TOXICOLOGICAL PROFILE FOR
CHLORFENVINPHOS

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

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DISCLAIMER

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

UPDATE STATEMENT

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 chlorfenvinphos. The panel consisted of the following members:

1.   Dr. Frederick Oehme, Professor, Kansas State University, Manhattan, KS;

2.   Dr. Casey Robinson, Professor of Pharmacology and Toxicology, University of Oklahoma, Oklahoma City, OK; and

3.   Dr. Syed Naqvi, Professor of Biology, Southern University Department of Biological Sciences, Baton Rouge, LA.

These experts collectively have knowledge of chlorfenvinphos' physical and chemical properties, toxico-kinetics, 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 chlorfenvinphos and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Chlorfenvinphos has been found in at least 1 of the 1,428 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 chlorfenvinphos 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 by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to chlorfenvinphos, 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 CHLORFENVINPHOS?

Chlorfenvinphos is the common name of an organophosphorus insecticide used to control insect pests on livestock. It was also used to control household pests such as flies, fleas, and mites. This chemical is synthetic and does not occur naturally in the environment. Chlorfenvinphos was sold under common trade names including Birlane®, Dermaton®, Sapercon®, Steladone®, and Supona®.

The pure chemical (100% chlorfenvinphos) is a colorless liquid with a mild odor. Commercial preparations commonly used in insecticides sold in stores were usually 90% chlorfenvinphos. Most of chlorfenvinphos was used in liquid form. The substance easily mixes with acetone, ethanol, and propylene glycol. It is slowly broken down by water and is corrosive to metal.

1.2 WHAT HAPPENS TO CHLORFENVINPHOS WHEN IT ENTERS THE ENVIRONMENT?

Chlorfenvinphos enters the environment from runoff after rainfall and leaching from hazardous waste sites. After it has leached, it may be present in the soil and underground water (wells). It may be present in surface water (rivers and ponds) after it has run off the land. From soil, it may also be washed into surface waters by rain. It may also move from soil to the air by evaporation or by being absorbed by plants. No information is available now to show that it can be found in fish or other freshwater animals, or in seafood, or in plants that are eaten by people.

1.3 HOW MIGHT I BE EXPOSED TO CHLORFENVINPHOS?

Most cases of unintentional chlorfenvinphos poisoning have resulted from short exposures to very high concentrations of this substance. Usually this occurred when people unintentionally swallowed it. Workers involved in pesticide application, or dairy farming, cattle or sheep holding, or poultry production, may have inhaled, swallowed, or contaminated their skin with a large amount of the substance if they did not properly protect themselves when using it. The most common way for people to be exposed to chlorfenvinphos is by eating imported agricultural products contaminated with it and by using pharmaceutical products that contain lanolin. Lanolin is a natural grease from sheep's wool wax that is used as a base for many medications, cosmetic skin lotions, and creams that are rubbed on the skin to keep the skin from drying. Chlorfenvinphos used to control flies in animal buildings and holding pens can contaminate sheep's wool. If you live in areas surrounding hazardous waste disposal sites or treatment facilities for chlorfenvinphos, you could be exposed to it by contact with soils, runoff water, surface water, or groundwater contaminated by spills or leaks on the site or facility. People who work in the disposal of chlorfenvinphos or its wastes are more likely to be exposed.

You are most likely to be exposed to chlorfenvinphos if you live near chemical plants where it was manufactured, or near dairy or poultry farms, or cattle or sheep holding areas where it was used; or if you live near hazardous waste sites that contain it.

1.4 HOW CAN CHLORFENVINPHOS ENTER AND LEAVE MY BODY?

If you breathe air containing chlorfenvinphos, you may absorb it into your body through your lungs. If you eat food or drink water containing this substance, it may be absorbed from your stomach and intestines. Chlorfenvinphos may also enter your body through your skin. Once in the body, it is rapidly broken down and eliminated from the body, mostly when you urinate. It does not build up in your tissues.

1.5 HOW CAN CHLORFENVINPHOS AFFECT MY HEALTH?

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.

Chlorfenvinphos affects the nervous system. In animals and people, high doses of the substance produce effects on the nervous system similar to those produced by high doses of muscarine and pure nicotine. Some mild symptoms of exposure are headache, dizziness, weakness, feelings of anxiety, confusion, runny nose, constriction of the pupils of the eye, and inability to see clearly. More severe symptoms may include nausea and vomiting, abdominal cramps, slow pulse, diarrhea, pinpoint pupils, difficulty in breathing, and passing out (fainting). These signs and symptoms may start to develop within 30–60 minutes and reach their maximum effect after

6–8 hours. Very high exposure to chlorfenvinphos has killed people who swallowed it by accident or who swallowed large amounts of the substance to commit suicide. We do not know if people who swallow small quantities of chlorfenvinphos over long periods of time will have permanent damage to their immune systems. In almost all cases, complete recovery occurred when exposure stopped. There is no evidence that long-term exposure to small amounts of the chlorfenvinphos causes any other harmful health effects in people. The substance has not been shown to cause birth defects or to prevent conception in people. The International Agency for Research on Cancer, the Environmental Protection Agency, and the National Toxicology Program have not yet studied chlorfenvinphos for cancer in people and animals. In animal studies, high doses of chlorfenvinphos produced effects on the nervous system similar to those seen in people.

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

Most of the signs and symptoms resulting from chlorfenvinphos poisoning are due to the inhibition of an enzyme called "acetylcholinesterase" in the nervous system. This enzyme is also found in your red blood cells and a similar enzyme (pseudocholinesterase) is found in blood plasma. The most common test for exposure to many pesticides (including chlorfenvinphos) that contain the element phosphorus is to determine the level of cholinesterase activity in the red blood cells or plasma. This test requires only a small amount of blood and can be done in your doctor's office. It takes weeks for this enzyme to completely recover to normal levels following exposure; therefore, a valid test may be conducted a number of days following the suspected exposure. This test indicates only exposure to a chemical substance of this type. It does not specifically show exposure to chlorfenvinphos. Other chemicals or disease conditions may also alter the activity of this enzyme. There is a wide range of normal cholinesterase activity among individual people in the general population. If your normal or baseline value has not been established through a previous test, you might have to repeat the test several times to determine if your enzyme activity is recovering.

Specific tests are available to identify chlorfenvinphos or its break-down products in your blood, body tissue, and urine. These tests are not usually available through your doctor's office and

require special equipment and sample handling. If you need the specific test, your doctor can collect the sample and send it to a special laboratory for analysis. Chlorfenvinphos is rapidly broken down to other chemicals and removed from the body (in urine), so this test must be done in the first few days after exposure to make sure that you have really breathed, swallowed, or got chlorfenvinphos on your skin.

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 can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (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 develop 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 reasons.

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.

The federal government has set standards or guidelines to protect people from the possible harmful health effects of chlorfenvinphos. These include regulated concentration limits for agricultural products, public right-to-know requirements about production and use of

chlorfenvinphos, and regulated quantities requiring emergency response procedures if an accidental release occurred.

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) 639-6315 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 22161
>   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 chlorfenvinphos. 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 lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in

determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (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.

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

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

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

2. HEALTH EFFECTS

2.2.1   Inhalation Exposure

2.2.1.1   Death

There are no reports of deaths in humans exposed by acute-, intermediate-, or chronic-duration inhalation to chlorfenvinphos.

No studies were located regarding lethality in animals after intermediate- or chronic-duration inhalation exposure to chlorfenvinphos. A study investigated whether the difference in the route of absorption or the mode of lethality is responsible for the higher lethality of the micron-sized (>1 µm) aerosols in male rats. The study reported 0, 60, and 100% mortality in rats at the 83, 144, and 236 mg/m^3 ambient air concentrations, respectively. The deaths occurred 3 and 4 hours after initiation of the exposure to micron-sized chlorfenvinphos aerosols. There was 0, 80, and 100% mortality in rats at the 254, 471, and 1,019 mg/m^3 ambient air concentrations, respectively. The LC$_{50}$ value calculated from the mortality of the rats was markedly increased by cannulation (from 133 mg/m^3 for non-cannulated to 489 mg/m^3 for cannulated rats) for the micron-sized aerosol ambient air concentrations. However, there was essentially no difference in the LC$_{50}$ values (509 mg/m^3 for non-cannulated and 475 mg/m^3 for cannulated rats) calculated from the mortality of the rats that were administered the more inhalable submicron-sized aerosols ambient air concentrations. These data indicate that the micron-sized aerosols were about 4 times more potent in producing lethality than the submicron-sized aerosols. This is also an indication that swallowed chlorfenvinphos contributed to the lethality; this was more evident for the less inhalable micron-sized aerosol ambient air concentrations. Elapsed time from the start of exposure to death was not changed by the cannulation in both the micron-sized and the submicron-sized aerosols. The authors surmised that death from acute exposure to chlorfenvinphos aerosols probably derives from inhibition of acetylcholinesterase(AChE) activity (Takahashi et al. 1994). In another study with rats, the acute lethality of chlorfenvinphos was unaffected in male rats in snout-only or whole body exposures (Tsuda et al. 1986). The LC$_{50}$ for death in rats is shown in Table 2-1 and plotted in Figure 2-1.

2.2.1.2   Systemic Effects

No studies were located regarding the gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to chlorfenvinphos. Existing human data on the metabolic effects of the

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

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference
					Less serious (mg/m3)	Serious (mg/m3)	
ACUTE EXPOSURE							
Death							
1	Rat (Fischer- 344)	once				133 M (LC$_{50}$)	Takahashi et al. 1994
Systemic							
2	Rat (Fischer- 344)	4 hr	Resp			390 M (apnea)	Takahashi et al. 1994
			Cardio			390 M (progressive increase in blood pressure, bradycardia)	
Neurological							
3	Rat (Fischer- 344)	4 hr				83 M (salivation, urination, exophthalmos, twitches, and tremors)	Takahashi et al. 1994

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

Cardio = cardiovascular; hr = hour; LC$_{50}$ = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed- adverse-effect level; Resp = respiratory

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

Acute (≤14 days)

Key

r   rat

■ LC$_{50}$ (animals)

● LOAEL for serious effects (animals)

◐ LOAEL for less serious effects (animals)

The number next to each point corresponds to entries in Table 2-1.
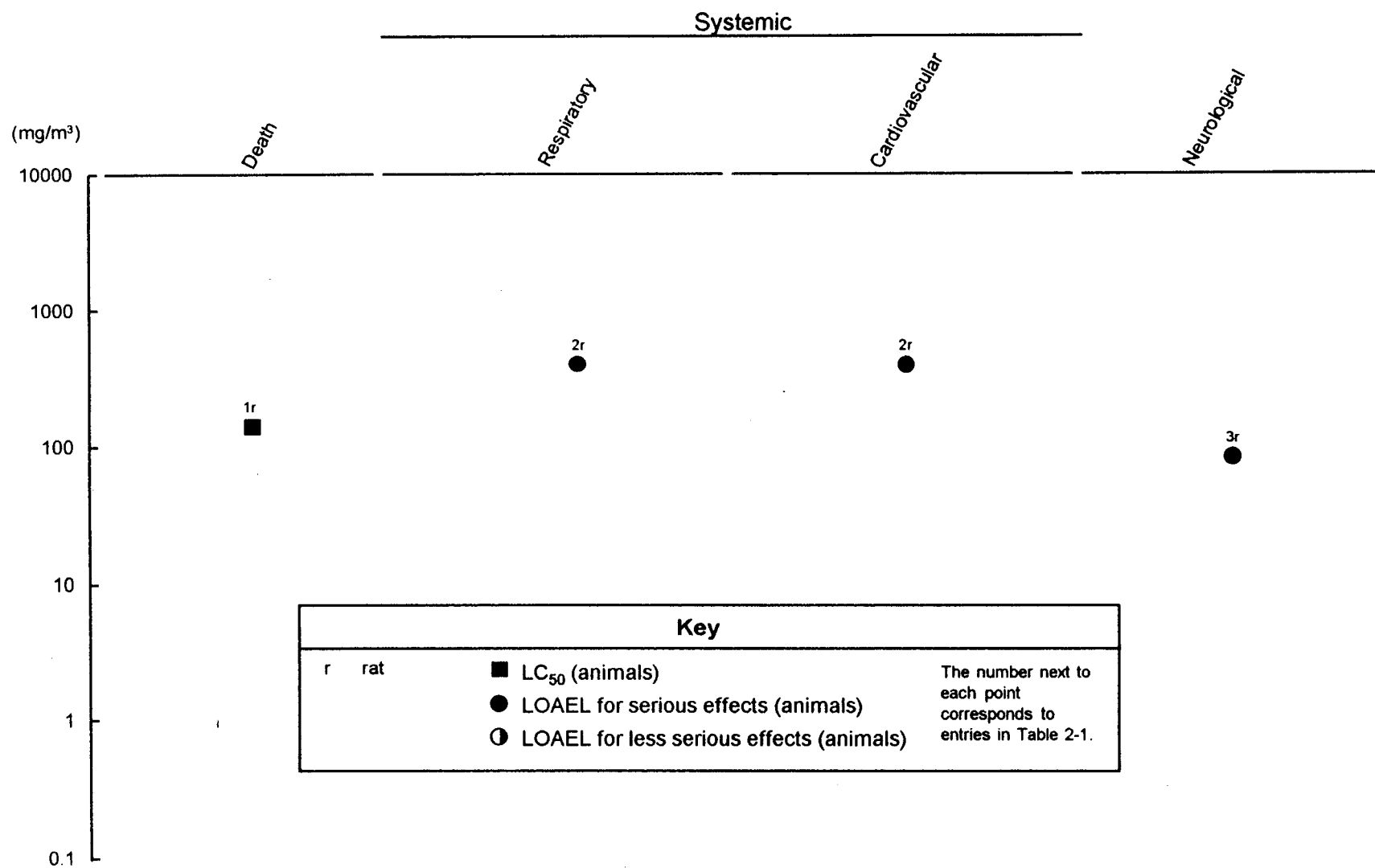
substance are limited to chronic-duration exposure. Existing animal data on the respiratory and cardiovascular effects are limited to acute-duration exposure.

The highest NOAEL value and all LOAEL values for adverse systemic effects in each reliable study for each species and duration category are shown in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects.   No studies were located regarding respiratory effects in humans after exposure to chlorfenvinphos for any duration category.

Acute-duration exposure of rats to inhalation aerosol chlorfenvinphos ambient air concentrations produced cardiorespiratory changes in the treated rats at high ambient air concentrations. Male Fischer 344 rats exposed to the micron-sized (>1 µm) or submicron-sized (<1 µm) chlorfenvinphos aerosols for 4 hours suffered cardiorespiratory effects. Rats exposed to the lethal concentration of 1,220 mg/m^3 of the submicron-sized aerosols showed a progressive increase in blood pressure followed by an apnea during which the blood pressure was maximally increased. Rats exposed to 390 mg/m^3 of the micron-sized aerosols also exhibited cardiorespiratory changes similar to changes caused by the submicron-sized aerosols (data were not shown in the report). No significant qualitative difference was observed in cardiorespiratory changes between the micron-sized and the submicron-sized aerosols, suggesting that the mode of lethality is not different between the two types of aerosols. A LOAEL of 390 mg/m^3 for apnea was established in this study (Takahashi et al.
1994). In a previous study (Takahashi et al. 1991), Sprague-Dawley rats exhibited similar signs at an intravenous dose of 16 mg/kg of chlorfenvinphos.

Cardiovascular Effects.   No studies were located regarding cardiovascular effects in humans after exposure to chlorfenvinphos for any duration category.

Acute exposure of rats to inhalation aerosol chlorfenvinphos ambient air concentrations produced cardiorespiratory changes in the treated rats at high ambient air concentrations. Adult male Fischer 344 rats exposed to the micron-sized (>1 µm) or submicron-sized (<1 µm) chlorfenvinphos aerosols for 4 hours suffered cardiorespiratory effects. Rats exposed to the lethal concentration of 1,220 mg/m^3 of the submicron-sized aerosols showed a progressive increase in blood pressure followed by apnea during which the blood pressure was maximally increased. Bradycardia was observed in the electrocardiograph (ECG) at the pressor period, which was characterized by a prolonged TP time without a change in PQ, QRS, and ST time. Rats exposed to 390 mg/m^3 of the micron-sized aerosols also exhibited cardiorespiratory changes similar to those

caused by the submicron-sized aerosols (data were not shown in the report). No significant
qualitative difference was observed in cardiorespiratory changes between the micron-sized and the
submicron-sized aerosols, suggesting that the mode of lethality is not different between the two
types of aerosols. A LOAEL of 390 mg/m^3 for progressive increased blood pressure and
bradycardia was established in this study (Takahashi et al. 1994).

Metabolic Effects.   The information on the metabolic effects of chronic-duration inhalation
exposure to chlorfenvinphos provides only inconclusive evidence. Examinations of
31 manufacturing workers who directly handled the chlorfenvinphos (and other similar compounds)
for 19–53 years revealed significantly lowered NBT (nitroblue tetrazolium)-dye reduction in both
stimulated and non-stimulated cells, as well as a significant decrease of the spontaneous E rosette
formation (not influenced by exposure time) in the blood (early E rosettes, 52%; late E rosettes,
57%) as compared to controls (early E rosettes, 57%; late E rosettes, 63%). No correlation was
found between the spontaneous E rosette formation and acetylcholinesterase activity. The authors
of this study concluded that depressed NBT-dye reduction and diminished spontaneous E rosette
formation may be regarded as a probable mode of the effect of organophosphoric chemicals on
metabolic and membrane damage to human cells. About half of the subjects in the study were
smokers (Wysocki et al. 1987). However, the data from this study are not reliable for evaluating the
inhalation toxicity of chlorfenvinphos because the workers were also concurrently exposed to
greater concentrations of other known toxic substances.

No studies were located regarding metabolic effects in animals after exposure to chlorfenvinphos
for any duration category.

2.2.1.3   Immunological and Lymphoreticular Effects

No studies were located regarding the immunological and lymphoreticular effects in humans
following acute- or intermediate-duration inhalation exposure to chlorfenvinphos. However, chronic-
duration inhalation exposure to organophosphoric pesticides caused a depression of immune
responses and, consequently, produced damage to humoral mechanisms in humans. Examination
of 31 manufacturing workers who directly handled the organophosphoric pesticide chlorfenvinphos
(and other compounds) for 19–53 years revealed significantly lowered NBT-dye reduction in
both stimulated and non-stimulated cells, and a decreased percentage of phagocytic cells
(P<0.001, 0.05, and 0.002, respectively) in pesticide workers occupationally exposed to an
estimated average ambient chlorfenvinphos concentration of 0.21 mg/m^3. These analyses
parameters of the NBT test showed a positive linear correlation with the degree of
acetylcholinesterase activity reduction. The exposure time had no effect on NBT reduction test

parameters, but there was a negative linear correlation with the phagocytic index of the NBT test
(r = -0.4879, P<0.01). A significant decrease of the spontaneous E rosette formation (not
influenced by exposure time) was found in the blood of the exposed workers (early E rosettes,
52%; late E rosettes, 57%), as compared to controls (early E rosettes, 57%; late E rosettes, 63%).
No correlation was found between the spontaneous E rosette formation and acetylcholinesterase
activity. No significant differences were found in number of white blood cells, mainly neutrophils, in
the two examined subgroups, but the absolute lymphocyte count in the peripheral blood of the
exposed subjects was lower when compared to controls (1,941.9 versus 2,380 cells/mm^3, P<0.05).
The authors of this study concluded that depressed NBT-dye reduction and diminished
spontaneous E rosette formation may be regarded as a probable mode of action of
organophosphoric chemicals on metabolic and membrane damage to human cells.
Acetylcholinesterase activity, which showed a time-independent positive linear relationship to
lowered NBT-dye reduction in the subjects, was above 2 µmol in 17 of the subjects (with an
average age of 38.5 years). Eighteen (58.1%) of the subjects examined showed symptoms of
chronic bronchitis; seven (23.3%) subjects in the control group also had signs indicating previous
(anamestic) chronic bronchitis. It is generally understood that chronic bronchitis stems from
changes in humoral rather than cellular immune response. About half of the subjects were
smokers. The maximal estimated airborne concentrations of substances in the workplace were:
0.654 mg/m^3 (formothion), 0.483 mg/m^3 (sumithion), trace (DDVP), 0.21 mg/m^3 (chlorfenvinphos),
and 1.09 mg/m^3 (malathion) (Wysocki et al. 1987). The data from this study are not reliable for
evaluating the inhalation toxicity of chlorfenvinphos because the workers were also concurrently
exposed to greater concentrations of other known immunotoxic substances.

No studies were located regarding immunological and lymphoreticular effects in animals after
acute-, intermediate-, or chronic-duration inhalation exposure to chlorfenvinphos.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after acute- or intermediate-
duration inhalation exposure to chlorfenvinphos. The single study that reported
neurological effects in humans from inhalation exposure to chlorfenvinphos involved occupational
exposure. A group of nine gardeners (pesticide mixers) who worked with the organo-
phosphates (dimethoate, formothion, isofenphos and occasionally chlorfenvinphos) for an
unspecified duration complained of headaches. The gardeners had a mean difference (before
and after exposure) of 0.56 nmol/mL for acetylcholinesterase and 2.67 nmol/mL for butyryl

cholinesterase. Since the symptoms could also result from exposure to the other organophosphates (dimethoate, formothion, isofenphos) to which the workers were also exposed, the role of chlorfenvinphos exposure in this incident is not certain. In addition, no data were given on air concentrations of the organophosphate pesticides (Kolmodin-Hedman and Eriksson 1987).

No studies were located regarding neurological effects in animals after intermediate- or chronic-duration inhalation exposure to chlorfenvinphos. Acute exposure of rats to aerosols of chlorfenvinphos produced neurological signs indicative of cholinergic response stemming from inhibition of acetylcholinesterase activity. Surviving adult male Fischer 344 rats (27 of 60) exposed to the micron-sized (>1 µm) or submicron-sized (<1 µm) chlorfenvinphos aerosols for 4 hours (83, 130, 144, 236, 254, 322, 471, 623, 1,019, or 1,065 mg/m^3) exhibited cholinergic signs: salivation, urination, exophthalmos, twitches, and tremors, at $83 mg/m^3. The inhalation experiments were conducted using a nose-only inhalation chamber. (To examine the toxicological significance of swallowed chlorfenvinphos, a drain cannula was placed in the esophagus under pentobarbital sodium anesthesia.) Toxic signs were not assessed in detail during the exposure because the rats were in the animal holder. There were no differences in toxic signs between the micron-sized and the submicron-sized aerosols (Takahashi et al. 1994).

All LOAEL values for neurological effects in each reliable study for each species and duration category are shown in Table 2-1 and plotted in Figure 2-1.

No studies were located regarding the following health effects in humans or animals after acute-, intermediate-, or chronic-duration inhalation exposure to chlorfenvinphos:

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Other genotoxicity studies for chlorfenvinphos are described in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals following inhalation exposure to chlorfenvinphos.

2.2.2 Oral Exposure

2.2.2.1 Death

There are no reports of deaths in humans exposed by intermediate- or chronic-duration ingestion of chlorfenvinphos. A 16-month-old child who accidentally drank an unspecified amount of chlorfenvinphos, used for flea treatment in the home, died despite treatment in a hospital (Felthous 1978).

Chlorfenvinphos is extremely toxic to rodents and dogs by the oral route in acute doses. The oral LD_{50} values for rats, rabbits, and dogs have been estimated to be 9.7, 300, 50.5 mg/kg, respectively (Ambrose et al. 1970). An acute oral LD_{50} of 23 mg/kg was calculated from the mortality data of an unspecified number of male Wistar rats that were given varying doses of chlorfenvinphos in olive oil (Hutson and Logan 1986). Similarly, the acute oral LD_{50} of chlorfenvinphos in male rats as a single dose in olive oil was estimated to be 15.4 mg/kg. Animals that died from the effects of chlorfenvinphos did so within 12 hours of dosing; no further deaths were noted up to 72 hours after dosing. The chlorfenvinphos LD_{50} value for rats pretreated with dieldrin (0.2 mg/kg) was estimated to be 157 mg/kg; thus, dieldrin pretreatment induced a 10-fold protective effect against the acute toxicity of the organophosphate (Hutson and Wright 1980). After prolonged (105 minutes) exhibition of cholinergic signs, death occurred at the 20 mg/kg dose when Sprague-Dawley rats were orally administered single doses of 1.25, 5, or 20 mg/kg chlorfenvinphos (Takahashi et al. 1991). In another study with Wistar rats, the acute oral LD_{50} was significantly decreased in rats fed a protein-deficient (4.5%) diet during the 60 days of administration. The 60-day rat LD_{50} value was reduced from a control value of 23.0 mg/kg to 7.4 mg/kg in males and 25.5 mg/kg to 10.2 mg/kg in females (Puzynska 1984). Pretreatment of male Fischer 344 rats with 15 mg/kg chlorfenvinphos followed by a further 15 mg/kg dose significantly reduced the male oral LD_{50} for chlorfenvinphos from a positive control value of 34.3 mg/kg to 105.6 mg/kg; about 3.08-fold (P<0.05). Deaths occurred between 2 hours and 1 day after oral administration of chlorfenvinphos (Ikeda et al. 1992).

2. HEALTH EFFECTS

Chlorfenvinphos appears to be less toxic to mice than to rats. In a lethality study with BDF1 mice of both sexes, the oral LD_{50} and maximum tolerated dose (MTD) for chlorfenvinphos (suspended in methylcellulose) were estimated to be 148 mg/kg and 109 mg/kg, respectively. The mice were evaluated 5 days after intragastric administration of the chlorfenvinphos doses (Kowalczyk-Bronisz et al. 1992). A mouse acute oral LD_{50} of 100–200 mg/kg for chlorfenvinphos was cited from an earlier study in which male CFI mice were used (Hutson and Logan 1986).

A rabbit acute oral LD_{50} of >500–1,000 mg/kg for chlorfenvinphos was cited from an earlier study in which male New Zealand White rabbits were used (Hutson and Logan 1986).

A dog acute oral LD_{50} of >5,000 mg/kg for chlorfenvinphos was cited from an earlier study in which female Beagle dogs were used (Hutson and Logan 1986).

In prolonged exposures, no significant effect on mortality and survival was reported for rats and dogs given chlorfenvinphos in the diet at doses as high as 90 mg/kg/day for 12 weeks or 24 mg/kg/day for 104 weeks (Ambrose et al. 1970).

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

2.2.2.2 Systemic Effects

No studies were located regarding the hematological, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or other systemic effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorfenvinphos. Existing human data on the respiratory and neurological effects are limited to acute-duration exposures. No studies were located regarding ocular effects in animals following acute-, intermediate-, or chronic-duration oral exposure to chlorfenvinphos.

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

Respiratory Effects.   No human studies were located that reported direct effects on the respiratory system following oral exposure to chlorfenvinphos. Respiratory effects in humans following accidental

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	once (GO)				9.7 M (LD$_{50}$)	Ambrose et al. 1970
2	Rat (Wistar)	once (GO)				23 M (LD$_{50}$)	Hutson and Logan 1986
3	Rat (Carworth Farm E)	once (GO)				15.4 M (LD$_{50}$)	Hutson and Wright 1980
4	Rat (Fischer- 344)	once (GO)				34.3 M (LD$_{50}$)	Ikeda et al. 1992
5	Rat (Sprague- Dawley)	once (NS)				20 (100% mortality)	Takahashi et al. 1991
6	Mouse (BDF1)	once (GO)				148 (LD$_{50}$) 109 (MTD)	Kowalczyk- Bronisz et al. 1992
7	Dog (Mongrel)	once (GO)				50.5 (LD$_{50}$)	Ambrose et al. 1970
8	Rabbit (NS)	once (GO)				300 M (LD$_{50}$)	Ambrose et al. 1970

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

Le

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic							
9	Rat (Wistar)	10 d ad libitum (F)	Bd Wt	2.4 F			Barna and Simon 1973
			Metabolic		2.4 F (30% increased gastrointestinal absorption of glucose; 32% decreased gastrointestinal absorption of Na+)		
10	Rat (Fischer- 344)	once (GO)	Hepatic		15M (30% increased P-450 activity; 40% increased aminopyrine-N-demethylase activity; 27% increased aniline hydroxylase activity)		Ikeda et al. 1991
11	Rat (Wistar)	once (GO)	Endocr		6.15M (>300% elevation of plasma corticosteroids)		Osicka-Koprowska et al. 1984
12	Rat (Wistar)	once (GO)	Hepatic		30M (51% increase in serum sorbitol dehydrogenase; 37% to 109% increase in liver aromatic aminotransferase activity) 30F (105% increase in serum sorbitol dehydrogenase; 32% decrease in serum glucose-6-phosphate isomerase)		Puzynska 1984

foo

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CHLORFENVINPHOS

2. HEALTH EFFECTS

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
13	Rat (Wistar)	10 d *ad libitum* (F)			2.4 [b] F (52% inhibition of plasma cholinesterase activity; 30% inhibition of erythrocyte activity)		Barna and Simon 1973
14	Rat (Wistar)	once (GO)			13 M (20% decrease in the noradrenaline level)		Brzezinski 1978
15	Rat (Fischer- 344)	once (GO)				30 M (salivation, fasciculation, lacrimation, tremors, irregular respiration, and prostration)	Ikeda et al. 1992
16	Rat (Wistar)	once (GO)			6.2 M (10-30% decrease in brain and blood cholinesterase activity)		Osicka-Koprowska et al. 1984
17	Rat (Wistar)	once (GO)		1 M	2 M (38% decrease in brain cholinesterase activity)		Osumi et al. 1975

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
18	Rat (Wistar)	once (GO)			30 M (87% inhibition of serum acetylcholinesterase activity; 58% inhibition of brain acetylcholin-esterase activity; 20% increase in brain aromatic amino-transferase activity) 30 F (93% inhibition of serum acetylcholinesterase activity; 39% inhibition of brain acetylcholinesterase activity; 30% to 42% increase in brain aromatic amino-transferase activity; 32% elevation of brain glucosephosphate isomerase)		Puzynska 1984
19	Rat (Sprague-Dawley)	once (NS)		1.25		5 M (>90% reduction of erythrocyte cholinesterase activity; fasciculations, twitches, convulsions, chromodacryorrhea, exophthalmos, gasping, lacrimation, prostration, salivation, Straub tail reflex, urination)	Takahashi et al. 1991

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Systemic							
20	Rat (Wistar)	12 wk ad libitum (F)	Resp	90 M			Ambrose et al. 1970
			Cardio	90 M			
			Gastro	90 M			
			Hepatic	90 M			
			Renal	0.9 M	2.7 M (significant reduction of relative kidney weight)		
				1 F	3 F (significant reduction of relative kidney weight)		
			Endocr	90 M			
			Dermal	90 M			
21	Rat (Wistar)	30 d ad libitum (F)	Bd Wt	0.8 F			Barna and Simon 1973
			Metabolic		0.8 F (12% increased gastrointestinal absorption of glucose; 23% decreased gastrointestinal absorption of Na⁺)		
22	Dog (Mongrel)	12 wk ad libitum (F)	Resp	10 M			Ambrose et al. 1970
			Cardio	10 M			
			Gastro	10 M			
			Musc/skel	10 M			
			Hepatic	10 M			
			Renal	10 M			
			Endocr	10 M			
			Bd Wt	10 M			
			Other	10 M			

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference
					Less Serious	Serious	

Immunological/Lymphoreticular

| 23 | Mouse (C57BL/ 6N) | 90 d 1 x/d (GO) | | 1.5 | 1.5[c] (190% increase of spleen endogenous colonies; 162% increase of spleen exogenous colonies; 50% reduction in thymus weight) 3 (15% decrease in plaque-forming cells; 25% reduction in EA rosettes-forming cells) | | Kowalczyk-Bronisz et al. 1992 |
| 24 | Rabbit (NS) | 90 d 1 x/d (GO) | | | 10 (16% elevation of serum hemagglutinin; 66% elevation of hemolysin activity; increased antibody production) | | Roszkowski 1978 |

Neurological

25	Rat (Wistar)	12 wk ad libitum (F)		2.7 3	9M (significant depression of plasma and erythrocyte cholinesterase activity) 10F (significant depression of plasma and erythrocyte cholinesterase activity)		Ambrose et al. 1970
26	Rat (Sprague- Dawley)	3-6 mo (F)			10.5 (38% inhibition of whole blood acetylcholinesterase)		Maxwell and LeQuesne 1982
27	Rat (Sprague- Dawley)	1 yr (F)			10.5 (abnormal response to muscle stimuli)		Maxwell and LeQuesne 1982

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

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference |
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
28	Rat (Sprague-Dawley)	3 mo (F)			10.5 (abnormal response to muscle stimuli)		Maxwell and LeQuesne 1982
Reproductive							
29	Rat (Wistar)	3 gen ad libitum (F)				3 F (50% decrease in fertility in F/2 generation)	Ambrose et al. 1970
Developmental							
30	Rat (Wistar)	12 wk ad libitum (F)		2.7	9 M (significant depression of growth)		Ambrose et al. 1970
				3	10 F (significant depression of growth)		
31	Rat (Wistar)	3 gen ad libitum (F)				10 (66% decrease in pup viability; 46% decrease in lactation index)	Ambrose et al. 1970

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Systemic							
32	Rat (Wistar)	104 wk *ad libitum* (F)	Resp	21 M			Ambrose et al. 1970
			Cardio	21 M			
			Gastro	21 M			
			Hemato	21 M			
			Musc/skel	21 M			
			Hepatic	2.1	7 M (significant increase in relative liver weight)		
			Renal	21 M			
			Endocr	21 M			
			Dermal	21 M			
			Bd Wt	2.4	8 F (significant decrease in body weight gain)		
33	Dog (Beagle)	104 wk *ad libitum* (F)	Cardio	10 M 50 F			Ambrose et al. 1970
			Hemato	10 M 50 F			
			Hepatic	10 M 50 F			
			Renal	10 M 50 F			
			Endocr	10 M 50 F			
			Bd Wt	10 M 50 F			

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

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
34	Rat (Wistar)	104 wk *ad libitum* (F)			0.7 [d] M (45% inhibition of plasma cholinesterase activity; 33% inhibition of erythrocyte cholinesterase activity) 0.8 F (48% inhibition of plasma cholinesterase activity; 20% inhibition of erythrocyte cholinesterase activity)		Ambrose et al. 1970
35	Dog (Beagle)	104 wk *ad libitum* (F)		2 10	10 M (36% inhibition of erythrocyte cholinesterase) 50 F (36% inhibition of erythrocyte cholinesterase)		Ambrose et al. 1970

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

| Key to[a] figure | Species/ (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference |
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Reproductive						
36	Rat (Wistar)	104 wk ad libitum (F)		21 M			Ambrose et al. 1970

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

[b]Used to derive an acute oral minimal risk level (MRL) of 0.002 mg/kg/day. Dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

[c]Used to derive an intermediate oral MRL of 0.002 mg/kg/day. Dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

[d]Used to derive a chronic oral MRL of 0.0007 mg/kg/day. Dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; d = day(s); EA = erythrocyte acetylcholinesterase; Endocr = endocrine; F = female; (GO) = gavage, oil; gen = generation; Hemato = hematological; Ld = lactation day(s); LD$_{50}$ = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; x = time(s); yr = year(s)

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

Acute (≤14 days)

Systemic

(mg/kg/day)

Death

Hepatic

Endocrine

Body Weight

Metabolic

Neurological

1000

100

10

1

0.1

0.01

0.001

0.0001

8h

6m

7d

2r
3r
4r
5r

1r

12r
10r

11r

9r   9r

13r

14r

15r

16r

17r

17r

18r

19r

19r

Key

r rat	■ LD$_{50}$ (animals)	¦ Minimal risk level
m mouse	● LOAEL for serious effects (animals)	for effects other
h rabbit	◑ LOAEL for less serious effects (animals)	∪ than cancer
d dog	○ NOAEL (animals)	The number next to each point corresponds to entries in Table 2-2.

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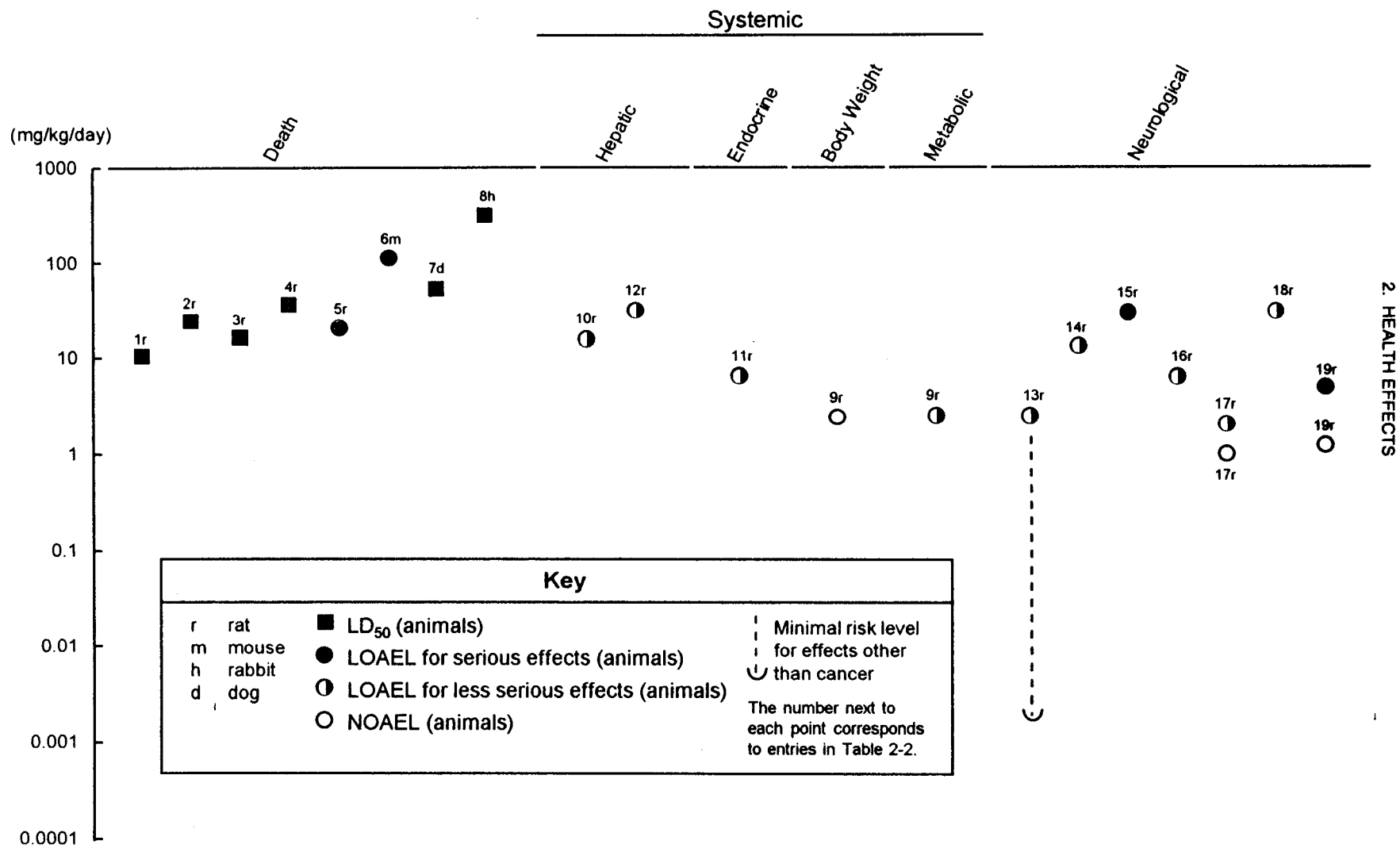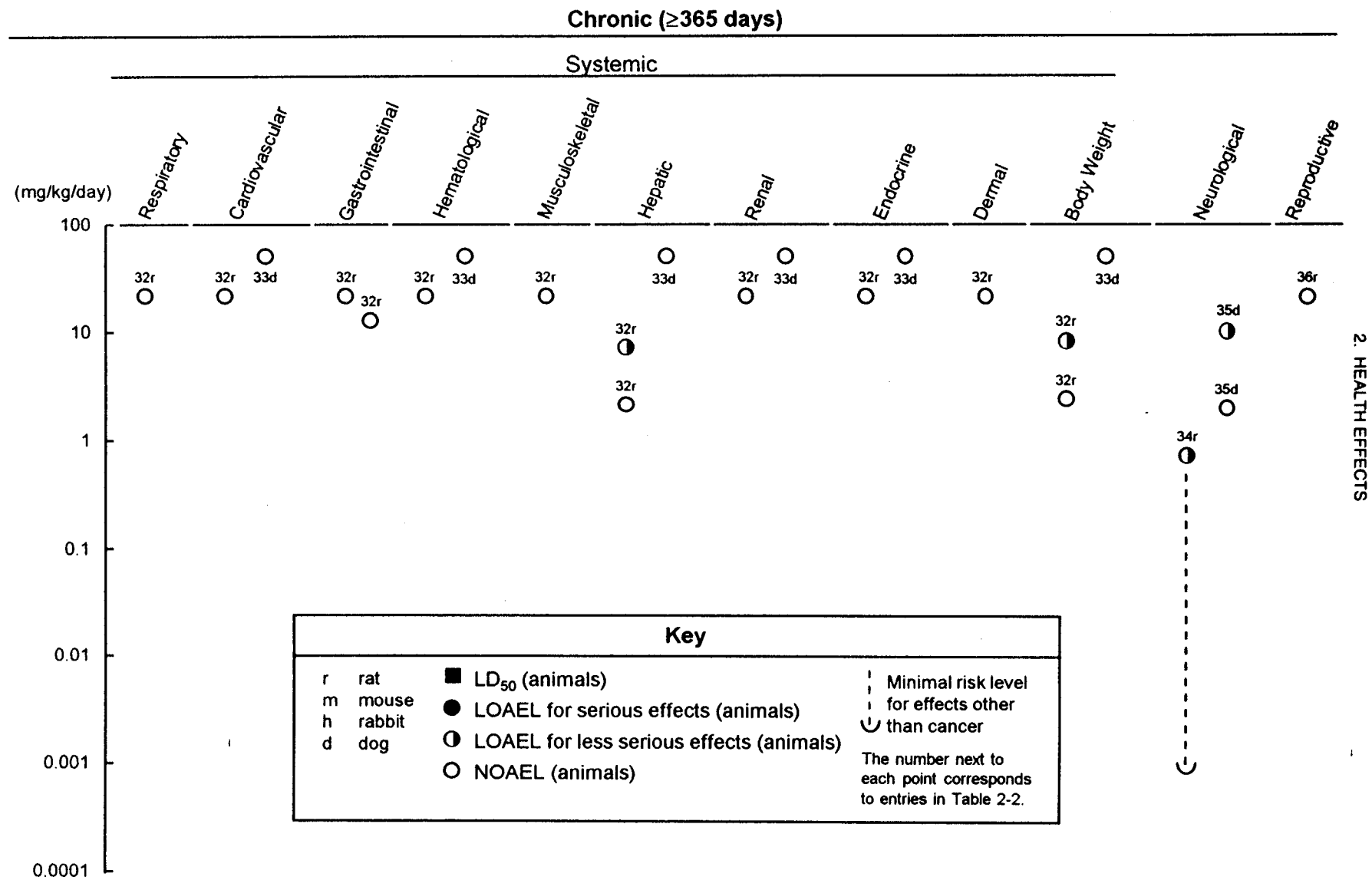
Intermediate (15-364 days)

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

Chronic (≥365 days)

ingestion of a mange-mite medication containing organic phosphate or intentional ingestion of the preparation Enolofos®, which contains 50% chlorfenvinphos, in suicide attempts reported in two clinical reports stemmed from central cholinergic disturbances (Cupp et al. 1975; Pach et al. 1987).

In animal studies, no effects on the respiratory system were noted in rats and dogs orally administered chlorfenvinphos at doses as high as 100 mg/kg/day (rats) or 50 mg/kg/day (dogs) for 12 weeks; or in rats at doses as high as 24 mg/kg/day for 104 weeks (Ambrose et al. 1970).

Cardiovascular Effects.   Evidence from animal studies indicates that chlorfenvinphos is not directly toxic to the cardiovascular system but may modulate the function of the cardiovascular system via its effect on the central nervous system. Relative heart-to-body weight ratios of weanling albino (Wistar) rats were not significantly altered when administered daily chlorfenvinphos doses of 0.27, 0.9, 2.7, 9, or 90 mg/kg/day (males): 0.3, 1, 3, 10, or 100 mg/kg/day (females) in the diet for 12 weeks. Similarly, no effects on relative heart-to-body weight ratios were reported for Wistar rats given chlorfenvinphos at doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females) in the diet for 104 weeks in another part of the same study (Ambrose et al. 1970). However, cardiovascular function was not assessed in these studies. No gross or microscopic histopathology in heart tissues or changes in relative heart weights were evident in mongrel dogs administered daily chlorfenvinphos doses of 0.01, 0.1, 1, or 10 mg/kg/day (males) or 0.05, 0.5, 5, or 50 mg/kg/day (females) for 12 weeks (Ambrose et al. 1970). However, cardiovascular function was not assessed in this study. Similarly, no effects on heart-to-body weight ratios were reported for Beagle dogs given chlorfenvinphos at doses of 0.3, 2, or 10 mg/kg/day (males), or 1.5, 10, 50 mg/kg/day (females) in the diet for 104 weeks in another part of the same study (Ambrose et al. 1970).

