desmethyl dichlorvos was detected in pigs exposed to 0.092 mg/m^3 (0.01 ppm) for 23 hours a day for 24 days. When young pigs were exposed for 24 days via inhalation to 0.15 mg/m^3 [l-^{14}C-vinyl]dichlorvos, radioactivity was detected in various tissues (blood, liver, lungs), but no intact dichlorvos was detected (Loeffler et al. 1976).

2.3.2.2 Oral Exposure

Little information is available on the distribution of dichlorvos after oral administration. It is probable that a large “first-pass effect” takes place in the liver when dichlorvos is absorbed from the gastrointestinal tract (Gaines et al. 1966). This may reduce intact dichlorvos concentrations below detection limits in tissues. Dichlorvos (0.18 mg/L) appeared in the blood of fetuses 5 minutes after oral administration of 6 mg/kg dichlorvos in sunflower oil to pregnant rabbits on the day of delivery (Maslinska et al. 1979). Organosoluble [^{32}P] (presumably dichlorvos or desmethyl dichlorvos) was detected in the milk of a lactating cow 30 minutes after oral administration of 1 mg/kg/day [^{32}P]dichlorvos for 7 days followed by a dose of 20 mg/kg on day 8 in gelatin capsules (Casida et al. 1962).

2.3.2.3 Dermal Exposure

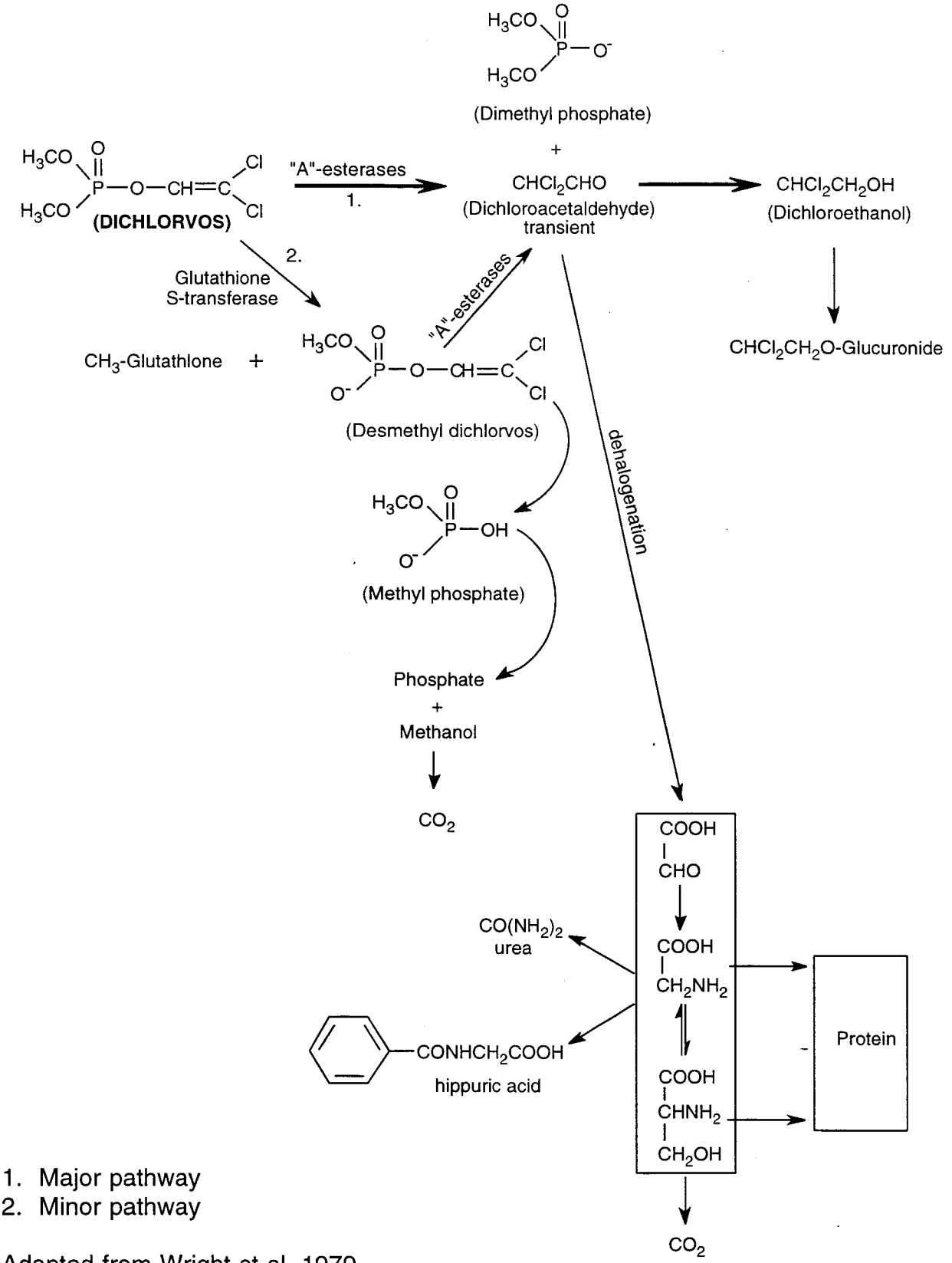
No information was located on tissue distribution after dermal exposure to dichlorvos.

2.3.3 Metabolism

In viva and in vitro studies have established the liver as the major site of dichlorvos detoxification (Casida et al. 1962; Gaines et al. 1966). Other tissues also metabolize dichlorvos *in vitro;* [^{32}P]dichlorvos was metabolized by blood, adrenal, kidney, lung and spleen tissue mostly to dimethyl phosphate. Other metabolites found were desmethyl dichlorvos, monomethyl phosphate, and inorganic phosphate (Loeffler et al. 1976). Pathways of metabolism for .dichlorvos are shown in Figure 2-3.

Metabolism studies of dichlorvos have been carried out in several animal species including human beings (Hutson and Hoadley 1972b), rats (Casida et al. 1962; Hutson and, Hoadley 1972a; Hutson et al. 1971), mice (Hutson and Hoadley 1972a, 1972b), Syrian hamsters (Hutson and Hoadley 1972b), pigs (Loeffler et al. 1976; Potter et al. 1973a, 1973b), goats (Casida et al. 1962), and cows (Casida et al. 1962) using radiolabeled dichlorvos and various routes of administration. These studies have shown that dichlorvos metabolism is generally similar in different species. Differences among species are mostly quantitative and related to the rate of metabolic pathways.

Figure 2-3. Mammalian Pathways of Metabolism of Dichlorvos



1. Major pathway
2. Minor pathway

Adapted from Wright et al. 1979

Dichlorvos breaks down via two enzymatic mechanisms. The first is glutathione-independent, catalyzed by "A"-type esterases, and produces dimethyl phosphate and dichloroacetaldehyde (Wright et al. 1979). The second is glutathione-dependent and results in formation of desmethyl dichlorvos and S-methyl glutathione (see Figure 2-3). Subsequent degradation of desmethyl dichlorvos to dichloroacetaldehyde and monomethyl phosphate is also catalyzed by "A"-type esterases (Wright et al. 1979). S-methyl-glutathione is broken down to methylmercapturic acid and excreted in the urine of animals treated with dichlorvos.

Several in vitro studies have examined the metabolism of dichlorvos in blood. An "A"-type esterase activity distinct from paraoxonase has been characterized in human serum (Traverso et al. 1989). A K_m of 7.1 mM was reported for the degradation of dichlorvos and a V_{max} of 143 nmol/min/mL. A K_m of 4 mM has also been reported in human serum for dichlorvos (Reiner et al. 1980). Half-times for degradation of dichlorvos in whole blood were 8.1 minutes for human males and 11.2 minutes for human females (Blair et al. 1975).

The vinyl moiety of the dichlorvos molecule undergoes two routes of biotransformation: conversion to dichloroethanol and subsequent formation of dichloroethanol glucuronide; or dehalogenation and incorporation of the carbon atoms into various metabolic pathways in the body. These pathways result in the production of hippuric acid, urea, carbon dioxide, and other endogenous compounds that result in a prolonged half-life of radioactivity in the tissues following the administration of [vinyl-^{14}C]dichlorvos. Both radiolabelled dichloroethanol glucuronide and urea have been identified in the urine of men treated with [vinyl-^{14}C]dichlorvos indicating that both pathways occur in humans (Hutson and Hoadley 1972b). In other animal species, most of the radioactivity in carcasses and tissues was identified as glycine, serine, and other body compounds resulting from the metabolism of the vinyl carbon atoms (Hutson and Hoadley 1972b; Loeffler et al. 1976). Neither dichlorvos nor its metabolites accumulated in any tissues of animals treated with dichlorvos.

The metabolism of some dichlorvos metabolites has been studied in experimental animals. Most of the single oral dose of 500 mg of [^{32}P]dimethylphosphate/kg body weight in rats was eliminated, with urine containing about 50% unmetabolized dimethylphosphate (Casida et al. 1962). On the other hand, when a single oral dose of 500 mg [^{32}P]desmethyl dichlorvos was administered to rats, 14% of the dose was recovered in the urine in 90 hours, with 86% of the radioactivity identified as phosphoric acid and 14% as unchanged desmethyl dichlorvos. The bone contained a high proportion of

radioactivity suggesting the incorporation of the phosphoric acid that was produced via rapid complete degradation of dichlorvos (Casida et al. 1962). Also, female rats given an intraperitoneal injection of [1-^{14}C]dichloroacetaldehyde excreted 32% of the radioactivity in expired air as carbon dioxide within 24 hours (Casida et al. 1962).

2.3.4 Elimination and Excretion

Following a single oral dose of 5 mg/kg body weight [^{14}C]dichlorvos in a human male, 27% of the radioactivity was eliminated as $^{14}CO_2$, while only 9% of the radioactivity was eliminated in the urine, Radioactivity excreted in urine decreased with time and none was detected by day nine (Hutson and Hoadley 1972b).

Rats given a single oral dose of 0.1-80 mg/kg body weight [^{32}P]dichlorvos excreted 66-70% of the dose in the urine and approximately 10% in the feces during a 6-day period after dosing (Casida et al. 1962). After a single oral dose of 1 mg (rats) or 0.5 mg (mice) [methyl-^{14}C]dichlorvos in 0.5 mL of arachis oil, approximately 65% of the radioactivity was eliminated in the urine, while only 15% was recovered in the expired air over the following 4 days (Hutson and Hoadley 1972a). Following the administration of a single oral dose of 20 mg [^{32}P]dichlorvos to a cow, 40% of the dose was eliminated in the urine and 50% in the feces (Casida et al. 1962). The milk contained organosoluble radioactivity that was significantly above background within two hours of dosing. The excretion of radioactivity via various routes 24 hours following the administration of a single oral dose of [vinyl-^{14}C] dichlorvos in human, rat, mouse, and hamster are listed in Table 2-5 (Hutson and Hoadley 1972b).

Several metabolism studies have shown the difficulty of determining the biological half-life of dichlorvos in animals. Orally administered dichlorvos undergoes rapid biotransformation, so that no intact dichlorvos could be detected in the blood or tissues of treated animals (Casida et al. 1962; Hutson and Hoadley 1972a, 1972b; Hutson et al. 1971; Potter et al. 1973a, 1973b). Intact dichlorvos has been detected in most tissues of the body only in rats and mice exposed by inhalation to the extremely high level of 90 mg dichlorvos/m3 (10 ppm) for 4 hours (Blair et al. 1975). The half-life of dichlorvos was 13.5 minutes in the kidney of rats exposed to 50 mg/m^3 for 2 or 4 hours.

Table 2-5. Percentage of Radioactivity Excreted by Males 24 Hours Following a Single Oral Dose of [^{14}C-vinyl]dichlorvos in Various Species

Species	Number of Animals	Carbon Dioxide	Urine	Feces
Human	1	27 (8 hours only)	7.6	No data
Rat	3	28.8	9.8	1.5
Mouse	1	23.1	27.4	3.2
Hamster	2	33.5	14.7	2.9

Source: Hutson and Hoadley 1972b

Neither dichlorvos nor any of its metabolites are stored in the tissues of exposed animals (Wright et al. 1979). Because small fractions of dichlorvos molecules, including carbon, phosphorus, and chlorine atoms, undergo reactions similar to natural components of the tissues, these dichlorvos-derived fractions are retained in the body for several days.

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

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

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

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

differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

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

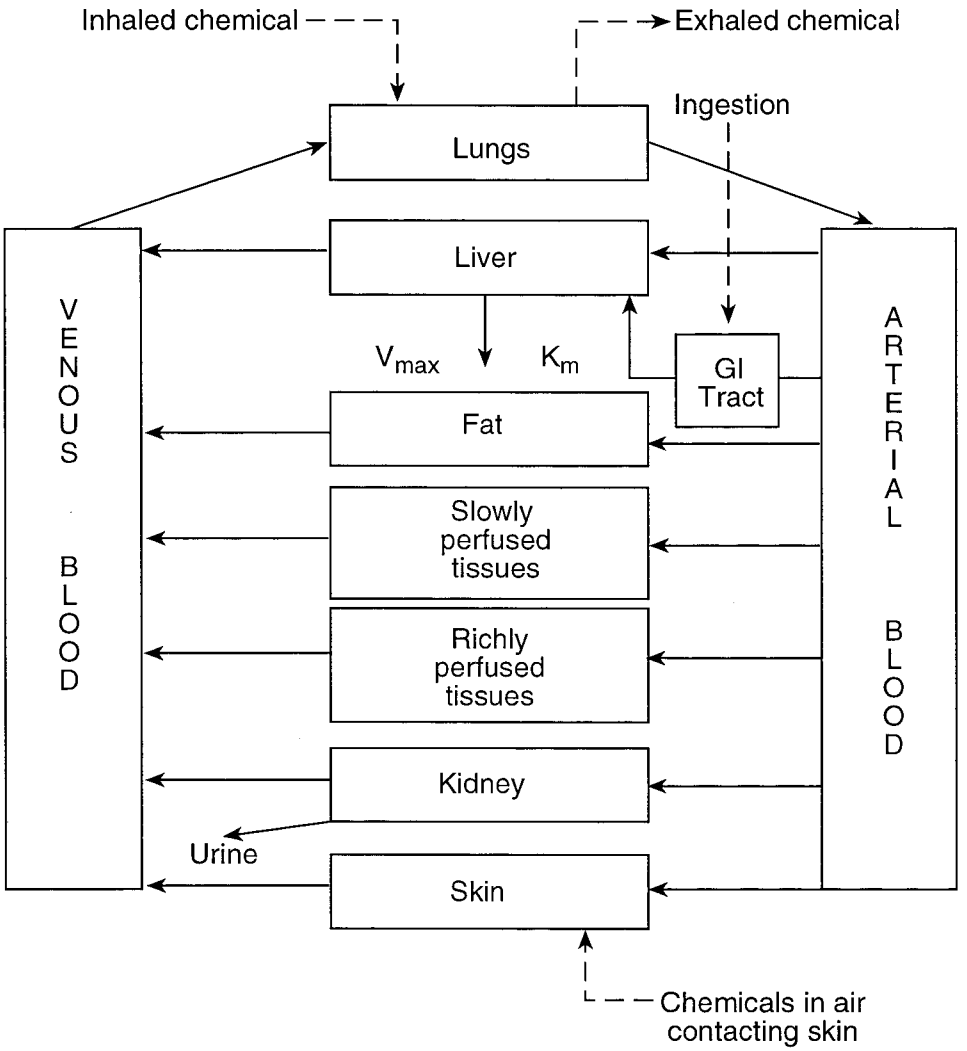
No PBPK models are available for dichlorvos.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

The major characteristics of the pharmacokinetics of dichlorvos are its rapid absorption and rapid metabolism. This metabolism is so rapid in mammals that distribution is very difficult to study. Dichlorvos is a small (molecular weight = 221 daltons), lipophilic molecule and would be expected to be absorbed rapidly across cell membranes. Dichlorvos is absorbed by passive diffusion from the gut, lungs, and skin to the blood. Some dichlorvos can be inactivated by serum cholinesterase or

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1992

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

erythrocyte and neural acetylcholinesterase, but based on total esterase activity in the body, the liver is probably the major site of metabolism. Glutathione-dependent demethylation can also take place, but this appears to be important only in high-dose situations (Wright et al. 1979). The toxicity of a given dose of dichlorvos depends on how rapidly neural acetylcholinesterase is inhibited; if this occurs before metabolic processes can reduce the blood level of dichlorvos, significant toxicity will take place.

Spontaneous reactivation of inhibited neural acetylcholinesterase has been studied *in vivo* (Pachecka et al. 1977; Reiner and Plestina 1979). After a single oral dose of 40 mg/kg dichlorvos in male rats (strain not stated), brain acetylcholinesterase was inhibited 47% after 5 minutes and 83% after 15 minutes (Pachecka et al. 1977). Brain acetylcholinesterase was 60% inhibited at 2 hours, 36% inhibited at 12 hours, and near control levels at 48 hours. Following intravenous administration of dichlorvos in male rats (Reiner and Plestina 1979), the highest degree of inhibition after a dose of 2.5 mg/kg was 85% at 30 minutes. Brain acetylcholinesterase inhibition returned to normal with a half-time of 2 hours. These relatively rapid times for reactivation indicate that recovery after a single dose is primarily by spontaneous reactivation.

2.4.2 Mechanisms of Toxicity

Dichlorvos exerts its toxicity by inhibiting neural acetylcholinesterase. The dichlorovinyloxy group of this molecule withdraws electrons from the phosphorus atom, leaving it susceptible to nucleophilic attack (Wright et al. 1979). One potential nucleophile is the serine hydroxyl group located at the active site of acetylcholinesterase. The products of this reaction are a dimethoxy-phosphorylated acetylcholinesterase molecule and dichloroacetaldehyde. The phosphorylated form of acetylcholin-esterase is incapable of hydrolyzing acetylcholine. If this enzyme is inhibited, acetylcholine accumulates in the synapse and can interfere with neuron functioning.. The consequences of the disturbed cholinergic neurotransmission in the parasympathetic autonomic nervous system can include lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, increased salivation, and increased urinary frequency and incontinence. Effects on motor nerve fibers in the skeletal muscles can include muscle fasciculations, cramps, muscle weakness, and flaccidity. Effects on cholinergic synapses in the central nervous system result in drowsiness, fatigue, mental confusion, headache, convulsions and coma.

There is also evidence that repeated exposure to dichlorvos (5 mg/kg/day by intraperitoneal injection for 30 consecutive days) depletes both oxidized and reduced glutathione levels in rat brain (Julka et al. 1992). Lowered glutathione levels may decrease the rate of detoxification of dichlorvos by the glutathione-dependent metabolic pathways. The full significance of depleted brain glutathione is not known for dichlorvos metabolism.

The nervous system can accept a certain amount of acetylcholinesterase inhibition without overt toxic effects. In humans and animals, toxic signs are generally not seen until at least 20% of this enzyme (erythrocyte acetylcholinesterase used as a marker) has been inhibited (Ecobichon 1991). In an animal study, brain acetylcholinesterase after a 2-year inhalation exposure to dichlorvos was inhibited more than 90% compared to control animals (Blair et al. 1976), yet signs of cholinergic overstimulation were not observed. With dichlorvos and other organophosphate compounds, the best predictor of toxicity is not necessarily the actual percentage inhibition of acetylcholinesterase, but rather how rapidly this inhibition has occurred. Rapid inhibition does not give the nervous system time to adapt to acetylcholinesterase inhibition. This adaptation appears to involve desensitization and downregulation of muscarinic receptors (Fitzgerald and Costa 1993).

2.4.3 Animal-to-Human Extrapolations

Metabolic pathways for dichlorvos do not appear to be significantly different among animal species or between animal species and humans (Wright et al. 1979). Degradation by “A”-type esterases is the major pathway in all species examined. Metabolism also appears to be independent of both duration and route of exposure. Given the lack of information on what levels of dichlorvos exposure are necessary to produce toxicity in humans, selection of a suitable animal model for human toxicity is difficult. There do appear to be differences in sensitivity to dichlorvos among animal species. Orally exposed greyhound dogs (Snow and Watson 1973) and rabbits exposed by inhalation (Thorpe et al. 1972) appear to be more susceptible to dichlorvos toxicity than mice or rats similarly exposed.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview

Dichlorvos is an organophosphorus insecticide that has been in use in the United States and elsewhere since the early 1960s. Like other insecticides in this class, dichlorvos is not only extremely toxic to insects, but also can be toxic to humans if high enough doses are received. The toxicity of dichlorvos results from its inhibition of neural acetylcholinesterase. This enzyme is necessary to hydrolyze acetylcholine and terminate its action at synapses and neuromuscular junctions. The clinical signs of dichlorvos toxicity are the result of overstimulation of the parasympathetic autonomic nervous system, somatic nerve fibers, and cholinergic pathways in the brain. After acute exposure to high concentrations of dichlorvos by any route, signs such as lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, bronchial secretion, dyspnea, increased salivation, and urinary frequency and incontinence can result from overstimulation of the parasympathetic autonomic nervous system. The actions of dichlorvos at neuromuscular junctions can result in muscle fasciculations (especially in fine facial muscles), cramps, muscle weakness, and paralysis. Dichlorvos can also act in the central nervous system to produce drowsiness, fatigue, mental confusion, headache, convulsions, coma, and depression of respiratory centers in the brain.

There is limited information on the toxicity of dichlorvos to humans. The potential hazards of this chemical were well known before it came into use because of experience with other organophosphorus compounds. Exposure to levels of dichlorvos high enough to cause clinical symptoms of organophosphorus poisoning has been very rare in the United States. Limited studies of volunteers show that dichlorvos is rapidly metabolized by esterases in the liver and the blood; intact dichlorvos has never been detected in humans. Studies in laboratory animals show similar results. The metabolites of dichlorvos are polar compounds that are excreted into the urine; thus, no potential for bioaccumulation exists. Limited laboratory studies in animals have not shown adverse reproductive or developmental effects. However, sperm abnormalities occurred in rats treated with dichlorvos by intraperitoneal injection.

Dichlorvos is mutagenic in a number of in vitro test systems. There is also evidence in studies on rats and mice that dichlorvos is carcinogenic in these species. Based on this evidence, the EPA has classified dichlorvos as a probable human carcinogen. There is no direct evidence that dichlorvos is

carcinogenic in humans; however. the animal data were used to predict exposure levels that would increase the risk of cancer in humans. The EPA has calculated that a lifetime of drinking water containing 0.1 μg/L would cause one extra case of cancer in one million people.

Dichlorvos evaporates readily, so the most likely human route of exposure is by inhalation. This is most likely to occur during and/or after pesticide application. The U.S. Occupational Safety and Health Administration (OSHA) has set a Permissible Exposure Limit (PEL) of 1 mg/m^3 (0.11 ppm) for dichlorvos in workplaces. Health effects could occur in workplaces if proper industrial hygiene and safety precautions are not followed. The exposure of the general population to dichlorvos is negligible. Dichlorvos has not been detected in drinking water in the United States and rarely in outdoor air (only at manufacturing sites). Monitoring of the food supply by the U.S. Food and Drug Administration (FDA) and other government agencies has very rarely detected dichlorvos. Thus, the risk of adverse health effects in the general population from dichlorvos exposure appears to be negligible. Dichlorvos is degraded by water and does not persist in the atmosphere or in bodies of water for more than a few days.

For people living near hazardous waste sites, the potential for adverse health effects would depend on the amount of dichlorvos to which they were exposed. Dichlorvos has been detected in at least 3 of the 1,416 hazardous waste sites that have been proposed for inclusion on the EPA National Priority List (NPL) (HAZDAT 1995). However, the number of sites evaluated for dichlorvos is not known. The most likely routes of exposure for people living near hazardous waste sites would be by breathing dichlorvos-contaminated air, drinking dichlorvos-contaminated water, or skin contact with dichlorvos-contaminated soil. Monitoring of the air, drinking water, and soil levels of dichlorvos at these sites is necessary to predict the possibility of adverse health effects.

Minimal Risk Levels for Dichlorvos

Six minimal risk levels (MRLs) have been derived from the database compiled for this-profile; three for inhalation exposure (acute, intermediate, and chronic duration) and three for oral exposure (acute, intermediate, and chronic duration). In all cases, the toxic end point used for MRL derivation is inhibition of either erythrocyte or neural acetylcholinesterase activity. The neural form of this enzyme is the target for dichlorvos toxicity; the erythrocyte form is genetically identical (Taylor et al. 1993) and can be used to approximate neural activity (Hayes 1982). There is no evidence for toxic effects

from dichlorvos exposure by any route or for any duration unless activity of either the erythrocyte or neural form of this enzyme is reduced by at least 20%.

Inhalation MRL.s

- An MRL of 0.002 ppm has been derived for acute-duration inhalation exposure (14 days or less) to dichlorvos.

This MRL is based on a study in male Sprague-Dawley rats which were exposed continuously to atmospheres containing 8 different concentrations of dichlorvos ranging from 0.02 to 6.3 ppm over a 3-day period (Schmidt et al. 1979). A NOAEL of 0.20 ppm was observed for inhibition of erythrocyte acetyl-cholinesterase. This NOAEL was adjusted by dividing by uncertainty factors of 10 for human variability and 10 for interspecies extrapolation. A clear dose-response relationship existed between exposure level and inhibition of erythrocyte acetylcholinesterase.

Limited information on volunteers exposed to dichlorvos-containing atmospheres indicates that the 0.002 ppm dichlorvos level should be protective for health effects in populations potentially exposed near hazardous waste sites. A group of volunteers exposed to 0.23 ppm dichlorvos (l00-fold higher than the MRL level) for 2 hours a day for 4 consecutive days had no inhibition of erythrocyte acetyl-cholinesterase 24 hours after the exposure or clinical signs of dichlorvos toxicity such as miosis (Witter et al. 1961). Miosis and significant depression of erythrocyte acetylcholinesterase activity (50%) were seen in this same study in rhesus monkeys exposed to 1.43 ppm (7 times higher than the humans). One volunteer exposed to 0.08 ppm dichlorvos for 20 hours also showed no clinical signs of dichlorvos toxicity (Blair et al. 1975).

OSHA has established a PEL for dichlorvos of 0.1 ppm for a l0-hour workday. Practical use levels for insect control with dichlorvos are approximately 0.02 ppm. No human toxicity has been associated with this level of exposure (Hayes 1982).

- An MRL of 0.0003 ppm has been derived for intermediate-duration inhalation exposure (14 days to one year) to dichlorvos.

This MRL was derived from a NOAEL of 0.03 ppm dichlorvos for inhibition of brain acetylcholin-esterase activity in a rat developmental study (Thorpe et al. 1972). The MFU was derived by

adjusting the NOAEL by a factor of 10 for animal to human extrapolation and another factor of 10 for human variability.

Groups of 15 pregnant Carworth E rats were exposed to atmospheres containing 0, 0.25, 1.25. or 6.25 mg/m^3 (0, 0.03, 0.14, or 0.69 ppm) throughout their 20-day gestation period. Exposure of dams to all 3 concentrations of dichlorvos had no effect on developmental parameters (the number of fetal resorptions, late fetal deaths, litter size, or mean weight per fetus). Exposure at 0.03 ppm had no effect on erythrocyte or brain acetylcholinesterase. Exposure at 0.14 ppm resulted in a 29% inhibition of erythrocyte and a 28% inhibition of brain acetylcholinesterase, while exposure at 0.69 ppm resulted in 88% inhibition of erythrocyte acetylcholinesterase and an 83% inhibition of brain acetyl-cholinesterase. Brain and erythrocyte acetylcholinesterase activities were inhibited 83 and 88%, respectively, in dams in the high exposure (0.69 ppm) group. A NOAEL of 0.03 ppm was established for the neurological effect of brain acetylcholinesterase inhibition. A NOAEL of 0.03 ppm for brain acetylcholinesterase inhibition was also noted for rabbits exposed for a 28-day gestation period in this study (Thorpe et al. 1972). Significant maternal toxicity was observed in rabbits exposed to 0.69 and 0.44 ppm dichlorvos, although this appears to have been related to mechanical failures that allowed higher concentrations of dichlorvos to enter the chambers for brief periods. However, no adverse developmental effects on the offspring were observed.

No human studies were available for intermediate-duration inhalation exposure to dichlorvos. A NOAEL for developmental effects of 0.69 ppm was also observed in the MRL study (Thorpe et al. 1972), but the NOAEL for neurological effects of 0.03 ppm was used to derive the MRL since the target of dichlorvos toxicity is, neural acetylcholinesterase. The database for intermediate-duration inhalation exposure to dichlorvos in animals is limited to the MRL study and a study in which pigs were exposed to dichlorvos at concentrations up to 0.015 ppm dichlorvos for 24 days (Loeffler et al. 1976). A NOAEL of 0.015 ppm dichlorvos was identified for erythrocyte acetylcholinesterase inhibition.

The intermediate-duration inhalation exposure MRL of 0.0003 ppm dichlorvos should be protective against health effects in populations potentially exposed at hazardous waste sites. This level is approximately l00-fold lower than that used in insect control (0.02 ppm), a level that has not resulted in human toxicity (Hayes 1982).

- An MRL of 0.00006 ppm has been derived for chronic-duration inhalation exposure (365 days or longer) to dichlorvos.

This MRL is based on a 2-year inhalation study in Carworth E rats (Blair et al. 1976). A NOAEL of 0.006 ppm in the male rats in this study was observed for inhibition of erythrocyte acetylcholinesterase. This NOAEL was adjusted by dividing by uncertainty factors of 10 for human variability and 10 for interspecies extrapolation. A dose-response relationship existed between exposure level and inhibition of erythrocyte acetylcholinesterase.

Groups of 50 Carworth E strain rats of both sexes were exposed to atmospheres containing 0, 0.05, 0.5, or 5 mg dichlorvos/m3 (0, 0.006, 0.06, or 0.6 ppm) for 23 hours a day for 2 years as part of a carcinogenicity study (Blair et al. 1976). At the end of the study, the surviving rats were killed, blood was collected, and half the brain was used to determine brain acetylcholinesterase. Plasma cholinesterase and erythrocyte acetylcholinesterase were also measured. In males treated at 0.006 ppm, a NOAEL for brain and erythrocyte acetylcholinesterase was identified. Females at this dose had a 12% reduction in erythrocyte acetylcholinesterase; this is also a NOAEL, since erythrocyte acetylcholinesterase inhibition of 20% or less is not considered an adverse effect.