A study concluded that the alteration of brain and liver activities of the aromatic amino acid transferases may be due to the inhibitory effect of chlorfenvinphos on noradrenaline (norepinephrine) activity (Puzynska 1984). In other studies, chlorfenvinphos was shown to independently inhibit noradrenaline (norepinephrine) activity *in vivo* in rats rapidly (3 hours) at doses as low as 4 mg/kg (Brzezinski 1978; Osumi et al. 1975). On this basis, it has been postulated that chlorfenvinphos may also act via central noradrenergic mechanisms, disturbing the dynamic equilibrium between the rate of formation and utilization of noradrenaline (norepinephrine). It was postulated that this action via central noradrenergic mechanisms by chlorfenvinphos may be responsible for the changes in blood pressure observed in other studies after chlorfenvinphos intoxication (Brzezinski 1978).

Gastrointestinal Effects.   No gross or microscopic histopathology was evident in the gastrointestinal tract of rats and dogs given oral doses of up to 100 mg/kg/day (female rats) or 50 mg/kg/day (female Beagle dogs) chlorfenvinphos for 12 weeks (Ambrose et al. 1970). Similarly, no gross or microscopic histopathology was evident in the stomach, or small and large intestine of weanling albino (Wistar) rats of both sexes chronically (104 weeks) given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females) (Ambrose et al. 1970).

Hematological Effects.   Information on the hematological effects from oral exposure to chlorfenvinphos is limited. Investigations conducted to evaluate the serological effects of chlorfenvinphos on 4 groups of rabbits of both sexes at a doses of 10 mg/kg for 90 days found significant increases of hemolysin and hemagglutinin serum titer, as compared to controls. Hemagglutinin and hemagglutinin IgG titer were increased by 16 and 18%, respectively, while hemolysin and hemolysin IgG titer were elevated by 66 and 102%, respectively (Roszkowski 1978). In a 104-week oral study in Beagle dogs, no effects were reported on monitored hematological parameters (hemoglobin, hematocrit, total/differential leucocyte counts) at doses of 10 mg/kg/day for male dogs and 50 mg/kg/day for female dogs (Ambrose et al. 1970). Similarly, no effects were seen on monitored hematological parameters (hemoglobin, hematocrit, total/differential leucocyte counts) in rats orally administered chlorfenvinphos (21 mg/kg/day, males; 24 mg/kg/day, females) for 104 weeks (Ambrose et al. 1970).

Musculoskeletal.   In animal studies, no gross or microscopic histopathology changes in the musculoskeletal system were observed in dogs orally administered chlorfenvinphos at doses as high as 50 mg/kg/day (females) for 12 weeks, or in rats at doses as high as 24 mg/kg/day (females) for 104 weeks (Ambrose et al. 1970).

Hepatic Effects.   The limited information on the hepatic effects of chlorfenvinphos indicates that the substance is not significantly hepatotoxic by the oral route in acute- or intermediate-duration exposure. No changes in liver weight (relative to body weight) were reported in Fischer 344 rats given a single oral chlorfenvinphos dose of 15 mg/kg. However, P-450 activity was increased by 30%. Aminopyrine-*N*-demethylase and aniline hydroxylase activities were also increased by 40 and 27%, respectively (Ikeda et al. 1991). Mature Wistar rats of both sexes were kept on diets containing 4.5% of casein (low-protein diet), 26% of casein (optimal-protein diet), or standard (Murigran) diet and 30 mg/kg/day of chlorfenvinphos for 30 days to evaluate the effects of oral chlorfenvinphos exposure on serum activity of sorbitol dehydrogenase (SDH), and on brain and liver activities of the aromatic amino acids transferases L-phenylalanine

aminotransferase (Phen AT), L-tyrosine aminotransferase (Tyr AT), and L-tryptophan aminotransferase (Try AT). Both male and female rats exhibited disturbances in the activities of these enzymes. Chlorfenvinphos significantly decreased the activities of Phen AT (females = 41%, P<0.01), Tyr AT (females = 30, P<0.01), and Try AT (males = 20%, females = 42%, P<0.01) in the brain of the rats. Concomitantly, chlorfenvinphos significantly increased the activities of Phen AT (males = 37%, females = 54%, P<0.01), Tyr AT (males = 75, female = 150%, P<0.001)), and Try AT (males = 109%, females = 62%, P<0.001) in the liver of the rats, and developed a rise in the activity of sorbitol dehydrogenase (SDH) in serum (4.5% protein diet, males = NS, females = 94%; standard diet, males = 51%, females = 105%). There was also a 32% decrease in serum glucose-6-phosphate isomerase in females. In general, these changes were more pronounced in female rats fed standard Murigran diet. However, no changes in protein levels were reported in the study (Puzynska 1984).

In other animal studies, no gross or microscopic histopathology in liver tissues was evident in weanling albino (Wistar) rats administered daily chlorfenvinphos doses of 0.27, 0.9, 2.7, 9, or 90 mg/kg/day (males) or 0.3, 1, 3, 10, or 100 mg/kg/day (females) in the diet for 12 weeks (Ambrose et al. 1970). In a chronic study (104 weeks) in which this strain of rats (both sexes) was given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females), increased relative liver weights were observed in males at the 7 mg/kg/day dose level. No gross or microscopic histopathology in the liver tissues examined or changes in relative liver weights were reported at any dose level (Ambrose et al. 1970). Hepatic function was not assessed in this study.

No gross or microscopic liver histopathology or changes in relative liver weights were evident in mongrel dogs administered daily chlorfenvinphos doses of 0.01, 0.1, 1, or 10 mg/kg/day (males) or 0.05, 0.5, 5, or 50 mg/kg/day (females) for 12 weeks (Ambrose et al. 1970). Similarly, no gross or microscopic liver histopathology or significant changes in relative kidney weights were evident in Beagle dogs (2/sex) fed daily dietary chlorfenvinphos doses of 0.3, 2, or 10 mg/kg/day (males), or 1.5, 10, or 50 mg/kg/day (females) for 104 weeks. No adverse effects on liver function as indicated by alterations in serum bromosulfalein (BSP), serum glutamic oxaloacetic transaminase (SGOT), and serum alkaline phosphatase (SAP) or in blood urea nitrogen (BUN) levels were reported for the test animals (Ambrose et al. 1970).

Renal Effects.   The relative kidney weight ratios of weanling albino (Wistar) rats administered daily chlorfenvinphos doses of 0.27, 0.9, 2.7, 9, or 90 mg/kg/day (males), or 0.3, 1, 3, 10, or 100 mg/kg/day (females) in the diet for 12 weeks were significantly and irreversibly decreased at

the 2.7 mg/kg/day (males) and 3 mg/kg/day (females) dose levels (Ambrose et al. 1970). However, no quantitative data on the reduction of relative kidney weight were provided in this study. No gross or microscopic histopathology in the kidney and urinary bladder tissues examined or changes in relative kidney weights were evident in Wistar rats of both sexes given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females) in a chronic study (104 weeks) (Ambrose et al. 1970). Renal function was not assessed in either study.

No gross or microscopic histopathology in kidney tissues or changes in relative kidney weights were evident in mongrel dogs administered daily chlorfenvinphos doses of 0.01, 0.1, 1, or 10 mg/kg/day (males) or 0.05, 0.5, 5, or 50 mg/kg/day (females) for 12 weeks (Ambrose et al. 1970). Similarly, no gross or microscopic renal histopathology or significant changes in relative kidney weights were evident in Beagle dogs fed daily dietary chlorfenvinphos doses of 0.3, 2, or 10 mg/kg/day (males), or 1.5, 10, or 50 mg/kg/day (females) for 104 weeks (Ambrose et al. 1970). However, renal function was not assessed in these studies.

Endocrine Effects. A significant increase (>300%) in plasma corticosterone was observed at 1 and 3 hours and in plasma aldosterone from 1 to 6 hours after treatment of male Wistar rats with a single chlorfenvinphos dose of 6.15 mg/kg (50% LD_{50}) by stomach tube. Maximal increase in plasma corticosteroid levels occurred within 1 hour, while the brain cholinesterase activity was only slightly inhibited at that time. The authors surmised that changes in plasma corticosteroids are not related to the decrease of cholinesterase activity in the brain (Osicka-Koprowska et al. 1984). The toxicological significance of these findings is unknown.

No gross or microscopic histopathology was evident in endocrine organs (pancreas, thyroid, adrenal, pituitary) of weanling albino (Wistar) rats or Beagle dogs given oral doses of up to 100 mg/kg/day (female rats) or 50 mg/kg/day (female Beagle dogs) chlorfenvinphos for 12 weeks (Ambrose et al. 1970). Similarly, no gross or microscopic histopathology was evident in endocrine organs (pancreas, thyroid, adrenal, pituitary) of weanling albino (Wistar) rats of both sexes chronically (104 weeks) given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females) (Ambrose et al. 1970).

Dermal Effects. No adverse changes were observed in the skin of weanling albino (Wistar) rats of both sexes given oral doses of up to 100 mg/kg/day (female rats) chlorfenvinphos for 12 weeks (Ambrose et al. 1970). Similarly, no adverse changes were observed in the skin of

weanling albino (Wistar) rats of both sexes chronically (104 weeks) given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females) (Ambrose et al. 1970).

Body Weight Effects.   A significant but slightly reversible depression on growth was observed at 9 mg/kg/day (males) or 10 mg/kg/day (females) in weanling albino (Wistar) rats. The rats were administered daily chlorfenvinphos doses of 0.27, 0.9, 2.7, 9, or 90 mg/kg/day (males) or 0.3, 1, 3, 10, or 100 mg/kg/day (females) in the diet for 12 weeks (Ambrose et al. 1970). In an accompanying chronic study (104 weeks) in which this strain of rats (both sexes) was given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females), no consistent difference in body weight gains in males was evident at any dose level tested, as compared to undosed controls. However, chlorfenvinphos exposure caused a significant decrease in body weight gain in females in the 8 and 24 mg/kg/day dose groups from the 26th week until near the end of the study. The decreased body weight gain became statistically insignificant at the end of the study (Ambrose et al. 1970). In another rat study, body weight gains in adult female albino (Wistar) rats were unaffected following orally administered Birlane® (chlorfenvinphos) at a dose of 0 or 2.4 mg/kg/day in the diet for 10 days or 0 or 0.8 mg/kg/day in the diet for 30 days (Barna and Simon 1973).

Likewise, no significant effect on body weight was observed in mongrel dogs following dietary chlorfenvinphos doses of 0.01, 0.1, 1, or 10 mg/kg/day (males), or 0.05, 0.5, 5, or 50 mg/kg/day (females) for 12 weeks (Ambrose et al. 1970). In a chronic study (104 weeks) in which Beagle dogs were given daily dietary chlorfenvinphos doses of 0.3, 2, or 10 mg/kg/day (males), or 1.5, 10, or 50 mg/kg/day (females), no significant changes in body weight were evident at any dose level tested, as compared to undosed controls (Ambrose et al. 1970).

Metabolic Effects.   In animal studies, pairs of Carworth Farm E strain male rats orally administered a single [^{14}C]chlorfenvinphos dose of 2.5 or 13.3 mg/kg in olive oil (with or without prior monooxygenase induction with dieldrin) exhibited minimal changes in the metabolic profiles (Hutson and Wright 1980).

Other Systemic Effects.   No significant effect on food consumption was observed in weanling albino (Wistar) rats administered daily chlorfenvinphos doses of 0.27, 0.9, 2.7, 9, or 90 mg/kg/day (males) or 0.3, 1, 3, 10, or 100 mg/kg/day (females) in the diet for 12 weeks (Ambrose et al. 1970). In a chronic study (104 weeks) in which weanling albino (Wistar) rats of both sexes were given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females), no consistent

difference in food consumption was evident at any dose level tested, as compared to undosed controls (Ambrose et al. 1970). In dog studies, no significant effect on food consumption was observed in mongrel dogs given dietary chlorfenvinphos doses of 0.01, 0.1, 1, or 10 mg/kg/day (males) or 0.05, 0.5, 5, or 50 mg/kg/day (females) for 12 weeks (Ambrose et al. 1970). Similarly, no significant changes in food consumption were evident at any dose level tested in a chronic study (104 weeks) in which Beagle dogs were given daily dietary chlorfenvinphos doses of 0.3, 2, or 10 mg/kg/day (males) or 1.5, 10, or 50 mg/kg/day (females) (Ambrose et al. 1970).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding the immunological and lymphoreticular effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorfenvinphos.

The limited information on the immunological and lymphoreticular effects of chlorfenvinphos indicates that the substance is moderately immunotrophic to the rodent immune system in oral exposures. The gastrointestinal absorption of glucose was increased by 30% over control values in adult female albino (Wistar) rats orally administered Birlane® (chlorfenvinphos) at a dose of 0 or 2.4 mg/kg/day in the diet for 10 days. Similarly, gastrointestinal absorption of glucose was increased by 12% over control values following orally administered Birlane® (chlorfenvinphos) at a dose of 0 or 0.8 mg/kg/day in the diet of Wistar rats for 30 days. The changes in glucose and Na^+ absorption were not considered statistically significant (P>0.05) by the investigators (Barna and Simon 1973). It has been observed in other studies that an increased metabolic activity of neutrophils and monocytes during phagocytosis is accompanied by higher consumption of glucose and oxygen. Hydrogen peroxide is then derived from the pentose cycle, NAD-, and NADP-oxidase action (Kolanoski 1977 as cited in Wysocki et al. 1977). The relationship between increased gastrointestinal absorption of glucose and increased glucose utilization is not clear.

In an intermediate-duration dietary study with albino (Wistar) rats, there was a significant and irreversible reduction in relative spleen weight of female rats given $3 mg/kg/day chlorfenvinphos for 12 weeks. However, no gross or microscopic histopathology was e vident in the spleen and bone marrow tissues of the rats upon examination (Ambrose et al. 1970). In dogs, relative spleen weights were unaffected following dietary doses of 10 mg/kg/ day (males) or 50 mg/kg/day (females) to mongrel dogs for 12 weeks. In addition, no gross or microscopic histopathology was evident in the spleen and bone marrow tissues of the

dogs upon examination (Ambrose et al. 1970). No quantitative data on the reduction of relative
spleen weights were provided in these studies.

A study was undertaken to evaluate selected serological and cytoimmunological reactions in
rabbits subjected to a long-term poisoning with subtoxic oral doses (10 mg/kg in a soya oil solution
with a small amount of food) of chlorfenvinphos for 90 days (shortened chronic poisoning). Both
control group (soya oil) and treatment group rabbits were immunized with sheep red blood cells
6 days prior to ending the experiment. Chlorfenvinphos treatment significantly elevated serum
hemagglutinin level (16%) and hemolysin activity (66%, P<0.05) and increased the number of
nucleated lymphoid cells producing hemolytic antibody to sheep erythrocytes as compared to
controls (treated 906, P<0.05 and controls 618). Spleen cytomorphology changes, manifested
mainly as transformation of primary follicles into secondary ones with well developed germinal
centers, were also observed (Roszkowski 1978). After 90 days of oral intoxication of C57BL/6
mice and (C57BL/6 x DBA/2)F1 (BDF1/Iiw) hybrid mice (6–8-weeks-old) with chlorfenvinphos
(suspended in 1% methylcellulose solution), a dose-related decrease in number of hemolysin-
producing cells was observed. Plaque-forming cells (PFC) were 58% at the 6 mg/kg dose group
and 85% at the 3 mg/kg dose level, as compared to control values. Chlorfenvinphos treatment
also caused reduction in E rosettes-forming cell numbers by 30% at the 6 mg/kg dose level, 25%
at the 3 mg/kg dose level, and 45% at the 6 mg/kg dose level. Spleen colonies were stimulated as
evidenced by the increase of endogenous spleen colonies; and exogenous spleen colonies
(CFU-S) increased 190% at the 1.5 mg/kg dose level, 137% at the 6 mg/kg dose level, 162% at
1.5 mg/kg dose level, and 70% at the 6 mg/kg dose level, respectively. When the IgM PFC
number was tested 3 weeks later, after the exposure to chlorfenvinphos in the small dose
(1.5 mg/kg), an increase (about 40%) in plaque number was observed. There was a 50%
reduction in thymus weight at the 1.5 mg/kg dose level, as compared to controls, as well as
significant involution of the thymus. IgM levels returned to normal values, indicating the reversible
nature of the immunotrophic effect of chlorfenvinphos (Kowalczyk-Bronisz et al. 1992). The
LOAEL of 1.5 mg/kg/day, based on adverse immunologic/lymphoreticular effects in this study, was
used to derive an intermediate oral MRL of 0.002 mg/kg/day for chlorfenvinphos.

In a chronic-duration (104 weeks) dietary study in which weanling albino (Wistar) rats of both
sexes were given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males)
or 0.8, 2.4, 8, or 24 mg/kg/day (females), no histopathological changes in the spleen or bone
marrow were evident at any dose level tested, as compared to undosed controls. In addition, no
changes in absolute or relative spleen weights were reported (Ambrose et al. 1970). Likewise, no

histopathological changes in the spleen or bone marrow were evident in Beagle dogs given daily dietary chlorfenvinphos doses of 0.3, 2, or 10 mg/kg/day (males) or 1.5, 10, or 50 mg/kg/day (females) for 104 weeks. In addition, no changes in absolute or relative spleen weights were reported (Ambrose et al. 1970).

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

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following intermediate- or chronic-duration oral exposure to chlorfenvinphos. In humans, chlorfenvinphos inhibits cholinesterase activity in the central and peripheral nervous system when ingested in acute-duration exposures (Cupp et al. 1975; Pach et al. 1987). A 16-year-old white male mistakenly took a full swallow of a mange-mite medication (identified as Dermaton® which contains 25% organophosphate, like chlorfenvinphos, as an active ingredient) prescribed by a veterinarian for his dog. Approximately 90 minutes later, he was hospitalized with symptoms of abdominal cramps, nausea, vomiting, generalized weakness, cold dry skin, constricted pupils, fine generalized muscular twitching, and apprehension. On physical examination, his blood pressure was 152/102, pulse was 96 and irregular, respiration was 24, and rectal temperature was 94.2 EF. While in the emergency room, gastric lavage of 4 L was done and 1 mg of atropine given intravenously. On transfer to the intensive care unit, respiration had increased in rate and depth, skin was warm and slightly diaphoretic, muscle twitching had increased, and he complained of double vision. Emesis persisted. The patient developed hypothermia which lasted for 2 hours. Four and one-half hours after admission, the patient was listless and apathetic, but oriented. Blood analysis showed plasma and erythrocyte cholinesterase levels of 0.3 and 1.1 µmol/minute, respectively. Twenty-four hours later, plasma and erythrocyte cholinesterase levels were 0.8 and 12.7 µmol/minute, respectively. He was given 1 g of pralidoxime intravenously over a 15-minute period, repeated in 1 hour. Forty-eight hours after admission, signs of improvement were evident. The patient was discharged 5 days after admission without residual effects (Cupp et al. 1975). Another clinical report described anticholinesterase symptoms (unconsciousness, absence of tendon reflexes, 80% reduction of erythrocyte acetylcholinesterase activity, 100% reduction in plasma pseudocholinesterase activity, respiratory failure, bronchial tree hypersecretion) in a 29-year-old male patient hospitalized 3 hours after a suicide attempt during which he drank about 50 mL of the preparation 'Enolofos®, which contains 50% chlorfenvinphos (Pach et al. 1987).

The existing information on neurological effects in animals following acute-, intermediate-, and chronic-duration oral exposures to chlorfenvinphos indicates that the substance causes disruptions in the central and peripheral nervous system in rats manifested as cholinesterase inhibition (Barna and Simon 1973; Osicka-Koprowska et al. 1984; Takahashi et al. 1991) and interference with noradrenaline (norepinephrine) activity in central adrenergic mechanisms (Brzezinski 1978; Osumi et al. 1975). Inhibition of acetylcholinesterase activity results in accumulation of acetylcholine at muscarinic and nicotinic receptors leading to peripheral and central nervous system effects. These effects usually appear within a few minutes to a few hours after exposure depending on the extent of exposure. When chlorfenvinphos was evaluated for acute lethality in animals, death occurred within 12 hours in tested rats, rabbits, and dogs and was usually preceded by the characteristic signs of cholinergic response—salivation, lacrimation, muscle fasciculation, diarrhea, emesis, tremors, irregular respiration, and prostration (Ambrose et al. 1970, Ikeda et al. 1992).

In acute-duration studies, brain cholinesterase activity was strongly inhibited in male Fischer 344 rats (8 weeks old) that were orally treated with 30 mg/kg chlorfenvinphos or pretreated with 15 mg/kg for 24 hours before treatment with 30 mg/kg chlorfenvinphos. This was accompanied by clinical anticholinesterase symptoms which included salivation, fasciculation, lacrimation, tremors, irregular respiration, and prostration which resulted in deaths 1–24 hours after administration of the chlorfenvinphos doses. Although chlorfenvinphos pretreatment did not change the nature of these symptoms, it aggravated the inhibition of brain cholinesterase activity (Ikeda et al. 1992). Plasma and erythrocyte cholinesterase activities were inhibited by 52 and 30%, respectively, at the only tested Birlane® (chlorfenvinphos) dietary dose of 2.4 mg/kg/day administered to adult female albino (Wistar) rats for 10 days (Barna and Simon 1973). The LOAEL of 2.4 mg/kg/day from the 10-day dosing protocol of this study, based on adverse neurological effects in rats was used to derive an acute oral MRL of 0.002 mg/kg/day for chlorfenvinphos.

Brain and erythrocyte acetylcholinesterase, and plasma pseudocholinesterase activities were reduced by $90% and 50%, respectively, following acute oral treatment of male Sprague-Dawley rats with chlorfenvinphos. Rats administered chlorfenvinphos orally attained maximum inhibition of cholinesterase activity in less than two hours. The rats also exhibited cholinergic signs that included fasciculations, twitches, convulsions, chromodacryorrhea, exophthalmos, gasping, lacrimation, prostration, salivation, Straub tail reflex, and urination. The clinical signs lasted for 8 hours. No effects were observed at the 1.25 mg/kg dose level (Takahashi et al. 1994). Cholinesterase activity in the brain of male Wistar rats was unaffected 3 hours after oral administration of 1 mg/kg of chlorfenvinphos. However, at doses of 2 and 4 mg/kg, oral chlorfenvinphos produced marked decreases in the brain cholinesterase activity to 38 and 18% of

control (P<0.001), respectively. The maximum inhibition occurred 3 hours after administration, after which the cholinesterase activity elevated gradually. Activity in the brain decreased steadily with time and, at 72 hours, still remained 67% of control. Erythrocyte acetylcholinesterase activity also decreased after 4 mg/kg of chlorfenvinphos; the lowest level (20%, P<0.001) was attained 3 hours after treatment (Osumi et al. 1975).

Acute oral exposure to chlorfenvinphos was also associated with reversible sleep disturbance in male Wistar rats. Single oral chlorfenvinphos doses up to 1 mg/kg did not affect the awake-sleep cycle in the rats, but spontaneous electroencephalogram (EEG) showed a prominent arousal pattern and appearance of slow wave sleep and parasleep was markedly depressed in doses over 2 mg/kg. The duration of arousal pattern was proportional to the doses but, nonetheless, the awake-sleep cycle returned to control values on the second day; a rebound increase in parasleep occurred on the third day at doses over 4 mg/kg. Atropine at a dose of 2 mg/kg (administered to one rat 2 hours after chlorfenvinphos administration) was antidotal to the chlorfenvinphos-induced disturbance of EEG arousal pattern, depressing the EEG arousal pattern without affecting cholinesterase activity in the brain. As a positive control, physostigmine, a reversible cholinesterase inhibitor, in doses of 0.05 and 0.1 mg/kg, produced an increase in wakefulness during the first hour. Thereafter, the arousal pattern was reduced, and slow wave sleep and parasleep patterns increased, as compared with the control, 3–5 hours after the administration of chlorfenvinphos. According to these investigators, appearance of EEG arousal pattern after treatment with chlorfenvinphos is indicative of central cholinergic activation. A LOAEL of 2 mg/kg with a NOAEL of 1 mg/kg for 38% decrease in brain cholinesterase activity and reversible sleep disturbances was determined in this study (Osumi et al. 1975). This study was not used to calculate an acute oral MRL because it was deemed less appropriate because of the gavage (oral) route of administration. An oral feeding study is preferred for this purpose by ATSDR.

In intermediate-duration studies, plasma and erythrocyte cholinesterase activities were inhibited by 36 and 3%, respectively, at a chlorfenvinphos dose of 0.8 mg/kg/day following dietary administration of 0 or 0.8 mg/kg/day Birlane® (chlorfenvinphos) to adult female albino (Wistar) rats for 30 days (Barna and Simon 1973). However, the change in erythrocyte acetylcholinesterase activity was not considered significant and therefore, this study was not used to derive an intermediate MRL. Similarly, the change in plasma pseudocholinesterase was not used to derive an intermediate MRL because while the inhibition of plasma pseudocholinesterase may have some physiological significance, alteration in the levels of this enzyme is generally regarded more as a biomarker of exposure to organophosphate compounds than as an adverse neurological effect. In other intermediate rat studies, mature rats of both sexes kept on diets containing 4.5%

of casein (low-protein diet), 26% of casein (optimal-protein diet), or standard (Murigran) diet for
30 days exhibited depressed cholinesterase activities following oral exposure to chlorfenvinphos.
These alterations consisted of significant inhibition in pseudocholinesterase activity in the serum (4.5%
protein diet: males = 97%, females = 96%; standard diet: males = 87%, females = 93%) and brain
(4.5% protein diet: males = 83%, females = 87%; standard diet: males = 58%, females = 39%), with
more pronounced effects in the brain of female rats fed low-protein diets (87%). The activity of this
enzyme returned to normal values 14 days after dosing (Puzynska 1984). Blood and plasma
cholinesterase activity was depressed at $9 mg/kg/day (males) or $10 mg/kg/day (females), with a
NOAEL of 2.7 mg/kg/day (males) or 3 mg/kg/day (females) following dietary administration of
chlorfenvinphos doses of 0.27, 0.9, 2.7, 9, or 90 mg/kg/day (males), or 0.3, 1, 3, 10, or 100 mg/kg/day
(females) in the diet to weanling albino (Wistar) rats for 12 weeks. No gross or microscopic
histopathology was evident in the brain tissues examined (Ambrose et al. 1970). Similarly, plasma
cholinesterase activity was consistently depressed, while erythrocyte cholinesterase activity was
sporadically depressed in all dose groups in mongrel dogs administered daily chlorfenvinphos doses
of 0.01, 0.1, 1, or 10 mg/kg/day (males) or 0.05, 0.5, 5, or 50 mg/kg/day (females) in the diet for
12 weeks. No gross or microscopic histopathology was evident in the brain and spinal cord tissues
examined (Ambrose et al. 1970). Due to incomplete reporting of this study, it was not clear if there
was a NOAEL for the inhibition of erythrocyte cholinesterase activity. No quantitative data on the
depression of plasma or erythrocyte cholinesterase activity were provided in this study.

In another intermediate-duration study, whole blood cholinesterase activity in Sprague-Dawley rats
was markedly inhibited at 3 and 6 months of exposure following exposure to 10.5 mg/kg/day
chlorfenvinphos (0.9 and $0.6x10^{-6}$ mol/minute; control, 2.4 and $1.9x10^{-6}$ mol/minute, respectively,
P<0.001). After 3 and 6 months of exposure to chlorfenvinphos, plasma cholinesterase activity was
also markedly inhibited (0.4 and $0.4x10^{-6}$ mol/minute; control, 1.9 and $1.6x10^{-6}$ mol/minute,
respectively; P<0.001). After 3–6 months, all 36 Sprague-Dawley rats in this study had repetitive and
increasingly diminishing muscle fiber depolarization when given double stimuli. The greatest
reduction in peak depolarization occurred with an interval of 4 muscle action potential amplitude (ms)
and a large but slightly smaller reduction at 7 ms. These phases probably coincide with refractoriness
of some muscle fibers due either to repetitive activity (at 4 ms) or reflex activity (at 7 ms). Double and
repetitive stimulation at rates even as low as 0.5 Hz reduced or abolished the prolonged negative
potential and repetitive activity. These abnormalities became more marked with time, even on
constant dosing. Spike potentials were recorded between the direct response and reflex responses
with latency similar to the repetitive activity potential. These electrophysiological abnormalities may be
attributable to acetylcholinesterase inhibition at neuromuscular junctions (Maxwell and LeQuesne
1982).

2. HEALTH EFFECTS

In chronic-duration studies, chlorfenvinphos significantly inhibited both plasma and erythrocyte cholin-
esterase activities in a dose-dependent manner in weanling albino (Wistar) rats fed daily
chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day
(females) mg/kg/day in the diet for 104 weeks. Plasma and erythrocyte cholinesterase activities were
inhibited by 48% in females and 45% in males in the first week of treatment and by 20% in females
and 33% in males in the fourth week of treatment, respectively, at the lowest dose tested
(0.7 mg/kg/day for males and 0.8 mg/kg/day for females). No gross or microscopic histopathology
was evident in the brain tissue examined (Ambrose et al. 1970). The LOAEL of 0.7 mg/kg/day, based
on adverse neurological effects in rats in this study, was used to derive a chronic oral MRL of
0.0007 mg/kg/day for chlorfenvinphos.

Similarly, chlorfenvinphos significantly inhibited both plasma and erythrocyte cholinesterase activities
in Beagle dogs fed daily chlorfenvinphos doses of 0.3, 2, or 10 mg/kg/day (males), or 1.5, 10, or
50 mg/kg/day (females) in the diet (moist) for 104 weeks. Plasma cholinesterase activities were
significantly inhibited at all dietary levels through week 39 of the study; 49% inhibition at ambient air
concentrations of 0.3 mg/kg/day (males) and 1.5 mg/kg/day (females) groups. During the first
12 weeks, erythrocyte cholinesterase activity was significantly and consistently inhibited (36%) only in
the 10 mg/kg/day (males) and 50 mg/kg/day (females) dose groups. No gross or microscopic
histopathology was evident in the brain and spinal cord tissues examined (Ambrose et al. 1970).

Besides its cholinergic action, chlorfenvinphos may also act via central noradrenergic mechanisms in
rats by accelerating the noradrenaline (norepinephrine) turnover in the brain *in vivo*. Three hours after
oral administration of 4 mg/kg of chlorfenvinphos, the brain noradrenaline (norepinephrine) level of
male Wistar rats was reversibly decreased by 16% (Osumi et al. 1975). In another study with male
Wistar rats, 13 mg/kg of oral chlorfenvinphos decreased cerebral noradrenaline (norepinephrine) level
by 20% as compared to the control rats. Other rats that received oral chlorfenvinphos 30 minutes after
pretreatment with disulfiram injection (400 mg/kg intraperitoneally) as positive controls exhibited a 50%
decrease of cerebral noradrenaline (norepinephrine); the level was observed in time intervals of
1–3 hours, peaking at 89% decrease after 6 hours. Based on these observations, it was suggested
that chlorfenvinphos accelerates the rate of noradrenaline (norepinephrine) disappearance from the rat
brain *in vivo*. Thus, besides being a cholinergic agent, chlorfenvinphos may also act via central
noradrenergic mechanisms, disturbing the dynamic equilibrium between the rate of formation and
utilization of noradrenaline (norepinephrine). It was postulated that this action via central
noradrenergic mechanisms by chlorfenvinphos may be responsible for the changes in blood pressure
observed in other studies after chlorfenvinphos intoxication (Brzezinski 1978).

Sprague-Dawley rats fed chlorfenvinphos doses of 10.5 mg/kg/day for 1 year had repetitive and increasingly diminishing muscle fiber depolarization when given double stimuli. The greatest reduction in peak depolarization occurred with an interval of 4 muscle action potential amplitude (ms) and a large but slightly smaller reduction at 7 ms. These phases probably coincide with refractoriness of some muscle fibers due either to repetitive activity (at 4 ms) or reflex activity (at 7 ms). These electrophysiological abnormalities may be attributable to acetylcholinesterase inhibition at neuromuscular junctions (Maxwell and LeQuesne 1982).

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

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorfenvinphos.

No studies were located regarding reproductive effects in animals following acute-duration oral exposure to chlorfenvinphos. The limited information on the reproductive toxicity of chlorfenvinphos indicates that chlorfenvinphos may interfere with the reproductive competence of rats. In a 3-generation reproductive study, chlorfenvinphos induced adverse reproductive effects (decreased fertility and maternal body weight gain) at a LOAEL of 2.7 mg/kg/day in albino (Wistar) rats given chlorfenvinphos at a doses of 2.7, 9, or 27 mg/kg/day (males) or 3, 10, or 30 mg/kg/day (females) in the diet for 11 weeks. The chlorfenvinphos dosed rats were mated for 20 days to produce an F/1a generation and remated, 10 days after weaning of the F/1a pups, to produce an F/1b generation. Each generation was fed the chlorfenvinphos doses for 11 weeks before mating. The study reported decreased maternal body weights of 3, 5, and 11%, respectively, for F/0 parental generation animals fed 0, 3, or 10 mg/kg/day; 9, 2, and 19%, respectively, for F/1 parental generation animals fed 0, 3, or 10 mg/kg/day; and 14 and 10%, respectively, for F/2 parental generation animals fed 0 or 3 mg/kg/day chlorfenvinphos. The changes in maternal body weight gain were not considered significant. However, fertility (pregnancy/mating x 100) was decreased by 49% in the F/1b parents at the 10 mg/kg/day dose level. In the F/2b parents, fertility was decreased by 50% at the 3 mg/kg/day dose level and by 84% in the 10 mg/kg/day dose level. No gross or microscopic histopathology was evident in male and female gonads examined. No adverse effects on gestation were noted at any exposure levels (Ambrose et al. 1970).

In intermediate-duration studies, chlorfenvinphos had no effect on relative testes weight at any of the doses tested in weanling albino (Wistar) rats administered daily chlorfenvinphos doses of 90 mg/kg/day (males) or 100 mg/kg/day (females) in diet for 12 weeks. No gross or microscopic histopathology was evident in any of the gonads (Ambrose et al. 1970).

In chronic-duration studies, no gross or microscopic gonad histopathology in either sex or changes in the relative weights of the testes in males were reported in albino (Wistar) rats administered daily chlorfenvinphos doses of 21 mg/kg/day (males) or 24 mg/kg/day (females) in the diet for 104 weeks (Ambrose et al. 1970). Similarly, no gross or microscopic gonad histopathology in either sex or changes in the relative weights of the testes in males were reported in mongrel dogs administered daily chlorfenvinphos doses of 0.01, 0.1, 1, or 10 mg/kg/day (males) or 0.05, 0.5, 5, or 50 mg/kg/day (females) in the diet for 12 weeks (Ambrose et al. 1970). Reproductive function was not evaluated in these studies.

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

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorfenvinphos.

No studies were located regarding developmental effects in animals following acute-duration oral exposures in animals. Oral chlorfenvinphos interfered with development in intermediate- and chronic-duration exposures as well as multigenerational studies in animals. Weanling albino (Wistar) rats administered daily dietary doses of chlorfenvinphos (0.27, 0.9, 2.7, 9, or 90 mg/kg/day for males; 0.3, 1, 3, 10, or 100 mg/kg/day for females) for 12 weeks exhibited slightly reversible but significant depression of growth at doses of 9 mg/kg/day (males) or 10 mg/kg/day (females). No quantitative data on the depression of growth were provided in the study (Ambrose et al.1970). In a chronic feeding study (104 weeks) in which weanling albino (Wistar) rats were given chlorfenvinphos in the diet at doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females) for 104 weeks, chlorfenvinphos significantly decreased body weight gain of females at the 8 and 24 mg/kg/day ambient air concentrations from the 26th week till towards the end of the study. The decrease in body weight gain was not statistically significant at the end of the study. An increased relative liver weight was observed in males at the 7 mg/kg/day dose level, but no other signs of hepatopathology were

reported. No consistent differences in body weight gains in males, survival of the test animals, food consumption, or mortality were evident at any dose level tested, as compared to undosed controls. No gross or microscopic histopathology was evident in any of the tissues (heart, lungs, liver, kidney, urinary bladder, spleen, stomach, small and large intestine, skeletal muscle, skin, bone marrow, pancreas, thyroid, adrenal, pituitary) examined to indicate teratogenicity. No changes in organ-to-body weight were observed in the heart and kidney (Ambrose et al. 1970). Dietary exposure to chlorfenvinphos exposure caused decreases in viability and lactational indices in a 3-generation reproductive study with albino (Wistar) rats. In this study, the rats were given chlorfenvinphos in the diet at doses of 2.7, 9, or 27 mg/kg/day (males) or 3, 10, or 30 mg/kg/day (females) for 11 weeks. The chlorfenvinphos-dosed rats were mated for 20 days to produce an F/1a generation and remated 10 days after weaning of the F/1a pups to produce an F/1b generation. Each generation was fed the chlorfenvinphos doses for 11 weeks before mating. The pup viability index (pups surviving 5 days/pups born alive x 100) decreased by 66% for F/1b pups at a maternal dose of 10 mg/kg/day. No offspring in the 27 mg/kg/day (males) or 30 mg/kg/day (females) dose group survived beyond the F1 generation. The lactation index was also decreased by 46% in the F/1b offsprings at the 10 mg/kg/day dose level. No gross or microscopic histopathology was evident in any of the tissues examined. There were no gross signs of teratogenicity (Ambrose et al. 1970).

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

2.2.2.7 Genotoxic Effects

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

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals following oral exposure to chlorfenvinphos.

2. HEALTH EFFECTS

Figure 2-3. Proposed Mammalian Metabolic Pathway for Chlorfenvinphos
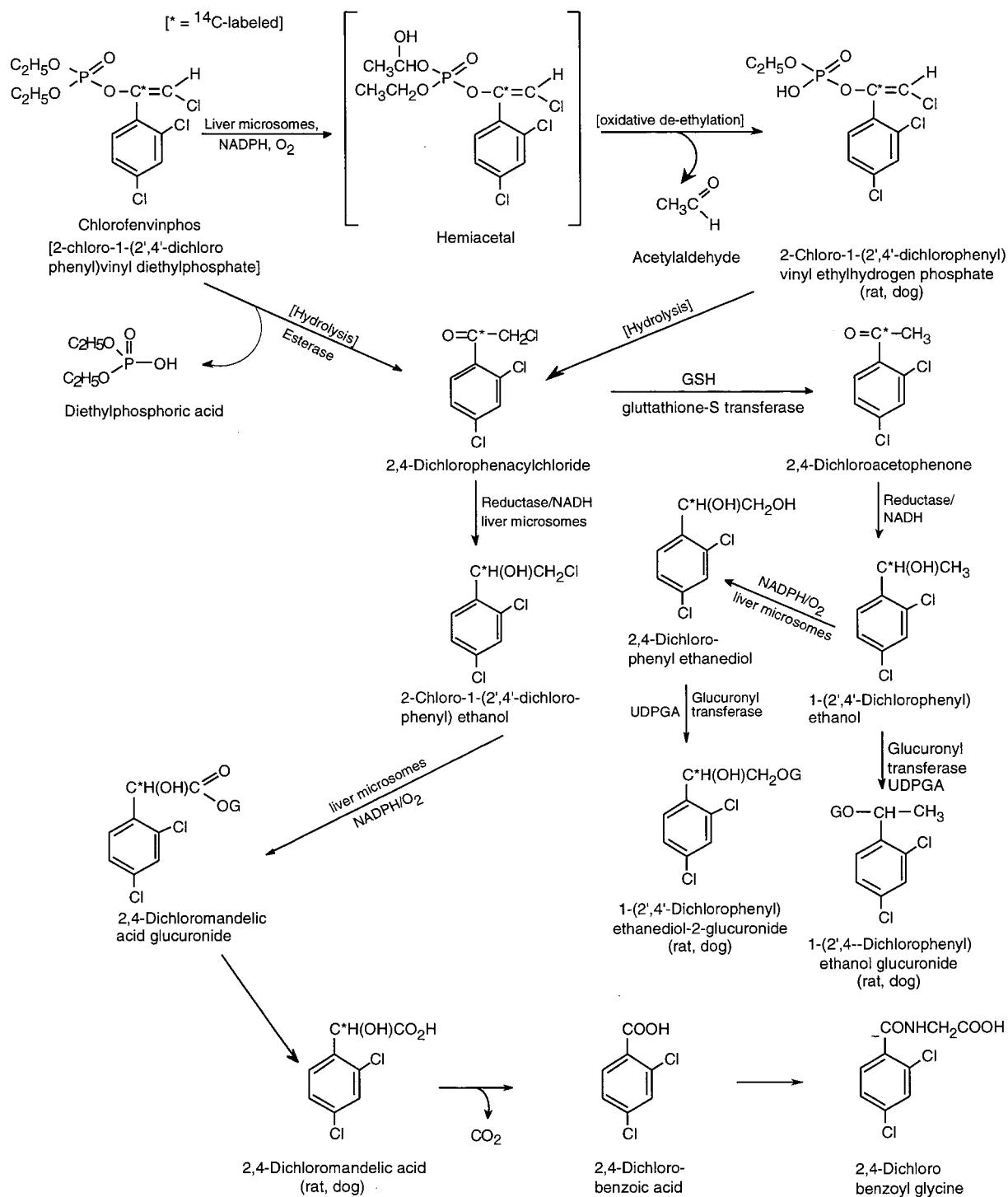
2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after acute-, intermediate-, or chronic-duration dermal exposure to chlorfenvinphos.

The dermal LD_{50} values in rabbits for undiluted chlorfenvinphos and emulsifiable concentrate have been estimated to be 400 and 1,087 mg/kg, respectively (Ambrose et al. 1970).

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, hepatic, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, metabolic, or other systemic effects in humans or animals following acute-, intermediate-, or chronic-duration dermal exposure to chlorfenvinphos.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after acute-, intermediate-, or chronic-duration dermal exposure to chlorfenvinphos.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after intermediate-, or chronic-duration dermal exposure to chlorfenvinphos. Dermally-applied chlorfenvinphos formulations significantly inhibited plasma cholinesterase activity in healthy human male volunteers without prior occupational exposure to the substance. Three different chlorfenvinphos formulations were used in this study: 80% weight per volume (w/v) emulsifiable concentrate (EC), mainly chlorfenvinphos and emulsifiers; 24% w/v EC, mainly isometric trimethyl benzenes with 4½% w/v emulsifiers; 25% w/w wettable powder (WP), mainly colloidal silica, florisil, triphenylphosphate, sodium triphosphates, empicol LZ and tamal. The formulations were administered separately in single applications to the forearm skin of 9 adult human males for periods up to 4 hours in doses of 4–10 mg chlorfenvinphos/kg body weight. The 80% EC and 25% EC formulations had no effect on cholinesterase activity levels in the volunteers. Only plasma and erythrocyte cholinesterase activities

of volunteers who received a single application of the 24% emulsifiable concentrate (5 and 10 mg chlorfenvinphos/kg body weight equivalent to a dermal dose of 5 mg/cm^2) were inhibited. Plasma and erythrocyte cholinesterase were inhibited by 53–76% and 9%, respectively (Hunter 1969).

No studies were located regarding neurological effects in animals after intermediate- or chronic-duration dermal exposure to chlorfenvinphos. Acute-duration dermal exposure of laboratory animals to chlorfenvinphos resulted in the depression of plasma cholinesterase without clinical symptoms. Two dogs of unspecified sex treated with a daily dose of 0.3% chlorfenvinphos applied topically to the spinal area from head to tail for 7 days (3 consecutive days, 1 day skipped, then 4 consecutive days) suffered 28% depression in plasma cholinesterase activity by day 8. No clinical signs resulting from cholinesterase depression were observed in any of the dogs (Vestweber and Kruckenberg 1972).

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after acute-, intermediate-, or chronic-duration dermal exposure to chlorfenvinphos.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after acute-, intermediate-, or chronic-duration dermal exposure to chlorfenvinphos.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects of chlorfenvinphos in humans or animals following dermal exposure.

Other genotoxicity studies for chlorfenvinphos are described in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to chlorfenvinphos.

2. HEALTH EFFECTS

2.3   TOXICOKINETICS

The absorption of chlorfenvinphos after inhalation exposure in humans or animals is unknown due to lack of data. Ingested chlorfenvinphos is rapidly absorbed in humans. In animals, oral chlorfenvinphos is also well absorbed to an extent of $67.1–72.5\%$ of the administered dose. Although no information on the dermal absorption of chlorfenvinphos in animals is available, dermally applied chlorfenvinphos formulations were rapidly and extensively absorbed in humans; the rate and extent of absorption was dependent on solvents used in the preparation.