This is the only chronic inhalation study available for the derivation of an MRL. The EPA used this study to derive a reference concentration (RfC) of 0.0005 mg dichlorvos/m^3 (0.00006 ppm) for lifetime exposure to dichlorvos, the same value as derived for the MRL. The RfC "is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (IRIS 1995).

Oral MRLs

- . An MRL of 0.004 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to dichlorvos.

This MRL is based on a study in male Sprague-Dawley rats that were treated for 14 days with dichlorvos by corn oil gavage (Teichert et al. 1976). A LOAEL of 4 mg/kg/day was identified on the basis of a 44% inhibition of brain acetylcholinesterase. The MRL was derived by dividing the

LOAEL value by 10 for use of a LOAEL (no NOAEL was identified in this study), by 10 for interspecies extrapolation, and by 10 for human variability.

Male Sprague-Dawley rats were treated daily for 14 days with 4 mg/kg dichlorvos by gavage in corn oil (Teichert et al. 1976). Dichlorvos purity was 99%. Control animals received corn oil only. Ten animals were used in the control group and 11 in the treatment group. At the end of the 14-day dosing period, the rats were decapitated; the brains were removed, homogenized in 10 volumes of 0.3% Triton X-100, and centrifuged for 10 minutes. Aliquots of the supematant were assayed for acetylcholinesterase activity by the hydrolysis of radioactive acetylcholine. Dichlorvos treatment at 4 mg/kg/day over a 14-day period resulted in a 44% depression of brain acetylcholinesterase activity, which is considered a less serious LOAEL for neurological effects. In this same study, a single gavage dose of 40 mg/kg dichlorvos resulted in a 70% depression of brain acetylcholinesterase 1 hour later, demonstrating, a dose-severity relationship.

This is the only reliable study located for acute-duration oral exposure to dichlorvos where doses ranging from 5 to 10% of the LD_{50} were administered on a daily basis and brain acetylcholinesterase (one of the targets for dichlorvos) was measured rather than erythrocyte acetylcholinesterase. Most of the acute-duration oral studies for dichlorvos in rodent species were LD_{50} studies; representative LD_{50}, values for the rat range from 56 to 97.5 mg/kg (Durham et al. 1957; Gajewski and Katkiewicz 1981; Ikeda et al. 1990). The 44% inhibition of brain acetylcholinesterase reported in this study is considered a less serious LOAEL; clinical signs were not reported in this study, but in another oral dosing study in Fischer 344 rats (NTP 1989) over an 11-day period, no clinical signs of dichlorvos neurotoxicity were reported in animals receiving up to 16 mg/kg/day dichlorvos. In a developmental study where CF-1 mice and New Zealand rabbits were orally exposed to dichlorvos during pregnancy (60 mg/kg/day over gestation days 6-l 5 in mice; 5 mg/kg/day over gestation days 6-l 8 in rabbits), no treatment-related effects were observed in the offspring.

This MRL should be protective against health effects in individuals potentially exposed to dichlorvos at hazardous waste sites. Oral exposure at this level would not be expected to have any effect on neural acetylcholinesterase activity, the target for dichlorvos toxicity. The FAO/WHO Joint Meeting on Pesticide Residues has established an acceptable daily intake of dichlorvos for humans of 0.004 mg/kg/day (FAO/WHO 1967).

- An MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to dichlorvos.

This minimal risk level is based on a 21-day study in male volunteers who consumed 0.033 mg/kg/day in either a capsule form or in a 3-ounce container of gelatin at meals (Boyer et al. 1977). A NOAEL of 0.033 mg/kg/day was observed for inhibition of erythrocyte acetylcholinesterase. The MRL was derived by dividing the NOAEL by an uncertainty factor of 10 for human variability.

Boyer et al. (1977) reported on a study designed to determine if different formulations would change the effect of dichlorvos on serum cholinesterase and erythrocyte acetylcholinesterase. Plasma cholinesterase and erythrocyte acetylcholinesterase were determined twice a week for 3 weeks in 30 male volunteers. The 24 men with the most stable enzyme activities were used in the study. Two treatment groups of 6 men each received 0.9 mg dichlorvos 3 times daily either in a pre-meal capsule filled with cottonseed oil or in a 3-ounce container of gelatin. Two other groups of 6 men each received placebo capsules or gelatin. The treated volunteers received 0.9 mg dichlorvos 3 times a day or 2.7 mg/day. The average weight of the volunteers was 81 kg, resulting in an average dose of 0.033 mg/kg/day. Dosing was started and carried out for a 21-day period during which plasma cholinesterase and erythrocyte acetylcholinesterase were measured twice a week by a pH titration method. Following the termination of dosing, plasma and erythrocyte activities were monitored twice weekly for 7 weeks. The observation of each individual's cholinesterase activities was converted to a percentage of his pretrial average determinations. No clinical signs of neurotoxicity were noted in any of the subjects (tremor, pupillary response to light, and skin moisture were assessed). A NOAEL of 0.033 mg/kg/day dichlorvos was observed for inhibition of erythrocyte acetylcholinesterase.

The reduction of serum cholinesterase observed in the study confirms that dichlorvos was absorbed by the volunteers under these conditions. No signs of clinical neurotoxicity were observed at any time in the volunteers. The dose given appeared to have been chosen for the express purpose of not causing erythrocyte acetylcholinesterase inhibition. This study was chosen for MRL derivation because it was the only one located that defined a NOAEL for humans for the end point of erythrocyte acetylcholinesterase inhibition. Several animal studies on intermediate-duration oral exposure to dichlorvos are available. NOAEL values for erythrocyte acetylcholinesterase inhibition were 3.5 mg/kg/day in Sherman rats exposed for 90 days by feed (Durham et al. 1957), 8 mg/kg/day in Fischer 344 rats

exposed by gavage for 32 days (NTP 1989) and 40 mg/kg/day in B6C3F$_1$ mice exposed by gavage for 33 days (NTP 1989).

This MRL should be protective against health effects in individuals potentially exposed to dichlorvos at hazardous waste sites. Oral exposure at this level would not be expected to have any effect on neural acetylcholinesterase activity, the target for dichlorvos toxicity. The FAO/WHO Joint Meeting on Pesticide Residues has established an acceptable daily intake of dichlorvos for humans of 0.004 mg/kg/day (FAO/WHO 1967).

- An MRL risk level of 0.0005 mg/kg/day has been derived for chronic-duration oral exposure (364 days or more) to dichlorvos.

This MRL level is based on a chronic feeding study in dogs (AVMAC Chemical Co. 1990; IRIS 1995). Groups of Beagle dogs (4 per sex per dose, approximately 6-7 months old) were administered dichlorvos daily by gelatin capsule for 52 weeks at dose levels of 0, 0.1, 1.0, and 3.0 mg/kg/day. The 0.1 mg/kg/day dose level was lowered to 0.05 mg/kg/day on day 22 due to inhibition of serum cholinesterase noted after 12 days on dichlorvos (the authors were attempting to assure a no-effect level for serum ChE). Observations included clinical signs, body weight, food consumption, ophthalmology, blood chemistry, necropsy, and histopathology. Serum cholinesterase and erythrocyte acetylcholinesterase were measured throughout the study. At termination of the study, the brain was weighed and brain acetylcholinesterase was measured. Histopathology was performed on the brain (with brainstem), cervical spinal cord, lumbar spinal cord, and the sciatic nerve. Serum cholinesterase and erythrocyte acetylcholinesterase were unchanged in the 0.05 mg/kg/day groups, and decreased in a dose-dependent manner at 1.0 and 3.0 mg/kg/day. Levels of inhibition did not increase over time of measurement (2-52 weeks). At termination of the study, brain acetylcholiesterase was unchanged at 0.05 mg/kg/day. It was decreased 22% in males at 1.0 mg/kg/day, but not in females. At 3.0 mg/kg/day, brain acetylcholinesterase was decreased 47% in males and 29% in females. No treatment-related changes were seen on histopathology for any of the tissues examined.

The MRL was derived from the NOAEL level of 0.05 mg/kg/day for inhibition of brain acetylcholinesterase by adjusting by a factor of 10 for human variability and 10 for animal-to-human extrapolation.

The EPA has derived a reference dose (RfD) of 0.0005 mg/lcg/day based on a NOAEL for brain acetylcholinesterase inhibition of 0.05 mg/kg/day dichlorvos based on this study (IRIS 1995).

Death. There have been several reports of deaths in humans as a result of exposure to dichlorvos (Hayes 1982). In one case, a woman who drank a pesticide containing dichlorvos died the following day, but the actual amount ingested was not determined. A 19-month-old girl died after eating a cakelike bait that contained dichlorvos. In this case, the amount of dichlorvos consumed was not determined. The bait also contained malathion, raising the possibility that an interaction may have occurred and contributed to the death. Two pesticide workers in Costa Rica were also reported to have died after spilling a dichlorvos-containing pesticide on their skin and failing to promptly wash it off (Hayes 1982). The concentration of dichlorvos in the pesticide was not reported, nor was the quantity spilled on the skin.

Deaths have been reported in rats and rabbits after inhalation exposure to dichlorvos. In an early toxicity study (Durham et al. 1957), rats exposed to air saturated with dichlorvos died between 7 and 62 hours after exposure began. Dichlorvos measured in the incoming air was 306 mg/m^3 (34 ppm). The signs of poisoning preceding death included slow labored respiration, sialorrhea, and paleness of the extremities. Deaths were also reported among pregnant rabbits exposed by inhalation to dichlorvos for 28 days at 4 and 6.25 mg/m^3 (0.44 and 0.69 ppm) (Thorpe et al. 1972). Before death, the animals were anorexic, lethargic, showed tremors, and had nasal discharges and diarrhea-all signs of dichlorvos neurotoxicity. Rats exposed to dichlorvos at levels up to 56 mg/m^3 (6.2 ppm) for up to 14 days survived (Schmidt et al. 1979) as did pregnant rats exposed by inhalation at levels up to 6.25 mg/m^3 (0.69 ppm) (Thorpe et al. 1972). No studies on inhalation of dichlorvos in non-pregnant rabbits were located, so whether this greater sensitivity is a species difference or a consequence of pregnancy cannot be determined. Exposure of rats by inhalation for 2 years at 5 mg/m^3 (0.55 ppm) did not increase the death rate over controls in males or females (Blair et al. 1976).

Deaths have been reported after single oral doses in a number of LD_{50} studies. LD_{50}values in rats range from 56 mg/kg in female Sherman rats (Durham et al. 1957) to 97.5 mg/kg in male Fischer 344 rats (Ikeda et al. 1990). In mice, LD_{50} values of 133 mg/kg for female CD-l mice and 139 mg/kg for males have been reported (Haley et al. 1975). In this study a reliable LD_1 value of 84 mg/kg in male mice and 95 mg/kg in female mice was reported. Single acute oral doses of 150 mg/kg in male Swiss mice caused 100% lethality within 9 minutes (Mohammad et al. 1989). An oral LD_{50} of 157 mg/kg

has also been reported in crossbred pigs (Stanton et al. 1979). In intermediate-duration studies, all rats died after being orally exposed by feed at 180 mg/kg/day dichlorvos or more for 6 weeks (NCI 1977). All Fischer 344 rats exposed by gavage to dichlorvos at levels of 32 or 64 mg/dichlorvos died within 13 weeks. as did 6 of 10 female rats exposed to 16 mg/kg/day dichlorvos (NTP 1989). Mice appear to be more resistant to dichlorvos toxicity in intermediate-duration studies. In a 6-week study where mice were orally exposed through feed, deaths were not reported until levels of 720 mg/kg/day were reached (NCI 1977). A 13-week gavage study in the same strain of mice reported deaths at 80 mg/kg/day (NTP 1989). These studies suggest that dichlorvos is less toxic when consumed in feed than when administered by gavage, possibly due to slower absorption and the intermittent nature of exposure when consumed in feed. In a 2-year study on Fischer 344 rats and $B6C3F_1$ mice, oral exposure to dichlorvos at doses of 4 and 8 mg/kg/day dichlorvos in rats, and 10, 20, and 40 mg/kg/day in mice had no effect on survival. Deaths have also been reported after dermal exposure in monkeys and rats (Durham et al. 1957; Gajewski and Katkiewicz 1981). Monkeys receiving daily doses of 50 mg/kg/day dichlorvos and above died within 10 days; LD_{50}, values of 70-107 mg/kg have been reported in rats.

Parenteral doses causing death are considerably lower than those required by the inhalation, oral or dermal routes. An intravenous dose of 2.2 mg/kg undiluted dichlorvos was fatal in a greyhound dog (Snow and Watson 1973). The clinical signs of toxicity before death (hyperpnea, dyspnea, severe and progressive cyanosis) were the same as those seen in dogs that had been acutely poisoned orally. The importance of the liver in reducing dichlorvos toxicity was demonstrated in a study where rats were perfused with dichlorvos either through the femoral vein (dichlorvos entering the circulation directly) or the intestinal vein (dichlorvos passing through the liver before reaching the general circulation) (Gaines et al. 1966). Time to onset of symptoms was delayed about 3 times as long in rats infused through the intestinal vein compared to rats perfused through the femoral vein. All the rats perfused through the femoral vein died within 31 minutes (total dose 5 mg/kg), while none of the rats perfused through the intestinal vein died even though their total dose was 3 times as high (15.2 mg/kg).

Systemic Effects. The systemic effects seen after dichlorvos exposure can generally be explained as the result of dichlorvos neurotoxicity.

Respiratory Effects. Labored breathing has been reported in greyhound dogs (Snow and Watson 1973) and monkeys (Durham et al. 1957) after acute oral exposure to high doses of dichlorvos. This

effect appears to be secondary to acetylcholinesterase inhibition in the respiratory tract. Increased cholinergic activity would be expected to cause increased bronchial secretions and bronchoconstriction and partial depolarization block at neuromuscular junctions could lead to labored breathing.

Gastrointestinal Effects. Diarrhea, sometimes bloody, has been reported after acute oral exposure to dichlorvos in greyhound dogs (Snow and Watson 1973) and after intermediate-duration inhalation exposure in rabbits (Thorpe et al. 1972). Cholinergic stimulation in the gastrointestinal tract would be expected to cause increased intestinal motility and result in diarrhea.

Dermal Effects. One case of contact dermatitis as a result of dichlorvos exposure was located. A 52-year-old male truck driver who had been hauling pesticide containers presented with dermatitis of his neck, anterior chest, dorsal hands, and forearms (Mathias 1983). On the previous day, several containers spilled in his truck and he apparently had direct dermal contact with a pesticide containing 5% dichlorvos, 15% petroleum distillates, and 80% trichloroethane. A faint papular dermatitis was present over the dorsal arms, hands, and V of the neck. Vertical erythematous, slightly scaling streaks were present over the lateral and posterior neck, a pattern suggesting that liquid droplets had produced the dermatitis. The dermatitis was treated with 1% hydrocortisone ointment. Follow-up examination 6 weeks later demonstrated persistent vertical, mildly erythematous streaks over the posterior and lateral neck; the arms and anterior chest had cleared. Dermatitis resolved completely approximately 10 weeks after onset. The persistence of dermatitis 2 months after exposure is very unusual, and the author speculated that this may be related to some unique local toxic effect of dichlorvos.

Ocular Effects. Miosis was observed in monkeys after inhalation exposure to dichlorvos at 12.9 mg/m^3 for 2 hours a day (Witter et al. 1961). This condition was no longer present the next morning.

Body Weight Effects. Male Carworth E rats exposed to atmospheres containing 5 mg/m^3 (0.6 ppm) for 2 years (Blair et al. 1976) were consistently 20% or more below the body weight ef control rats from the tenth week of treatment. However, no significant changes in body weight were noted in rats or mice of either sex after a 2-year oral exposure at doses ranging from 4 to 40 mg/kg for 5 days a week (NIT 1989).

Immunological and Lymphoreticular Effects. Twelve of 18 subjects in an occupational study of flower growers who had positive patch test reactions to triforine (1,4-bis [2,2,2-trichlor-I-formamidoethyl] piperazine) also showed positive reactions to dichlorvos (Ueda et al. 1994). These subjects may have also been occupationally exposed to dichlorvos.

Immunosuppression after oral exposure to dichlorvos in rabbits has been reported in two studies (Desi et al. 1978, 1980). A dose-related suppression of the humoral immune response induced by *S. typhimurium* was observed in rabbits administered 0.3-2.5 mgikg dichlorvos 5 days a week for 6 weeks (Desi et al. 1978). A single oral dose of 120 mg/kg dichlorvos in male C57B1/6 mice that had been inoculated with sheep erythrocytes 2 days earlier suppressed the primary IgM response observed 48 hours later (Casale et al. 1983). Severe signs of dichlorvos neurotoxicity were noted and the authors stated that the immunosuppression observed in this study may have been mediated indirectly by toxic chemical stress.

In a guinea pig maximization test conducted in this study, induction with dichlorvos by intradermal injection and topical application and subsequent challenge with topical dichlorvos solutions showed sensitization (Ueda et al. 1994). Cross-reactivity with dichlorvos was demonstrated in animals that had been induced with triforine. It is unknown if the immunosuppression seen with dichlorvos in animals is a direct effect or mediated by a cholinergic pathway.

Neurological Effects. Dichlorvos exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase. This enzyme is present at cholinergic synapses throughout the central and peripheral nervous systems and is responsible for hydrolyzing acetylcholine released from the presynaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased firing of the post-synaptic neuron or increased contractions in muscle. The consequences of this increased cholinergic activity in the parasympathetic autonomic nervous system can include lacrimation, perspiration, miosis, nausea, vomiting, diarrhea, excessive bronchial secretions, bradycardia, increased salivation, increased urinary frequency, and incontinence. Effects on motor nerve fibers in the skeletal muscles can include muscle fasciculations, cramps, muscle weakness, and paralysis. Effects on cholinergic synapses in the central nervous system result in drowsiness, fatigue, mental confusion, headache, convulsions, and coma.

This same enzyme is present in erythrocytes, where it is known as erythrocyte acetylcholinesterase. Both forms of acetylcholinesterase are produced by the same gene (Taylor et al. 1993). Erythrocyte and neural acetylcholinesterase are inhibited to roughly the same extent by exposure to dichlorvos and other organophosphorus compounds, and measurement of erythrocyte acetylcholinesterase is used as an indicator of the extent of inhibition of neural acetylcholinesterase (Hayes 1982). Another enzyme capable of hydrolyzing acetylcholine circulates in the blood and is called serum cholinesterase. The activity of this enzyme is inhibited by dichlorvos at lower levels of exposure than required for inhibition of erythrocyte acetylcholinesterase and is often used as a biomarker of exposure.

Male volunteers exposed to atmospheres containing 0.25 or 0.7 mg/m^3 showed no symptoms of neurological toxicity (Blair et al. 1975). One volunteer was exposed to 0.25 mg/m^3 for 10 hours, and another was exposed to 0.7 mg/m^3 for 20 hours.

Another group of seven male volunteers was exposed to dichlorvos-containing atmospheres in a simulated aircraft cabin to determine safe levels for aircraft insect control (Witter et al. 1961). In this study, the volunteers were exposed to dichlorvos on 4 consecutive days for either 1 or 2 hours. The average dichlorvos concentration in the first experiment was 0.49 mg/m^3 (0.05 ppm); in a second experiment with the same group, it was 2.1 mg/m^3 (0.23 ppm). In the first experiment at 0.49 mg/m^3, no changes were observed in serum cholinesterase or erythrocyte acetylcholinesterase in any of the men whether they had been exposed for 1 or 2 hours a day over the 4-day exposure period. There was a small inhibition of serum cholinesterase (about 20%) in 2 of 3 volunteers exposed for 2 hours a day for 4 consecutive days at 2.1 mg/m^3. No changes were seen in erythrocyte acetylcholinesterase in any of the men exposed to 2.1 mg/m^3 for either 1 or 2 hours a day over the 4-day period. In this study, there was a 24-hour interval between exposure and the time blood was sampled for cholinesterase activities.

In the same study, groups of 2 rhesus monkeys (one of each sex) were exposed to atmospheres containing 0.48, 2.3, 2.6, or 12.9 mg/m^3 (0.05, 0.25, 0.29, or 1.43 ppm) for 2 hours a day on 4 consecutive days (Witter et al. 1961). Exposure for 2 hours a day on 4 consecutive days at 0.48 mg/m^3 had no effect on serum cholinesterase or erythrocyte acetylcholinesterase. Similar exposures at 2.3 and 2.6 mg/m^3, and the same sampling interval, had no effect on erythrocyte acetylcholinesterase but caused about a 20% inhibition of serum cholinesterase. Exposure at 12.9 mg/m^3 had significant toxic effects. The monkeys exposed at this level showed substantial inhibition of both

cholinesterases from the first day of exposure. Activity fell throughout the 4-day exposure period; serum cholinesterase was inhibited about 40-50% in both monkeys while erythrocyte acetylcholinesterase fell about 40% in one monkey and 67% in the other. Miosis was also noted in both monkeys at the end of each 2-hour exposure period. but was no longer present the following morning. Cholinesterase determinations after exposure was terminated indicated that 40-50 days were required for a return to pre-exposure levels.

Rhesus monkeys housed in a chamber whose walls and ceiling had been sprayed with an emulsion of dichlorvos were observed for 2 weeks (Durham et al. 1957). The original concentration in the chamber was approximately 6 mg/m^3 (0.66 ppm); it fell to about 1 mg/m^3) (0.11 ppm) after 3 days and was about 0.1 mg/m^3 (0.01 ppm) for the remainder of the 2 weeks. No signs of neurological toxicity were observed. By the end of the first week, both serum cholinesterase and erythrocyte acetylcholinesterase had fallen from their pre-exposure levels. Inspection of a graph in this report indicates that levels of both blood cholinesterases fell about 50-60% during the first week of the study. Serum cholinesterase recovered partially in the second week, but erythrocyte acetylcholinesterase did not. After exposure was terminated, the activities of both enzymes were normal in about 5 weeks.

Ten Sherman rats of each sex housed in the same chamber as the monkeys were also monitored in this experiment (Durham et al. 1957). No clinical signs of neurological toxicity were observed in the rats over the 2-week exposure period. There was a slight decrease in serum cholinesterase and erythrocyte acetylcholinesterase at the end of the first week (about 10% for each enzyme). At the end of 2 weeks, there was no difference between exposed rats and controls. Bronchial and erythrocyte acetylcholinesterase were measured in male Sprague-Dawley rats exposed to atmospheres ranging from 0 to 56.64 mg/m^3 (0-6.3 ppm) over a 3-day period (Schmidt et al. 1979). A dose-dependent reduction in both bronchial and erythrocyte acetylcholinesterase was observed. Bronchial tissue acetylcholinesterase measured in homogenates from treated rats at 0.83 and 1.82 mg/m^3 (0.09 and 0.20 ppm) was lower than in control rats; 50% inhibition of bronchial tissue acetylcholinesterase took place at a dose (1.82 mg/m^3) that had no effect on erythrocyte acetylcholinesterase. Erythrocyte cholinesterase was inhibited more than 80% at 8.2 mg/m^3 (0.91 ppm) after 3 days exposure. Clinical signs were not reported in this study, so the toxicological significance of this level of inhibition in the male Sprague-Dawley rats cannot be assessed.

Several studies in animals have addressed neurological end points after intermediate-duration inhalation exposure to dichlorvos. In a study of pregnant Carworth E rats exposed over their gestation period (20 days), dams exposed to atmospheres containing 6.25 mg/m^3 (0.69 ppm) were less active than controls (Thorpe et al. 1972). Exposure at 0.25 mg/m^3 (0.03 ppm) had no effect on erythrocyte or brain acetylcholinesterase. Exposure at 1.25 mg/m^3 (0.14 ppm) resulted in a 30% inhibition of erythrocyte and brain acetylcholinesterase, while exposure at 6.25 mg/m^3 resulted in 88% inhibition of erythrocyte acetylcholinesterase and an 83% inhibition of brain acetylcholinesterase. A similar experiment with pregnant Dutch rabbits over 28 days (Thorpe et al. 1972) showed inhibition of 14% and l0%, respectively, in erythrocyte and brain acetylcholinesterase at exposure of 0.25 mg/m^3. At exposures of 1.25 mg/m^3, erythrocyte acetylcholinesterase was inhibited 68% and brain acetyl-cholinesterase was inhibited 56% compared to controls.

In a 2-year chronic inhalation study with dichlorvos (Blair et al. 1976), 50 Carworth E rats of each sex were exposed to atmospheres containing 0, 0.05, 0.5, or 5 mg/m^3 (0, 0.0055, 0.055, or 0.55 ppm). No clinical signs of neurological toxicity were seen in any of the groups, although 6 control rats and 9 treated rats were reported as showing involuntary convulsive movements when being weighed. Acetylcholinesterase activity was measured in brain and erythrocytes, as was serum cholinesterase at the termination of this study. In male animals exposed to 0.05 mg/m^3, no significant differences with control animals were seen for any of the cholinesterases. Female animals at this dose had a statistically significant decrease of 12% in erythrocyte acetylcholinesterase. At 0.5 mg/m^3, brain cholinesterase was 10% lower compared to controls in both male and female rats. Females at this dose also showed erythrocyte acetylcholinesterase inhibition of 31%, while the males were unaffected. At 5 mg/m^3, brain acetylcholinesterase was inhibited by 79 and 81% in male and female rats, respectively. Erythrocyte acetylcholinesterase inhibition at this dose was 96% in the male rats and 95% in the female rats.

Neurological effects have been seen in a number of studies in animals after acute oral exposure to dichlorvos. Male Fischer 344 rats exposed to dichlorvos by olive oil gavage during an LD_{50}, study had signs of excessive cholinergic stimulation including salivation, tremors, lacrimation, fasciculations, irregular respiration, and prostration (Ikeda et al. 1990). In greyhound dogs receiving 11 or 22 mg/kg in a single dose, signs of neurological toxicity appeared within 7-15 minutes of dosing (Snow and Watson 1973). Restlessness was seen initially, followed by increased salivation, muscle fasciculations, involuntary urination, and repeated diarrhea, sometimes bloody. There was no apparent difference in

severity of clinical signs between dogs given 11 or 22 mg/kg. In dogs where erythrocyte acetylcholinesterase was determined (7 of 9), activity was decreased by at least 75%. One dog with 97% inhibition of erythrocyte acetylcholinesterase survived although suffering severe symptoms. Crossbred pigs receiving single doses from 18 to 560 mg/kg had clinical signs of neurological toxicity including hypoactivity, vomiting, ataxia, muscle fasciculations, uncoordinated movements, frothy salivation, and defecation (Stanton et al. 1979).

In a 21-day study in volunteers given dichlorvos orally, no signs of neurological toxicity were seen at doses of 0.033 mg/kg/day. They were then given 0.9 mg dichlorvos 3 times a day for 21 days in either a pre-meal capsule or in a 3-ounce container of gelatin. Serum cholinesterase and erythrocyte acetylcholinesterase were measured twice a week during the exposure period. Once a week each volunteer had his vital signs measured and an examination made for tremor, pupillary response to light, and skin moisture. Following the termination of the study, serum cholinesterase and erythrocyte acetylcholinesterase were measured weekly for the next 7 weeks. No clinical signs of neurological toxicity were observed in any of the volunteers. Erythrocyte acetylcholinesterase was not inhibited at 0.033 mg/kg/day in either the gelatin or capsule formulation. Serum cholinesterase was inhibited on average 38% in the group given the pre-meal capsule and 28% in the gelatin group. Measurements after the dosing period indicated that the half-life for regeneration of serum cholinesterase was 13.7 days.

In a 90-day study in female Sherman rats, groups of 10 animals were exposed to doses ranging from 0 to 69.9 mg/kg/day in their feed. Two animals from each group were bled on days 3, 11, 60, and 90, and sernm cholinesterase and erythrocyte acetylcholinesterase were determined. No clinical signs of neurological toxicity were noted in any dosage group. Cholinesterase data were presented graphically so the percentage inhibition of the cholinesterases can only be estimated. For serum cholinesterase, doses of 0.4 and 1.5 mg/kg/day appeared to have no effect. Doses of 3.5 and 14.2 mg/kg/day appeared to have been inhibited by 25-40% of control by the third day of feeding, remained at this level up to 60 days, and rose to near control level by the termination of the experiment at 90 days. Serum cholinesterase in rats consuming 35.7 and 69.9 mg/kg/day fell by 50% after 3 days and remained at this level throughout the experiment. Erythrocyte acetylcholinesterase was unaffected at doses up to 3.5 mg/kg/day. Activity was inhibited by 30% after 3 days at 14.2 mg/kg/day and remained at this level until the end of the experiment. At 35.7 and 69.9 mg/kg/day, erythrocyte

acetylcholinesterase was inhibited by about 50% after 3 days and 80% after 10 days. There appeared to be some recovery to about 50% of control by the end of the experiment.

Inhibition of erythrocyte and brain acetylcholinesterase, but not signs of neurotoxicity, were reported in Beagles receiving 0.05, 1.0, or 3 mg/kg/day dichlorvos in capsules for 52 weeks (AMVAC Chemical Corp. 1990; IRIS 1995). No changes were noted at 0.05 mg/kg/day, but erythrocyte acetyl-cholinesterase was inhibited 43-53% in dogs receiving 1 mg/kg/day and 81-87% in dogs receiving 3 mg/kg/day. Brain acetylcholi-esterase was inhibited 22% in dogs receiving 1 mg/kg/day and 47% in dogs receiving 3 mg/kg/day.

In a study where 3 cynomolgus monkeys were exposed to dichlorvos in xylene by daily dermal doses on a shaved area between the shoulder blades (Durham et al. 1957), cholinergic signs appeared within 10-20 minutes of dosage. Signs of toxicity in general order of appearance were nervousness, incoordination, muscle fasciculations, excessive salivation, labored breathing, miosis, and inability to move. The authors stated that at any given dose, the cholinergic signs tended to become more severe with subsequent doses. Serum cholinesterase and erythrocyte acetylcholinesterase were measured in one of the monkeys which received 75 mg/kg/day. After 2 doses, erythrocyte acetylcholinesterase had declined by about 67%, while serum cholinesterase was unchanged. When these values were measured shortly after the next day's dosage, the serum cholinesterase had fallen by about 33%, while erythrocyte acetylcholinesterase remained inhibited by about 67%. The serum cholinesterase recovered after 2 days without dosing, but the erythrocyte acetylcholinesterase did not. After 5 doses, the erythrocyte acetylcholinesterase had fallen by 90% and stayed there until death occurred after 12 days, during which 10 doses were administered.