In humans, absorbed chlorfenvinphos is widely distributed and has been detected in compartments that include serum, cervical mucus, follicular and sperm fluids, and milk at levels of up to 0.42 µg/kg for environmental exposures and 15 ng/mL in an acute poisoning case. The distribution of absorbed chlorfenvinphos in animals is unknown because of lack of data.

In humans, absorbed chlorfenvinphos is extensively metabolized via oxidative dealkylation by liver microsomal fractions. Based on human and animal data, the mechanism for oxidative dealkylation of chlorfenvinphos proceeds initially via monooxygenation of the *alpha*-carbon atom of the alkoxy group to produce an unstable hemiacetal which breaks down by oxidative *O*- and *N*-alkylation mechanisms to acetaldehyde and 2-chloro-1-(2,4-dichlorophenyl) vinylethylhydrogen phosphate. Acetophenone produced in the succeeding step is reduced to the alcohol and conjugated by glutathione transferases. Data from animal studies suggest that electrophilic metabolic intermediates or epoxides may be produced in the metabolism of chlorfenvinphos.

The elimination or excretion of chlorfenvinphos in humans and animals after inhalation or dermal exposures is unknown due to lack of data. In humans, ingested chlorfenvinphos is rapidly removed from the blood and passed into the tissues. Chlorfenvinphos has been detected in human sperm fluid and milk samples. In animals, ingested chlorfenvinphos is rapidly eliminated via the urine (70–90%), feces (about 16%), and expired air (0.5%).

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

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

2.3.1.2 Oral Exposure

A 29-year-old male was hospitalized with severe respiratory distress and bronchial tree hypersecretion. The patient had ingested about 50 mL of the preparation Enolofos®, which contains 50% chlorfenvinphos, in a suicide attempt. The concentration of chlorfenvinphos in the serum was 300 ng/mL upon admission. This is the only known human chlorfenvinphos poisoning case in which hemoperfusion intervention was employed. The mean clearance of chlorfenvinphos during hemoperfusion was low (68 mL/min) and only 0.42 mg of the poison was recovered. The poison level in the serum was low (15 ng/mL) immediately before the procedure, and gradually rose in successive blood samples indicating that chlorfenvinphos passes fairly easily from the tissues into blood. This may be related to secondary resorption from the digestive tract. The highest value of clearance was observed in the fourth hour of hemoperfusion, in contrast to the observations during hemoperfusion performed for other drug poisoning, when the value of the clearance was lowest in the last hour. The serum chlorfenvinphos levels decreased temporarily within a few hours even prior to the beginning of hemoperfusion, either due to rapid inactivation or to rapid passage into the tissues where the organophosphates accumulate (Pach et al. 1987).

In animal studies, a total of 67.1–72.5% of the administered radioactivity was recovered from the urine of pairs of Carworth Farm E strain male rats administered [^{14}C]chlorfenvinphos orally at doses of 2.5 or 13.3 mg/kg in olive oil (with or without prior monooxygenase induction with dieldrin). This is suggestive of gastrointestinal absorption of $67.1–72.5% (Hutson and Wright 1980).

2.3.1.3 Dermal Exposure

A study conducted to assess the potential dermal absorption of chlorfenvinphos for humans (since the most likely route of entry is through the skin in occupational exposures) applied the substance to the forearm skin of nine healthy human male volunteers who had no prior occupational exposure to the

substance. Three different chlorfenvinphos formulations were used in this study: 80% w/v EC, mainly chlorfenvinphos and emulsifiers; 24% w/v EC, mainly isometric trimethyl benzenes with 4.5% w/v emulsifiers; 25% weight per weight (w/w) wettable powder, mainly colloidal silica, florisil, triphenylphosphate, sodium triphosphates, empicol LZ and tamal. The formulations were administered separately in single applications to the forearm skin of nine adult human males for periods up to 4 hours in doses of 4–10 mg chlorfenvinphos/kg body weight. The 80% EC formulation was applied at doses of 4, 5, 10, or 10 mg/kg body weight for periods of 4, 3.7, 3.8, or 4 hours on approximate skin areas of 36, 38, 320, or 336 cm^2, respectively. The 24% EC formulation was applied at doses of 5, 5, 10, 10, or 10 mg/kg body weight for periods of 4, 3.8, 4.1, 4, or 4 hours on approximate skin areas of 272, 420, 800, 600, or 880 cm^2, respectively. The 25% WP formulation was applied at doses of 5 or 5 mg/kg body weight for periods of 4.2 or 3.8 hours on approximate skin areas of 80 or 70 cm^2, respectively. The extent and ease of absorption or permeability factor of the applied doses depended on the formulation, relating to solvents in the preparation. The dermal absorption of the 80% EC formulation was 1.43, 1.81, 0.06, or 0.32 mg/cm^2/hour, corresponding to applied doses of 4, 5, 10, or 10 mg/kg body weight for periods of 4, 3.7, 3.8, or 4 hours on approximate skin areas of 36, 38, 320, or 336 cm^2, respectively. The dermal absorption of the 24% EC formulation was 0.18, 0.12, 0.14, 0.20, or 0.08 mg/cm^2/hour corresponding to applied doses of 5, 5, 10, 10, or 10 mg/kg body weight for periods of 4, 3.8, 4.1, 4, or 4 hours on approximate skin areas of 272, 420, 800, 600, or 880 cm^2, respectively. The dermal absorption of the 25% wettable powder formulation was 0.35 mg/cm^2/hour corresponding to applied doses of 5 mg/kg body weight for periods of 4.2 hours on approximate skin areas of 80 cm^2. Concentrations of intact chlorfenvinphos of 14.4, 12.0, or 0.5 µg/L were found 24 hours post-exposure in the blood of volunteers for whom chlorfenvinphos absorption rates of 0.20, 0.14, or 0.08 mg/cm^2/hour, respectively, had been estimated. Concentrations of intact chlorfenvinphos of 22, 3.8, <2.8, 2.9, 2.6, 0.2, or <0.7 µg/L were found 8 hours later in the blood of volunteers for whom chlorfenvinphos absorption rates of 1.81, 1.43, 0.32, 0.18, 0.12, and 0.06 mg/cm^2/hour, respectively, had been estimated (Hunter 1969).

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

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

As an organophosphorus compound, chlorfenvinphos is not expected to accumulate in the body tissues because of its expected short half-life. However, chlorfenvinphos was found in some of the

41 specimens of cervical mucus, follicular and sperm fluids, and human milk that were examined in Germany. Chlorfenvinphos levels of 13.66, 1.69, 2.02, and 1.89 µg/kg were detected in 4 of the 11 samples of cervical mucus. Chlorfenvinphos levels of 0.42 µg/kg were detected in 1 of the 10 sperm fluid samples and 1 of the 10 human milk samples, respectively. The detection of chlorfenvinphos in the cervical mucus, which showed the highest levels, was unexpected because it was believed to be the most unlikely site for accumulation in the body. It was suggested that a connection exists between the activities of the cervical glands of the endocervix and the appearance of some pesticides in the cervical mucus which might show a new way for accumulation. Accordingly, the data indicate that organophosphorus environmental pollutants, like chlorfenvinphos, can appear in the human reproductive organs, exposing even germ-cells and, thus, present a risk of interference with the process of reproduction (Wagner et al. 1990). Since the data were generated from environmental exposure, the combined route of exposure may include inhalation.

No studies were located regarding the distribution of chlorfenvinphos after inhalation exposure in animals.

2.3.2.2 Oral Exposure

Although chlorfenvinphos is a hydrophilic substance, it has hitherto not been widely found in human tissues because it is not expected to persist in these tissues. As an organophosphorus compound, chlorfenvinphos is not expected to accumulate in the body tissues because of its expected short half-life. However, chlorfenvinphos was found in some of the 41 specimens of cervical mucus, follicular and sperm fluids, and human milk that were examined. Chlorfenvinphos levels of 13.66, 1.69, 2.02, and 1.89 µg/kg were detected in 4 of the 11 samples of cervical mucus. Chlorfenvinphos levels of 0.42 µg/kg were detected in 1 of the 10 sperm fluid samples and 1 of the 10 human milk samples, respectively. The detection of chlorfenvinphos in the cervical mucus, which showed the highest levels, was unexpected because it is the most unlikely compartment for accumulation in the body. It was suggested that a connection exists between the gland's activities and the appearance of some pesticides in the cervical mucus, which might show a new way for accumulation. Accordingly, these data indicate that new environmental pollutants, like chlorfenvinphos, can appear in the human organs, exposing even germ-cells and, thus, present a risk of adverse effects on reproduction (Wagner et al. 1990). Since the data were generated from environmental exposure, the combined route of exposure possibly include oral.

A 29-year-old male was hospitalized with severe respiratory distress and bronchial tree hypersecretion. The patient had ingested about 50 mL of the preparation Enolofos®, which contains

50% chlorfenvinphos, in a suicide attempt. The concentration of chlorfenvinphos in the serum was 300 ng/mL upon admission. This is the only human chlorfenvinphos poisoning case in which hemoperfusion intervention was employed. The mean clearance of chlorfenvinphos during hemoperfusion was low (68 mL/minute) and only 0.42 mg of the poison was recovered. The poison level in the serum was low (15 ng/mL) immediately before the procedure, and gradually rose in successive blood sampling indicating that chlorfenvinphos passes fairly easily from the tissues into blood. This may be related to secondary resorption from the digestive tract. The highest value of clearance was observed in the fourth hour of hemoperfusion, in contrast to the observations during hemoperfusion performed for other drug poisoning, when the value of the clearance was lowest in the last hour. The serum chlorfenvinphos levels decreased temporarily within a few hours even prior to the beginning of hemoperfusion, either due to rapid inactivation or to rapid passage into the tissues where the organophosphates accumulate (Pach et al. 1987).

No studies were located regarding the distribution of chlorfenvinphos in animals after oral exposure.

2.3.2.3 Dermal Exposure

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

Although chlorfenvinphos is a hydrophilic substance, it has hitherto not been widely found in human tissues because it is not expected to persist in these tissues. As an organophosphorus compound, chlorfenvinphos is not expected to accumulate in the body tissues because of its expected short half-life. However, chlorfenvinphos was found in some of the 41 specimens of cervical mucus, follicular and sperm fluids, and human milk that were examined. Chlorfenvinphos levels of 13.66, 1.69, 2.02, and 1.89 µg/kg were detected in 4 of the 11 samples of cervical mucus. Chlorfenvinphos levels of 0.42 µg/kg were detected in 1 of the 10 sperm fluid samples and 1 of the 10 human milk samples, respectively. The detection of chlorfenvinphos in the cervical mucus, which showed the highest levels, was unexpected because it is the most unlikely compartment for an accumulation in the body. It was suggested that a connection exists between the gland activities and the appearance of some pesticides in the cervical mucus, which might show a new way for accumulation. Accordingly, this data indicate that new environmental pollutants, like chlorfenvinphos, can appear in the human organs, contacting even germ-cells and, thus, present risk of adverse effects on reproduction (Wagner et al. 1990). Since the data were generated from environmental exposure, the combined route of exposure possibly includes dermal.

2.3.3 Metabolism

An adapted scheme for the mammalian metabolic pathway of chlorfenvinphos (Akintonwa 1984; Akintonwa 1985; Akintonwa and Itam 1988; Hunter et al. 1972; Hutson and Millburn 1991; Hutson and Wright 1980) is presented in Figure 2-3.

2.3.3.1 Inhalation Exposure

No studies were located regarding the metabolism of chlorfenvinphos after inhalation exposure in humans or animals.

2.3.3.2 Oral Exposure

In humans, the rates of chlorfenvinphos de-ethylation by liver microsomal fractions are 0.36 nmol/minute per mg protein (range 0.11–0.82) without induction and 1.03 nmol/minute per nmol of cytochrome P-450 (range 0.42–1.78) with induction (Hutson and Logan 1986).

In animal studies, pairs of Carworth Farm E strain male rats administered [^{14}C]chlorfenvinphos orally at doses of 2.5 or 13.3 mg/kg in olive oil (with or without prior monooxygenase induction with dieldrin) exhibited minimal changes in the metabolic profiles. Urine samples were collected at 12 and 32 hours and analyzed by chromatography for metabolites of chlorfenvinphos using authentic standards: de-ethylchlorfenvinphos or 2-chloro-1-(2',4'-dichlorophenyl) vinylethylhydrogen phosphate, 1-(2',4'-dichlorophenyl) ethanol, 1-(2',4'-dichlorophenyl) ethanediol, 2,4-dichloromandelic acid, and 2,4-dichlorobenzoyl glycine. The metabolites 2-chloro-1-(2,4-dichlorophenyl) vinylethylhydrogen phosphate, 1-(2,4-dichlorophenyl) ethanol, 1-(2,4-dichlorophenyl) ethanediol, 2,4-dichloromandelic acid, and 2,4-dichlorobenzoyl glycine were identified in the urine by this method. Increased monooxygenase induction (dieldrin pretreatment) favored the production of the glucuronide of 1-(2,4-dichlorophenyl) ethanol and decreased yield of 2,4-dichloromandelic acid and 2,4-dichloro-benzoyl glycine at a low dose level. At the high dose level, an increased yield of 1-(2,4-dichlorophenyl) ethanol, an increase in the relative yield of 2,4-dichloromandelic acid and 2,4-dichlorobenzoyl glycine, and a doubling in the relative yield of de-ethylchlorfenvinphos occurred with a concomitant reduction in the relative yields of the glucuronides. The authors suggested that the relatively low amount of radioactivity eliminated within 0–32 hours via the urine of high-dose rats was probably due to limited absorption/metabolism. The results support the conclusion that the effect of enzyme induction on the

metabolism of substrates of that enzyme are dose-dependent with respect to enzyme saturation. Therefore, alterations in metabolism are not necessarily a consequence of enzyme induction alone (Hutson and Wright 1980). The tissue distribution of organophosphoric ester metabolizing enzymes in the livers of mammalian species has been suggested to be an important factor in accounting for species specificity of the toxicity of some phosphate triester anticholinesterase agents, including chlorfenvinphos. These enzymes were identified as microsomal monooxygenases, esterases, and glutathione-s-transferases. The acute oral LD_{50} values of chlorfenvinphos for the rat, mouse, rabbit, and dog which have been estimated as 10, 100, 500, and 12,000 mg/kg, respectively, correlated fairly well with the relative rates of chlorfenvinphos O-dealkylation and relative *in vivo* chlorfenvinphos-induced decreases in the rates of hexobarbital metabolism in these species. The relative rates of dealkylation in the rat, mouse, rabbit, and dog have been estimated as 1, 8, 24, and 80, respectively. The relative rates of chlorfenvinphos-induced decreases in hexobarbital metabolism in the rat, mouse, rabbit, and dog have been estimated as 4, 17, 5, and 1, respectively (Hansen 1983).

An investigator in an earlier study had suggested that the enzyme system responsible for this reaction was found to be microsomal and required molecular oxygen and $NADPH_2$ for activity. The activity of this enzyme system in isolated washed rat, mouse, and dog liver microsomes had rates of product formation of 0.02, 0.65, and 2.00 nmol (per mg of microsomal protein per minute), respectively. The activity of this enzyme system in isolated washed rabbit liver microsomes had a rate of product formation similar to the other species used in this study. The maximum specific activity of liver microsomes with respect to the dealkylation of chlorfenvinphos achieved in dieldrin-pretreated and phenobarbital-pretreated mice was 3.6 nmol at 1.6 mg/kg daily for 62 weeks and 6.0 nmol at 12 mg/kg daily for 40 weeks, respectively. The maximum specific activity of liver microsomes with respect to the dealkylation of chlorfenvinphos achieved in dieldrin-pretreated and phenobarbital-pretreated dogs was 4.1 nmol (per mg of microsomal protein per minute) at 2.0 mg/kg daily for 4 weeks and 9.2 nmol (per mg of microsomal protein per minute) at 20 mg/kg daily for 4 weeks, respectively. The activity of the enzyme system oxygen: $NADPH_2$ oxidoreductase (with chlorfenvinphos as substrate) in isolated washed monkey liver microsomes had a rate of product formation of 1.00 nmol (per mg of microsomal protein per minute). The maximum specific activity of liver microsomes with respect to the dealkylation of chlorfenvinphos achieved in dieldrin-pretreated monkeys given oral chlorfenvinphos doses of 0.03 mg/kg/day for 6.15 years was 1.8 nmol (per mg of microsomal protein per minute). The mechanism of this reaction has been proposed to be mediated by oxidative dealkylation of chlorfenvinphos to the relatively nontoxic metabolite, 2-chloro-1-(2,4-dichlorophenyl) vinyl ethylhydrogen phosphate and acetaldehyde. The enzyme system was

readily inducible, especially in the rat, by the administration of phenobarbital or dieldrin. The maximum specific activity of liver microsomes with respect to the dealkylation of chlorfenvinphos achieved in dieldrin-pretreated and phenobarbital-pretreated rats was 12.4 nmol at 8 mg/kg/day for 4 weeks and 5.7 nmol at 14 mg/kg/day for 4 weeks, respectively. A 600-fold increase in specific activity was observed in the liver of dieldrin-pretreated rats. In rats pretreated with dieldrin at 200 ppm in the diet for 12 days, the acute LD_{50} for chlorfenvinphos was increased by a factor of 6–8 (Donninger 1971).

A quantitative study of the species distribution of phosphate esterases and glutathione *S*-alkyl transferase found that these enzymes are significantly less in quantity in the pig than in all the other species studied, suggesting a significantly varied distribution among some mammalian species. The author of the study concluded that the distribution of these enzymes is an important factor in accounting for the species specificity of at least some anticholinesterase agents and that the glutathione-dependent alkyl transferase is predominantly a methyl transferase. The contribution of these two enzyme systems to the detoxification of any particular phosphate triester is dependent on the structure and solubility of the molecule (Donninger 1971).

These findings were confirmed by three other reports. In the report by Hutson and Millburn (1991), the oral LD_{50} values for rat, mouse, rabbit, and dog are 10–30 mg/kg, 150, 500, and >5,000 mg/kg, respectively. The oral LD_{50} in the rabbit has been reported to be as high as >12,000 mg/kg in some studies. The difference in toxicity in rats and dogs was found to be due to differences in several pharmacokinetic and pharmacodynamic factors. These factors include differences in the rates of absorption and metabolism, bioavailability in blood, and rates of uptake by the brain, as well as the sensitivity of brain cholinesterase to the phosphorylating action of the compound. In studies using rats and dogs, the most important reaction in detoxification is the conversion of chlorfenvinphos to de-ethylchlorfenvinphos by oxidative de-ethylation. The reaction is catalyzed by a hepatic microsomal monooxygenase, probably cytochrome P-450. The relative rates of de-ethylation in liver slices were 1, 8, 24, and 88 for the rat, mouse, rabbit, and dog, respectively. Thus, an excellent inverse correlation between oral LD_{50} and rate of de-ethylation was established. Also evidence for the significance of the reaction *in vivo* was provided from experiments in which rats were protected 7-fold from the action of chlorfenvinphos by pre-treatment with dieldrin in the diet for 12 days. This treatment induces cytochrome P-450 microsomal monooxygenase and, thus, chlorfenvinphos de-ethylation. However, the author cautioned that species differences in toxicity response are often multi-factorial, and metabolism can be a minor component (Hutson and Millburn 1991).

In the second report, Ikeda et al. (1991) found the metabolism of chlorfenvinphos in kidney subcellular fractions and in the serum of Fischer 344 rats (orally pretreated with chlorfenvinphos followed by oral treatment with a similar chlorfenvinphos dose or 50 mg/kg phenobarbital in 24 hours), with or without the NADPH-generating system, to be negligible. Metabolism of chlorfenvinphos in the liver subcellular fraction without the NADPH-generating system was also practically negligible. However, when the NADPH-generating system was added to the liver subcellular fraction, chlorfenvinphos metabolism increased significantly (203% in the 9,000 g fraction and 178% in the microsomes) in the chlorfenvinphos-pretreated animals and in the phenobarbital-pretreated animals (565%). Additionally, chlorfenvinphos pretreatment increased cytochrome P-450 content (30%) in the hepatic microsomal fraction; phenobarbital pretreatment caused a 180% increase. Hepatic microsomal cytochrome b5 content and cytochrome P-450 reductase activity were also increased by chlorfenvinphos and phenobarbital pretreatment (121 and 130%, respectively, for chlorfenvinphos, and 126 and 139%, respectively, for phenobarbital). Both chlorfenvinphos and phenobarbital pretreatment significantly increased protein content ($P<0.001$) in the microsomal fraction. Chlorfenvinphos treatment did not increase liver weight (relative to body weight). Increases were also noted in cytochrome P-450-linked activities such as aminopyrine *N*-demethylase (40%) and aniline hydroxylase (27%) content in the hepatic microsomal fraction and hexobarbital sleeping time and zoxazolamine paralysis time. Both chlorfenvinphos and phenobarbital are potent inducers of cytochrome P-450, which is involved in the metabolic detoxication of chlorfenvinphos. Thus, the authors concluded that the increase in hepatic chlorfenvinphos metabolism may be due to the induction of the hepatic cytochrome P-450 system caused by the single oral short-term treatment with chlorfenvinphos. Also this induction may be one of the reasons for the decrease in plasma chlorfenvinphos concentration which may be responsible for the reduction in toxicity of subsequent exposure to chlorfenvinphos (Ikeda et al. 1991).

The third report was a theoretical analysis that predicted the mammalian biotransformation products based on the recognition of the structure of chlorfenvinphos, understanding of Types I and II metabolism of foreign compounds, and mechanistic biochemistry (Akintonwa 1984). This analysis also acknowledged that cytochrome P-450 monooxygenase (an inducible enzyme) is the relevant enzyme which mediates the biotransformation of chlorfenvinphos via oxidative dealkylation of to the relatively nontoxic metabolite, 2-chloro-1-(2,4-dichlorophenyl) vinyl ethylhydrogen phosphate or de-ethylchlorfenvinphos. Thirteen metabolites of chlorfenvinphos were predicted for mammals from theoretical biotransformation as justified by the known structure of chlorfenvinphos and understanding of biochemical reactions of monooxygenation, reduction, hydrolysis, glucuronidation, glutathione-S-transferase conjugation, and amino acid conjugation. The 13 metabolites predicted are: 2-chloro-

1-(2',4'-dichlorophenyl) vinyldiethyl phosphate; acetaldehyde; 2-chloro-1-(2',4'-dichlorophenyl) vinyl-
ethylhydrogen phosphate; 2,4-dichlorophenacylchloride; 2-chloro-1-(2',4'-dichlorophenyl) ethanol;
2,4-dichloromandelic acid; 2,4-dichloromandelic acid ester glucuronide; 2,4-dichloroacetophenone;
1-(2',4'-dichlorophenyl) ethanol; 1-(2',4'-dichlorophenyl) ethanediol; 1-(2',4'-dichlorophenyl) ethanediol-
2-glucuronide; 1-hydroxy-1-(2',4'-dichlorophenyl) acetyl glycine; and 1-(2',4'-dichlorophenyl)
ethanediol. 2-Chloro-1-(2',4'-dichlorophenyl) vinylethylhydrogen phosphate, 2,4-dichloromandelic acid,
1-(2',4'-dichlorophenyl) ethanediol-2-glucuronide, and 1-(2',4'-dichlorophenyl) ethanediol are predicted
specifically for the dog and rat. 1-Hydroxy-1-(2',4'-dichlorophenyl) acetyl glycine (the glycine conjugate
of 2,4-dichloromandelic acid) was not confirmed in the rat while 2,4-dichlorohippuric acid was present
in the dog, but not in the rat. While the theoretical or predictive approach to metabolite identification
elucidates all the possible mechanistic pathways in the derivation of each metabolite and identifies all
toxic or hazardous intermediates, only actual experimentation, which begins with theoretical prediction,
can provide species differences in the proportion of metabolites and the toxicity of these metabolites.
Thus, the theoretical approach to chlorfenvinphos metabolism in mammals effectively reveals that the
monooxygenation of the vinyl group would produce an unstable epoxide (2-hydroxyl groups attached
to a carbon) to yield 2,4-dichlorophenyl glyoxylate and 2,4-dichlorobenzoic acid through
decarboxylation and oxygenation. The author of this study postulated that the 2,4-dichlorobenzoyl
glycine (2,4-dichlorohippuric acid) was produced in the rat by this mechanism. The production of
electrophilic metabolic intermediates or epoxides in the metabolism of chlorfenvinphos, which could
react with nucleophilic cellular components (DNA, RNA, and proteins) leading to carcinogenesis, was
considered unlikely by this theoretical approach (Akintonwa 1984).

2,4-Dichlorophenacyl chloride, an intermediary metabolite of chlorfenvinphos and dimethylvinphos, is
excreted from mammals mainly as 1-(2,4-dichlorophenyl)ethyl glucuronide (Hutson et al. 1977). The
authors assumed that this arose via the reductive dechlorination of the phenacyl halide to the
acetophenone, which was then reduced to the alcohol and conjugated. A further investigation of the
proposed reductive dechlorination step (using subcellular fractions of rat liver) led the authors to
conclude that it is likely that the mechanism of reaction is a nucleophilic attack by sulphur (of the
second GSH) on sulphur (of the chlorfenvinphos/GSH conjugate), with the expulsion of the phenacyl
anion as the leaving group. The enzyme may be regarded as one of the glutathione transferases
(Hutson et al. 1977).

An assay developed for determining monooxygenase activity in human fetal livers, as a measure of
the rate of decrease in substrate (Supona®, chlorfenvinphos) concentration, was found reliable for
incubations at 37 EC for periods up to 10 minutes. Incubations in excess of 10 minutes were

unreliable due to an unexpected increase in $E_{246\,nm}$ readings. The investigators concluded that hydrolysis, rather than monooxygenation, of chlorfenvinphos, was probably responsible for the observed increase in readings. Using 5- and 10-minute incubations, specific activity values for monooxygenase in whole liver homogenates of 13- and 16-week-old human fetuses were determined to be 6.47±0.84 and 5.26±0.46 µg/mg, respectively; no monooxygenase activity could be detected in whole liver homogenates of 24-week-old fetuses. The authors concluded that, similar to *in vivo* observations, the mechanism for oxidative dealkylation of chlorfenvinphos proceeds initially via monooxygenation of the *alpha*-carbon atom of the alkoxy group to produce an unstable hemiacetal which breaks down by oxidative *O*- and *N*-alkylation mechanisms to acetaldehyde and 2-chloro-1-(2,4-dichlorophenyl) vinylethylhydrogen phosphate (Akintonwa and Itam 1988).

2.3.3.3 Dermal Exposure

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

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

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

2.3.4.2 Oral Exposure

A male patient, aged 29, was admitted to the hospital 3 hours after a suicide attempt during which he drank about 50 mL of the preparation Enolofos® which contains 50% chlorfenvinphos. The concentration of chlorfenvinphos in the serum was 300 ng/mL upon admission. In this, the only human chlorfenvinphos poisoning in which hemoperfusion intervention was employed, the mean clearance of chlorfenvinphos during hemoperfusion was low, 68 mL/minute; and only 0.42 mg of the poison was recovered. The level of the poison in the serum was low (15 ng/mL) immediately before the procedure and gradually rose in successive blood sampling. At all times in successive blood samples during the procedure, there was an increase of chlorfenvinphos level in the serum, indicating that chlorfenvinphos passes fairly easily from the tissues into blood. This may be related to secondary

resorption from the digestive tract. The highest value of clearance was observed in the fourth hour of
hemoperfusion, in contrast to the observations during hemoperfusion performed for other drug
poisoning, when the value of the clearance was lowest in the last hour. The serum chlorfenvinphos
levels decreased temporarily within a few hours even prior to the beginning of hemoperfusion, either
due to rapid inactivation or to rapid passage into the tissues where the organophosphates accumulate
(Pach et al. 1987).

In animal studies, pairs of Carworth Farm E strain male rats administered [^{14}C]chlorfenvinphos orally at
doses of 2.5 or 13.3 mg/kg in olive oil (with or without prior monooxygenase induction with dieldrin)
eliminated about 50% of the administered radioactivity in the urine in the first 12 hours, 9–13% in the
next 12 hours, 3.5–6% in the subsequent 16 hours, and 4.2–5% in the final 42 hours of monitoring. A
total of 67.1–72.5% of the administered radioactivity was recovered from the urine. Only 15.2–16.9%
of the administered radioactivity was eliminated in the urine in the first 12 hours, 2.5–8.2% in the next
12 hours, 6.1–6.6% in the subsequent 18 hours, and 0.7–1.4% in the final 42 hours of monitoring.
Only 26.2–31.7% of the total dose was recovered in the urine in the high-dose animals. Dieldrin
pretreatment resulted in a more rapid elimination as well as a greater percentage elimination of the
administered [^{14}C]chlorfenvinphos doses (Hutson and Wright 1980). All of the Birlane®
(chlorfenvinphos) dose of 0.8 mg/kg/day administered in the diet for 30 days to 2 groups of adult
female albino (Wistar) rats was removed from the body (excreted or metabolized) in 4 days. The dose
was excreted mostly in the urine (70–90%) and feces (about 16%) with minor amounts (0.5%) in
expired air (Barna and Simon 1973).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of chlorfenvinphos after dermal exposure in humans or
animals.

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.

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

Inhaled chemical — — — ┐   ┌ — — → Exhaled chemical

Ingestion

Lungs

Liver

V_{max} K_m

GI Tract

VENOUS BLOOD

Fat

Slowly perfused tissues

Richly perfused tissues

Kidney

Urine

Skin

ARTERIAL BLOOD

└ — — Chemicals in air contacting skin
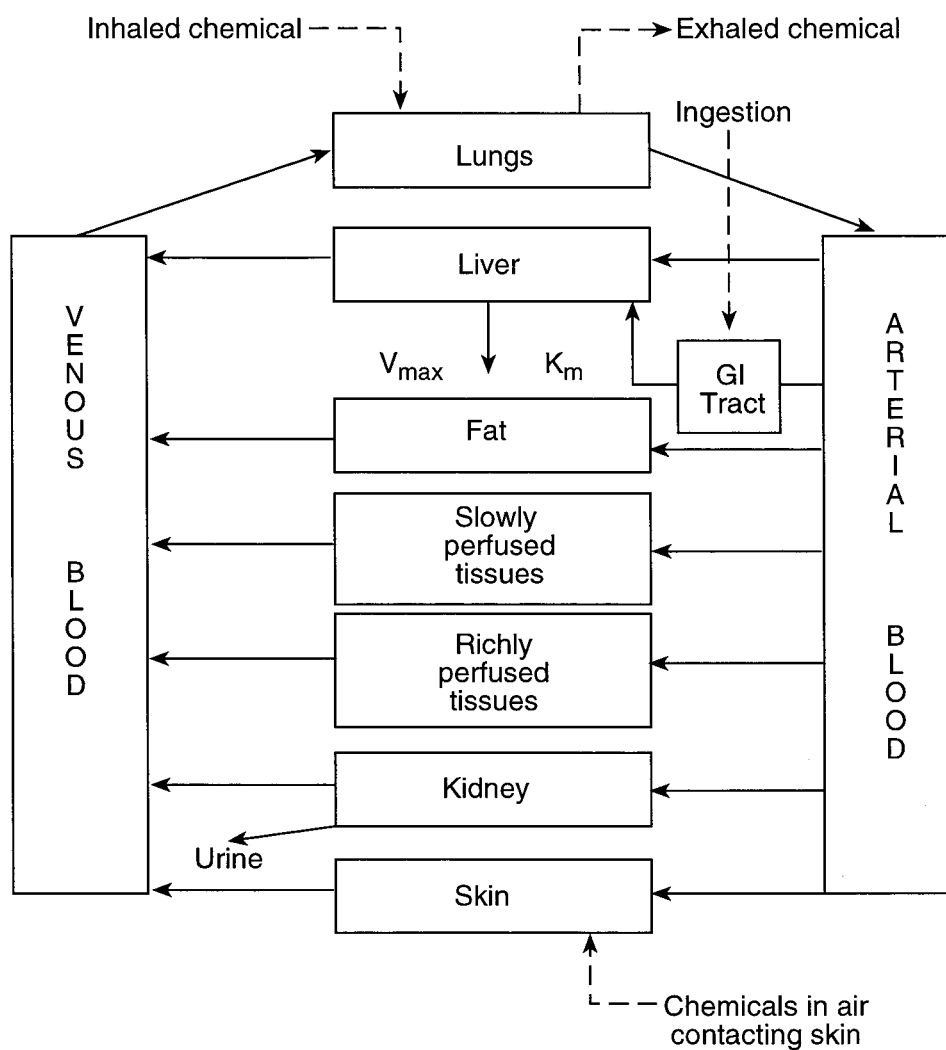
Source: adapted from Krishnan et al. 1994

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

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

A physiologically based pharmacokinetic (PBPK) analysis used data from a study with 8-week old Fischer 344 rats as a model to study the mechanism of protection by initial chlorfenvinphos exposure against the toxicity of a subsequent exposure. The analysis concluded that, contrary to expectation, the body burden of chlorfenvinphos decreased after the initial exposure upon subsequent challenge exposure. The model predicted that decreased body burden of oral chlorfenvinphos dose might be due to the decrease in the plasma concentration after a challenge with chlorfenvinphos. In the rat study on which the model is based, the acute oral toxicity of chlorfenvinphos was reduced by the oral pretreatment of rats with chlorfenvinphos after a subsequent challenge dose. This was accompanied by reduction in brain cholinesterase, liver, and plasma concentrations of chlorfenvinphos (by one-third and 4–10 times, respectively). Unbound fractions of chlorfenvinphos in blood and liver were estimated by the *in vitro* experiments and pretreatment did not change the unbound fraction of chlorfenvinphos. The authors stated that, according to the PBPK model, the decrease in body burdens of the oral chlorfenvinphos dose may be caused mainly by an increase in intrinsic clearance of chlorfenvinphos by the liver and a decrease in the partition coefficient of chlorfenvinphos between the emergent blood and he liver. The increase in the intrinsic clearance was suggested to be related to the metabolic induction of P-450 observed *in vitro*. Additionally, pretreatment decreased the absorption rate constant of the oral chlorfenvinphos dose. Essentially, this is responsible for the protection afforded against toxicity of subsequent exposure to chlorfenvinphos (Ikeda et al. 1992).

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

The level of activity of cholinesterases in the livers of mammalian species and the distribution of these enzymes have been suggested to be important factors in accounting for species specificity of some phosphate triester anticholinesterase agents, including chlorfenvinphos. These factors may account for the great variation in the toxicity of chlorfenvinphos among different animal species. The acute oral LD_{50} values of chlorfenvinphos for the rat, mouse, rabbit, and dog are 10, 100, 500, and 1,200 mg/kg, respectively. The relative conversion rates of chlorfenvinphos (by *O*-dealkylation) to the diester by liver slices from the rat, mouse, rabbit, and dog were 1, 8, 24, and 80 hours, respectively; these values correlate well with the published acute oral LD_{50} values for the species. The enzyme system responsible for this reaction was found to be microsomal and required molecular oxygen and $NADPH_2$

for activity. The activity of this enzyme system in isolated rat, mouse, and dog liver (washed) microsomes had rates of product formation of 0.02, 0.65, and 2.00 nmol (per mg of microsomal protein per minute), respectively. The activity of this enzyme system in isolated washed rabbit liver microsomes had a rate of product formation similar to that of other species used in this study.

The maximum specific activity of liver microsomes with respect to the dealkylation of chlorfenvinphos achieved in dieldrin-pretreated and phenobarbital-pretreated mice was 3.6 nmol at 1.6 mg/kg/day for 62 weeks and 6.0 nmol at 12 mg/kg/day for 40 weeks, respectively. The maximum specific activity of liver microsomes with respect to the dealkylation of chlorfenvinphos achieved in dieldrin- and phenobarbital-pretreated dogs was 4.1 nmol (per mg of microsomal protein per minute) at 2.0 mg/kg/day for 4 weeks and 9.2 nmol (per mg of microsomal protein per minute) at 20 mg/kg/day for 4 weeks, respectively. The activity of the enzyme system oxygen: $NADPH_2$ oxidoreductase (with chlorfenvinphos as substrate) in isolated washed monkey liver microsomes had a rate of product formation of 1.00 nmol (per mg of microsomal protein per minute). The maximum specific activity of liver microsomes with respect to the dealkylation of chlorfenvinphos achieved in dieldrin-pretreated monkeys given oral chlorfenvinphos doses of 0.03 mg/kg/day for 6.15 years was 1.8 nmol (per mg of microsomal protein per minute). It has been proposed that the mechanism of this reaction is mediated by oxidative dealkylation of chlorfenvinphos to the relatively nontoxic metabolite, 2-chloro-1-(2,4-dichlorophenyl) vinyl ethylhydrogen phosphate and acetaldehyde. The enzyme system was readily inducible, especially in the rat, by the administration of phenobarbital or dieldrin.

The maximum specific activity of liver microsomes with respect to the dealkylation of chlorfenvinphos achieved in dieldrin- and phenobarbital-pretreated rats was 12.4 nmol at 8 mg/kg/day for 4 weeks and 5.7 nmol at 14 mg/kg/day for 4 weeks, respectively. A 600-fold increase in specific activity was observed in the liver of dieldrin-pretreated rats; in rats pretreated with dieldrin at 200 ppm in the diet for 12 days, the acute LD_{50} for chlorfenvinphos was increased by a factor of 6–8. A quantitative study of the species distribution of phosphate esterases and glutathione *S*-alkyl transferase found that these enzymes are significantly less in the pig than all the other species studied, suggesting a significantly varied distribution among some mammalian species. The author of the study concluded that the distribution of these enzymes is an important factor in accounting for the species specificity of at least some anticholinesterase agents and that the glutathione-dependent alkyl transferase is predominantly a methyl transferase; the contribution of these two enzyme systems to the detoxification of any particular phosphate triester is dependent on the structure and solubility of the molecule (Donninger 1971).

These findings were confirmed by two other reports. In one, the oral LD_{50} values for rat, mouse, rabbit, and dog were 10–30, 150, 500, and >5,000 mg/kg, respectively; it can be >12,000 mg/kg in the rabbit. The difference in toxicity in rats and dogs was found to be due to rates of absorption and metabolism, bioavailability in blood, and rates of uptake by the brain and sensitivity of brain cholinesterase to the phosphorylating action of the compound. In studies using rats and dogs, the most important reaction in detoxification is the conversion of chlorfenvinphos to de-ethylchlorfenvinphos by oxidative de-ethylation. The reaction is catalyzed by a hepatic microsomal monooxygenase, probably cytochrome P-450. The relative rates of de-ethylation in liver slices were 1, 8, 24, and 88 for the rat, mouse, rabbit, and dog, respectively. Thus, an excellent inverse correlation between oral LD_{50} and rate of de-ethylation was established. Also evidence for the significance of the reaction *in vivo* was provided from experiments in which rats were protected 7-fold from the action of chlorfenvinphos by pre-treatment with dieldrin in the diet for 12 days. This treatment induces cytochrome P-450 microsomal monooxygenase and, thus, chlorfenvinphos de-ethylation. The de-ethylation was induced about 40-fold (measured *in vitro*) relative to cytochrome P-450 concentration. However, the author cautioned that species differences in toxicity response are often multi-factorial, and metabolism can be a minor component (Hutson and Millburn 1991).

In the second report, the metabolism of chlorfenvinphos in kidney subcellular fraction and in the serum of Fischer 344 rats (orally pretreated with chlorfenvinphos followed by an oral treatment with a similar chlorfenvinphos dose or 50 mg/kg phenobarbital in 24 hours), with or without the NADPH-generating system, was found to be negligible. Metabolism of chlorfenvinphos in the liver subcellular fraction without the NADPH-generating system was also practically negligible. However, when the NADPH-generating system was added to the liver subcellular fraction, chlorfenvinphos metabolism increased significantly (203% in the 9,000 g fraction and 178% in the microsomes) in the chlorfenvinphos-pretreated animals and in the phenobarbital-pretreated animals (565%). Additionally, chlorfenvinphos pretreatment increased cytochrome P-450 content (30%) in the hepatic microsomal fraction; phenobarbital pretreatment caused a 180% increase. Hepatic microsomal cytochrome b5 content and cytochrome P-450 reductase activity were also increased by chlorfenvinphos and phenobarbital pretreatment (121 and 130%, respectively, for chlorfenvinphos and 126 and 139%, respectively, for phenobarbital). Both chlorfenvinphos and phenobarbital pretreatment significantly increased protein content (P<0.001) in the microsomal fraction. Chlorfenvinphos treatment did not increase liver weight (relative to body weight). Increases were also noted in cytochrome P-450-linked activities such as aminopyrine *N*-demethylase (40%) and aniline hydroxylase (27%) content in the hepatic microsomal fraction and hexobarbital sleeping time and zoxazolamine paralysis time. Both chlorfenvinphos and phenobarbital are potent inducers of cytochrome P-450, which is involved in the metabolic detoxication of chlorfenvinphos. Thus, the

authors concluded that the increase in hepatic chlorfenvinphos metabolism may be due to the induction of the hepatic cytochrome P-450 system caused by the single oral short-term treatment. Also this induction may be one of the reasons for the decrease in plasma chlorfenvinphos concentration, which may be responsible for the reduction in toxicity of subsequent exposure to chlorfenvinphos (Ikeda et al. 1991).

Some of the major sites and enzyme systems involved in the detoxication of direct-acting neurotoxic organophosphates, like chlorfenvinphos, are NADPH-P-450, GSH transferase, FAD-monooxygenase and esterases; the most important of these is monooxygenase. The major activation step for microsomal monooxygenases is of critical importance for the toxicity of organophosphate compounds like chlorfenvinphos. According to this study, the relative rates of chlorfenvinphos *O*-dealkylation in rats, mice, rabbits, and dogs are 1, 8, 24, and 88, respectively. These rates correlated well with the oral LD_{50} values for these species, which were given as 10, 100, 500, and 12,000 mg/kg for rats, mice, rabbits, and dogs, respectively. According to the author, the potential for oxidative *O*-dealkylation in the P-450 pathway varies widely with species, with activity toward chlorfenvinphos correlating well with species selectivity. The author concluded that the biotransformation of delayed neurotoxicants will certainly influence relative potencies, but the distinction between a delayed neurotoxicant and the neurotoxicity of organophosphate compounds, which is mainly limited to acute effects, depends more heavily on pharmacodynamic than pharmacokinetic considerations. Thus, the pharmacokinetics of delayed neurotoxicants differ from the pharmacokinetics of neurotoxic organophosphates, like chlorfenvinphos (Hansen 1983).

2.4.2   Mechanisms of Toxicity

Most chlorfenvinphos toxicity results from the inhibition of cholinesterase activity in the central and peripheral nervous system when administered by the oral (Cupp et al. 1975; Pach et al. 1987) or inhalation route in acute-duration exposures in humans (Kolmodin-Hedman and Eriksson 1987), and when administered by the oral (Barna and Simon 1973; Osicka-Koprowska et al. 1984; Takahashi et al. 1991) or dermal route in acute-duration exposures in animals. Inhibition of cholinesterase activity results in accumulation of acetylcholine at muscarinic and nicotinic receptors leading to peripheral and central nervous system effects. These effects usually appear within a few minutes to a few hours after exposure depending on the extent of exposure. The enzyme is responsible for terminating the action of the neurotransmitter acetylcholine in the synapse of the pre- and post-synaptic nerve endings or in the neuromuscular junctions. On arrival of a nerve impulse at the synaptic gutter between the pre- and post-synaptic nerve endings or effector muscle fiber endplates, there is a

release of acetylcholine from the pre-synaptic terminals. At the post-synaptic nerve ending, acetylcholine acts as a chemical mediator to perpetuate the action potential. However, the action of - acetylcholine does not persist long as it is hydrolyzed by the enzyme, acetylcholinesterase, and rapidly removed.

As an anticholinesterase organophosphate, chlorfenvinphos inhibits the activity of the acetylcholinesterase enzyme by reacting with the esteratic sites of the enzyme to form a stable phosphorylated complex which is incapable of destroying acetylcholine at the synaptic gutter between the pre- and post-synaptic nerve endings in the central and peripheral nervous system or neuromuscular junctions of skeletal muscles, resulting in the accumulation of acetylcholine at these sites. This leads to continuous or excessive stimulation of cholinergic fibers in the post-ganglionic parasympathetic nerve endings, neuromuscular junctions of the skeletal muscles, resulting in hyperpolarization of nerve or muscle fibers and receptor desensitization until hydrolysis of the phosphorylated cholinesterase occurs. In some cases, a dealkylation and stabilization of the phosphorylated enzyme ("aging") occurs such that hydrolysis can no longer take place and the enzyme is irreversibly inhibited. In such cases, return of acetylcholinesterase activity parallels the time required to resynthesize this enzyme.

In the parasympathetic system, stimulation of postganglionic fibers on the effector organs is mimicked by muscarine, and the receptors for the transmitters are called muscarinic receptors. They are found primarily in smooth muscle, the heart, and the exocrine glands. Stimulation of these receptors by inhibition of acetylcholinesterase activity produces signs and symptoms of cholinergic poisoning that include bronchoconstriction and increased bronchial secretions, increased salivation and lacrimation, exophthalmos, increased sweating, increased gastrointestinal tone and peristalsis, nausea, vomiting, abdominal cramps, diarrhea, hypotension and bradycardia that can lead to heart block, involuntary urination caused by contraction of the smooth muscle of the bladder, and constriction of the pupils or miosis.

At the autonomic ganglia and neuromuscular junctions, stimulation of transmission is mimicked by the action of nicotine, and the receptors are called nicotinic receptors. Inhibition of acetylcholinesterase activity leads to abnormal continuous or excessive stimulation of the receptor muscle fibers, causing weakness of the muscles, involuntary twitching, fasciculations, cramps, and eventual paralysis of the muscles. Paralysis of the respiratory muscles leads to respiratory failure and death. The central nervous system effects are due to accumulation of acetylcholine at various cortical, subcortical, and spinal levels (primarily in the cerebral cortex, hippocampus, and extrapyramidal motor system). Accumulation of acetylcholine in the central nervous system causes tension, anxiety, restlessness,

insomnia, headache, emotional instability, neurosis, excessive dreaming and nightmares, apathy, drowsiness, confusion, slurred speech, tremor, ataxia, convulsions, depression of respiratory and circulatory centers, and coma. The most likely cause of death in fatal organophosphate poisoning is paralysis associated with respiratory failure (Cupp et al. 1975; Klaassen et al. 1986; Shankar; Takahashi et al. 1991; Williams and Burson 1985).

The results of pretreatment of New Zealand white rabbits with 0.007 mg/kg oxotremorine, a direct agonist of muscarinic receptors, followed by treatment with 0.5 mg/kg chlorfenvinphos by hypothalamic infusion suggests that the chlorfenvinphos is neither an agonist nor antagonist of the muscarinic receptors in the rabbit hypothalamus. No overt changes in behavior or changes in hippocampal EEG were observed in the rabbits following infusion with 0.5 mg/kg chlorfenvinphos (Gralewicz et al. 1995).

Organophosphate-induced hypotension (reported for chlorfenvinphos only in rats receiving intravenous doses) (Takahashi et al. 1991) has been suggested to be due to factors other than inhibition of cholinesterase activity (Kojima et al. 1992). A study concluded that the alteration of brain and liver activities of the aromatic amino acid transferases may be due to the inhibitory effect of chlorfenvinphos on noradrenaline (norepinephrine) activity (Puzynska 1984). In other studies, chlorfenvinphos was shown to independently inhibit noradrenaline (norepinephrine) activity *in vivo* in rats rapidly (3 hours) at doses as low as 4 mg/kg (Brzezinski 1978; Osumi et al. 1975). On this basis, it has been postulated that chlorfenvinphos may also act via central noradrenergic mechanisms, disturbing the dynamic equilibrium between the rate of formation and utilization of noradrenaline (norepinephrine). This action via central noradrenergic mechanisms by chlorfenvinphos may be responsible for the changes in blood pressure observed in other studies after chlorfenvinphos intoxication (Brzezinski 1978).

It has also been suggested that the cholinergic action of organophosphates like chlorfenvinphos may interfere with the pathways controlling the secretory activity of the anterior pituitary lobe and the adrenal cortex whose hormones influence the activities of many enzymes, including aromatic amino acid transferases (Puzynska 1984). Interference with the secretory activity of the adrenal cortex may lead to a disruption in the normal activities of one or more components of the renal blood pressure regulatory systems (Klaassen et al. 1986).

2.4.3   Animal-to-Human Extrapolations

In one study, the rates of chlorfenvinphos de-ethylation by human liver microsomal fractions are 0.36 nmol/minute per mg protein (range 0.11–0.82) without induction and 1.03 nmol/minute per nmol

of cytochrome P-450 (range 0.42–1.78) with induction. The rates of chlorfenvinphos de-ethylation by liver microsomal fractions are 0.62 nmol/minute/mg protein (range 0.36–0.93) and 1.30 nmol/minute/nmol cytochrome P-450 (range 0.81–1.74) for uninduced rabbits. The rabbit is considered relatively resistant to the acute toxic action of chlorfenvinphos, with an LD_{50} of 500–1,000 mg/kg (provided in another study). These results demonstrate that human hepatic cytochrome P-450 is almost as active as that of rabbits. However, the authors stressed that these results refer to the total cytochrome P-450 complement of the cells and take no account of the several forms known to exist which differ from species to species, or of the environmental factors, and the other factors involved in the acute toxicity of chlorfenvinphos in humans. Based on the findings in this study, it appears that humans may de-ethylate chlorfenvinphos more like rabbits or mice than like rats (Hutson and Logan 1986).

2.5   RELEVANCE TO PUBLIC HEALTH

Overview

Chlorfenvinphos is an insecticide that was broadly used in the United States in both agriculture and control of pests in residential dwellings, gardens, and on household pets from 1963 until 1991, when all products containing chlorfenvinphos as an active ingredient were canceled (REFS 1995).

The absorption of chlorfenvinphos after inhalation exposure in humans or animals is unknown due to lack of data. Ingested and dermally contacted chlorfenvinphos is rapidly absorbed in humans and animals; the rate of absorption is dependent on the solvent in which the substance is dissolved. In humans, absorbed chlorfenvinphos is widely distributed and has been detected in compartments that include serum, cervical mucus, follicular and sperm fluids, and milk. It is extensively metabolized via oxidative dealkylation by liver microsomal fractions. Data from animal studies suggest that electrophilic metabolic intermediates or epoxides may be produced in the metabolism of chlorfenvinphos. There is no information on the elimination or excretion of chlorfenvinphos in humans and animals after inhalation or dermal exposures; however, ingested chlorfenvinphos is rapidly eliminated via the urine and feces, and expired air in animals. In humans, ingested chlorfenvinphos is rapidly removed from the blood and passed into the tissues; chlorfenvinphos has been detected in human sperm fluid and milk samples.

As an anticholinesterase organophosphate, the principal toxic effect of chlorfenvinphos is the inhibition of cholinesterase activity in the central and peripheral nervous system when administered by the oral

or inhalation route in acute-duration exposures in humans and the inhibition of cholinesterase activity in the central and peripheral nervous system when administered by the oral, or dermal route in acute-duration exposures. Inhibition of cholinesterase activity results in the accumulation of acetylcholine at acetylcholine receptors leading to cholinergic responses in the peripheral (muscarinic and nicotinic) and central nervous system and neuromuscular junctions. Severe inhibition of acetylcholinesterase activity often leads to cholinergic symptoms in humans and laboratory animals, which include excessive glandular secretions (salivation, lacrimation, rhinorrhea, miosis), exophthalmos, bronchoconstriction, vasodilation, hypotension, diarrhea, nausea, vomiting, urinary incontinence, and bradycardia. Tachycardia, mydriasis, fasciculations, cramping, twitching, muscle weakness, and muscle paralysis are associated with nicotinic receptor stimulation. Central nervous system toxicity may be mediated by either muscarinic or nicotinic receptors and includes respiratory depression, anxiety, insomnia, headache, apathy, drowsiness, dizziness, loss of concentration, confusion, tremors, convulsions, and coma. In non-fatal exposures, the effects are transient and recovery is rapid and complete following cessation of exposure. In sufficiently high doses, chlorfenvinphos exposure has resulted in death of humans, rats, and mice. These effects usually occur within a few minutes to a few hours after dosing, depending on the extent of exposure. In addition, chlorfenvinphos may interfere with the activity of noradrenaline (norepinephrine) in central adrenergic mechanisms in animals.

The greatest potential for significant exposure to this compound is found in occupational settings (i.e., manufacture and application of chlorfenvinphos). Currently, the most common exposure scenario for the general population comes from home use of imported foods and lanolin-containing pharmaceutical products. Workers involved in disposal of chlorfenvinphos-contaminated wastes are at a higher risk of exposure. Populations potentially at higher risk of exposure are: people living in the vicinity of plants where chlorfenvinphos was manufactured; people living near dairy farms, cattle or sheep holding areas, or poultry producing-facilities where chlorfenvinphos was used; and populations living near hazardous waste sites containing chlorfenvinphos. No association has been reported between chlorfenvinphos toxicity and low-level environmental contamination.

Minimal Risk Levels for Chlorfenvinphos

Inhalation MRLs.

Inhalation MRLs for acute-, intermediate-, or chronic-duration exposure to chlorfenvinphos have not been calculated because adequate data for developing these MRLs are not available. The available human reports involve mixed exposures. The available animal studies reported serious effects.

A human study reported immunological effects at a LOAEL of 0.21 mg/m^3 following prolonged occupational exposure to chlorfenvinphos by the inhalation route. However, the subjects of this study were also concurrently exposed to greater concentrations of other potentially immunotoxic substances such as formothion, sumithion, and malathion (Wysocki et al. 1987). In another human study, a group of nine gardeners (pesticide mixers) exposed to unknown concentrations of a mixture of pesticides (chlorfenvinphos, dimethoate, formothion, isofenphos), complained of headaches and had a mean difference (before and after exposure) of 0.56 nmol/mL for acetylcholinesterase and 2.67 nmol/mL for butyrylcholinesterase (Kolmodin-Hedman and Eriksson 1987). However, since these symptoms could also result from exposure to the other organophosphate pesticides in the mixture, the etiology for these symptoms is uncertain. Therefore the study was not useful for developing inhalation MRLs.

The available inhalation animal studies reported only serious effects (mortality, apnea, salivation, urination, exophthalmos, twitches, and tremors) (Takahashi et al. 1994; Tsuda et al. 1986) following exposure to chlorfenvinphos. Therefore, the data from these studies are not appropriate for use in the calculation of MRLs.

Oral MRLs.

C   An MRL of 0.002 mg/kg/day has been developed for acute-duration oral exposure (14 days or less) to chlorfenvinphos.

This MRL for chlorfenvinphos is based on a LOAEL of 2.4 mg/kg/day for neurological effects (38% erythrocyte cholinesterase inhibition) in female rats (Barna and Simon 1973). In the study, two groups of adult female albino (Wistar) rats weighing 208 g were orally administered Birlane$^®$ (chlorfenvinphos) at dose of 0 or 2.4 mg/kg/day in the diet for 10 days. The study was designed to investigate the

effects of oral chlorfenvinphos on body weight increase, the gastrointestinal absorption of glucose, Na^+, and Ca^{2+}, and the effects of oral chlorfenvinphos on plasma and erythrocyte cholinesterase activity levels. Plasma cholinesterase activity was inhibited by 52%, and erythrocyte cholinesterase activity level was inhibited by 30% at a dose of 2.4 mg/kg/day (the only dose tested). Gastrointestinal absorption of glucose was increased by 30% over control values while Na^+ absorption was decreased by 32% below control values. Gastrointestinal absorption of Ca^{2+} and body weight increases were unaffected by chlorfenvinphos exposure. These changes in the gastrointestinal absorption of glucose, but Na^+ were not considered statistically significant ($P>0.05$) by the investigators.

The central nervous system is the principal target of chlorfenvinphos toxicosis. Chlorfenvinphos, an anticholinesterase organophosphate, inhibits cholinesterase activity in the central and peripheral nervous system in humans and animals (Cupp et al. 1975; Gralewicz et al.1990; Hunter 1969; Maxwell and LeQuesne 1982; Osumi et al. 1975; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972). Chlorfenvinphos also inhibits noradrenaline (norepinephrine) activity in the central nervous system in animals (Brzezinski 1978; Osumi et al. 1975). Human subjects exposed to large acute doses of chlorfenvinphos exhibited severe cholinergic signs. These cholinergic signs were relieved by the administration of atropine and/or pralidoxime, indicating cholinesterase inhibition etiology (Cupp et al. 1975; Pach et al. 1987). In rats, low to moderate doses (2.4–30 mg/kg) of oral chlorfenvinphos significantly inhibited cholinesterase activities in a number of tissues: the brain, erythrocyte, and plasma (Barna and Simon 1973; Osicka-Koprowska et al. 1984; Puzynska 1984). An acute-duration oral study also found alterations in noradrenaline (norepinephrine) level in rat brain following exposure to chlorfenvinphos. A chlorfenvinphos dose of 13 mg/kg decreased noradrenaline (norepinephrine) levels in rat brains by 20%, as compared to control rats. According to the investigators, chlorfenvinphos accelerated the rate of NA disappearance from the brain (Brzezinski 1978).

Therefore, it is appropriate to base the acute oral MRL for chlorfenvinphos on cholinesterase inhibition.

It should be noted that a study by Osumi et al. (1975) which determined a NOAEL of 1 mg/kg/day and a LOAEL of 2 mg/kg/day for 38% inhibition of brain cholinesterase in rats was not used to calculate an acute oral MRL because it was deemed less appropriate due to the gavage (oral) route of administration of the test substance. An oral feeding study is preferred by ATSDR.

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

The MRL is based on a LOAEL of 1.5 mg/kg/day for adverse immunological/lymphoreticular effects in
mice (Kowalczyk-Bronisz et al. 1992). In this study male and female inbred C57BL/6 mice and
(C57BL/6 x DBA/2)F1 (BDF1/liw) hybrid mice (6–8 weeks old) were orally dosed with chlorfenvinphos
(suspended in 1% methylcellulose solution) and evaluated for 5 days for the effect of chlorfenvinphos
exposure on the mouse immune system. The mice were exposed to oral chlorfenvinphos doses of 0,
1.5, 3, or 6 mg/kg (0, 1/100, 1/50, or 1/25 LD_{50}) daily for 3 months; the control group was given 1%
methylcellulose. Then exposed and control mice were immunized by intraperitoneal injections of
0.2 mL 10% sheep red blood cells. The IgM-PFC (plaque-forming or antibody-producing cells)
number in spleen cell suspension was tested on day 4 after immunization and the procedure
repeated 3 weeks after the exposure to chlorfenvinphos had been ceased. Exposed and control
groups were subjected to immunological tests and hematological examinations. Lymphatic organs
were histologically examined. A dose-related decrease in the number of hemolysin-producing cells
was observed: plaque-forming cells (PFC) were 58% at the 6 mg/kg dose group and 85% at the
3 mg/kg dose level as compared to control values. Chlorfenvinphos treatment also caused reduction
in the number of E rosette-forming cells by 30% at the 6 mg/kg dose level and by 25% at the 3 mg/kg
dose level. Increases in Interlukin-1 (Il-1) activity and delayed-type hypersensitivity (DTH) reaction
were observed 24 hours after challenge. Spleen colonies were stimulated, as evidenced by the
increase of endogenous spleen colonies and exogenous spleen colonies (CFU-S). CFU-S increased
190% at the 1.48 mg/kg dose level; 137% at the 6 mg/kg dose level; 162% at 1.5 mg/kg dose level;
and 70% at the 6 mg/kg dose level. When the IgM PFC number was tested 3 weeks later, after the
exposure to chlorfenvinphos in the small dose (1.5 mg/kg), an increase (about 40%) in number of
plaques was observed. There was a 50% reduction in thymus weight at the 1.5 mg/kg dose level,
compared to controls; significant involution of the thymus was also noted.

In other studies, adverse immunologic/lymphoreticular effects have been associated with exposure to
oral chlorfenvinphos. In an intermediate-duration dietary study with albino (Wistar) rats, there was a
significant and irreversible reduction in relative spleen weight of female rats given $3 mg/kg/day
chlorfenvinphos for 12 weeks (Ambrose et al. 1970). A study was undertaken to evaluate selected
serological and cytoimmunological reactions in rabbits subjected to a long-term poisoning with
subtoxic oral doses (10 mg/kg in a soya oil solution with a small amount of food) of chlorfenvinphos
for 90 days. Chlorfenvinphos treatment significantly elevated serum hemagglutinin levels (16%) and

hemolysin activity (66%, P<0.05), and also increased the number of nucleated lymphoid cells producing hemolytic antibody to sheep erythrocytes, compared to controls (treated 906, P<0.05 and controls 618). Spleen cytomorphology changes, manifested mainly as transformation of primary follicles into secondary ones with well developed germinal centers, were also observed (Roszkowski 1978).

Therefore, it is appropriate to base the intermediate oral MRL for chlorfenvinphos on immunological effects.

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

This MRL for chlorfenvinphos was developed from a LOAEL of 0.7 mg/kg/day for adverse neurological effects in rats (Ambrose et al. 1970). In this study, four matched groups of weanling albino (Wistar) rats were culled to a narrow starting weight range and fed daily GC-4072 (technical chlorfenvinphos) doses of 0, 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0, 0.8, 2.4, or 8, or 24 mg/kg/day (females) in the diet for 104 weeks. An additional group of non-littermate rats were administered 21 mg/kg/day (males) or 24 mg/kg/day (females) chlorfenvinphos for 104 weeks. Plasma and erythrocyte cholinesterase (ChE) activity levels were obtained from 4 rats of each sex per dose group at 1, 4, 8, and 12 weeks. At 13 weeks, 4 rats/sex/dose group were sacrificed for histopathologic examination. The rats in the 21 mg/kg/day (males) and 24 mg/kg/day (females) were sacrificed on the 95th week, and all other dose group animals were sacrificed on the end of the study (104 weeks). At each autopsy, relative organ weights were determined for heart and kidneys. All animals sacrificed in moribund condition, as well as those sacrificed at week 13, 95, and 104 weeks were examined grossly and microscopically, and organs (heart, lungs, liver, kidney, urinary bladder, spleen, stomach, small and large intestine, skeletal muscle, skin, bone marrow, pancreas, thyroid, adrenal, pituitary) from these animals were histopathologically examined. Chlorfenvinphos significantly decreased body weight gain of females at the 8 and 24 mg/kg/day dose groups from the 26th week until near the end of the study, although the decreased body weight gain became statistically insignificant at the end of the study. Increased relative liver weights were observed in males at the 7 mg/kg/day dose level, but no other signs of hepatopathology were reported. Compared to undosed controls, no consistent differences in body weight gains in males, survival of the test animals, food consumption, or mortality were evident at any dose level tested. No gross or microscopic histopathology was evident in any of the organs (heart, lungs, liver, kidney, urinary bladder, spleen, stomach, small and large intestine, skeletal muscle, skin, bone marrow, pancreas, thyroid, adrenal, pituitary) and tissues examined. No changes in organ-to-body weight were observed in the heart, kidney, spleen and testes.

Although the neurological effects of prolonged human exposure to low oral doses of chlorfenvinphos are not known due to a lack of studies, clinical reports of accidental and intentional acute exposure to relatively high doses of chlorfenvinphos-containing organic phosphate products indicate that neurological effects, mediated by cholinesterase inhibition (Cupp et al. 1975; Pach et al. 1987), may be the most sensitive toxicological consequences of human exposure to chlorfenvinphos. Similarly, chlorfenvinphos significantly inhibited both plasma and erythrocyte cholinesterase activities in Beagle dogs fed daily chlorfenvinphos doses of 0.3, 2, or 10 mg/kg/day (males), or 1.5, 10, or 50 mg/kg/day (females) in the diet (moist) for 104 weeks. Plasma cholinesterase activities were significantly inhibited at all dietary levels through week 39 of the study; 49% inhibition was noted at the 0.3 mg/kg/day (males) and 1.5 mg/kg/day (females) dose levels. Erythrocyte cholinesterase activity was significantly and consistently inhibited (36%) during the first 12 weeks only in the 10 mg/kg/day (males) and 50 mg/kg/day (females) dose levels (Ambrose et al. 1970).

Death.   Data are not available to estimate the lethal dose of chlorfenvinphos by any route or for any duration of exposure in humans. However, one study reported the death of a 16-year-old victim following unintentional ingestion of an unspecified amount of chlorfenvinphos (Felthous 1978). In animal studies, the acute inhalation LC_{50} for rat is estimated as 130 mg/m^3 (Tsuda et al. 1986). The acute oral LD_{50} for technical chlorfenvinphos for both sexes of rat is variously estimated as 15.4 mg/kg (Hutson and Wright 1980); 22.8 mg/kg (Hutson and Logan 1986); 34.3 mg/kg (Ikeda et al. 1992); and 9.7 mg/kg/day (Ambrose et al. 1970). The acute oral LD_{50} values for male and female rats have been given as 23 mg/kg and 25.5 mg/kg, respectively (Puzynska 1984). Chlorfenvinphos appears to be less acutely toxic to mice than to other experimental animals, with estimated LD_{50} values of 148 mg/kg (male) and 109 mg/kg (female) (Kowalczyk-Bronisz et al. 1992). The LD_{50} for rabbits has been estimated to be 300 mg/kg (Ambrose et al. 1970) and 500–1,000 mg/kg (Hutson and Logan 1986); the estimated LD_{50} for dogs is 50.5 mg/kg/day (Ambrose et al. 1970).

The dermal LD_{50} values for undiluted chlorfenvinphos and emulsifiable concentrate for rabbits have been estimated as 400 and 1,087 g/kg, respectively (Ambrose et al. 1970). No reports of human deaths resulting from dermal exposure to chlorfenvinphos were located, but evidence from non-lethal human data and animal studies (Hunter 1969; Vestweber and Kruckenberg 1972) indicates that human lethality by this route of exposure is unlikely.

Systemic Effects.

Respiratory Effects. No studies were located regarding respiratory effects in humans following acute-, intermediate- or chronic-duration inhalation, oral, or dermal exposure to chlorfenvinphos. Respiratory effects were noted in two clinical reports of human ingestion: accidental ingestion of a mange-mite medication containing organic phosphate; and intentional ingestion in a suicide attempt of the preparation Enolofos®, which contains 50% chlorfenvinphos. In both cases, effects stemmed from central cholinergic disturbances (Cupp et al. 1975; Pach et al. 1987). Animal data indicate that acute-duration inhalation exposure to high doses of chlorfenvinphos (16–390 mg/m^3) may be accompanied by transient apnea (Takahashi et al. 1991, 1994). No effects on the respiratory system were noted in rats and dogs orally administered chlorfenvinphos at doses as high as 100 mg/kg/day (rats) or 50 mg/kg/day (dogs) for 12 weeks; or in rats at doses as high as 24 mg/kg/day for 104 weeks (Ambrose et al. 1970). Due to inadequate data, it is unknown whether human exposure to environmental concentrations of chlorfenvinphos could result in adverse respiratory effects.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal exposure to chlorfenvinphos. Animal data indicate that acute-duration inhalation exposure to high doses of chlorfenvinphos (16–390 mg/m^3) may be preceded by an initial hypotension followed by steadily increasing hypertension and abnormal cardiac conductivity (Takahashi et al. 1991, 1994). Evidence from animal studies also indicates that oral chlorfenvinphos is not directly toxic to the cardiovascular system, but may modulate the function of the cardiovascular system via its effect on the central nervous system (Ambrose et al. 1970; Klaassen et al. 1986; Puzynska 1984). Although this route of exposure may not be relevant to human exposure to chlorfenvinphos, Sprague-Dawley rats also exhibited similar signs at a dose of 16 mg/kg following intravenous administration of the chlorfenvinphos (Takahashi et al. 1991). Due to inadequate data, it is unknown whether human exposure to environmental concentrations of chlorfenvinphos could result in adverse cardiovascular effects.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorfenvinphos. Acute- and intermediate-duration oral exposures to chlorfenvinphos increased gastrointestinal absorption of glucose, while decreasing the gastrointestinal absorption of Na$^+$; however, Ca^{2+} absorption was unaffected in adult Wistar rats. These changes in glucose and Na$^+$ absorption were not considered statistically significant ($P>0.05$) by the investigators (Barna and Simon 1973). Weanling albino (Wistar) rats of both sexes chronically administered daily dietary chlorfenvinphos doses of 21 mg/kg/day (males) or 24 mg/kg/day (females) exhibited no gross or microscopic histopathology in

the stomach or small and large intestine at autopsy (Ambrose et al. 1970). Based on the available information, human exposure to chlorfenvinphos at hazardous waste sites is not likely to result in any significant adverse gastrointestinal effects.

Hematological Effects. The hematological effects from inhalation exposure to chlorfenvinphos are not known due to lack of data in humans and laboratory animals. Similarly, the hematological effects of oral chlorfenvinphos exposure are not certain because of limited and inconclusive data in animals. Uncorroborated investigations conducted on 4 groups of male and female rabbits (13 each) at a dose of 10 mg/kg for 90 days to evaluate the serological effects of chlorfenvinphos reported significant increases of hemolysin and hemagglutinin serum titers as compared to controls. Hemagglutinin and hemagglutinin IgG titers were increased by 16 and 18%, respectively, while hemolysin and hemolysin IgG titers were elevated by 66 and 102%, respectively (Roszkowski 1978). However, no effects were observed on monitored hematological parameters in rats and Beagle dogs given oral chlorfenvinphos (up to 24 mg/kg/day for rats and 50 mg/kg/day for dogs) for 104 weeks (Ambrose et al. 1970). Due to the lack of data on the hematological effects of chlorfenvinphos in humans and scarcity of data in animals, the hematological effects of human exposure to chlorfenvinphos are uncertain.

Musculoskeletal Effects. No studies were found regarding musculoskeletal effects in humans or animals following inhalation or dermal exposure to chlorfenvinphos. In animal oral studies, no effects on the musculoskeletal system were noted in dogs orally administered chlorfenvinphos at doses as high as 50 mg/kg/day (females) for 12 weeks; or in rats at doses as high as 24 mg/kg/day (females) for 104 weeks (Ambrose et al. 1970). Therefore, adverse musculoskeletal effects in humans from exposure to chlorfenvinphos at hazardous waste sites are not likely.

Hepatic Effects. Based on the currently available data, chlorfenvinphos exposure at environmental levels is not likely to present risk of liver injury to humans. No hepatic effects were reported in humans from exposure to chlorfenvinphos by any route. Although chlorfenvinphos proved to be porphyrinogenic in tissue culture without induction and markedly porphyrinogenic with induction (Koeman et al. 1980), no such evidence was found in the currently available *in vivo* studies. The limited information on the hepatic effects of chlorfenvinphos indicates that the substance is not significantly hepatotoxic by the oral route in acute-, intermediate-, or chronic-duration exposures. While no changes in liver weight (relative to body weight) were reported in Fischer 344 rats given a single oral chlorfenvinphos dose of 15 mg/kg, P-450 activity was increased by 30%. Aminopyrine-*N*-demethylase and aniline hydroxylase activities were also increased by 40 and 27%, respectively

(Ikeda et al. 1991). Although intermediate oral administration of doses of chlorfenvinphos induced alterations in serum sorbitol dehydrogenase and brain and liver levels of aromatic amino acids transferases L-phenylalanine aminotransferase, L-tyrosine aminotransferase, and L-tryptophan aminotransferase in mature Wistar rats (Puzynska 1984), no gross or microscopic histopathology in liver tissues was evident in weanling albino (Wistar) rats administered daily dietary chlorfenvinphos doses of 90 mg/kg/day (males) or 100 mg/kg/day (females) or in mongrel dogs given daily dietary doses of 10 mg/kg/day (males) or 50 mg/kg/day (females) for 12 weeks. However, relative liver weights were significantly and irreversibly decreased in the rats at a dose of 2.7 mg/kg/day (males) or 3 mg/kg/day (females) (Ambrose et al. 1970). In chronic (104 weeks) feeding studies, increased relative liver weights were observed in males at a dose of 7 mg/kg/day following dietary administration of chlorfenvinphos to both sexes. No liver histopathological or adverse liver function effects were reported in Beagle dogs fed daily dietary chlorfenvinphos doses of 10 mg/kg/day (males) or 50 mg/kg/day (females) for 104 weeks (Ambrose et al. 1970).

Renal Effects. No studies were located regarding renal effects in humans or animals following acute-, intermediate-, or chronic-duration oral exposure to chlorfenvinphos. In one study, no gross or microscopic histopathology in kidney tissues was evident in weanling albino (Wistar) rats administered daily dietary chlorfenvinphos doses of 90 mg/kg/day (males) or 100 mg/kg/day (females), or in mongrel dogs given daily dietary doses of 10 mg/kg/day (males) or 50 mg/kg/day (females) for 12 weeks. However, relative kidney weights were significantly and irreversibly decreased in the rats at a dose of 2.7 mg/kg/day (males) or 3 mg/kg/day (females) (Ambrose et al. 1970). In chronic (104 weeks) feeding studies, no gross or microscopic histopathology in the kidney and urinary bladder tissues examined or changes in relative kidney weights were evident in this strain of rats following daily doses of 21 mg/kg/day (males) or 24 mg/kg/day (females) (Ambrose et al. 1970). No kidney histopathological or adverse kidney function effects were reported in Beagle dogs fed daily dietary chlorfenvinphos doses of 10 mg/kg/day (males) or 50 mg/kg/day (females) for 104 weeks (Ambrose et al. 1970). Renal function was not assessed in these studies. Due to the lack of adequate data on the renal effects on chlorfenvinphos in humans and animals, the renal effects of human exposure to chlorfenvinphos are not known.

Endocrine Effects. There are no reports of endocrine effects in humans exposed by acute-, intermediate-, or chronic-duration ingestion of chlorfenvinphos. No studies were located regarding endocrine effects in animals after intermediate- or chronic-duration oral exposure to this insecticide. Although a significant increase (>300%) of plasma corticosterone was observed at 1 and 3 hours, and

of plasma aldosterone from 1 to 6 hours after treatment of male Wistar rats with a single chlorfenvinphos dose of 6.15 mg/kg (50% LD_{50}) by stomach tube (Osicka-Koprowska et al. 1984), the toxicological significance of these findings and relevance to human health are unknown.

Dermal Effects. No studies were found regarding dermal effects in humans or animals following inhalation or dermal exposure to chlorfenvinphos. In animal oral studies, no adverse changes were seen in the skin of weanling albino (Wistar) rats of both sexes given oral doses of up to 100 mg/kg/day (female rats) chlorfenvinphos for 12 weeks (Ambrose et al. 1970). Similarly, no adverse changes were seen in the skin of weanling albino (Wistar) rats of both sexes chronically (104 weeks) given daily dietary chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females) (Ambrose et al. 1970). Therefore, adverse dermal effects in humans from exposure to chlorfenvinphos at hazardous waste sites are not likely.

Ocular Effects. No studies were located regarding ocular effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal exposure to chlorfenvinphos. Consequently, it is not known whether human exposure to environmental concentrations of chlorfenvinphos could result in adverse ocular effects.

Body Weight Effects. No studies were located regarding body weight effects in humans following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal exposure to chlorfenvinphos. In animal studies, acute-duration exposure of adult rats to oral Birlane® (chlorfenvinphos) at a dose of 2.4 mg/kg/day in the diet for 10 days did not affect body weight increases. Body weight increases were also unaffected following oral doses of 0.8 mg/kg/day in the diet for 30 days (Barna and Simon 1973). Similarly, no body weight changes were seen in mongrel dogs exposed to dietary chlorfenvinphos at a dose of 10 mg/kg/day (males) or 50 mg/kg/day (females) for 12 weeks (Ambrose et al. 1970). However, oral exposure of weanling rats for the same duration was associated with a significant but slightly reversible depression on growth, observed at a dose of 9 mg/kg/day (males) or 10 mg/kg/day (females). In an accompanying chronic-duration oral study (104 weeks), chlorfenvinphos also significantly and reversibly decreased body weight gain of female weanlings at dose levels of $8 mg/kg/day. Beagle dogs given daily dietary chlorfenvinphos doses of 10 mg/kg/day (males) or 50 mg/kg/day (females) for the same duration (104 weeks) exhibited no significant changes in body weight (Ambrose et al. 1970). Based on the available information, human exposure to environmental concentrations of chlorfenvinphos is not likely to result in any significant adverse body weight effects.

Metabolic Effects. Occupational exposure to airborne chlorfenvinphos significantly lowered NBT-dye reduction in both stimulated and non-stimulated cells, and caused a significant decrease of the spontaneous E rosette formation (not influenced by exposure time) in the blood (early E rosettes, 52%; late E rosettes, 57%). The authors of this study concluded that this may be regarded as a probable mechanism by which organophosphoric chemicals interfere with metabolism and cause membrane damage in human cells. About half of the subjects in the study were smokers (Wysocki et al. 1987). In animal studies, Carworth Farm E strain male rats orally administered a single [^{14}C]chlorfenvinphos dose of 2.5 or 13.3 mg/kg in olive oil (with or without prior monooxygenase induction with dieldrin) exhibited minimal changes in the metabolic profiles (Hutson and Wright 1980). However, the gastro-intestinal absorption of glucose was increased by 30% over control values, while Na$^+$ absorption was decreased by 32% below control values in adult female albino (Wistar) orally administered Birlane$^®$ (chlorfenvinphos) at a dose of 2.4 mg/kg/day in the diet for 10 days, although, Ca^{2+} absorption was unaffected. Similarly, oral chlorfenvinphos increased glucose absorption 12% while decreasing Na$^+$ absorption by 23% at a dose of 0.8 mg/kg/day in the diet to this strain of rats for 30 days. Gastro-intestinal absorption of Ca^{2+} was, likewise, unaffected by chlorfenvinphos exposure in this intermediate exposure to oral chlorfenvinphos. The changes in glucose and Na$^+$ absorption were not considered statistically significant ($P>0.05$) by the investigators (Barna and Simon 1973). The LOAEL of 2.4 mg/kg/day from the 10-day dosing protocol of this study, based on adverse neurological effects in rats was used to derive an acute oral MRL of 0.002 mg/kg/day for chlorfenvinphos.

Evidence from rat studies indicates that the alteration of brain and liver activities of the aromatic amino acid transferases by chlorfenvinphos may be due to the inhibitory effect of the substance on noradrenaline (norepinephrine) activity, since noradrenaline (norepinephrine) has been shown to affect amino acid transferase (L-tyrosine aminotransferase) activity in another study (Puzynska 1984).

Based on the available information, human exposure to environmental concentrations of chlorfenvinphos is not likely to result in any significant adverse metabolic effects.

Other Systemic Effects. No studies were located regarding other systemic effects in humans following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal systemic effects from exposure to chlorfenvinphos. In animal studies, no significant effect on food consumption was evident in weanling albino (Wistar) rats administered daily dietary chlorfenvinphos doses of 90 mg/kg/day (males) or 100 mg/kg/day (females) or in mongrel dogs given daily dietary doses of 10 mg/kg/day (males) or 50 mg/kg/day (females) for 12 weeks. Similarly, in chronic (104 weeks) feeding studies, no

significant effect on food consumption was evident in rats and Beagle dogs following daily doses of 21 mg/kg/day (males) or 24 mg/kg/day (females) and 10 mg/kg/day (males) or 50 mg/kg/day (females), respectively (Ambrose et al. 1970). Based on the available information, human exposure to environmental concentrations of chlorfenvinphos is not likely to result in any significant adverse effects on food consumption effects.

Immunological and Lymphoreticular Effects.   Only one study was located that reported immunological effects in humans. In this report, occupational exposure to inhaled chlorfenvinphos for an average of 15 years was associated with damage to humoral mechanisms in humans. The subjects exhibited significant decrease of the spontaneous E rosette formation and lowered absolute lymphocyte count in the peripheral blood. However, the subjects were also concurrently exposed to greater concentrations of other potentially immunotoxic substances such as formothion, sumithion, and malathion (Wysocki et al. 1987). In animal studies, the gastrointestinal absorption of glucose was increased by 30% over control values in adult female albino (Wistar) rats orally administered Birlane® (chlorfenvinphos) at a dose of 0 or 2.4 mg/kg/day in the diet for 10 days. Similarly, gastrointestinal absorption of glucose was increased by 12% over control values following orally administered Birlane® (chlorfenvinphos) at a dose of 0 or 0.8 mg/kg/day in the diet to this strain of rats for 30 days. However, the changes in glucose and Na^+ absorption were not considered statistically significant (P>0.05) by the investigators (Barna and Simon 1973). It has been observed in other studies that an increased metabolic activity of neutrophils and monocytes during phagocytosis is accompanied by higher consumption of glucose and oxygen. Hydrogen peroxide is then derived from the pentose cycle, NAD-, and NADP-oxidase action (Kolanoski 1977 as cited in Wysocki et al. 1977). However, the relationship between increased gastrointestinal absorption of glucose and increased glucose utilization is not clear. In other animal studies, rabbits orally exposed to chlorfenvinphos for 90 days also exhibited significantly elevated serum hemagglutinin level (16%) and hemolysin activity (66%, P<0.05) as well as increased numbers of nucleated lymphoid cells producing hemolytic antibodies to sheep erythrocytes. Spleen cytomorphology changes, manifested mainly as transformation of primary follicles into secondary ones with well developed germinal centers, were also observed (Roszkowski 1978). Intermediate-duration dietary exposure of rats resulted in a significant and irreversible reduction in relative spleen weight of female rats given $3 mg/kg/day chlorfenvinphos for 12 weeks. However, no gross or microscopic histopathology was evident in the spleen and bone marrow tissues of the rats upon examination (Ambrose et al. 1970). No histopathological changes in the spleen or bone marrow or changes in absolute or relative spleen weights were noted in rats or Beagle dogs of both sexes given dietary chlorfenvinphos doses of 21 mg/kg/day (males) or 24 mg/kg/day (females), or 10 mg/kg/day (males) or 50 mg/kg/day (females), respectively, for 104 week (Ambrose et al. 1970). C57BL/6 mice and (C57BL/6 x DBA/2)F1 (BDF1/Iiw) hybrid mice (6–8 weeks old) orally exposed to

chlorfenvinphos for 90 days exhibited a reversible reduction in the number of E rosette-forming cells as well as a dose-related decrease in the number of hemolysin-producing cells, reduction in the number of plaque-forming cells, increases in Interlukin-1 activity and DTH reaction, stimulation of spleen colonies, and disturbance in humoral immune factors (immunoglobulins) at a LOAEL of 1.5 mg/kg (Kowalczyk-Bronisz et al. 1992). The LOAEL of 1.5 mg/kg/day, based on adverse immunolymphoreticular effects in this study, was used to derive an intermediate oral MRL of 0.002 mg/kg/day for chlorfenvinphos. While the existing human inhalation study and the animal oral studies provide some indication that chlorfenvinphos exposure is associated with immunological changes, these changes were not consistent with depressive effect on immune reactions. Thus, the changes reported in these studies may simply be immunological mobilizations of the organisms to xenobiotics as opposed to damage to the major histocompatibility complex. Consequently, it is not certain that human inhalation or oral exposure to chlorfenvinphos can result in immune dysfunction.

Neurological Effects.   No studies were located regarding neurological effects in humans after acute- or intermediate-duration inhalation exposure to chlorfenvinphos, or after intermediate- or chronic-duration dermal exposure. Chlorfenvinphos inhibits cholinesterase activity in the central and peripheral nervous system of humans and animals (Ambrose et al. 1970; Barna and Simon 1973; Cupp et al. 1975; Gralewicz et al. 1989a, 1989b, 1990; Hunter 1969; Maxwell and LeQuesne 1982; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972). It also interferes with noradrenaline (norepinephrine) activity in central adrenergic mechanisms in animals (Brzezinski 1978; Osumi et al. 1975). Inhibition of acetylcholinesterase activity results in accumulation of acetylcholine at muscarinic and nicotinic receptors leading to peripheral and central nervous system effects. These effects usually appear within a few minutes to a few hours after exposure, depending on the extent of exposure. In a human case report, a 16-year-old white male who mistakenly ingested a formulation (identified as Dermaton[®]) was hospitalized 90 minutes afterward with symptoms of abdominal cramps, nausea, vomiting, generalized weakness, cold dry skin, hypothermia, listlessness, constricted pupils, hypertension, respiratory distress, fine generalized muscular twitching, and apprehension. Plasma and erythrocyte activity levels were significantly inhibited. All vital signs returned to normal after gastric lavage and treatment with atropine and pralidoxime (Cupp et al. 1975).

The available information indicates that chlorfenvinphos has similar neurological effects in animals. The information indicates that the substance causes disruptions in the central and peripheral nervous system in rats and dogs following acute-, intermediate-, or chronic-duration exposures via the oral route at doses as low as 0.8 mg/kg/day (Ambrose et al. 1970; Barna and Simon 1973; Maxwell and

LeQuesne 1982; Osumi et al. 1975; Puzynska 1984; Takahashi et al. 1994). These disruptions are mediated by the inhibition of cholinesterase activity in the peripheral and central nervous tissue and are manifested as abnormal muscle reflex, muscle fasciculations, Straub tail reflex, twitches, convulsions, chromodacryorrhea, exophthalmos, gasping, lacrimation, prostration, salivation, sleep disturbances, diarrhea, emesis, and urination (Ambrose et al. 1970; Maxwell and LeQuesne 1982; Osumi et al. 1975; Puzynska 1984; Takahashi et al. 1991). Cholinesterase activity in the brain of male Wistar rats was unaffected 3 hours after oral administration of 1 mg/kg of chlorfenvinphos. However, at doses of $2 mg/kg, oral chlorfenvinphos produced a marked decrease in the brain cholinesterase activity to 18–38% of the control (P<0.001) value. The maximum inhibition occurred 3 hours after the administration, after which the cholinesterase activity increased gradually. Erythrocyte cholinesterase activity also decreased after 4 mg/kg of chlorfenvinphos; the lowest level (20%, P<0.001) was attained 3 hours after treatment (Osumi et al. 1975). This study was not used to calculate an acute oral MRL because it was deemed less appropriate due to the gavage (oral) route of administration. An oral feeding study is preferred for this purpose by the ATSDR MRL Workgroup. In a chronic-duration study, chlorfenvinphos significantly inhibited both plasma and erythrocyte cholinesterase activities in a dose-dependent manner in weanling albino (Wistar) rats fed daily chlorfenvinphos doses of 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0.8, 2.4, 8, or 24 mg/kg/day (females) mg/kg/day in the diet for 104 weeks. Plasma and erythrocyte cholinesterase activities were inhibited by 48% in females and 45% in males in the first week of treatment and by 20% in females and 33% in males in the fourth week of treatment, respectively, at the lowest dose tested (0.7 mg/kg/day for males and 0.8 mg/kg/day for females). No gross or microscopic histopathology was evident in the brain tissue examined (Ambrose et al. 1970). The LOAEL of 0.7 mg/kg/day, based on adverse neurological effects in rats in this study, was used to derive a chronic oral MRL of 0.0007 mg/kg/day for chlorfenvinphos. In another study, all 36 Sprague-Dawley rats exposed to chlorfenvinphos doses of 10.5 mg/kg/day in the diet for 3–6 months exhibited repetitive muscle activity when given two electrical stimuli simultaneously. This is indicative of hyper stimulation due to depletion or inactivation of neuromuscular junction cholinesterase. The abnormality became more marked with time, even on constant dosing (Maxwell and LeQuesne 1982). The indications from this study may be useful in explaining electrophysiological abnormalities described in some workers chronically exposed to some organophosphorus compounds.

Besides its cholinergic action, there is limited evidence that chlorfenvinphos acts via central noradrenergic mechanisms in rats by accelerating the noradrenaline (norepinephrine) turnover in the brain *in vivo* by the release of noradrenaline (norepinephrine) from brain tissue stores (Brzezinski 1978).

On the basis of the existing evidence, human exposure to chlorfenvinphos is likely to result in neurological effects stemming from interference with both the central cholinergic and adrenergic mechanisms.

Reproductive Effects.   No studies were located regarding reproductive effects in humans following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal exposure to chlorfenvinphos. Reports from single-generation, intermediate- or chronic-duration rat and dog studies are largely negative for reproductive effects (Ambrose et al. 1970). However, these studies did not evaluate reproductive function. A 3-generation reproductive study in albino (Wistar) rats reported significant (50%) reduction in fertility in the F/2 generation at a LOAEL of 3 mg/kg/day (Ambrose et al. 1970). Although human data are lacking, the indications provided by the animal data suggest that adverse reproductive effects may result from prolonged human exposure to chlorfenvinphos at levels found at hazardous wastes sites.