Symptoms of neurological toxicity were also observed in Sherman rats dermally exposed to dichlorvos during an LD_{50}, experiment (Durham et al. 1957). Rats which survived exhibited bulging eyes, excessive lacrimation, and generalized muscle fasciculation and tremors. Surviving rats appeared to be completely recovered after 24 hours.

In a study involving daily dermal dosage in white Leghorn chickens, 3 hens receiving 2.8-3.8 mg/kg/day exhibited a staggering gait after 14 days of treatment (Francis et al. 1985). Three hens receiving doses between 0.54 and 0.71 mg/kg/day showed no signs of neurotoxicity over 90 days of dosing.

Dichlorvos does not appear to cause organophosphate-induced delayed neurotoxicity (OPIDN. Certain organophosphate compounds can inhibit an enzyme called neuropathy target esterase (NIT), as well as neural acetylcholinesterase. Significant inhibition of NTE followed by irreversible binding to this enzyme (aging) results in a progressive, irreversible neuropathy in humans and experimental mammals and hens (Coppock et al. 1995; Johnson 1981). The in viva substrate for this enzyme is unknown, as is the biochemical mechanism underlying the subsequent development of neuropathy. In hens that had been pre-medicated with atropine to protect against the acute cholinergic effects of dichlorvos, subcutaneous injection of dichlorvos did not result in OPIDN (Durham et al. 19.56; Lotti and Johnson 1978). Mild signs of ataxia were noted in atropine-pretreated hens 2 weeks after a single subcutaneous dose of 100 mg/kg dichlorvos (Caroldi and Lotti 1981). Subcutaneous administration of 100 mg/kg dichlorvos to atropine pre-treated hens followed by the same dose within l-3 days produced ataxia in the hens (Johnson 1978). When dichlorvos was administered by a single intraperitoneal injection (5-60 mg/kg in hens and 5-30 mg/kg in rats), no significant pathological lesions of the OPIDN type were observed (Ehrich et al. 1995), or gait alterations characteristic of this neuropathy.

Hens protected from the parasympathomimetic effects of dichlorvos by atropine developed clinical signs of ataxia (Francis et al. 1985; Johnson 1978). However, the apparent clinical signs of axonalpathy in the hens were not confirmed by histopathology. A number of different animal species have been experimentally intoxicated with dichlorvos. It has also been used as a systemic parasiticide in a number of domestic animal species (Hayes 1982). Humans have been intoxicated with dichlorvos and, because of medical intervention, recovered. In none of these studies and human poisoning incidents has OPIDN been reported. It is unlikely that dichlorvos OPIDN will occur in humans even in victims who have high levels of exposure and survive because of timely medical intervention. However, the interactions between dichlorvos and other pesticides for inducing OPIDN is not known.

While signs of delayed neuropathy can be produced in animal models, this only occurs at doses far above the LD_{50}. It is unlikely that dichlorvos would produce OPIDN in humans at doses that were not lethal because of acute cholinergic effects.

Several effects on brain chemistry have been observed in studies where dichlorvos was administered intraperitoneally. Glutathione peroxidase activity was inhibited and the reduced and oxidized forms of

glutathione were depleted in female Wistar rats receiving 5 mg/kg/day (Julka et al. 1992). This suggests that glutathione-dependent metabolism of dichlorvos depletes glutathione levels and possibly leaves the brain vulnerable to oxidative damage. Dopamine, norepinephrine, and 5-hydroxy tryptamine levels were also reported depleted in the brain after 10 days of intraperitoneal administration at 3 mg/kg/day in male rats (Ali et al. 1979).

Reproductive Effects. No incident reports or epidemiological studies in humans on reproductive effects associated with dichlorvos exposure are available. In a reproductive toxicity study involving male CF-1 mice, groups of 16 mice were exposed to atmospheres containing 0, 30, or 55 mg/m^3 (0, 3.3, or 6.1 ppm, respectively) for 16 hours (Dean and Thorpe 1972). There were no differences between control and treated mice in the number of early fetal deaths, late fetal deaths, or live fetuses found in the pregnant females. The percentage of pregnancies for females mated to males exposed to 30 and 55 mg/m^3 (3.3 and 6.1 ppm) for 16 hours was similar to the controls (73-88%, mean 80.9%). Under these exposure conditions, dichlorvos does not appear to affect the fertility of male CF-1 mice.

Sperm abnormalities were seen in C57BL/C3H mice injected intraperitoneally with 10 mg/kg/day for 5 days (Wyrobek and Bruce 1975). About 6% of the sperm from dichlorvos-treated animals was abnormal compared to 1.8% of sperm from untreated animals.

Developmental Effects. No studies in humans on developmental effects associated with dichlorvos exposure are available. Several animal studies examining developmental toxicity during continuous inhalation exposure to dichlorvos are available. Groups of 15 pregnant Carworth E rats were exposed to atmospheres containing 0, 0.25, 1.25, or 6.25 mg/m^3 throughout their 20-day gestation period (Thorpe et al. 1972). At the end of 20 days, the rats were sacrificed and the uteri removed for examination. The number of live fetuses, stillbirths, and resorption sites were noted, and live fetuses were examined for external malformations. Exposure of dams to all three concentrations of dichlorvos had no effect on the number of fetal resorptions, late fetal deaths, litter size, or mean weight per fetus. One fetus in the litter of one dam in the 0.25 mg/m^3 group had skeletal defects and gastroschisis. No other fetuses from dams exposed to the same or higher concentrations had these defects, so the authors concluded that they were not exposure related. Brain and erythrocyte acetyl-cholinesterase activities were inhibited 83% and 88%, respectively, in dams in the high-dose (6.25 mg/m^3) group, suggesting that even very high levels of acetylcholinesterase inhibition are not associated with teratogenicity.

In a parallel experiment conducted on groups of 20 pregnant Dutch rabbits in this same study (Thorpe et al. 1972), similar results were seen. Dams exposed to 6.25 mg/m^3 in the previous study had high mortality (16 of 20 died) so the doses used in this experiment were 0, 0.25, 1.25, 2, and 4 mg/m^3 over the 28 day rabbit gestational period. Sizes of litters, fetal resorptions, and late fetal deaths were unaffected by inhalation exposure to dichlorvos. Mean weight per fetus was slightly depressed in dams exposed to 4 mg/m^3, but the authors ascribed this to maternal toxicity. (Clinical signs were not reported, but 6 dams out of 20 in this group died during the study.) Three fetuses from groups that had not been exposed to dichlorvos had gastroschisis. Two dead fetuses from one litter in the 4 mg/m^3 had cleft palates.

No adverse developmental effects were observed in CF-1 mice treated by gavage with 60 mg/kg/day dichlorvos during gestation days 6-15 (Schwetz et al. 1979). There was no significant effect on implantations, mean number of fetuses per litter, incidence or distribution of resorptions, or on fetal body measurements. Similar results were observed in New Zealand rabbits treated by gavage with 5 mg/kg/day over gestation days 6-18 (Schwetz et al. 1979).

Genotoxic Effects. Dichlorvos is an electrophile and possesses a structural alert for methylating activity. Dichlorvos has been tested for genotoxicity in a number of in viva and *in vitro* systems. In general, dichlorvos was not genotoxic in *in vivo* studies (see Table 2-6) but was generally genotoxic or mutagenic in *in vitro* tests when metabolizing enzymes (S9 fraction) were not present (see Table 2-7).

In the sex-linked lethal mutation test in *Drosophila melunogaster,* dichlorvos gave negative results when the flies were exposed by inhalation (Jayasuriya et al. 1973; Sobels and Todd 1979). Multiple generations of flies exposed to food containing dichlorvos for 18 months had increased mutations (Hanna and Dyer 1975). Salivary gland chromosome abnormalities were reported in larvae fed 1 ppm dichlorvos in food in one study (Gupta and Singh 1974), while another study at lower levels showed no effect (Kramers and Knaap 1978).

No dominant lethal mutations were reported in ICR mice given a single intraperitoneal dose or consecutive daily doses of 5 or 10 mg/kg orally (Epstein et al. 1972). In a similar study where dichlorvos was administered by inhalation (30 or 55 mg/m^3 (3.3 or 6.1 ppm) to CF-1 mice, no dominant lethal mutations were observed (Dean and Thorpe 1972).

Table 2-6. Genotoxicity of Dichorvos *In Vivo*

Species (test system)	Test	Results	Reference
Drosophila melanogaster	sex-linked lethal mutation	—	Jayasuriya et al. 1973
D. melanogaster	sex-linked lethal mutation	—	Sobels and Todd 1979
D. melanogaster	sex-linked lethal mutation	—	Kramers and Knapp 1978
D. melanogaster	chromosome abnormalities	+	Gupta and Singh 1974
Mouse (ICR/Ha)	dominant lethal	—	Epstein et al. 1972
Mouse (CF-1)	dominant lethal	—	Dean and Thorpe 1972
Mouse (Q)	dominant lethal	—	Degraeve et al. 1972
Mouse (CF1)	dominant lethal	—	Dean and Blair 1976
Mouse (Q)	dominant lethal	—	Degraeve et al. 1972
Mouse (Q)	chromosome damage	—	Moutschen-Dahmen et al. 1981
Mouse (Swiss)	chromosome aberrations	—	Paik and Lee 1977
Mouse (F-1)	chromosome aberrations	—	Dean and Thorpe 1972
Hamster (Chinese)	chromosome aberrations	—	Dean and Thorpe 1972
Hamster (Syrian)	chromosome aberrations	—	Dzwonkowska and Hubner 1986

+ = Positive result; – = negative result

Table 2-7. Dichlorvos Genotoxicity *In Vitro*

Species (test system)	Reverse test	Result: With activation	Result: Without activation	Reference
Salmonella typhimurium				
TA98	mutation	–		Braun et al. 1982
TA100		+		
TA1535		–		
TA1536		–		
TA1537		–	–	
TA1538		–	–	
S. typhimurium				
TA98	reverse mutation		–	Moriya et al. 1982
TA100			+	
TA1535		–	+	
TA1536			–	
TA1537			–	
TA1538			–	
S. typhimurium				
TA1530	reverse mutation		+	Hanna and Dyer 1975
TA1535			+	
LTZ his C117			–	
his G 46			–	

Table 2-7. Dichlorvos *In Vitro* (continued)

Species (test system)	Reverse test	Result: With activation	Result: Without activation	Reference
S. typhimurium				
TA1535	reverse mutation		+	Shirasu et al. 1976
TA1536			–	
TA1537			–	
TA1538			–	
Mammalian cells				
Hamster (Chinese U79)	mutation induction		–	Aquilina et al. 1984
Hamster (Chinese U79)	DNA strand breakage		+	Green et al. 1974
Hamster (Chinese ovary)	nuclease resistance		+	Nishio and Uyeki 1982
Hamster (Chinese ovary)	sister chromatid exchange		+	Nishio and Uyeki 1982
Hamster (Chinese U79)	sister chromatid exchange		+	Tezuka et al. 1980
Hamster (Syrian embryo)	adenovirus transformation		+	Hatch et al. 1986
Mouse (Peripheral blood lymphocyte)	sister chromatid exchange		–	Kligerman et al. 1985
Human (epithelial line EUE)	unscheduled DNA synthesis		+	Aquilina et al. 1984
Human (kidney T-cells)	DNA single-strand breakage		–	Bootsman et al. 1991
Human (lympocytes, fetal lung fibroblasts)	exchange		–	Nicholas et al. 1978

NA = not applicable; ND = no data; – = negative results; + = positive results

Male Q strain mice which received drinking water containing 2 mg/L dichlorvos for 7 weeks did not show chromosome damage in bone marrow cells, spermatogonia, or primary spermatocytes (Moutschen-Dahmen et al. 1981). In a micronucleus test, Swiss mice given daily intraperitoneal injections of dichlorvos (0.0075 or 0.015 mg/kg) for 2 days showed no aberrations in structure or number of chromosomes in bone marrow cells. CF-1 mice exposed to 64-72 mg/m^3 for 16 hours or to 5 mg/m^3 for 21 days did not show chromosome abnormalities (Dean and Thorpe 1972). In Syrian hamsters, however, intraperitoneal injections at 3, 6, 15, and 30 mg/kg did cause increases in the number of cells with aberrant chromosomes (Dzwonkowska and Hubner 1986).

Dichlorvos was positive for binding to calf thymus DNA in vitro (Lofroth 1970; Segerbeck 1981). Dichlorvos was negative for DNA binding in viva in rats (Wooder et al. 1977) and in mice (Segerbeck 1981).

In mutagenicity tests with *S. typhimurium* tester strains, dichlorvos has generally been positive without metabolic activation and negative in the presence of S9. Dichlorvos in the presence of metabolic activation was negative in strains TA 98 (Braun et al. 1982), TA 1535 (Braun et al. 1982; Carere et al. 1976; Moriya et al. 1978) and TA 1536, 1537, and 1538 (Braun et al. 1982; Carere et al. 1976). Without metabolic activation, dichlorvos was positive in strain TA 100 (Moriya et al. 1978), strain 1530 (Hanna and Dyer 1975), strain 1535 (Carere et al. 1978; Hanna and Dyer 1975; Moriya et al. 1978; Shirasu et al. 1976), but negative in strains 1536, 1537, and 1538 (Moriya et al. 1983; Shirasu et al. 1976).

The lack of dichlorvos genotoxicity in *in vivo* studies is most likely due to the fact that while dichlorvos possesses methylating activity, the phosphorous atom of the molecule is a stronger electrophile than the methyl carbon atoms (Wright et al. 1979). In tissues and blood, dichlorvos is much more likely to react with “A”-type esterases, serum cholinesterase, or acetylcholinesterase than with DNA (WHO 1989).

Cancer. In a 2-year carcinogenicity study of inhalation exposure to dichlorvos, groups of 50 Carworth rats of each sex were exposed at levels of 0, 0.05, 0.5, or 5 mg/m^3 (Blair et al. 1976). Only 11 of the unexposed male controls and 25 of the unexposed female controls survived to the end of the study. Survival was actually highest in the rats receiving the highest dose of dichlorvos (32 of 50 males and 34 of 50 females). Microscopic examination revealed a wide range of lesions in all

groups; the authors stated that these are commonly seen in old rats of this strain. There was a high incidence in all groups of chronic nephrosis, focal myocardial fibrosis, degenerative artery disease, lymphoid hyperplasia of the spleen. and testicular atrophy. Common tumors in all groups were adenomas of the anterior pituitary gland, parafollicular cell adenomas, and carcinomas of the thyroid gland, adrenal pheochromocytomas, and mammary fibroadenomas in the females. Examination of the lungs (presumably the tissue receiving the highest dose) revealed minor changes in all groups. Peribronchial and perivascular lymphoid aggregates, mild degrees of bronchiolitis and focal alveolar thickening were noted. Electron microscopic examination of bronchi, bronchioli, and alveoli of a small number of control and high-dose group animals showed no differences between the groups. None of the lesions in the study was associated with dichlorvos exposure.

The high mortality of the control animals in this study makes interpretation of the carcinogenicity data problematic. The possibility also exists that exposure by the oral and dermal routes may have occurred. However, no significant increase in neoplastic or non-neoplastic lesions was found in the nasal and respiratory tract tissues that received the highest dose of dichlorvos.

In a carcinogenicity study in Osborne-Mendel rats, groups of 50 animals of each sex were originally dosed through feed at levels of 45 and 90 mg/kg/day (NCI 1977). During the initial 3 weeks of dosage, acute signs of toxicity were observed including tremor and diarrhea in the 90 mg/kg/day group. For this reason, the dosages were then lowered to 30% of the original. The TWA doses over the go-week period of dosing were 13.5 and 29.3 mg/kg/day. After the go-week dosing period, the animals were observed for a further 30 weeks until sacrifice. Adverse clinical signs (hematuria, rough coats, epistaxis) were noted in control and dosed animals, gradually increasing during the second year of the study. The authors stated that at the end of the study the rats were in generally poor condition. The matched control groups had significantly lower survival than the treated groups at the end of the study, mainly due to deaths during the 30-week observation period after treatment. At the termination of the study, only 2 of 10 male rats and 5 of 10 female rats survived in the matched control groups. For this reason, these control rats were pooled with control rats from concurrent studies for comparison with the treated groups. Of the male rats, 76% of the high-dose and 64% of the low-dose group survived to the end of the study as did 84% of the high-dose and 80% of the low-dose females.

Numerous inflammatory, degenerative, and proliferative lesions commonly seen in aged rats occurred with approximately equal frequency in the treated and the pooled control rats. Several non-neoplastic

lesions occurred more frequently in the treated rats than in the controls. These included aggregates of alveolar macrophages in the lungs, interstitial fibrosis of the myocardium, and focal follicular cell hyperplasia of the thyroid gland in the male rats. Benign endocrine neoplasms occurred frequently in both test and control rats. There was a high incidence of benign mammary neoplasms in both control and treated rats. Because of the low survival of the matched control rats, control animals from other concurrent studies were pooled for statistical analysis. The authors stated that on the basis of variability of both the incidence and type of spontaneous lesions and the lack of significant proportions of tumors in the dosed groups compared to the controls, no statistical significance could be attached to the incidence of the tumors seen in the dichlorvos-treated rats in this study. Because of the poor survival of control animals in this study, the results are difficult to interpret.

In another carcinogenicity study in rats, groups of 50 Fischer 344 rats of each sex were dosed with dichlorvos by oral gavage in corn oil at levels of 0, 4, or 8 mg for 5 days a week for 103 weeks (NTP 1989). No significant differences in survival were noted between any groups. Survival rates were: 31 of 50 for male and female controls, 25 of 50 males and 26 of 50 females in the low-dose group, and 24 of 50 males and 26 of 50 females in the high-dose group.

Statistically significant increases in neoplasms were observed in the pancreas and hematopoietic system in male rats and in the mammary gland in female rats. Adenoma of the exocrine pancreas exhibited a significant positive trend and the incidences were greater in treated than control groups (15 of 50 in vehicle control, 23 of 49 in the low-dose group and 30 of 50 in the high-dose group). When horizontal sections of the pancreas were examined, additional adenomas were observed. When the data from both methods were combined, the incidences of pancreatic adenoma were 25 of 50 in the controls, 30 of 50 in the low-dose, and 33 of 50 in the high-dose group. The incidence for the treated groups was statistically significant compared to the vehicle controls.

A significant positive trend for mononuclear cell leukemia was also observed in the male rats. This neoplasm was found in 11 of 50 controls, 20 of 50 in the low-dose group, and 21 of 50 in the high-dose group. A significant positive trend also occurred for mammary gland tumors in female rats. Fibroadenoma, adenoma, or carcinoma occurred in 11 of 50 control rats, 20 of 50 in the low-dose group, and 17 of 50 in the high-dose group. Peer review panels characterized these results as “some evidence” of carcinogenic activity in male rats and “equivocal evidence” in female rats. The control

animals in these studies had substantially higher incidences of neoplasms at these sites than the historical incidence compiled from other studies.

Dichlorvos was also tested for carcinogenicity in male and female $B6C3F_1$ mice by a similar 2-year protocol (NTP 1989). Because of higher toxicity in male mice during the dose-finding study, groups of 50 male mice were dosed by corn oil gavage at 0, 10, or 20 mg/kg for 5 days a week, and the females dosed at 0, 20, or 40 mg/kg for 5 days a week.

The only neoplasm that occurred with a significant positive trend in treated compared to control mice was squamous cell papilloma and carcinoma of the forestomach. The overall incidence of this lesion in male mice was 1 of 50 in the controls, 1 of 50 in the low-dose group, and 5 of 50 in the high-dose group. In the females, overall incidences were 5 of 49 in the control group, 6 of 49 in the low-dose group and 18 of 50 in the high-dose group. Incidence in male controls was near the historical incidence of l%, but was higher in the female controls (10% compared to 1%). Peer review panels characterized the level of carcinogenic activity as “some evidence” in male mice and “clear evidence” in female mice.

The mechanism of dichlorvos-induced carcinogenicity is not known. A study of $B6C3F_1$ mouse forestomach from mice treated with dichlorvos by gavage in corn oil (Benford et al. 1994) showed increases in replicative DNA synthesis (associated with increased cell proliferation). Unscheduled DNA synthesis (associated with DNA repair) was not increased by dichlorvos treatment, but was increased by 1 -methyl-3-nitro-1 -nitrosoguanidine, a known genotoxic forestomach carcinogen. The authors concluded that the forestomach tumors seen in the 2-year carcinogenicity study (NTP 1989) may have been mediated by enforced cellular proliferation rather than by a genotoxic mechanism.

Two organizations have reviewed the evidence for dichlorvos carcinogenicity in humans from the results obtained in test systems. The EPA has classified dichlorvos as a probable human carcinogen (Category B2) on the basis of significant increases of forestomach tumors in mice and-leukemias and pancreatic acinar adenomas in rats. Supporting evidence included observation of tumors at other sites in the rat and the observation that dichlorvos and a major metabolite, dichloroacetaldehyde, are mutagenic in in vitro test systems. A structurally related compound, dichloropropene, also causes forestomach tumors in rodents (IRIS 1995). The International Agency for Research on Cancer (IARC) has classified dichlorvos as possibly carcinogenic to humans (Group 2B) based on inadequate evidence

in humans for the carcinogenicity of dichlorvos and sufficient evidence in experimental animals for the carcinogenicity of dichlorvos (IARC 1991).

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to dichlorvos are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAWNRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by dichlorvos are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Dichlorvos

Dichlorvos at high doses will cause classical symptoms of organophosphate toxicity, such as miosis, tremor, increased salivation, lacrimation, pulmonary secretions, and perspiration. If these symptoms occur together and the individual has recently been in contact with pesticides containing dichlorvos, it is highly likely that exposure to dichlorvos has occurred. Exposure to toxic concentrations of dichlorvos or other organophosphates can be confirmed by blood tests. Dichlorvos can reduce the activity of two enzymes in the blood, serum cholinesterase and erythrocyte acetylcholinesterase. Serum cholinesterase appears to be more sensitive to inhibition by dichlorvos and other organophosphates than erythrocyte acetylcholinesterase. However, serum cholinesterase activity recovers more rapidly than erythrocyte acetylcholinesterase because of the higher turnover rate of serum proteins compared to erythrocytes. Exposures that occurred two weeks or more before testing probably would not be reflected in an inhibition of serum cholinesterase. Because of the human variability in activity of these enzymes, follow-up determinations showing a rise back to a constant activity are more reliable evidence that an exposure has taken place than a single determination.

Confirmation that specific exposure to dichlorvos has taken place is difficult and requires sophisticated analytical chemistry. Intact dichlorvos has not been detected in humans and only rarely in animals. This is because of the rapid metabolism of dichlorvos by esterases in the liver and blood (see Section 2.3). The major metabolic products of dichlorvos are dimethyl phosphate and the glucuronide conjugate of dichloroethanol. These compounds are rapidly excreted into the urine and will have left the body within a day or two of cessation of exposure. Dimethyl phosphate has been measured in the urine of pesticide applicators by extraction with an ion exchange resin, derivitization, and gas chromatography (Das et al. 1983). Dichloroethanol has been detected in the urine of a human volunteer after glucuronidase treatment and gas-liquid chromatography (Hutson and Hoadley 1972b). However, because of interference by endogenous urine components, the measurement had a relatively high error. Exposure to naled and trichlorphon, two organophosphates that are converted in the body

to dichlorvos, would also have to be ruled out before a definitive determination of dichlorvos exposure could be made (Hayes 1982).

2.6.2 Biomarkers Used to Characterize Effects Caused by Dichlorvos

The toxic effects of dichlorvos are caused by its inhibition of neural acetylcholinesterase in the peripheral and central nervous systems. This inhibition is reflected by the level of depression of erythrocyte acetylcholinesterase activity in the blood.

The nervous system can accept a certain amount of acetylcholinesterase inhibition without overt toxic effects. In humans and animals, toxic signs are generally not seen until at least 20% of this enzyme (measured as erythrocyte acetylcholinesterase) has been inhibited (Ecobichon 1991). In an animal study, brain acetylcholinesterase after a 2-year inhalation exposure to dichlorvos was inhibited more than 90% compared to control animals (Blair et al. 1976), yet no symptoms of cholinergic overstimulation were observed. With dichlorvos and other organophosphate compounds, the best predictor of toxicity is not necessarily the actual percent inhibition of acetylcholinesterase, but rather how rapidly this inhibition has occurred. Rapid inhibition does not give the nervous system time to physiologically adapt to acetylcholinesterase inhibition. This adaptation appears to involve desensitization and down-regulation of muscarinic receptors (Fitzgerald and Costa 1993).

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

2.7 INTERACTIONS WITH OTHER CHEMICALS

The major interaction of dichlorvos with other chemicals would be with chemicals that have the same mechanism of action (i.e., organophosphate and carbamate pesticides). Simultaneous exposure to dichlorvos and one of these chemicals could possibly have an additive effect on inhibition of neural acetylcholinesterase. There has been one case of serious human toxicity caused by ingestion of a bait cake that contained both dichlorvos and malathion (Hayes 1982). Chemicals which can react with the serine residue at the active site of the “A”-type esterases (e.g., diisopropylfluorophosphate [DEP]) could also increase the toxicity of dichlorvos by interfering with metabolism.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to dichlorvos than will most persons exposed to the same level of dichlorvos in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of dichlorvos, or compromised function of target organs affected by dichlorvos. Populations who are at greater risk due to their unusually high exposure to dichlorvos are discussed in Section 5.6, Populations With Potentially High Exposure.

People with impaired “A”-type esterase function would be unusually susceptible to dichlorvos exposure , because of an impaired ability to metabolize dichlorvos absorbed by the body. This population would primarily be composed of people suffering from liver diseases. Pregnant women have lower levels of serum cholinesterase and are more susceptible to agents such as succinylcholine which is metabolized by this enzyme. Dichlorvos can bind stoichiometrically to this enzyme and inhibit its activity, so pregnant women are at least hypothetically more susceptible to dichlorvos exposure than other populations. A similar effect could be expected in individuals with inherited abnormally low serum cholinesterase levels.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to dichlorvos. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to dichlorvos. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to dichlorvos:

> “Cholinesterase inhibitor pesticides” in *Handbook* of Poisonilzg, 1987, Appleton and Lange, Norwalk, CT; R.H. Dreisbach and W.O. Robertson. pp 11 l-l 18.
>
> “Organophosphates and other insecticides” in *Clinical Management of Poisoning and Drug Overdose,* 2nd. edition, 1990, W.B. Saunders, Philadelphia; L.M. Haddad and J.F. Winchester, eds. pp 10761087.

"Insecticides: organophosphates and carbamates" in *Goldfrank's Toxicologic Emergencies,* 5th edition, 1994, Norwalk, CT; L.R. Goldfrank, N.E. Flomenbaum, N.A. Lewis, R.S. Weisman, M.A. Howland, and R. S. Hoffman. pp 1105-l 119.

2.9.1 Reducing Peak Absorption Following Exposure

If exposure has occurred by the oral route, gastric lavage would reduce peak absorption following exposure. Dichlorvos generally does not absorb to other materials. so treatment with activated charcoal, for example would probably be ineffective. If exposure has occurred by the dermal route, rinsing the exposed skin with large amounts of flowing water and soap would greatly reduce exposure.

2.9.2 Reducing Body Burden

Because dichlorvos does not accumulate in the body and is rapidly metabolized to less toxic metabolites which are rapidly excreted into the urine, specific efforts to reduce the body burden would not appear to be necessary.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Dichlorvos has the same mechanism of action as other organophosphorus insecticides. Poisonings with these types of chemicals are common enough that specific and effective medical interventions have been developed. The life-threatening effects of dichlorvos poisoning are related to its effects on the respiratory system (respiratory depression, bronchospasm, increased bronchial secretions, pulmonary edema. muscular weakness). If these symptoms are present, artificial respiration and suctioning are performed via an endotracheal tube. Atropine is used to counteract the muscarinic effects of dichlorvos with care being taken that symptoms of atropine overdose do not occur (dry mouth, dilatation of the pupils). The inhibited neural acetylcholinesterase can be reactivated by intravenous administration of specific antidotes such as pralidoxime.

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of dichlorvos is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to

assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of dichlorvos.

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

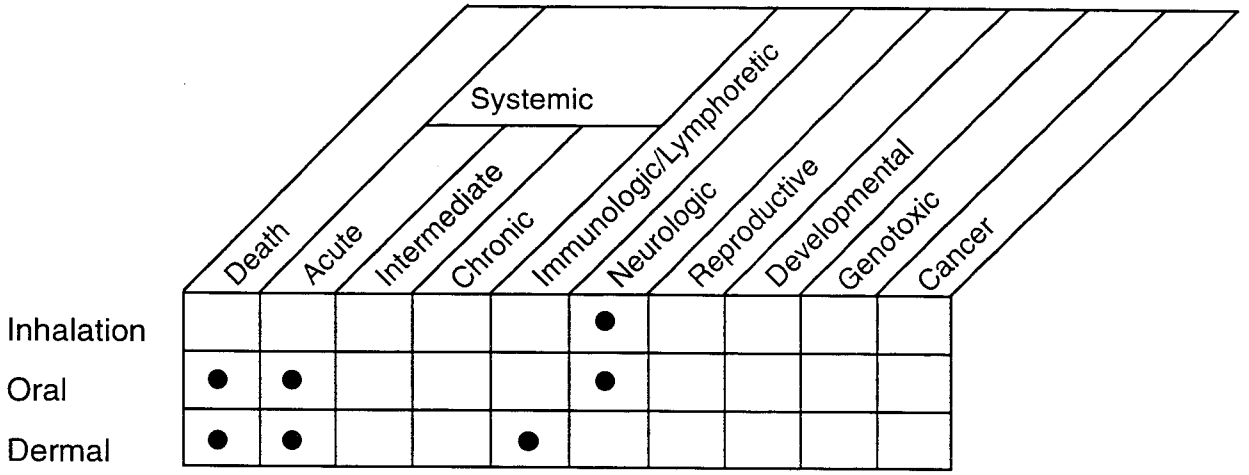
2.10.1 Existing information on Health Effects of Dichlorvos

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to dichlorvos are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of dichlorvos. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

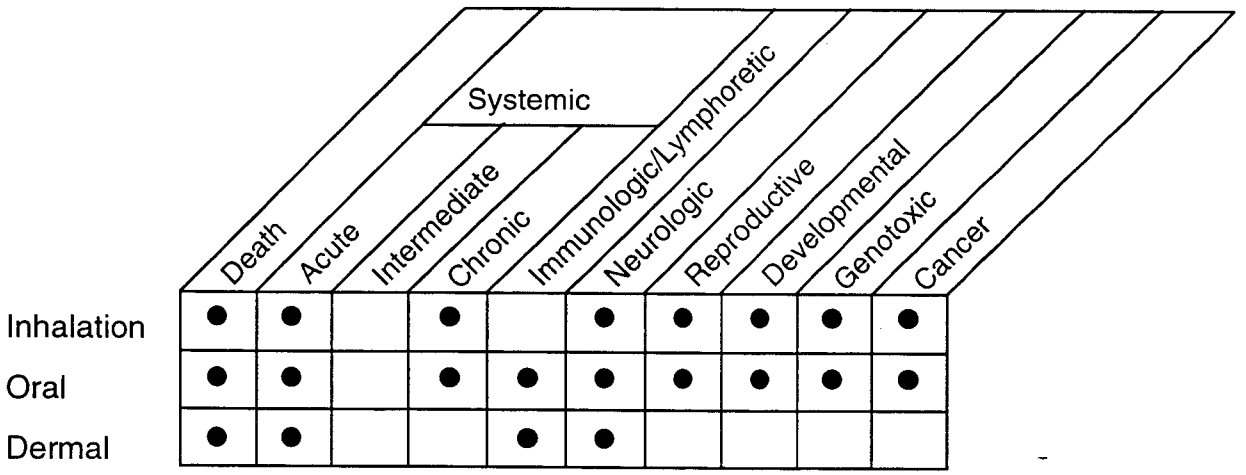
As shown in Figure 2-5, information is available for humans on death after oral and dermal exposure, and on systemic and neurological effects after inhalation and oral exposure. This information is generally for acute-duration exposure only, except for one 21-day study of oral exposure in volunteers that examined the neurological end point of erythrocyte acetylcholinesterase inhibition. Nonneurological end points generally have not been observed in humans, except those that result secondarily from the neurological toxicity of dichlorvos.