Developmental Effects.   No studies were located regarding developmental effects in humans following acute-, intermediate-, or chronic-duration inhalation exposure to chlorfenvinphos; or regarding acute-duration exposure of animals to chlorfenvinphos. A statistical model for hazard identification concluded that chlorfenvinphos is likely to interfere with development in rabbits and hamsters but not in rats. The model was essentially a database of 175 probable, suspected, unknown, and probably negative teratogenic or embryotoxic drugs and chemical compounds. For each of the compounds, including chlorfenvinphos, the results of any developmental toxicity testing in up to 14 animal species and any reports of mutagenicity or carcinogenicity were recorded. The compounds were categorized with respect to their human developmental toxicant effect: -1.0 testing negative, 0.0 not tested (unknown), 0.5 tested with equivocal results (suspicious), and 1.0 testing positive. Although the model did not evaluate the adverse reproductive effects potential of chlorfenvinphos in primates, mice, and dogs, it correctly classified the study compounds 63–91% of the time. The model had a sensitivity of 62–75%, and a positive predictive value of 75–100%. However, the model had a negative predictive value of 64–91%, indicating the model is not optimal for hazard identification (Jelovsek et al. 1989). In acute exposures, chlorfenvinphos inhibited respiratory efficiency of juvenile rats in a dose-dependent manner at a LOAEL of 29 mg/kg/day. At 300 mg/kg/day, chlorfenvinphos completely arrested respiration in these rats (Skonieczna et al. 1981). In a 3-generation rat study, chlorfenvinphos induced significant but slightly reversible body weight gains in female rats at a LOAEL of $8 mg/kg/day as well as increased pup mortality and reduced lactational index at a LOAEL of 2.7 mg/kg/day. However, no teratogenic effects were reported in offspring rats (Ambrose et al. 1970). In single-generation intermediate- and chronic-duration studies with juvenile rats in which the rats were given dietary chlorfenvinphos doses of 90 mg/kg/day (males) or 100 mg/kg/day (females) for 12 weeks, or 21 mg/kg/day (males) or 24 mg/kg/day (females) in the

diet for 104 weeks, no significant effects on development were reported (Ambrose et al. 1970). Although human data are lacking, the indications provided by the animal data suggest that adverse developmental effects may result from prolonged human exposure to chlorfenvinphos at levels found at hazardous wastes sites.

Genotoxic Effects.   No studies were located regarding genotoxic effects of chlorfenvinphos in humans or animals following any route of exposure. Chlorfenvinphos was negative for mutagenicity in both base-pair change-type strains microorganisms (WP2 *hcr* of *Escherichia coli*; TA1535, TA1537, TA1538, TA98 of *Salmonella typhimurium*). In a mutagenicity study, the dose-response curve at doses of 0, 50, 500, and 5,000 µg/plate, for the mutagenic activity of chlorfenvinphos for the *S. typhimurium* strain TA100 was reduced by the S9 mix (metabolic activation). At present, no mutagenic pesticide whose activity decreases in the presence of the S9 mix is carcinogenic except captan (F-28) (Moriya et al. 1983). The mutagenic potency of chlorfenvinphos for strain TA100 has been reported as 0.038 revertants/nmol, indicative of a positive response (Dean 1972; Moriya et al. 1983; Vishwanath and Kaiser 1986). A mixture of 15 pesticides (containing 0.3% chlorfenvinphos) tested negative for mutagenicity in the *Salmonella* microsome assay, with or without metabolic activation with PCB-induced rat liver S9, at concentrations up to 500 µg/plate in the *Salmonella*-microsome assay. The mixture also failed to induce SCEs in human lymphocytes *in vitro* as well as *in vivo* mutagenicity in the micronucleus bone marrow assay in male Wistar rats at concentrations proportional to the ratio determined in foods ranging from 0.1 to 20 µg/mL (Dolara et al. 1993). In other large-scale screening programs which revealed microbial mutagenic activity in four new compounds (all fungicides), chlorfenvinphos (without metabolic activation) exhibited no mutation induction capacity in a rec-assay procedure (prescreening of DNA-damaging chemicals) utilizing strains of *Bacillus subtilis*, H17 Rec+ and M45 Rec-. Also, no mutation potential was evident in a reversion-assay (determination of mutation specificities) in which two tryptophan-requiring strains (auxotrophic) of *E. coli* (B/r try WP2 and WP2 *try hcr*) and four strains of *S. typhimurium* (TA1535, TA1536, TA1537, TA1538) were used. The *E. coli* auxotrophic strains and *Salmonella* TA1535 are reversible by base-pair change-type mutagens and the three *Salmonella* strains (TA1536, TA1537, and TA1538) are reversible by frameshift mutagens (Shirasu 1973; Shirasu et al. 1976).

There are no unequivocal data to indicate that chlorfenvinphos reacts directly with DNA *in vivo* or *in vitro* to produce mutations in either germ or somatic cells. In a study to determine the ability of vinyl phosphate esters, like chlorfenvinphos, to form methylated bases in DNA of calf thymus failed to detect 6-methyl guanine, a known mutagen. In both the reaction with dsDNA and ssDNA, 7-methyl guanine was the main methylation product. However, all methyl derivatives of adenine constituted

about 40% and 50% of all methylation products in the case of dsDNA and ssDNA, respectively. 3-Methylcytosine was the only methyl derivative of a pyrimidine identified (Wiaderkiewicz et al. 1986). In another study, tetrachlorvinphos (Gardona®) was evaluated for its potential to induce chromosomal aberrations and SCEs *in vitro* in a primary culture of Swiss mice spleen cells at concentrations of 0.25, 0.50, 1.0, or 2.0 µg/mL. After 4 hours of treatment, tetrachlorvinphos induced a high percentage of metaphases with chromosomal aberrations in the mouse spleen cells in a dose-dependent manner. According to the authors, the results indicate that tetrachlorvinphos in the tested concentrations is mutagenic in mouse spleen cell cultures (Amer and Aly 1992). In this study, a structural analog of chlorfenvinphos (tetrachlorvinphos) was used; therefore, the data are difficult to relate to chlorfenvinphos without extensive structure-activity relationship analysis. Data from these studies are shown on Tables 2-3 and 2-4.

Cancer   There are no epidemiological or laboratory animal data to evaluate the carcinogenicity of chlorfenvinphos in humans by any route of exposure. However, a study to determine the ability of vinyl phosphate esters, like chlorfenvinphos, to form methylated bases in DNA of calf thymus failed to detect 6-methyl guanine, a known mutagen. In both the reaction with dsDNA and ssDNA, 7-methyl guanine was the main methylation product. However, all methyl derivatives of adenine constituted about 40% and 50% of all methylation products in the case of dsDNA and ssDNA, respectively. 3-Methylcytosine was the only methyl derivative of pyrimidine identified (Wiaderkiewicz et al. 1986). It is noteworthy that the production of electrophilic metabolic intermediates or epoxides in the metabolism of chlorfenvinphos, which could react with nucleophilic cellular components (DNA, RNA, and proteins) leading to carcinogenesis, was considered unlikely by a theoretical analysis (Akintonwa 1985).

In a mutagenicity study, the dose-response curve, at doses of 0, 50, 500, and 5,000 µg/plate, for the mutagenic activity of chlorfenvinphos for the *S. typhimurium* strain TA100 was reduced by the S9 mix (metabolic activation). At present, no mutagenic pesticide whose activity decreases in the presence of the S9 mix is carcinogenic except captan (F-28) (Moriya et al. 1983). A theoretical analysis that predicted the mammalian biotransformation products based on the recognition of the structure of chlorfenvinphos, understanding of Types I and II metabolism of foreign compounds, and mechanistic biochemistry, also acknowledged that cytochrome P-450 monooxygenase (an inducible enzyme) is the relevant enzyme which mediates the biotransformation of chlorfenvinphos. The author of this study postulated that the 2,4-dichlorobenzoyl glycine (2,4-dichlorohippuric acid) was produced in the rat by this mechanism. The production of electrophilic metabolic intermediates or epoxides in the metabolism of chlorfenvinphos, which could react

Table 2-3. Genotoxicity of Chlorfenvinphos *In Vivo*

End point	Species (Test System)	Exposure Route	Results	Reference
Mammalian systems:				
bone marrow micronucleus test	rat	Oral	–	Dolara et al. 1993

– = negative result; ± = weakly positive

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

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms: Reverse mutation				
Salmonella typhimurium TA1535, TA1537, TA1538, TA98	Gene mutation	–	–	Moriya et al 1983
S. typhimurium TA1535, TA1536, TA1537, TA1538	Gene mutation	–	–	Shirasu et al. 1976
S. typhimurium TA97, TA98, TA100, TA1530, TA1535	Gene mutation	–	–	Vishwanath and Kaiser 1986
S. typhimurium TA100	Gene mutation	±	+	Moriya et al 1983
S. typhimurium	Gene mutation	–	–	Dolara et al. 1993
Escherichia coli B/r try WP2 *and* WP2 *try hcr*	Gene mutation	–	–	Shirasu et al. 1976
E. coli WP2 *hcr*	Gene mutation		–	Shirasu 1973; Dean 1972
Bacillus subtilis H17 Rec+ and M45 Rec-	Gene mutation	–	–	Shirasu et al. 1976
Eukaryotic cells: Human peripheral blood lymphocytes	Chromosomal aberration	–	–	Dolara et al. 1993
Calf thymus	DNA binding	–	–	Wiaderkiewicz et al. 1986

- = negative result; + = positive result; ± = weakly positive

with nucleophilic cellular components (DNA, RNA, and proteins) leading to carcinogenesis, was considered unlikely by this theoretical approach (Akintonwa 1984).

In contrast, tetrachlorvinphos (Gardona®), a structural analog to chlorfenvinphos, was evaluated for potential to induce chromosomal aberrations and SCEs *in vitro* in a primary culture of Swiss mice spleen cells at concentrations of 0.25, 0.50, 1.0, or 2.0 µg/mL. After 4 hours of treatment, tetra-chlorvinphos induced a high percentage of metaphases with chromosomal aberrations in the mouse spleen cells in a dose-dependent manner. The corresponding number of metaphases for tetra-chlorvinphos doses of 0.25, 0.50, 1.0, and 2.0 µg/m were 150, 590, 590, 600, and 600. According to the authors, the results of this evaluation indicate that tetrachlorvinphos (in the tested concentrations) ismutagenic in mouse spleen cell cultures (Amer and Aly 1992). However, in both of these studies, structural analogs of chlorfenvinphos (methylbromophenvinphos and tetrachlorvinphos, respectively) were used; therefore, the data are difficult to relate to chlorfenvinphos without extensive structure-activity relationship analysis.

Although neither human epidemiological evidence or evidence from rodent cancer bioassays is available, the current theoretical evidence indicates that human exposure to chlorfenvinphos is not likely to present cancer risk.

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 chlorfenvinphos are discussed in Section 2.6.1.

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

Chlorfenvinphos is rapidly absorbed from the gastrointestinal tract and widely distributed throughout the body in humans (Pach et al. 1987; Wagner et al. 1990). Traces of unchanged chlorfenvinphos have been detected in animal urine following exposure (Hunter 1972; Szczepaniak and Sienkiewitcz 1980). Chlorfenvinphos undergoes biotransformation to a variety of polar metabolites, including 2-chloro-1-(2,4-dichlorophenyl) vinylethylhydrogen phosphate; 1-(2,4-dichlorophenyl) ethanol; 1-(2,4-dichlorophenyl) ethanediol; 2,4-dichloromandelic acid; and 2,4-dichlorobenzoyl glycine (Hutson and Wright 1980), which have been detected in animals. Analysis of urine samples for the presence of these metabolites represents a potentially preferable means of assessing exposure since this method is non-invasive. However, as an organophosphate, chlorfenvinphos is rapidly metabolized and excreted from the body; therefore, urinary metabolite analysis is useful only in the evaluation of recent exposures.

The major action resulting from human exposure to chlorfenvinphos is the inhibition of cholinesterase activity (see Section 2.4). Two pools of cholinesterases are present in human blood: - acetylcholinesterase in erythrocytes and pseudocholinesterase in plasma. Acetylcholinesterase, present in human erythrocytes, is identical to the enzyme present in neuromuscular tissue (the target of chlorfenvinphos action), while plasma pseudocholinesterase has no known physiological function. Inhibition of both forms of cholinesterase activities has been associated with exposure to chlorfenvinphos in humans and animals (Cupp et al. 1975; Gralewicz et al. 1989a, 1989b, 1990; Hunter 1969; Maxwell and LeQuesne 1982; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972). Inhibition of erythrocyte, plasma, or whole blood cholinesterase activities may be used as a marker of exposure to chlorfenvinphos. However, inhibition of cholinesterase activity is a common action of anticholinesterase compounds, which include organophosphates, like chlorfenvinphos, and carbamate compounds. In addition, a wide variation in normal cholinesterase values exists in the general population, and there are no studies which report a quantitative association between cholinesterase activity levels and exposure to chlorfenvinphos in humans. Thus, the inhibition of cholinesterase activity is not a specific biomarker of effect for chlorfenvinphos exposure; it is indicative only of effect and is not useful for dosimetric analysis. It should be noted that changes in plasma cholinesterase (pseudocholinesterase) activity are considered a more sensitive biomarker of exposure for organophosphate exposure than changes in erythrocyte cholinesterase activity (Endo et al. 1988; Hayes et al. 1980). It has been suggested that in the absence of baseline values for cholinesterase activity, sequential post-exposure cholinesterase analyses be used to confirm a diagnosis of organophosphate (like chlorfenvinphos) poisoning (Coye et al. 1987).

This method of using the inhibition of cholinesterase activity as an indicator for exposure to organophosphate exposure lacks even greater specificity when used to assess exposure to compounds like chlorfenvinphos which are weak cholinesterase inhibitors. As a vinyl phosphate, chlorfenvinphos is metabolized to desethyl chlorfenvinphos which could be detected in urine as a specific biomarker of exposure to chlorfenvinphos or other vinyl phosphates. The method of detection involves conversion of urinary desethyl chlorfenvinphos to the more easily measurable methyl desethyl chlorfenvinphos with diazomethane. The analyses of 24-hour samples of urine from 14 male volunteers were made at 14-day intervals on four occasions (days 10, 24, 38, and 52) during exposure, and on one occasion, 15–16 days after cessation of exposure, using this novel detection method. The average daily excretion of *beta*-methyl desethyl chlorfenvinphos during exposure was 120 µg, which was 4.7% of the dose. In post-exposure urine, the concentrations of *beta*-methyl desethyl chlorfenvinphos were 0 in most cases, and no greater than 5–10 µg/day in the remainder. The excretion rate of *alpha*-methyl desethyl chlorfenvinphos was 15 ±5 µg/day during exposure, but

fell to 0 or <5 µg/day post-exposure. Thus, the higher level of excretion of desethyl chlorfenvinphos in the urine found in an acute dosing experiment was not maintained when the dose was diminished four-fold and administered daily. However, since desethyl chlorfenvinphos accounts for only about 5% of the dose at this low exposure level, its concentration in urine would lack sensitivity when used as an index of exposure to chlorfenvinphos (Hunter et al. 1972). Although this method of assessing chlorfenvinphos exposure may not be useful in low exposure conditions, the method could be used to evaluate exposure to high doses of chlorfenvinphos such as occurs in human acute poisoning cases. It has been suggested that the concentration of chlorfenvinphos (or its unique metabolites) in the blood may be a better index of exposure than inhibition of cholinesterase activity (Hunter 1968, 1969).

2.6.2 Biomarkers Used to Characterize Effects Caused by Chlorfenvinphos

Inhibition of erythrocyte, plasma, or whole blood cholinesterase activities in humans and animals that results from chlorfenvinphos exposure (Barna and Simon 1973; Brzezinski 1978; Cupp et al. 1975; Pach et al. 1987; Kolmodin-Hedman and Eriksson 1987; Osicka-Koprowska et al. 1984; Osumi et al. 1975; Takahashi et al. 1991) may be used as a marker of effect for chlorfenvinphos exposure. However, inhibition of cholinesterase activity is a common action of anticholinesterase compounds, which include organophosphates, like chlorfenvinphos, and carbamate compounds. In addition, a wide variation in normal cholinesterase values exists in the general population, and there are no studies which report a quantitative association between cholinesterase activity levels and exposure to chlorfenvinphos in humans. Thus, inhibition of cholinesterase activity is not a specific biomarker of effect for chlorfenvinphos exposure; it is indicative only of effect and not useful for chlorfenvinphos-specific dosimetric analysis.

It should be noted that plasma cholinesterase (pseudocholinesterase) activity is considered a more sensitive biomarker of effect for organophosphate exposure than erythrocyte cholinesterase activity (Endo et al. 1988; Hayes et al. 1980). It has been suggested that in the absence of baseline values for cholinesterase activity, sequential post-exposure cholinesterase analyses be used to confirm a diagnosis of organophosphate poisoning (Coye et al. 1987).

In combination with analysis of reductions in the level of cholinesterase activity, the manifestations of severe organophosphate (chlorfenvinphos) poisoning, clinically characterized by a collection of cholinergic signs and symptoms, which may include dizziness, fatigue, tachycardia or bradycardia, miosis, diarrhea, and vomiting (Chambers and Levi 1992; Cupp et al. 1975; Klaassen et al. 1986;

Takahashi et al. 1991; Williams and Burson 1985), are useful biomarkers of effect for identifying poisoned victims of organophosphates (chlorfenvinphos). Also, these manifestations are not specific to chlorfenvinphos but to anticholinesterase compounds (such as organophosphates and carbamate compounds) in general. A positive response to atropine treatment is considered a confirmation of organophosphate poisoning.

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

2.7   INTERACTIONS WITH OTHER CHEMICALS

The toxicity of chlorfenvinphos may be affected by other substances. Some chemicals may increase the toxicity of chlorfenvinphos in an additive manner. Chemical substances such as other anticholinesterase organophosphates, carbamates, or some pyrethroid insecticides that cause neurotoxicity are expected to act in an additive manner with chlorfenvinphos with respect to its potential to induce cholinergic toxicity.

As a direct-acting cholinesterase activity inhibitor (P=O type in contradistinction from P=S types), other chemicals may interfere with the toxicity of chlorfenvinphos indirectly by accelerating its metabolism to less toxic metabolites through their actions on drug-metabolizing enzymes, specifically, glutathione-S-transferase and P-450 or mixed function monooxygenases (Akintonwa 1984, 1985; Akintonwa and Itam 1988; Donninger 1971; Hansen 1983; Hutson and Logan 1986; Hutson and Millburn 1991; Hutson and Wright 1980). The duration and intensity of action of chlorfenvinphos is largely determined by the speed at which it is metabolized via oxidative *O*-dealkylation in the body by liver microsomal cytochrome P-450 or mixed function monooxygenases (MFO). More than 200 drugs, insecticides, carcinogens, and other chemicals are known to induce the activity of liver microsomal drug-metabolizing enzymes. The characteristic biological actions of these chemicals are highly varied. Although there is no relationship between their actions or structures and their ability to induce enzymes, most of the inducers are lipid-soluble at physiological pH. These inducers of the MFO system include the following classes of drugs: hypnotic and sedatives (barbiturates, ethanol, tetrahydrofuran, metyrapone); anesthetic gases (methoxyflurane, halothane); central nervous system stimulants (amphetamine); anticonvulsants (diphenylhydantoin); tranquilizers (meprobamate); antipsychotics (triflupromazine); hypoglycemic agents (carbutamide); anti-inflammatory agents (phenylbutazone); muscle relaxants (orphenadrine); analgesics (aspirin, morphine); antihistaminics (diphenhydramine); alkaloids (nicotine); polychlorinated aromatic hydrocarbons; insecticides

(chlordane, DDT, BHC, aldrin, dieldrin, heptachlorepoxide); pyrethrins; steroid hormones (testosterone, progesterone, cortisone); and polycyclic aromatic hydrocarbons (3-methylcholanthrene, 3,4-benzpyrene, α-naphthoflavone) (Akintonwa 1984; Hansen 1983; Hutson and Logan 1986; Hutson and Millburn 1991; Hutson and Wright 1980; Ikeda et al. 1991; Klaassen et al. 1986; Williams and Burson 1985). Thus, exposure to any of these enzyme inducers prior to, or concurrent with, exposure to chlorfenvinphos may result in accelerated biotransformation of chlorfenvinphos to its less toxic metabolites. Conversely, since chlorfenvinphos is active *per se*, concurrent exposure to chlorfenvinphos and MFO enzyme-inhibiting substances (e.g., carbon monoxide; ethylisocyanide; SKF 525A, halogenated alkanes, such as CCl_4; alkenes, such as vinyl chloride; and allylic and acetylenic derivatives) would increase the mammalian half-life and, thus, the toxicity of chlorfenvinphos (Akintonwa 1984; Akintonwa and Itam 1988; Donninger 1971; Hansen 1983; Hutson and Logan 1986; Hutson and Millburn 1991; Hutson and Wright 1980; Williams and Burson 1985).

Chlorfenvinphos exposure may interfere with the short-acting muscle relaxant succinylcholine used concurrently with anesthetics. The action of succinylcholine is terminated by means of its hydrolysis by plasma cholinesterase (Klaassen et al. 1986). Since plasma cholinesterase activity is strongly inhibited by chlorfenvinphos in humans (Cupp et al. 1975; Kolmodin-Hedman and Eriksson 1987; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972) and animals (Gralewicz et al. 1989a, 1989b, 1990; Kolmodin-Hedman and Eriksson 1987; Maxwell and LeQuesne 1982; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972), it is expected that concurrent exposure to chlorfenvinphos may result in the prolongation of the action of succinylcholine leading to prolonged muscular paralysis.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chlorfenvinphos than will most persons exposed to the same level of chlorfenvinphos 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 chlorfenvinphos, or compromised function of target organs affected by chlorfenvinphos. Populations who are at greater risk due to their unusually high exposure to chlorfenvinphos are discussed in Section 5.6, Populations With Potentially High Exposure.

The magnitude of chlorfenvinphos toxicity, like the toxicity of any xenobiotic, is affected by the rate of its metabolic biotransformation to less toxic substances (Klaassen et al. 1986). Therefore, low xenobiotic metabolizing activity would result in greater toxicity. The newborn of several animal species, including humans, have an almost complete lack of ability to metabolize xenobiotics and may be more sensitive to chlorfenvinphos toxicity. Studies on experimental animals showed that starvation depressed P-450 activity due to actual loss of the enzyme protein (Boyd and Carsky 1969; Puzynska 1984). Thus, it is expected that dietary deficiency in protein would increase chlorfenvinphos toxicity by diminishing its metabolism in the liver. Hereditary factors may also contribute to population sensitivity to chlorfenvinphos. Atypical plasma cholinesterase with low activity is present in a small percentage of the human population. This is the result of an hereditary factor with 0.04% occurrence in the population. Since plasma cholinesterase activity is strongly inhibited by chlorfenvinphos (Cupp et al. 1975; Gralewicz et al. 1989a, 1989b, 1990; Kolmodin-Hedman and Eriksson 1987; Maxwell and LeQuesne 1982; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972), it is expected that individuals who have atypical ChE (or low plasma cholinesterase activity) will be unusually sensitive to the muscle relaxant succinylcholine (Klaassen et al. 1986) and may suffer prolonged muscle paralysis if administered succinylcholine while exposed to chlorfenvinphos. Congenital low plasma cholinesterase activity may also increase subpopulation sensitivity to chlorfenvinphos exposure. This is because, after exposure, plasma cholinesterase acts as a depot for chlorfenvinphos due to its strong affinity for the substance (Davies and Holub 1980; Edson and Noakes 1960; Klemmer et al. 1978; Williams et al. 1959), thus decreasing the availability of the chlorfenvinphos dose to neuromuscular tissue, the target of chlorfenvinphos toxicity in the population with normal plasma cholinesterase levels. In individuals with congenital low plasma cholinesterase activity, less chlorfenvinphos is bound in the blood and more unbound chlorfenvinphos is in circulation to reach neuromuscular tissue, the target of chlorfenvinphos toxicity.

Individuals who have abnormally low tissue cholinesterase due to prior exposure to cholinesterase activity inhibitors are also exceptionally susceptible to the cholinesterase activity-inhibiting toxicity of chlorfenvinphos. These individuals may include those who are occupationally exposed to anticholinesterases, such as other cholinesterase activity inhibiting organophosphate or carbamate pesticides. In this regard, patients on medication that inhibit cholinesterase activity may also be unusually susceptible to the cholinesterase activity inhibiting toxicity of chlorfenvinphos.

2.9   METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chlorfenvinphos. 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 chlorfenvinphos. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following text provides specific information about treatment following exposures to chlorfenvinphos.

2.9.1   Reducing Peak Absorption Following Exposure

Organophosphate insecticides like chlorfenvinphos are rapidly absorbed after inhalation, ingestion, or dermal contact (Hutson and Wright 1980; Ikeda et al. 1991; Wagner et al. 1990). In oral exposures, emesis is not indicated because of the danger of aspiration of stomach contents by an obtunded patient. Gastric lavage, with a solution of 5% sodium bicarbonate or 2% potassium permanganate, may be indicated within the first 60 minutes after ingestion to get rid of unabsorbed chlorfenvinphos in the stomach (Cupp et al. 1975; Pach et al. 1987; Shankar 1967, 1978). Activated charcoal can also be used, but cathartics are not necessary due to the diarrhea induced by muscarinic activity. However, if diarrhea is not present in the patient, cathartics, mixed with activated charcoal, can be used.

Decontamination is the first step in reducing dermal or conjunctival absorption. This decontamination should begin immediately after the exposure is recognized. Contaminated clothing should be removed, and skin, hair, and nails should be washed with soap and plenty of water. Health care workers and emergency responders should be protected from secondary contamination, and clothes and other contaminated material should be treated as contaminated waste. Eyes should be irrigated with copious amounts of room-temperature water or saline, if available, for at least 15 minutes. If irritation, lacrimation, or especially pain, swelling, and photophobia persist after 15 minutes of irrigation, expert ophthalmologic care should be sought (Ellenhorn and Barceloux 1988).

If exposure is via inhalation, the exposed individual should be moved to fresh air and efforts should be directed toward the maintenance of an open airway, airway suctioning, endotracheal intubation. Artificial ventilation with supplemental oxygen may be helpful (Ellenhorn and Barceloux 1988).

2.9.2 Reducing Body Burden

Chlorfenvinphos is rapidly metabolized, with an estimated mammalian biological half-life of
12–15.13 hours (Akintonwa 1984; Akintonwa and Itam 1988; Donninger 1971; Hutson and Millburn
1991; Hutson and Wright 1980). Consequently, efforts at reducing body burdens of poisoned persons
may not be critical to the outcome. Although hemoperfusion has been successfully used in one case
of chlorfenvinphos poisoning (Pach et al. 1987), dialysis and hemoperfusion are not recommended in
organophosphate poisonings because of the extensive tissue distribution of the absorbed doses
(Mücke et al. 1970; Poklis et al. 1980). The use of P-450-inducing substances such as some
antipsychotics (triflupromazine) and analgesics (aspirin, morphine) would tend to accelerate the
metabolism of chlorfenvinphos, thereby decreasing its toxicity (Akintonwa 1984; Akintonwa and Itam
1988; Donninger 1971; Hutson and Millburn 1991; Hutson and Wright 1980; Klaassen et al. 1986;
Williams and Burson 1985).

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

As an anticholinesterase organophosphate, the principal toxic effects of chlorfenvinphos in humans
and laboratory animals derive from inhibition of cholinesterase activity (Cupp et al. 1975; Gralewicz et
al. 1989a, 1989b, 1990; Hunter 1969; Kolmodin-Hedman and Eriksson 1987; Maxwell and LeQuesne
1982; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and
Kruckenberg 1972). Severe inhibition of the activities of these enzymes results in accumulation of -
acetylcholine at its sites of action, and excessive or interminable stimulation of both sympathetic and
parasympathetic cholinergic receptors leading to muscarinic and nicotinic effects (Klaassen et al.
1986; Williams and Burson 1985).

Timely treatment of chlorfenvinphos poisoning cases with atropine and cholinesterase regeneration
with pralidoxime and other oximes, significantly reduces the cholinergic effects (Cupp et al. 1975; Pach
et al. 1987).

Pralidoxime acts by hydrolyzing phosphorylated acetylcholinesterase and is effective in counteracting
the paralytic effects (muscular weakness and fasciculations) of anticholinesterase agents, such as
chlorfenvinphos, if it is administered prior to the "aging" (See Mechanisms of Toxicity) of the
phosphorylated enzyme (Williams and Burson 1985). Pralidoxime is most effective if started within the
first 24 hours, preferably within 6–8 hours of exposure, prior to the irreversible phosphorylation of the
enzyme (Shankar 1967, 1978; Schenker 1992).

Atropine is an anti-muscarinic agent which, in large doses, alleviates bronchoconstriction and reduces secretion in the oral cavity and the airway. Atropine also counters some of the central nervous system effects (Cupp et al. 1975; Pach et al. 1987). It is recommended that atropine be given immediately by intravenous injection at a dose of 2 mg and every 10–20 minutes thereafter at an intramuscular dose of 0.67 mg until evidence of "atropinization" or muscarinic blockade, such as flushing, dry mouth, dilated pupils, and tachycardia is seen (Shankar 1978). Atropine therapy is required for less than 24 hours because of the shorter duration of effect (Schenker et al. 1992). The most clinically important indication for continued atropine treatment is persistent wheezing (pulmonary rales) or bronchorrhea (Woo 1990). Pralidoxime acts to regenerate inhibited cholinesterase enzyme activity at all affected sites (Shankar 1967, 1978; Schenker 1992; Taitelman 1992).

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 chlorfenvinphos 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 chlorfenvinphos.

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 Chlorfenvinphos

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chlorfenvinphos are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of chlorfenvinphos. 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, or should missing information in this figure be interpreted as a "data

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

Human

Animal

● Existing Studies

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.

The available information indicates that chlorfenvinphos is a toxic substance to most species of experimental animals, deriving its toxicity principally from the inhibition of cholinesterase activity. All three reports concerning the health effects of chlorfenvinphos in humans described individuals or group of individuals exposed either occupationally or in the home by accident. The route in the occupational exposure reports is believed to be dermal, although an occupational exposure was reported as inhalation. The route for the accidental exposure case was oral. Thus, Figure 2-5 reflects that information exists for oral and inhalation exposures in humans. However, all of the human reports on inhalation exposures are limited because of probable concurrent or sequential exposures to other substances of similar qualitative toxicity present in the environment (workplace or home), such as other organophosphate pesticides present as components of organophosphate-containing household products. In all cases, the doses at which these effects occurred in the human studies are not known and the purity of the material to which these subjects were exposed is questionable because of the accidental nature of the exposures, thus rendering evaluation of substance-relatedness to these reported toxicities uncertain. The availablehuman data, therefore, fail to fully characterize the human health effects from acute-, intermediate-, or chronic-duration inhalation exposures to chlorfenvinphos.

Information regarding the health effects of chlorfenvinphos following ingestion in laboratory animals is also limited due to a paucity of definitive studies. Only limited information is available on the health effects resulting from dermal exposures. In all health effects categories, acute-, intermediate-, and chronic-duration exposure data for inhalation exposure are limited for both humans and laboratory animals. Consequently, it was not possible to develop acute-, intermediate-, or chronic-duration inhalation MRLs for chlorfenvinphos. Furthermore, no information on the carcinogenic effects of chlorfenvinphos exposure is available for humans or laboratory animals by any route of exposure.

An acute oral MRL of 0.002 mg/kg/day has been derived for chlorfenvinphos from a LOAEL of 2.4 mg/kg/day, based on adverse neurological effects in rats (Barna and Simon 1973). An intermediate oral MRL of 0.002 mg/kg/day for chlorfenvinphos has been developed from a LOAEL of 2 mg/kg/day, based on adverse immunolymphoreticular effects in mice (Kowalczyk-Bronisz et al.

1992). A chronic oral MRL of 0.0007 mg/kg/day for chlorfenvinphos has been developed from a
LOAEL of 0.7 mg/kg/day, based on adverse neurological effects in rats (Ambrose et al. 1970).

2.10.2 Identification of Data Needs

Acute-Duration Exposure.   No data are available on the acute-duration effects of human inhalation
exposure to chlorfenvinphos. The available animal inhalation studies reported only serious effects
(mortality, apnea, salivation, urination, exophthalmos, twitches, and tremors) (Takahashi et al. 1994;
Tsuda et al. 1986) following exposure to chlorfenvinphos. Therefore, the data from these studies are
not appropriate for use in the derivation of an acute-duration inhalation MRL.

The information available on acute oral human exposures consists primarily of studies that reported
interference with central cholinergic and adrenergic mechanisms (disturbances in cholinesterase and
noradrenaline (norepinephrine) levels) and secondary effects resulting from these disturbances
manifested as neurological symptoms and death in some cases. The adverse effects reported in
humans included death (Felthous 1978) and neurological effects (Cupp et al. 1975; Kolmodin-Hedman
and Eriksson 1987; Pach et al. 1987). In animals effects noted from acute oral exposure to
chlorfenvinphos included death in rats (Ambrose et al. 1970; Hutson and Logan 1986; Hutson and
Wright 1980; Ikeda et al. 1991, 1992; Puzynska 1984; Takahashi et al. 1991), mice (Hutson and
Logan 1986; Kowalczyk-Bronisz et al. 1992; Wysocka-Paruszewska et al. 1980), dogs (Hutson and
Logan 1986; Ambrose et al. 1970), and rabbits (Ambrose et al. 1970; Hutson and Logan 1986);
systemic effects in rats, i.e., hepatic (Ikeda et al. 1991; Puzynska 1984), endocrine (Osicka-Koprowska
et al. 1984), and metabolic (Barna and Simon 1973); and neurological effects in rats (Barna and
Simon 1973; Brzezinski 1978; Ikeda et al. 1992; Osicka-Koprowska et al. 1984; Osumi et al. 1975;
Puzynska 1984; Takahashi et al. 1991). Thus, the acute effects of oral chlorfenvinphos are relatively
well-characterized, stemming principally from the inhibition of cholinesterase activity.

No effects were noted in humans dermally exposed to chlorfenvinphos for acute durations (Hunter
1968). In animals, death (Ambrose et al. 1970) and neurological effects (Vestweber and Kruckenberg
1972) have resulted from dermal exposure to chlorfenvinphos.

Additional studies via the inhalation and dermal routes of exposure would be helpful for establishing a
dose-response relationship and for identifying thresholds for adverse effects for these routes of

exposure to chlorfenvinphos. This information is necessary for determining levels of significant exposure to chlorfenvinphos that are associated with adverse health effects for the protection of potentially exposed populations living near hazardous waste sites that contain chlorfenvinphos.

Intermediate-Duration Exposure.   No information is available on the effects of human intermediate-duration exposure, by any route (inhalation, oral, dermal). No animal studies were available on intermediate-duration inhalation or dermal exposure to chlorfenvinphos.

Available information on the adverse effects resulting from intermediate-duration oral exposure of animals to chlorfenvinphos include death in rats and dogs (Ambrose et al. 1970); systemic effects in rats, i.e., renal (Ambrose et al. 1970) and metabolic (Barna and Simon 1973); immunological/lymphoreticular effects in rats (Ambrose et al. 1970: Kowalczyk-Bronisz et al. 1992; Roszkowski 1978); neurological effects in rats (Ambrose et al. 1970; Barna and Simon 1973; Maxwell and LeQuesne 1982) and dogs (Ambrose et al. 1970); reproductive effects in rats (Ambrose et al. 1970); developmental effects in rats (Ambrose et al. 1970). Additional available studies found no effects on mortality in rats and dogs (Ambrose et al. 1970); no significant systemic effects, i.e., respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, and body weight in dogs or respiratory, cardiovascular, gastrointestinal, hepatic, renal, endocrine, dermal effects in rats (Ambrose et al. 1970) endocrine system effects in mice (Kowalczyk-Bronisz et al. 1992), or body weight changes in rabbits (Roszkowski 1978) and rats (Barna and Simon 1973; Maxwell and LeQuesne 1982); no immunological/lymphoreticular effects in rats and dogs (Ambrose et al. 1970); and no reproductive effects in rats (Ambrose et al. 1970). Data from these studies sufficiently demonstrate that chlorfenvinphos interferes with the immunological/ lymphoreticular system. An intermediate oral MRL of 0.002 mg/kg/day for chlorfenvinphos has been developed from a LOAEL of 2 mg/kg/day, based on adverse immunolymphoreticular effects in mice (Kowalczyk-Bronisz et al. 1992).

Due to the lack of adequate human or animal data for effects from intermediate-duration inhalation exposure to chlorfenvinphos, no intermediate-duration inhalation MRL was derived for chlorfenvinphos. Additional studies via the inhalation and dermal routes of exposure would be helpful for establishing a dose-response relationships and for identifying thresholds for adverse effects for chlorfenvinphos exposure. This information is necessary for determining levels of significant exposure to chlorfenvinphos that are associated with adverse health effects for the protection of potentially exposed populations living near hazardous waste sites that contain chlorfenvinphos.

Chronic-Duration Exposure and Cancer.   No controlled epidemiological studies regarding the
systemic toxicities of chlorfenvinphos resulting from chronic-duration inhalation exposure are available.
However, two retrospective epidemiological studies regarding the systemic toxicities of
chlorfenvinphos resulting from chronic-duration inhalation exposures are available. Although the
existing human studies reported immunological (Wysocki et al. 1987) and neurological effects
(Kolmodin-Hedman and Eriksson 1987), the subjects in the Wysocki et al. (1987) report were also
concurrently exposed to greater concentrations of other potentially immunotoxic substances such as
formothion, sumithion, and malathion while the subjects in the Kolmodin-Hedman and Eriksson (1987)
study were exposed to unknown concentrations of a mixture of potentially neurotoxic pesticides which
included dimethoate, formothion, and isofenphos. Therefore, data from these studies were not useful
for developing a chronic inhalation MRL for chlorfenvinphos.

There is no information on the effects of chronic human oral exposure to chlorfenvinphos. In animals
the existing information on adverse effects from chronic oral exposure to chlorfenvinphos is limited to
systemic effects, i.e., hepatic and body weight effects in rats (Ambrose et al. 1970); and neurological
effects in rats and dogs (Ambrose et al. 1970). Additional available studies found no effects on
mortality in rats and dogs (Ambrose et al. 1970); no significant systemic effects, i.e., cardiovascular,
hematological, hepatic, renal, endocrine, or body weight in dogs, or respiratory, cardiovascular,
gastrointestinal, hematological, musculoskeletal, renal, endocrine, or dermal effects in rats (Ambrose
et al. 1970); no immunological/ lymphoreticular effects in rats and dogs (Ambrose et al. 1970); and no
reproductive effects in rats (Ambrose et al. 1970). Data from these studies sufficiently demonstrate
that chlorfenvinphos is an anticholinesterase organophosphate. A chronic oral MRL of
0.0007 mg/kg/day for chlorfenvinphos has been developed from a LOAEL of 0.7 mg/kg/day, based on
adverse neurological effects in rats (Ambrose et al. 1970).

No information on the effects of chronic-duration dermal exposure to chlorfenvinphos is currently
available.

No epidemiological studies or chronic rodent cancer bioassays are available for assessing the
carcinogenic potential of chlorfenvinphos. However, a study to determine the ability of vinyl phosphate
esters (like chlorfenvinphos) to form methylated bases in DNA of calf thymus failed to detect 6-methyl
guanine, a known mutagen. In both the reaction with dsDNA and ssDNA, 7-methyl guanine was the
main methylation product. However, all methyl derivatives of adenine constituted about 40% and 50%
of all methylation products in the case of dsDNA and ssDNA, respectively. 3-Methylcytosine was the

only methyl derivative of pyrimidine identified. An analog of chlorfenvinphos, methylbromo-phenvinphos, was used in this study (Wiaderkiewicz et al. 1986); therefore, the data are difficult to relate to chlorfenvinphos without extensive structure-activity relationship analysis. In a mutagenicity study, the dose-response curve, at doses of 0, 50, 500, 5,000 µg/plate for the mutagenic activity of chlorfenvinphos for the *S. typhimurium* strain TA100 was reduced by the S9 mix (metabolic activation). At present, no mutagenic pesticide for which activity decreases in the presence of the S9 mix is carcinogenic except captan (F-28) (Moriya et al. 1983).

Additional studies via the inhalation and dermal routes of exposure would be helpful for establishing a dose-response relationships and for identifying thresholds for adverse effects for prolonged exposure to chlorfenvinphos. This information is necessary for determining levels of significant exposure to chlorfenvinphos that are associated with adverse health effects for the protection of potentially exposed populations living near hazardous waste sites that contain chlorfenvinphos. Inhalation, oral, and dermal bioassays would be helpful to determine whether populations with long-term inhalation, oral, or dermal exposure (especially those living near hazardous waste sites or establishments where wastes containing chlorfenvinphos are released into the air or water) are at risk of developing cancers.

Genotoxicity.   No studies were located regarding genotoxic effects of chlorfenvinphos in humans following inhalation, oral, or dermal exposure. Chlorfenvinphos was negative for mutagenicity in both base-pair change-type strains microorganisms (WP2 *hcr* of *E. coli*; TA1535, TA1537, TA1538, TA98 of *S. typhimurium*). In a mutagenicity study, the dose-response curve, at doses of 0, 50, 500, and 5,000 µg/plate, for the mutagenic activity of chlorfenvinphos for the *S. typhimurium* strain TA100 was reduced by the S9 mix (metabolic activation). At present, no mutagenic pesticide whose activity decreases in the presence of the S9 mix is carcinogenic except captan (F-28) (Moriya et al. 1983). The mutagenic potency of chlorfenvinphos for strain TA100 has been reported as 0.038 revertants/nmol, indicative of a positive response (Dean 1972; Moriya et al. 1983; Vishwanath and Kaiser 1986). A mixture of 15 pesticides (containing 0.3% chlorfenvinphos) tested negative for mutagenicity in the *Salmonella* microsome assay, with or without metabolic activation with PCB-induced rat liver S9, at concentrations up to 500 µg/plate in the *Salmonella*-microsome assay. The mixture also failed to induce SCEs in human lymphocytes *in vitro* as well as *in vivo* mutagenicity in the micronucleus bone marrow assay in male Wistar rats at concentrations proportional to the ratio determined in foods (range = 0.1–20 µg/mL) (Dolara et al. 1993). In other large-scale screening programs, which revealed microbial mutagenic activity in four new compounds (all fungicides), chlorfenvinphos (without metabolic activation) exhibited no mutation induction capacity in a rec-assay procedure (prescreening of DNA-damaging chemicals) utilizing strains of *B. subtilis*, H17 Rec+ and

M45 Rec-. Also, no mutation potential was evident in a reversion-assay (determination of mutation specificities) in which two tryptophane-requiring strains (auxotrophic) of *E. coli* (B/r *try* WP2 and WP2 *try hcr*) and four strains of *S. typhimurium* (TA1535, TA1536, TA1537, TA1538) were used. The *E. coli* auxotrophic strains and *Salmonella* TA1535 are reversible by base-pair change-type mutagens and the three *Salmonella* strains (TA1536, TA1537, and TA1538) are reversible by frameshift mutagens (Shirasu 1973; Shirasu et al. 1976).

There are no unequivocal data to indicate that chlorfenvinphos reacts directly with DNA *in vivo* or *in vitro* to produce mutations in either germ or somatic cells. In a study to determine the ability of vinyl phosphate esters (like chlorfenvinphos) to form methylated bases in DNA of calf thymus, DNA failed to detect 6-methyl guanine, a known mutagen. In the reaction both with dsDNA and ssDNA, 7-methyl guanine was the main methylation product. However, all methyl derivatives of adenine constituted about 40% and 50% of all methylation products in the case of dsDNA and ssDNA, respectively. 3-Methylcytosine was the only methyl derivative of pyrimidine identified (Wiaderkiewicz et al. 1986). In another study, tetrachlorvinphos (Gardona®) was evaluated for potential to induce chromosomal aberrations and SCEs *in vitro* in a primary culture of Swiss mice spleen cells at concentrations of 0.25, 0.50, 1.0, or 2.0 µg/mL. Tetrachlorvinphos induced a high percentage of metaphases with chromosomal aberrations in the mouse spleen cells after 4 hours of treatment in a dose-dependent manner. According to the authors, the results indicate that tetrachlorvinphos in the tested concentrations are mutagenic in mouse spleen cell cultures (Amer and Aly 1992). In both of these studies, structural analogs of chlorfenvinphos (methylbromophenvinphos and tetrachlorvinphos, respectively) were used; therefore, the data are difficult to relate to chlorfenvinphos without extensive structure-activity relationship analysis. These limited data suggest that chlorfenvinphos might not be genotoxic. Thus, the existing information on the mutagenic potential of chlorfenvinphos is equivocal. Additional genotoxicity assays in microorganisms and mammalian cells (*in vivo* and *in vitro*) will be helpful in determining if the substance is clastogenic or can cause mutation in somatic or germ cells. This information is necessary to determine whether potentially exposed populations, especially those living near hazardous waste sites, are at risk of developing genetic diseases.

Reproductive Toxicity.   No studies were located regarding reproductive effects in humans following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal exposure to chlorfenvinphos. Animal studies regarding reproductive effects after acute-, intermediate-, or chronic- inhalation or dermal exposure to chlorfenvinphos, or acute-duration oral exposure to chlorfenvinphos are also lacking. A 3-generation reproductive study in albino (Wistar) rats orally exposed to chlorfenvinphos

reported significant (14%) reduction in fertility and decrease in maternal body weight gains at a LOAEL of 2.7 mg/kg/day (Ambrose et al. 1970). Single-generation studies, in which rats and dogs were exposed to chlorfenvinphos for intermediate- or chronic-durations found no histopathology or changes in relative weights of the testes and ovaries of the tested animals (Ambrose et al. 1970). However, these studies did not evaluate reproductive function. Consequently, additional reproductive toxicity studies in animals exposed to chlorfenvinphos via inhalation, oral, or dermal route would be helpful in evaluating the potential for chlorfenvinphos to cause adverse reproductive effects in humans. This information is necessary to determine whether potentially exposed populations, especially those living near hazardous waste sites, are at risk of developing reproductive diseases.

Developmental Toxicity.   No studies were located regarding developmental effects in humans following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal exposure to chlorfenvinphos. Animal studies regarding developmental effects after acute-, intermediate- or chronic-duration inhalation and dermal exposure to chlorfenvinphos are also lacking. The limited information on the developmental toxicity of oral chlorfenvinphos exposure indicates that the substance may interfere with the normal development of rats by inhibiting cellular respiration (Skonieczna et al. 1981) and interfering with maternal body weight gains, and reducing lactational index and offspring survivability in the developing rodents (Ambrose et al. 1970). A statistical model for hazard identification developed for use in predicting the developmental toxicity of 175 chemicals, including chlorfenvinphos, produced equivocal results concerning the developmental toxicity of chlorfenvinphos to the rat, rabbit, and hamster. The model was essentially a database of 175 probable, suspected, unknown, and probably negative teratogenic or embryotoxic drugs and chemical compounds. For each of the compounds, including chlorfenvinphos, the results of any developmental toxicity testing in up to 14 animal species and any reports of mutagenicity or carcinogenicity were recorded. The compounds were categorized with respect to their human developmental toxicant effect: -1.0 testing negative, 0.0 not tested (unknown), 0.5 tested with equivocal results (suspicious), and 1.0 testing positive. However, the model had a sensitivity of 62–75%, a positive predictive value of 75–100%, and a negative predictive value of 64–91%, indicating that it is not optimal for hazard identification (Jelovsek et al. 1989). Additional information on the developmental effects in animals exposed to chlorfenvinphos via the inhalation, oral, or dermal route would be helpful in evaluating the potential for chlorfenvinphos to cause developmental toxicity in humans. This information is necessary to determine whether offspring of potentially exposed populations, especially those living near hazardous waste sites, are at risk of developmental adverse effects.

Immunotoxicity. No studies were located regarding immunological and lymphoreticular effects in humans following acute- or intermediate-duration inhalation exposure to chlorfenvinphos, or regarding immunological and lymphoreticular effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorfenvinphos. No studies were available regarding immunological and lymphoreticular effects in animals following acute-, intermediate-, or chronic-duration inhalation or dermal exposure to chlorfenvinphos.

Only one study was located that reported immunological effects in humans. In this report, occupational exposure to inhaled chlorfenvinphos for an average of 15 years was associated with damage to humoral mechanisms in humans. This study is not suitable for assessing the immunological and lymphoreticular effects of human exposure to chlorfenvinphos because the subjects of this study were also concurrently exposed to greater concentrations of other potentially immunotoxic substances such as formothion, sumithion, and malathion (Wysocki et al. 1987). In animal studies, intermediate-duration dietary exposure of rats resulted in a significant and irreversible reduction in relative spleen weight of female rats given $3 mg/kg/day chlorfenvinphos for 12 weeks. However, no gross or microscopic histopathology was evident in the spleen and bone marrow tissues of the rats upon examination (Ambrose et al. 1970). A chronic study in dogs and rats did not note any histopathological changes in the spleen or bone marrow or changes in absolute or relative spleen weights in Wistar rats or Beagle dogs of both sexes given dietary chlorfenvinphos doses of 21 mg/kg/day (males) or 24 mg/kg/day (females), or 10 mg/kg/day (males) or 50 mg/kg/day (females), respectively, for 104 week (Ambrose et al. 1970). In other animal studies, C57BL/6 mice and (C57BL/6 x DBA/2)F1 (BDF1/liw) hybrid mice (6–8 weeks old) orally exposed to chlorfenvinphos for 90 days exhibited a reversible reduction in the number of E rosettes-forming cells as well as a dose-related decrease in number of hemolysin producing cells; reduction in the number of plaque-forming cells; increases in Interlukin-1 activity and DTH reaction; stimulation of spleen colonies; and disturbance in humoral immune factors (immunoglobulins) at a LOAEL of 1.5 mg/kg (Kowalczyk-Bronisz et al. 1992).

Rabbits orally exposed to chlorfenvinphos for 90 days also exhibited significantly elevated serum hemagglutinin level (16%) and hemolysin activity (66%, P<0.05) as well as increased number of nucleated lymphoid cells producing hemolytic antibody to sheep erythrocytes. Spleen cytomorphology changes, manifested mainly as transformation of primary follicles into secondary ones with well developed germinal centers, were also observed (Roszkowski 1978). While the existing human inhalation study and the animal oral studies provide some indication that chlorfenvinphos exposure is associated with immunological changes, these changes were not consistent with depressive effect on immune reactions. Thus, the changes reported in these studies

may simply be immunological mobilizations of the organisms to xenobiotics in contradistinction from immune system damage. Consequently, additional TIER II animal immunotoxicity testing (cell-mediated immunity, cell surface marker profile immunopathology, humoral immunity, cytolytic macrophage function, and bone marrow tests) via the inhalation, oral, or dermal route for chlorfenvinphos would be helpful to more fully assess the potential of chlorfenvinphos to cause immunotoxicity in humans. This information is necessary to determine whether potentially exposed populations, especially those living near hazardous waste sites, are at risk of developing immunological diseases.

Neurotoxicity.   No studies were located regarding neurological effects in humans after acute- or intermediate-duration inhalation exposure to chlorfenvinphos; or following acute-, intermediate-, or chronic-duration oral exposure; or after intermediate- or chronic-duration dermal exposure. In humans, chlorfenvinphos inhibits cholinesterase activity in the central and peripheral nervous system when administered by the oral (Cupp et al. 1975; Pach et al. 1987) or inhalation route in acute-duration exposures (Kolmodin-Hedman and Eriksson 1987). Inhibition of cholinesterase activity results in accumulation of acetylcholine at muscarinic and nicotinic receptors leading to peripheral and central nervous system effects. These effects usually appear within a few minutes to a few hours after exposure depending on the extent of exposure. In a human case report, a 16-year-old white male who mistakenly ingested a formulation (identified as Dermaton[®]) was hospitalized 90 minutes afterward with symptoms of abdominal cramps, nausea, vomiting, generalized weakness, cold dry skin, hypothermia, listlessness, constricted pupils, hypertension, respiratory distress, fine generalized muscular twitching, and apprehension. Plasma and erythrocyte activity levels were significantly inhibited. All vital signs returned to normal after gastric lavage and treatment with atropine and pralidoxime (Cupp et al. 1975).

No studies were located regarding neurological effects in animals after acute- or intermediate-duration inhalation or dermal exposure to chlorfenvinphos. The available information indicates that chlorfenvinphos has similar neurological effects in animals. In animals, chlorfenvinphos inhibits cholinesterase activity in the blood and neuromuscular tissue by the oral route in acute-duration exposures in rats at doses as low as 2 mg/kg (Barna and Simon 1973; Osicka-Koprowska et al. 1984; Osumi et al. 1975; Puzynska 1984; Takahashi et al. 1991); in rats following intermediate-duration exposures via the oral route at doses as low as 9 mg/kg/day (Ambrose et al. 1970; Maxwell and LeQuesne 1982); and in dogs following chronic-duration exposure via the oral route at doses as low as 0.7 mg/kg/day (Ambrose et al. 1970). These disruptions in cholinesterase activity resulted in cholinergic responses manifested as abnormal muscle reflex, muscle fasciculations, Straub tail reflex, twitches, convulsions, chromodacryorrhea, exophthalmos, gasping,

lacrimation, prostration, salivation, sleep disturbances, diarrhea, emesis, and urination (Ambrose et al. 1970; Maxwell and LeQuesne 1982; Osumi et al. 1975; Puzynska 1984; Takahashi et al. 1991). In one of these studies, all 36 Sprague-Dawley rats exposed to chlorfenvinphos doses of 10.5 mg/kg/day in the diet for 3–6 months exhibited repetitive muscle activity when given two simultaneous stimuli. This abnormality became more pronounced with time, even on constant dosing (Maxwell and LeQuesne 1982). The findings from this study may be useful in explaining electrophysiological abnormalities described in some workers chronically exposed to some organophosphorus compounds.

Intraperitoneal administration of daily doses of 100, 150, 200, or 300 mg/kg/day chlorfenvinphos to White Leghorn hens for 10 days or until death resulted in cholinergic signs. Typical cholinergic signs, including inability to stand, salivation, and retching (as well as some deaths) were observed immediately after the administration of any dose level of chlorfenvinphos, with or without atropine coadministration. No signs of delayed neurotoxicity or evidence of neurological lesions suggestive of demyelination or neural damage were observed in the brain and sciatic nerve tissues examined (Ambrose 1970). Although all doses of chlorfenvinphos elicited cholinergic responses (leg weakness, salivation, and retching) from hens given 100, 150, 200, or 300 mg/kg by intraperitoneal injection, no signs of delayed neurotoxicity was evident after 20 days of observation (Ambrose et al. 1970).

Besides its cholinergic action, chlorfenvinphos also acts via central noradrenergic mechanisms in rats by accelerating the noradrenaline (norepinephrine) turnover in the brain *in vivo* by the release of noradrenaline (norepinephrine) from brain tissue stores (Brzezinski 1978).

Although the available toxicity information in humans and animals is sufficient to establish that short- and long-term exposure to chlorfenvinphos results in adverse neurological effects, additional animal studies by the inhalation, oral, and dermal routes will be helpful in the more accurate assessment of the exposure levels at hazardous waste sites at which these effects are likely to occur.

Epidemiological and Human Dosimetry Studies.   Although the available epidemiological studies sufficiently identify inhibition of cholinesterase activity as the characteristic and most critical effect of human exposure to chlorfenvinphos, these studies inadequately identify the dose at which this effect occurs (Cupp et al. 1975; Kolmodin-Hedman and Eriksson 1987; Pach et al. 1987; Wysocki et al. 1987). Well-conducted acute-, intermediate-, and chronic-duration (for effects other than inhibition of cholinesterase activity) human dosimetry studies are not available. Therefore, well conducted

retrospective epidemiological studies would be helpful in determining and quantifying the effects (including neurologic, immunologic, and reproductive effects) of inhalation, oral, or dermal chlorfenvinphos exposure on human health; such studies would also provide useful data regarding the carcinogenic potential of chlorfenvinphos in humans, especially people living around hazardous waste sites or establishments where wastes containing chlorfenvinphos are released into the air or water, and people who are occupationally exposed to chlorfenvinphos for long periods of time.

Biomarkers of Exposure and Effect.

Exposure. The major action resulting from human exposure to chlorfenvinphos is the inhibition of acetylcholinesterase activity (see Section 2.4). Two pools of cholinesterases are present in human blood: acetylcholinesterase in erythrocytes and neuromuscular tissue and butyrylcholinesterase (pseudocholinesterase) in plasma. Acetylcholinesterase, present in human erythrocytes, is identical to the enzyme present in neuromuscular tissue (the target of chlorfenvinphos action). While plasma cholinesterase (pseudocholinesterase or butyrylcholinesterase) has no known physiological function, it has been suggested that it scavenges acetylcholine that gets into the plasma. Inhibition of the activity of both forms of cholinesterase has been associated with exposure to chlorfenvinphos in humans and animals (Cupp et al. 1975; Gralewicz et al. 1989a, 1989b, 1990; Hunter 1969; Kolmodin-Hedman and Eriksson 1987; Maxwell and LeQuesne 1982; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972). Inhibition of erythrocyte, plasma, or whole blood cholinesterase may be used as a marker of exposure to chlorfenvinphos. However, inhibition of cholinesterase activity is a common action of anticholinesterase compounds, which include organophosphates like chlorfenvinphos, and carbamate compounds. In addition, a wide variation in normal cholinesterase values exists in the general population, and there are no studies which report a quantitative association between cholinesterase activity levels and exposure to chlorfenvinphos in humans.

Chlorfenvinphos undergoes biotransformation to a variety of polar metabolites, including 2-chloro-1-(2,4-dichlorophenyl) vinylethylhydrogen phosphate; 1-(2,4-dichlorophenyl) ethanol; 1-(2,4-dichloro-phenyl) ethanediol; 2,4-dichloromandelic acid; and 2,4-dichlorobenzoyl glycine (Hutson and Wright 1980), which have been detected in animals. Analysis of blood samples for the presence of these metabolites represents a potential means of assessing exposure. Analysis of urine samples for metabolic products provides a non-invasive method for detecting exposure. As an organophosphate, chlorfenvinphos is rapidly metabolized and excreted from the body; therefore, urinary metabolite analysis is useful only in the evaluation of recent exposures (Hutson and Wright 1980). There are no

studies which report a quantitative association between metabolite levels and exposure to chlorfenvinphos in humans. Therefore, these biomarkers are only indicative of exposure and are also not useful for dosimetric analysis. The inhibition of cholinesterase activity method as a measure of organophosphate exposure lacks even greater specificity when used to assess exposure to compounds which are weak inhibitors of cholinesterase activity, like chlorfenvinphos (Hunter et al. 1972). As a vinyl phosphate, chlorfenvinphos is metabolized to desethyl chlorfenvinphos, which could be detected in urine as a specific biomarker of exposure to chlorfenvinphos, or other vinyl phosphates (Akintonwa 1984, 1985; Akintonwa and Itam 1988; Donninger 1971; Hansen 1983; Hutson and Logan 1986; Hutson and Millburn 1991; Hutson and Wright 1980). The method of detection involves conversion of urinary desethyl chlorfenvinphos to the more easily measurable methyl desethyl chlorfenvinphos with diazomethane. This method is a more specific biomarker for chlorfenvinphos exposure and has been successfully used as such in a case of 14 male volunteers exposed to chlorfenvinphos for 53 days. However, since desethyl chlorfenvinphos accounts for only about 5% of the dose at this low exposure level, its concentration in urine would lack sensitivity when used as an index of exposure to chlorfenvinphos (Hunter et al. 1972). Although this method of assessing chlorfenvinphos exposure may not be useful in low exposure conditions, the method could be used to evaluate exposure to high doses that occur in human acute poisoning cases. Further research in the adaptation of this method for low-dose exposure would be useful.

Effect. Inhibition of the activities of erythrocyte, plasma, or whole blood cholinesterase in humans and animals that results from chlorfenvinphos exposure (Cupp et al. 1975; Gralewicz et al. 1989a, 1989b, 1990; Hunter 1969; Kolmodin-Hedman and Eriksson 1987; Maxwell and LeQuesne 1982; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972) may be used as a marker of effect for chlorfenvinphos exposure. However, the inhibition of cholinesterase activity is a common action of anticholinesterase compounds, which include organophosphates like chlorfenvinphos, and carbamate compounds. In addition, a wide variation in normal cholinesterase values exists in the general population, and there are no studies which report a quantitative association between cholinesterase activity levels and exposure to chlorfenvinphos in humans. Thus, the inhibition of cholinesterase activity is not a specific biomarker of effect for chlorfenvinphos exposure; it is indicative only of effect and is not useful for chlorfenvinphos-specific dosimetric analysis. In combination with analysis of reductions in the level of cholinesterase activity, the manifestations of severe organophosphate (chlorfenvinphos) poisoning, clinically characterized by a collection of cholinergic signs and symptoms (which may include dizziness, fatigue, tachycardia or bradycardia, miosis, and vomiting) (Chambers and Levi 1992; Cupp et al. 1975; Klaassen et al. 1986; Pach et al. 1987; Takahashi et al. 1991; Williams and Burson 1985), are useful biomarkers of effect for identifying victims of organophosphates (chlorfenvinphos) poisoning. These manifestations, however,

are also not specific to chlorfenvinphos, but to anticholinesterase compounds, such as organophosphates and carbamate compounds, in general. A study conducted in rats reported that 1–6 hours after administration, chlorfenvinphos (13 mg/kg) decreased the noradrenaline (norepinephrine) level in rat brain by 20% as compared to controls (Brzezinski 1978). A similar study in Wistar rats found a 16% transient reduction in brain noradrenaline (norepinephrine) 3 hours after oral dosing with 4 mg/kg chlorfenvinphos (Osumi et al. 1975). Further research on the adrenergic effects of chlorfenvinphos exposure might provide a more specific biomarker for chlorfenvinphos when used in combination with inhibition of cholinesterase activity and clinical signs of interference with the central cholinergic mechanism.

Absorption, Distribution, Metabolism, and Excretion.   No studies were located regarding the absorption of chlorfenvinphos after inhalation exposure; or regarding the distribution or metabolism of chlorfenvinphos after inhalation or dermal exposure; or regarding excretion of chlorfenvinphos after inhalation or dermal exposure in humans. In humans, dermally applied chlorfenvinphos was absorbed in a concentration-dependent manner with rates of 0.06–1.43 mg/cm^2/hour. Concentrations of intact chlorfenvinphos of <0.7–22 µg/L were found in the blood of volunteers 8 hours later (Hunter 1969). The rates of chlorfenvinphos de-ethylation by liver microsomal fractions are 0.36 nmol/minute per mg protein (range 0.11–0.82) without induction and 1.03 nmol/minute per nmol of cytochrome P-450 (range 0.42–1.78) with induction (Hutson and Logan 1986). Chlorfenvinphos levels of 13.66, 1.69, 2.02, and 1.89 µg/kg were detected in 4 of the 11 samples of cervical mucus in environmentally exposed persons. Chlorfenvinphos levels of 0.42 µg/kg were detected in 1 of the 10 sperm fluid samples and 1 of the 10 human milk samples, respectively (Wagner et al. 1990). A serum concentration of 300 ng/mL chlorfenvinphos was reported for a 29-year-old patient who had attempted suicide by ingesting about 50 mL of the preparation Enolofos®, which contains 50% chlorfenvinphos. The authors of this report surmised that orally absorbed chlorfenvinphos is widely and rapidly distributed (Pach et al. 1987).

No studies were located regarding the absorption of chlorfenvinphos after inhalation or dermal exposure; or regarding the distribution or metabolism of chlorfenvinphos after inhalation, oral, or dermal exposure; or regarding excretion of chlorfenvinphos after inhalation or dermal exposure in animals. The available animal studies indicate that orally administered chlorfenvinphos is minimally absorbed and metabolized in rats (Hutson and Wright 1980). The metabolism of oral doses of the substance is mediated by hepatic microsomal monooxygenase (cytochrome P-450) via oxidative dealkylation (Donninger 1971; Hutson and Millburn 1991; Ikeda et al. 1991). Thirteen metabolites of chlorfenvinphos have been identified in animal studies or predicted from theoretical biotransformation as justified by the known structure of chlorfenvinphos and understanding of biochemical reactions of

monooxygenation, reduction, hydrolysis, glucuronidation, glutathione-S-transferase conjugation, and amino acid conjugation. The 13 metabolites identified or predicted are: 2-chloro-1-(2',4'-dichlorophenyl) vinyldiethyl phosphate; acetaldehyde; 2-chloro-1-(2',4'-dichlorophenyl) vinylethylhydrogen phosphate; 2,4-dichlorophenacylchloride; 2-chloro-1-(2',4'-dichlorophenyl) ethanol; 2,4-dichloromandelic acid; 2,4-dichloromandelic acid ester glucuronide; 2,4-dichloroacetophenone; 1-(2',4'-dichlorophenyl) ethanol; 1-(2',4'-dichlorophenyl) ethanediol; 1-(2',4'-dichlorophenyl) ethanediol-2-glucuronide; 1-hydroxy-1-(2',4'-dichlorophenyl) acetyl glycine; and 1-(2',4'-dichlorophenyl) ethanediol (Akintonwa 1984, 1985; Akintonwa and Itam 1988; Hunter et al. 1972; Hutson and Millburn 1991; Hutson and Wright 1980). Orally absorbed chlorfenvinphos is eliminated mainly in the urine in rats in 0-32 hours (Hutson and Wright 1980). Additional studies in animals, designed to measure the rate of inhalation, gastrointestinal, and dermal absorption, distribution, and excretion of chlorfenvinphos would be useful in extrapolating the toxicokinetics of chlorfenvinphos in humans, especially those living around hazardous waste sites.

Comparative Toxicokinetics.   Chlorfenvinphos inhibits cholinesterase activity in the central and peripheral nervous system, resulting in cholinergic symptoms as reported in several human poisoning incidents (Cupp et al. 1975; Hunter 1969; Pach et al. 1987; Kolmodin-Hedman and Eriksson 1987). However, the purity of the material to which these subjects were exposed is questionable, and the doses at which these effects occurred are unknown because of the accidental nature of the exposures. Therefore, it is difficult to determination whether the adverse effects reported in these human studies are attributable to exposure to technical chlorfenvinphos. Although information is available that indicates that dermally applied chlorfenvinphos was absorbed in a concentration-dependent manner (with rates of 0.06–1.43 mg/cm^2/hour), inhibiting cholinesterase in a dose-dependent in the human subjects (Hunter 1969), information on the toxicokinetics of chlorfenvinphos in humans is limited to serum levels following ingestion (Pach et al. 1987).

Similarly, chlorfenvinphos inhibits cholinesterase activity in the central and peripheral nervous system in animals (Gralewicz et al. 1989a, 1989b, 1990; Kolmodin-Hedman and Eriksson 1987; Maxwell and LeQuesne 1982; Osicka-Koprowska et al. 1984; Pach et al. 1987; Takahashi et al. 1991; Vestweber and Kruckenberg 1972).

The level of activity of cholinesterases in the livers of mammalian species and the distribution of these enzymes have been suggested to be important factors in accounting for species specificity of some phosphate triester anticholinesterase agents, including chlorfenvinphos. These factors may account for the great variation in the conversion of chlorfenvinphos to less toxic metabolites and, consequently, the

toxicity of chlorfenvinphos among different animal species. The relative rates of conversion of chlorfenvinphos (by *O*-dealkylation) to the diester by liver slices from the rat, mouse, rabbit, and dog are 1, 8, 24, and 80 hours, respectively; evidently correlating with the published acute oral LD_{50} values for the species. A quantitative study of the species distribution of phosphate esterases and glutathione *S*-alkyl transferase found that these enzymes are significantly less in the pig than all the other species studied (Donninger 1971; Hansen 1983; Ikeda et al. 1991). The ease of absorption, bioavailability in blood, and rates of uptake by the brain and sensitivity of brain cholinesterase to the phosphorylating action of the compound may be additional factors in species sensitivity to the toxicity of chlorfenvinphos as demonstrated in the dog and rabbit (Hutson and Millburn 1991).

Additional comparative studies regarding the absorption, distribution, and excretion of chlorfenvinphos after inhalation, oral, or dermal exposure in animals would be useful in species or route-route extrapolation. This information could be used to determine an appropriate animal model for the evaluation of the toxicokinetics of chlorfenvinphos.

Methods for Reducing Toxic Effects. Although dialysis and hemoperfusion are currently not recommended in organophosphate poisonings because of the extensive tissue distribution of the absorbed doses (Mücke et al. 1970; Poklis et al. 1980), hemoperfusion has been successfully used in one chlorfenvinphos poisoning treatment (Pach et al. 1987). Further studies are necessary in view of the relatively few clinical observations concerning the use of hemoperfusion in the treatment of acute poisoning caused by vinyl phosphate compounds like chlorfenvinphos.

2.10.3 Ongoing Studies

No information on ongoing studies in humans or laboratory animals for chlorfenvinphos was located.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY
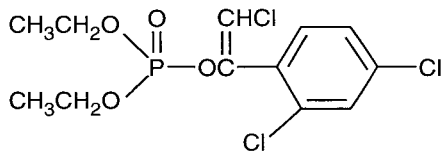
Chlorfenvinphos is a synthetic organophosphorus insecticide that has been used as a soil or foliar insecticide. It was also used to control insect pests on livestock and to control household pests. Information regarding the chemical identity of chlorfenvinphos is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Chlorfenvinphos is a vinyl organophosphate insecticide. The technical material is an amber liquid with a mild odor containing about 80–90% chlorfenvinphos (trans and cis isomers with a typical ratio of 8.5:1). It is sparingly soluble in water, but miscible with most organic solvents. It hydrolyzes slowly in water, but is unstable in alkali (Worthing 1983). Information regarding the physical and chemical properties of chlorfenvinphos is located in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-1. Chemical Identity of Chlorfenvinphos

Characteristic	Information	Reference
Chemical name	2-chloro-1-(2,4-dichlorophenyl) vinyl diethyl phosphate	Worthing 1983
Synonym(s)	Phosphoric acid 2-chloro-1-(2,4-dichlorophenyl)ethenyl diethyl ester; O,O-diethyl O-[2-chloro-1-(2,4-dichlorophenyl)vinyl] phosphate; 2,4-dichloro-α-(chloromethylene)benzyl alcohol diethyl phosphate	Merck 1989
Registered trade name(s)	CVP; SD 7859; Compound 4072; Birlane; Dermaton; Sapecron; Steladone; Supona	Merck 1989
Chemical formula	$C_{12}H_{14}Cl_3O_4P$	Worthing 1983
Chemical structure		Worthing 1983

Identification numbers:		
CAS Registry	470–90–6	Merck 1989
NIOSH RTECS	TB 8750000	HSDB 1996
EPA Hazardous Waste	No data	
OHM/TADS	810041	HSDB 1996
DOT/UN/NA/IMCO	UN 2783 Organophosphorus pesticide	HSDB 1996
HSDB	1540	HSDB 1996
NCI	No data	

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

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-2. Physical and Chemical Properties of Chlorfenvinphos

Property	Information	Reference
Molecular weight	359.56	Merck 1989
Color	Amber liquid (Technical) Colorless liquid	Merck 1989 Hartley 1987
Physical state	Liquid	Merck 1989
Melting point	−19 to −23 °C (Technical) −16 to −22 °C	Worthing 1987 Ouellette 1977
Boiling point at 0.01 mm Boiling point at 0.5 mm	120 °C (Technical) 167–170 °C (Technical)	Merck 1989 Merck 1989
Density at 25 °C	1.5272 g/mL	Merck 1989
Odor	Mild odor	Merck 1989

Odor threshold:
  Water
  Air
	
	No data
	No data	

Solubility: Water at 23 °C	 145 ppm	 Merck 1989
Organic solvent(s)	Miscible with acetone, ethanol, propylene glycol, dichloro-methane, hexane, xylene	Merck 1989; Worthing 1983

Partition coefficients:
  Log K_{ow}
  Log K_{oc}
	
	3.806
	2.45
		
		Bowman and Sans 1983
		Kenaga 1980

Vapor pressure at 25 °C	4×10^{-6} mm Hg 7.5×10^{-6} mm Hg 1.7×10^{-7} mm Hg	Worthing 1983 Merck 1989 Verschueren 1983
Henry's law constant: at 25 °C	1.53×10^{-8} atm-m^3/mol 2.76×10^{-9} atm-m^3/mol	HSDB 1996 Domine et al. 1992
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits at 25 °C	No data	
Conversion factors (25 °C)	1 ppm = 14.7 mg/m^3 1 mg/m^3 = 0.068 ppm	
Explosive limits	No data	

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

4.1 PRODUCTION

Chlorfenvinphos was introduced into the United States in 1963 (Hayes 1982), by the Shell International Chemical Company Ltd., Ciba AG (now Ciba-Geigy AG), and by Allied Chemical Corporation (Worthing 1983). The Burroughs Wellcome Company produced several chlorfenvinphos-containing formulated products including Dermaton® dust, Dermaton® dip, Dermaton® II, and Dermaton® flea and tick collars (EPA 1978a, 1978b, 1979, 1982a, 1982b, 1983). Information on current production of chlorfenvinphos is conflicting. One source lists current base producers of the compound as American Cyanamid Company (under the trade names Birlane® and Supona®) and Ciba Ltd. (under the trade names Sapecron® and Steladone®) (Farm Chemicals Handbook 1993). However, no producers of chlorfenvinphos were identified in a recent Directory of Chemical Producers for the United States of America (SRI 1993).

Chlorfenvinphos is produced by reaction of triethyl phosphite with 2,2,2',4'-tetrachloroacetophenone (Worthing 1983). The technical grade material contains greater than 92% chlorfenvinphos as both the Z (trans) and E (cis) isomers in a ratio (Z:E) of 8.5:1 (Spencer 1982; Worthing 1983).

No information on historic production volumes was found; however, there are currently no registered uses for chlorfenvinphos in the United States (REFS 1995).

No information is available in the Toxics Release Inventory (TRI) database on total environmental releases of chlorfenvinphos from production facilities because chlorfenvinphos is not included under SARA, Title III (40 CFR 372.65), and, therefore, is not one of the toxic chemicals that facilities are required to report to the Toxics Release Inventory database (EPA 1995).

4.2 IMPORT/EXPORT

Chlorfenvinphos is not likely to be imported as there are currently no registered uses for this compound as a pesticide in the United States (REFS 1995). No definitive information on recent or historic import volumes was found.

Current production of chlorfenvinphos in the United States could not be verified (SRI 1993), but production for domestic consumption is not permitted as all registered uses in the United States were canceled in 1991 (REFS 1995). Production of pesticides for export whose registered uses in the United States have been cancelled is legal under U.S. law. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) generally prohibits the EPA from releasing complete information on pesticide production, sales, and distribution. In a recent report by the Foundation for the Advancement of Science and Education, the authors report that no government agency maintains current records concerning what specific pesticides are exported (FASE 1996). No definitive information on recent or historic export volumes was found.

4.3   USE

In the United States, chlorfenvinphos was registered for a variety of uses from 1963 until 1991 when all products containing chlorfenvinphos as an active ingredient were canceled (REFS 1995). Chlorfenvinphos was first registered in 1963 under the trade name Dermaton® as an insecticide/ acaricide dip for veterinary use in controlling fleas and ticks on domestic pets and other animals. During the mid-1960s and early 1970s, chlorfenvinphos was registered for additional uses as a residual fly spray, surface spray, and larvicide. As part of these registrations, chlorfenvinphos was used to control adult flies in dairy barns, milk rooms, poultry houses and yards, other animal buildings, feedlots, and animal holding pens; and to control larval flies in manure storage pits and piles, and in other refuse accumulation areas around dairies and feedlots (REFS 1995). Beginning in the early 1980s, it was registered for additional uses under the trade name Dermaton®, in a dust formulation for use in dog kennels and in dog collars for the control of fleas and ticks (Farm Chemicals Handbook 1984, 1993; Hayes 1982; REFS 1995).

Available formulations of chlorfenvinphos included a 0.5% dust, 10% pelletized granules, 21% emulsifiable concentrate, 24.5% emulsifiable concentrate, 25% wettable powder(WP), and 40% seed dressing (with 2% mercury compounds); however, some of these formulations were not registered for use in the United States (Hayes 1982; REFS 1995; Spencer 1982). A summary of the registered uses of chlorfenvinphos in the United States prior to the cancellation of its registration is given in Table 4-1 (REFS 1995).

Chlorfenvinphos was subject to re-registration by the Office of Pesticide Programs of EPA in the mid-1980s. At that time, the sole manufacturer, Shell International Chemical Company decided not to support reregistration and allowed its registration of both the technical compound 4072 and of a variety of formulated

Table 4-1. Previously Registered Uses of Chlorfenvinphos

Site	Pest	Dosage	Tolerance, Use, and Limitations
Dairy barns and milk rooms; indoor surfaces	Housefly (adults)	3.5 fl. oz. of 21.1% conc./gal. water (EC)	0.1 ppm (milk fat). Apply to surfaces such as walls, ceilings, partitions and stalls where flies congregate or rest. Apply as a coarse spray to thoroughly wet the surfaces—approximately one gallon of spray per 500-1,000 sq. ft. Remove livestock from barns before spraying. Cover feed and water containers. Remove all milking utensils and milk containers. Do not apply directly to livestock.
Poultry houses and yards	Housefly (adults)	4.0 fl. oz. of 21.1% conc./gal. water (EC)	0.005 ppm (eggs and fat of poultry). Apply as a coarse spray to surfaces inside and outside poultry houses such as ceilings, partitions, walls, posts and yards. Thoroughly wet surfaces—apply about one gallon of spray per 1,000 sq. ft. Do not apply directly to birds. Do not treat litter or surfaces with which poultry may come in contact.
Droppings (beneath caged birds or birds on wire); effluents from houses; manure storage pits and piles	Flies (larvae)	3.0-10 fl oz. of 21.1% conc./gal water (EC)	Apply as a coarse spray with pressure or by sprinkling at the rate of one gallon of spray per 100 sq. ft. Thorough coverage and penetration is essential. Increase volume of water if penetration is in doubt. Use higher dosage for initial cleaning or severe infestations. Repeat as needed. Do not apply directly to birds. Do not treat litter or surfaces with which poultry may come in contact. Do not contaminate feed or water containers.
Animal buildings other than dairy and poultry; feed lots and holding pens; indoor surfaces	Housefly (adults)	3.5 fl. oz. of 21.1% conc./gal. water (EC)	0.005 ppm (fat of goats, hogs, horses). Apply to surfaces such as walls, ceilings, partitions and stalls where flies congregate or rest. Apply as a coarse spray to thoroughly wet the surfaces—approximately one gallon of spray per 500-1,000 sq. ft. Remove livestock from barns before spraying. Cover feed and water containers. Do not apply directly to livestock.
Outdoor areas; manure and refuse accumulations (including those around dairies and feed lots)	Flies (larvae)	0.75-1.5 fl. oz. of 21.1% conc./ gal. water (EC)	Apply as a coarse spray with low pressure at a rate of one gallon of spray per 25 sq. ft. Thorough coverage and penetration is essential. Increase volume if penetration is in doubt. Use higher dosage for severe infestations. Repeat as needed. Do not apply directly to livestock. Do not contaminate feed or water containers.
Exterior surfaces	Fleas; housefly (adults); ticks	3.5 fl. oz. of 21.1% conc/gal. water (EC)	Apply to surfaces such as fence posts, walls and yards where insects congregate or rest. Apply as a coarse spray to thoroughly wet the surfaces—approximately one gallon of spray per 1,000 sq. ft. Do not apply directly to livestock. Do not contaminate feed or water containers.

Table 4-1. Previously Registered Uses of Chlorfenvinphos (continued)

Site	Pest	Dosage	Tolerance, Use, and Limitations
Humans; pets and other animals	Fleas; ticks	0.5 fl. oz. of 24.5% conc./ gal. water (ED)	For use by or on the order of licensed veterinarians only. Bathe or dip dog, making sure it is thoroughly wet. Repeat as needed, but not more often than once a week. Do not use diluted emulsion stored more than 30 days.
Dog kennels; yards	Fleas; ticks	2.5 fl. oz. of 24.5% conc./gal. water (EC)	Spray or sprinkle at a rate of 1 gallon of spray per 1,000 sq. ft. Be sure to treat hiding places such as cracks, around dogs bedding, and debris.
Dog kennels; yards	Housefly (adults)	3.5 fl. oz. of 21.1% conc./gal. water (EC)	Apply to surfaces such as walls, ceilings, and partitions where flies congregate or rest. Apply as a coarse spray to thoroughly wet the surfaces—approximately one gallon of spray per 1,000 sq. ft.

EC = effective concentration; ED = effective dose

products to lapse and be canceled (EPA 1994). A summary of chlorfenvinphos product registrations and their effective dates of cancellation are given in Table 4-2.

Outside the United States, chlorfenvinphos is registered for use under the trade names Birlane®, C8949, CGA 26351, Sapecron®, Steladone® and Supona® (Farm Chemicals Handbook 1993). Chlorfenvinphos (under the trade name Birlane®) is used as a soil insecticide for controlling root maggots, root worms, and cutworms (Farm Chemicals Handbook 1984; Spencer 1982; Worthing 1983). As a foliar insecticide, it controls Colorado beetles, *Leptinotarsa decemlineata* on potatoes, and scale insects on citrus, where it also exhibits ovicidal activity against mite eggs. It also controls stem borers on maize, rice, and sugarcane, and whiteflies (*Benusia* sp.) on cotton (Farm Chemicals Handbook 1984; Worthing 1983). Birlane® 24 controls root flies, phorid and sciarid fly larvae, fruit flies on maize and sweet corn, and wheat bulb flies in winter wheat. Birlane® 10% granules are used to control root flies and Birlane® Liquid Seed Treatment is used to control wheat bulb flies in winter wheat. Supona® is used to control ticks, flies, lice and mites on cattle; blowflies, lice ked, and itchmites on sheep; and fleas and ticks on dogs. Steladone® and Sapecron® are used as cattle dips or sprays to control ectoparasites on cattle (Farm Chemicals Handbook 1984; REFS 1995; Spencer 1982). Chlorfenvinphos is also used in public health applications for control of mosquito larvae (The Agrochemicals Handbook 1991).

No quantitative information on the volume of chlorfenvinphos use in the United States or on historic trends in use was found. It is known, however, that chlorfenvinphos was first introduced for use in the United States on October 3, 1963, and that the last EPA approved label date for a chlorfenvinphos-containing product was September 1986. Use is likely to have declined from 1986 until January 22, 1991, when all uses of the chemical were canceled in the United States (REFS 1995).

4.4   DISPOSAL

Chlorfenvinphos is considered to be an extremely hazardous substance (EPA 1988). The recommended disposal method for chlorfenvinphos consists of hydrolysis and subsequent transport to a landfill (IRPTC 1985). Chlorfenvinphos and chlorfenvinphos-containing wastes should be treated by alkali and then mixed with a portion of soil which is rich in organic matter before burial (at least to a depth of 0.5 meters) in a pit or in clay soil. For disposal of large quantities of chlorfenvinphos, incineration at high temperatures in a unit equipped with an effluent gas scrubbing device is recommended (IRPTC 1985). See Chapter 7 for further information on regulations and advisories.

Table 4-2. Chlorfenvinphos Product Registrations and Dates of Cancellation in the United States

Percent chlorfenvinfos	ID number	Product name	Initial registration date	Effective cancellation date
21.10	218-608	Arcadian Residual Fly Spray	09-29-66	02-21-86
21.10	59-144	Residual Surface Spray and Larvicide	03-25-66	02-21-86
21.10	59-173	Coopona Poultry Premise Larvicide	03-07-73	02-21-86
24.50	59-136	Dermaton® Dip	10-03-63	07 -01-87
92.00	201-209	Shell Technical Compound 4072, Insecticide for Manufacturing Purposes Only	12-13-66	10-10-89
92.00	31629-1	Technical Compound 4072 Insecticide (for Manufacturing Purposes Only)	06-07-74	10-10-89
00.50	59-189	Dermaton Dust	07-14-80	01-22-91
15.00	59-197	Dermaton Dog Collar	08-10-82	01-22-91
12.25	59-203	Dermaton III	05-15-84	01-22-91

Source: EPA 1994

5. POTENTIAL FOR HUMAN EXPOSURE

5.1   OVERVIEW

Chlorfenvinphos is currently released to the environment in the United States from runoff and leaching from hazardous waste disposal sites. Soil is the environmental medium most likely to be contaminated with chlorfenvinphos. The processes that may transport chlorfenvinphos from soil to other media include volatilization to the air, leaching to groundwater, runoff to surface water, and absorption by plants. Biodegradation appears to be the dominant process responsible for chlorfenvinphos loss from soil (Miles et al. 1979, 1983). Biodegradation, hydrolysis, and adsorption to organic matter are likely to be responsible for the loss of chlorfenvinphos from water (Beynon et al. 1971, 1973; Rouchaud et al. 1988).

If released to air from soil or water via volatilization, chlorfenvinphos is expected to exist primarily in the vapor phase, but can also be found associated with particulate matter (Eisenreich et al. 1981). In the vapor phase, chlorfenvinphos can react with hydroxyl radicals (estimated half-life value of 7 hours) or with ozone (estimated half-life value of 92 hours) (Atkinson and Carter 1984; Lyman et al. 1990; Meylan and Howard 1993).

If released to water, moderate adsorption to particulate matter will transport chlorfenvinphos from the water column and partition it to suspended solids and sediment (Swann et al 1983). The hydrolysis half-life value for chlorfenvinphos in water is highly dependent on pH and temperature. At a pH of 6 and 8 and a temperature of 20–30 EC, the half-life values were 170 and 80 days, respectively (Beynon et al. 1971).

Chlorfenvinphos does not appear to partition extensively from water into aquatic organisms. Estimated whole-body concentration factors for chlorfenvinphos were significant, but relatively low, ranging from 37 to 460 (Mackay 1982; Veith et al. 1979; Veith et al. 1980 in Bysshe 1990). No experimentally measured bioconcentration factor (BCF) values were located in the literature for any aquatic invertebrate or fish species. Chlorfenvinphos is absorbed by plants primarily from the soil, but residues generally decline fairly rapidly in the tissues through the course of the growing season (Beynon et al. 1968; Suett 1971, 1975a).

The estimated half-life value of chlorfenvinphos in sandy soil ranges from 28 days (4 weeks) to 210 days (30 weeks) (Beynon et al. 1973; Williams 1975a). The rate of degradation is influenced greatly by the soil type, amount of organic matter in the soil, soil temperature, soil moisture content, and

the history of chlorfenvinphos use. Repeated application of chlorfenvinphos to agricultural soils enhanced microbial degradation of the pesticide (Rouchaud et al. 1989a, 1991).

No information was found on concentrations of chlorfenvinphos in ambient air samples or in drinking water in the United States. Chlorfenvinphos was detected in surface and groundwater samples (concentrations not specified) at the one hazardous waste site where chlorfenvinphos was detected (HazDat 1996). Chlorfenvinphos was also detected in soil samples (concentrations not specified) at the one hazardous waste site where chlorfenvinphos was detected (HazDat 1996). It should be noted that the amount of chlorfenvinphos found by chemical analysis is not necessarily the amount that is bioavailable.

Currently, both domestic and imported foods (fresh fruits and vegetables) and lanolin-containing pharmaceutical products appear to be sources of some exposure for the general population. In the past, occupational exposure to chlorfenvinphos may have occurred through dermal contact and inhalation of dusts and sprays especially to workers applying the compound as a pesticide. Occupational exposure to chlorfenvinphos was reported in California in workers who handled flea control products (Ames et al. 1989).

Workers involved in disposal of chlorfenvinphos or chlorfenvinphos-contaminated wastes are also at a higher risk of exposure than the general population. People living in the vicinity of plants where chlorfenvinphos was manufactured or formulated, or living near dairy farms, cattle or sheep holding areas, or poultry producing facilities where chlorfenvinphos was used; and people living near hazardous waste sites containing chlorfenvinphos also are potentially at higher risk of exposure.

Chlorfenvinphos has been identified in at least 1 of the 1,428 current or former EPA National Priorities List (NPL) hazardous wastes sites (HazDat 1996). However, the number of sites evaluated for chlorfenvinphos 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

Information on historic production of chlorfenvinphos (including producers, production sites, production volumes and years of production) in the United States was not found. Releases of chlorfenvinphos are not required to be reported under SARA Section 313; consequently there are no data for this chemical in the 1993 Toxics Release Inventory (EPA 1995).