Animal data exist for death by inhalation, oral, and dermal routes for acute durations, and inhalation and oral routes for intermediate and chronic durations. Data also exist for systemic effects that are secondary to the neurotoxicity of dichlorvos. Limited immunological data are available only for the oral route for the acute and intermediate duration. Data are available for neurological effects for all

Figure 2-5. Existing Information on Health Effects of Dichlorvos



Human



Animal

● Existing Studies

routes and all durations except dermal intermediate and chronic. Reproductive and developmental studies are available for the inhalation and oral route. Genotoxic and cancer studies are available for the inhalation and oral route.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. Populations in the vicinity of hazardous waste sites may be exposed to dichlorvos for brief periods. Exposure would most likely occur by the inhalation route, but dermal exposure by contact with contaminated soil is also possible. Cases of accidental and intentional poisonings in humans (Hayes 1982) indicate that the central and peripheral nervous systems are the major target organs for dichlorvos toxicity by the oral and dermal routes. It can be inferred from animal studies that this is true for inhalation exposure as well (Durham et al. 1957). The specific target of dichlorvos is the enzyme which catalyzes the hydrolysis of the neurotransmitter acetylcholine, neural acetylcholinesterase. Minimal risk levels (MRLs) have been derived for the acute duration for both the inhalation route (0.002 ppm) (Schmidt et al. 1979) and the oral route (0.004 mg/kg/day) (Teichert et al. 1976) based on inhibition of erythrocyte acetylcholinesterase and neural acetyl-cholinesterase activity. The study used for the acute-duration oral MRL (Teichert et al. 1976) did not include a dose at which no adverse effects occurred (NOAEL); an acute-duration oral study in animals which included doses of dichlorvos that produced both a NOAEL and a LOAEL would be valuable. Little information on acute-duration dermal exposure is available except for lethality studies. Since this is a possible route of exposure from contaminated soil at hazardous waste sites, studies which establish a threshold value for acetylcholinesterase inhibition in a sensitive species would be useful.

Intermediate-Duration Exposure. A well-conducted study is available for human intermediateduration oral exposure to dichlorvos (Boyer et al. 1977). This study was used to derive an oral MRL of 0.003 mg/kg/day dichlorvos based on a NOAEL of 0.033 mg/kg/day for erythrocyte acetyl-cholinesterase inhibition. An intermediate-duration inhalation study in rats (Thorpe et al. 1972) was used to derive an inhalation MRL of 0.0003 ppm dichlorvos based on a NOAEL of 0.03 ppm for brain acetylcholinesterase inhibition. Results in animal studies indicate that the toxic effects of intermediate-duration exposure dichlorvos are similar to those for the acute duration. Several studies have identified immunosuppression in rats treated orally with dichlorvos over the intermediate duration (Desi et al. 1978, 1980). This effect may be secondary to central cholinergic stimulation; further studies are needed to clarify this point. No studies on intermediate-duration dermal exposure to

dichlorvos were located: studies on this topic would be helpful to establish threshold values of acetylcholinesterase inhibition.

Chronic-Duration Exposure and Cancer. Chronic-duration exposure is the most likely type of exposure that would be experienced by people living near hazardous waste sites. Because of the physical properties of dichlorvos, this exposure is most likely to be by the inhalation route. The only chronic-duration study by the inhalation route was done on rats in 1976 (Blair et al. 1976). A chronicduration inhalation MRL of 0.00006 ppm was derived, based on brain acetylcholinesterase inhibition in this study. While this study found no evidence of an increased incidence of cancer in these rats, it does not meet present-day standards for carcinogenicity studies of this type. A chronic-duration oral study has been done in rats and mice, and produced evidence of carcinogenicity by this route (NTP 1989). Since inhalation is the most likely route of exposure in humans for dichlorvos, a chronic duration inhalation study in rats and mice could help public health assessment of potential risks of dichlorvos.

Genotoxicity. Dichlorvos has been tested in virtually every available genotoxicity test. In bacteria, dichlorvos bound covalently to DNA and caused DNA damage and point mutations. Dichlorvos induced gene conversion, mutation and aneuploidy in yeast and fungi. In *D. melunogasrer*, chromosomal but not sex-linked recessive lethal mutations were produced. In mammalian cells *in vitro,* dichlorvos caused DNA strand breaks, mutation, sister chromatid exchange, chromosomal aberrations and cell transformation. The effects on *in vitro* systems were in general greatly reduced when metabolic activation was present. Dichlorvos was negative for genotoxicity in *in vivo* tests for the induction of unscheduled DNA synthesis, sister chromatid exchange, micronucleus formation, chromosomal aberrations, or dominant lethal mutation by the inhalation route. The database for dichlorvos genotoxicity is extensive and no data needs have been identified.

Reproductive Toxicity. No information on reproductive toxicity in humans after dichlorvos exposure is available. Dichlorvos did not cause reproductive toxicity by the inhalation route over the acute duration in male mice (Dean and Thorpe 1972). No gross or histological evidence of treatmentrelated damage to reproductive tissues (prostate, testes, epididymis, ovaries or uterus) was seen in rats (4 or 8 mg/kg/day) or mice (10, 20, or 40 mg/kg/day) orally exposed to dichlorvos by gavage for 2 years (NTP 1989). No reproductive studies on dichlorvos by the oral or dermal routes are available;

animal reproductive toxicity studies by these routes would be useful. No multi-generational reproductive studies on dichlorvos are available.

Developmental Toxicity. No information on developmental toxicity in humans after dichlorvos exposure is available. Dichlorvos did not cause developmental toxicity in rats exposed throughout pregnancy by the inhalation route to up to 0.69 ppm or up to 0.44 ppm in rabbits (Thorpe et al. 1972). Similar results were obtained with mice and rabbits exposed to 0.44 ppm dichlorvos for 7 hours a day during the organogenesis period of gestation (Schwetz et al. 1979). Developmental toxicity was not observed in mice exposed orally by gavage to 60 mg/kg/day dichlorvos over gestation days 6-15, or in rabbits exposed similarly to 5 mg/kg/day dichlorvos over gestation days 6-18 (Schwetz et al. 1979). The database for dichlorvos developmental toxicity is adequate, except that a multi-generation developmental study in rabbits would be useful.

Immunotoxicity. No information was located on immunotoxicity in humans after dichlorvos exposure. Only a few studies were located that addressed immunotoxicity in animals after dichlorvos exposure. Immunosuppression after oral exposure to dichlorvos in rabbits has been reported in three studies (Casale et al. 1983; Desi et al. 1978, 1980). A dose-related suppression of the humoral immune response induced by *S. typhimurium* was observed in rabbits (Desi et al. 1978). A single oral dose of 120 mg/kg dichlorvos in male C57B l/6 mice that had been inoculated with sheep erythrocytes 2 days earlier suppressed the primary IgM response observed 48 hours later (Casale et al. 1983). Severe signs of dichlorvos neurotoxicity were noted, and the authors stated that the immuno-suppression observed in this study may have been mediated indirectly by toxic chemical stress. It is unknown if the immune suppression noted after dichlorvos exposure in these studies is secondary to cholinergic stimulation. Immunotoxicity studies employing atropine prophylaxis to counteract the anticholinesterase effect of dichlorvos are necessary to resolve this question. Additional studies examining potential longer-term effects of dichlorvos on the immune system by all three routes as well as short-term effects by the inhalation and dermal routes would be important for estimating human susceptibility for populations exposed for varying lengths of time at hazardous waste sites.

Neurotoxicity. A few case reports in humans indicate that the central and peripheral nervous systems are the targets of dichlorvos toxicity after oral and dermal exposure (Hayes 1982). Numerous animal studies by the inhalation, oral and dermal routes corroborate these findings (Durham et al. 1957; Snow and Watson 1973; Stanton et al. 1979) and have identified the molecular target for

dichlorvos neurotoxicity, neural acetylcholinesterase. The database for neurotoxicity was sufficient to derive MRLs for acute-, intermediate-, and chronic-duration inhalation exposure and for acute- and intermediate-duration oral exposure based on observation of NOAELs and one less serious LOAEL for inhibition of neural and/or erythrocyte acetylcholinesterase. Further studies are needed to elucidate the mechanism of adaptation to dichlorvos neurotoxicity. In longer term experiments (Blair et al. 1976), levels of inhibition that would cause serious toxicity if caused by an acute dose (up to 90% for neural acetylcholinesterase) are tolerated without clinical signs of dichlorvos neurotoxicity. Studies that determine a threshold dose for dichlorvos neurotoxicity by the dermal route are also needed since this is a potential route for exposure to populations near hazardous waste sites.

The adverse neurological effects of dichlorvos can be explained largely by its inhibition of neural acetylcholinesterase, but the possibility exists that other potential targets in the nervous system exist. For example, there is evidence that chlorpyrifos oxon (the active metabolite of the organophosporus insecticide chlorpyrifos) can inhibit muscarinic receptor binding *in vitro.* This inhibition occurs at concentrations lower than those necessary to inhibit neural acetylcholinesterase (Huff et al. 1994). *In vitro* receptor binding in brain membrane preparations or in cultured cells would determine if dichlorvos has a similar effect on muscarinic receptor function. Little is known about the potential for interaction between dichlorvos and other neurotoxic agents; further studies on this topic would be useful.

Epidemiological and Human Dosimetry Studies. At the present time, very few people are exposed to dichlorvos outside occupational groups. The major group potentially exposed, pest control workers, generally use several different pesticides, and it would be virtually impossible to identify a group exposed primarily to dichlorvos. The lack of adequate analytical methods that would specifically quantify dichlorvos exposure (as opposed to other organophosphorus or carbamate pesticides) precludes human dosimetry studies. Thus, no data needs for epidemiological or human dosimetry studies were identified.

Biomarkers of Exposure and Effect.

Exposure. Reliable biomarkers for exposure to dichlorvos already exist (serum cholinesterase, erythrocyte acetylcholinesterase, and clinical symptoms of neurotoxicity). However, reliable methods

to distinguish dichlorvos intoxication from that caused by other organophosphorus compounds do not exist.

Effect. Reliable biomarkers for the effect of dichlorvos exist (cholinergic symptoms of neurotoxicity and erythrocyte acetylcholinesterase). There is no evidence that toxic effects occur in humans at levels of dichlorvos that do not significantly inhibit erythrocyte acetylcholinesterase.

Absorption, Distribution, Metabolism, and Excretion. Very little information is available on the toxicokinetics of dichlorvos in humans. Dichlorvos appears to be rapidly absorbed by all routes of exposure. This rapid rate of absorption is inferred from the time to onset of clinical signs and/or cholinesterase inhibition because of the difficulty in assaying dichlorvos in biological tissues. This is due to the rapid hydrolysis of dichlorvos by tissue esterases, particularly in the liver and the serum. The half-life of dichlorvos in human blood *in vitro* is about 10 minutes (Blair et al. 1975). Distribution is also inferred from cholinesterase inhibition, but there does not appear to be any preferential distribution to particular tissues. Dichlorvos does not appear to be stored or concentrated in any tissue (Casida et al. 1962). The major metabolites of the esterase-catalyzed degradation of dichlorvos are dimethyl phosphate and dichloroacetaldehyde (Wright et al. 1979). Dimethyl phosphate is excreted in the urine, while dichloroacetaldehyde can be reduced to dichlorethanol or dehalogenated to glyoxal, which enters 2-carbon metabolism (Hutson et al. 1971). Dichloroethanol is either conjugated to glucuronic acid and excreted or dehalogenated and further metabolized. There is also some evidence that dichlorvos can be demethylated in a glutathione-dependent process (Blair et al. 1975).

Further characterization of the esterases involved in dichlorvos degradation is necessary to determine if any possibility exists that human polymorphism may make some groups more susceptible to dichlorvos toxicity than others. Since inhalation exposure is the most likely route of exposure at hazardous waste sites, determination of the blood-gas partition coefficient for dichlorvos in human blood is needed to more accurately quantify the potential health risks for a given atmospheric level of dichlorvos.

Comparative Toxicokinetics. Differences in sensitivity to dichlorvos toxicity appear to exist in mammalian test animal species. Generally, for a given dose, rabbits are the most sensitive, followed in order by dogs, rats, and mice (NTP 1989; Snow and Watson 1973; Thorpe et al. 1972). The comparative toxicokinetic parameters that might explain these differences are unknown. Further

studies via all three exposure routes in test species would be useful in determining similarities and differences between humans and animals and the effects of pregnancy on dichlorvos metabolism.

Methods for Reducing Toxic Effects. Further studies on retarding gastrointestinal absorption of dichlorvos would be useful in the treatment of poisoning. No methods exist for reducing the body burden of dichlorvos. The medical management of the toxic effects of dichlorvos (respiratory support, atropine treatment, reactivation of neural acetylcholinesterase with oximes) is similar to that for poisoning by other organophosphorus pesticides. Any improvements in the management of organophosphorus poisoning would apply to dichlorvos.

2.10.3 Ongoing Studies

M. Cunningham of the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, is conducting feeding studies in mice with dichlorvos and several other chemicals to investigate the relationship between cell proliferation and carcinogenesis.

3. CHEMICAL AND PHYSICAL INFORMATION

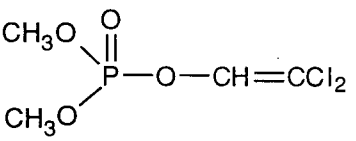
3.1 CHEMICAL IDENTITY

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

3.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 3-1. Chemical Identity of Dichlorvos

Characteristic	Information	Reference
Chemical name	O,O-dimethyl-O-(2,2-dichlorovinyl)phosphate	Merck 1989
Synonym(s)	Phosphoric acid 2,2-dichloroethenyl dimethyl ester; phosphoric acid 2,2-dichlorovinyl dimethyl ester; 2,2-dichlorovinyldimethyl phosphate; dichlorophos; dichlorovos; DDVP; dichlorvos	Merck 1989; Worthing 1983
Registered trade name(s)	SD 1750; Astrobot; Atgard; Canogard; Dedevap; Dichlorman; Divipan; Equigard; Equigel; Estrosol; Herkol; Nogos; Nuvan; Task; Vapona; Verdisol	Merck 1989
Chemical formula	$C_4H_7Cl_2O_4P$	Merck 1989
Chemical structure		Worthing 1983
Identification numbers:		
CAS Registry	62-73-7	Merck 1989
NIOSH RTECS	TC 0350000	HSDB 1996
EPA Hazardous Waste	No data	
OHM/TADS	7800015	HSDB 1996
DOT/UN/NA/IMCO	NA 2783 Dichlorvos UN 3018 Organophosphorus pesticides, liquid, toxic IMO 6.1	HSDB 1996
HSDB	319	HSDB 1996
NCI	C00113	HSDB 1996

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

Table 3-2. Physical and Chemical Properties of Dichlorvos

Property	Information	Reference
Molecular weight	220.98	Merck 1989
Color	Colorless to amber	Worthing 1983
Physical state	Liquid	Merck 1989
Melting point	No data	
Boiling point at 0.05 mm Hg	35 °C	Worthing 1983
at 20 mm Hg	140 °C	Merck 1989
at 14 mm Hg	120 °C	Sunshine 1969
at 760 mm Hg	221 °C	Aster 1996 (calculated)
Density at 25 °C	1.415 g/mL	Merck 1989
Odor	mild chemical odor	Mackison 1981
	aromatic odor	Worthing 1983
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20 °C	10 mg/mL	Worthing 1983; Merck 1989
Water at 25 °C	16 mg/mL	Kawamoto and Urano 1989
Organic solvent(s)	Miscible with alcohol and most organic solvents	Merck 1989;
	Miscible with aromatic chlorinated hydrocarbons	Sunshine 1969
Partition coefficients:		
Log K_{ow}	1.16	Kawamoto and Urano 1989
	1.47	Bowman and Sans 1983
Log K_{oc}	1.45	Kenaga 1980
Vapor pressure at 20 °C	1.2×10^{-2} mm Hg	Sunshine 1969; Merck 1989
Henry's law constant		
at 25 °C	6.61×10^{-7} atm-m^3/mol	Domine et al. 1992
	7.01×10^{-8} atm-m^3/mol	ASTER (1996) (calculated)
	8.58×10^{-7} atm-m^3/mol	SRC 1994
Autoignition temperature	No data	
Flashpoint	>79 °C	HSDB 1996
Flammability limits		
at 25 °C	Nonflammable	Merck 1989

Table 3-2. Physical and Chemical Properties of Dichlorvos (continued)

Property	Information	Reference
Atmospheric reaction rate constants		
Hydroxyl radicals	9.408 x 10^{-12} cm^3/molecule-sec	SRC 1995
Half-life with 5x10^5 hydroxyl radicals per cm^3	2 days	Howard 1991
Ozone reaction	0.003579 x 10^{-17} cm^3/molecule-sec	SRC 1995
Half-life with 7.0x10^{11} ozone molecules per cm^3 (first order)	320 days	Howard 1991
Hydrolysis half-lives		
pH = 5.4	3.2 days	Latif et al. 1984
pH = 6	0.32 days	Latif et al. 1984
pH = 7	0.2 days	Latif et al. 1984
T = 10 °C	240 days	Faust and Suffet 1966
T = 20 °C	61.5 days	Faust and Suffet 1966
T = 30 °C	1.7 days	Faust and Suffet 1966
Other	Readily decomposes in strong acid or alkali; hydrolyzes in water	Sunshine 1969
	Decomposition products may include hydrogen chloride gas, phosphoric acid mist, and carbon monoxide	NIOSH, OSHA 1981
	Corrosive to iron and mild steel	Worthing 1983
Conversion factors (25 °C)	ppm (v/v) = 9.02 mg/m^3	Calculated
	mg/m^3 = 0.11 ppm (v/v)	Calculated
Explosive limits	No data	

HSDB = Hazardous Substance Data Bank; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; v/v = volume per volume

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

4.1 PRODUCTION

Initially synthesized in the late 1940s, dichlorvos was not registered for insecticidal use in the United States under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) until 1948 (EPA 1987b). Until large scale production of dichlorvos began in the late 1950s, the compound was chiefly encountered as an impurity in the pesticide trichlorfon (IARC 1979). One method of production is the dehydrochlorination of trichlorfon in aqueous alkali at 40-50°C (WHO 1989). Dichlorvos is also produced commercially by a reaction of trimethyl phosphite and chloral (Cremlyn 1978; Sittig 1980; WHO 1989).

As a pesticide, dichlorvos is commonly referred to as DDVP, which is an abbreviation for 2,2-dichlorovinyl dimethyl phosphate (Farm Chemical Handbook 1984). Commercially available formulations include aerosols and soluble concentrates. Historically, product formulations have also included dusts, granules, emulsifiable concentrates, wettable powders, flea collars, baits, and impregnated resin strips, and pellets/tablets (EPA 1990b; Farm Chemical Handbook 1984; IARC 1991; PIP-Dichlorvos 1993; The Agrochemicals Handbook 1991). Dichlorvos is also formulated in combination with a variety of other pesticides including dimethoate, dinocap, fenchlorphos, fenitrothion, iodofenphos, lindane, malathion, methoxychlor, phosalone, piperonyl, pirimiphos-methyl, propoxpur, tetrasul, pyrethrins, and trichlorfon (IARC 1991; The Agrochemicals Handbook 1991). By September 1987, the EPA had issued 885 end-use registrations for dichlorvos products. Of this total, 94 products were formulation intermediates, 24 were special local need registrations, 13 were technical products, and 49 were intrastate products (EPA 1987b).

In the past, basic producers of dichlorvos in the United States have included: Denka Chemia B.V., E.I. du Pont de Nemours and Company, Fermenta Animal Health, Kenco Chemical and Manufacturing Corporation, McLaughlin Cormley King Company, Prentiss Drug and Chemical Company, and SDS Biotech Corporation (EPA 1987b). Currently, only one manufacturer, AMVAC Chemical Corporation in Los Angeles, California, can be clearly documented as producing technical grade dichlorvos in the United States (Farm Chemical Handbook 1994; SRI 1994).

Information on historic production volumes of dichlorvos in the United States is limited. Production volumes based on estimates of annual use of dichlorvos in the United States for the years 1971, 1976, and 1980, suggest production levels as high as 4.6 million pounds (2.1 million kg) per year (IARC 1991; WHO 1989). In 1984, estimated production of dichlorvos in the United States was 500,000 kg (1.1 million pounds) (IARC 1991). In 1985, the estimated production of dichlorvos (active ingredient) in the United States was 2 million pounds (0.9 million kg) (EPA 1988a). Estimates of annual use of dichlorvos (active ingredient) in the United States during 1989 were less than 450,000 kg (992,000 pounds) and this use level was significantly lower than the total use in previous years (IARC 1991). It is unlikely, therefore, that production volumes for dichlorvos in the United States increased significantly between 1985 and 1989. Information on more recent production volumes was not found; however, it is likely that production volumes have decreased since the late 1980s due to changes in use patterns and registration cancellations (see Section 4.3).

Table 4-l lists the facilities in each state that manufacture or process dichlorvos, the intended use, and the range of maximum amounts of dichlorvos that are stored on site. The data listed in Table 4-l are derived from the Toxics Release Inventory (TR193 1995). Only certain types of facilities were required to report (EPA 1995a). Therefore, this is not an exhaustive list.

4.2 IMPORT/EXPORT

Official government statistics on imports and exports for chemicals such as dichlorvos are summarized under broad generic categories such as “pesticides” or “organophosphates.” No quantitative data on current or historic import volumes of dichlorvos were located in the available literature. With respect to exports, FIFRA generally prohibits the EPA from releasing complete information on pesticide production, sales, and distribution. No governmental agency maintains current records concerning what specific pesticides are exported. No quantitative data on current or historic export volumes of dichlorvos were located in the available literature.

4.3 USE

Dichlorvos has been used widely as an insecticide and miticide since 1961 to control internal and external parasites in livestock and domestic animals, to control insects in houses, and for crop protection (IARC 1991). It is an organophosphorus insecticide with fumigant and penetrant action that

Table 4-1. Facilities That Manufacture or Process Dichlorvos

Facility	Location [a]	Range of maximum amounts on site in pounds	Activities and uses
AMERICAN VANGUARD CO.	LOS ANGELES, CA	10,000-99,999	Produce; For on-site use/processing; For sale/distribution; As a reactant; As a formulation component
NA	SANDERSVILLE, GA	1,000-9,999	As a formulation component
NA	PLEASANTVILLE, IA	1,000-9,999	As a formulation component
NA	ELWOOD, KS	10,000-99,999	As a formulation component; As a product component
NA	ADDISON, TX	1,000-9,999	As a product component

Source: TRI93 1995

[a] Post office state abbreviations used

NA = not available

exhibits anticholinesterase effects (EPA 1987b, 1990a; Worthing 1983). Dichlorvos is poisonous if swallowed, inhaled, or absorbed through the skin; therefore, it acts as a contact and stomach poison (WHO 1985). Because dichlorvos is one of the more volatile pesticides in this class of compounds, it has been used primarily for its fumigant action (Cremlyn 1978). It is effective in controlling nuisance pests (e.g., caterpillars, flies, mosquitoes, and cockroaches) in and around domestic dwellings, stored products, commercial transportation vehicles, and livestock buildings. In 1974, dichlorvos was ranked as one of three active ingredients most frequently used by pest control operators. The aerosol formulation of dichlorvos was viewed as the most popular (EPA 1976). In 1975, it was estimated that approximately 80% of the dichlorvos produced in the United States was formulated into polyvinylchloride resin strips containing 20% by weight of dichlorvos (EPA 1976; IARC 1979, 1991). Prior to marketing this formulation for controlling flies and mosquitoes in the home in 1967, resin strips were introduced to the dairy and poultry industries (IARC 1991). According to the National Household Pesticide Usage Study of 1976 and 1977, the most frequently observed pesticide in a sample of 8,254 households was dichlorvos (EPA 1987b). Other uses have included direct application to packaged nonperishable processed or bulk-stored raw agricultural commodities (EPA 1990b, 1993b). Dichlorvos also has therapeutic uses; it has been incorporated in animal feed as an antihelminthic to treat a variety of internal and external parasites in swine, horses, and dogs (Farm Chemical Handbook 1984; HSDB 1996; PIP-Dichlorvos 1993).

Until the early 1970s, dichlorvos or mixtures containing dichlorvos were routinely used by fisheries biologists for the control of nuisance species such as carp (Marking 1992). Dichlorvos also has been added directly to water to control parasites in intensive fish farming (WHO 1989). Concern over problems associated with toxic and environmentally persistent organochlorine and organophosphate pesticide agents has led to restrictions on the use of such agents in natural lakes or other waterbodies, but dichlorvos has continued to be used in aquaculture to control various types of fish parasites. The use of such methods is very common in some European countries; for example, in Norway it is used in the aquaculture production of Atlantic salmon and rainbow trout (Cusack and Johnson 1990; Hoey et al. 1991; Horsberg and Hoey 1990; McHenery et al. 1991). Information on the current use of dichlorvos in aquaculture in the United States was not found.

In 1971, a total of 1,116,000 kg (2.44 million pounds) of dichlorvos were used in agricultural applications with 16,000 kg (35,000 pounds) being used on crops and 1.1 million kg (2.4 million pounds) being used on livestock and livestock buildings (IARC 1979). In 1980, the total usage of

dichlorvos (active ingredient) in the United States was estimated to range from 1.58 to 2.1 million kg (3.5-4.6 million pounds) (EPA 1980 as cited in IARC 1991). This includes 0.68-1.2 million kg (1.5-2.6 million pounds) for agricultural uses, 450,000 kg (1 million pounds) for public health applications, and about 450,000 kg (1 million pounds) for household use. With respect to agricultural uses of dichlorvos during 1980, approximately 340,000 kg (748,000 pounds) were used on dairy cattle, 30,000 kg (66,000 pounds) on beef cattle, 6,000 kg (13,200 pounds) on hogs, 2,000 kg (4,400 pounds) on poultry, 14,000 kg (30,800 pounds) on other livestock, and 50,000 kg (110,000 pounds) for treatment of tobacco. The estimated annual agricultural use of dichlorvos on crops in the United States during 1982 was 112,500 kg (248,000 pounds) of active ingredient (Gianessi 1986). From the mid- to late-1980s, agricultural applications represented 60% of the total annual usage in the United States: 35% was used on beef and dairy cattle, swine, and livestock buildings; and 25% was used on sheep, poultry, other livestock, tobacco, and greenhouse-grown food crops including lettuce, mushrooms, and tomatoes. Commercial, institutional, and industrial uses accounted for 25% of the annual usage; and domestic uses, including household pesticides and pet collars, accounted for 15% of the usage. The annual usage of dichlorvos (active ingredient) for 1989 was estimated to be less than 450,000 kg (990,000 pounds) (IARC 1991). This use level was significantly lower than the total use in previous years (IARC 1991). No information on more current use levels was identified in the available literature.

Drastic changes in use patterns (EPA 1993a) and restrictions on or cancellations of some registrations (EPA 1991a) are likely to have resulted in decreasing production of dichlorvos. For example, there has been a decline in the use of dichlorvos in unique agricultural applications such as ornamental perennials (EPA 1993a), and its use on figs was canceled in October 1989 (EPA 1991a). As a result of scientific investigations initially begun in the early 1980s and determination that exposure to dichlorvos from the registered uses may pose a carcinogenic risk, the EPA announced in February 1988 that it was initiating a Special Review for products containing dichlorvos (EPA 1991a). Dichlorvos has since been classified as a probable human carcinogen based on effects observed in mice and rats. The EPA has required cautionary warning labels on products containing dichlorvos; and the FDA has required warnings for pest strip products to discourage their use around kitchens, restaurants, or other areas where food is prepared. Recently, the EPA issued a “stay” on the effective date for the revocation of the food additive regulation for residues of dichlorvos in or on certain packaged processed foods (EPA 1993b, 1994a).