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

SITES

▨ 1
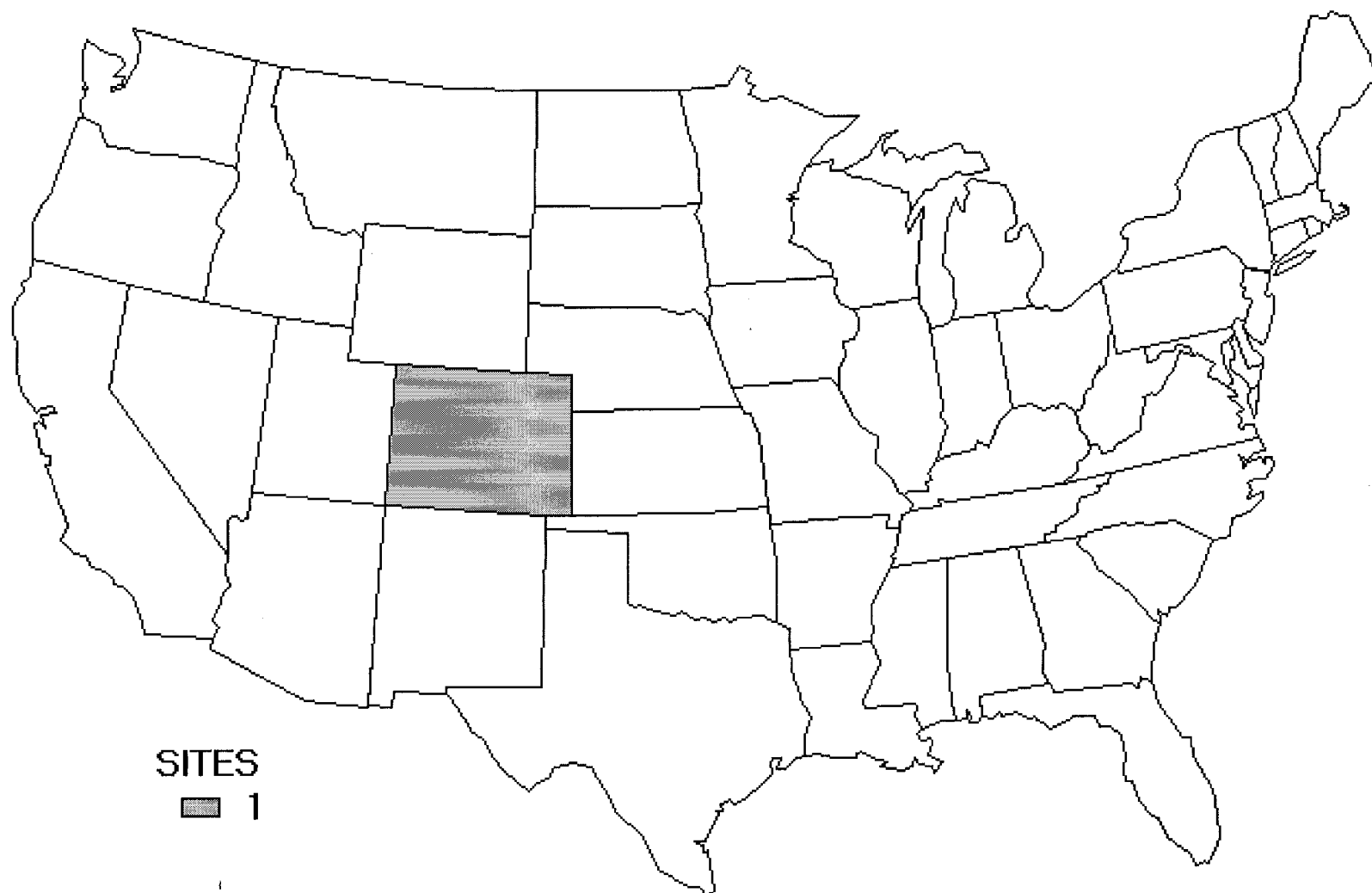
Derived from HazDat 1996

There is one NPL hazardous waste site where chlorfenvinphos has been identified (HazDat 1996). Hazardous waste disposal sites appear to be the major source for release of this compound into the environment since there are currently no registered uses for it in the United States (REFS 1995).

5.2.1 Air

Chlorfenvinphos may have been released into the air in the past, during its production and processing. Historically, chlorfenvinphos may have volatilized into the air during its use in sprays applied to dairy, poultry, and cattle facilities to control flies and fly larvae, or from the skin of animals exposed to chlorfenvinphos in cattle dips or sprays. Because of the relatively low volatility of the compound and lack of registration for crop use in the United States (REFS 1995), releases to the air from registered uses would be expected to be negligible.

Chlorfenvinphos was not detected in air samples collected at the one NPL hazardous waste site where it was detected in some environmental media (HazDat 1996). No other information on releases of chlorfenvinphos to air was located; however, there are no current registered uses of this compound in the United States (REFS 1995; SRI 1993).

5.2.2 Water

In the past, chlorfenvinphos may have been released to surface water during its production and processing. Chlorfenvinphos also may have been released to water via runoff after its application to dairy, poultry, and cattle facilities to control flies and fly larvae, or when residues from sheep or cattle dip tanks were discharged onto soil (Inch et al. 1972). Because chlorfenvinphos was never registered for use on crops in the United States (REFS 1995), its releases to water from its registered uses would be expected to be minimal. Adsorption to particulate matter will eventually transport chlorfenvinphos from water to suspended solids and sediment.

Chlorfenvinphos has been detected in surface water and groundwater samples collected at the one NPL hazardous waste site where it was detected (concentrations unspecified) in some environmental media (HazDat 1996). No other information on releases of chlorfenvinphos to water was located; however, there are no current registered uses of this compound in the United States (REFS 1995; SRI 1993).

5.2.3   Soil

Chlorfenvinphos may have been released directly to soil during its production and processing and is likely to have been released during its disposal as the recommended disposal practice for small quantities was burial in a disposal pit or in clay soil (IRPTC 1985). The chemical may also have been released to soil and sediment indirectly from runoff from treated manure storage areas, and areas around poultry or cattle holding areas, or when residues from sheep or cattle dip tanks were discharged onto soil (Inch et al. 1972). Adsorption to particulate matter will eventually transport chlorfenvinphos from water to suspended solids and sediment. Because chlorfenvinphos was not registered for crop use in the United States, its releases to soil from its registered uses would be expected to be minimal.

Chlorfenvinphos has been detected in soil samples collected at the one NPL hazardous waste site where it was detected in some environmental media (HazDat 1996). No other information on releases of chlorfenvinphos to soil or sediments was located; however, there are currently no registered uses of this chemical in the United States (REFS 1995; SRI 1993).

5.3   ENVIRONMENTAL FATE

5.3.1   Transport and Partitioning

There is a paucity of experimental data regarding the transport and partitioning of chlorfenvinphos in the air. Given a vapor pressure ranging from 4.0×10^{-6} mm Hg (Worthing 1983) to 7.5×10^{-6} mm Hg (Merck 1989), chlorfenvinphos should exist in the atmosphere in the vapor phase, but will also partition to available airborne particulates (Eisenreich et al. 1981). The solubility of 145 mg/L (Merck 1989) ensures that at least partial removal of atmospheric chlorfenvinphos will occur by wet deposition.

The transport of chlorfenvinphos from water to air can occur due to volatilization. Henry's law constant provides a qualitative indication of the importance of volatilization. Compounds with a Henry's law constant (H) of $<10^{-5}$ atm-m^3/mol volatilize slowly from water (Thomas 1990). Chlorfenvinphos with an H value of 2.76×10^{-9} atm-m^3/mol (Domine et al. 1992), therefore, will volatilize slowly from water. Since H $<10^{-9}$ atm-m^3/mol, chlorfenvinphos is less volatile than water and its concentration in water may increase as water evaporates. Humidity in the air reduces the volatilization rate of water somewhat so the lower limit can be set at 10^{-7}; this means that chlorfenvinphos could be considered essentially nonvolatile (Thomas 1990).

Adsorption to particulate matter will transport chlorfenvinphos from water and partition it to suspended solids and sediment in water. The estimated organic carbon-adjusted soil sorption coefficient (K_{oc}) for chlorfenvinphos is 280 (Kenaga 1980). This K_{oc} value suggests that chlorfenvinphos in the water column adsorbs moderately to suspended solids and sediments based on criteria established by Swann et al. (1983), and this process may transport considerable amounts of chlorfenvinphos from water to particulate matter. Partitioning of chlorfenvinphos from water to solid suspended matter was studied in a field experiment. Chlorfenvinphos was sprayed at a rate of 74 kg/ha on to the surface of a pond so the water contained an average concentration of 6.1 ppm (Beynon et al. 1971). The concentration decreased to 2.0 ppm after 5 hours, and to 0.12 ppm after 1 month. The sediment concentrations increased and persisted for at least 34 days after treatment. Chlorfenvinphos disappears from water in two distinct phases, a rapid initial phase and a much slower second phase. It is suggested that the first phase represents the initial precipitation of the heavier particles and uptake in plankton containing the adsorbed pesticide. Later, chlorfenvinphos is gradually adsorbed to other suspended matter, which then precipitates much more slowly, or the second phase may represent the slower removal of the residues by biotic processes.

Based on structure and activity relationships, certain regression equations have been developed to estimate the bioconcentration factor (BCF) value for chlorfenvinphos from its water solubility and organic carbon partition coefficent (K_{oc}) values. Using these regression equations, the BCF value for chlorfenvinphos in aquatic organisms is estimated to be 37 (Kenaga 1980). A log octanol-water partition coefficient (K_{ow}) value of 3.806 was reported by Bowman and Sans (1983). Using regression equations involving log K_{ow}, the following BCF values were estimated; 306 (Mackay 1982), 343 (Veith et al. 1979), and 460 (Veith et al. 1980 in Bysshe 1990). No experimentally measured BCF values were located in the literature for any aquatic invertebrate or fish species. However, bioconcentration of chlorfenvinphos in aquatic organisms, although relatively low, ranging from 37 to 460, may have some environmental significance. No information was found on the biomagnification of chlorfenvinphos through aquatic or terrestrial food chains.

The transport processes that may move chlorfenvinphos from soil to other media are volatilization, leaching, runoff, and absorption by plants. Based on the estimated Henry's law constant, volatilization is not expected to be an important transport process for moving chlorfenvinphos from soil to other media. Like other pesticides, chlorfenvinphos in soil partitions between soil-sorbed and soil-water phases (Racke 1992). This latter phase may be responsible for the volatilization of chlorfenvinphos from soil; however, due to the low Henry's law constant value, the rate of chlorfenvinphos volatilization from the soil-water phase to the atmosphere would be low. In a laboratory study of volatilization from

soil, chlorfenvinphos was incorporated into sterilized sand and into a sterilized sandy loam at a
concentration of 50 ppm. The media contained 25% moisture and were maintained at 20 EC in an
open beaker. Forty-five days after incorporation, more than 95% of the chlorfenvinphos was still
present in the beaker (Rouchaud et al. 1988). However, in a field study conducted by Williams (1975a),
the author suggests that rapid loss (42% in 2 days) of surface-applied chlorfenvinphos (granular) was
probably due to volatilization and/or photodecomposition. Subsurface application of the granular
formulation at the same concentration showed only a 6% loss in 2 days post-application. In another
field study, Suett (1977) reported that the combination of sunlight and warm wet soil for 48 hours
immediately after application of chlorfenvinphos marginally increased isomerization on both the coarse
and fine soil tilthes, but did not enhance volatilization.

The reported K_{oc} value of 280 (Kenaga 1980) suggests that the adsorption of chlorfenvinphos to soil is
moderately strong; therefore, the rates of leaching and runoff will be relatively minor processes in most
soils. Very little leaching of chlorfenvinphos and no leaching of its degradation products was observed
in several field studies. The leaching characteristics of chlorfenvinphos were studied by applying it to
sloping arable land at 22 kg active ingredient/hectare (a.i./ha) and following its movement down a slope
(Edwards et al. 1971). Only 0.18% of the chlorfenvinphos applied was leached through the soil, but this
was nine times more than was observed with dieldrin in a similar experiment. Only very small amounts
of chlorfenvinphos moved down the slope and were present in runoff. In one of the experiments there
was a pond located at the bottom of the slope and residues could not be detected in the mud or water
from this pond. Residues of the main soil degradation products were not detected in the pond water at
23 or 36 weeks post-application. More chlorfenvinphos leached vertically into drainage water than
laterally over the soil surface. Chlorfenvinphos residues in soil following broadcast applications on the
surface showed that even after 150 days, only 1–1.5% of the applied chlorfenvinphos leached to a
depth of 7.5–15 cm despite 12 cm of rainfall that occurred during the first 60 days post-application
(Williams 1975a). Furthermore, when the granular formulation was applied at a depth of 7.5 cm, there
was little movement of chlorfenvinphos below a depth of 10 cm. In a similar study by Agnihotri et al.
(1981), when chlorfenvinphos granules were applied to the 0–15 cm soil layer, no leaching of the
compound occurred below the 15 cm depth over a period of 120 days.

Chlorfenvinphos is also transported from the soil of one area to soil of another area or from soil to
surface water (rivers, lakes, and streams) via runoff. Pesticides with a water solubility >10 mg/L move
mainly in solution phase in runoff water (Racke 1992). Chlorfenvinphos with a water solubility of
145 mg/L (Merck 1989) is expected to be found mainly in runoff water. This does not seem to be
completely substantiated, however, by results of several field studies conducted in agricultural

watersheds. In one field study, only 0.3–0.6% of the applied chlorfenvinphos was found in runoff water after a rainfall event (Racke 1992). Braun and Frank (1980) analyzed pesticide residues in surface water samples over a 3-year period (1975–77) collected in 11 agricultural watersheds in Southern Ontario, Canada. Although chlorfenvinphos was known to have been used as a soil pesticide in at least one of the watersheds, it was not detected in any surface water samples (detection limit 1 µg/L [1 ppb]). In a more recent study, Frank et al. (1991) analyzed pesticide residues in surface water samples over a 5-year period (1986–90) collected from the mouths of the 3 major agricultural watersheds, the Grand, the Saugeen, and the Thames Rivers in Ontario, Canada. All three rivers flow into Lake Erie. Although it was known to have been used as a soil pesticide in the Thames River basin in 1988, no chlorfenvinphos residues were detected in any surface water samples during the study period (detection limit <1.0 µg/L [ppb]). Most recently, Wan et al. (1994) studied residues of several organophosphate pesticides including chlorfenvinphos in farm ditch water, and sediments and farm soils in the lower Fraser Valley of British Columbia, Canada, from July through December 1991. The farm ditches drained into three rivers: the Fraser, the Niicomekl, and the Sumas. During the study period, no sales of chlorfenvinphos were reported. Chlorfenvinphos was used as a soil insecticide in 1990, but was not recommended for this use in Canada in 1991. Although chlorfenvinphos was not detected in any of the farm ditch water or sediment samples analyzed at the 7 sampling sites, it was detected in 7% of the soil samples. Adsorption of chlorfenvinphos to particulate matter will transport the pesticide from the water column and partition it to suspended solids and sediment. From these results, it seems clear that surface water runoff and leaching of chlorfenvinphos into drainage water from treated agricultural fields is not likely to be a serious problem.

Adsorption of chlorfenvinphos from water solutions of hydrogen, calcium, sodium, and potassium ions were studied (Barba et al. 1991). In all cases, the saturating cations influenced the Freundlich-type adsorption, with adsorption decreasing in the following sequence: $H^+ > Ca^{2+} > Na^+ > K^+$ for adsorption on two clays, kaolinite and bentonite. The extent of adsorption of chlorfenvinphos was generally slower in kaolinite than in bentonite.

When it was first introduced, chlorfenvinphos was generally considered to be a non-systemic pesticide (i.e., when it is applied to soil it should not move into plants and when sprayed on plant foliage, it should not move from the treated leaves into other untreated parts of the plant) (Rouchaud et al. 1989b). This view was based on the fact that at plant maturity or at harvest, very low residues (<0.02 mg/kg [0.02 ppm]) were found in turnips, carrots, cabbages, white radishes, and potatoes planted or sown in chlorfenvinphos-treated soil (Beynon and Wright 1968; Beynon et al. 1968). In addition, no

translocation of chlorfenvinphos from treated leaves to other parts of plants was observed (Beynon et al. 1973). Earlier work with potato tubers under recommended field conditions also confirmed this finding (Beynon et al. 1968). Rouchaud et al. (1989b), however, found that in the foliage of the spring cauliflower, the concentration of chlorfenvinphos increased, reaching a peak concentration 15 days after soil treatment, then progressively decreased until harvest. The presence of chlorfenvinphos and two metabolites, trichloroacetophenone and 2,4-dichlorobenzoic acid, was the result of their absorption by the plant from the soil and of their biodegradation by the plant. Two crops were studied for their chlorfenvinphos uptake (Rouchaud et al. 1991). The periods of time required for chlorfenvinphos foliage concentrations to attain residues of 1 mg/kg (1 ppm) fresh weight were: cauliflower, 24–37 days; and Brussels sprouts, 41–45 days. Suett (1974, 1975a) also reported that carrots accumulated high residue concentrations of chlorfenvinphos applied to the soil and continued to accumulate the pesticide during the entire period of active plant growth. Thirty weeks after carrot seed was sown in soil treated with chlorfenvinphos at a depth of 10 cm, the peel of the carrots contained 88% of the total chlorfenvinphos residues found in the carrots. The upper 6 cm of carrot root always contained most of the chlorfenvinphos residue irrespective of the application mode. Significant residues of chlorfenvinphos were detected in immature onion bulbs (64–76 days after seeding), with the level of chlorfenvinphos residue being much higher in the roots and outer skin (Ritcey et al. 1991). The chlorfenvinphos concentrations in the bulbs dropped below the detection limit (unspecified) by 96 days after seeding (2 months before harvesting).

In recent experiments, plant cuticle was investigated as the first and rate-limiting barrier in foliar uptake of chlorfenvinphos. Mobility studies of chlorfenvinphos across the cuticular membranes of bitter orange (*Citrus aurantium*) leaves and green pepper (*Capsicum annuum*) fruits gave first-order rate constants of 6.7 ($\pm$3.3)x10^8/second and 10.2 ($\pm$3.4)x10^7/second, respectively (Bauer and Schönherr 1992). These correspond to penetration half-lives of 120 days (2,874 hours) and 7.8 days (189 hours), respectively.

5.3.2   Transformation and Degradation

5.3.2.1   Air

One of the important reactions for most organic pollutants in the atmosphere is with hydroxyl radicals. No rate constant for the reaction of hydroxyl radicals with chlorfenvinphos in air has been experimentally determined. Using an estimation method, the estimated rate constant value for the vapor-phase reaction of chlorfenvinphos with hydroxyl radicals is 5.31x10^{-11} cm^3/radical-sec at 25 EC (Atkinson 1988; Meylan and Howard 1993). Based on this value, and assuming an average annual

atmospheric concentration of hydroxyl radicals in the northern hemisphere of 4.8×10^5 radicals/cm^3 (Lyman et al. 1990), the estimated half-life value (first-order kinetics) of chlorfenvinphos in the atmosphere due to this reaction is 7 hours. Thus, chlorfenvinphos is short-lived in the atmosphere. Chlorfenvinphos can also be degraded by ozonation in the atmosphere. However, no rate constant for the reaction of ozone with chlorfenvinphos in air has been experimentally determined. An estimated value of the rate constant is $3 \times 10^{-18}cm^3$/molecule-sec at 25 EC (Atkinson and Carter 1984; Meylan and Howard 1993). Based on this value and assuming an average atmospheric ozone concentration of 9.6×10^{11} molecules/cm^3 (Lyman et al. 1990), the estimated half-life value (first-order kinetics) of chlorfenvinphos in the atmosphere due to this reaction is 92 hours (3.4 days). Photolysis is probably the least significant of the atmospheric degradation processes. Chlorfenvinphos is not susceptible to direct photolysis in sunlight because its maximum absorption for ultraviolet light is 228 nm (Schlett 1991), which is less than the 290 nm wavelength limit for sunlight absorption to occur.

5.3.2.2 Water

The processes that can result in the transformation and degradation of chlorfenvinphos in water are hydrolysis, photosensitized oxidation, and biodegradation. Hydrolysis pathways for chlorfenvinphos in water are shown in Figure 5-2. Chlorfenvinphos is most stable in water at ambient temperatures and neutral pH. Chlorfenvinphos hydrolyzed slowly in water resulting in a half-life (first-order kinetics) value of 170 days at pH 6 and 80 days at pH 8 at 20–30 EC (Beynon et al. 1971). In laboratory studies, hydrolysis was observed under conditions of high temperature and extreme pH (highly alkaline or highly acidic), resulting in a half-life of >400 hours (>33 days) at pH 9.1, and >700 hours (58 days) at pH 1.1 at 38 EC (Agrochemicals Handbook 1991; Beynon et al. 1973; Hayes 1982). Hydrolysis probably does not contribute much to the initial disappearance of chlorfenvinphos from natural waters (Beynon et al. 1971). Based on hydrolysis studies (Ruzicka et al. 1967) conducted at 70 EC and correcting for temperature differences assuming an environmental temperature of 20 EC, the aqueous hydrolysis half-life (first-order kinetics) value of chlorfenvinphos is approximately 1–1.3 years (Harris 1990). Direct photolysis of chlorfenvinphos is negligible, since the compound does not significantly absorb ultraviolet wavelength light >290 nm. No information was found in the literature regarding the photosensitized reaction of chlorfenvinphos in water with ozone, hydroxyl radicals or singlet oxygen. Therefore, biodegradation appears to be the dominant degradation process in natural waters. This is likely, as microbial degradation is the dominant degradation process in soils (Miles et at. 1979, 1983; Rouchaud et al. 1988).

Figure 5-2. Hydrolysis Pathways for Chlorfenvinphos in Water

Chlorfenvinphos

Acidic, 100°C

Basic, 10% NaOH, 100° C

Neutral

Trichloroacetophenone

Stable

Trichloroacetophenone

+

+

Diethyl phosphoric acid

2,4-Dichlorophenylglycolic acid

+

Diethyl phosphoric acid, sodium
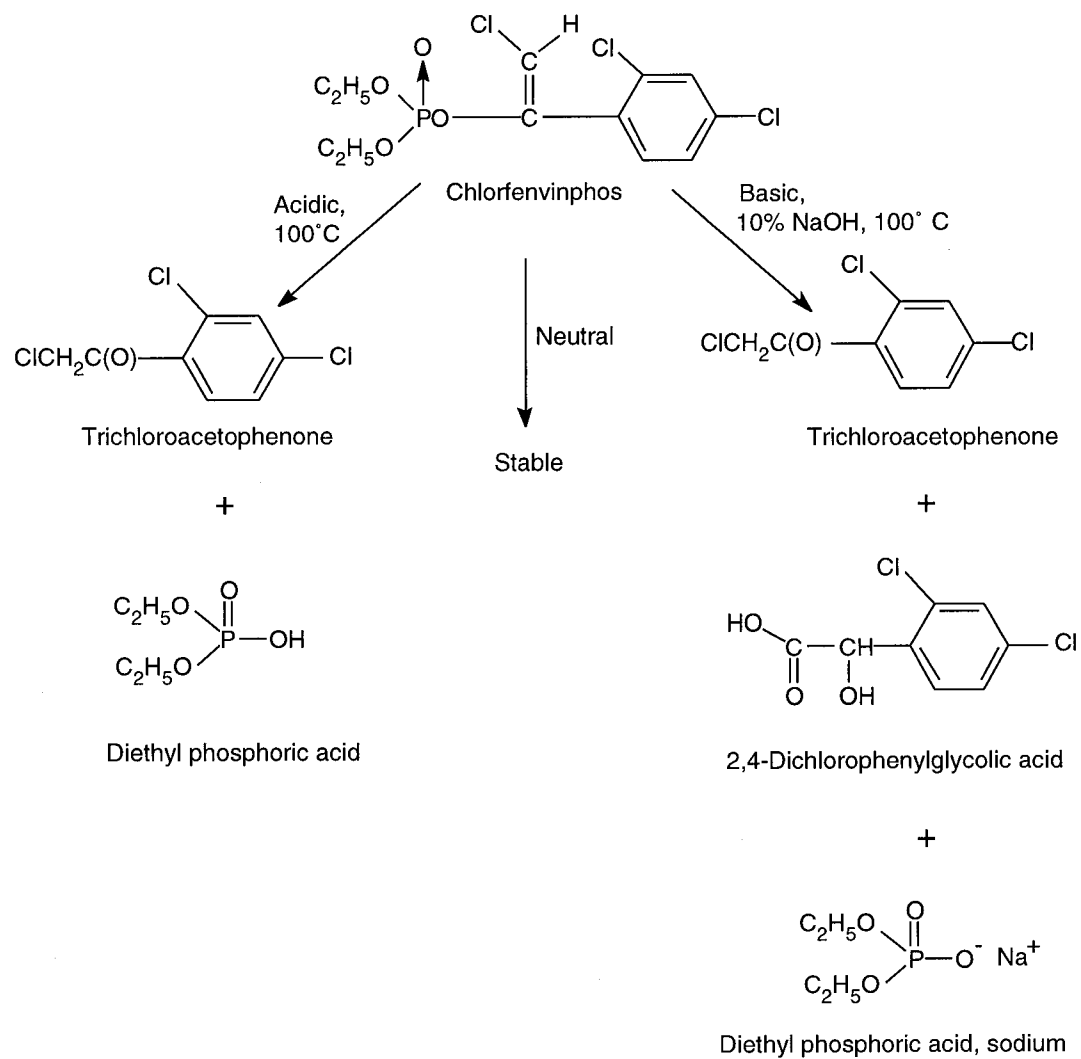
5.3.2.3   Sediment and Soil

Chlorfenvinphos in soil and sediment may undergo degradation and transformation by hydrolysis, and biotic processes. Various screening studies have demonstrated that microbial degradation is the dominant degradation process in soil (Miles et al. 1979, 1983; Rouchaud et al.1988, 1989a, 1989b). The hydrolysis of chlorfenvinphos may occur in the soil/sediment-water phase, as opposed to the soil/ sediment-sorbed phase. As a result, the rate of hydrolysis is expected to be comparable to that in water. Based on the slow hydrolysis rates observed in water (see Section 5.3.2.2), hydrolysis of chlorfenvinphos in soil is not expected to be significant. In the laboratory, chlorfenvinphos was incubated in sterilized and unsterilized soil for more than 2 months at 20 EC. The rate of disappearance of chlorfenvinphos from the sterilized soil was more than 15 times slower than that observed in unsterilized soil. The persistence of chlorfenvinphos was examined in sterile and natural mineral (sandy loam/organic matter = 2.7%, pH = 7.2) and organic (muck, organic matter = 48%, pH = 6.5) soils at a range of temperatures (3–28 EC) for 24 weeks (Miles et al. 1979, 1983). In general, chlorfenvinphos is less stable in sandy loam than in muck, less stable at higher temperatures (the exception was the stability of chlorfenvinphos in sterile sandy loam at all temperatures studied), and considerably less stable in natural soils (half-lives #11 weeks at 15 and 28 EC) compared to sterile soils (half-lives >24 weeks at all temperatures), indicating the major role microbes play in degrading chlorfenvinphos in soil. A summary of degradation pathways of chlorfenvinphos in soil is presented in Figure 5-3.

Chlorfenvinphos is degraded in soil to trichloroacetophenone, 2,4-dichloroacetophenone, α-(chloro-methyl)-2,4-dichlorobenzyl alcohol, and 1-(2',4'-dichlorophenyl)-ethan-1-ol (Rouchaud et al. 1988, 1991). Other degradation products identified are 2,4-dichlorobenzoic acid, 2-hydroxy-4-chlorobenzoic acid, and 2,4-dihydroxybenzoic acid. None of the degradation products retain any pesticide characteristics. Trichloroacetophenone is the main transformation product; when hydrolyzed, oxidized and decarboxylated, it becomes 2,4-dichlorobenzoic acid. Reduction of trichloroacetophenone to α-(chloromethyl)-2,4-dichlorobenzyl alcohol is a slow process, and replacement of a chlorine atom by a hydrogen atom to become 2,4-dichloroacetophenone and 1(-2',4'-dichlorophenyl)-ethan-1-ol is also slow. The degradation products 2-hydroxy-4-chlorobenzoic acid and 2,4-dihydroxybenzoic acid are produced from 2,4-dichlorobenzoic acid by replacement of chlorine atoms by hydroxyl groups.

Biodegradation of chlorfenvinphos is influenced by several factors: soil type, presence of organic matter, moisture content, soil temperature, and a history of chlorfenvinphos use. Chlorfenvinphos degrades fastest in

Figure 5-3. Environmental Degradation Pathways for Chlorfenvinphos in Soil
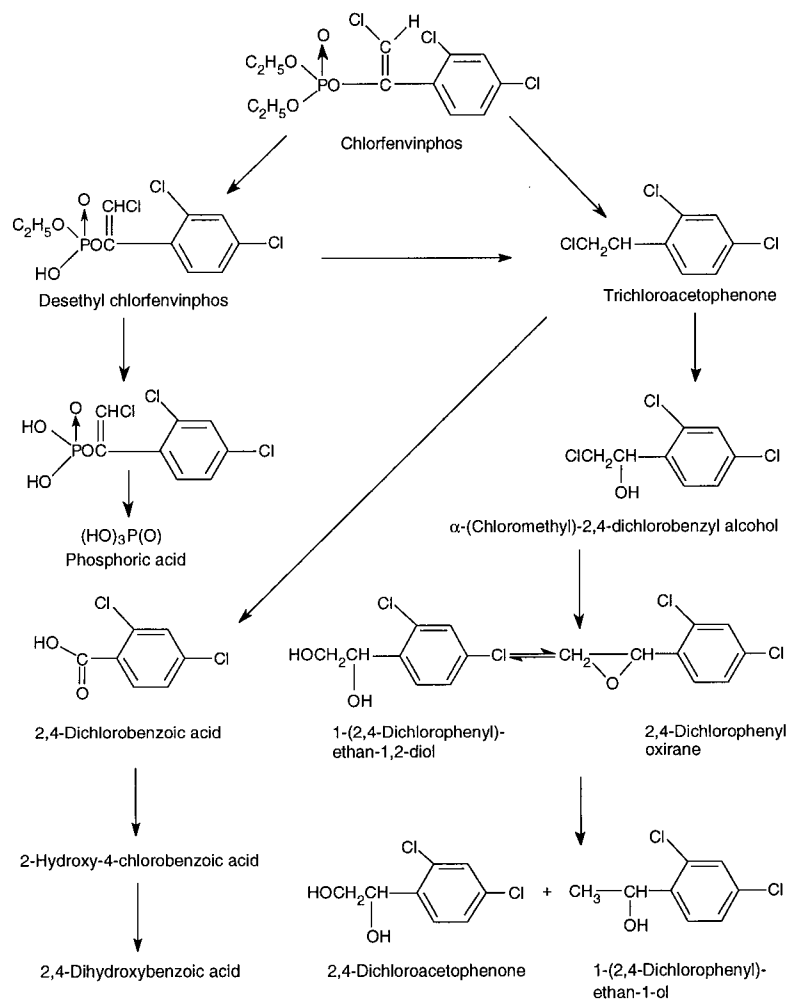
sandy soils and slowest in peat, probably because of its degree of adsorption to organic matter (Beynon et al. 1973; Williams 1975a). Because the rate of degradation by hydrolysis is greater than expected, breakdown is assumed to be mainly biotic. Initial half-life values of 4–30 weeks have been determined for sandy soils. In peat, chlorfenvinphos persists longer. Chlorfenvinphos was found to be very slowly degraded in a peat soil (47.8% organic matter), but was much less persistent on several sandy soils (1.6–2.2% organic matter) (Williams 1975a). In the peat (soil water pH = 6.0), 70% of the applied chlorfenvinphos remained after 21 weeks and 30% remained after nearly 12 months. In sandy soil (soil water pH = 6.9–7.5) only 3–15% of the applied chlorfenvinphos remained after a period of 15 weeks. The persistence in peat was attributed to strong adsorption rendering the pesticide unavailable to microorganisms and to plant roots. In sandy soil, rainfall was also correlated to increased loss of chlorfenvinphos.

Chlorfenvinphos was more stable and had increased persistence in soils that had been treated with organic fertilizer such as pig slurry, cow manure, city refuse, or mushroom cultivation composts compared to untreated control plots (Rouchaud et al. 1992a, 1992b). For example, the half-life of chlorfenvinphos at the Gembloux site was 18, 36, 35, and 43 days for the control, city refuse compost, cow manure, and mushroom compost plots, respectively. At another site (St. Katelijne-Waver), both a spring and summer application study were conducted. In the spring study, the half-life of chlorfenvinphos was 9, 13, 14, and 21 days and in the summer study, the half-life was 23, 42, 46, and 53 days for the control, city refuse compost, cow manure, and mushroom compost plots respectively. The humic acid concentrations and the total soil organic matter content were always higher in the organic fertilizer treated plots.

Rates of chlorfenvinphos loss from soil also appear to be related to soil moisture conditions. In dry seasons, although the initial rate of loss was high, the subsequent rate of degradation was slower than in wetter seasons of higher soil moisture content (Williams 1975a). Under conditions of average summer rainfall and relatively moist soils, the residues were less than 5% of applied dose, but when the soils were much drier than normal, residues were higher at 15% of applied dose after the same period of time (Miles et al. 1984).

Degradation of chlorfenvinphos ceases in soil at low temperatures (below 6–7 EC) (Suett 1975b). A granular formulation of chlorfenvinphos was broadcast at 2 kg active ingredient per hectare and incorporated to 10 cm into sandy-loam soil in May and in September 1971. When applied in September, the chlorfenvinphos persisted for a longer period than when applied in May. Degradation was slower during the winter while the mean soil temperature remained below 6–7 EC. Rising soil temperature during the following spring rapidly increased the rate of degradation. The late summer-

early fall applications to control carrot flies would leave appreciable residues of chlorfenvinphos in the soil at the beginning of the next growing season which might contribute to the terminal crop residues. Residues of chlorfenvinphos applied in May declined to less than 20% of the initially applied dose, and there was little loss subsequent to the December sampling. In the September application, more than 60% of the chlorfenvinphos applied still remained when the loss rates decreased in October. The relatively high concentration of chlorfenvinphos remaining then continued to decline only slowly throughout the winter until March when the rate of loss of chlorfenvinphos residues increased to rates similar to those of the previous September.

The catalytic degradation of chlorfenvinphos on H^+, Ca^{2+}, Na^+, and K^+ mono-ionic kaolinite and bentonite was found to be influenced by the nature of the exchange cations and their degree of hydration in the order $K^+ > Na^+ > Ca^{2+} > H^+/Al^{3+}$ (Cámara et al. 1992). In both types of clays, the process of hydrolysis occurred in two stages involving first-order kinetics, giving different hydrolysis rates. The first stage is characterized by a rapid hydrolysis rate of short duration; the second phase is long with a slow but continuous hydrolysis rate.

An inverse relationship between the history of chlorfenvinphos use in the soil and foliage concentrations was found that suggested enhanced biodegradation (Rouchaud et al. 1991). The longer the history of chlorfenvinphos use in a field, the lower the chlorfenvinphos residues and residues of its metabolites that were found; this suggests that specific soil microbial fauna adaptation was due to previous soil treatments. In soil from cauliflower, Brussels sprouts, and Chinese cabbage fields, the half-life of chlorfenvinphos was found to vary from 9 to 35 days; for chlorfenvinphos plus degradation products, the half-life ranged from 50 to 80 days (Rouchaud et al. 1989a). The fields in which chlorfenvinphos exhibited the shorter half-lives were those with the longer histories of chlorfenvinphos use in the soil, suggesting enhanced biodegradation was occurring.

Environmental transformation pathways for chlorfenvinphos in plants are summarized in Figure 5-4. A trans to cis rearrangement of chlorfenvinphos sprayed on plant foliage has been observed (Beynon et al. 1973). This conversion has been attributed to photochemical processes. The same conversion has not been observed for chlorfenvinphos applied directly to soil. The initial half-life value of chlorfenvinphos on foliage is 2–3 days, and the rate of degradation decreases thereafter. Over 50% of the radioactivity from [14]C-(vinyl)-trans-chlorfenvinphos disappeared from foliage in 4–7 days. It is not known whether it is released as chlorfenvinphos or as a degradation product. The major breakdown product of chlorfenvinphos on plant foliage is a conjugate of the ethan-1-ol [8], probably with a sugar.

Figure 5-4. Environmental Transformation Pathways for Chlorfenvinphos in Plants

Chlorfenvinphos

Desethyl chlorfenvinphos

Trichloroacetophenone

(HO)₃P(O)
Phosphoric acid

α-(Chloromethyl)-2,4-dichlorobenzyl alcohol

2,4-Dichlorobenzoic acid

1-(2,4-Dichlorophenyl)-
ethan-1,2-diol

2,4-Dichlorophenyl
oxirane

2-Hydroxy-4-chlorobenzoic acid

2,4-Dihydroxybenzoic acid

2,4-Dichloroacetophenone

1-(2,4-Dichlorophenyl)-
ethan-1-ol
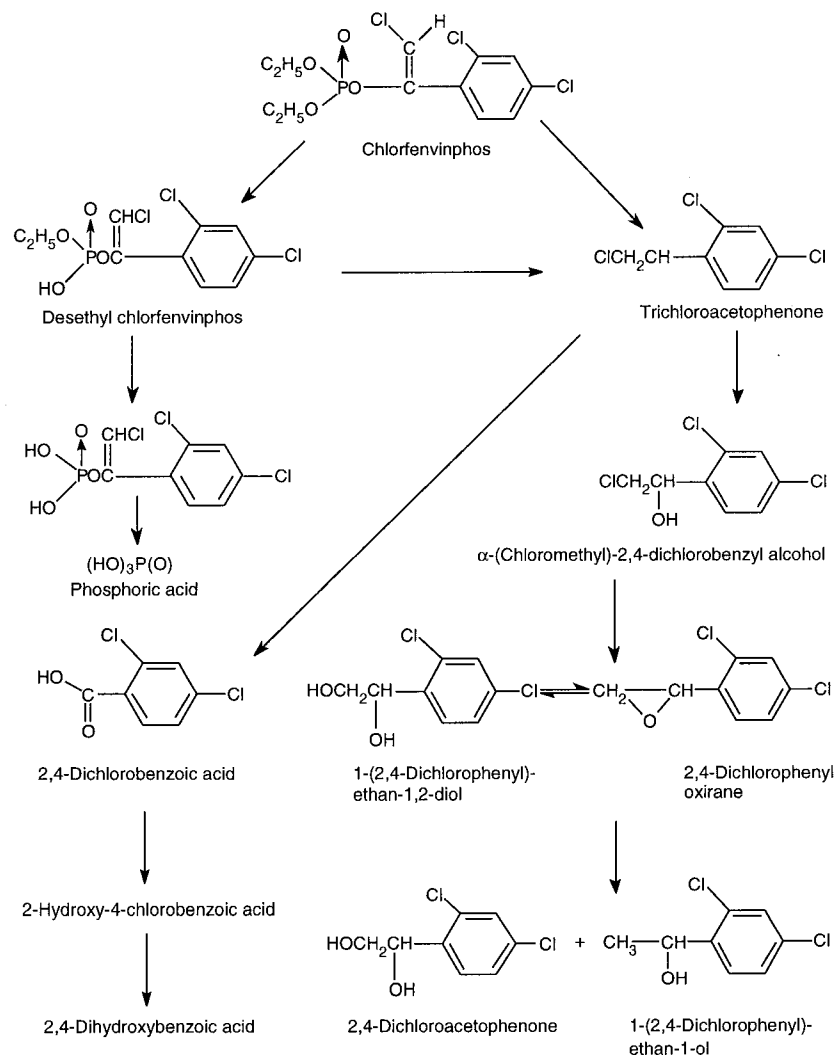
5.4   LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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

5.4.1   Air

No information was located on the ambient concentrations of chlorfenvinphos in the atmosphere or on concentrations associated with domestic or occupational indoor air exposures in the United States.

5.4.2   Water

No information was located on the ambient concentrations of chlorfenvinphos in drinking water, surface water, or groundwater in the United States. Chlorfenvinphos was detected (concentration unspecified) in surface water and groundwater samples collected at the only hazardous waste site where it was detected in some environmental media (HazDat 1996).

Environmental monitoring data are available for surface waters from Canadian studies in the Great Lakes region and from British Columbia. Braun and Frank (1980) analyzed pesticide residues in surface water samples collected over a 3-year period (1975–77) in 11 agricultural watersheds in Southern Ontario, Canada. Although chlorfenvinphos was known to have been used as a pesticide in at least one of the watersheds, it was not detected in any surface water samples (detection limit 1 µg/L [1 ppb]). Frank et al. (1991) analyzed pesticide residues in water samples collected over a 5-year period (1986–90) from the mouths of the three major agricultural watershed rivers in Ontario, Canada: the Grand, the Saugeen, and the Thames. All three rivers flow into Lake Erie. Although it was known to have been used as a soil pesticide in the Thames River basin in 1988, no chlorfenvinphos residues were detected in any water samples during the study period (detection limit <1.0 µg/L [<1 ppb]). Most recently, Wan et al. (1994) studied residues of several organophosphate pesticides including chlorfenvinphos in farm ditch water and farm soils in the lower Fraser Valley of British Columbia, Canada, from July through December 1991. The farm ditches drained into three rivers: the Fraser, the Niicomekl, and the Sumas. During the study period, no sales of chlorfenvinphos were reported. Chlorfenvinphos was used as a soil insecticide in 1990, but was not recommended for this use in

Canada in 1991. Although chlorfenvinphos was not detected in any of the farm ditch water or sediment samples analyzed at the 7 sampling sites, it was detected in 7% of the soil samples. Residue results obtained in these Canadian studies may be inappropriate for estimating water residues in the United States, as chlorfenvinphos was never registered for use as a soil insecticide in the United States (REFS 1995).

5.4.3   Sediment and Soil

Chlorfenvinphos was detected (concentration not specified) in topsoil and subsoil samples (>3 inches deep) collected at one NPL hazardous waste site where it was detected in some environmental media (HazDat 1996). No other information was located on the concentrations of chlorfenvinphos detected in soil or sediment samples collected in the United States.

Environmental monitoring data are available, however, for agricultural soils from Canadian studies in the Great Lakes region and from British Columbia. Chlorfenvinphos residues in organic farm soils of the Holland Marsh in Ontario, Canada, were analyzed each fall from 1972 to 1975 and residue levels generally exceeded 0.1 ppm (Miles et al. 1978). The annual mean residues (dry weight basis) of chlorfenvinphos sampled in 13 farm soils were as follows: 1972, 0.12 ppm; 1973, 0.05 ppm; 1974, 0.36 ppm; and 1975, 0.13 ppm. Wan et al. (1994) studied residues of several organophosphate pesticides including chlorfenvinphos in farm soils from seven different sites in the lower Fraser Valley of British Columbia, Canada, from July through December 1991. Chlorfenvinphos was used as a soil insecticide in 1990, but was not recommended for this use in Canada, in 1991 (during the study period). Despite the fact that chlorfenvinphos was not used during the study period, it was detected in 7% of the soil samples analyzed. The mean chlorfenvinphos concentration found in soil at the Cloverdale site was 31 µg/kg (0.031 ppm), with a range of 12 to 60 µg/kg (0.012–0.060 ppm). The authors believed that these residues were a carryover from the previous years. Residue results obtained in these Canadian studies may be inappropriate for estimating soil residues in the United States, as chlorfenvinphos was never registered for use as a soil insecticide in the United States (REFS 1995).

5.4.4   Other Environmental Media

Chlorfenvinphos was not monitored in many of the federal, regional, and state food studies conducted from the late 1960s through the mid-1980s (Corneliussen 1970; Duggan and Corneliussen 1972; Duggan et al. 1983; Gartell et al. 1986; Gunderson 1988; Hundley et al. 1988). The FDA's monitoring

program for domestic and imported food commodities detected chlorfenvinphos in unspecified foods at unspecified concentrations during fiscal years 1978–82 (Yess et al. 1991a) and during fiscal years 1983–86 (Yess et al. 1991b). During 1982–86, the FDA Los Angeles District Laboratory analyzed 19,851 samples of domestic and imported food and feed commodities (Luke et al. 1988). Chlorfenvinphos was not detected in any sample of the 6,391 domestic agricultural commodities or in any of the 12,044 imported agricultural commodities analyzed. Chlorfenvinphos was detected in unspecified foods at unspecified concentrations and at an unspecified detection frequency in 14,492 domestic and imported food samples analyzed as part of the FDA pesticide monitoring program for 1986–87 (FDA 1988). In a pesticide residue screening program conducted in 1989–91 in San Antonio, Texas, on 6,970 produce samples, chlorfenvinphos was detected (0.75 ppm detection limit) in one produce sample of tomatoes (frequency of <0.5%) (Schattenburg and Hsu 1992). In a similar study conducted by Agriculture Canada of 13,230 domestic and imported food items analyzed during the same period (1989–91), chlorfenvinphos was not detected in any domestic foods, but was detected in 13 imported food samples (frequency <0.1%) (Neidert et al. 1994). Detectable residues were found in fresh oranges, peppers, pineapples, and spinach. As part of the FDA's Pesticide Monitoring Program for domestic and imported foods, chlorfenvinphos residues have been detected in unspecified foods at unspecified concentrations and at unspecified detection frequencies during 1988–89, 1989–90, 1990–91, 1991–92, 1992-93 (FDA 1990, 1991, 1992, 1993, 1994), but residues were not detected in 1993–94 during the most recent regulatory monitoring period (FDA 1995).

The effect of cooking on chlorfenvinphos concentrations in raw foods was examined by Askew et al. (1968). These authors spiked samples of raw potato and cabbage mash with 2 ppm of chlorfenvinphos and boiled the samples for 30 minutes to simulate the effect of cooking raw vegetables contaminated with chlorfenvinphos. Total residues were reduced by 37–53% for potato and 56–86% for cabbage mash. A cooking process such as boiling leads to a partial reduction of chlorfenvinphos residues, but does not completely eliminate the pesticide. A similar study examined the effects of milk processing procedures on organophosphate residues in milk (Skibniewska and Smoczynski 1985). These authors reported that boiling in an enamel vessel to simulate home cooking, and three pasteurization procedures involving heating for 30 minutes at 62 EC, for 2 minutes at 72 EC, and for 5 seconds at 85 EC, resulted in about a 20% decrease in the residues of organophosphates including chlorfenvinphos. Reduction of the pesticide residues was more affected by the duration of heating rather than the temperature to which the milk was heated.