As of September 28, 1995, the EPA proposed cancellation of most uses of the pesticide dichlorvos and proposed restrictions on retained uses (TOXLIST 1995). The proposed uses to be cancelled included all home uses such as hanging pest strips, room foggers, and pet flea collars. EPA also proposed that most retained uses be restricted to specially trained certified applicators. Because of dietary cancer risk, the EPA also proposed cancelling uses of dichlorvos on non-perishable raw and processed agricultural commodities which are stored in bulk, packages, or bags. The following uses are being proposed for cancellation because of unacceptable risks to persons applying dichlorvos or persons who live or work in areas where the chemical is applied: all warehouses, including tobacco warehouses; commercial, institutional, and industrial areas including food service, food manufacturing and food processing facilities; dichlorvos applied by hand to farm livestock (except poultry); all home uses (including uses by residents and commercial applicators); uses on ornamental lawns, turf and plants; and in airplanes. The EPA proposes to retain the following uses: mushroom houses and greenhouses (only automatic foggers or fogging through a port), kennels, feedlots, insect traps, garbage dumps, direct application to poultry, automated application to livestock, animal premises, manure, and in passenger buses. The uses in mushroom houses, greenhouses, and passenger buses will also be cancelled unless specified re-entry period statements (no re-entry within 48 hours after application except in emergency) are added to the product labels. Because of the uncertainty associated with continuing the registration of a number of registered uses, it is difficult to predict future production or use patterns for the United States.

4.4 DISPOSAL

Dichlorvos was designated as a hazardous substance under the Federal Resource Conservation and Recovery Act, and the clean-up of discharges of dichlorvos to the environment are further regulated by the Clean Water Act (CWA) Amendments of 1977 and 1987 and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Regulations and advisories governing the treatment and disposal of dichlorvos-containing waste are detailed in Section 7. Generally, the recommended disposal methods for dichlorvos include alkaline hydrolysis, landfilling,and incineration. Prior to disposal, the product from the alkali treatment is mixed with soil that is rich in organic matter. Another possible disposal technology is to combine residues of dichlorvos with sawdust followed by incineration at high temperature in a unit equipped with effluent gas scrubbers (IRPTC 1985).

No historic or current information was located on the volume of dichlorvos disposed of or on the specific disposal method used.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Dichlorvos is released to the environment solely by human activity. Before the mid-1950s, releases of dichlorvos were largely associated with the environmental transformation of the agricultural pesticide trichlorfon. Dichlorvos is significantly more volatile than trichlorfon or most other organophosphate pesticides. While the relatively high volatility of dichlorvos makes it impractical for application to field crops, this property makes the chemical useful as a fogger and fumigant capable of penetrating into small interstitial areas in walls and other structural surfaces to kill insects (Hayes 1982). Some of the earliest applications were around confined animal-feeding operations to control flies and other pests. By the mid-1960s, dichlorvos preparations were developed that could control the release of the vapor in a concentration range from 0.015 mg/m^3 (considered the minimum needed to kill flies or mosquitoes after an exposure of several hours) to 0.25 mg/m^3. This higher concentration would kill insects after exposures of half an hour or less while providing an adequate margin of safety for shortterm human exposures (Hayes 1982).

Some of the earliest applications outside animal agriculture were for the disinsection (to kill insects, mites, and other invertebrate pests) of commercial aircraft subject to quarantine requirements when crossing international boundaries (Rasmussen et al. 1963); in museum storage areas (Deer et al. 1993); and in warehouses, greenhouses, or containerized ships (Hayes 1982). By the late 1960s polyvinylchloride plastic resin strips became popular as a way to dispense dichlorvos in a time-release fashion. These strips were widely adopted in livestock holding or feeding operations and also were widely used in homes. A variety of pest strip products became popular to control insects around kitchens or otherhousehold areas, and dichlorvos strips became widely used as an ingredient in pet flea and tick collars (Hayes 1982; IARC 1991; PIP-Dichlorvos 1993). During the 1980s, these household uses were progressively reduced as the EPA began a Special Review process for existing registered uses of dichlorvos. While the Special Review was still ongoing as of the end of 1994, EPA precautionary actions by 1988 required household products containing dichlorvos to display the words “Danger-Poison.” Manufacturers began switching to other pesticide agents, mostly on a voluntary basis, so that by the early 1990s, consumer use of dichlorvos had declined dramatically (EPA 1988a; Mueller 1992; PIP-Dichlorvos 1993). Its uses in agriculture and commercial buildings continue. Dichlorvos has also found applications in aquaculture to rid fish of various skin parasites (Hoey and Horsberg 1991). In

addition, both dichlorvos and trichlorfon have veterinary and human medicinal uses in the control of severe internal and external parasite infestations (IARC 1991; PIP-Dichlorvos 1993).

Whether applied in a liquid form or dispensed through plastic resin strips or granules, dichlorvos is most commonly released to the atmosphere in a gaseous form and will predominate in the vapor phase (Eisenreich et al. 1981). Dichlorvos is not expected to undergo degradation from direct photolysis in the atmosphere (Gore et al. 1971). While degradation by ozone in the atmosphere is possible, the main degradation pathway involves the vapor phase reaction of dichlorvos with photochemically produced hydroxyl radicals. The half-life (first-order kinetics) for dichlorvos in the atmosphere has been estimated to be less than 2 days (Howard 1991; Kelly et al. 1994). Dichlorvos can be removed from the air through rainfall scavenging. When released to water, hydrolysis is the major degradation process which proceeds much more rapidly under alkaline pH conditions and with increasing temperature. The hydrolysis half-life of dichlorvos in water is highly variable and is dependent both on pH and temperature, but is typically on the order of days or weeks (Faust and Suffet 1966; Lamoreaux and Newland 1978; Lartiges and Garrigues 1995; Latif et al. 1984). Because of its high solubility in water, dichlorvos would not be expected to bioconcentrate in fish or other aquatic life. When released to soils, hydrolysis and other non-biological processes account for 70% or more of the total degradation of dichlorvos, while bacterial degradation accounts for only 30% (Lamoreaux and Newland 1978). In field studies, Menzie (1972) reported a half-life value (first-order kinetics) of 17 days for dichlorvos in soil (soil type unspecified). Because, dichlorvos does not readily sorb to soil particles, spills, or other large amounts of the pesticide, especially when released in a liquid form or dissolved in solvent carriers, may migrate through soil profiles or sediments and into groundwater. Since dichlorvos will degrade within a few days in the air, surface waters, or wetted soils due primarily to hydrolysis reactions, it is not expected to enter into large-scale regional or hemispheric fate and transport processes.

Dichlorvos has not been extensively monitored in most environmental media. It has been detected at very low concentrations in outdoor air, but has been detected at higher concentrations-in indoor air associated with its use as a fumigant pesticide in homes or during occupational exposures in manufacturing and production facilities. It has not been detected in drinking water and no environmental monitoring data were found for dichlorvos in surface or groundwater or in soils and sediment. Dichlorvos has been detected infrequently and never at concentrations of concern in both raw and processed food items.

Since dichlorvos is a breakdown product of trichlorfon and can be generated in many plants through the metabolism of the pesticide naled (EPA 1988a; Menzie 1972; PIP-Naled 1994; PIP-Trichlorfon 1993), it is often difficult to ascertain the original source of the chemical when dichlorvos is detected in environmental media. In addition, trichlorfon and naled can be transformed to dichlorvos during sample preparation and analysis procedures. The general population may be exposed to dichlorvos primarily by inhaling contaminated air or by absorption via dermal exposure during application of liquid formulations. Both inhalation of indoor air and direct dermal contact have been identified as primary sources of human exposure at the present time. The risk of exposure is greatest to the general populations during and/or immediately after its application. Exposures of the general population to dichlorvos via consumption of contaminated food and drinking water are negligible to insignificant. Because it is rapidly metabolized, dichlorvos has not been detected in blood, adipose tissue, breast milk, or any other tissue samples from the general population or from populations with occupational exposures. In occupational settings, exposure is via inhalation of contaminated air and/or via dermal contact with dichlorvos formulations.

Dichlorvos has been identified in at least 3 of the 1,428 current or former hazardous wastes sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HAZDAT 1996). However, the number of sites evaluated for dichlorvos is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

Releases of dichlorvos are required to be reported under the Superfund Amendments and Reauthorization Act (SARA) Section 313; consequently, data are available for this compound in the Toxic Release Inventory (TRI) (EPA 1995a). According to the TRI, in 1993 a total of 1,562 pounds (709 kg) of dichlorvos were released to the environment from 5 large processing facilities (TR193 1995). In addition, an estimated 4,660 pounds (2,114 kg) were transferred off-site (TR193 1995). Table 5-l lists these releases. The TRI data should be used with caution because only-certain types of facilities are required to report (EPA 1995a). This is not an exhaustive list.

Dichlorvos has been identified in a variety of environmental media collected at 3 of the 1,428 former or current NPL hazardous waste sites (HazDat 1996).

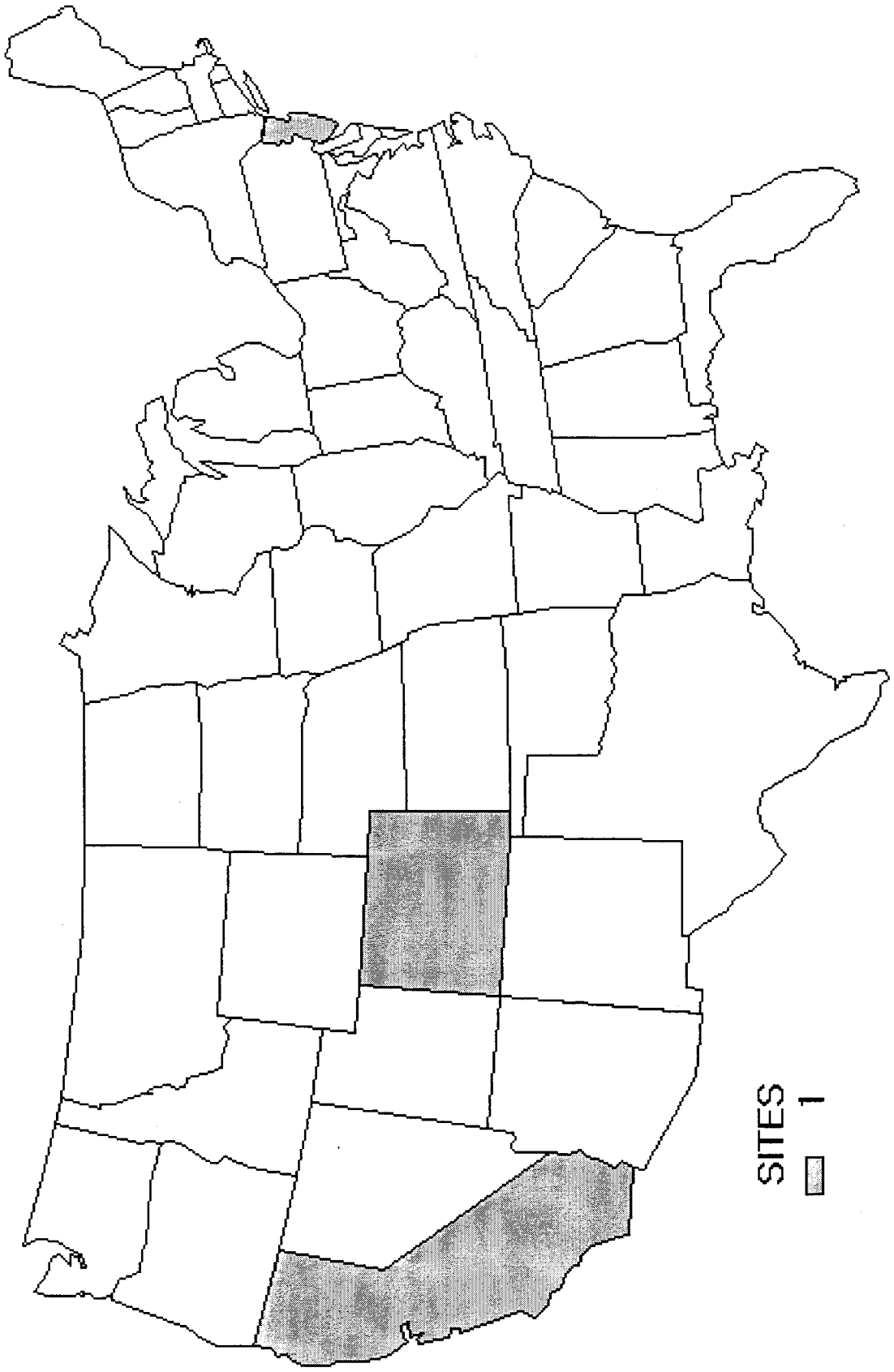


Figure 5-1. Frequency of NPL Sites with Dichlorvos Contamination

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Dichlorvos

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
CA	LOS ANGELES	AMERICAN VANGUARD CO.	250				250		1,005
GA	SANDERSVILLE	NA	52				52		
IA	PLEASANTVILLE	NA	250				250		
KS	ELWOOD	NA	255	5			260		3,655
TX	ADDISON	NA	500		250		750		
		Totals	1,307	5	250		1,562		4,660

Source: TRI93 1995

[a] Post office state abbreviations used
[b] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

NA = not available; POTW = publicly owned treatment works

5.2.1 Air

Dichlorvos may be released to the air during production and processing activities or during its various use applications as a pesticide. Based on its vapor pressure of $1.2x10^{-2}$ mm Hg at 20ºC (see Table 3-2), a large portion of the dichlorvos contained in plastic or resin strips, or applied in concentrated liquid formulations to surfaces within buildings or other enclosures with low humidities would be expected to volatilize to the air. However, no data were located providing comprehensive estimates of releases to the air.

According to the TRI, in 1993, releases of 1,307 pounds (593 kg) dichlorvos to the air from 5 large processing facilities accounted for about 84% of the estimated total environmental releases (TR193 1995). Table 5-l lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995a). This is not an exhaustive list.

Dichlorvos has not been found in air samples collected at any of the 3 NPL sites where it was detected in some environmental media (HazDat 1996).

5.2.2 Water

Dichlorvos may be released to surface water in waste waters generated by its production or fabrication into resin strips or other formulations. Some releases to surface water would also occur when dichlorvos is used in aquaculture to control fish parasites. Other releases to water might take place as the result of spills or other accidents. No data were found providing comprehensive estimates of intentional and unintentional releases into water.

According to the TRI, estimated releases of 5 pounds (2.3 kg) of dichlorvos to surface water from one large processing facility in 1993, accounted for about 0.3% of the estimated total environmental releases (TR193 1995). Table 5-l lists these releases. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995a). This is not an exhaustive list.

Dichlorvos has been found in groundwater samples (concentrations unspecified) at 1 of the 3 NPL sites where it was detected in some environmental medium (HAZDAT 1996).

5.2.3 Soil

Dichlorvos may be released to the soil as a result of intentional uses, spills or through waste disposal practices associated with its various formulations. According to the TRI, estimated releases of 250 pounds (113 kg) of dichlorvos to the land from one large processing facilities in 1993 accounted for about 16% of the total environmental emissions. In addition, over 4,660 pounds (2,113 kg) were disposed of via offsite waste transfer (TR193 1995). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995a). This is not an exhaustive list.

Environmental releases of dichlorvos to agricultural soils have occurred from its intentional use in livestock feeds to control internal parasites and flies (IARC 1979, 1991; OSU 1992) and its use in specialty crops (e.g., tobacco and greenhouse-grown food crops) (IARC 1991). Land application of the treated livestock manures may contribute to soil releases of dichlorvos (OSU 1992). Any improper disposal of plastic resin material wastes containing dichlorvos or other formulations of dichlorvos could also release the chemical to soils. The most recent use application data from the mid- to late 1980's suggests that agricultural applications of dichlorvos represented 60% of the total annual use of dichlorvos in the United States. Commercial, institutional, and industrial uses accounted for 25% of annual usage; while domestic uses, including household pest control and pet collars accounted for only 15% of annual usage (IARC 1991). Releases of dichlorvos to soils in urban areas have occurred from its intentional uses in residential, industrial, and commercial areas including food services, food manufacturing and processing facilities; in horticultural and turf applications for pest control; and in flea collars, room foggers, and no-pest strips. For products composed of polyvinylchloride plastic resins impregnated with dichlorvos, such as flea collars, the collar materials were designed to shed off small fragments of the plastic material (exfoliation). These small particles tend to spread throughout the animal's coat, which would assist in delivering the pesticide to fleas and other insect parasites. Such small particles could also be spread onto floors or land surfaces, where they could be released to the soil. Drastic changes in recent use patterns (EPA 1993a) and restrictions on or cancellations of some registrations (EPA 1991a) make it difficult to determine the magnitude of current uses/applications of dichlorvos are greater in both agricultural and in urban settings

Dichlorvos has been found in soil samples (concentrations unspecified) at 1 of the 3 NPL sites where dichlorvos was detected in some environmental media (HAZDAT 1996).

5.3 ENVIRONMENTAL FATE

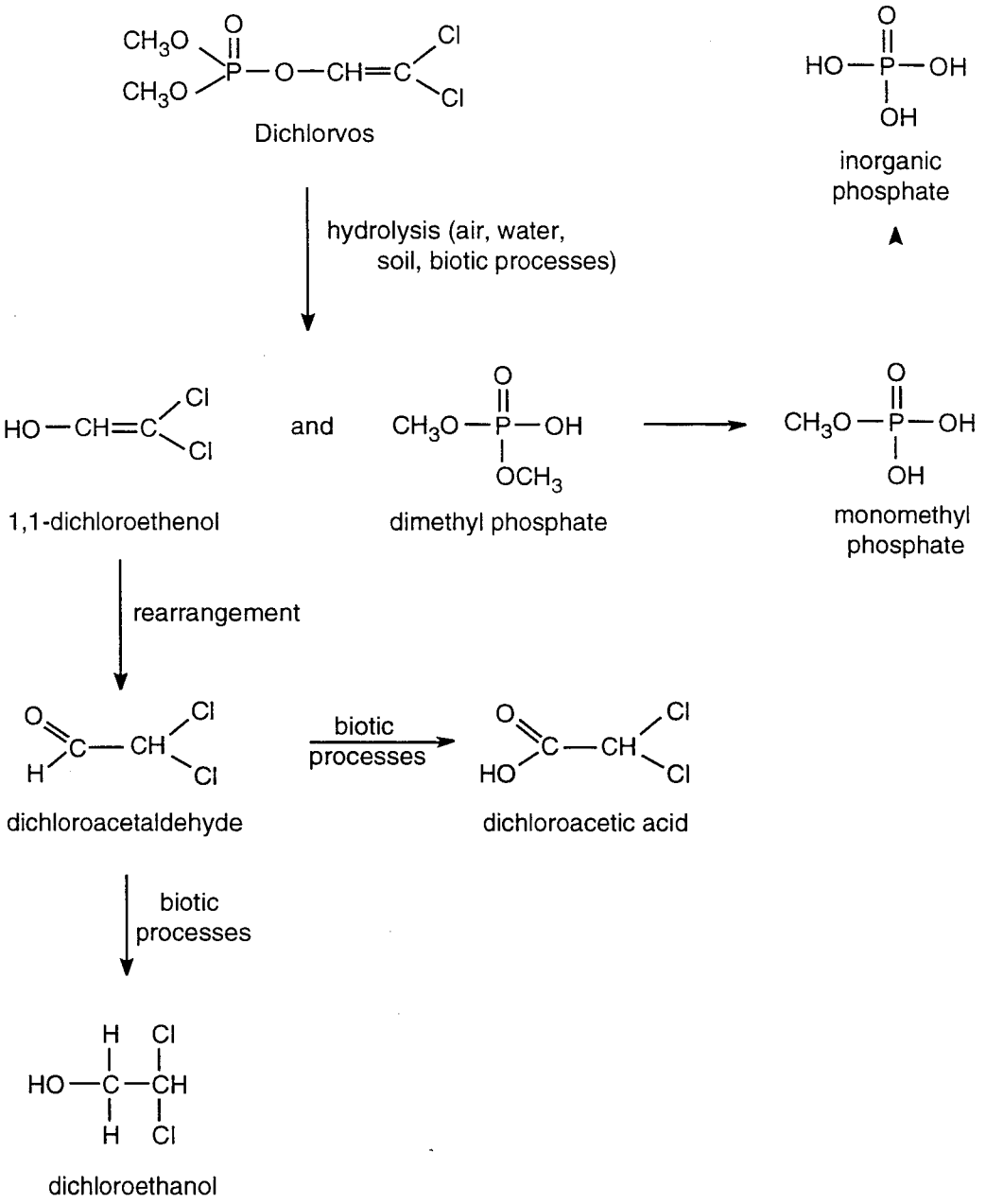
While most initial releases of dichlorvos will be to the air, the solubility of dichlorvos in water will quickly lead to its partitioning to water. Once in contact with water. hydrolysis reactions become the predominant mechanisms for degradation, with hydrolysis proceeding more rapidly with increasing pH and temperatures (Faust and Suffet 1966; Lamoreaux and Newland 1978). In the environment, abiotic degradation via hydrolysis is the primary transformation process, although biodegradation by some microorganisms also occurs (see Figure 5-2). Dichlorvos shows little tendency to sorb to soil particles or bioconcentrate in living tissues, which creates the potential for dichlorvos to leach through soil and sediments into groundwater (PIP-Dichlorvos 1993).

5.3.1 Transport and Partitioning

Dichlorvos has a high vapor pressure ($1.2x10^{-2}$ mm Hg) and if released to the atmosphere, it will be found predominately in the vapor phase (Eisenreich et al. 1981). Most dichlorvos releases are initially intended to reach the air, but if there is high humidity or rain scavenging, dichlorvos will partition into water. The Henry's law constant for dichlorvos has been calculated as 7.01x10-^{8} atm-m^3/mole at 25˚C (see Table 3-2), which is a fairly low value and suggests that dichlorvos, once dissolved in water, will remain in aqueous solution for an appreciable period of time. The solubility of dichlorvos in water is 16,000 mg/L (Table 3-2), which is quite high compared to other common organophosphate pesticides (e.g., <10 mg/L for malathion or parathion and <100 mg/L for diazinon). Based on the Henry's law constant and for aqueous systems with initial dichlorvos concentrations less than the saturation levels, the volatilization half-life from a model river was estimated at 57 days, while the volatilization half-life from a model pond was estimated at over 400 days (Howard 1991).

The log K_{oc} (organic carbon partition coefficient) for dichlorvos has been calculated to be 1.45 (Kenaga 1980), which is very low. This K_{oc} value suggests dichlorvos will not appreciably sorb to soil particles; therefore, dichlorvos can be expected to leach through soil columns or sediments and into groundwater (Swann et al. 1983). Since natural soils and sediments contain water, hydrolysis reactions will also occur as the dichlorvos moves downward through the soil horizon, and this will reduce the amount of dichlorvos transported to groundwater.

Figure 5-2. Environmental Transformation for Dichlorvos in Soil and Sediment



Because of its high water solubility, dichlorvos would not be expected to show a significant tendency to bioconcentrate in fish or other aquatic animals. A commonly used quantitative measure of the tendency of some chemicals to partition from the water column into the tissues of aquatic organisms is the bioconcentration factor (BCF). This BCF value can be empirically determined by measuring the chemical concentration in an organism's tissues after exposing it over a period of time to a specified concentration of the chemical in water. The empirical BCF is calculated as the concentration of the chemical in an organism divided by the concentration of the chemical in water. BCFs can sometimes be estimated based on regression equations developed from data on physical properties such the octanol/water partition coefficient and the water solubility. The larger the value of the BCF, the greater the tendency for partitioning into the tissues of an organism. No experimental BCF values for dichlorvos have been reported for any aquatic species. A calculated BCF of 2.8 has been reported (Kenaga 1980), which is intended to be applicable to many fishes. More recently, the EPA's ASTER Toxicology profile database reported a calculated BCF of 1 for the fathead minnow *(Pimephales promefus)* (ASTER 1996). Such BCF values suggest there is no marked tendency for bioaccumulation or biomagnification of dichlorvos through the food chain. One short-term exposure study was conducted to test the efficacy of dichlorvos as a pest control agent for sea lice on penned salmon. Atlantic salmon *(Salmo salar)* were exposed to dichlorvos at 2 ppm at either 4 or 12 ºC for 60 minutes as a treatment to remove ectoparasitic copepods (Horsberg and Hoy 1990). These authors found that at 4 ºC, dichlorvos residues averaged 0.094 μg/g (ppm) in muscle and <0.01 μg/g in liver tissue immediately post-treatment. At 12 ºC, dichlorvos residues averaged 0.046 μg/g (ppm) in muscle and 0.041 μg/g (ppm) in liver tissue. At 4 ºC, residues in muscle and liver were not detected after 3 days post-treatment and at 12 ºC, residues were not detected in muscle tissue after 1 day posttreatmentand in liver tissue 6 days post-treatment. The rapid clearance of dichlorvos from the fish tissues was similar to results obtained in other species (see Chapter 2).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Dichlorvos does not strongly absorb ultraviolet (UV) light above 240 nm (Gore et al. 1971; Howard 1991) and is, therefore, unlikely to be subject to direct photolysis in the atmosphere. Based on theoretical considerations, dichlorvos may be susceptible to degradation in the air from free radicals such as hydroxyl groups or ozone. Figure 5-2 shows the transformation pathways for dichlorvos in the

atmosphere. A calculated half-life, assuming first-order kinetics, for a vapor-phase reaction of dichlorvos with photochemically produced hydroxyl radicals was reported to be 2 days, assuming an atmospheric concentration of $5x10^5$ hydroxyl radicals per cm^3 (Howard 1991). With an assumed level of $7.0x10^{11}$ ozone molecules per cm^3, an estimated half-life (first-order kinetics) for dichlorvos of 320 days was reported (Howard 1991).

5.3.2.2 Water

Dichlorvos is highly soluble in water and tends to remain in solution, with very little tendency to sorb to sediments. While dichlorvos can re-volatilize to the air, re-volatilization of dichlorvos once it is dissolved in water is a fairly slow process.

When dissolved in water, dichlorvos becomes subject to both abiotic and biological degradation. The predominant degradation mechanism is hydrolysis, and dichlorvos is hydrolyzed into dichlorethanol, dichloroacetaldehyde, dichloracetic acid, dimethyl phosphate and dimethyl phosphoric acid (WHO 1989). The hydrolysis reaction is sensitive to pH, with much more rapid degradation taking place at higher, more alkaline pH levels. Chemical hydrolysis of dichlorvos in aqueous, buffered, soil-free systems showed that hydrolysis did not occur in very acid systems (pH <3.3), but increased with increasing pH values (26% in 4 days at pH 6.9), and was most rapid at pH 9.3 (>99% in 2 days). At pH values of 2.0, 3.3, 6.2, 6.9, 7.8, 8.2, 8.7, and 9.3, the percent of initial dichlorvos remaining in buffered, aqueous solutions after 96 hours was 99, 100, 92, 89, 84, 82, 36, and 10%, respectively (Lamoreaux and Newland 1978). Latif et al. (1984)m reported half-life (first-order kinetics) values for dichlorvos of 4,620 minutes (3.2 days), 2,100 minutes (1.46 days), 462 minutes (0.32 days), and 301 minutes (0.2 days) in water at pH 5.4, 6, 7, and 8, respectively.

In addition to pH, hydrolysis kinetics are affected by temperature. Faust and Suffet (1966) reported that the half-life (first-order kinetics) values for dichlorvos in water were 240, 61.5, 17.3, 1.7, and 0.2 days at 10, 20, 30, 50, and 70 °C, respectively. Lartiges and Garrigues (1995) studied degradation of dichlorvos in different types of water (filtered water, natural seawater, natural river water, and filtered river water) under different environmental conditions (temperatures of 6 and 22 “C to simulate winter and summer conditions, respectively, and pH values ranging from 6.1 to 8.1). The authors reported that at the winter temperature, dichlorvos was still present in the filtered water (pH 6.1) after 180 days. Residues in river water (pH 7.3) and filtered river water (pH 7.3) disappeared after 81 days

and residues in seawater (pH 8.1) disappeared after 34 days. At summer temperatures, dichlorvos residues disappeared in filtered water after 81 days. Residues in river water disappeared after 55 days, residues in filtered river water disappeared in 34 days, and residues in seawater persisted for 180 days. At pH values of 7.8-8.2, reported half-disappearance times were approximately 96 and 48 hours, respectively (Lamoreaux and Newland 1978). At pH values of 8.7 and 9.3, the half-disappearance time was less than 24 hours and at pH values of less than 6.9, the half-disappearance time was more than 96 hours. Therefore, under pH conditions encountered in most natural waters in contact with the atmosphere, hydrolysis can degrade dichlorvos at rates considerably more rapid than the rate of dichlorvos re-volatilization to the air. Only at low pHs (less than 4) would dichlorvos show persistence. The hydrolysis half-life or half-disappearance time in water is highly variable and is dependent both on pH and temperature, but is typically on the order of days to weeks.

Microorganisms found in sewage sludges apparently can biodegrade dichlorvos, but a period of acclimation may be needed and the rate of biodegradation may be much less than that from abiotic transformation processes (Lieberman and Alexander 1983). Abiotic hydrolysis rates will generally far outstrip the biodegradation rate, and the biotic transformations will be sensitive to pH, temperature, and the concentrations of dichlorvos or other toxic chemicals present. The environmental transformation pathways for dichlorvos in water are shown in Figure 5-2.

Since the hydrolysis reaction in water is both pH- and temperature-dependent, caution should be exercised in making predictions for dichlorvos in groundwater. In groundwater with low pH (pH <4), dichlorvos would be expected to persist for moderate periods, with half-disappearance times greater than 4 days (PIP-Dichlorvos 1993).

5.3.2.3 Sediment and Soil

In soils containing any appreciable amount of moisture, hydrolysis reactions similar to those in aqueous solutions are expected to occur (PIP-Dichlorvos 1993), although few quantitative studies of half-life or half-disappearance times could be identified in the literature. In field trials, Menzie (1972) reported a half-life (first-order kinetics) value for dichlorvos of 17 days; however, the soil type was not specified by the author. In laboratory experiments using natural and sterilized Houston black clay soils, the rate of dichlorvos disappearance in the soil was related directly to the presence of the bacterium *Bacillus cereus*, the pH of the soil perfusion system, and the extent of dichlorvos adsorption.

Dichlorvos disappearance was most rapid when *B. cereus* was added to a previously unsterilized soil (half-life value of 3.9 days), while under sterile conditions, a half-life value of 10 days was reported (Lamoreaux and Newland 1978). Hydrolysis and other non-biological processes accounted for 70% of the total degradation of dichlorvos, while bacterial degradation accounted for only 30% in the soil perfusion system (Lamoreaux and Newland 1978).

For sediments, biodegradation processes may often be similar to the results documented for sewage sludges. A sewage sludge culture containing the bacterium *Pseudomonas aeruginosa* and other bacteria from the same genus was shown to convert dichlorvos into several metabolites, including dichloroethanol, dichloroacetic acid, ethyl dichloroacetate, and inorganic phosphate (Lieberman and Alexander 1983). Dichlorvos was still present in the cultures after 7 days of incubation at 29 ºC both in the presence or absence of microbes. The environmental transformation pathways for dichlorvos in soil and sediment are shown in Figure 5-2. Abiotic hydrolytic cleavage of the parent molecule presumably gives rise to dichloroacetaldehyde (via rearrangement of l,l-dichloroethenol) and dimethyl phosphate. The dichloroacetaldehyde then is converted enzymatically to dichloroethanol, or to dichloroacetic acid (Lieberman and Alexander 1983). The dimethyl phosphate is converted to inorganic phosphate with monomethyl phosphate being a likely intermediate.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Dichlorvos has not been routinely included in most national environmental monitoring programs, so that broad-based data are lacking for most environmental media. Results from several special studies suggest that dichlorvos should not be found above very low levels on a widespread basis in either air or in water. Data for soils and sediments are even more limited. When dealing with soils and sediments, a complicating factor is that dichlorvos may be found associated with fragments of discarded resin strips or in other plastics wastes or containers impregnated with dichlorvos.

Where dichlorvos is detected in the environment, it may be impossible to determine whether the initial release was from dichlorvos directly or from the application of the pesticide trichlorfon which can degrade to form dichlorvos or the pesticide naled which can be transformed in some plant tissues to dichlorvos. In addition, dichlorvos can be produced from trichlorfon and naled during sample preparation and analysis (see Section 6.2). For these reasons, caution must be used in the interpretation of data from environmental samples found to contain dichlorvos. Reliable evaluation of

the potential for human exposure to dichlorvos depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on levels monitored or estimated in the environment, it should be noted that the amount of the chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

Most of the available measurements of dichlorvos in the air have focused on indoor-air settings where dichlorvos has been most commonly used as a fumigant-type pesticide agent; however, limited information is available for ambient outdoor air. Kelly et al. (1994) reported that dichlorvos concentrations measured in 288 samples of ambient outdoor air collected from 2 locations ranged from not detected to 150 ng/m^3. As part of the Non-Occupational Pesticide Exposure Study based on the EPA's Total Exposure Assessment Methodology (TEAM) approach, dichlorvos was monitored in outdoor air samples collected in Springfield, Massachusetts and in Jacksonville, Florida. While dichlorvos was not detected in ambient outdoor air in Springfield, Massachusetts, it was detected at 3.2 ng/m^3 in winter samples collected in Jacksonville, Florida (Whitmore et al. 1994).

Much of the historic indoor-air monitoring literature deals with product uses that have declined dramatically, or ceased altogether, since the late 1980s. For instance, air monitoring data were gathered while dichlorvos was a major ingredient in pest strips which were widely used in homes, hospitals, restaurants, and other public places to kill flies, cockroaches, and other nuisance insects (Elgar and Steer 1972; Leary et al. 1974). Other valuable information comes from studies on potential occupational exposure to personnel in museums where dichlorvos was used to kill insects in closed display cases or storage areas (Deer et al. 1993), exposures to employees at professional pest control companies (Wright and Leidy 1980), and exposures to flight crews while it was used as a disinsection agent (prophylactic insecticide) in commercial aircraft (Rasmussen et al. 1963).

By the late 1960s the design of resin strips or application rates of dichlorvos in liquid or fogger formulations was guided by the goals of achieving dichlorvos concentrations in the air of at least 0.015 mg/m^3 for a period of several hours; this goal to achieve good kills of nuisance insects was balanced against the rule of thumb that concentrations below 0.25 mg/m^3 provided an adequate margin of safety for human health (Hayes 1982). Where adequate precautions are observed, and barring

accidents. concentrations above this 0.25 mg/m^3 threshold are uncommon in studies accompanied by good sampling programs.

Results from early work on the use of dichlorvos-impregnated polyvinylchloride resin pest strips for insect control in homes in the United Kingdom, Australia, and France suggest that indoor-air concentrations in houses that are well ventilated (especially using open windows) will be very low (range, 0.01-0.24 μg/L [mg/m^3]) (Elgar and Steer 1972). Leary et al. (1974) monitored the concentrations of dichlorvos in indoor-room air in homes in Arizona using polyvinylchloride resin strips containing dichlorvos. Homes were treated at a rate of one strip per 1,000 cubic feet and typically averaged 8-18 strips per residence. One month after installation, new pest strips were placed in the kitchen and dining areas at a rate of one strip per 500 cubic feet. Air samples were collected prior to installation of the strips and at 1, 2, 3, 4, 6, 7, 10, 13, 16, 21, and 28 days post-application. Dichlorvos concentrations in the air peaked at 0.12-0.13 mg/m^3 within several days and then declined to a plateau level of 0.08-0.09 mg/m^3 from day 12 to 28 post-application. The replacement and doubling of the number of strips in the dining room and kitchen produced a maximum concentration of 0.16 mg/m^3 within 2 days and a subsequent decrease to 0.11 mg/m^3 by day 15. Removal of all the pest strips from the residence resulted in a rapid decline in dichlorvos residues to zero within 17 days.

In the EPA TEAM study of indoor-air levels of common household pesticides, dichlorvos was included as a target analyte, but was not commonly detected in the indoor air of the homes sampled (detected in only 1 out of 9 homes sampled) (Lewis et al. 1988). Most recently, as part of the Non-Occupational Pesticide Exposure Study based on the EPA's TEAM approach, dichlorvos was monitored in indoor-air samples collected in Springfield, Massachusetts and in Jacksonville, Florida. Dichlorvos was detected in ambient indoor air in Springfield, Massachusetts at concentrations of 4.3 and 1.5 ng/m^3 in spring and winter air samples, respectively. This pesticide was detected at much higher concentrations of 134.5, 86.2, and 24.5 ng/m^3 in summer, spring, and winter samples, respectively, collected in Jacksonville, Florida (Whitmore et al. 1994).

The highest occupational exposure reported was 3 mg/m^3 (mean concentration of 0.7 mg/m^3) that was monitored in a vaporizer production plant and its packaging rooms (Menz et al. 1974 in IARC 1991). Other valuable information comes from studies on potential occupational exposure to personnel in museums where dichlorvos was used to kill insects in closed display cases or storage areas (Deer et al. 1993), exposures to employees at professional pest control companies (Wright and Leidy 1980), and

exposure to flight crews while it was used as a disinsection agent in commercial aircraft (Rasmussen et al. 1963). Air samples were collected in several locations within a museum of natural history's entomological curation area (Deer et al. 1993). The authors reported a significant difference in the mean concentrations of dichlorvos in the air collected with the ventilation system on (0.005 mg/m^3) and the ventilation system off (0.14 mg/m^3). Ambient air in the storage rooms (where concentrates of various chemicals were stored and mixed to appropriate dilutions) and main office areas of four North Carolina commercial pest control firms were monitored for dichlorvos for a 4-hour sampling period (Wright and Leidy 1980). These authors found that concentrations in the storage rooms averaged 617 ng/m^3 (range, 147-1,501 ng/m^3) and concentrations in the office areas averaged 41 ng/m^3 (range, 19-66 ng/m^3). In addition, mean dichlorvos concentrations of 110 ng/m^3 (range, 16-231 ng/m^3) were detected in the ambient air inside company pickup trucks and vans used by professional pest control technicians (Wright and Leidy 1980). The proposed use of dichlorvos as an aircraft disinsectant was studied by Rasmussen et al. (1963). Volunteers were exposed to dichlorvos at concentrations varying from 0.14 to 0.33 µg/L (mg/m^3) in a setting designed to simulate the maximal exposure that airline flight crew personnel could possibly receive during the maximum period of scheduled duty flights (39 doses in a 14-day period).

5.4.2 Water

Dichlorvos was included as one of 101 pesticide target analytes in EPA's National Pesticide Survey of Drinking Water Wells (EPA PIN 1994). This survey included wells from community systems used in towns and cities, non-community systems found in such public places as truck stops, and private domestic wells. Dichlorvos was not found above detection limits in any of the drinking water wells sampled. While dichlorvos is not ordinarily included in sampling programs for community systems that rely on surface water supplies, the nature of the treatment processes used in most community systems tends to minimize the possibilities for dichlorvos to persist in the final tap water. In most larger community drinking water systems in the United States that use surface water supplies, conventional treatment technologies using lime and soda ash will temporarily raise the alkalinity (pH >9). These elevated pHs, combined with the ample opportunities for hydrolysis degradation before the treated water reaches end users, virtually eliminate any exposure possibilities to dichlorvos in treated drinking water.

No other information was found on the concentrations of dichlorvos in surface water or groundwater in the United States. While dichlorvos could be released to surface waters during production or on an episodic basis as a result of spills, prompt sample collection and analysis would likely be needed to document the presence of dichlorvos. For instance, a dichlorvos formulation known as Nuvan® is widely used in Europe to control skin parasites in fish culture, especially in the caged cultures of Atlantic salmon. In a coastal bay in Ireland, monitoring was carried out during the summer period when salmon were being tended in cages in the bay and for a period after the summer to document the possible persistence of dichlorvos in seawater and sediments (Tully and Morrissey 1989). In all but one of the ambient water samples from the Beirtreach Bay study, dichlorvos levels were below the detection limit of 0.02 μg/L (ppb), suggesting that dichlorvos rapidly dissipates or degrades in large natural waterbodies. The exceptional seawater sample in which the pesticide was detected, contained 0.13 μg/L (ppb) of dichlorvos.

5.4.3 Sediment and Soil

No information was found on background levels of dichlorvos in either agricultural or urban soils or in sediments in the United States. Given the relatively high volatility of dichlorvos combined with its low potential to sorb to soil particles, and its rapid degradation via hydrolysis, dichlorvos does not appear to be a good candidate analyte for soil or sediment sampling programs.
Dichlorvos has been identified at unspecified concentrations in soil samples at 1 of the 3 NPL sites where it was detected in some environmental media (HazDat 1996).

5.4.4 Other Environmental Media

Dichlorvos has been detected in some foods as part of standard FDA residue monitoring or regional or state sampling activities using protocols patterned after the FDA methods. FDA regulatory surveillance monitoring extends back to the 1970s. The food items sampled include common fruits and vegetables, coffee, wine, and milk. In summaries of the FDA pesticide residue monitoring of foods, dichlorvos is reported among those chemicals where some detections were documented, but never at concentrations of concern. Positive samples have been detected for some food items for which tests were performed in the FDA program from 1978 to 1982 (Yess et al. 1991a), from 1983 to 1986 (Yess et al. 1991b), for 1987 (FDA 1988), 1988 (FDA 1989), 1989 (FDA 1990), 1990 (FDA 1991), 1991 (FDA 1992), 1992 (FDA 1993), 1993 (FDA 1994), and 1994 (FDA 1995). For chemicals

with such a low incidence of detection, the published literature does not generally record concentrations detected, the food items in which the residues were detected or detection limits. Concentrations of dichlorvos in ready-to-eat foods were monitored for 10 years from 1982 through 1991 through the FDA Revised Market Basket Survey (KAN-DO Office and Pesticide Team 1995). Dichlorvos was detected in one sample of one food item (rye bread) at a concentration of 0.01 μg/g ppm.

A summary of the results of chemical residue monitoring conducted by 10 state food laboratories from 1988 to 1989 showed 2 detections of dichlorvos out of 13,085 food items sampled (0.015% positive detections), with neither of these detections exceeding any federal or state tolerance limits (Minyard and Roberts 1991). A summary of food residue sampling by the State of California included dichlorvos in its screening list, but no detections were reported for testing carried out in 1989 (Okumura et al. 1991). A special study on pesticide residues in infant formulas carried out for the National Academy of Sciences included dichlorvos as a target analyte, but no detections were reported based on analysis of 24 milk-based and 19 soy-based infant formula samples (Gelardi and Mountford 1993). Very low percentages of detections and concentrations well below any thresholds of concern are typical of food residue monitoring programs in Canada and the United Kingdom (IARC 1991).

While detections have been documented in food surveys, dichlorvos residues in food are normally destroyed by washing and cooking (IARC 1991); therefore, the risk to the general population in the United States is insignificant. In a study from Japan, residues of dichlorvos were found on harvested rice, where dichlorvos and other pesticide or fumigant agents had been applied to control insects during shipping and storage (Nakamura et al. 1993). The levels of dichlorvos decreased during storage, falling to below detection levels within 45 days after the initial treatments. In addition, ordinary washing and cooking to prepare the rice for human consumption essentially removed all of the dichlorvos residues.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

While no quantitative information is available on the percentage of dichlorvos released to each environmental compartment, dichlorvos can be released to any or all environmental media (air, surface water, groundwater, and soil). The general population is exposed to dichlorvos primarily through inhalation and dermal contact. Exposure to dichlorvos via consumption of contaminated food is

insignificant because daily intakes are extremely low, and washing and general food preparation procedures further remove dichlorvos residues (IARC 1991; Nakamura et al. 1993). Based on the results of the 2 recent FDA Total Diet Studies conducted in 1991 and 1992, the estimated mean daily dietary intakes of dichlorvos were <0.000l, <0.000l, and 0.0001 µg/kg body weight for 6-l l-month-old infants, 14-16-year-old males, and 60-65year-old women, respectively (FDA 1992). Based on the results of the recent analysis of data from the FDA Total Diet Studies conducted from 1986 to 1991, the estimated mean daily dietary intakes of dichlorvos were <0.000l, <0.000l, and <0.000l µg/kg body weight for 6-l l-month-old infants, 14-16-year-old males, and 60-6.5year-old women, respectively (FDA 1993). Exposure to dichlorvos via consumption of contaminated drinking water also is insignificant.

The general population is exposed to dichlorvos primarily through inhalation of contaminated indoor air either during and/or immediately after application or through use of polyvinylchloride resin strips. Exposure would be of most concern in buildings with inadequate or defective ventilation. Since many commercial and residential buildings are sprayed with dichlorvos formulations or use pest control strips that vaporize dichlorvos, there is the possibility of widespread low-level exposure to many individuals in the general population from inhalation of residual vapors in these dichlorvos-treated indoor-air spaces. The second major route of exposure to dichlorvos for the general population is through direct dermal contact with the chemical spray during domestic applications, contact with dichlorvos-treated plant materials such as grass or ornamental plants, or contact with other treated surfaces (e.g., furniture) in domestic or office buildings. Through the late 1980s the widespread use of dichlorvos in resin strips for the control of insects within houses or other public buildings created the potential for widespread low-level exposures to many individuals in the general population. After 1988, concerns over the carcinogenic potential of dichlorvos led the EPA to require warning labels on pest strips. The FDA then disallowed the use of these products in kitchens, restaurants, or other places where food is prepared. This led to a dramatic reduction in dichlorvos formulations for home use. As of September 28, 1995, the EPA proposed cancellation of dichlorvos for all home uses (pest strips, flea collars, room foggers, and on ornamental lawns and plants) and for many commercial and industrial uses (TOXLIST 1995). In addition, the EPA proposed that most retained uses be restricted to specially trained certified applicators. The current potential for exposure of the general population to dichlorvos appears to be very limited compared to past exposures. In addition, if the proposed cancellation of all home use and many commercial and industrial uses of dichlorvos becomes final, this will further reduce risks to the general population.

Dichlorvos may still be applied by professional exterminators for insect control in buildings (Berteau et al. 1989; Gold and Holcslaw 1985; Wright and Leidy 1980) and in turf grass treatments (Goh et al. 1986). These applications create potential for some exposure for the general population through inhalation, dermal contact, and (especially in children) oral intake. These exposure risks would be highest for periods immediately following dichlorvos applications and would be of most concern in buildings with inadequate or defective ventilation (Gold and Holcslaw 1985).

Because dichlorvos is metabolized so rapidly by esterases in the liver and blood, it has not been found in human adipose tissue, milk, blood or in urine (see Section 2.5). Even the major metabolic products of dichlorvos, dimethyl phosphate and the glucuronide conjugate of dichloroethanol, are rapidly excreted from the body and will have left the body completely within a day or two of cessation of dichlorvos exposure.

Although many of the uses of dichlorvos have been restricted, occupational exposures may still occur among workers at facilities that manufacture or process dichlorvos, among professional exterminators or certified pesticide applicators involved in applying dichlorvos, and among workers at hazardous waste sites involved in the disposal of dichlorvos. Retained uses under the proposed EPA rule (September 28, 1995), would be restricted to trained, certified applicators, thereby eliminating most risks associated with application of this pesticide to all but occupational exposures (TOXLIST 1995). Dichlorvos is still widely used in agriculture, especially in confined animal breeding and feeding operations. Failure to wear protective clothing (especially gloves) or to rinse hands would increase the potential risks from dermal exposure for persons handling dichlorvos in concentrated liquid or resin-impregnated forms. Where dichlorvos is applied in concentrated liquid forms in interior spaces with poor ventilation (e.g., applications for termite control), inhalation risks could be significant without the use of protective clothing and equipment. Gold and Holcslaw (1985) evaluated dermal and inhalation exposure of pesticide applicators involved in spraying dichlorvos in domestic residences. Applicators wore a one-piece polyester jumpsuit with an open collar and long sleeves, a hard hat, respirator, and rubber gloves. The subject applicators were fitted with both inside and outside dermal exposure pads placed on the outer clothing and on the skin beneath the clothing. The total exposure calculated for the applicators was 0.0284 mg/kg/hour with 0.028 mg/kg/hour coming from dermal exposure and 0.0004 mg/kg/hour from respiratory exposure.

Information in the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 provides estimates of the number of workers and the different types of occupations and industries where workers could be potentially exposed to dichlorvos (NOES 1991). The NOES survey estimated 24,204 potential occupational exposures. Approximately 95% of these exposures are from four Standard Industrial Classification (SIC) codes: (1711) Plumbing, Heating and Air Conditioning; (2048) Prepared Feed Products; (2339) Women's and Misses' Outerwear; and (7342) Disinfecting and Exterminating Services.

The Occupational Safety and Health Administration (OSHA) has set a Permissible Exposure Limit (PEL) of 1.0 mg/m^3 (0.11 ppm) for dichlorvos in the workplace (OSHA 1974). The National Institute for Occupational Safety and Health (NIOSH 1992) also recommends an occupational exposure limit (time-weighted average [TWA]) of 1.0 mg/m^3 based on a 10-hour average workday and has designated a concentration exceeding 200 mg/m^3 as immediately dangerous to life and health (NIOSH 1990). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Threshold Limit Value (TLV-TWA) of 0.90 mg/m^3 (skin) for occupational exposures (ACGIH 1994). The notation "skin" refers to the potential contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or by direct skin contact with dichlorvos. The use of this notation is intended to alert the reader that air sampling alone is insufficient to accurately quantitate exposure and that measures to prevent significant cutaneous absorption many be required (ACGIH 1994).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to those individuals occupationally exposed to dichlorvos identified in Section 5.5, several groups within the general population may receive potentially higher inhalation exposures to dichlorvos. These groups include individuals living near facilities where dichlorvos is produced or processed and those individuals living near the 3 NPL hazardous waste sites where this compound is present. Although dichlorvos is not tightly bound to soil particles, ingestion of dichlorvos contaminated soil or soil where polyvinylchloride resin strips have been disposed of, may be a route of exposure particularly for children living in areas near production facilities or near hazardous waste sites. Ingestion of contaminated groundwater by individuals living in the vicinity of hazardous waste sites may be another possible source of exposure for both adults and children if these individuals use untreated well water as their primary source of drinking water.

5.7 ADEQUACY OF THE DATABASE

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

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

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The relevant physical and chemical properties of dichlorvos (listed in Table 3-2), are generally known (ASTER 1996; Bowman and Sans 1983; Kenaga 1980; Kowamoto and Urano 1989; Merck 1989; Sunshine 1969; Worthing 1983). No major data needs were identified for physical and chemical properties.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1993, became available in May of 1995. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

As with most pesticide agents, it is virtually impossible to make quantitative estimates of dichlorvos production, use, disposal, and imported and exported volumes. While regulations govern the registration and labeling of pesticide agents, no national statistics are maintained on the amounts sold or actually used. For pesticide agents where production has shown major declines and there are few

remaining plants manufacturin g the pesticide for domestic use, confidentiality considerations may prevent the public reporting of production data. Import and export statistics are generally maintained only for very broad categories of insecticides and not for specific pesticide agents. Under the federal Resource Conservation and Recovery Act (RCRA) system, pesticides are similarly covered under very broad waste categories that make it virtually impossible to track disposal patterns for specific pesticide agents. This presents some fundamental problems in making more than the most general sorts of exposure assessments. While some historic information is available on production and use (Cremlyn 1978; EPA 1976, 1987b, 1988a. 1991a, 1993a, 1994a; Gianessi 1986; IARC 1979, 1991; Marking 1992; Menz et al. 1974 in IARC 1991; PIP-Dichlorvos 1993; WHO 1989), current information for any of these categories (production. use, import/export, and disposal) is considered a major data need. This information would be helpful in evaluating potential exposures and risks to human health.

Environmental Fate. Empirical data on the environmental fate of dichlorvos are almost completely lacking. Because dichlorvos tends to undergo rapid hydrolysis (Howard 1991; PIP-Dichlorvos 1993) under typical environmental conditions, it has been assumed to degrade rapidly and to pose few risks to humans. Dichlorvos is an environmental degradation product of the pesticide trichlorfon and can also be metabolized in many plants from the pesticide naled (EPA 1988a; Menzie 1972; PIP-Naled 1994; PIP-Trichlorfon 1993). In addition, the pesticides trichlorfon and naled can decompose to dichlorvos during sample preparation and analysis. These two factors add further complications to interpreting detections of dichlorvos in environmental media. Since dichlorvos found at NPL or other waste sites may be in the form of discarded resin-plastic materials, further fate and transport research would be valuable in explaining how the dichlorvos impregnated in such plastics is actually released to air, water, or soils.

Bioavailability from Environmental Media. Dichlorvos can be absorbed following inhalation of contaminated workplace air, through derrnal contact, and through consumption of contaminated food or water. Exposure to dichlorvos through inhalation or dermal contact directly with liquid formulations or with dichlorvos pest strips and residues on treated surfaces are probably the largest sources of exposure for the general population. Exposure to dichlorvos through ingestion of contaminated drinking water is expected to be insignificant since the compound is readily hydrolyzed in water, except at very low pH values (pH <4). Well water from areas around hazardous waste sites where dichlorvos has been detected should be monitored to determine whether exposures are insignificant. Exposure to dichlorvos through ingestion of contaminated foods also is expected to be insignificant

since this pesticide is rarely found in raw foods at concentrations of concern and because routine food preparation procedures (i.e., washing and cooking) further reduce dichlorvos residues (IARC 1991; Nakamura et al. 1993). The lack of information on current levels of use makes precise exposure assessments extremely difficult. Since resin-strips are no longer used in households, risks to the general population are likely to have declined since the mid-1980s. Risks may still remain for persons in some occupations (e.g., professional pesticide applicators or workers in confined animal-feeding operations where dichlorvos is still used for pest control, and in veterinary applications) and for those people living near production or processing facilities or those living near waste disposal sites. The main occupational exposure pathways are from inhalation or dermal exposures. Although dichlorvos is not tightly bound to soil particles, dermal contact with or ingestion of dichlorvos contaminated soil or soil where polyvinylchloride resin strips have been disposed of, may be a route of exposure particularly for children living in areas near hazardous waste sites. Improvements in current estimates of the numbers of people in these various groups is a major data need. Information regarding the bioavailability of dichlorvos from dermal contact and from ingestion of soil-bound dichlorvos, particularly in children, and the levels of dichlorvos in contaminated groundwater would be helpful in assessing health risks to populations living near hazardous waste sites.

Food Chain Bioaccumulation. While virtually no experimental data could be identified, the BCF values calculated based on the physical and chemical properties of dichlorvos strongly suggest that there is very limited potential for bioaccumulation or biomagnification in the food chain (ASTER 1996; Kenaga 1980). Additional experimentally determined estimates of BCF in edible fish or shellfish would be helpful in verifying that bioaccumulation of dichlorvos is not an important process in the transfer of residues to humans.

Exposure Levels in Environmental Media. Dichlorvos is not commonly included in routine monitoring programs for air, water or soil. Additional monitoring data, at least in the form of national surveys such as the EPA's Pesticides in Groundwater project, would be very valuable in assessing ambient dichlorvos concentrations. Dichlorvos has been included in the FDA food surveillance program, and these data suggest there is no significant risk to the general U.S. population from eating dichlorvos in the food supply (FDA 1989, 1990, 1991, 1992, 1993, 1994c, 1995; KAN-DO Pesticide Team 1995). Available information also suggests there are few risks associated with ingestion of treated drinking water from larger community systems because water treatment procedures operate in alkaline conditions that would facilitate more rapid hydrolysis of dichlorvos. Exposures to dichlorvos

from ingestion of contaminated groundwater from domestic wells are not well known. Additional monitoring data are needed to determine dichlorvos concentrations in domestic well water, especially from wells near waste disposal sites where dichlorvos has been identified and where the well water is being used as a drinking water source by local residents. This information is needed to determine whether any additional risks exist for populations living in proximity to these hazardous waste sites. Since dichlorvos found at NRL or other waste sites may be in the form of discarded resin-plastic materials, further research on the degradation of dichlorvos impregnated in such plastics would be useful in assessing exposure levels particularly in soil and sediment.

Exposure Levels in Humans. There are no data concerning levels of dichlorvos in human tissues (including adipose tissues, blood, milk, or urine) for members of the general U.S. population or in populations with occupational exposure to dichlorvos. Dichlorvos has not been detected in the human body and only rarely in animals because of its rapid metabolism by esterases in the liver and blood. Additional information on exposure levels in the general population and in individuals in occupational settings would be useful. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for dichlorvos were found. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

The U.S. Department of Agriculture (USDA) is currently sponsoring several research projects related to migration of the pesticide trichlorfon following application to turfgrass (FEDRP 1996). This research is important in studying the movement of dichlorvos which is a major degradation product of trichlorfon. Researchers at the New York Agricultural Experimental Station in Geneva, New York are conducting experiments to determine the extent of downward movement of the pesticide trichlorfon commonly applied to creeping bentgrass turf grown on various soil types. Leachates and soils from

the Automated Rain Exclusion System for Turfgrass Studies in Ithaca, New York will be analyzed for chemical residues.

Researchers at Cornell University in Ithaca, New York are conducting experiments to determine the extent of downward movement of the pesticide trichlorfon applied to several major soil types using normal management practices. The leaching characteristics of trichlorfon will be studied on creeping bentgrass turf plots. Leachates and soils from the Automated Rain Exclusion System for Turfgrass Studies in Ithaca, New York will be analyzed for chemical residues.

Researchers at Pennsylvania State University in University Park, Pennsylvania are conducting experiments to determine the extent of downward movement of the pesticide trichlorfon applied to several major soil types using normal management practices. The runoff and leaching characteristics of trichlorfon will be studied on creeping bentgrass turf plots. Leachates and soils from the Automated Rain Exclusion System for Turfgrass Studies in Ithaca, New York will be analyzed for chemical residues.

Researcher at the University of Massachusetts at Amherst, Massachusetts are conducting experiments to determine the rate of volatile loss and the amount of dislodgeable residues from pesticide-treated turfgrass. One of the pesticides being studied is trichlorfon. The fate of the pesticide will be evaluated. Concentrations of trichlorfon will be measured in air samples and in dislodgeable residues from a one square foot area of treated sod. Preliminary investigations have found that dichlorvos concentrations in air may be of concern even three days post-application of trichlorfon on the grass.

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL SAMPLES

Analytical methods for the determination of dichlorvos in human biological samples are listed in Table 6-l.

Dichlorvos can be recovered from biological media through extraction with an organic solvent (Nordgren 1981; Tewari and Harpalani 1977; Tewari et al. 1974), through the use of solid phase extraction (SPE) (Kawasaki et al. 1992; Liu et al. 1989), or through a clean-up of the matrix with no additional isolation steps (Unni et al. 1992). Determination is via gas chromatography (GC) with mass spectrometry (MS), electron capture (ECD), nitrogen-phosphorus (NPD), flame photometric (PPD), or flame ionization (FID) detectors, high performance liquid chromatography (HPLC) with spectrophotometric detection, or thin layer chromatography (TLC). Limits of detection are generally in the sub-ppm range. Reported recoveries for dichlorvos range from 74 to 85% based on measurements of dichlorvos made immediately after addition of the compound to the tissue or plasma.

Dichlorvos is formed in viva from trichlorfon (metrifonate; (o,o-dimethyl-(1 -hydroxy-2,2,2-trichloroethyl) phosphonate), a drug used to treat schistosomiasis (Nordgren 1981; Unni et al. 1992). In addition, the pesticides naled (o,o-dimethyl-o-(1,2-dibromo-2,2-dichloroethyl)phosphate) and trichlorfon can decompose to dichlorvos during sample preparation (see Section 6.2). In light of these

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

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma	Dilution with saline, addition of deuterated internal standards, and extraction with hexane. Hexane washed with saturated NaCl solution, dried, solvent exchange to chloroform.	GC/MS-SIM	No data	No data	Nordgren 1981
Plasma	Addition of HCl, centrifugation, filtration.	HPLC/UV	40 ng/mL (40 ppb, w/v)	85 (8% RSD) at 0.15 µg/mL (0.15 ppm, w/v)	Unni et al. 1992
Liver, stomach fluid (autopsy)	Acidification of minced liver or stomach fluid with phosphoric acid, steam distillation, extraction with hexane.	TLC	No data	No data	Tewari et al. 1974
Stomach contents	Equilibration of sample at 60 °C for 30 minutes after addition of HCl and acetone. Extraction of cooled and filtered mixture with chloroform and solvent exchange to acetone.	TLC	500 ppb (500 ng/mL, w/v)	Stomach contents: 74 at 500 µg/mL (500 ppm, w/v) Liver: No data	Tewari and Harpalani 1977
Visceral tissue (stomach, intestine, liver)	Mincing of tissue followed by extraction with diethyl ether, evaporation of solvent and redissolution in ethanol.	TLC (visualization by spraying with 2% NaOH followed by 0.5% orcinol)	2 µg/g (2 ppm, w/w)	90	Mali et al. 1995

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

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma, urine	Isolation via C_{18} SPE after dilution of sample with water followed by elution with chloroform:isopropanol (9:1) and solvent exchange to acetonitrile.	GC/FID	approx 400 ppb (400 ng/mL, w/v)	No data	Liu et al. 1989
Serum	Dilution of sample with pH 7 phosphate buffer followed by SPE, elution with *n*-hexane:diethyl ether (8:2, v/v) followed by solvent exchange to methanol:water (70:30, v/v).	HPLC/APCI-MS (SIM)	2 ppb (ng/mL, w/v)	80 at 2 µg/mL (2 ppm, w/v)	Kawasaki et al. 1992
Urine (dichloroethanol)	Adjustment of pH to 3.9 with acetic acid, incubation with β-glucuronidase at 37 °C for 20 hours, and extraction with ether.	GC/ECD	No data	90 at 1.22 µg/mL (1.22 ppm, w/v)	Hutson and Hoadley 1972b
Urine (dimethyl phosphate)	Removal of inorganic phosphate with $Ca(OH)_2$, centrifugation, removal of impurities via cation exchange, formation of pentafluorobenzyl derivative.	GC/FPD	approx 0.02 ppm (0.02 µg/mL, w/v)	149 (9% RSD) at 0.50 ppm (0.50 µg/mL, w/v)	Takamiya 1994

[a] Unless otherwise indicated, the target analyte was dichlorvos.

APCI = atmospheric pressure chemical ionization; ECD = electron capture detector; FID = flame ionization detector; FPD = flame photometric detector; GC = gas chromatography; HPLC = high performance liquid chromatography; MS = mass spectrometry; RSD = relative standard deviation; SIM = selected ion monitoring; SPE = solid phase extraction; TLC = thin layer chromatography; UV = ultraviolet absorbance detector; v/v= volume:volume; w/v = weight:volume;w/w = weight:weight

transformations, caution must be used in the interpretation of data from samples found to contain dichlorvos. It is quite possible that the measured dichlorvos did not arise from exposure to dichlorvos, but rather from exposure to trichlorfon or naled.

6.2 ENVIRONMENTAL SAMPLES

Analytical methods for the determination of dichlorvos in environmental samples are listed in Table 6-2.

Most of the methods for the determination of dichlorvos in air are based on the interaction of the vapor with an adsorbent as air is drawn through a sorbent tube with a sampling pump. Early methods used potassium nitrate for adsorption followed by recovery of dichlorvos via elution with hexane (Bryant and Minett 1978), or dissolution in water of the salt containing adsorbed dichlorvos (Heuser and Scudamore 1966). The dichlorvos in the resulting solution was then determined. The relatively high water solubility of dichlorvos allowed for its collection in water as an air sample was bubbled through a Drechsel bottle (Elgar and Steer 1972). Quantitation was often based on the ability of the desorbed sample to inhibit the enzyme cholinesterase (Elgar and Steer 1972; Heuser and Scudamore 1966). More recent methods use polymeric sorbents such as polyurethane foam (PUP) (EPA 1988d), SPE disks (Markell et al. 1994), XAD (Brouwer et al. 1994; OSHA 1986) or Tenax TA (Roinestad et al. 1993). Analyte recovery was via extraction of the polymeric material with organic solvent, and determination typically by GC. With very few exceptions, detection was achieved using the nitrogen/ phosphorus thermionic detector (NPD), the flame photometric detector (FPD) in the phosphorus mode, or the electron capture detector. Confirmation was obtained using MS. Limits of detection were often in the sub-ppb and sub-ppt range (OSHA 1986; Roinestad et al. 1993).

Methods for the recovery of dichlorvos from water, soil, and wastes are based on liquid/liquid extraction (ASTM 1994; EPA 1991b, 1992a, 1992b; Kadokami et al. 1991) or SPE (DiCorcia et al. 1993; Wang and Huang 1994) followed by extract volume reduction or solvent exchange followed by volume reduction. Supercritical fluid extraction (SFE) also holds promise for the extraction of dichlorvos from soils (Lopez-Avila et al. 1990; Snyder et al. 1992) or as a means to recover dichlorvos from an SPE cartridge (Barnabas et al. 1994). The water solubility of dichlorvos can often result in poor recoveries from aqueous matrices (EPA 1992b); salt is often added during extraction to favor dichlorvos partition into the organic phase (ASTM 1994; EPA 1991b; Kadokami et al. 1991).

Table 6-2. Analytical Methods for Determining Dichlorvos in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Pesticide formulations (sand/sugar base fly bait and 4 pounds/gallon emulsifiable concentrates)	Sand/sugar base: Dispersion with diatomaceous earth and elution with chloroform followed by volume reduction. Emulsifiable concentrates:dissolution of known mass of sample to give approx. 1 g DDVP/100 mL chloroform.	IR absorbance (Method 964.04)	No data	No data	AOAC 1990
Pesticide formulations (0.5% spray solution and 1% cattle spray in hydrocarbon solvent)	None for sample; reference solvent preparation by extraction of DDVP from sample with 0.5N NaOH and water removal using sodium sulfate.	IR absorbance (Method 966.07)	No data	No data	AOAC 1990
Air	Known volume of air drawn through polyurethane foam (1–5 L/minute) followed by extraction with 5% diethyl ether in hexane and extract volume reduction.	GC/ECD (EPA Method TO-10)	No data (depends on volume)	72 (13% RSD) at 0.22 $\mu g/m^3$ and 0.9 m^3 sample volume	EPA 1988d
Air	Known volume of air drawn through SPE disk containing styrene-divinylbenzene copolymer. DDVP recovery via extraction with ethyl acetate.	GC/NPD	No data (depends on volume)	97.8 at 450 ng/m^3 (49.5 ppt, v/v)	Markell et al. 1994
Air	Known volume of air drawn through XAD-2 adsorbent followed by extraction with toluene.	GC/FPD (OSHA Method 62)	0.0019 mg/m^3 (0.21 ppb, v/v) based on 480 L air volume	97.4 (10% RSD) at 0.11 ppm	OSHA 1986
Air (personal air)	Known volume of air drawn through cartridge containing XAD-2 and polyurethane foam followed by extraction with toluene.	GC/NPD or GC/FID	No data	94 at 9.9 and 479 µg and 45% and 95% relative humidity (98% retention of 0.6 µm particles)	Brouwer et al. 1994

Table 6-2. Analytical Methods for Determining Dichlorvos in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air, dust	**Air:** Adsorption of DDVP in 1 m^3 of air onto Tenax TA via an air sampling pump followed by desorption with acetone. **Dust:** Extraction of 1 g homogenized dust (from vacuum cleaner bag) with acetone.	GC/MS	Air: 1 ng/m^3 (0.11 ppt, v/v) Dust: 50 ng/g (50 ppb, w/w)	Air: 94 (10.4% RSD) at 0.1 ppb (v/v). Dust: 111 (3.7% RSD) at 50 ng/g (50 ppb)	Roinestad et al. 1993
Drinking water, groundwater	Adjustment of pH to 7, addition of NaCl and extraction with methylene chloride. Removal of water with sodium sulfate and extract volume reduction.	GC/NPD (ASTM Method D5475)	Approx. 0.5 µg/L (0.5 ppb, w/v)	102 (8.8% RSD) at 1 µ/L	ASTM 1994
Drinking water, groundwater	Adjustment of pH to 7, addition of NaCl and extraction with methylene chloride. Removal of water with sodium sulfate and extract volume reduction.	GC/NPD (EPA Method 507)	2.5 µg/L (2.5 ppb, w/v)	86–100 (15% RSD) at 25 µg/L	EPA 1991b
Groundwater	Addition of sodium chloride to water and extraction with methylene chloride. Water removal using sodium sulfate and solvent exchange to acetone.	GC/MS (SIM)	0.017 µg/L (0.017 ppb, w/v)	99.4 (1.9% RSD) at 0.1 µg/L (0.1 ppb, w/v)	Kadokami et al. 1991
Urban precipitation	Filtration of precipitation and passage through a column packed with XAD-2 resin. Elution from XAD using dichloromethane followed by removal of water from dichloromethane with anhydrous sodium sulfate and volume reduction to 1 mL using Kuderna-Danish concentrator and nitrogen stream. Addition of internal standards just prior to analysis.	GC/MS (SIM)	0.015 µg/L (ppb)	84 (16% RSD) at 0.01 µg/l; 93 (9.1% RSD) at 0.1 µg/L	Haraguchi et al. 1995
Water	Adsorption of DDVP onto graphitized carbon black, elution in reverse direction using methylene chloride/methanol (80:20) and volume reduction.	HPLC/UV	22 ng/L (22 ppt, w/v)	85 (10% RSD) at 1–4 µg/L (ppb, w/v)	Di Corcia et al. 1993
Water	Adsorption of DDVP onto SPE (C_{18}, Florisil) and elution with ethyl acetate.	GC/FPD	No data	98.6 (2.8% RSD) from C_{18} at 0.21 ppm	Wang and Huang 1994

Table 6-2. Analytical Methods for Determining Dichlorvos in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Waste water	Adjustment of pH to 7 and extraction with methylene chloride, water removal, and solvent exchange to hexane.	GC/NPD, GC/FPD, or GC/MS (EPA Method 622)	0.1 µg/L (0.1 ppb, w/v)	72 (7.7% RSD) over concentration range 15–517 µg/L	EPA 1992a
Water, soil, sludges, and waste	Liquid/liquid extraction of water at pH = 7 using methylene chloride. Extraction of solid samples using methylene chloride/acetone (1:1). Column chromatography clean-up if needed.	GC/FPD or GC/NPD (EPA Method 8141A)	8 µg/L (8 ppb, w/v) for water to 40 mg/kg (ppm, w/w) for non- water-miscible waste	Water: 79 (11% RSD) at 14.3 µg/L (14.3 ppb, w/v). Soil: 13 (9% RSD) at 475 µg/kg (0.475 ppb, w/v)	EPA 1992b
Non-fatty foods	Sample homogenization with acetone followed by filtration. Residues partitioned into methylene chloride and petroleum ether after addition of NaCl. Alternatively, acetone solution passage through Hydromatrix (diatomaceous earth) and residue elution with methylene chloride.	GC/FPD, GC/HECD, GC/NPD (US FDA PAM1 Method 302)	Approx. 20 ppb (w/w, µg/kg) depending on analytical system used.	>80	FDA 1994a
Vegetables and fruits; brown rice	**Vegetables and fruits:** Sample blended with acetone, filtered, and blended with a fresh aliquot of acetone; filtrates were combined, subjected to volume reduction, mixed with Celite 545, filtered and rinsed with acetone: water. Cleanup using liquid/liquid partition and volume reduction. **Brown rice:** Ground sample blended with acetonitrile, filtered, and extracted with another aliquot of acetonitrile; extracts combined and extracted with hexane, acetonitrile volume reduced and taken to liquid/liquid partition for cleanup as for vegetables and fruits.	GC/FPD	No data	76–113 (%RSD range 1–10%) at 0.05 ppm.	Nakamura et al. 1994

Table 6-2. Analytical Methods for Determining Dichlorvos in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Produce, wheat, soybeans	**Non-fatty samples (<2% fat):** homogenization with sodium sulfate and ethyl acetate; solvent evaporation, redissolution in acetone. **Fatty samples (>5% fat):** Preparation as for non-fatty samples with the addition of a hexane/ acetonitrile partitioning step.	GC/FPD; GC/MS	No data	61–111 (%RSD 0.1–18%) at 0.5 and 1 ppm	Miyahara et al. 1994
Potatoes	Sample blended and combined with Hydromatrix, addition of internal standards, and SFE.	GC/ITMS	6 ng/g	72 (12% RSD) at 0.5 µg/g (0.5 ppm)	Lehotay and Eller 1995
Cauliflower	Extraction of homogenized plant material with acetone and saturation of this extract with NaCl and dilution with methylene chloride. Clean-up of organic phase using GPC.	GC/NPD (German Pesticide Commission Method S17)	Approx. 0.1 mg/kg (ppm, w/v)	>80	Thier and Zeumer 1987
Various produce	Extraction of finely chopped sample with acetonitrile or ethyl acetate. DDVP extraction into chloroform or clean-up using column chromatography.	GC/FPD	No data	87–94 at 0.5 mg/kg (0.5 ppm, w/v)	Ministry of Agriculture, Fisheries, and Food 1977
Wheat	Homogenization of grain with methanol and clean-up on a charcoal column.	GC/NPD	0.005 ppm	92 (6% RSD) at 0.25 ppm	Crisp and Tarrant 1971
Lettuce	Homogenization of sample and extraction with acetone:dichloromethane:petroleum ether (1:1:1) followed by solvent exchange to acetone.	SFC/NPD	Approx. 25 µg/kg (25 ppb, w/w)	86 at 50–100 µg/kg	Zegers et al. 1994
Various crops	Adsorption of homogenized sample onto Florisil to obtain free-flowing powder. Extraction in glass column with ethyl acetate or methylene chloride:acetone (9:1).	GC/NPD	5 µg/kg (5 ppb, w/w)	84–92 at 0.01–0.5 mg/kg (ppm, w/w)	Kadenczki et al. 1992
Wine	Adsorption onto C_{18} SPE cartridge, washing with 20% ethanol in water and elution with ethyl acetate.	GC/ECD/NPD	0.01 mg/L (0.01 ppm, w/v)	93 (4% RSD) at 0.2 mg/L (0.2 ppm, w/v)	Holland et al. 1994

Table 6-2. Analytical Methods for Determining Dichlorvos in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Various produce	Dispersion of homogenized sample with anhydrous sodium sulfate followed by extraction with ethyl acetate, water removal, and volume reduction.	GC/FPD, GC/MS	Approx. 10 µg/kg (10 ppb, w/w)	83 (6.9% RSD) at 0.2–0.3 mg/kg (ppm, w/w)	Agüera et al. 1993
Milk (whole, skim, chocolate, infant formula)	Sample extracted with 1:4 acetone: acetonitrile followed by centrifugation. Extraction of precipitate twice more with acetone: acetonitrile. Extraction of supernatant from centrifugation combined with extracts followed by back-extraction into dichloromethane. Water removal and evaporation of solvent, redissolution in acetonitrile followed by SPE and solvent exchange to acetone.	GC/FPD	No data	Mean of 54 (18% RSD) at 0.02 ppm.	Erney 1995
Various produce, swine/cattle liver	Maceration of sample with anhydrous sodium sulfate and extraction with ethyl acetate followed by GPC clean-up.	GC/NPD	No data	>90	Roos et al. 1987
Honey	Sample extracted with acetonitrile: water (2:1, v/v), filtered, and extracted with hexane; volume reduction, cleanup using Florisil, evaporation to dryness, and redissolution in hexane.	GC/NPD	0.030 ng/g (ppb)	83 (4.3% RSD) at 1 µg/g (1 ppm)	García et al. 1995
Bovine liver, rumen content	Homogenization with sodium sulfate and extraction with methanol: methylene chloride (1:9), solvent evaporation, redissolution in hexane:ethylacetate (60:40), GPC clean-up.	GC/FPD	0.01–0.05 µg/g (ppm, w/w) using 5 g samples	Rumen content: 81 (2% RSD) at 1 µg/g Liver: 74 (6% RSD) at 0.5 µg/g	Holstege et al. 1991

Table 6-2. Analytical Methods for Determining Dichlorvos in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Pig tissue (brain, liver, muscle, kidney, fat), blood and urine (DDVP, desmethyldichlorvos, dichloroacetaldehyde, dichloroethanol, dichloroacetic acid)	**DDVP:** lean tissue–homogenization/extraction with sodium sulfate and ethyl acetate; water removal from extract; fat–extraction with diethyl ether followed by solvent exchange to hexane-saturated acetonitrile, washing with hexane, and solvent exchange to ethyl acetate. **Blood and urine:** dilution with ethanol and extraction with ethyl acetate followed by water removal using anhydrous sodium sulfate.	GC/NPD (DDVP and methylated desmethyl-dichlorvos); GC/ECD for others	0.05–0.1 ppm (mg/kg, w/w)	Recovery from brain, liver, muscle, kidney 86–100 for all analytes at concentrations greater than 0.2 ppm	Schultz et al. 1971
Pig tissue (brain, liver, muscle, kidney, fat), blood and urine (DDVP, desmethyldichlorvos, dichloroacetaldehyde, dichloroethanol, dichloroacetic acid) (continued)	**Dichloroacetaldehyde:** Tissue and blood–Treatment of macerated sample or blood with sodium sulfate and sulfuric acid followed by extraction with diethyl ether. **Dichloroethanol:** Lean tissue and blood–Hydrolysis with 3 N sulfuric acid followed by protein precipitation, removal, and extraction with ethyl ether:benzene (1:1) and water removal using sodium sulfate. Derivatization with trifluoroacetic anhydride. Fat–Hydrolysis with 3 N sulfuric acid over steam bath and processing as for lean tissue and blood. **Dichloroacetic acid and desmethyl-dichlorvos:** Tissue and liquid samples–Homogenization, hydrolysis, extraction with ethyl ether, drying, formation of methyl esters.		No data		
Milk, eggs, body tissues	**Milk:** dispersion of milk with silicic acid, application to a chromatographic column packed with sodium sulfate and silicic acid, elution with methylene chloride:hexane (3:2), concentration and solvent exchange to hexane.	GC/FPD	Milk: 0.003 ppm;	77–97 at 0.01 ppm for all matrices except liver; poor recovery from liver	Ivey and Claborn 1969

Table 6-2. Analytical Methods for Determining Dichlorvos in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Fat and chicken skin: homogenization with sodium sulfate with heat to liquify fat and extraction with hexane. Back-extraction into acetonitrile and solvent exchange to hexane. Clean-up using silicic acid column chromatography.		Tissues: 0.002 ppm		
Milk, eggs, body tissues (continued)	**Muscle:** homogenization with sodium sulfate, extraction with acetonitrile, and filtration. Extraction of acetonitrile with hexane to remove fat and solvent exchange to hexane. Clean-up using silicic acid column chromatography. **Blood and eggs:** blending of sample with acetonitrile and sodium sulfate, solvent exchange to hexane. Clean-up of egg extract with silicic acid chromatography. Drying and volume reduction of blood hexane extract.				

[a] Unless otherwise indicated, the target analyte was dichlorvos.

ASTM = American Society for Testing and Materials; DDVP = dichlorvos; ECD = electron capture detector; EPA = Environmental Protection Agency; FID = flame ionization detector; FPD = flame photometric detector; GC = gas chromatography; GPC = gel permeation chromatography; HECD = Hall electrolytic conductivity detector; HPLC = high performance liquid chromatography; IR = infrared absorbance spectroscopy; ITMS = ion trap mass spectrometry; MS = mass spectrometry; NPD = nitrogen phosphorus detector; OSHA = Occupational Safety and Health Administration; RSD = relative standard deviation; SFE = supercritical fluid extraction; SFC = supercritical fluid chromatography; SIM = selected ion monitoring; SPE = solid phase extraction; UV = ultraviolet absorbance detection; v/v = volume/volume; w/v = weight/volume; w/w = weight/weight;

The pH of liquid samples is often adjusted to 7 prior to extraction to minimize the hydrolysis of dichlorvos during extraction (ASTM 1994; EPA 1991b, 1992a, 1992b).

The determination of dichlorvos in the resulting extracts is typically by GC with selective detection such as NPD, FPD, or MS, although HPLC with ultraviolet (UV) absorbance detection (DiCorcia et al. 1993) and TLC have also been reported (Askew et al. 1969; Shevchuk et al. 1987). Limits of detection range from low parts per trillion (ppt) (ng/L) for relatively clean water (ground, drinking water) to the mgkg (ppm) range for non-water-miscible wastes.

Electrochemical sensors have been developed and applied in a research setting. Potentiometric sensors (Imato and Ishibashi 1995; Ivnitskii and Rishpon 1994) and amperometric sensors (Hartely and Hart 1994; Martorell et al. 1994) based on immobilized acetyl- or butyrylcholinesterase have been described. Inhibition of the enzyme activity in proportion to the concentration of organophosphorus pesticides, including dichlorvos, in water is the basis of their operations. Sensitivities as low as sub-micromolar concentrations of dichlorvos in water have been demonstrated. However, they are not specific to dichlorvos and have not undergone testing for ruggedness in environmental use.

Significant losses of dichlorvos can occur during preparation of samples for analysis. Some types of boiling chips have been found to facilitate the decomposition of dichlorvos during extract volume reductions (Hsu et al. 1988). The volatility of dichlorvos can also result in losses during volume reductions of extracts (Holland 1977; Lartiges and Garrigues 1993) so care must be taken to avoid taking extracts to dryness during solvent exchange operations. Loss of dichlorvos can also result from improper storage of soil samples (Snyder et al. 1992) prior to extraction; samples should be kept cold and processed as soon as possible. The storage of SPE cartridges onto which dichlorvos has been adsorbed, as after collection of dichlorvos from water, can also result in losses (Lacorte et al. 1995). It is very important that appropriate control samples be used and that the method be validated prior to its use in a critical study.

Dichlorvos can be produced from other chemicals during sample preparation and analysis. Trichlorfon rearranges and is dechlorinated in acidic, neutral, or basic media to form dichlorvos and hydrochloric acid (EPA 1992b). In addition, naled can be converted to dichlorvos during sample workup (EPA 1992b). The analyst must be aware that such transformations can lead to incorrect or misleading results for dichlorvos quantitations. High temperatures in the GC injector or oven can facilitate the

transformation of naled and trichlorfon to dichlorvos (EPA 1992b; Yamashita et al. 1991) and lead to incorrect quantitative results for dichlorvos. The use of cool on-column injection can minimize injector-related transformations of trichlorfon (Yamashita et al. 1991), but transformation on-column can still occur and can be minimized through the use of short, thin-film columns to facilitate elution at lower temperatures (FDA 1994a).

Dichlorvos residues have been determined in a variety of foods including produce, grain, meats, milk, honey, and wine. Dichlorvos is most easily recovered from low-moisture foods, such as grain, by homogenization with an organic solvent (Crisp and Tarrant 1971). For non-fatty, high moisture foods, the sample is typically homogenized in the presence of a salt such as sodium sulfate and an organic solvent (Agiiera et al. 1993; FDA 1994a; Ministry of Agriculture, Fisheries and Food 1977; Roos et al. 1987; Thier and Zeumer 1987; Zegers et al. 1994). The salt serves to absorb water and to favor the partition of dichlorvos into the organic phase. In some cases, homogenized sample is mixed with Florisil, as for produce in Kadenczki et al. (1992), or silicic acid, as for milk in Ivey and Clabom (1969) to obtain a free-flowing powder that is packed into a column and eluted with organic solvent to recover dichlorvos. Column chromatography (gel permeation, adsorption) is often used to remove impurities that could interfere with analysis. For fatty foods such as meats, additional chromatographic or solvent partition clean-up operations are needed to remove the fats that can foul chromatographic systems. Careful use of controls and method validation is indicated because of the sample losses that can occur during clean-up. For example, significant losses of dichlorvos occur during clean-up steps in FDA PAM1 Method 304 for fatty foods (FDA 199413). Emey (1995) hypothesizes that loss of dichlorvos during sample workup of skim milk arises from lack of a fatty “keeper” and subsequent volatilization losses of the analyte. The transformation products of dichlorvos, including desmethyldichlorvos, dichloroacetaldehyde, dichloroethanol, and dichloroacetic acid have also been recovered from pork and other pig tissues and fluids (Schultz et al. 1971). In this case, the chemical derivatives of the transformation products are formed before chromatographic analysis. The same concerns about chemical transformations during sample preparation discussed above also apply to foods.

Dichlorvos is most often determined in the extracts using GC with selective detection, although one method was reported that employed supercritical fluid chromatography (SFC) (Zegers et al. 1994). Limits of detection for dichlorvos in produce were reported to be in the ppm to low-ppb range and those in animal samples were reported to be in the high-ppb to low-ppb range.

6.3 ADEQUACY OF THE DATABASE

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

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Exposure to dichlorvos can occur from environmental exposure as a result of contacting air (inhalation), water (ingestion), food (ingestion), or dermal contact. Methods exist for the determination of dichlorvos in blood and tissues; limits of detection in plasma have been reported to be 40 ppb with 8% relative standard deviation (RSD) (Unni et al. 1992) and 2 ppb (Kawasaki et al. 1992). Their utility is limited, however, because of the short half-life of dichlorvos in these media (Blair et al. 1975; Unni et al. 1992). Dimethyl phosphate is more persistent in urine (Das et al. 1983; Takamiya 1994), but is not specific to dichlorvos; any organophosphate that contains a dimethyl phosphate moiety will produce dimethyl phosphate upon hydrolysis. Dimethyl phosphate can be detected in urine down to concentrations of 0.02 ppm, although a high (149%) recovery was reported at a concentration of 0.50 ppm (Takamiya 1994). The bias at the limit of detection is unclear. Additional information would make the method more meaningful. Additional transformation products include dichloroacetaldehyde, dichlorethanol, and dichloracetic acid (Schultz et al. 1971), which are specific to dichlorvos exposure. Dichloroethanol has been detected in human urine after treatment with more glucuronidase followed by GC (Hutson and Hoadley 1972b). However, an endogenous interferant resulted in a large measurement error and limited application of the method to high exposures. Additional method work

could improve that situation. Exposures to naled and trichlorphon, two organophosphates that are converted in the body to dichlorvos, would also have to be ruled out before a definitive determination of dichlorvos exposure could be made.

The most sensitive biomarker for exposure to dichlorvos is inhibition of the activity of serum cholinesterase. This enzyme is related to the target for dichlorvos toxicity, neural acetylcholinesterase. Neural and erythrocyte acetylcholinesterase are produced by the same gene and a reasonable correlation exists in animal studies between neural and erythrocyte acetylcholinesterase inhibition resulting from organophosphate exposure. Volunteers who consumed 0.033 mg/kg/day dichlorvos over a 21-day period demonstrated a 30% inhibition of serum cholinesterase activity without effect on erythrocyte acetylcholinesterase activity or clinical signs of organophosphate neurotoxicity (Boyer et al. 1977).

Serum cholinesterase and erythrocyte acetylcholinesterase are measured by the spectrophotometric method of Ellman (Ellman et al. 1961). Blood samples are centrifuged and aliquots of serum are used for assay. Erythrocyte acetylcholinesterase can be determined by lysing the pellet in hypotonic solution and washing the erythrocyte membranes where the enzyme is located. Samples are added to buffer containing the substrate acetylthiocholine and 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB). The product of the reaction, thiocholine, reacts with the DTNB to give a yellow product which is measured spectrophotometrically. Kits are available from a number of manufacturers to perform these assays using autoanalyzer equipment.

Normal ranges for enzyme activity have been established. Dichlorvos inhibits serum cholinesterase at levels that have no effect on erythrocyte acetylcholinesterase in most species, including humans (Hayes 1982). Given the variability in normal activities in humans (especially for serum cholinesterase), confirmation of exposure is best established by repeated determinations demonstrating an increase in activity to a constant level after exposure has ceased. Information on cholinesterase activities can be combined with the measurement of other transformation products to increase the certainty that exposure to dichlorvos has occurred.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. If an MRL of 0.00006 ppm (0.0005 mg/m^3) for chronic inhalation exposure is assumed, an analytical method for dichlorvos in air must have a limit of detection of

0.00006 ppm (0.0005 mg/m^3) or less. Limits of detection for dichlorvos in air of 1 ng/m^3 (0.11 ppt) (Roinestad et al. 1993) and 0.0019 mg/m^3 (OSHA 1986) have been reported. The Roinestad method is sufficiently sensitive to permit determination of potential inhalation exposures below the MRL. No new methods are needed.

An oral MRL for chronic exposure to dichlorvos has been established as 0.0005 mg/kg/day which corresponds to a dose of 0.035 mg/day for a 70-kg person. If a 2 L/day consumption of water is assumed, this corresponds to a required limit of detection (LOD) of 0.0175 mg/L (0.0175 ppm, weight per volume [w/v]) for drinking water. Most of the methods for drinking water report LODs in the low-ppb range (ASTM 1994; DiCorcia et al. 1993; EPA 1991b) and are adequate. No new methods for drinking water are needed. If a 2 kg/day consumption of food is assumed, this corresponds to a needed LOD in food of 0.0175 mg/kg (0.0175 ppm, weight per weight [w/w]). The FDA method for dichlorvos in non-fatty foods (FDA 1994a) has an LOD of 20 ppb and is just outside of the adequate range. The methods of Crisp and Tarrant (1971) for wheat (LOD=0.005 ppm) and Kadenczki et al. (1992) for dichlorvos on various crops (LOD=5 ppb) are adequate. However, methods for dichlorvos in fatty foods are more problematic. The method of Schultz et al. (1971) for dichlorvos in pig tissue has an LOD of 0.05-0.1 ppm and is not adequate. The FDA method for fatty foods requires additional column chromatography clean-up and is not satisfactory for dichlorvos (FDA 1994b). Thus, additional methods for fatty foods are needed. Virtually no information was found on methods for environmental transformation products. Methods are needed for these compounds in foods.

6.3.2 Ongoing Studies

No ongoing research was found in which new methods for detecting dichlorvos are being developed.

7. REGULATIONS AND ADVISORIES

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

ATSDR has derived an acute-duration inhalation minimal risk level (MRL) of 0.002 ppm for dichlorvos based on a NOAEL of 1.82 mg/m^3 dichlorvos for inhibition of erythrocyte acetylcholin-esterase (biomarker for dichlorvos neurotoxicity) in a study in male Sprague-Dawley rats which were exposed to atmospheres containing dichlorvos over a 3-day period (Schmidt et al. 1979).

ATSDR has derived an intermediate-duration inhalation MRL of 0.0003 ppm for dichlorvos based on a NOAEL of 0.03 ppm for the neurological effect of brain acetylcholinesterase inhibition in a study in pregnant Carworth E rats exposed to atmospheres containing dichlorvos during their 20-day gestation period (Thorpe et al. 1972).

ATSDR has derived a chronic-duration inhalation MRL of 0.00006 ppm for dichlorvos based on a NOAEL of 0.006 ppm in male rats for brain and erythrocyte acetylcholinesterase in a 2-year inhalation study in Carworth E rats (Blair et al. 1976). Females at this dose had a 12% reduction in erythrocyte acetylcholinesterase; this is also a NOAEL, since erythrocyte acetylcholinesterase inhibition of 20% or less is not considered an adverse effect.

ATSDR has derived an acute-duration oral MRL of 0.004 mg/kg/day for dichlorvos based on a LOAEL of 4 mg/kg/day for inhibition of brain acetylcholinesterase based on a 14-day study in male Sprague-Dawley rats that received 4 mg dichlorvos daily by gavage in corn oil (Teichert et al. 1976).

ATSDR has derived an intermediate-duration oral MRL of 0.003 mg/kg/day for dichlorvos based on a NOAEL of 0.033 mg/kg/day for inhibition of erythrocyte acetylcholinesterase in a 21-day study in male volunteers who consumed 0.033 mg/kg/day in either a capsule form or in a 3-ounce container of gelatin at meals (Boyer et al. 1977).

ATSDR has derived a chronic-duration oral MRL of 0.0005 mg/kg/day for dichlorvos based on a NOAEL of 0.05 mg/kg/day for inhibition of brain acetylcholinesterase in a 52-week feeding study in dogs which consumed 0.05 mg/kg/day by gelatin capsule (AVMAC Chemical Co. 1990; IRIS 1995).

The EPA has established a reference concentration (RfC) of 0.0005 mg/m^3 (0.0006 ppm) for dichlorvos (IRIS 1996). The EPA has established a reference dose (RfD) of 0.0005 mg/kg/day for dichlorvos (IRIS 1996).

The EPA has identified dichlorvos as a probable human carcinogen (IRIS 1995). The International Agency for Research on Cancer (IARC) has determined that dichlorvos is possibly carcinogenic to humans (IARC 1991). In studies conducted under the National Toxicology Program (NTP), female mice showed some evidence of carcinogenic effect; male rats and mice some evidence; and female rats equivocal evidence (NTP 1995).

Dichlorvos is one of the chemicals regulated under "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 1987b). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to dichlorvos to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an g-hour TWA of 1 mg/m^3. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1974).

Dichlorvos is designated a hazardous substance and subject to regulations implementing Section 311 of the Federal Water Pollution Act (EPA 1978) and Section 311 of the Clean Water Act (EPA 1986).

Table 7-1. Regulations and Guidelines Applicable to Dichlorvos

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
WHO		NA	
IARC	Group (cancer ranking)	2B[a]	IARC 1991
NATIONAL			
Regulations:			
a. Air:			
EPA OAR	Proposed Rule: De Minimis Emissions for Determinations Regarding Modifications to Major Sources	Yes	59 FR 15504 40 CFR 63 EPA 1994b
OSHA	Permissible Exposure Limit (TWA)	1 mg/m^3	29 CFR 1910.1000 OSHA 1974
b. Water			
EPA OW	Designation of Hazardous Substances	Yes	40 CFR 116.4 EPA 1978
	Reportable Quantities of Hazardous Substances Pursuant to the Clean Water Act	10 lbs.	40 CFR 117.3 EPA 1986
	National Pollutant Discharge Elimination System (NPDES) -- List of Toxic Pollutants and Hazardous Substances	Yes	40 CFR 122, App. D EPA 1983
	Instructions -- Form 2c, NPDES Criteria and Standards	Yes	40 CFR 125 EPA 1984
c. Other:			
EPA OERR	Reportable Quantity	10 lbs.	40 CFR 302.4 DOT 1989
	Threshold Planning Quantity (TPQ)	1,000 lbs.	40 CFR 355, App. A EPA 1987b
	Toxic Chemical Release Reporting: Community Right-to-Know	Yes	40 CFR 372.65 EPA 1988c
	Proposed Rule: Reportable Quantity Adjustments	Yes	58 FR 54836 40 CFR 302.4 EPA 1993c
EPA OPP	Deletion of Certain Uses and Directions	Yes	60 FR 19580 EPA 1995a
	Notice of Preliminary Determination to Cancel Certain Registrations and Draft Notice of Intent to Cancel	Yes	60 FR 50338 EPA 1995b
Guidelines:			
a. Air:			
ACGIH	Threshold Limit Value (TLV-TWA)	0.90 mg/m^3 (skin)	ACGIH 1994

Table 7-1. Regulations and Guidelines Applicable to Dichlorvos (continued)

Agency	Description	Information	References
National (cont.)			
NIOSH	Recommended Exposure Limit for Occupational Exposure (TWA)	1 mg/m^3 (skin)	NIOSH 1992
	Immediately Dangerous to Life & Health	200 mg/m^3	NIOSH 1990
OSHA	Carcinogen	CA[b]	Sittig 1994
b. Water:			
EPA	q_1* Cancer Slope Factor (oral exposure)	1.22x10^{-1} per mg (kg/day)	60 FR 50338 EPA 1995b
c. Other			
EPA	Cancer Classification	B2[c]	60 FR 50338 EPA 1995b
	Reference Dose (RfD)	5x10^{-4} mg/kg/day	IRIS 1996
	Reference Concentration (RfC)	5x10^{-4} mg/m^3	IRIS 1996
NTP	Cancer Classification		
	Male rat, gavage	SE[d]	NTP 1995
	Female rat, gavage	EE[e]	
	Male mouse, gavage	SE	
	Female mouse, gavage	CE[f]	
STATE			
Regulations or Guidelines:			
a. Air	Acceptable Ambient Air Concentration Guidelines or Standards		
CT	8 hr. avg. time	20 µg/m^3 (2.21x10^{-3} ppm)	Sittig 1994
M	8 hr. avg. time	10 µg/m^3 (1.11x10^{-3} ppm)	
	24 hr. avg. time	2.4 µg/m^3 (2.66x10^{-3} ppm)	
ND	8 hr. avg. time	9 µg/m^3 (9.96x10^{-4} ppm)	
OK	24 hr. avg. time	10 µg/m^3 (1.11x10^{-3} ppm)	
TX	0.5 hr. avg. time	9 µg/m^3 (9.96x10^{-4} ppm)	
	Annual	0.9 µg/m^3 (1.0x10^{-4} ppm)	
VA	24 hr. avg. time	15 µg/m^3 (1.66x10^{-3} ppm)	

Table 7-1. Regulations and Guidelines Applicable to Dichlorvos (continued)

Agency	Description	Information	References
State (cont.)			
WA	24 hr. avg. time	3.3 $\mu g/m^3$ ($3.65x10^{-4}$ ppm)	
b. Water:			
OH	Aquatic Life Habitat - Cold Water Outside Mixing Zone, 30-day average	0.001 µg/L	
MI	Domestic/Drinking Water	0.12 µg/L	Sittig 1994
	Hazardous Waste Constituents		CELDs 1994
ME		Yes	
NJ		Yes	
SD		Yes	
	Restricted Use Pesticides		CELDs 1994
ME		Yes (above 25%)	
NH		Yes (Above 25%)	
NM		Yes	

[a] Possible carcinogenic to humans
[b] CA =Potential occupational carcinogen
[c] Possible human carcinogen
[d] Some evidence
[e] Equivocal evidence
[f] Clear evidence

ACGIH = American Conference of Governmental Industrial Hygienists; CELDs = Computer-assisted Environmental Legislative Data System; CFR = Code of Federal Regulations; DOT = Department of Transportation; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; STEL = Short-term Exposure Limit: TLV = Threshold Limit Value; TWA = Time Weighted Average

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9. GLOSSARY

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

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

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

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

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

Carcinogen-A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

In Viva-Occurring within the living organism.

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

Lethal Concentration$_{(50)}$ (LC_{50})-A calculated concentration of a chemical in air to which exposure for a specific length of time 1s expected to cause death in 50% of a defined experimental animal population.

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

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

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

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

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

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

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

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

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

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

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

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

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

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 3 11 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

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

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

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

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

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

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

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty- in extrapolating animal data to the case of human, (3) the uncertainty in

extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorizarion Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

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

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

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1996
Profile status: Post-Public Comment, Final
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ]Intermediate [ ] Chronic
Key to figure: 2
Species: rat

MRL: 0.002 [ ] mg/kg/day [x] ppm [ ] mg/m^3

Reference: Schmidt G, Schmidt M, Nenner M, and Vetterlein F 1979 Effects of dichlorvos (DDVP) inhalation on the activity of acetylcholinesterase in the bronchial tissue of rats Arch. Toxicol 42: 191-198.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Schmidt et al. (1979) reported on a study where male Sprague-Dawley rats were exposed to atmospheres containing dichlorvos for 3, 7, or 14 days to determine its effect on acetylcholinesterase activity in the bronchi and the blood. Groups of 3 rats were kept in 0.55 m^3 gas cages and the dichlorvos atmosphere generated by suspended polyvinyl chloride strips impregnated with dichlorvos. These strips were hung in the cages 24 hours before the beginning of the experiment and the dichlorvos concentration determined by withdrawing a 10-liter sample of air and passing it through 2 wash bottles containing water. This water was then tested for its ability to inhibit a standard preparation of bovine erythrocyte membrane acetylcholinesterase. Comparison with known concentrations of dichlorvos in this assay allowed an estimate of dichlorvos concentration in the cage air to be made. Different sizes of dichlorvos strips were used to generate dichlorvos concentrations ranging from 0 to 56.64 mg dichlorvos/m^3. At the end of the exposure, blood samples were taken and the pulmonary and bronchial arteries were perfused to remove blood. The bronchial tree was scarified under a dissecting microscope, rinsed, and homogenized. Acetylcholinesterase activity was measured by automatic pH titration after the addition of acetylcholine iodide. Acetylcholinesterase activity was also detected histochemically by the thiolacetic acid method using neostigmine as a specific blocker. A NOAEL of 1.82 mg dichlorvos/m^3 (0.20 ppm) was identified for inhibition of erythrocyte acetylcholinesterase. This enzyme is always inhibited in cases of dichlorvos neurotoxicity.

APPENDIX A

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Acetylcholinesterase Activity

Dose	Bronchial AChE (% inhibition)	Erythrocyte AChE (% inhibition)
0 mg dichlorvos/m^3	0	0
0.83 mg/m^3 (0.09 ppm)	40	0
1.82 mg/m^3 (0.20 ppm)	46	0
4.32 mg/m^3 (0.48 ppm)	60	60
8.20 mg/m^3 (0.91 ppm)	90	80
16.32 mg/m^3 (1.80 ppm)	90	80
56.64 mg/m^3 (6.3 ppm)	85	100

Dose end point used for MRL derivation: 1.82 mg/m^3 (0.20 ppm) for inhibition of erythrocyte acetylcholinesterase.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
$NOAEL_{[HEC]} = NOAEL_{[ANIMAL]}$ x (human blood-gas partition coefficient/animal blood-gas partition coefficient). Since the blood-gas partitioning coefficients of dichlorvos are unknown for humans or rats, a default value of 1 is being used for this ratio. Thus, $NOAEL_{[HEC]} = NOAEL_{[ANIMAL]} = 0.2$ ppm dichlorvos. Data were reported as μg dichlorvos per liter air; this value was converted to the recommended units for gases (ppm) by multiplying μg/L by 24.45 liters/mole (the standard value for the volume of a mole of contaminant at 760 mm Hg and 25 °C) and then dividing by the molecular weight of dichlorvos in grams per mole (220.98). The result is expressed as μg/g, which is equivalent to ppm.

Was a conversion used from intermittent to continuous exposure?
If so, explain: No, exposure was continuous.

Other additional studies or pertinent information that lend support to this MRL:
This is the only acute inhalation study available for derivation of an MRL. Bronchial homogenate acetylcholinesterase showed significant inhibition at 0.09 ppm. The authors stated that lengthening the exposure period to 7 or 14 days produced similar results, but did not provide any data.

The Permissible Exposure Level (PEL) for dichlorvos established by OSHA is 0.1 ppm for a 10-hour workday. Practical insecticidal use concentrations for dichlorvos are 0.025 ppm.

APPENDIX A

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1996
Profile status: Post-Public Comment, Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 7
Species: rat

MRL: 0.0003 [ ] mg/kg/day [x] ppm [ ] mg/m^3

Reference: Thorpe E, Wilson AB, Dix KM, and Blair D. (1972) Teratological studies with dichlorvos vapor in rabbits and rats. Arch. Toxikol. 30 29-38.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 15 pregnant Carworth E rats were exposed to atmospheres containing 0, 0.25, 1.25, or 6.25 mg/m^3 (0, 0.03, 0.14, or 0.69 ppm) throughout their 20-day gestation period. At the end of 20 days, the rats were sacrificed and the uteri removed for examination. The number of live fetuses, late fetal deaths, and resorption sites were noted, and live fetuses were weighed and examined for external malformations. Exposure of dams to all three concentrations of dichlorvos had no effect on the number of fetal resorptions, late fetal deaths, litter size, or mean weight per fetus. Some of the dams exposed to atmospheres containing 0.69 ppm dichlorvos were less active than controls. Exposure at 0.03 ppm had no effect on erythrocyte or brain acetylcholinesterase. Exposure at 0.14 ppm resulted in a 29% inhibition of erythrocyte and a 28% inhibition of brain acetylcholinesterase, while exposure at 6.25 mg/m^3 resulted in 88% inhibition of erythrocyte acetylcholinesterase and an 83% inhibition of brain acetylcholinesterase. Brain and erythrocyte acetylcholinesterase activities were inhibited 83% and 88% in dams in the high exposure (0.69) group, suggesting that acetylcholinesterase inhibition is not associated with teratogenicity. Measurement of acetylcholinesterase activities in the pups was not performed. A NOAEL of 0.03 ppm was established for the neurological effect of brain acetylcholinesterase inhibition.

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Acetylcholinesterase Activity

Dose	Brain AChE (% inhibition)	Erythrocyte AChE (% inhibition)
0 ppm	0%	0%
0.03 ppm	0%	0%
0.14 ppm	28%	29%
0.69 ppm	83%	88%

Dose end point used for MRL derivation: 0.03 ppm for neurological effects of acetylcholinesterase inhibition.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
$NOAEL_{[HEC]} = NOAEL_{[ANIMAL]}$ x (human blood-gas partition coefficient/animal blood-gas partition coefficient). Since the blood-gas partitioning coefficients of dichlorvos are unknown for humans or rats, a default value of 1 is being used for this ratio. Thus, $NOAEL_{[HEC]} = NOAEL_{[ANIMAL]} = 0.03$ ppm. Data were reported in the study as µg dichlorvos per liter air; this value was converted to the recommended units for gases (ppm) by multiplying µg/L by 24.45 liters/mole (the standard value for the volume of a mole of contaminant at 760 mm Hg and 25 °C) and then dividing by the molecular weight of dichlorvos in grams per mole (220.98). The result is expressed as µg/g, which is equivalent to ppm.

Was a conversion used from intermittent to continuous exposure?
If so, explain: Rats were exposed for 23 hours a day; 0.03 ppm x 23/24 = 0.0288 ppm = 0.03 ppm.

Other additional studies or pertinent information that lend support to this MRL:
A NOAEL for developmental effects of 0.69 ppm dichlorvos was established in this study; however, the neurological NOAEL of 0.03 ppm was chosen for derivation of the MRL because it is more relevant to the principal toxicity of dichlorvos.

The Permissible Exposure Level (PEL) for dichlorvos established by OSHA is 0.1 ppm for a 10-hour workday. Practical insecticidal use concentrations for dichlorvos are 0.025 ppm.

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1997
Profile status: Post-Public Comment, Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 16
Species: rat

MRL: 0.00006 [ ] mg/kg/day [x] ppm [ ] mg/m^3

Reference: Blair D, Dix KM, Hunt PF, Thorpe E, Stevenson DE, and Walker AIT 1976 Dichlorvos - A 2-year inhalation carcinogenesis study in rats. Arch. Toxicol 35:281-294.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 50 Carworth E strain rats of both sexes were exposed to atmospheres containing 0, 0.05, 0.5, or 5.0 mg dichlorvos/m^3 (0, 0.006, 0.06, or 0.6 ppm) for 2 years for 23 hours per day as part of a carcinogenicity study. At the end of the study, the surviving rats were killed, blood was collected and half the brain was used to determine brain acetylcholinesterase. Plasma cholinesterase and erythrocyte acetylcholinesterase were also measured. In males treated at 0.006 ppm a NOAEL for brain and erythrocyte acetylcholinesterase was identified. Females at this dose had a 12% reduction in erythrocyte acetylcholinesterase, this is also a NOAEL, since erythrocyte acetylcholinesterase inhibition of 20% or less is not considered an adverse effect.

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Acetylcholinesterase Activity

Dose	Brain AChE (% inhibition)	Erythrocyte AchE (% inhibition)
0 ppm	0	0
0.006 ppm	0 (M) 0 (F)	0 (M) 12 (F)
0.06 ppm	10 (M) 10 (F)	0 (M) 31 (F)
0.6 ppm	79 (M) 81 (F)	96 (M) 95 (F)

Dose end point used for MRL derivation: 0.006 ppm for brain and erythrocyte acetylcholinesterase inhibition in male rats.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
$NOAEL_{[HEC]} = NOAEL_{[ANIMAL]}$ x (human blood-gas partition coefficient/animal blood-gas partition coefficient). Since the blood-gas partitioning coefficients of dichlorvos are unknown for humans or rats, a default value of 1 is being used for this ratio. Thus, $NOAEL_{[HEC]} = NOAEL_{[ANIMAL]}$ = 0.006 ppm. Data were reported as µg dichlorvos per liter air; this value was converted to the recommended units for gases (ppm) by multiplying µg/L by 24.45 liters/mole (the standard value for the volume of a mole of contaminant at 760 mm Hg and 25 °C) and then dividing by the molecular weight of dichlorvos in grams per mole (220.98). The result is expressed as µg/g, which is equivalent to ppm.

Was a conversion used from intermittent to continuous exposure?
If so, explain: Rats were exposed for 23 hours a day; 0.006 ppm x 23/24 = 0.0058 ppm = 0.006 ppm.

Other additional studies or pertinent information that lend support to this MRL:
This is the only chronic inhalation study available for the derivation of an MRL. The EPA used this study to derive an RfC of 0.0005 mg dichlorvos/m^3 for lifetime exposure to dichlorvos.

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1997
Profile status: Post-Public Comment, Final
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ]Intermediate [ ] Chronic
Key to figure: 14
Species: rat

MRL: 0.004 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Teichert K, Szymczyk T, Consolo S, and Ladinsky H. (1976) Effect of acute and chronic treatment with dichlorvos on rat brain cholinergic parameters. Toxicol and Appl Pharmacol 35 77-81.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Male Sprague-Dawley rats were treated daily for 14 days with 4 mg/kg dichlorvos by gavage in corn oil. Dichlorvos purity was 99%. Control animals received corn oil only. Ten animals were used in the control group and 11 in the treatment group. At the end of the 14 day dosing period, the rats were decapitated, the brains removed, homogenized in 10 volumes of 0.3% Triton X-100, and centrifuged for 10 minutes. Aliquots of the supernatant were assayed for acetylcholinesterase activity by the hydrolysis of radioactive acetylcholine.

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Brain Acetylcholinesterase Activity
(μmoles acetylcholine hydrolyzed/gram wet weight/hour)

0 mg/kg/day	4 mg/kg/day (from Table 1 of reference)
559.3 +/- 5.2	314.91 +/- 1.97

Dichlorvos treatment at 4 mg/kg/day over a 14-day period resulted in a 44% inhibition of brain acetylcholinesterase activity, which is considered a less serious LOAEL for neurological effects.

Dose end point used for MRL derivation: 4 mg/kg/day for a 44% inhibition of brain AChE activity.

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

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

Was a conversion used from intermittent to continuous exposure?
If so, explain: No

Other additional studies or pertinent information that lend support to this MRL:
This is the only reliable study located for acute duration oral exposure to dichlorvos where doses ranging from 5 to 10% of the LD_{50} were administered on a daily basis and brain acetylcholinesterase (one of the targets for dichlorvos) was measured rather than erythrocyte acetylcholinesterase. Most of the acute duration oral studies for dichlorvos in rodent species were LD_{50} studies; representative LD_{50} values for the rat range from 56 to 97.5 mg/kg (Durham et al. 1957; Gajewski and Katkiewicz 1981; Ikeda et al. 1990). The 44% inhibition of brain acetylcholinesterase reported in this study is considered a less serious LOAEL; clinical signs were not reported in this study, but in another oral dosing study in Fischer 344 rats (NTP 1989) over an 11-day period, no clinical signs of organophosphate neurotoxicity were reported in animals receiving up to 16 mg/kg/day dichlorvos. The major limitation of the study used to derive the MRL is that because of its design, a dose-response relationship was not demonstrated.

The FAO/WHO Joint Meeting on Pesticide Residues has established an acceptable daily intake of dichlorvos for humans of 0.004 mg/kg/day (FAO/WHO 1967).

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1996
Profile status: Post-Public Comment, Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 27
Species: human

MRL: 0.003 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Boyer AC, Brown LJ, Slomka MB, and Hine CH (1977) Inhibition of human plasma cholinesterase by ingested dichlorvos: effect of formulation vehicle. Toxicol. Appl. Pharmacol. 41 389-394.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Boyer et al. (1977) reported on a study designed to determine if different formulations would change the effect of dichlorvos on serum cholinesterase and erythrocyte acetylcholinesterase. Plasma cholinesterase and erythrocyte acetylcholinesterase were determined twice a week for 3 weeks in 30 male volunteers. Twenty-four men with the most stable activities were used in the study. Two treatment groups of 6 men each received 0.9 mg dichlorvos 3 times daily either in a premeal capsule filled with cottonseed oil or in a 3-ounce container of gelatin. Two other groups of 6 men each received placebo capsules or gelatin. The treated volunteers received 0.9 mg dichlorvos 3 times a day or 2.7 mg/day. The average weight of the volunteers was 81 kg, resulting in an average dose of 0.033 mg/kg/day. Dosing was started and carried out for a 21-day period during which plasma cholinesterase and erythrocyte acetylcholinesterase were measured twice a week by a pH titration method. Following the termination of dosing, plasma and erythrocyte activities were monitored twice weekly for seven weeks. Each individual's observation of cholinesterase activities was converted to a percentage of his pretrial average determinations. No clinical signs of neurotoxicity were noted in any of the subjects (tremor, pupillary response to light and skin moisture were assessed). A NOAEL of 0.033 mg dichlorvos/kg/day was observed for inhibition of erythrocyte acetylcholinesterase.

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Cholinesterase Activity

Dose	Serum ChE (% inhibition)	Erythrocyte AChE (% inhibition)
0.033 mg/kg/day	38% (capsule)	0% (capsule)
	28% (gelatin)	0% (gelatin)

Dose end point used for MRL derivation: 0.033 mg/kg/day for inhibition of AchE activity.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

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

Was a conversion used from intermittent to continuous exposure?
If so, explain: NA

Other additional studies or pertinent information that lend support to this MRL:
The reduction of serum cholinesterase observed in the study confirms that dichlorvos was absorbed by the volunteers under these conditions. No signs of clinical neurotoxicity were observed at any time in the volunteers. The dose given appeared to have been chosen expressly to not cause inhibition of erythrocyte acetylcholinesterase. This study was chosen for MRL derivation because it was the only one located that defined a NOAEL for humans for the end point of erythrocyte acetylcholinesterase inhibition.

The FAO/WHO Joint Meeting on Pesticide Residues has established an acceptable daily intake of dichlorvos for humans of 0.004 mg/kg/day (FAO/WHO 1967).

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1996
Profile status: Post-Public Comment, Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 38
Species: dog

MRL: 0.0005 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: AMVAC Chemical Corp. 1990 A 52-week chronic toxicity study on DDVP in dogs. Unpublished report dated August 6, 1990 submitted by AMVAC Chemical Corporation, Los Angeles CA. EPA-41593101.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): In a chronic feeding study, groups of Beagle dogs (4 per sex per dose, approximately 6–7 months old) were administered dichlorvos daily by gelatin capsule for 52 weeks at dose levels of 0, 0.1, 1.0, and 3.0 mg/kg/day. Observations included clinical signs, body weight, food consumption, ophthalmology, blood chemistry, necropsy, and histopathology. The 0.1 mg/kg/day dose level was lowered to 0.05 mg/kg/day on day 22 due to inhibition of serum cholinesterase noted after 12 days on dichlorvos (the authors were attempting to assure a no-effect level for serum ChE). Serum cholinesterase and erythrocyte acetylcholinesterase were measured throughout the study (3 times prior to treatment, and during weeks 2, 6, 13, 26, 39, and 52). At termination of the study, the brain was weighed and brain acetylcholinesterase was measured. Histopathology was performed on the brain (with brainstem), cervical spinal cord, lumbar spinal cord and the sciatic nerve.

Effects noted in study and corresponding doses: The main clinical observations were soft feces and emesis. Soft feces did not appear to be related to dichlorvos administration. One male treated at 3.0 mg/kg/day experienced emesis on 29 different days in the study. One male experienced ataxia, salivation, and dyspnea on one day during week 33, these classical symptoms of organophosphate toxicity were thought to be from an accidental overdose although this was not confirmed. Serum cholinesterase was unchanged in the 0.05 mg/kg/day groups for both sexes. At 1.0 mg/kg/day, serum cholinesterase was decreased by 52.9% in males and 51.8% in females. Erythrocyte acetylcholinesterase was decreased by 53.4% in males and 45.2% in females. At 3.0 mg/kg/day, serum cholinesterase was decreased 71.5% in males and 64.6% in females. Erythrocyte acetylcholinesterase was decreased 85.1% in males and 81.1% in females. Levels of inhibition did not increase over time of measurement (2–52 weeks). At termination of the study, brain acetylcholinesterase was decreased 22% in males at 1.0 mg/kg/day, but not in females. At 3.0 mg/kg/day, brain acetylcholinesterase was decreased 47% in males and 29% in females. No treatment-related changes were seen on histopathology for the following tissues: brain with brainstem, cervical spinal cord, lumbar spinal cord, optic nerve, thoracic spinal cord, and sciatic nerve.

APPENDIX A

Effect of Dichlorvos on Acetylcholinesterase Activity

Dose (mg/kg/day)	Brain AChE (% inhibition)	Erythrocyte (% inhibition)
0	0	0
0.05	0	0
1.0	53.4 (M) 45.2 (F)	22 (M) 0 (F)
3.0	85.1 (M) 81.1 (F)	47 (M) 29 (F)

Dose end point used for MRL derivation: NOAEL of 0.05 mg/kg/day for erythrocyte and brain acetylcholinesterase inhibition

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

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

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: The EPA used this as the principal study to establish an RfD for dichlorvos of 0.0005 mg/kg/day.

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

See LSE Table 2-1

(1) Route of Exuosure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
(2) Exuosure Period Three exposure periods - acute (less than 15 days), intermediate (1.5-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference

to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a'NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.0005 ppm (see footnote 'lb").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompames the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious

effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0005 ppm.

LEGEND

See Figure 2-1

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

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day .

(16) NOAEL In this example, 1% NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (ql*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

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

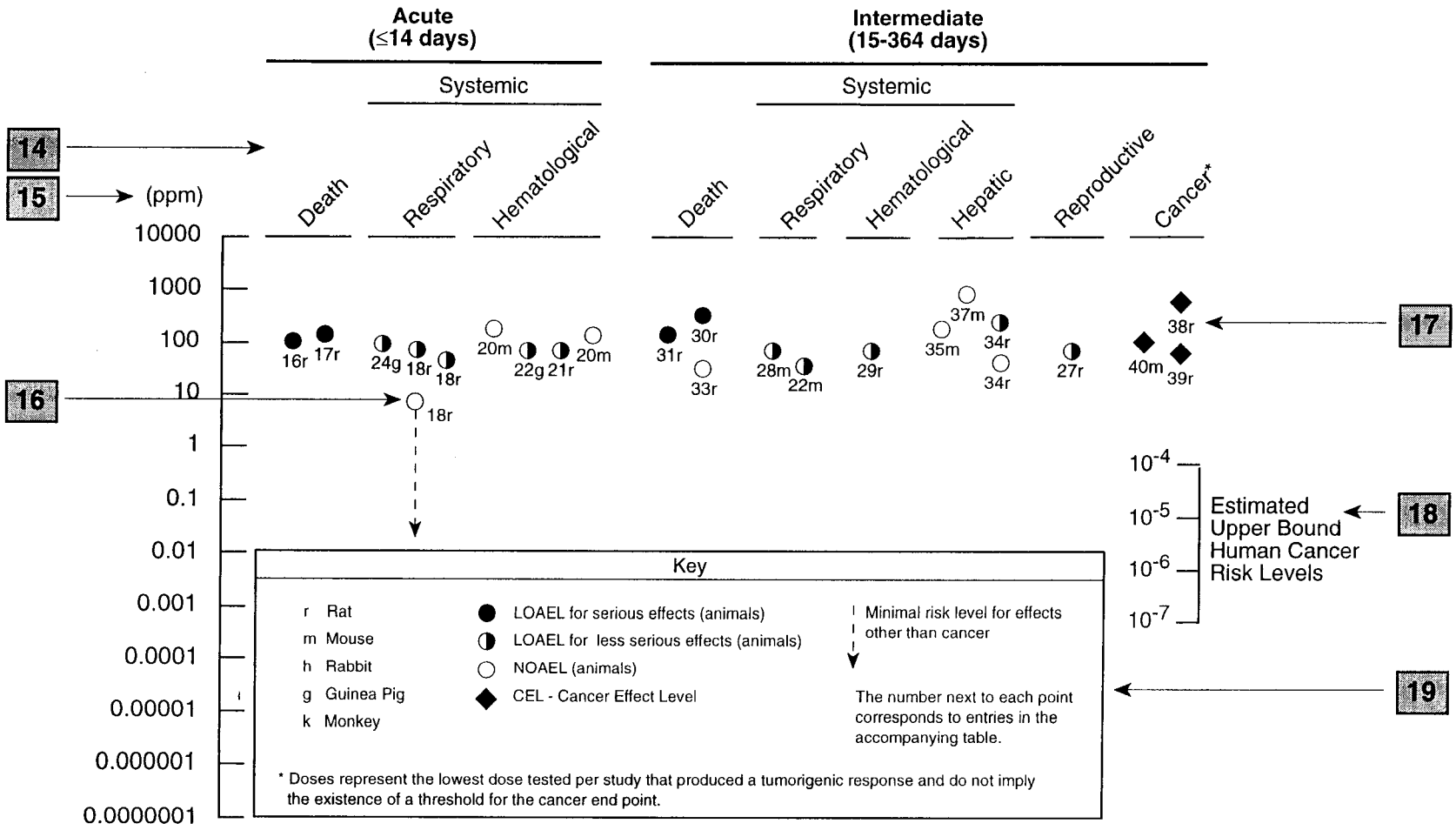
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

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

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

SAMPLE

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



Chapter 2 (Section 2.4)

Relevance to Public Health

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

1. What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

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

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

Interpretation of Minimal Risk Levels

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

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

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

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

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography

APPENDIX C

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

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