Nagayama et al. (1989) studied the residue levels of chlorfenvinphos on commercial tea leaves grown in Japan and the leaching of the pesticide into tea. Chlorfenvinphos was detected at concentrations

ranging from trace to 3.4 ppm on tea leaves and more that 12% of the chlorfenvinphos was found to leach from the leaves into the tea.

Heikes and Craun (1992) analyzed the residues of several pesticides including chlorfenvinphos in anhydrous lanolin and lanolin-containing pharmaceutical preparation sampled from 1988 through 1992. Concentrations of chlorfenvinphos in anhydrous lanolin samples collected in 1989 ranged from 0.60 to 5.9 mg/kg; those collected in 1991 ranged from 0.81 to 10 mg/kg. In 1988, chlorfenvinphos was detected in a wide range of pharmaceutical preparations including A & D ointment, analgesic balm, nitroglycerin cream, atropine sulfate ointment, and dibucaine ointment at concentrations ranging from 0.08 to 1.1 mg/kg (ppm). In 1992, chlorfenvinphos was detected in antibiotic, cold sore, and ophthalmic ointments at concentrations ranging from trace to 0.32 mg/kg (ppm).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Currently, the general population is primarily exposed to chlorfenvinphos by ingesting food containing chlorfenvinphos, particularly fresh fruits and vegetables imported from countries where this pesticide still is used. In addition, the general population may be dermally exposed to chlorfenvinphos concentrations in lanolin and lanolin-containing pharmaceutical products.

No information is available on the concentrations of chlorfenvinphos in ambient air. However, because this pesticide currently has no registered uses in the United States, the extent of exposure of the general population to chlorfenvinphos from inhalation is probably insignificant. No information is available on the concentrations of chlorfenvinphos in drinking water. Because chlorfenvinphos was not used as an agricultural pesticide on crops in the United States, it was not monitored extensively in groundwater. As a result of its relatively limited use, current exposure of the general population to chlorfenvinphos from consumption of drinking water is probably negligible.

Chlorfenvinphos has been detected in both domestic and imported foods, but especially in imported fresh fruits and vegetables (see Section 5.4.4). Thus, consumers can be exposed to chlorfenvinphos by ingesting contaminated food. No information was available on the FDA-estimated daily food intakes of chlorfenvinphos for different age/sex groups in the United States for fiscal years 1982–84 (Gunderson 1988) or 1986–91 (FDA 1993). However, because exposure to the general population from consumption of chlorfenvinphos-contaminated foods comes primarily from imported foods and

because residues in raw vegetables and fruits are reduced during food preparation by washing and
cooking procedures, the risk to the general U.S. population appears negligible.

Workers who were involved in the manufacture, formulation, handling, or application of chlorfenvinphos
are likely to have been exposed to higher concentrations by dermal exposure and inhalation of
chlorfenvinphos particles than the general population. Workers who are currently involved in the
disposal of chlorfenvinphos-contaminated wastes are likely to be exposed to higher concentrations by
dermal contact and inhalation of chlorfenvinphos particles or chlorfenvinphos-contaminated soil
particles than the general population. Occupational exposure to chlorfenvinphos was reported to have
occurred in workers in California who handled flea control products. However, chlorfenvinphos was not
associated with statistically elevated symptom frequency (Ames et al. 1989).

No information was found in the National Occupational Exposure Survey (NOES) conducted by NIOSH
from 1981 to 1983 on the number of workers and the number of facilities where workers could be
potentially exposed to chlorfenvinphos in the United States (NOES 1990). NIOSH (1992) did not
provide recommendations for occupational exposure levels to chlorfenvinphos for a 10-hour time
weighted average (TWA) workday. An Occupational Safety and Health Administration (OSHA)
permissible exposure limit (PEL) for workplace air does not exist (OSHA 1974).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In the past, individuals who were occupationally exposed to chlorfenvinphos during its production,
formulation, packaging, distribution, use, or disposal, were exposed to higher-than-background
concentrations of chlorfenvinphos.

At the present time, several groups within the general population may receive potentially high
exposures to chlorfenvinphos. These groups include individuals living near chemical manufacturing or
processing sites or those currently involved in the disposal of chlorfenvinphos or chlorfenvinphos-
contaminated materials, those living on dairy, beef, sheep, or poultry farms where chlorfenvinphos was
extensively used, and those living near hazardous waste sites. Individuals living near these sites may
be exposed to potentially higher concentrations of chlorfenvinphos or its metabolites in their drinking
water if they obtain tap water from wells near these sources. Children playing in chlorfenvinphos-
contaminated soils may consume this pesticide or its degradation products from their exposed hands.

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 chlorfenvinphos 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 chlorfenvinphos.

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.   As seen in Table 3-2, the relevant physical and chemical
properties of chlorfenvinphos are known (Bowman and Sans 1983; Domine et al. 1992; HSDB 1994;
Kenaga 1980; Merck 1989; Worthing 1983) and predicting the environmental fate and transport of
this compound based on the K_{oc}, K_{ow}, and Henry's law constant is possible. No further information is
required.

Production, Import/Export, Use, Release, and Disposal.   Chlorfenvinphos was introduced into
the United States in 1963 (Hayes 1982) by the Shell International Chemical Company, Ciba-Geigy
AG, and by Allied Chemical Corporation (Worthing 1983). No historic import/export information was
available for this chemical. In the United States, chlorfenvinphos use appears to have been limited to
uses in dairies, feedlots, or poultry yards to reduce adult fly populations; in manure containment
areas to reduce adult and larval fly populations; as a cattle and sheep dip to reduce ectoparasites,
and as a wettable powder (WP), granular form, or contained in a collar for killing fleas and ticks in
dogs (EPA 1994; REFS 1995). While chlorfenvinphos has been extensively used in agricultural
applications in other countries, especially for root and cole crops, this pesticide was not used for crop
applications in the United States (Farm Chemicals Handbook 1984, 1993; Spencer 1982; The
Agrochemicals Handbook 1991; Worthing 1983). More complete information on the production and

import/export of chlorfenvinphos would be useful to assess the possible routes of exposure, potential for environmental contamination and human exposure. Information on the number of producers and production sites, locations of production facilities, years of production, and the volume of production in the United States would be helpful. Information on import/export volumes and estimates of yearly usage during those years prior to the cancellation of its pesticide registration would also be useful. While adequate information on disposal procedures exists (IRPTC 1985), more recent information would be helpful.

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. No information is available from TRI93 because chlorfenvinphos is not one of the toxic chemicals that producers currently are required to report (EPA 1995).

Environmental Fate.   Information regarding the fate of chlorfenvinphos in the air was not located in the literature. Given a vapor pressure ranging from $4x10^{-6}$ to $7.5x10^{-6}$ mm Hg (Merck 1989; Worthing 1983), chlorfenvinphos should exist in the atmosphere in the vapor phase, but will also partition to available airborne particulates (Eisenreich et al. 1981). The solubility of 145 mg/L (Merck 1989) ensures that at least partial removal of atmospheric chlorfenvinphos will occur by wet deposition. Based on these chemical and physical properties, the atmospheric concentrations of chlorfenvinphos are expected to be low because chlorfenvinphos is not highly volatile. Additional information would help predict the residence time and distance of its aerial transport. The fate of chlorfenvinphos in water has been more extensively studied (see Section 5.3.1) (Barba et al. 1991; Beynon et al. 1971, 1973; Braun and Frank 1980; Frank et al. 1991; Wan et al. 1994), including information on its degradation under various environmental conditions. The fate of chlorfenvinphos in soil, including information on its mobility and biodegradation, has also been well documented (see Section 5.3.1) (Beynon et al. 1973; Edwards et al. 1971; Miles et al. 1979, 1983; Racke 1992; Rouchaud et al. 1988, 1989a, 1989b, 1989c, 1991, 1992a, 1992b; Williams 1975a). Additional information on the degradation of chlorfenvinphos in air and groundwater would be helpful in estimating exposure to chlorfenvinphos under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

Bioavailability from Environmental Media.   Available information regarding the rate of chlorfenvinphos absorption following inhalation, oral, and dermal contact has been discussed in the

Toxicokinetics section (see Section 2.3) (Hunter 1969; Hutson and Wright 1980; Pach et al. 1987). Although no data on chlorfenvinphos' bioavailability from contaminated air are available, the bioavailability from inhalation exposure is expected to be relatively low because the compound is likely to partition to available particulates. No data are available on the bioavailability of chlorfenvinphos from water, soil, or plant material. Chlorfenvinphos is adsorbed moderately to soil (Beynon et al. 1973; Edwards et al. 1971; Racke 1992). Chlorfenvinphos is expected to have reduced bioavailability from soil and water, since the part that remains adsorbed to soil or sediment may be only partially bioavailable. Additional data on the bioavailability of chlorfenvinphos from environmental media and the difference in bioavailability from different media would be helpful in assessing the potential body burdens that may occur as a result of exposure to environmental concentrations.

Food Chain Bioaccumulation.   The only information on bioconcentration factors for chlorfenvinphos was derived from equations based on information on physical and chemical properties (see Section 5.3.1) Estimated whole-body concentration factors calculated for chlorfenvinphos were significant, but relatively low, ranging from 37 to 460 (Mackay 1982; Veith et al. 1979; Veith et al. 1980 in Bysshe 1990). No measured BCFs for any aquatic organisms were found in the literature. Available data indicate that chlorfenvinphos applied to plant foliage is transported across the cuticular membrane (Bauer and Schönherr 1992). Chlorfenvinphos applied to the soil is accumulated in the roots, stem and leaves of plants (Ritcey et al. 1991; Rouchaud et al. 1989b; Suett 1974, 1975b). No information was found on the biomagnification of chlorfenvinphos in aquatic or terrestrial food chains. These data would be helpful in assessing the potential for human exposure as a result of consuming contaminated food.

Exposure Levels in Environmental Media.   No data were located on the concentrations of chlorfenvinphos in ambient air or in occupational settings; therefore, no estimate of inhalation exposure to chlorfenvinphos can be obtained for the general population, or for any occupationally exposed groups. No data on the concentration of chlorfenvinphos in drinking water, surface water, or groundwater in the United States were located in the literature. Monitoring data for surface waters are available from several Canadian studies conducted in the Great Lakes region and British Columbia; however, monitoring results from these Canadian studies may be inappropriate for estimating water residues in the United States, as chlorfenvinphos was never registered for agricultural use as a soil insecticide. Current monitoring data on the concentrations of chlorfenvinphos in ambient air, in drinking water, surface water, groundwater, and in soil from the United States would be helpful. Many of the federal, regional, and state food studies conducted from the late 1960s through the mid-1980s did not monitor chlorfenvinphos concentrations in foods

(Corneliussen 1970; Duggan and Corneliussen 1972; Duggan et al. 1983; Gartell et al. 1986; Gunderson 1988; Hundley et al. 1988), despite the fact that chlorfenvinphos was most extensively used in the United States during this period (see Section 4.3). Recent FDA monitoring studies on imported and domestic foods have detected chlorfenvinphos residues; however, the foods in which chlorfenvinphos was detected and the residue concentrations were not specified (FDA 1990, 1991, 1992, 1993). Additional quantitative information on chlorfenvinphos concentrations in food and the estimated daily human intake of chlorfenvinphos from foods would be helpful in assessing current exposure levels to this pesticide.

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

Exposure Levels in Humans.   No data on chlorfenvinphos levels in various human tissues and body fluids of unexposed populations, populations near hazardous waste sites, or occupationally exposed groups in the United States are available. Although chlorfenvinphos is a hydrophilic substance, it has not been widely found in human tissues because of its relatively short half-life. However, in a recent study conducted in the Federal Republic of Germany, chlorfenvinphos was found in some of the 41 specimens of cervical mucus, follicular and sperm fluids, and human milk that were examined. Chlorfenvinphos concentrations of 13.66, 1.69, 2.02, and 1.89 µg/kg were detected in 4 of the 11 samples of cervical mucus. Chlorfenvinphos was also detected at concentrations of 0.42 µg/kg in 1 of the 10 sperm fluid samples and 1 of the 10 human milk samples, respectively (Wagner et al. 1990). Additional data on the concentrations of chlorfenvinphos and its metabolites in body tissues and fluids are needed to estimate the extent of exposure to chlorfenvinphos. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries.   No exposure registries for chlorfenvinphos were located. 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

A search of the Federal Research in Progress database (FEDRIP 1995) indicated that no research studies are in progress to fill the data gaps discusses in Section 5.7.1.

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 chlorfenvinphos, its metabolites, and other biomarkers of exposure and effect to chlorfenvinphos. 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

Few methods are available for the determination of chlorfenvinphos in biological samples. Some methods which may be applicable to biological media are summarized in Table 6-1. Most methods involve an extraction step followed by one or more purification and fractionation procedures, then analysis, usually by gas chromatography (GC). Two detection methods are commonly used, nitrogen-phosphorus detection (NPD) (Thier and Zeumer 1987; Wagner et al. 1990) and flame photometric detection (FPD) (Ivey et al. 1973). Both of these methods are specific for phosphorus-containing compounds and are very sensitive (low- to sub-ppb levels). Recovery, where reported, is very good (>80%).

Several cautions should be noted. First, the stability of chlorfenvinphos in biological media is unknown. The cold-storage stability (5 to –20 EC) of chlorfenvinphos in crops and soil has been reported (Kawar et al. 1973). However, enzymes present in biological media may reduce levels of organophosphate pesticides (Singh et al. 1986). Second, it is difficult to eliminate or reduce interfering compounds and maintain acceptable recovery of chlorfenvinphos. Quality control procedures are recommended to assure that the method performance is acceptable. Third, other organophosphorus pesticides may co-elute with chlorfenvinphos (Sasaki et al. 1987), so a confirmatory method is recommended A few methods are available for measuring metabolites of chlorfenvinphos. Chlorfenvinphos undergoes biotransformation to a variety of polar metabolites including diethyl phosphate. Methods for measurement of dialkyl phosphates involve extraction from urine using an ion exchange resin and derivatization prior to GC analysis (Bradway et al. 1981; Lores and Bradway 1977). The

Table 6-1. Analytical Methods for Determining Chlorfenvinphos in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human milk, cervical fluid, sperm fluid	Solvent extraction; clean-up on Florisil	GC/NPD	0.040 µg/kg	No data	Wagner et al. 1990; Thier and Zeumer 1987
Rat liver, muscle, whole blood	Solvent extration; clean-up	GC/thermionic detection	0.10–0.02 ppm	92 (muscle, liver)	Hladká et al. 1975
Rat liver, blood	Solvent extraction	TLC/enzyme-inhibition detection	sub-nanogram levels	94–96 (blood); 84–89 (liver)	Vitorović 1982
Cattle and chicken fat, skin, muscle, liver, heart, kidney, feces	Fat, skin: isolation by filtration through celite; solvent partition Tissues, feces: solvent extraction; solvent partition All: clean-up on sodium sulfate/silicic acid column	GC/FPD	0.001 ppm	83–100	Ivey et al. 1973

GC = gas chromatography; FPD = flame photometric detection; NPD = nitrogen/phosphorus detection; TLC = thin layer chromatography

performance of the methods is variable; extraction is not always complete, and GC interferences often present problems.

6.2   ENVIRONMENTAL SAMPLES

Representative analytical methods for determining chlorfenvinphos in environmental samples are summarized in Table 6-2. Methods involve solvent extraction, purification and fractionation, and gas chromatographic analysis. Although most methods for measuring chlorfenvinphos in environmental samples involve GC coupled with specific detectors (including MS), other methods are available, including high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection (Bagon and Warwick 1982; Schlett 1991), and thin layer chromatography (TLC) (Roberts and Stoydin 1976).

Methods for determining chlorfenvinphos in aqueous samples include solvent extraction (EPA 1992b; Wan et al. 1994) or isolation using solid phase extraction (SPE) (Schlett 1991). Further clean-up of the extract may not be required prior to analysis by HPLC (Schlett 1991) or GC (EPA 1992b; Wan et al. 1994). For GC analysis, confirmation using a second column is recommended (EPA 1992b; Wan et al. 1994). Detection limits are in the sub-ppb range; recovery was not reported.

Similarly, methods for determining chlorfenvinphos in sediments, solid wastes, and soils use a solvent extraction procedure. A variety of clean-up procedures are used, including Florisil column purification (Beynon et al. 1966), solvent partition (Miles et al. 1979; Williams 1975b), and gel permeation chromatography (Wan et al. 1994). Extracts are analyzed by GC with electron capture detection (ECD) (Beynon et al. 1966; Edwards et al. 1968) or phosphorus-specific detectors (Wan et al. 1994; Williams 1975b). Detection limits are in the low-ppb range (1–20); recovery is excellent ($95%).

A chemiluminscence assay has been developed that should be a useful screening tool for environmental media. It is not as sensitive as GC methods, but is inexpensive, fast, and may be used as a portable detection system (Moris et al. 1995). Capillary electrophoresis is a relatively new technique for environmental analysis. It is rapid, but does not yet achieve detection limits needed for environmental analysis (Süsse and Müller 1995).

Methods for determining chlorfenvinphos on a variety of foods and crops have been reported. Most involve solvent extraction followed by clean-up using adsorption column techniques (FDA 1979; Kadenczki et al.

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Workplace air	Collection on filters/Tenax traps, desorption	HPLC/UV	2 µg/m³ [a]	No data[b]	Bagon and Warwick 1982
Drinking and surface water	Filtration; solid-phase extraction (SPE)	HPLC/UV	≈0.025 µg/L	No data	Schlett 1991
Drinking and surface water	On-line enrichment (SPE)	Thermospray LC/MS	15 ng/L	52	Sennert et al. 1995
Waste water (EPA Method 1657)	Solvent extraction; optional clean-up using GPC and/or SPE	Capillary GC/FPD; confirmation on second GC column	2 ng/L	No data	EPA 1992b
Water and sediments	Water: solvent extraction Sediments: solvent extraction; clean-up by GPC	Dual column/dual detector: capillary GC/NPD, FPD	0.01 µg/L (water); 1 µg/kg (soil, sediment)	99 (water); 97 (soil); 96 (sediment)	Wan et al. 1994
Solid wastes (EPA Method 8141A)	Solvent extraction; optional cleanup using Florisil column or GPC	Capillary GC/NPD	No data	No data	(SW-846) EPA 1992a
Soil	Samples are tumbled with solvent; optional clean-up on Florisil column	GC/ECD	0.01 ppm	95	Beynon et al. 1966
Soil	Ultrasonic extraction; solvent partition	GC	No data	95 ave.	Miles et al. 1979
Soil	Solvent extraction	GC/ECD	<0.02 ppm	95–115	Edwards et al. 1968
Pesticide formulations	Solvent extraction	GC/FID	Not applicable	92–97 for mg quantities	Paterson 1970

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Animal tissue, milk	Solvent extraction; clean-up on Florisil column	GC/thermoionic detection	0.001 ppm (milk); 0.005 ppm (tissue)	73–87 (beef fat); 84–105 (milk)	FDA 1979
Fruits and vegetables	Solvent extraction	Capillary GC/FPD; confirmation by capillary GC/MS	10 µg/kg	90.5	Agüera et al. 1993
Vegetables	Solvent extraction and partition	GC	0.02 mg/kg	85–97 ave.	Frank et al. 1990
Foods	Solvent extraction; column clean-up	capillary GC/FPD; confirmation by GC/MS or GC/FPD	≈9 ppb (trans isomer), ≈7 ppb (cis isomer)	89–97 (trans isomer); 72–101 (cis isomer)	Leoni et al. 1992
Fruits and vegetables	Prepared food is adsorbed onto Florisil, extracted with solvent	Capillary GC/PFD or NPD	0.01 mg/kg	80–89	Kadenczki et al. 1992
Fruit (apples)	Soxhlet extraction	Capillary GC/NPD	0.099 µg/mL	98	Barrio et al. 1994
Crops (lipid-containing)	Solvent extraction; cleanup by solvent partitioning	Capillary GC/FPD	1 ppb	79	Nakamura et al. 1994
Milk	Solvent extraction; clean-up by solvent partitioning	GC/FPD or thermoionic detector; confirmation by TLC	≥0.01 mg/kg	81–96	Stijve 1984
Pharmaceuticals	Disolution in solvent, filtration; GPC clean-up	Capillary GC/ELCD; confirmation by second column or MS	<0.05 mg/kg	97–110 (all pesticides)	Heikes and Craun 1992

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Cosmetics	Solvent extraction utilizing adsorption columns; GPC clean-up	GC/FPD	≤0.2 mg/kg	98-108	Specht 1990

[a] Based on instrumental detection limits; value will vary with volume of air sampled.
[b] Desorption efficiency from Tenax is 100%.

GC = gas chromatography; ELCD = electrolytic conductivity detection; FID = flame ionization detection; FPD = flame photometric detection; GPC = gel permeation chromatography; HPLC = high performance liquid chromatography; LC = liquid chromatography; MS = mass spectrometry; NPD = nitrogen/phosphorous detection; SPE = solid-phase extraction; TLC = thin layer chromatography; UV = visible/ultraviolet detection

1992; Leoni et al. 1992) or solvent partitioning (Frank et al. 1990; Stijve 1984). Chlorfenvinphos is determined by GC with phosphorus-specific detectors (flame photometric [FPD]; and nitrogen-phosphorus [NPD]) (Agüera et al. 1993; Leoni et al. 1992; Kadenczki et al. 1992; Stijve 1984). Chlorfenvinphos in sample extracts is confirmed using GC with MS (Agüera et al. 1993; Leoni et al. 1992) or TLC (Stijve 1984). Detection limits are in the low-ppb range; recovery is acceptable (>80%).

A summary of methods for determination of chlorfenvinphos environmental degradation products is shown in Table 6-3. The breakdown products 2,4-dichloroacetophenone, 1-(2,4-dichlorophenyl)-1-ethan-1-ol, and 2,4-dichlorophenacyl chloride can be determined in soil and earthworms using solvent extraction and GC/ECD (Edwards et al. 1968). Detection limits are approximately 0.05 ppm and recovery is excellent (95–115%). The hydrolysis product 2,2',4'-trichloroacetophenone has been determined in corn extracts using GC/ECD and GC/FPD. Detection limits are 0.02 ppm (ECD) and 0.002 (FPD), and recovery is excellent (Beroza and Bowman 1966). Free and conjugated degradation products have been determined in soils and crops by GC/ECD (Beynon et al. 1968). Free products are extracted with solvent; conjugated products are hydrolyzed with sulfuric acid. Recovery is acceptable (80–100% for soils, 50–90% for crops); detection limits range from 0.01 to 0.2 ppm for soils (varies with compound) and from 0.005 to 0.05 ppm for crops. Degradation products, including soil-bound (polar) compounds, were determined by GC/ECD of soil extracts. The polar compounds were methylated prior to GC analysis. Recovery is acceptable (65–105%); detection limits are approximately 0.02 ppm.

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 chlorfenvinphos 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 chlorfenvinphos.

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

Table 6-3. Analytical Methods for Determining Biomarkers for Chlorfenvinphos

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Acetylcholinesterase in erythrocytes			No data	No data	Zwiener and Ginsburg 1988
Free tryptophan in plasma		Spectrophotometry	No data	No data	Dudka and Szczepaniak 1993
Urine levels of desethyl chlorfenvinphos metabolite	Solvent extraction; methyation	GC/FPD	0.002 ppm	97%	Hunter et al. 1972
Blood levels of chlorfenvinphos	Headspace	GC/FID;GC/ thermionic detection	No data	No data	Klys 1985

GC = gas chromatography; FID = flame ionization detection

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.   Few methods are available for measuring exposure to chlorfenvinphos. These are summarized in Table 6-4. Blood levels of chlorfenvinphos were determined in a case of human poisoning (Klys 1985); however, sensitivity and reliability were not reported. Chlorfenvinphos is metabolized in the body to esters of phosphoric acid, and methods are available for determining urine levels of these metabolites (Bradway et al. 1981; Lores and Bradway 1977). However, these phosphate compounds are not specific for chlorfenvinphos, but are common to all organophosphate pesticides. Decreased levels of acetylcholinesterase in plasma or erythrocytes have been reported to be indicative of chlorfenvinphos poisoning (Zwiener and Ginsberg 1988). Again, this assay is not specific for chlorfenvinphos. An increase in the level of tryptophan after exposure to chlorfenvinphos has been reported in rats (Dudka and Szczepaniak 1993). Good precision and accuracy were reported for the method; however, specific values were not given. It is not known if the available analytical methods will be sensitive enough to measure chlorfenvinphos levels in body tissues and fluids of the background population. Since chlorfenvinphos is apparently not produced or imported into this country, it should not be necessary to determine these background levels. It would be helpful to have methods which would permit assessment of the severity of exposure of a highly exposed population.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media.   Methods are available for determining chlorfenvinphos in water, soils and sediments, and foods (Table 6-2). A summary of available methods for determining the environmental degradation products of chlorfenvinphos in soils (Beynon et al. 1968; Rouchaud et al. 1988), crops (Beynon et al. 1968; Beroza and Bowman 1966), and worms (Edwards et al. 1968) is shown in Table 6-3. Sensitive methods (sub-ppb levels) are available for determining chlorfenvinphos in water; however, better information is needed regarding the recovery and precision of the methods (EPA 1992b; Schlett 1991; Wan et al. 1994). Methods for determining chlorfenvinphos in soils and sediments are sensitive (low ppb levels) and good recovery ($95%) has been reported (Beynon et al. 1966; Edwards et al. 1968; Wan et al. 1994). Methods for measuring chlorfenvinphos in some foods are sensitive (low ppb levels) with acceptable recovery (72–105%) (Agüera et al. 1993; FDA 1979; Frank et al. 1990; Kadenczki et al. 1992; Leoni et al. 1992; Stijve 1984). Available methods have

Table 6-4. Analytical Methods for Determining Environmental Degradation Products of Chlorfenvinphos

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil, worms	Solvent extraction	GC/ECD	≈0.05 ppm	No data	Edwards et al. 1968
Soil	Solvent extraction; clean-up on alumina	GC/ECD	0.01–0.2 ppm	80–100	Beynon et al. 1968
Crops	Maceration with solvent; clean-up on alumina. Hydrolysis of conjugates are hydrolyzed with sulfuric acid/heat; solvent extraction; clean-up on alumina	GC/ECD	0.005–0.15 ppm	50–90	Beynon et al. 1968
Soil	Solvent extraction; solvent partition; clean-up by TLC. Soil bound compounds: extraction at basic pH; pH adjustment and solvent extraction; clean-up by TLC; methylation	GC/ECD; confirmation by GC/MS	≈0.02 mg/kg	65–105	Rouchaud et al. 1988
Corn	Sample is blended with solvent	GC/ECD; GC/FPD	0.02 ppm (ECD); 0.002 ppm (FPD)	94–101	Beroza and Bowman 1966

GC = gas chromatography; ECD = electron capture detection; FPD = flame photometric detection; MS = mass spectrometry; TLC = thin layer chromatography

sufficient sensitivity for measuring chlorfenvinphos in water, soils and sediments, and foods at background levels. Information on the precision of these methods would be helpful. No methods are available for measuring chlorfenvinphos in ambient air. Given its low volatility, chlorfenvinphos is not likely to be detected in ambient air. Methods are available for monitoring occupational exposure to chlorfenvinphos (Bagon and Warwick 1982). Research investigating the relationship between levels of chlorfenvinphos measured in water, soils and sediments, and food and health effects would be helpful.

6.3.2   Ongoing Studies

No ongoing studies involving chlorfenvinphos were located.

7. REGULATIONS AND ADVISORIES

The national regulations and guidelines regarding chlorfenvinphos in air, food, and other media are summarized in Table 7-1. No international or state regulations were identified for chlorfenvinphos, nor were regulations and guidelines identified for chlorfenvinphos in air or water.

ATSDR has not derived MRLs for inhalation exposure for any duration of exposure.

An acute oral MRL of 0.002 mg/kg/day for chlorfenvinphos has been developed from a LOAEL of 2.4 mg/kg/day, based on adverse neurological effects in rats (Barna and Simon 1973).

An intermediate oral MRL of 0.002 mg/kg/day for chlorfenvinphos has been developed from a LOAEL of 1.5 mg/kg/day, based on adverse immunological/lymphoreticular effects in mice (Kowalczyk-Bronisz et al. 1992).

A chronic oral MRL of 0.0007 mg/kg/day for chlorfenvinphos has been developed from a LOAEL of 0.7 mg/kg/day, based on adverse neurological effects in rats (Ambrose et al. 1970).

No reference concentration or dose exists for chlorfenvinphos, and no IARC or EPA cancer classification exists.

Chlorfenvinphos is one of the chemicals regulated under "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 1987). 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.

An Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for chlorfenvinphos does not exist, nor is it regulated by the Clean Water Effluent Guidelines contained in Title 40, Sections 400-475, of the Code of Federal Regulations.

Tolerances for chlorfenvinphos in agricultural products have been established (EPA 1982b).

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Chlorfenvinphos

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	None	
NATIONAL			
Regulations:			
a. Food			
FDA	FDA action level	None	
EPA OPTS	Tolerances for Related Pesticide Chemicals	Yes	40 CFR 180.3, EPA 1976
	Tolerance Range for Agriculture Products	0.005–0.2 ppm	40 CFR 180.322, EPA 1982b
b. Other			
EPA	Carcinogen Classification	None	IRIS 1995
	Reference Dose (RfD)	None	IRIS 1995
	Reference Concentration (RfC)	None	IRIS 1995
EPA OERR	Threshold Planning Quantity	500 lb.	40 CFR 355, App A, EPA 1987
	Reportable Quantity	500 lb.	40 CFR 355, App A, EPA 1996
	App. B - National Priorities List	Yes	40 CFR 300, EPA 1992d

EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; LDR = Land Disposal Restrictions; NIOSH = National Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Response; OSW = Office of Solid Wastes; REL = Recommended Exposure Limit; 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 Vivo—Occurring within the living organism.

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

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

Lethal Dose$_{(LO)}$ (LD$_{LO}$)—The lowest dose of a chemical introduced by a route other than inhalation that 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 q$_1$* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

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

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deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

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

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

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

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

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

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

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

Toxic Dose (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.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

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

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

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

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

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

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chlorfenvinphos
CAS number: 470-90-6
Date: August 21, 1996
Profile status: Final
Route: [] Inhalation [x] Oral
Duration: [x] Acute []Intermediate [] Chronic
Key to figure: 13
Species: Rat

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

Reference: Barna J, Simon G. 1973. The effect of chlorfenvinphos insecticide in small often repeated dose. Cereal Research Commun. Vol.1, No. 3: 33-44.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Two groups (55/group) of adult female albino (Wistar) rats weighing 208 g were orally administered Birlane$^®$ (chlorfenvinphos) at dose of 0 or 2.4 mg/kg/day in the diet for 10 days. The study was designed to investigate the effects of oral chlorfenvinphos on body weight increase, the gastrointestinal absorption of glucose, Na$^+$, and Ca^{2+}, as well as he effects of oral chlorfenvinphos on plasma and erythrocyte cholinesterase activity levels.

Effects noted in study and corresponding doses:

Plasma cholinesterase activity was inhibited by 52% while erythrocyte cholinesterase activity level was inhibited by 30% at a dose of 2.4 mg/kg/day (the only dose tested). Gastrointestinal (g.i.) absorption of glucose was increased by 30% over control values while Na$^+$ absorption was decreased by 32% below control values. Gastrointestinal absorption of Ca^{2+} and body weight increases were unaffected by chlorfenvinphos exposure. These changes in the gastrointestinal absorption of glucose and Na$^+$ were not considered statistically significant (P>0.05) by the investigators.

Dose endpoint used for MRL derivation:

[] NOAEL [x] LOAEL

2.4 mg/kg/day; 30% decrease in erythrocyte cholinesterase activity in female rats.

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: No, the doses used are author-provided.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Not applicable.

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Was a conversion used from intermittent to continuous exposure?
Not applicable.

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

Neurological effects, mediated by cholinesterase inhibition, is the principal and most sensitive
toxicological consequence of acute-duration exposure to chlorfenvinphos in humans (Cupp et al. 1975;
Pach et al. 1987). Chlorfenvinphos also inhibits noradrenaline in the central nervous system
(Brzezinski 1978). Human subjects, exposed to large acute doses of chlorfenvinphos, exhibited
severe cholinergic signs. These cholinergic signs were relieved by the administration of atropine
and/or pralidoxime, indicating cholinesterase inhibition etiology (Cupp et al. 1975; Pach et al. 1987). In
rats, relatively moderate to low doses (2.4–30 mg/kg) of oral chlorfenvinphos significantly inhibited
cholinesterase activities in a number of tissue including the brain, erythrocyte, and plasma (Osumi et
al. 1975; Osicka-Koprowska et al. 1984; Puzynska 1984). An acute-duration oral study also found
alterations in noradrenaline level in rat brain following exposure to chlorfenvinphos. A chlorfenvinphos
dose of 13 mg/kg decreased noradrenaline levels in rat brains by 20%, as compared to control rats.
According to the investigators, chlorfenvinphos accelerated the rate of NA disappearance from the
brain (Brzezinski 1978).

Therefore, it is appropriate to base the acute oral MRL for chlorfenvinphos on cholinesterase inhibition.

It should be noted that a study by Osumi et al. (1975) which determined a NOAEL of 1 mg/kg/day and
a LOAEL of 2 mg/kg/day for 38% inhibition of brain cholinesterase in rats was not used to calculate an
acute oral MRL because of the gavage (oral) route of administration of the test substance which was
deemed less appropriate by the ATSDR MRL Workgroup. An oral feeding study is preferred by the
ATSDR MRL Workgroup.

Agency Contact (Chemical Manager): Alfred Dorsey.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chlorfenvinphos
CAS number: 470-90-6
Date: August 21, 1996
Profile status: Final
Route: [] Inhalation [x] Oral
Duration: [] Acute [x]Intermediate [] Chronic
Key to figure: 23
Species: Mouse

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

Reference: Kowalczyk-Bronisz S, Gieldanowski J, Bubak , Kotz J. 1992. Studies on the effect of pesticide chlorfenvinfos on mouse immune system. Arc Immunol Ther Exp (Warsz) 40(5-6):283-289.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

The authors investigated the effect of chlorfenvinphos on mouse immune system. In the study, male and female inbred C57BL/6 mice and (C57BL/6 x DBA/2)F1 (BDF1/liw) hybrids mice (6-8 weeks old) were orally dosed with chlorfenvinphos (suspended in 1% methylcellulose solution) and evaluated for 5 days for the effect of chlorfenvinphos exposure on the mouse immune system. The rats were exposed to oral chlorfenvinphos doses of 0, 1.5, 3, and 6 mg/kg (0, 1/100, 1/50, and 1/25 LD$_{50}$) daily for 3 months; control group was given 1% methylcellulose. Then exposed and control mice were immunized by intraperitoneal injections of 0.2 mL 10% SRBC. IgM-PFC (plaque-forming or antibody-producing cells) number in spleen cell suspension was tested on day 4 after immunization and the procedure repeated 3 weeks after the exposure to chlorfenvinphos had been ceased. Exposed and control groups were subjected to immunological tests and hematological examinations. Lymphatic organs were histologically examined.

Effects noted in study and corresponding doses:

A dose-related decrease in number of hemolysin producing cells was observed: plaque-forming cells (PFC) were 58% at the 6 mg/kg dose group and 85% at the 3 mg/kg dose level as compared to control values. Chlorfenvinphos treatment also caused reduction in E rosettes forming cell number by 30% at the 6 mg/kg dose level and by 25% at the 3 mg/kg dose level. Increases in Interlukin-1 (Il-1) activity and DTH reaction were observed 24 hours after challenge. Spleen colonies were stimulated as evidenced by the increase of endogenous spleen colonies and exogenous spleen colonies (CFU-S) increased 190% at the 1.48 mg/kg dose level and 137% at the 6 mg/kg dose level, and 162% at 1.5 mg/kg dose level and 70% at the 6 mg/kg dose level, respectively). When the IgM PFC number was tested 3 weeks latter, after the exposure to chlorfenvinphos in the small dose (1.5 mg/kg), and increase (about 40%) in plaques number was observed. There was a 50% reduction in thymus weight at the 1.5 mg/kg dose level as compared to controls as well as significant involution of thymus was noted.

Dose endpoint used for MRL derivation:

[] NOAEL [x] LOAEL

1.5 mg/kg/day; 190% increase of spleen endogenous colonies; 162% increase of spleen exogenous colonies; 50% reduction in thymus weight.

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: Doses were provided as 1/100, 1/50, and 1/25 of the LD_{50} (148 mg/kg) by the authors, resulting in doses of 1.5, 3, and 6 mg/kg, respectively.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Not applicable.

Was a conversion used from intermittent to continuous exposure?
Not applicable.

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

In other studies, adverse immunolymphoreticular effects has been associated with exposure to oral chlorfenvinphos. In an intermediate-duration dietary study with albino (Wistar) rats, there was a significant and irreversible reduction in relative spleen weight of female rats given $3 mg/kg/day chlorfenvinphos for 12 weeks (Ambrose et al. 1970). A study was undertaken to evaluate selected serological and cytoimmunological reactions in rabbits subjected to a long-term poisoning with subtoxic oral doses (10 mg/kg in a soya oil solution with a small amount of food) of chlorfenvinphos for 90 days. Chlorfenvinphos treatment significantly elevated serum hemagglutinin level (16%) and hemolysin activity (66%, $P<0.05$) as well as increased the number of nucleated lymphoid cells producing hemolytic antibody to sheep erythrocytes as compared to controls (treated 906, $P<0.05$ and controls 618). Spleen cytomorphology changes, manifested mainly as transformation of primary follicles into secondary ones with well developed germinal centers, were also observed (Roszkowski 1978).

Therefore, it is appropriate to base the intermediate oral MRL for chlorfenvinphos on immunological effects.

Agency Contact (Chemical Manager): Alfred Dorsey.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chlorfenvinphos
CAS number: 470-90-6
Date: August 21, 1996
Profile status: Final
Route: [] Inhalation [x] Oral
Duration: [] Acute []Intermediate [x] Chronic
Key to figure: 34
Species: Rat

MRL: 0.0007 [x] mg/kg/day [] ppm [] mg/m^3

Reference: Ambrose AM, Larson PS, Borzelleca JF, Hennigar GR. 1970. Toxicologic studies on diethyl-1-(2,4-dichlorophenyl)-2-chlorovinyl phosphate. Toxicology and Applied Pharmacology, 17:323-336.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

The authors conducted toxicological studies with chlorfenvinphos in weaning albino (Wistar) rats. In the study, four matched groups of weaning albino (Wistar) rats (30 rats/sex/group) were culled to a narrow starting weight range and fed daily GC-4072 (technical chlorfenvinphos) doses of 0, 0.7, 2.1, 7, or 21 mg/kg/day (males) or 0, 0.8, 2.4, or 8, or 24 mg/kg/day (females) in the diet for 104 weeks. An additional group of non-littermate rats (30/sex) were administered 21 mg/kg/day (males) or 24 mg/kg/day (females) chlorfenvinphos for 104 weeks. Plasma and erythrocyte cholinesterase (ChE) activity levels were obtained from 4 rats of each sex per dose group at 1, 4, 8, and 12 weeks. At 13 weeks, 4 rats/sex/dose group were sacrificed for histopathologic examination. At 13 weeks, 4 rats/sex/dose group were sacrificed for histopathologic examination. The rats in the 21 mg/kg/day (males) and 24 mg/kg/day (females) were sacrificed on the 95th week while all other dose group animals were sacrificed on the end of the study (104 weeks). At each autopsy, relative organ weights were determined for heart and kidneys. All animals sacrificed in moribund condition as well as those sacrificed at week 13, 95, and 104 weeks were examined grossly and microscopically and organs (heart, lungs, liver, kidney, urinary bladder, spleen, stomach, small and large intestine, skeletal muscle, skin, bone marrow, pancreas, thyroid, adrenal, pituitary) from these animals were histopathologically examined. Chlorfenvinphos significantly decreased body weight gain of females at the 8 and 24 mg/kg/day dose groups from the 26th week till towards the end of the study, although, the decreased body weight gain became not statistically significant at the end of the study. Increased relative liver weights were observed in males at the 7 mg/kg/day dose level but no other signs of hepatopathology was reported. No consistent difference in body weight gains in males, survival of the test animals, food consumption, or mortality was evident at all dose levels tested, as compared to undosed controls. Essentially, no gross or microscopic histopathology were evident in all the organs (heart, lungs, liver, kidney, urinary bladder, spleen, stomach, small and large intestine, skeletal muscle, skin, bone marrow, pancreas, thyroid, adrenal, pituitary) tissues examined. No changes in organ-to-body weight were observed in the heart, kidney, spleen and testes (Ambrose et al. 1970).

Dose endpoint used for MRL derivation:

[] NOAEL [x] LOAEL

0.7 mg/kg/day; 45% inhibition of plasma cholinesterase activity; 33% inhibition of erythrocyte cholinesterase activity

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: Doses, provided as food concentrations (10, 30, 100, or 300 ppm), were converted to doses in mg/kg/day using rat daily food intake factor for chronic Wistar rat obtained from EPA (1988).

CALCULATIONS: 10 ppm =10 mg/kg; Male - 10 mg/kg x 0.07 mg/kg/day (chronic male Wistar rat food factor) = 0.7 mg/kg/day; 30 ppm = 2.1 mg/kg/day; 100 ppm = 7 mg/kg/day; 300 ppm = 21 mg/kg/day: Female - 10 mg/kg x 0.08 mg/kg/day (chronic female Wistar rat food factor) = 0.8 mg/kg/day; 30 ppm = 2.4 mg/kg/day; 100 ppm = 7 mg/kg/day; 300 ppm = 24 mg/kg/day.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

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

Although the neurological effects of human prolonged exposure to low oral doses of chlorfenvinphos is not known due to a dearth of studies, acute-duration exposure data indicate that neurological effects, mediated by cholinesterase inhibition, is the most sensitive toxicological consequence of human exposure to chlorfenvinphos(Cupp et al. 1975; Pach et al. 1987; Taitelman 1992). Similarly, chlorfenvinphos significantly inhibited both plasma and erythrocyte cholinesterase activities in Beagle dogs (2/sex) fed daily chlorfenvinphos doses of 0, 0.3, 2, or 10 mg/kg/day (males), or 0, 1.5, 10, or 50 mg/kg/day (females) in the diet (moist) for 104 weeks. Plasma cholinesterase activities were significantly inhibited at all dietary levels through week 39 of the study; 49% inhibition at the 0.3 mg/kg/day (males) and 1.5 mg/kg/day (females) dose levels. Erythrocyte cholinesterase activity was significantly and consistently inhibited (36%) during the first 12 weeks only in the 10 mg/kg/day (males) and 50 mg/kg/day (females) dose levels (Ambrose et al. 1970).

Therefore, it is considered appropriate to use this endpoint for developing a chronic oral MRL for chlorfenvinphos.

Agency Contact (Chemical Manager): Alfred Dorsey.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an 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 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND
See LSE Table 2-1

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

(2)   Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

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(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 2-1).

(5)   Species The test species, whether animal or human, are identified in this column. Section 2.5, "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 0.005 ppm (see footnote "b").

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

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

(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 0.005 ppm.

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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) <u>Exposure Period</u> 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) <u>Health Effect</u> These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) <u>Levels of Exposure</u> 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) <u>NOAEL</u> In this example, 18r 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 0.005 ppm (see footnote "b" in the LSE table).

(17) <u>CEL</u> 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) <u>Estimated Upper-Bound Human Cancer Risk Levels</u> This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).

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

SAMPLE

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

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

- -

CHRONIC EXPOSURE						[11]	
Cancer						9	
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.

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

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

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

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

Acute (≤14 days) — Systemic: Death, Respiratory, Hematological

Intermediate (15-364 days) — Systemic: Death, Respiratory, Hematological, Hepatic, Reproductive, Cancer*

14, **15** (ppm), **16**, **17**, **18**, **19**

Data points:
- 16r, 17r (Death, ~100)
- 24g, 18r, 18r (Respiratory)
- 18r (~7, NOAEL with arrow)
- 20m, 22g, 21r, 20m (Hematological)
- 31r, 30r, 33r (Death, Intermediate)
- 28m, 22m, 29r (Respiratory)
- 37m, 35m, 34r, 34r (Hematological/Hepatic)
- 27r (Reproductive)
- 38r, 40m, 39r (Cancer)

Estimated Upper Bound Human Cancer Risk Levels: 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}

Key

r Rat
m Mouse
h Rabbit
g Guinea Pig
k Monkey

● LOAEL for serious effects (animals)
◑ LOAEL for less serious effects (animals)
○ NOAEL (animals)
◆ CEL - Cancer Effect Level

| Minimal risk level for effects other than cancer

The number next to each point corresponds to entries in the accompanying table.

* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

Chapter 2 (Section 2.5)

Relevance to Public Health

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

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill

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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
mm Hg	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

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yr	year
WHO	World Health Organization
wk	week
>	greater than
$\geq$	greater than or equal to
=	equal to
<	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram