SERA TR 04-43-05-05b

Control/Eradication Agents for the Gypsy Moth - Human Health and Ecological Risk Assessment for DDVP (Dichlorvos) FINAL REPORT

Prepared for:

USDA, Forest Service

Forest Health Protection

GSA Contract No. **GS-10F-0082F**
USDA Forest Service BPA: **WO-01-3187-0150**
Requisition No.: **43-3187-1-0269**
Task No. **5**

Submitted to:
Dave Thomas, COTR
Forest Health Protection Staff
USDA Forest Service
Rosslyn Plaza Building C, Room 7129C
1601 North Kent Street
Arlington, VA 22209

Prepared by:
Patrick R. Durkin and Mark H. Follansbee [a]
Syracuse Environmental Research Associates, Inc.
5100 Highbridge St., 42C
Fayetteville, New York 13066-0950
Telephone: (315) 637-9560

[a] Syracuse Research Corporation, 301 Plainfield Road, Suite 350, Syracuse, New York 13212

August 20, 2004

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

LIST OF TABLES

LIST OF FIGURES

NOTE: Tables followed by figures are placed after Section 5, References.

LIST OF APPENDICES

LIST OF SUPPLEMENTS

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AEL	adverse-effect level
ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
a.i.	active ingredient
BCF	bioconcentration factor
bw	body weight
CBI	confidential business information
ChE	pseudo-cholinesterase
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
d.f.	degrees of freedom
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FOIA	Freedom of Information Act
FQPA	Food Quality Protection Act
g	gram
ha	hectare
HQ	hazard quotient
IAA	indole-3-acetic acid
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level

LOC	level of concern
m	meter
M	male
MCL	mononuclear cell carcinoma
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
MRID	Master Record Identification Number
MSDS	material safety data sheet
MW	molecular weight
NCAP	Northwest Coalition for Alternatives to Pesticides
NCI	National Cancer Institute
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPIDN	organophosphate-induced delayed neurotoxicity
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
ppm	parts per million
PVC	polyvinyl chloride
RBC	red blood cell
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRC	Syracuse Research Corporation
STS	Slow the Spread
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
WCR	water contamination rate
WHO	World Health Organization
µ	micron

COMMON UNIT CONVERSIONS AND ABBREVIATIONS

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4,047
atmospheres	millimeters of mercury	760
	Fahrenheit	1.8 °C+32
centimeters	inches	0.3937
		1,000
Fahrenheit	centigrade	0.556 °F-17.8
		0.6818
gallons (gal)	liters (L)	3.785
		9.34
grams (g)	ounces, (oz)	0.03527
		0.002205
hectares (ha)	acres	2.471
		2.540
kilograms (kg)	ounces, (oz)	35.274
		2.2046
kilograms per hectare (hg/ha)	pounds per acre (lb/acre)	0.892
		0.6214
liters (L)	cubic centimeters (cm^3)	1,000
		0.2642
liters (L)	ounces, fluid (oz)	33.814
		1.609
miles per hour (mi/hr)	cm/sec	44.70
		0.000035
meters (m)	feet	3.281
		28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
		0.0701
ounces fluid	cubic centimeters (cm^3)	29.5735
		453.6
pounds (lb)	kilograms (kg)	0.4536
		1.121
pounds per acre (lb/acre)	mg/square meter (mg/m^2)	112.1
		11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
		0.155
square centimeters (cm^2)	square meters (m^2)	0.0001
		10,000
yards	meters	0.9144

Note: All references to pounds and ounces refer to avoirdupois weights unless otherwise specified.

CONVERSION OF SCIENTIFIC NOTATION

Scientific Notation	Decimal Equivalent	Verbal Expression
$1 \cdot 10^{-10}$	0.0000000001	One in ten billion
$1 \cdot 10^{-9}$	0.000000001	One in one billion
$1 \cdot 10^{-8}$	0.00000001	One in one hundred million
$1 \cdot 10^{-7}$	0.0000001	One in ten million
$1 \cdot 10^{-6}$	0.000001	One in one million
$1 \cdot 10^{-5}$	0.00001	One in one hundred thousand
$1 \cdot 10^{-4}$	0.0001	One in ten thousand
$1 \cdot 10^{-3}$	0.001	One in one thousand
$1 \cdot 10^{-2}$	0.01	One in one hundred
$1 \cdot 10^{-1}$	0.1	One in ten
$1 \cdot 10^{0}$	1	One
$1 \cdot 10^{1}$	10	Ten
$1 \cdot 10^{2}$	100	One hundred
$1 \cdot 10^{3}$	1,000	One thousand
$1 \cdot 10^{4}$	10,000	Ten thousand
$1 \cdot 10^{5}$	100,000	One hundred thousand
$1 \cdot 10^{6}$	1,000,000	One million
$1 \cdot 10^{7}$	10,000,000	Ten million
$1 \cdot 10^{8}$	100,000,000	One hundred million
$1 \cdot 10^{9}$	1,000,000,000	One billion
$1 \cdot 10^{10}$	10,000,000,000	Ten billion

EXECUTIVE SUMMARY

OVERVIEW

The USDA uses DDVP in its program to manage the gypsy moth. The primary use of DDVP is as a component in the pheromone baited milk carton style traps that are used primarily for surveying and monitoring gypsy moth populations. Because of this a very limited use in USDA programs, the potential for exposures to humans or nontarget ecological species is extremely limited. Because of this limited use and limited potential for exposure, this risk assessment focuses on the information that has the greatest impact on potential hazard rather than a summary of all of the available information that is available on DDVP and this risk assessment utilizes several detailed reviews conducted by agencies responsible for assessing chemical risks

PROGRAM DESCRIPTION

In USDA programs for the control of the gypsy moth, DDVP is used only in a 1" x 4" inch polyvinyl chloride (PVC) strip that contains 590 mg of DDVP. These strips are used to kill insects that are attracted to and enter milk carton style traps baited with the gypsy moth pheromone. Typically milk carton traps are deployed in widely spaced grids (inter-trap distances ranging from 500 m to 7 km) to survey for the presence of gypsy moth populations in the STS or eradication areas. Only rarely are milk carton traps deployed in mass trapping grids to control isolated infestations. When used in mass trapping control efforts, milk carton traps are deployed in tightly spaced grids (inter-trap distance of 20 to 30 meters). Mass trapping is a rarely used eradication tactic that targets low-density infestations (<10 egg masses per acre) occupying relatively small areas (<100 acres) .

HUMAN HEALTH RISK ASSESSMENT

Hazard Identification **–** DDVP is an organophosphorus insecticide that works by inhibiting cholinesterase. DDVP has been used since the early 1960's and has been the subject of many toxicity studies and review articles. Information is available on a number of case reports of accidental and suicidal exposures as well as human monitoring data from normal use. The toxicity of DDVP has been adequately evaluated using laboratory animals, although not all of these studies are available in the open literature.

DDVP is readily absorbed into the body of mammals via all routes of exposure, where it is rapidly metabolized and eliminated. In general, the systemic effects observed after oral, inhalation, or dermal exposure of humans or laboratory animals to DDVP result from the inhibition of acetylcholinesterase. Inhibition of this enzyme in mammalian systems produces a variety of systemic effects, including salivation, urination, lacrimation, convulsions, increased bronchial secretions, respiratory depression, and even death. The nature and magnitude of the toxic effects produced by a given exposure to DDVP by any route are directly related to the dose and rate at which the exposure occurs. In the case of the USDA programs for the management of the gypsy moth, the use of milk carton traps containing Vaportape II (slow-release of DDVP from PVC strips) essentially precludes rapid exposures to high doses of DDVP.

Short-term animal studies have shown that oral exposures to doses below about 0.5 mg/kg-day (or inhalation exposures to 1–2 mg/m³) do not result in meaningful reductions in cholinesterase activity. Experiments in laboratory mammals that were exposed to DDVP during pregnancy (by oral or inhalation route) did not show any effect on fertility or health of the offspring, even at levels that produced maternal toxicity. The latest evaluation of data from assays for carcinogenicity and genetic toxicity classify DDVP as a "suggestive" carcinogen and determined that a quantitative assessment of cancer risk is not applicable. The literature contains some data suggesting that contact dermatitis (as well as cross-sensitization to other pesticides) may occur; although, this appears to be an infrequent occurrence in the general population.

Exposure Assessment – Under normal conditions, exposure to both workers and members of the general public should be negligible. Workers will handle DDVP strips only during the assembly of milk cartoon traps. If workers wear gloves and assemble the traps outdoors or in very well ventilated rooms, both inhalation and dermal exposures should be negligible. Inhalation exposure to DDVP during transport of the traps should also be negligible if the traps are not transported inside of the passenger compartments of vehicles. Worker exposures will also be limited in most programs because foil wrapping in which the strip is distributed will not be removed until after the trap is transported to the field. Milk carton traps will generally be placed about four feet above the ground (Leonard 2004) and exposure of members of the general public to DDVP contained in the milk carton traps should also be negligible except in the case of intensional tampering.

Notwithstanding the above assertions, exposure assessments are developed for workers who do not use gloves in the assembly of the milk carton traps and who assemble the traps indoors and transport the traps in the passenger compartments of vehicles. All of these exposure scenarios should be considered atypical and some are extreme. The intent is to illustrate the consequences of mishandling or imprudent handling. During assembly, the central estimate of dermal exposures in workers not wearing gloves leads to an absorbed dose of about 0.0008 mg/kg with a range of about 0.0003 mg/kg to 0.004 mg/kg. Inhalation exposures in workers may be highly variable depending on the ventilation rates in an enclosed space and the number of traps that are handled. Based on the handling and transport of 75 traps, inhalation exposures could reach up to about 0.6 mg/m^3 in an enclosed and unventilated room and up to about 1.8 mg/m^3 in the passenger compartment of a vehicle. These exposure assessments are based on several site and situation specific assumptions which are intended to reflect plausible upper bounds of exposures.

Exposure assessments are also developed for children who might come in contact with an accidentally discarded or misplaced DDVP strip. Estimated dermal doses are much higher than those for workers: a central estimate of about 0.02 mg/kg with a range of 0.003 mg/kg to 0.1 mg/kg. Oral exposures from a small child sucking on the pest strip are about a factor of 10 higher than dermal exposures: a central value of about 0.2 mg/kg with a range of 0.04 mg/kg to 0.6 mg/kg.

Under normal circumstances, the use of DDVP in PVC strips is not likely to result in contamination of water or other materials that might be consumed by members of the general public. Nonetheless, an exposure assessment is developed for the accidental contamination of a small pond by a pest strip. In this scenario, dose estimates range from about 0.000003 mg/kg to 0.00007 mg/kg with a central estimate of about 0.00001 mg/kg.

Dose-Response Assessment – The extensive toxicology data base has been evaluated by a number of governmental organizations including the U.S. EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration, and the World Health Organization. Following the approach taken in most USDA risk assessments, these sources are used for selecting levels of acceptable exposure. Because all of the scenarios considered in this risk assessment involve only acute exposures, only acute exposure criteria are considered.

For both oral and dermal exposures, the acute RfD established by the U.S. EPA, 0.0017 mg/kg, is used for the risk characterization. This is based on an acute oral NOAEL of 0.5 mg/kg from a study in rats with the application of an uncertainty factor of 300. Acute exposure criteria proposed by other groups are comparable to but somewhat higher than the acute RfD. Because some of the accidental acute exposures may substantially exceed the acute RfD, some attempt is made to characterize the consequences of high oral exposures. A human NOAEL of 1 mg/kg for AChE inhibition has been identified. While this NOAEL is not used to modify the acute RfD, it can be used to assess plausible consequences of exceeding the RfD. The human data on DDVP, although extensive, are not sufficient to identify a minimal lethal dose. For the current risk assessment, the lowest reported lethal dose (16 mg/kg) is used to assess the plausibility of observing serious adverse effects in cases of accidental over-exposure to DDVP.

A number of inhalation criteria for DDVP are available. Since potentially significant inhalation exposures are likely only in workers, the occupational exposure criteria of 0.1 mg/m^3 proposed by American Conference of Governmental Industrial Hygienists is used. This value is a factor of 10 below the occupational criteria proposed by NIOSH and OSHA.

Risk Characterization – In most cases, exposures to both workers and members of the general public should be negligible. If workers take prudent steps to limit both dermal and inhalation exposures, the likelihood of exposures to DDVP reaching a level of concern appears to be very low. Similarly, members of the general public should not be exposed to substantial amounts of DDVP. The DDVP is contained within a PVC strip to insure that the active ingredient is slowly released over a long period of time. The strip, in turn, is placed within a trap and the trap is placed so that the that will not be accessed except in the case of intentional tampering or trap monitoring.

Nonetheless, this risk assessment develops exposure scenarios for both workers and members of the general pubic that are intended to illustrate the potential effects of mishandling or tampering with DDVP strips. For workers, the greatest risks are associated with inhalation exposures from

assembling the traps in enclosed and poorly ventilated spaces or transporting the traps in the passenger compartments of vehicles. These risks can be readily avoided. Dermal exposures can also lead to lesser but sill undesirable levels of exposure. For members of the general public, all of the exposure scenarios are accidental and some are extreme. The most likely of these is the accidental contamination of a small body of water. This scenario leads to exposures that are below the level of concern by a factor of about 25. If a child were to come into contact with a DDVP strip, however, both dermal and oral exposures could substantially exceed a level of concern. While such exposures should clearly be avoided, it does not seem likely that frank signs of toxicity would be observed. This is consistent with human experience in the use of DDVP resin strips.

ECOLOGICAL RISK ASSESSMENT

Hazard Identification – The available data suggest that invertebrates are more sensitive to DDVP than other organisms. For example, the oral LD_{50} in honey bees is 0.29 µg/g bee, and the topical LD_{50} is 0.65 µg/g bee. DDVP is also toxic to birds with an oral LD_{50} value of < 10 mg/kg for the most sensitive species. Short-term repeat dose studies in mammals found that oral exposures to doses below about 0.5 mg/kg-day or inhalation exposures to 1–2 mg/m³ generally do not result in adverse effects.

Aquatic animals are also sensitive to DDVP and, as with terrestrial animals, invertebrates may be more sensitive than vertebrates. The lowest reported LC_{50} value in fish is approximately 0.2 mg/L. Some aquatic invertebrates are much more sensitive to DDVP than fish. For daphnids, the most sensitive group of invertebrate species, reported EC_{50} values range from 0.00007 mg/L to 0.00028 mg/L.

The majority of the toxicity data in ecological receptors is limited to free DDVP, rather than a slow-release formulation such as the Vaportape II product used in USDA programs for control of the gypsy moth. Hence, the toxicity values reported for indicator species will likely be conservative (i.e., suggest greater toxicity) as compared to Vaportape II. U.S. EPA has assessed the ecological effects of DDVP; however, the exposures assessed by U.S. EPA are not specific to formulations where DDVP is encapsulated in PVC resin. In general, aside from those organisms that enter the milk carton trap or those that remove the PVC strip form the trap, toxicity resulting from exposure of ecological receptors to DDVP in Vaportape II milk carton traps is not likely.

Exposure Assessment – As in the human health risk assessment, exposure of terrestrial mammals to DDVP from the VaporTape strips used in milk carton traps is likely to be negligible under most circumstances. Nonetheless, it is conceivable that some mammals such as racoons or bears could easily access and tamper with the milk carton trap. Depending on the proportion of the DDVP strip that is consumed, doses (as DDVP in the PVC strip) are estimated to range from 10.5 mg/kg (10% of strip) to 105 mg/kg (100% of strip) and the central estimate is taken as 31.6 mg/kg (30% of strip). In addition, contamination of water with a pest strip is plausible, although probably rare, and is considered in a manner similar to the corresponding scenario in the human health risk assessment (Section 3.2.3.4). This scenario is based on the consumption of

contaminated water by a small mammal and the dose to the animal is estimated at about 0.00003 mg/kg with a range of 0.000009 mg/kg to 0.00009 mg/kg. Other exposure scenarios for terrestrial vertebrates, while possible, seem far less plausible and are not considered quantitatively. No quantitative exposure assessments for terrestrial invertebrates are developed because the milk carton trap will attract only male gypsy moths. Nontarget insects that incidentally enter the trap are likely to be killed by exposure to the DDVP vapor. Exposures to aquatic species are based on the same water concentrations used for terrestrial species: 0.000177 mg/L with a range of 0.000059 mg/L to 0.00059 mg/L.

Dose-Response Assessment – Given the limited nature of the use of DDVP in programs to control the gypsy moth and consequent limited number of exposure assessments, the dose-response assessment for DDVP is relatively simple. For terrestrial mammals, a value of 240 mg/kg from a study using DDVP in a PVC formulation is used for direct exposure to the DDVP-PVC strip – i.e., a raccoon tampering with a milk carton trap and consuming all or part of the DDVP strip. At the dose of 240 mg/kg, no mortality or frank signs of AChE inhibition were observed. For the contaminated water scenario, the NOAEL of 0.5 mg/kg from a study involving exposure to free or unformulated DDVP is used. This NOAEL is from the study that forms the basis for the acute RfD used in the human health risk assessment. Although DDVP is classified as highly toxic to fish, the estimated levels of acute exposure for fish are far below the 30-day NOEC of 0.03 mg/L. Thus, this value is used for all fish and no attempt is made to consider differences in sensitivity among fish. A somewhat different approach is taken with aquatic invertebrates, some of which are more sensitive to DDVP than fish by a factor of over 2500. Risks to sensitive species of aquatic invertebrates – i.e., daphnids and other small arthropods – are characterized based on the lowest reported LC_{50} value, 0.00007 mg/L from a 48-hour bioassay in *Daphnia pulex*. Some other groups of aquatic invertebrates, such as snails, appear to be much less sensitive than small arthropods. Risks to such tolerant species are based on a LC_{50} value of 21 mg/L in a freshwater snail.

Risk Characterization – As with the human health risk assessment, it is anticipated that typical exposures and consequent risks to nontarget species should be negligible. As with the human health risk assessment, it is anticipated that typical exposures and consequent risks to most nontarget species should be negligible. The containment of the DDVP within a slow release PVC strip combined with the target specific nature of pheromone baited traps should reduce the risks of inadvertent effects in non-target species. Other insects and arthropods that may inadvertently enter the trap will probably be killed by DDVP vapor. While such inadvertent contact may occur, it is not likely to impact substantial numbers of nontarget insects or arthropods.

Because of the limited use of DDVP, a relatively small number of exposure scenarios – all of which might be considered accidental or incidental – are developed. For terrestrial mammals, contact with the pest strip could occur by an animal directly tampering with a trap or by an animal consuming water that had been accidentally contaminated with a DDVP strip. Adverse effects would not be expected in either case. In the case of accidental contamination of a small

body of water with a DDVP strip, concentrations of DDVP in the water would be below the level of concern for fish by factors of about 50 to 500. Some aquatic invertebrates, however, might be affected. For the most sensitive species of aquatic invertebrates – i.e., small aquatic arthropods such as daphnids – exposures could substantially exceed laboratory LC_{50} values by factors of up to about 8. Exposures to tolerant aquatic invertebrates – such as snails – would be below a level of concern by a substantial margin – i.e., factors of about 30,000 to 300,000.

The exposure assessments that serve as the bases for these risk characterizations are highly dependent on specific conditions – i.e., how much DDVP was in the strip at the time that the contamination occurred and the size of the body of water that was contaminated. Because the hydrolysis of DDVP in water is rapid, the estimates of adverse effects in some aquatic invertebrates would probably apply only to a very limited area near the pest strip rather than to the larger area of the body of water that is contaminated.

1. INTRODUCTION

The USDA uses DDVP in its program to manage the gypsy moth. The primary use of DDVP is as a component in the pheromone baited milk carton style traps that are used primarily for surveying and monitoring gypsy moth populations. This document is an update to a risk assessment prepared in 1995 (USDA 1995a,b) and provides risk assessments for human-health effects and ecological effects to support an assessment of the environmental consequences of these uses.

This document has four chapters, including the introduction, program description, risk assessment for human health effects, and risk assessment for ecological effects or effects on wildlife species. Each of the two risk assessment chapters has four major sections, including an identification of the hazards associated with DDVP, an assessment of potential exposure to the product, an assessment of the dose-response relationships, and a characterization of the risks associated with plausible levels of exposure. These are the basic steps recommended by the National Research Council of the National Academy of Sciences (NRC 1983) for conducting and organizing risk assessments.

Although this is a technical support document and addresses some specialized technical areas, an effort was made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts, methods, and terms common to all parts of the risk assessment are described in plain language in a separate document (SERA 2001).

The human health and ecological risk assessments presented in this document are not, and are not intended to be, comprehensive summaries of all of the available information. This is particularly true for DDVP used in gypsy moth programs. There is an extremely large and relatively complex database of literature on DDVP. For example, TOXLINE, one of several commonly used commercial databases containing information on toxic chemicals, has over 14,000 citations on DDVP. DDVP, however, has a very limited use in USDA gypsy moth programs (Section 2) and the potential for exposures to humans (Section 3.2) or nontarget ecological species (Section 4.2) is extremely limited. Because of this limited use and limited potential for exposure, this risk assessment focuses on the information that has the greatest impact on potential hazard rather than a summary of all of the available information that is available on DDVP and this risk assessment utilizes several detailed reviews conducted by agencies responsible for assessing chemical risks (e.g., ATSDR 1997; U.S. EPA 1999a, 2000a,b; WHO 1988, 1989).

This risk assessment involves numerous calculations. Many of the calculations are relatively simple and the very simple calculations are included in the body of the document. Some of the calculations, however, are complex. For the more complex calculations, worksheets are included as an attachment to the risk assessment. The worksheets provide the detail for the estimates cited in the body of the document. The worksheets for DDVP are contained in an EXCEL workbook

and are included as Supplement 1 to this risk assessment and general documentation for the use of these worksheets is given in SERA (2004).

The USDA will update this and other similar risk assessments on a periodic basis and welcomes input from the general public on the selection of studies included in the risk assessment. This input is helpful, however, only if recommendations for including additional studies specify why and/or how the new or not previously included information would be likely to alter the conclusions reached in the risk assessments.

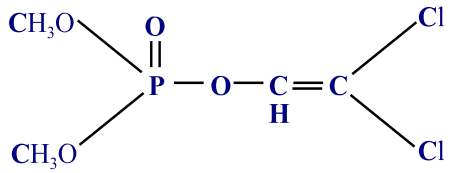
2. PROGRAM DESCRIPTION

2.1. OVERVIEW

DDVP is an organophosphate insecticide that acts by inhibiting acetylcholinesterase, an enzyme that is very important in the nervous system of all vertebrates and many invertebrates including all arthropods. Thus, DDVP is not specific to the gypsy moth or other insects. In USDA programs for the control of the gypsy moth, DDVP is used only in a 1" x 4" inch polyvinyl chloride (PVC) strip that contains 590 mg of DDVP. These strips are used to kill insects that are attracted to and enter milk carton style traps baited with the gypsy moth pheromone. Typically milk carton traps are deployed in widely spaced grids (inter-trap distances ranging from 500 m to 7 km) to survey for the presence of gypsy moth populations in the STS or eradication areas. Only rarely are milk carton traps deployed in mass trapping grids to control isolated infestations. When used in mass trapping control efforts, milk carton traps are deployed in tightly spaced grids (inter-trap distance of 20 to 30 meters). Mass trapping is a rarely used eradication tactic that targets low-density infestations (<10 egg masses per acre) occupying relatively small areas (<100 acres) .

2.2. CHEMICAL DESCRIPTION AND COMMERCIAL FORMULATIONS

DDVP is the common name for O,O-dimethyl O-(2,2-dichlorovinyl) phosphate:



Other synonyms for DDVP as well as selected chemical and physical properties of DDVP are summarized in Table 2-1.

DDVP is a contact and stomach organophosphate insecticide (Gallo and Lawryk 1991, IARC 1991). As detailed further in the human health risk assessment (Section 3) and the ecological risk assessment (Section 4), DDVP acts by inhibiting acetylcholinesterase, an enzyme that is very important in the nervous system of all vertebrates (including humans) and most other animals including all arthropods.

DDVP is currently undergoing reregistration (http://www.epa.gov/pesticides/op/ddvp.htm; Mennear 1998) and is being considered in the U.S. EPA's cumulative risk assessment of organophosphates (http://www.eps.gov/pesticides).

Various DDVP pest strips for residential or industrial use have been registered with the U.S. EPA and are manufactured by AMVAC Chemical Corporation, Loveland Industries, and Spectrum Group (http://www.cdpr.ca.gov/docs/pressrls/ddvp.htm). However, the only strip used by the USDA in gypsy moth programs is the Vaportape II strip provided by Hercon Environmental Corp, Emigsville, PA (Hercon 1993). A contract for the supply of these strips to

the USDA gypsy moth program was awarded to Hercon Environmental Corp on March 23, 1999 (www.fbodaily.com/cbd/archive/1999/03 (March)23/Mar-1999/87awdoo1.htm).

Vaportape II is distributed in packages of 50 strips, each of which comes in a protective pouch. Each strip consists of a 1" x 4" inch red, multi-layered polyvinyl chloride (PVC) strip containing 590 mg of DDVP. The average thickness of the strip is 67.5 mil with a range of 65–70 mil or 0.0675 inches with a range of 0.065–0.07 inches (Hercon 1994). Additional details concerning the composition of the strips have been disclosed to U.S. EPA (Health-Chem Corporation 19??; Herculite Products Incorporated 19??a,b; Starner 1993). Note that the 19?? designation indicates that the material is not dated and that the U.S. EPA cannot determine when the information was submitted. This is not uncommon for submissions that occurred in the early 1970's. The details of the information contained in these submissions are classified as CBI (confidential business Information) under Section 7(d) and Section (10) of FIFRA and this information cannot be specifically disclosed in this risk assessment.

The product label specifies that in addition to DDVP, each strip contains 0.75% compounds that are related to DDVP and 89.25% inerts (Hercon 2004). Further details are not provided on the label; nonetheless the impurities in commercial DDVP have been characterized (Gillett and others 1972a, IARC 1991). The impurities include: Dipterex (O,O-dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate); O,O-dimethyl 2-chlorovinyl phosphate; O,O-dimethyl methylphosphonate; O,O,O-trimethyl phosphate; and trichloroacetaldehyde. These impurities are known to be or are likely to be toxic (Gillett and others 1972a, WHO 1989). These impurities are encompassed in the risk assessment because the dose-response assessment is based on studies that used commercial grade DDVP. Consequently, the results of these studies are directly applicable to the risk assessment for human health (Section 3) and ecological effects (Section 4).

2.3. APPLICATION METHODS

The Vaportape II strips are used as an insecticide in large capacity pheromone traps to monitor gypsy moth populations. DDVP is also used in a similar way in monitoring populations of the beet armyworm (Lopez 1998).

In order to minimize the ecological effects and human health effects of gypsy moth infestations, the USDA adopted various intervention strategies that are roughly categorized as suppression, eradication, and Slow the Spread (STS). Suppression efforts are conducted by the USDA Forest Service in areas of well established gypsy moth infestations to combat or interdict periodic gypsy moth population outbreaks. Eradication efforts are conducted by USDA/APHIS to completely eliminate gypsy moth populations in areas where new populations of the gypsy moth are found. Slow the spread, as the name implies, is a program to reduce the expansion of gypsy moth populations from areas of established populations to adjacent non-infested areas (Liebhold and McManus 1999). The STS project is the primary user of DDVP and milk carton traps. STS has purchased DDVP in the following amounts: 2002 - 540 packs (540x50 strips=27,000 strips); 2003 - 540 packs (27,000 strips); 2004 - 500 packs (25,000 strips) (Leonard 2004).

As in the previous gypsy moth programs, a Vaportape II strip is contained in the milk carton trap together with together with a slow release dispenser containing disparlure, the gypsy moth pheromone. The milk carton traps containing the strips are placed in selected areas to monitor gypsy moth infestations. When used in eradication efforts for mass trapping, milk carton traps are typically used only in low density infestations – i.e., 10 egg masses per acre or less. In addition, because of the labor involved in mass trapping, this method is applied to relatively small areas – i.e., about 100 acres or less (USDA 2001, p. 1-7 to 1-8).

As discussed in the exposure assessments for human health (Section 3.2) and ecological effects (Section 4.2), the nature of the exposures to humans and other nontarget species will typically be extremely small and it is unlikely that significant exposures will occur under normal circumstances. For workers, the nature of exposure to DDVP depends on program handling practices, which vary from state to state. In most cases, dermal and inhalation exposure will be minimal, provided that recommended work practices are followed. In some states, inhalation exposure will be minimal because strip installation takes place outdoors, at the trap placement site. In other states, traps may be assembled the day before placement. Even so, the workers are instructed to assemble the traps only in a well-ventilated area, and the traps are sealed in plastic bags after assembly and prior to transport. Dermal exposure is also likely to be minimal. In most states, workers are given plastic gloves and instructed to use them. In other states, workers are instructed to touch only the plastic wrapper in which the strip is shipped.

3. HUMAN HEALTH RISK ASSESSMENT

3.1. HAZARD IDENTIFICATION

3.1.1. Overview

DDVP is an organophosphorus insecticide that works by inhibiting cholinesterase. DDVP has been used since the early 1960's and has been the subject of many toxicity studies and review articles. Information is available on a number of case reports of accidental and suicidal exposures as well as human monitoring data from normal use. The toxicity of DDVP has been adequately evaluated using laboratory animals, although not all of these studies are available in the open literature.

DDVP is readily absorbed into the body of mammals via all routes of exposure, where it is rapidly metabolized and eliminated. In general, the systemic effects observed after oral, inhalation, or dermal exposure of humans or laboratory animals to DDVP result from the inhibition of acetylcholinesterase. Inhibition of this enzyme in mammalian systems produces a variety of systemic effects, including salivation, urination, lacrimation, convulsions, increased bronchial secretions, respiratory depression, and even death. The nature and magnitude of the toxic effects produced by a given exposure to DDVP by any route are directly related to the dose and rate at which the exposure occurs. In the case of the USDA programs for the control of the gypsy moth, the use of milk carton traps containing Vaportape II (slow-release of DDVP from PVC strips) essentially precludes rapid exposures to high doses of DDVP.

Short-term animal studies have shown that oral exposures to doses below about 0.5 mg/kg-day (or inhalation exposures to 1–2 mg/m^3) do not result in meaningful reductions in cholinesterase activity. Experiments in laboratory mammals that were exposed to DDVP during pregnancy (by oral or inhalation route) did not show any effect on fertility or health of the offspring, even at levels that produced maternal toxicity. The latest evaluation of data from assays for carcinogenicity and genetic toxicity classify DDVP as a "suggestive" carcinogen and determined that a quantitative assessment of cancer risk is not applicable. The literature contains some data suggesting that contact dermatitis (as well as cross-sensitization to other pesticides) may occur; although, this appears to be an infrequent occurrence in the general population.

3.1.2. Mechanism of Action

The mechanism of action of DDVP in target organisms and its principal toxic effects in humans and animals result from inhibiting neural acetylcholinesterase (AChE). DDVP shares this mechanism of action with other organophosphate insecticides. A number of excellent reviews on the mechanism of action of the organophosphate insecticides are available in various texts (Wills 1972; Gallo and Lawryk 1991; Taylor 1996; Ecobichon 2001). The AChE enzyme is present at cholinergic synapses (spaces between the nerve cells) throughout the nervous systems, and it is responsible for hydrolyzing acetylcholine released from the pre-synaptic terminal. If this enzyme is inhibited, acetylcholine accumulates in the synapse, resulting in increased stimulation of the postsynaptic neuron and cholinergic overstimulation. The consequences of increased cholinergic activity in various organ systems are listed in Table 3-1. These classical symptoms of

organophosphate neurotoxicity increase in severity and rapidity of onset in a dose-dependent manner.

Acetylcholinesterase is also present in erythrocytes where it is known as erythrocyte or red blood cell acetylcholinesterase (RBC AChE). *In vitro* assays have found that the erythrocyte and neural forms of AChE are inhibited to roughly the same extent by exposure to DDVP (ATSDR 1997). Measurement of RBC AChE is used as a surrogate of the inhibition of neural AChE. One of the major diagnostic tools and measures of exposure to DDVP and other organophosphate insecticides is the determination of cholinesterase activity in various tissues, most often red blood cells and plasma (Ecobichon 2001; Gallo and Lawryk 1991; Murphy 1980). Plasma cholinesterase, sometimes referred to as pseudo-cholinesterase or ChE, is produced by the liver and differs from AChE in structure and substrates (ATSDR 1993). Although the normal physiological role of plasma ChE is not known, it is also inhibited by DDVP and is often used as a marker for exposure. Inhibition of RBC AChE is generally regarded as a more clinically significant index of organophosphate exposure, compared with inhibition of plasma ChE, as plasma ChE is inhibited by DDVP at lower levels of exposure than required to inhibit neural or erythrocyte AChE (ATSDR 1997).

3.1.3. Kinetics and Metabolism

DDVP is a small, lipid-soluble molecule (see Table 2-1) that is readily absorbed by passive diffusion through the lungs, gastrointestinal tract, or skin. Little information is available on the pulmonary absorption rate of DDVP, but it appears to be rapidly absorbed by the inhalation as well as oral and dermal routes of exposure. Due to the rapid degradation of DDVP by tissue esterases, particularly in the liver and the serum, measuring DDVP *in vivo* is difficult. Laws (1966) reported that DDVP is absorbed primarily by hepatic portal venous system after oral administration and is subject to first pass metabolism by the liver. Because of the difficulty in measuring DDVP *in vivo*, the rate of absorption is typically inferred from the time to onset of clinical signs of AChE inhibition (see Table 3-1). Determination of the tissue distribution of DDVP is also difficult to study because of rapid metabolism, but the data do not suggest preferential distribution or sequestration in any tissue (ATSDR 1997). A compartmental model has been proposed by Garcia-Repetto et al. (1995) to describe the toxicokinetics of DDVP following oral exposure. The model was composed of two compartments: central and peripheral. The central compartment was blood, and the peripheral compartment encompassed adipose, muscle, and liver.

3.1.3.1. Oral Absorption – Oral absorption of DDVP is rapid. Acute oral toxicity studies have demonstrated toxic effects from oral DDVP exposure within minutes. ATSDR (1997) noted that animal studies demonstrated lethality from single gavage doses of DDVP within 9 minutes for Swiss mice and 15–30 minutes in crossbred swine; signs of cholinergic toxicity (vomiting and diarrhea) were noted in greyhound dogs 7–15 minutes after receiving oral doses of DDVP in gelatin capsules. Based on a suicide case, Shimizu et al. (1996) have reported the tissue distribution of DDVP in humans following oral exposure. Tissue to blood ratios in this individual ranged from <1 for brain and liver to 28 for heart and 115 for the spleen. The authors

reported that the high-tissue concentrations in the heart and spleen were likely due to diffusion from the stomach to nearby organs (postmortem, the stomach contained approximately 250 mL of fluid equivalent to 300 g of DDVP). Studies in swine treated with DDVP-impregnated PVC pellets (veterinary use as anthelminthic) show that DDVP is absorbed from the PVC resin after oral exposure (Jacobs 1968, Potter et al. 1973).

3.1.3.2. Dermal Absorption – No studies have been found on the dermal absorption rate of DDVP in humans. As a small, lipid-soluble compound (see Section 2.2), DDVP would likely be rapidly absorbed through the skin. Dermal absorption in rats has been studied by Jeffcoat (1990). Groups of rats were dosed with ^{14}C-DDVP at 3.6, 36, and 360 µg/rat by applying the compound to the shaved back. The treated area was isolated with a protective cover for a 10-hour period. After 10 hours, the remaining DDVP was washed from the treated surface and animals were sacrificed over 24- to 102-hour periods. Based on the ^{14}C recovered from the rats, the amount penetrating the skin ranged from 21.9 to 30.1% with no substantial variation among dose groups. For this type of a study, first order dermal absorption coefficients (***k***) can be calculated as:

$$\boldsymbol{k} = -\ln(1-\boldsymbol{f})/\boldsymbol{t}$$

where ***f*** is the fraction absorbed and ***t*** is the duration of exposure. Based on absorption fractions of 0.219 to 0.301, the first-order dermal absorption rates can be calculated as 0.025 hour^{-1} [-ln(1-0.219)/10 hours] to 0.036 hour^{-1} [-ln(1-0.301)/10 hours]. These calculations are based on the cumulative amount of DDVP recovered from urine, feces, expired air, blood, carcass, and treated skin). Excluding treated skin, only 6.4 to 11.4% of the dose was actually absorbed. These correspond to first order dermal absorption rates of 0.0066 hour^{-1} [-ln(1-0.064)/10 hours] to 0.012 hour^{-1} [-ln(1-0.114)/10 hours] and these estimates are consistent with the dermal absorption rate selected by EPA (2000a) for occupational and residential exposures (11% in 10 hours of exposure).

3.1.3.3. Metabolism – As noted above, DDVP is rapidly degraded by tissue esterases, particularly in the liver and the serum. The products of the esterase-catalyzed degradation of DDVP are dimethyl phosphate and dichloroacetaldehyde. Dimethyl phosphate is excreted in the urine, while dichloroacetaldehyde can be reduced to dichloroethanol or dehalogenated to glyoxal, which enters 2-carbon metabolism. Dichloroethanol is either conjugated to glucuronic acid and excreted in the urine or dehalogenated and further metabolized. There is also evidence that DDVP can be demethylated in a glutathione-dependent reaction (WHO 1989, ATSDR 1997). The *in vitro* half-life of DDVP in human blood is about 10 minutes (Blair et al. 1975).

3.1.4. Acute Oral Toxicity

As described in Section 3.1.2, DDVP exposure can result in increased cholinergic activity in the nervous system, producing the classical symptoms of organophosphate poisoning (See Table 3-1). The life-threatening effects of acute exposure to DDVP are usually related to its cholinergic effects on the respiratory system (respiratory depression, bronchospasm, increased bronchial secretions, pulmonary edema, and muscle weakness). DDVP is moderately to highly

toxic by the oral route when administered in single doses to a variety of animal species, and several cases of acute DDVP poisoning in humans have reported in the literature. Some individuals have committed suicide by intentionally ingesting DDVP pesticide formulations (e.g., Shimizu et al. 1996). This study is discussed further in Section 3.3 (Dose-Response Assessment). In an attempted suicide, a 56-year old woman who ingested about 100 mg/kg DDVP survived following intensive care for 14 days (WHO 1989). Two workers who had skin exposure to a concentrated dichlorvos formulation, and failed to wash it off, died of poisoning. In addition, four patients suffering from severe poisoning from oral exposure to dichlorvos survived, although they later showed delayed neurotoxic effects (WHO 1989). Thus, although the possibility of neuropathy in humans cannot be excluded, it is likely to occur only after almost lethal oral doses (see also Section 3.1.6).

Oral LD_{50} values for experimental mammals range from 25 to 300 mg/kg (Jones et al. 1968, Gaines 1969, Muller 1970, Wagner and Johnson 1970). Signs of intoxication in these studies are consistent with cholinergic overstimulation, typically salivation, lacrimation, urination, defecation, tremors, convulsions, and death from respiratory failure.

EPA (2000a, p. 18) identified an unpublished neurotoxicity study in rats as the basis for establishing a risk level for acute oral exposure to unformulated DDVP – i.e., DDVP not in a PVC strip. In this study (Bast et al. 1997), Sprague Dawley rats (12/sex/dose) received a single oral dose of DDVP (97.8%) at doses of 0, 0.5, 35, or 70 mg/kg. Behavioral testing, including a functional observation battery and motor activity, was conducted pretest, 15 minutes after treatment, and on days 7 and 14 after exposure. Cholinesterase activity was not measured in any tissue. The acute NOAEL was 0.5 mg/kg and the LOAEL was 35 mg/kg based on neurological effects related to AChE inhibition.

The containment of DDVP in a slow-release vehicle, however, such as the PVC in the Vaportape II strips, will reduce the likelihood of acute toxic effects. The kinetics of DDVP release from PVC were investigated in a study in which DDVP was incorporated into PVC at 20% (w/w) (Slomka and Hine 1981). The PVC was extruded, cut into pellets, and encased in a hard gelatin capsule. The release of DDVP from the capsules was assayed *in vitro* using an artificial gastric fluid and *in vivo* in swine and humans. The release rates in the three assays were comparable; approximately 30% was released in the first 24 hours, and the subsequent release appeared to follow a first order function with a release rate of approximately 0.1 day^{-1}.

The effect of PVC encapsulation on the toxicity of DDVP has been quantified in parallel acute assays in young pigs (Stanton et al. 1979) using unformulated DDVP (undiluted technical grade administered in gelatin capsules) and DDVP in PVC resin (administered by gavage). For the technical grade liquid formulation, the LD_{50} was 157 (113–227) mg/kg. Signs of toxicity in these animals were consistent with the general signs of AChE inhibition (Table 3-1) and included decreased general activity, vomiting, poor coordination, and twitching. In the bioassay using the PVC formulation, no deaths occurred at any of the administered doses – i.e., 180 mg/kg, 240 mg/kg, 320 mg/kg or 1,000 mg/kg. Higher doses of the DDVP-PVC formulation could not be

administered because these doses produced vomiting. While not specified by Stanton et al. (1979), vomiting at doses >1,000 mg/kg may have been due to the physical stress associated with such a large gavage dose. Although no animals died, vomiting was observed at all DDVP-PVC doses. At the lowest dose, 180 mg/kg, vomiting with no other signs of AChE inhibition were observed. At the next higher dose, 240 mg/kg, no adverse effects are reported.

Stanton et al. (1979) also conducted 30-day assays using only the PVC formulation. Aside from alterations in cholinesterase activity, 30 consecutive days of exposure of young swine or gravid sows to doses as high as 25 mg/kg-day of the DDVP-PVC formulation produced no adverse effect on any physical or biochemical parameter measured. The authors suggest that the lack of serious adverse effects was related to the slow-release of DDVP from the PVC pellet (Stanton et al. 1979).

In an abstract, Singh et al. (1968) evaluated free DDVP (200 or 400 mg/day) or DDVP in V-13 pellet (800 mg/day; 9% DDVP, 91% inert [NOS]) in gravid sows. The DDVP, whether in free form or in the pellet, produced no adverse effects on the number of pigs born alive, number of pigs born dead, average birth weight, average number of pigs weaned at 35 days, or the average weanling weight. Minor gross signs of organophosphate poisoning (NOS) were observed only in the group receiving 400 mg/day free DDVP.

3.1.5. Subchronic or Chronic Systemic Toxic Effects

Subchronic and chronic toxicity bioassays have been conducted in several laboratory animal species (e.g., rats, mice, dogs, pigs, and monkeys), exploring the adverse effects of DDVP exposure by oral and inhalation routes of exposure. Generally, the toxic effects of DDVP exposure (regardless of route of administration) are due to the inhibition of AChE (Table 3-1). Consequently, plasma, erythrocyte, and brain cholinesterase activity are metrics of exposure and toxicity. Studies have demonstrated more sensitive neurological effects than cholinesterase inhibition; however, the toxicologic implications of these early biomarkers of exposure are uncertain. For example, the correlations between the relatively low level, chronic dichlorvos (DDVP) exposure and early electrophysiological changes (assessed by electrocorticogram, cortical evoked potentials, conduction velocity, and refractory periods of peripheral nerve) showed the electrophysiological parameters to be sensitive biomarkers of the exposure in humans (Desi et al. 1998).

In a long-term dietary study, rats fed diets containing DDVP for 2 years showed no signs of toxicity until the dietary exposures reached 2.5 mg/kg-day or more (WHO 1989). EPA (2000a) identified an unpublished dietary study in dogs (MRID No. 41593101 as summarized by U.S. EPA 1994) as the basis for establishing a risk level for chronic oral exposure. Groups of beagle dogs received DDVP orally in capsules at dose levels of 0, 0.1, 1.0, and 3.0 mg/kg/day for 52 weeks. The 0.1 mg/kg/day dose was lowered to 0.05 mg/kg/day on day 22 due to the inhibition of plasma ChE noted after 12 days (the magnitude of the reduction was 21.1% in males and 25.7% in females). After week 2, plasma ChE activity was only significantly reduced in males (39.1–59.2%) and females (41.0–56.7%) in the mid-dose group and in males (65.1–74.3%) and

females (61.1–74.2%) in the high-dose group at all other later time intervals. RBC AChE activity was reduced in males (23.6%) and females (50.1%) at week 6 in the low-dose group. The authors attributed this to a residual effect on RBC AChE of the earlier dose of 0.1 mg/kg/day, because much less inhibition was observed in this group after week 6. After week 6, RBC AChE activity was only significantly decreased in males (43.0–53.9%) and females (38.0–51.9%) in the mid-dose group and in males (81.2–86.9%) and females 79.2–82.5%) in the high-dose groups at all other later time intervals. Brain AChE activity was significantly reduced in males (22%) in the mid-dose group and in males (47%) and females (29%) in the high-dose group. The NOAEL and LOAEL selected by EPA (2000a) for chronic oral risk exposure are 0.05 and 0.1 mg/kg/day, respectively. These effect levels are based on plasma ChE and RBC AChE inhibition in male and female dogs as early as the first time point measure and brain AChE inhibition in male dogs.

3.1.6. Effects on Nervous System

A neurotoxicant is a chemical that disrupts the function of nerves, either by interacting with nerves directly or by interacting with supporting cells in the nervous system (Durkin and Diamond 2002). This definition of neurotoxicant distinguishes agents that act directly on the nervous system (direct neurotoxicants) from those agents that might produce neurologic effects that are secondary to other forms of toxicity (indirect neurotoxicants). As discussed in Section 3.1.2, DDVP, like all organophosphate insecticides, is a direct-acting neurotoxicant. DDVP combines with and inhibits AChE. The biochemical basis for the toxic effects of DDVP is related to the normal function of AChE. In the cholinergic system, neural impulses are transmitted between nerve cells or between nerve cells and an effector cell (such as a muscle cell) by the acetylcholine. When the acetylcholine reaches a certain level, the receptor cell is stimulated. Normally, the acetylcholine is then rapidly degraded to inactive agents (acetic acid and choline) by AChE. When AChE activity is inhibited by organophosphate agents (such as DDVP), acetylcholine persists and continues to accumulate at the synapse (the space between the nerve cells). Initially, this accumulation causes continuous stimulation of the cholinergic system, which may be followed by paralysis because of nerve cell fatigue (ATSDR 1993).

The cholinergic effects of DDVP intoxication are well documented in studies involving humans, wildlife, and experimental mammals (Gillett et al. 1972a,b; IARC 1979, 1991; WHO 1989). DDVP also inhibits other cholinesterases and many other esterases outside of the nervous system and induces clinical signs of intoxication that are dependent upon the dose and duration of exposure (Table 3-1). In addition, some studies of lifetime exposure of rats to DDVP suggest that oral exposures to doses $\geq$0.97 mg/kg-day result in behavioral changes (Schultz et al. 1995, Institäoris et al. 1997).

RBC AChE activity follows a circadian oscillation in both mice and humans (Jian and Zhiying 1990). Furthermore, mortality in mice associated with exposure to DDVP is inversely related to the oscillation in AChE activity. These investigators report that DDVP interferes with the normal circadian rhythm of RBC AChE in mice and humans, although this interference is secondary to pronounced AChE inhibition.

The effect of DDVP on AChE activity in humans has been assayed by Gledhill (1997). In this study, DDVP was administered to 6 male volunteers as a single dose of 70 mg DDVP in a corn oil solution in a gelatin capsule. The body weights of 6 individuals ranged from 67 kg to 80 kg (Gledhill 1997) and thus the individual dose rates ranged from 0.70 to 1.04 mg/kg bw. No effect on AChE activity was observed and there were no signs or symptoms of cholinergic overstimulation.

Normal ChE activities can be highly variable among individuals. Consequently, interpreting differences between cholinesterase levels in exposed groups and control groups is more difficult than interpreting differences between individual ChE levels before and after exposure (ATSDR 1993). All of the human and animal studies on PVC-DDVP formulations report AChE levels using the method involving treated groups and control groups. For all of the human studies on DDVP (Cervoni et al. 1969; Pena-Chavarria et al. 1969; Hine and Slomka 1970; Slomka and Hine 1981), the interpretation is further complicated because ChE levels are reported as ranges of inhibition, rather than mean values with standard errors.

As discussed in the general literature and illustrated in the human studies on DDVP, inhibition of cholinesterase in plasma and blood is not necessarily associated with clinically significant adverse effects (Gage 1967; Wills 1972). ATSDR (1997) noted that the nervous system can accept a certain amount of acetylcholinesterase inhibition without overt toxic effects. In humans and animals, toxic signs are generally not seen until at least 20% of this enzyme (RBC AChE used as a marker) has been inhibited (ATSDR 1997). In a rat study, brain AChE after a 2-year inhalation exposure to DDVP was inhibited more than 90% compared to control animals (Blair et al. 1976), yet signs of cholinergic overstimulation were not observed. ATSDR (1997) suggests that the best predictor of toxicity is not necessarily the actual percentage inhibition of AChE, but rather how rapidly this inhibition has occurred. Rapid inhibition does not afford the nervous system time to adapt to AChE inhibition. This adaptation appears to involve desensitization and down regulation of muscarinic receptors (ATSDR 1997).

A significant characteristic of some organophosphate insecticides is that the reversibility of enzyme inhibition is slow (Murphy 1980). Relatively little information is available on the reversibility of inhibition due to DDVP. There is one case report indicating substantial inhibition of ChE, 36% of normal, in an individual exposed to DDVP 3 days before the assay of ChE activity (Bisby and Simpson 1975), and other data suggest that cholinesterase activity levels do not return to normal for several months (ATSDR 1997).

Exposure to some organophosphorus compounds cause delayed neuropathy in humans (also known as organophosphate-induced delayed neurotoxicity or OPIDN). Clinical manifestations include motor dysfunction, tingling in the extremities, and in some cases paralysis. These effects usually appear 7–14 days after exposure, when signs of cholinergic toxicity have resolved, and can persist for weeks or years (ATSDR 1997). The data concerning the potential for DDVP-induced OPIDN are inconsistent and controversial. Several studies that demonstrate that DDVP does not induce delayed neuropathy (WHO 1989), including a recent study in adult hens

(Abdelsalam 1999). On the other hand, very high doses of DDVP (doses in excess of the LD_{50}) produced clinical neuropathy when administered to hens (Johnson 1978, 1981). These data are consistent with human cases of poisoning where recovery was followed by delayed neurotoxicity (see Section 3.1.4) (WHO 1989). Subcutaneous doses of DDVP (single dose of 200 mg/kg or 6 mg/kg-day for 8 weeks) in rats led to motor deficit or biochemical and behavioral deficits (Sarin and Gill 2000, 1998, respectively). The potential for OPIDN in humans resulting from exposure to DDVP in PVC resin strips is unknown.

3.1.7. Effects on Immune System

Immunotoxicants are chemical agents that disrupt the function of the immune system. Two general types of effects, suppression and enhancement, may be seen and both of these are generally regarded as adverse. Agents that impair immune responses (*immune suppression*) enhance susceptibility to infectious diseases or cancer. Enhancement or *hyperreactivity* can give rise to *allergy* or hypersensitivity, in which the immune system of genetically predisposed individuals inappropriately responds to chemical or biological agents (e.g., plant pollen, cat dander, flour gluten) that pose no threat to other individuals or *autoimmunity*, in which the immune system produces antibodies to self components leading to destruction of the organ or tissue involved (Durkin and Diamond 2002).

Although the literature contains some evidence that organophosphate insecticides can impair immunological markers (Colosio et al. 1999), no human data are available to describe a dose-response relationship for the immunotoxic potential of DDVP. Animal studies suggest that exposure to DDVP may be associated with immunosuppression. Treating rabbits with oral doses of 0.31–2.5 mg/kg DDVP (2.5–20% of the LD_{50}) 5 days per week for 6 weeks resulted in inhibition of both humoral and cell-mediated immune response to *S. typhimurium* (Desi et al. 1978, 1980). Immunosuppression (suppressed IgM response at 48 hours) was also observed in mice treated with a single oral dose of 120 mg/kg DDVP (Casale et al. 1983). A decrease in relative spleen weight was also noted in this study; however, severe signs of DDVP neurotoxicity were noted and the authors stated that the immunosuppression observed in this study may have been related to toxic chemical stress. In addition, *in vitro* studies on cells from embryonic renal tissue of carp demonstrated a dose-related decrease in lymphocyte proliferation and myeloid cell respiratory burst activities, both of which indicate immunosuppression; however, no effects on antibody production were noted in an *in vivo* study of carp (Dunier et al. 1991). Bryant (1985) has associated the precipitation of preexisting asthma to small doses (NOS) of DDVP.

Aside from the few positive reports above, there is very little direct information on which to assess the immunotoxic potential of DDVP in humans. The extrapolation of the observed alterations in the immune system response of experimental animals to humans is uncertain, since the functional relevance of these deficits in humans is unknown. The immune system has a functional reserve and modifications in the immune response do not always correlate with a measurable health effect (Vial et al. 1996; Voccia et al. 1999).

The systemic toxicity of DDVP has been adequately examined in numerous acute, subchronic, and chronic bioassays. Although many of these studies did not focus on the immune system, changes in the immune system (which could potentially be manifest as increased susceptibility to infection among DDVP-exposed animals compared to controls) were not observed in any of the available long-term animal studies. In a three-generation study of Wistar rats, neurologic endpoints were found to be more sensitive markers of exposure than immunologic endpoints in all three generations (Institäoris et al. 1997).

3.1.8. Effects on Endocrine System

In terms of functional effects that have important public health implications, some of the effects on endocrine function would be expressed as diminished or abnormal reproductive performance. This issue is addressed specifically in the following section (Section 3.1.9). As discussed in Durkin and Diamond (2002), mechanistic assays are generally used to assess the potential for direct action on the endocrine system. DDVP has not been tested for activity as an agonist or antagonist of the major hormone systems (e.g., estrogen, androgen, thyroid hormone), nor have the levels of these circulating hormones been adequately characterized following DDVP exposures. Alterations in the diurnal rhythm of the pituitary/adrenal axis were observed in rats exposed to 2 ppm (approximately 0.3 mg/kg) DDVP in drinking water. Although effects on plasma ChE activity were not noted, levels of plasma adrenocorticotrophic hormones and adrenal cholesterol ester were altered (Civen et al. 1980). In the absence of mechanistic studies of the endocrine system, any judgments concerning the potential effect of DDVP on endocrine function must be based largely on inferences from standard toxicity studies, none of which provide evidence for an endocrine effect.

3.1.9. Reproductive and Teratogenic Effects

No data are available in humans concerning the potential for DDVP-induced reproductive or developmental toxicity. As a small, lipid-soluble molecule, DDVP would be expected to cross the placental barrier and be excreted into breast milk (Desi et al. 1998). According to some studies, exposure to DDVP caused reproductive and teratogenic effects in laboratory animals; on the other hand, there are several breeding studies in which no adverse reproductive or teratogenic effects were observed in rabbits or swine after exposure to DDVP (ATSDR 1997). In a study in which female rats were given intraperitoneal injections of 15 mg/kg DDVP on day 11 of gestation, herniation of the umbilical cord was observed in 3 of 41 offspring from the treated group (Kimbrough and Gaines 1969). The effect was not observed in offspring from the control group (0/65) but the effect is not statistically significant using the Fisher Exact test (p=0.074) – i.e., the conventional criterion for statistical significance is a p-value of $\leq$ 0.05. In a three-generation study of Wistar rats, oral gavage doses of approximately 1, 1.3, or 1.9 mg/kg-day 5 days/week for 28 weeks found no consistent toxicity (systemic, reproductive, or immunologic) across generations (e.g., birth body weight was statistically decreased in generation 2 and increased in generation 3) (Institäoris et al. 1995, 1997).

When rabbits were treated with 6 mg/kg DDVP during the last 10 days of gestation and the brain tissue of the offspring was examined by electron microscopy, there was an incidence of

immaturity or delay in brain development that was not apparent in the offspring of the untreated rabbits (Dambska et al. 1979). The method of dosing the animals is not specified in this study. Groups of New Zealand White rabbits (16/dose) received DDVP (97% purity in distilled water) orally at dose levels of 0, 0.1, 2.5, or 7.0 mg/kg/day on gestation days 7 through 19 (U.S. EPA 2000a, p. 19). The NOAEL for maternal toxicity was 0.1 mg/kg/day and the LOAEL was 2.5 mg/kg/day, based on decreases in maternal body weight gain during gestation days 7–19. The U.S. EPA (2000a) considered the decrease in weight gain to be biologically significant even though the effect was not statistically significant. A dose-related increase in maternal mortality also was noted at 2.5 and 7 mg/kg/day. Cholinergic signs were observed at 7 mg/kg/day. No adverse developmental effects were noted in the fetuses. Cholinesterase activity was not determined.

An early study by Schwetz et al. (1979) in New Zealand White rabbits and CF-1 mice using the MTD dose (based on signs of cholinesterase inhibition) for both oral (gavage of 5 mg/kg-day DDVP in corn oil on gestation days 5–18 and 60 mg/kg-day DDVP in corn oil on gestation days 5–16 for rabbits and mice, respectively) and inhalation (whole body exposure to atmospheres containing 4 µg/dL (0.4 mg/L or 400 mg/m^3) DDVP for 7 hours/day on gestation days 5–18 or 5–16 for rabbits and mice, respectively) routes of exposure found no teratogenic effects that could be attributed to DDVP. These studies suggest that DDVP is not a selective developmental toxin, since adverse developmental effects only occur at doses that are maternally toxic.

At toxic doses (i.e., where signs of organophosphorus poisoning are evident), DDVP may produce reversible adverse effects on spermatogenesis (WHO 1989). Adverse testicular effects were observed in mice after chronic exposure to average daily doses of 0, 58, or 94.8 mg/kg/day DDVP in drinking water (MRID 41041801 as cited by U.S. EPA 1994). There was a dose-related decrease in the absolute and relative weight of the testes, and testicular atrophy was increased at 94.8 mg/kg/day. In addition, sperm abnormalities were seen in C57BL/C3H mice injected intraperitoneally with 10 mg/kg/day for 5 days (Wyrobek and Bruce 1975). About 6% of the sperm from DDVP-treated animals was abnormal compared to 1.8% of sperm from untreated animals. In a reproductive toxicity study involving male CF-1 mice, groups of 16 mice were exposed to atmospheres containing 0, 30, or 55 mg/m³ (0, 3.3, or 6.1 ppm, respectively) for 16 hours or to 0, 2.1, or 5.8 mg/m³ 23 hours/day for 4 weeks (Dean and Thorpe 1972). No differences between control and treated mice were observed in the number of early fetal deaths, late fetal deaths, or live fetuses found in the pregnant females. The percentage of pregnancies for females mated to males exposed to DDVP was also similar to the controls (73–88%, mean 80.9%). Under these exposure conditions, DDVP does not appear to affect the fertility of male CF-1 mice. No gross or histological evidence of treatment-related damage to reproductive tissues (prostate, testes, epididymis, ovaries, or uterus) was seen in F344 rats (4 or 8 mg/kg/day) or B6C3F1 mice (10, 20, or 40 mg/kg/day) orally exposed to DDVP by gavage for 2 years (NTP 1989).

3.1.10. Carcinogenicity and Mutagenicity

Adequate data regarding the carcinogenic potential of DDVP in humans by any route of exposure are not available. Studies of human populations exposed to DDVP (including workplace and residential exposures) are constrained by the lack of adequate exposure data and other limiting issues. As reported in a series of case studies, some evidence suggests an association between childhood cancer and exposures to DDVP in resin strips during childhood or during gestation (Reeves et al. 1981, Davis et al. 1992, 1993, Liess and Savitz 1995). These studies have been reviewed by U.S. EPA (2000a) which concluded:

> "*[r]eviews of these studies have identified biases and confounders that could explain the observed associations. The Agency concludes that the biases are a more likely explanation for the findings of increased cancer than exposure to resin strips. Additional studies that correct for the control of potential biases and problems of exposure determination are needed before an association between Dichlorvos and childhood cancer can be established*" (U.S. EPA, 2000a, p. 26).

The carcinogenic potential of DDVP has been evaluated in several animal species (mice, rats, dogs, and swine) via the oral route and in rats via the inhalation route. The weight of evidence suggests that the cancer bioassays do not offer sufficient evidence to treat DDVP as a potential human carcinogen (U.S. EPA 2000a,b). DDVP produced positive results in mammalian bioassays for carcinogenicity by the oral, but not the inhalation route of exposure. A cancer bioassay was conducted in which male and female mice were given gavage doses of DDVP (NCI 1977). The doses levels were 10 and 20 mg/kg for males and 20 and 40 mg/kg for females. There was a significant dose-related increase in squamous-cell papillomas of the forestomach in both sexes. In females at the high-dose level, the incidence of squamous-cell carcinomas was significantly greater than in the control group ($p=0.004$ using the Fisher Exact test). In the same study, male rats were given 4 mg/kg/day DDVP by gavage and female rats were given 8 mg/kg/day. A significant ($p<0.001$) dose-related increase in the incidence of acinar-cell adenomas of the pancreas was observed in the males. The increased incidence of fibroadenomas and adenomas of the mammary gland was significant ($p=0.028$) in the females. The increased incidence of the pancreatic acinar cell carcinomas in male rats and squamous cell tumors in male mice reported by NCI (1977) has been discounted by WHO (1989) and Mennear (1994, 1998). The relevance of the sex-specific increase in mononuclear cell carcinoma (MCL) reported by NCI (1977) has also been questioned (Manley et al. 1997, Mennear 1998, U.S. EPA 2000b). The issues of concern regarding the increased incidence of MCL in male rats are not dose-related increases in mortality or disease severity (Mennear 1998), incidence rates among DDVP-treated rats statistically increased as compared to matched controls but within historical control incidence, and similarity in histopathology between the MCL tumors and spontaneous tumors in control animals (Manley et al. 1997). U.S. EPA (2000b) found compelling evidence to disregard the MCL finding in Fisher rats, concluding that "*the high background and variability in the incidence of this tumor, as well as its species and strain specificity, make it an invalid response for human risk assessment*". Two other bioassays conducted on the carcinogenicity of DDVP

after oral exposure are reviewed by IARC (1991). Neither study indicated significant evidence of carcinogenicity (IARC 1991).

DDVP has been tested extensively for mutagenicity, and the results of the tests are available in several reviews (IARC 1979, 1991, Ramel et al. 1980, Mennear 1998, U.S. EPA 2000a,b). Mutagenic effects as well as covalent binding to RNA and DNA have been demonstrated in bacterial systems. Generally, mutagenicity is decreased by the presence of liver microsomal preparations; however, chromosome abnormalities in peripheral lymphocytes have been reported in pesticide workers who use DDVP (no quantitative exposure data are available and this appears to be from workers using a spray formulation of DDVP) (Desi et al. 1998). EPA (2000b) concluded that "*the results from whole animal bioassays supercede the results in vitro tests... [C]ompounds that are positive in mutation tests but do not cause cancer in whole animals should be regulated as noncarcinogens*".

A more detailed review of the cancer and mutagenicity literature database on DDVP is beyond the scope of this risk assessment. Owing to the extraordinary level of effort and Special Agency Reviews of the issue (U.S. EPA 2000a,b), this risk assessment will defer to the EPA's latest position (U.S. EPA 2000a) concerning the carcinogenic and mutagenic potential of DDVP. In that assessment (U.S. EPA 2000a), which included an open meeting to discuss the issues (U.S. EPA 2000b), it was decided that "[*t]he carcinogenicity potential of Dichlorvos has been classified as 'suggestive' under the 1999 Draft Agency Cancer Guidelines and no quantitative assessment of cancer risk is required"*. Thus, this risk assessment for DDVP does not include a quantitative assessment of cancer risk.

3.1.11. Irritation and Sensitization (Effects on the Skin and Eyes)

The available human data, supported by studies on experimental animals, suggest that exposure to DDVP may cause skin irritation or allergic reactions. Human data regarding the dermal effects of DDVP are relatively sparse. In a case report, relatively severe contact dermatitis developed in an adult male after a 1% solution of DDVP leaked onto his skin (Bisby and Simpson 1975). This effect was accompanied by signs of cholinergic toxicity, including fatigue, dizziness, and labored respiration. Cases of dermatitis and skin sensitization due to DDVP have been described in workers handling and spraying different types of pesticides and cross-sensitization with certain pesticides has been seen (WHO 1989).

The data from animal testing supports the results of human case reports. In New Zealand white rabbits, the application of an aqueous solution of 5–20% DDVP to the skin caused relatively severe irritation (Arimatsu et al. 1977). In a skin sensitization assay, 1% DDVP in olive oil induced no visible effects in male albino guinea pigs (Kodama 1968). In a guinea pig assay for allergenicity, 35% of the tested guinea pigs had a positive response to a 0.5% solution of DDVP (Fujita 1985). In a sensitization assay, Ueda et al. (1994) reported that 1% DDVP was a threshold irritation concentration in guinea pigs and that cross-sensitization occurred between DDVP and triforine. WHO (1989) reported that in Hartley guinea pigs the primary irritant threshold limit value for DDVP was $\geq$2%.

3.1.12. Systemic Toxic Effects from Dermal Exposure

Most of the systemic effects observed after dermal exposure of laboratory animals (including monkeys, rats, and chickens) to DDVP were the result of the neurotoxicity of this chemical. In its risk assessment for DDVP, U.S. EPA (2000a) selected studies for short-term and intermediate-term risk assessment that reflect the systemic toxicity resulting from dermal exposures to DDVP. In both of these studies, the toxicity of DDVP is secondary to inhibition of cholinesterase activity. Data concerning the dermal absorption kinetics of DDVP are discussed in Section 3.1.3.2.

A number of fatalities have been reported from dermal exposures to concentrated formulations of DDVP (spilling or splashing onto skin) (WHO 1989). The data suggests that, in those cases where the spilled solution was immediately washed off, the victims developed symptoms of organophosphorus poisoning but they recovered after treatment (WHO 1989). Such exposures are not relevant to this risk assessment, as the encapsulation of DDVP in PVC used in Vaportape II precludes rapid exposure to high doses of DDVP.

3.1.13. Inhalation Exposure

Exposure of pesticide manufacturing plant workers to concentrations in the air of up to 0.5 mg/m^3 were without clinical effects, and no, or only insignificant, inhibition of blood ChE activity was noted (WHO 1989). When DDVP is used properly, air levels of 0.01–0.03 ppm are achieved (ATSDR 1997). This level kills most insects within 1 hour; whereas, in human volunteers, exposure at about 20 times this level (0.23 ppm) for 2 hours a day for 4 days had no harmful effects (ATSDR 1997). Consistent with the human exposure data, harmful effects have not been seen in laboratory animals exposed to air levels of dichlorvos below 0.5 ppm (about 4.5 mg/m^3) (ATSDR 1997), and exposure of laboratory animals to DDVP air concentrations between 0.2–1 mg/m^3 do not affect ChE activity significantly (WHO 1989). In a 2-year study in rats, breathing air every day containing low-to-moderately high levels (0.006–0.6 ppm or about 0.05 to 5 mg/m^3) of DDVP had no effect on survival or general health (ATSDR 1997). Generally, the systemic effects observed after inhalation exposure of laboratory animals to higher levels of DDVP were the result of the neurotoxicity (cholinesterase inhibition) (U.S. EPA 2000a). Chronic inhalation exposure of laboratory animals to DDVP produced no compound-related pulmonary toxicity (U.S. EPA 2000a).

EPA (1994) selected the chronic inhalation study in rats (Blair et al. 1976) as the basis for establishing an RfC for DDVP. Groups of 50/sex/group Carworth E Farm (CFE) rats were exposed (whole body exposures) for 23 hours/day, 7 days/week to DDVP vapor (>97% purity) at atmospheric concentrations of 0, 0.05, 0.5, and 5 mg/m^3 for 2 years. The rats were observed for clinical signs of toxicity, hematology, and clinical chemistry. Plasma, RBC, and brain cholinesterase activity were determined at study termination, but not prior to the study. No clinical signs of toxicity were observed, and no organ weight or organ to body weight changes or hematological changes were associated with DDVP exposure. Body weights were decreased as compared to control rats in high-dose male (up to 20% vs. control) and female rats (up to 14% vs. control) for large portions of the study. Dose-dependent reductions in plasma, RBC, and

brain cholinesterase activity were observed. This study establishes a NOAEL of 0.05 mg/m³ and a LOAEL of 0.5 mg/m³ based on reductions in brain cholinesterase activity (U.S. EPA 2000a).

3.1.14. Inerts and Adjuvants

As discussed in Section 2.2, the DDVP used in gypsy moth control programs is contained in a multi-layered polyvinyl chloride (PVC) strip. The manufacturer (Hercon 2004) indicates that the product contains 10% DDVP, 0.75 % related compounds (Section 3.1.15), and 89.25% inert ingredients. The only toxicity data available on this strip itself (i.e., without DDVP) is an acute oral toxicity study in rats (Braun and Killeen 1975). This study used a DDVP-free strip ground to a "grayish-green powder". The strip was tested at the limit dose of 5,000 mg/kg bw by gavage with a 14-day post-dosing observation period in 5 male and 5 female rats. No adverse effects were noted in any of the rats based on mortality, gross observations, body weight gain, and gross necropsy. While this single study has its limitations, it suggests that the PVC strip alone (i.e., without DDVP) is unlikely to produce acute adverse effects. Given the limited nature of the exposure scenarios assessed herein, these data may be sufficient information for the likely exposure scenario (i.e., a child putting a strip in his/her mouth). Section 3.1.17 focuses on the toxicity studies concerning DDVP embedded in the PVC strips.

3.1.15. Impurities and Metabolites

The product label Hercon (2004) specifies that, in addition to DDVP (10%), each strip contains 0.75% compounds that are related to DDVP. Further details are not provided on the label; nonetheless, the impurities in commercial DDVP have been characterized (Gillett et al. 1972a; IARC 1991). The impurities include: Dipterex (O,O-dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate); O,O-dimethyl 2-chlorovinyl phosphate; O,O-dimethyl methylphosphonate; O,O,O-trimethyl phosphate; and trichloroacetaldehyde. These impurities are known to be or are likely to be toxic (Gillett et al. 1972a, WHO 1989). These impurities are encompassed in the risk assessment because the effect levels are based on studies that used commercial grade DDVP. Consequently, the results of these studies are directly applicable to the risk assessment for human health.

3.1.16. Toxicologic Interactions

The major toxicologic interaction of concern is concurrent exposure to other cholinesterase inhibitors (e.g., organophosphate or carbamate insecticides) or cholinomimetic agents (e.g., agents such as pilocarpine or carbachol that mimic the action of acetylcholine). In either case, simultaneous exposure would likely enhance the cholinergic toxicity produced by DDVP. Potentiation studies using DDVP in combination with 22 other organophosphate pesticides, however, found little or no potentiation (WHO 1989). Chemicals that react with the serine residue at the active site of the "A"-type esterases (e.g., diisopropylfluorophosphate [DEP]) could also increase the toxicity of DDVP by interfering with its metabolism (ATSDR 1997).

In addition, experimental data suggest that repeated exposures of rats to DDVP (5 mg/kg/day by intraperitoneal injection for 30 consecutive days) depletes brain glutathione levels (Julka et al. 1992). Reduced glutathione levels may decrease the rate of detoxification of DDVP by the

glutathione-dependent metabolic pathways. The toxicologic significance of depleted brain glutathione on DDVP metabolism is not known. In contrast with the potentiation of DDVP toxicity observed when rats are pretreated with diethylmaleate (Fukami 1980), Costa and Murphy (1984) reported that pretreatment with 600 mg/kg acetaminophen (which is also detoxified by and thus reduces glutathione levels) did not have any effect on the toxicity of DDVP. Although no data are available, these experiments suggest that repeat exposure to DDVP (resulting in a depletion of glutathione levels) may increase an organism's susceptibility to toxicity by another chemical if that chemical is also detoxified by glutathione-dependent pathways.

3.1.17. Studies on PVC Formulations of DDVP

In the EPA risk assessment for DDVP (U.S. EPA 2000a), EPA noted that DDVP resin strips (such as the Vaportape II strip used in USDA programs) "*account for a very small proportion of total incidences* [e.g., reports of poisonings]*, about 33 cases per year (1% of total incidences). Incidence reports involving exposure to resin strips usually do not involve any significant acute symptoms that would require medical treatment*". In a review of DDVP-impregnated PVC strips (Gillett 1972a,b concluded that "*even when chewed or applied directly to the skin for short intervals, the strips do not release excessive or hazardous amounts of DDVP*".

When DDVP was administered orally to human volunteers (single or repeated doses of a slow-release PVC formulation), significant inhibition of RBC ChE activity was found only at 4 mg/kg body weight or more (Hine and Slomka 1970; Slomka and Hine 1981). Single oral doses (1–32 mg/kg) of DDVP in a slow-release PVC formulation was administered to 107 male volunteers. Measurable reductions in erythrocyte ChE activity was observed at dose levels above 4 mg/kg, with a maximum reduction of 46% at 32 mg/kg. Plasma ChE activity was affected at lower doses, with 50% reduction at 1 mg/kg and about 80% reduction at 6 mg/kg or more. Repeated oral doses of 1–16 mg/kg bw per day were given to 38 male volunteers for up to 3 weeks. Plasma ChE activity was depressed at all dose levels, and RBC AChE activity depression was dose-related and statistically significant at doses of 2 mg/kg or more. Blood cell count, urine, liver function, prothrombin time, and blood urea nitrogen were all normal (Hine and Slomka 1968, 1970, Slomka and Hine 1981, WHO 1989). Among these individuals, the clinical signs of DDVP exposure were minimal (nausea, diarrhea, lassitude, restlessness, and light-headedness).

Data from 32 rhesus monkeys receiving orally administered DDVP in PVC resin (as an anthelminthic) at 0, 5, 10, 20, 40, or 80 mg/kg once daily or 0, 8, or 20 mg/kg twice daily for 10 to 21 days support the human data (Hass et al. 1971). None of the monkeys died or exhibited debilitating symptoms of organophosphorus poisoning, although some cholinergic effects were noted (a loss of appetite and emesis [LOAEL = 20 mg/kg]; diarrhea and salivation [LOAEL = 80 mg/kg]). A semi-quantitative assay for cholinesterase activity demonstrated inhibition. Studies in swine treated with DDVP-impregnated pellets (veterinary use as anthelminthic) suggest that DDVP is absorbed from the pellets after oral exposure (Jacobs 1968, Potter et al. 1973). Neither study was reported in sufficient detail to develop dose-response relationships.

Two reproduction studies investigated exposure to PVC-DDVP formulations. In one of the studies, swine were exposed to 5 or 25 mg/kg/day DDVP during the last 30 days of gestation (Stanton et al. 1979). Sows and fetuses were monitored for changes in ChE. Both plasma ChE and RBC AChE were inhibited in sows, and brain AChE was increased in fetuses. In a separate experiment conducted by these investigators, there were no significant effects on reproductive capacity in sows treated with 25 mg/kg/day DDVP during the last 30 days of gestation. In an abstract concerning DDVP encapsulated in PVC, Vogin (1971) reported that no adverse effects on reproduction or developmental parameters were observed in dams exposed to DDVP concentrations that did not cause maternal toxicity (up to 12 mg/kg). Maternal toxicity was evident in dams treated with 34 mg/kg. This abstract also employed exposures to PVC resin and dioctylphthalate to assess the potential developmental toxicity of inerts. No teratogenic effect was reported for any exposure regimen.

When DDVP pesticide strips were used in hospital wards, exposure of hospitalized adults and children, as well as healthy pregnant women and newborn babies, did not produce any significant effects on plasma ChE or RBC AChE activity. Exposures were estimated TWA concentrations of 0.05, 0.152, and 0.159 mg/m^3 based on 18 hours/day (Vigliani 1971). Only those subjects exposed 24 hours/day to concentrations above 0.1 mg/m^3 or patients with liver insufficiency showed a moderate decrease in plasma ChE activity (Cavagna et al. 1969). Cavagna et al. (1969) also calculated DDVP inhalation exposure doses (based on inhalation volumes of 10 m^3/day for adults and 1.4 m^3/day for children and continuous exposures) that would be required to produce a significant reduction in plasma ChE activity (25–54% reduction in activity) for healthy adults and children (approximately 0.03 mg/kg-day) and adults and children with liver insufficiency (approximately 0.006 mg/kg-day). Note that these exposure doses are not anticipated to produce signs or symptoms of cholinesterase inhibition (Cavagna et al. 1969). No significant effects on plasma ChE or RBC AChE activity were observed in people exposed to the recommended rate of one strip per 30 m^3 in their homes over a period of 6 months, even when the strips were replaced at shorter intervals than that normally recommended (Zavon and Kindel 1966). The maximum average concentration in the air of the homes was approximately 0.1 mg/m^3 (WHO 1989). In factory workers exposed to an average of 0.7 mg/m^3 for 8 months, significant inhibition of plasma ChE and RBC AChE activity was found (WHO 1989).

In a study evaluating the effects of 30 minutes of dermal exposure to a DDVP pest strip on AChE activity, no dermal effects were noted in 21 individuals (Zavon and Kindel 1966). Zavon and Kindel (1966) also reported no inhibition of plasma or erythrocyte cholinesterase from the 30 minute dermal exposure as well as 5 consecutive days of 30 minutes of continuous dermal exposure to DDVP resin strips. EPA (1981) provides a summary or exposure incidents involving DDVP in the general public. The reports involving DDVP-impregnated resin strips involved dermal contact which largely resulted in DDVP-induced allergic reactions or contact dermatitis (this is consistent with the effects of DDVP reported in dermal contact bioassays as described in Section 3.1.12). Flea collar dermatitis (primary contact dermatitis) has been reported in dogs and cats wearing DDVP-impregnated PVC flea collars (Muller 1970), and four people who handled dogs wearing flea collars containing 9–10% DDVP developed contact dermatitis (patch tests

using 0.25–1% DDVP in these individuals were positive). The data suggest that a very small proportion of the general population is susceptible to dermal irritation by DDVP (WHO 1989).

3.2. EXPOSURE ASSESSMENT

3.2.1. Overview.

Under normal conditions, exposure to both workers and members of the general public should be negligible. Workers will handle strips only during the assembly of milk carton traps. If workers wear gloves and assemble the traps outdoors or in very well ventilated rooms, both inhalation and dermal exposures should be negligible. Inhalation exposure to DDVP during transport of the traps should also be negligible if the traps are not transported inside of the passenger compartments of vehicles. Worker exposures will also be limited in most programs because foil wrapping in which the strip is distributed will not be removed until after the trap is transported to the field. Milk carton traps will generally be placed about four feet above the ground and exposure of members of the general public to DDVP contained in the milk carton traps should also be negligible except in the case of intensional tampering.

Notwithstanding the above assertions, exposure assessments are developed for workers who do not use gloves in the assembly of the milk carton traps and who assemble the traps indoors, remove the protective foil strip during assembly, and transport the traps in the passenger compartments of vehicles. All of these exposure scenarios should be considered atypical and some are extreme. The intent is to illustrate the consequences of mishandling or imprudent handling. During assembly, the central estimate of dermal exposures in workers not wearing gloves leads to an absorbed dose of about 0.0008 mg/kg with a range of about 0.0003 mg/kg to 0.004 mg/kg. Inhalation exposures in workers may be highly variable depending on the ventilation rates in an enclosed space and the number of traps that are handled. Based on the handling and transport of 75 traps, inhalation exposures could reach up to about 0.6 mg/m^3 in an enclosed and unventilated room and up to about 1.8 mg/m^3 in the passenger compartment of a vehicle. These exposure assessments are based on several site and situation specific assumptions which are intended to reflect plausible upper bounds of exposures.

Exposure assessments are also developed for children who might come in contact with an accidentally discarded or misplaced strip. Estimated dermal doses are much higher than those for workers: a central estimate of about 0.02 mg/kg with a range of 0.003 mg/kg to 0.1 mg/kg. Oral exposures from a small child sucking on the pest strip are about a factor of 10 higher than dermal exposures: a central value of about 0.2 mg/kg with a range of 0.04 mg/kg to 0.6 mg/kg.

Under normal circumstances, the use of DDVP in PVC strips is not likely to result in contamination of water or other materials that might be consumed by members of the general public. Nonetheless, an exposure assessment is developed for the accidental contamination of a small pond by a pest strip. In this scenario, dose estimates range from about 0.000003 mg/kg to 0.00007 mg/kg with a central estimate of about 0.00001 mg/kg.

3.2.2. Workers

3.2.2.1. General Considerations – The EPA (2000a) concluded that human exposures would be negligible from DDVP-impregnated strips in insect traps (such as those used in USDA programs). Consequently, the EPA (2000a) did not quantitatively assess the exposure or

potential risks posed by the use of PVC formulations of DDVP for any route of exposure. While this may be a reasonable approach, the current risk assessment develops quantitative exposure assessments for both workers and the general public that could occur in cases of poor handling practices.

The milk carton traps can be assembled in two stages. The most time consuming stage is the carton assembly, in which two pre-cut perforated pieces of heavy waxed paper, similar to those used in milk cartons, are configured. In the second stage, the DDVP strip and disparlure wick are attached to the twist tie, and the twist tie is placed in the trap. The second stage should proceed much more rapidly than the first. During assembly, two routes of exposure may be significant, inhalation and dermal. As discussed in the program description (Section 2.2), however, both routes of exposure will be negligible if proper handling procedures are followed (that is, if the strips are installed outdoors or in a well ventilated area, if foil wrapping in which the strip is distributed is removed until after the trap is transported, and dermal contact with the strip is avoided).

3.2.2.2. Inhalation Exposures – During normal use and assembly, either outdoors or in well ventilated areas, inhalation exposures to DDVP should be negligible. The material safety data sheet for VaporTape II (Hercon 1993) calls for local exhaust and respirators under conditions of continuous handling. Estimates of concentrations of DDVP in air from release of DDVP by VaporTape strips under different conditions of ventilation can be based on estimates of release rates (Hercon 1994) and a more general air model for DDVP pest strips proposed by Gillett et al. (1972a).

Hercon (1994) conducted a study on the release of DDVP from Vaportape II strips. In this study, two samples (referred to as **A** and **B**) were weighed and assayed for DDVP at various intervals for up to 12 weeks after placement outdoors. The results, expressed as the proportion of DDVP remaining in the strip at various intervals, are detailed in Worksheet A01. As also detailed in Worksheet A01, the release data fit a first order model extremely well with an adjusted squared correlation coefficient of 0.97 and a p-value of 2×10^{-23}. The estimated first-order release coefficient is 0.04 day^{-1} with very narrow confidence intervals – i.e., 0.037 to 0.043 day^{-1}.

Gillett et al. (1972a) proposed the following model for estimating concentrations of DDVP in air from the release of DDVP from pest strips:

$$C_t = \frac{8}{\pi^2}\,\frac{M_0}{Va(1+\gamma)}\,\frac{\exp(-\lambda t) - \exp\left(\frac{-(kRH + \frac{At}{Va})}{1+\gamma}\,t\right)}{\frac{(kRH + \frac{At}{Va})}{\lambda\,(1+\gamma) - 1}} \qquad \text{(Eq. 3-1)}$$

The terms in the above equation are defined as follows:

t	time after start of release
C_t	concentration of DDVP in air at time, *t* (days)
M_0	mass of DDVP in strip or strips at time zero (mg)
Va	volume of room or other space (m^3)
γ	apparent adsorption coefficient of DDVP on to surfaces
exp(***x***)	the exponential function, e^x, where ***e*** is the constant 2.718 and ***x*** is any numeric expression
λ	first-order release rate constant ($days^{-1}$)
RH	relative humidity (proportion)
A_t	air flow rate (m^3/day)
k	first-order vapor phase hydrolysis rate ($days^{-1}$)

The parameters used in the model are summarized in Table 3-2. The fit of the Gillett et al. (1972a) model to the data from Slomka (1970) using the apparent adsorption coefficient (γ) of 37.5 is illustrated in Figure 3-1 (which is in turn taken from Worksheet A02b). Technical details of the application of the model and optimization of the model parameter for adsorption (γ) are given in Appendix 1.

For the current risk assessment, two scenarios are considered for inhalation exposures of workers to DDVP: assembly of traps with strips in a garage and driving in a vehicle containing assembled traps with the strips. Both scenarios assume that the worker has removed the protective foil from the strip during assembly of the trap. These exposure scenarios are detailed in Worksheets A03a (garage) and A03b (vehicle). It should be noted that these exposure assessments are based on a number of plausible but conservative exposure assumptions – i.e., number of traps assembled or transported, volume of the space in which the traps are assembled or transported, and the ventilation rates of these spaces. The worksheets in which these exposure assessments are given are designed so that these parameters may be varied and applied to specific uses of the DDVP strips in specific USDA programs.

A major factor in exposure will be the number of traps that are assembled. In the previous risk assessment (USDA 1995a), it was assumed that a workers would assemble up to 75 traps at a time. No more recent information has been encountered on the number of traps that might be assembled by a worker or workers and the value of 75 traps is maintained in the current risk assessment.

For exposures in a garage involving the assembly of the milk carton traps, the dimensions of the garage are assumed to be 1,500 ft^3 (10 feet · 10 feet · 15 feet) or 42.48 m^3 [1 ft^3=0.02832 m^3]. For the exposure assessment involving transport of the strips in a vehicle, the volume of the

driving cabin is assumed to be 160 ft^3 (8 feet · 5 feet · 4 feet) or 4.5 m^3. Again, these assumptions are somewhat arbitrary but are identical to the assumption used in the previous risk assessment (USDA 1995a).

The other major assumptions used in these exposure scenarios involve ventilation rates and release rates. The release rate is taken as 0.04 day^{-1} from the study by Hercon (1994) discussed above and detailed in Worksheet A01. It should be noted that the study by Hercon (1994) was conducted outdoors over a period of 12 weeks. Hercon (1994) does not specify the average temperature or range of temperatures. As discussed in Gillett et al. (1972a), the release rate of DDVP from PVC test strips will increase with increasing temperature, doubling from a temperature of 25°C to 38°C. This variability is not explicitly incorporated into the model used in this risk assessment (Eq. 3-1) and release rates higher than 0.04 day^{-1} are possible at high ambient temperatures.

Ventilation rates are likely to be highly variable. In most cases, it is likely that the milk carton traps will be assembled outdoors and will be transported in a cargo area and not in the driving cabin. In such cases, inhalation exposure would likely be negligible. For the purpose of illustrating the consequence of assembling traps in a garage or similar structure or transporting assembled traps in a vehicle, three ventilation rates (number of air turnovers per day) are used for each scenario. Rates of 0 day^{-1} (no ventilation) and 60 day^{-1} (poor ventilation) are used in both scenarios. An additional rate of 300 day^{-1} is used in the garage scenario and an additional rate of 3000 $day^{-1}$is used in the vehicle scenario. These rates are referred to as *"Adequate"* in Worksheets A03a and A03b. As discussed further in Section 3.4.2, this term is used because these ventilation rates lead to concentrations in air that are about 0.1 mg/m^3, the chronic NOAEL from animal studies and the TLV recommended by ACGIH (2004).

As detailed in Worksheet A03a, the garage scenario models concentrations over a 24 hour period. This duration period is selected under the assumption that traps might be stored for a day prior to use. The modeled concentrations reach up to about 0.5 mg/m^3 for no ventilation and 0.3 mg/m^3 for poor ventilation. As noted above, peak concentrations of 0.1 mg/m^3 are obtained with a ventilation rate of about 300 day^{-1}. The vehicle scenario (Worksheet A03b) covers a period of only 6 hours. It is likely that the duration of transport would typically be much less. Peak concentrations are somewhat higher – 1.8 mg/m^3 for no ventilation and about 1.5 mg/m^3 for poor ventilation. It is unclear if the no ventilation or poor ventilation assumptions are reasonable for a vehicle. As discussed by Fedoruk and Kerger (2003), concentrations of volatile organic compounds in vehicles suggest that substantial air turnover rates are likely in vehicles even when the ventilation system is turned off and the windows are closed. Quantitative estimates of air turnover rates in vehicle passenger cabins, however, have not been encountered. Nonetheless, it seems that turnover rates of 0 day^{-1} or 60 day^{-1} will lead to overestimates of concentrations of DDVP in the air of passenger compartments. Adequate ventilation for a vehicle is defined as a turnover rate of 3000 day^{-1}, the rate required to reach a concentration in air of about 0.1 mg/m^3.

3.2.2.3. Dermal Exposures – For assessing the likelihood of systemic toxic effects from dermal exposures, such as handling a pest strip during assembly, some estimate of absorbed dose is necessary. The method for making such an assessment for DDVP test strips, however, is highly uncertain.

As an individual manipulates the strip, some material will be transferred to the surface of the skin. Some of the chemical will be absorbed and some will volatilize. Assuming that the nature of the manipulation is such that a film of DDVP is maintained on the contaminated surface, Fick's first law may be used to estimate absorption (U.S. EPA/ORD 1992). Fick's first law requires an estimation of the K_p in cm per hour, the concentration of the chemical in a solution in contact with the skin, the area of the body surface that is contaminated, and the duration of exposure. There is no experimentally determined K_p for DDVP. Based on structure-activity relationships proposed by the U.S. EPA/ORD (1992), K_p for DDVP is may be estimated at about 0.00090 cm/hour with a 95% confidence interval of 0.00061 cm/hr to 0.0013. Details of these calculations are given in Appendix 2.

In this and other similar scenarios considered in this risk assessment, the DDVP is not in solution; instead, the skin is in contact with neat or undiluted DDVP. Following the recommendations of U.S. EPA/ORD (1992), the functional concentration of DDVP on the surface of the skin is assumed to be the solubility of DDVP in water, 10 mg/mL (Table 2-2) – i.e., the concentration of DDVP in pore water of the skin will be limited by the solubility of the chemical in water.

For workers wearing gloves, dermal absorption will be negligible. For workers who do not wear gloves, it is possible that the tips of the fingers and perhaps other surfaces on the hands would be contaminated. The most likely surface for contamination would be the finger tips. The precise area that might be contaminated, however, is difficult to estimate. The finger tip of each digit will be taken as 1 cm^2, except for the thumb that will be taken as 2 cm^2. Thus, the total surface area of the finger tips of both hands will be taken as 12 cm^2. This value will be used to calculate both lower and central estimates of absorbed dose. To account for the potential contamination of other parts of the hand, the upper range of exposed surface area will be taken as 24 cm^2. The duration of exposure is difficult to estimate. Most of the time spent in assembling the milk carton trap will not involve the DDVP strip. For this exposure assessment, a central estimate of 0.5 hours of total contact time with the strip is used and the range is taken as 0.25 hours to 1 hour. As detailed in Worksheet B01a, the assumptions used in this exposure scenario lead to estimates of absorbed dose of about 0.0008 mg/kg with a range of about 0.0003 mg/kg to 0.004 mg/kg.

3.2.3. General Public

3.2.3.1. General Considerations – Milk carton traps contain the strip of Vaportape II attached to a twist tie or simply placed in the bottom of the trap. The DDVP strip can be accessed easily and removed. As summarized by U.S. EPA (2000a, p. 26), incidents involving contact with DDVP resin strips have been reported but these incidents account for only a small proportion of the total

incidents involving DDVP (1% or about 33 cases per year) and the reported incidents involving DDVP strips typically to do not lead to overt signs of toxicity that require medical treatment.

In the current risk assessment, two routes of exposure are considered for the general public: dermal contact and ingestion. Milk carton traps will generally be placed about four feet above the ground (Leonard 2004) and exposure of members of the general public to DDVP contained in the milk carton traps should also be negligible except in the case of intensional tampering. Although any member of the general public could tamper with a trap, incidents such as these seem to be more plausible for children, compared with adults. While the traps may be place out of the reach of young children, the potential for exposure to the DDVP strip could occur if traps were accidentally dislodged or misplaced. In addition, using children as the exposed group is conservative because dose estimates for children, in units of mg/kg body weight, will be higher than those for adults.

3.2.3.2. Dermal Contact – The exposure assessment for dermal contact with a VaporTape II strip is detailed in Worksheet B01b. This scenario is very similar to that for dermal contact in a worker (Worksheet B01a). The major differences involve body weight, the dermal surface area that is considered, and the duration of exposure. The body weight is taken as 13.3 kg, the standard value for a 2-3 year old child (U.S. EPA/ORD 1996). In this scenario, it is assumed that a young child comes in contact with a pest strip and holds the strip against the surface of the skin for a period of time. Thus, the exposed skin surface area is taken as the dimensions of the strip – i.e., 1" x 4" inches or about 26 cm^2). The duration of exposure must be set somewhat arbitrarily. It does not seem reasonable to assume that a 2-3 year old child would be unsupervised for a prolonged period of time. Consistent with the approach taken in the 1995 risk assessments (USDA 1995a), the central estimate of exposure will be taken as 1 hour with an upper range of 4 hours. In the current risk assessment, a lower range of 15 minutes (0.25 hours) is also used and may be a more reasonable estimate of a plausible duration of exposure. Other assumptions and calculations are identical to those in the corresponding worker exposure assessment (Worksheet B01a, Section 3.2.2.3). As indicated in Worksheet B01b, this exposure assessment for a young child handling a DDVP strip leads to an estimated dose of about 0.02 mg/kg with a range of 0.003 mg/kg to 0.1 mg/kg.

3.2.3.3. Oral Exposure to DDVP Strip – As with dermal exposure, it is unlikely that children would experience any oral exposure to DDVP strips. The strips are placed within the milk carton traps and 2-3 year old children will generally be closely supervised. Thus, this exposure assessment for oral exposure, as with the above scenario for dermal exposure, should be regarded as accidental.

An assessment of oral exposure might be based on incidental sucking on a pest strip. The amount of DDVP that a child might absorb will depend on the proportion of the strip that is in the mouth, the release rate of DDVP from the strip, and duration of the activity. The durations will be taken as the same as in the dermal exposure scenario, a central estimate of 1 hour with a range of 0.25 to 4 hours. The initial release rate will be taken as 0.015 $hour^{-1}$. This is calculated

from the study by Slomka and Hine (1981) which indicated that approximately 30% of the DDVP was released in the first 24 hours – i.e., k = -ln(1-f)/t = ln(1-0.3)/24 hours = 0.01486 $hour^{-1}$.]. The proportion of the strip that might be in the mouth of the child will be taken as 0.25 – i.e., a area of about 1 square inch. As indicated in Worksheet B02, this exposure assessment results in estimates of absorbed doses of about 0.2 mg/kg with a range of 0.04 mg/kg to 0.6 mg/kg. This scenario would also involve some dermal exposure. As indicated in Section 3.4, any plausible dermal exposure would likely be much less than the oral exposure and would have no impact on the characterization of risk.

3.2.3.4. Oral Exposure to Contaminated Water – Under normal circumstances, the use of DDVP in PVC strips is not likely to result in contamination of water or other materials that might be consumed by members of the general public. In the recent risk assessment by U.S. EPA (2000a), no exposure assessment for water contamination by DDVP in PVC formulations is presented.

The approach taken by U.S. EPA (2000a) seems reasonable in that the slow release DDVP from the test strip and rapid hydrolysis of DDVP in water is likely to limit the concentration of DDVP in ambient water. For example, the halftimes for the hydrolysis of DDVP in water range from about 11.65 days at pH 5 to 0.88 days at pH 9, with a hydrolysis halftime of 5.19 days at pH 7 (U.S. EPA 1999a, p. 3). These values correspond to hydrolysis rates – i.e., $k = \ln(2)/t_{50}$ – of 0.06 day^{-1} [pH 5], 0.13 day^{-1} [pH 7], and 0.78 day^{-1} [pH 9]. All of these hydrolysis rates are more rapid than the release rate of DDVP in air from the Hercon pest strip – i.e., 0.04 day^{-1} as discussed in Section 3.2.2.2.

For this risk assessment, the assumption will be made that a VaporTape strip accidentally contaminates a small pond (e.g., it is inadvertently dropped into a pond during placement of a trap or a trap is dislodged and falls or is blown into a pond). No data are available to directly estimate the amount of DDVP that might be released over the course of a single day. For this exposure assessment, the assumption will be made that 30% of the DDVP in a fresh strip might be released over the course of a single day. This is based on the study by Slomka and Hine (1981), discussed in Section 3.1.4, in which 30% of the DDVP was released from a pest strip into gastric juices over a 24 hour period. Thus, the central estimate of the amount of DDVP in water is taken as 177 mg [590 mg × 0.3]. The upper range of the amount of DDVP in water is taken simply as the amount of DDVP in a new pest strip – 590 mg. The selection of a lower is somewhat arbitrary and a value of 10% or 59 mg is used. Other details of this exposure assessment are given in Worksheet B03 and involve standard assumptions concerning the size of the pond and the amount of water that might be consumed. These assumptions are standard in risk assessments (SERA 2001). As detailed in Worksheet B02, dose estimates range from about 0.000003 mg/kg to 0.00007 mg/kg with a central estimate of about 0.00001 mg/kg.

As noted above, this very simple exposure scenario does not consider the degradation or dissipation of DDVP. As discussed further in Section 3.4, however, this exposure assessment leads to concentrations in water that are far below a level of concern. Thus, the overestimates of

concentrations in water developed in this section have no impact on the risk characterization for potential effects in humans.

3.3. DOSE-RESPONSE ASSESSMENT

3.3.1. Overview

The extensive toxicology data base has been evaluated by a number of governmental organizations including the U.S. EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration, and the World Health Organization. Following the approach taken in most USDA risk assessments, these sources are used for selecting levels of acceptable exposure. Because all of the scenarios considered in this risk assessment involve only acute exposures, only acute exposure criteria are considered.

For both oral and dermal exposures, the acute RfD established by the U.S. EPA, 0.0017 mg/kg, is used for the risk characterization. This is based on an acute oral NOAEL of 0.5 mg/kg from a study in rats with the application of an uncertainty factor of 300. Acute exposure criteria proposed by other groups are comparable to but somewhat higher than the acute RfD. Because some of the accidental acute exposures may substantially exceed the acute RfD, some attempt is made to characterize the consequences of high oral exposures. A human NOAEL of 1 mg/kg for AChE inhibition has been identified. While this NOAEL is not used to modify the acute RfD, it can be used to assess plausible consequences of exceeding the RfD. The human data on DDVP, although extensive, are not sufficient to identify a minimal lethal dose. For the current risk assessment, the lowest reported lethal dose (16 mg/kg) is used to assess the plausibility of observing serious adverse effects in cases of accidental over-exposure to DDVP.

A number of inhalation criteria for DDVP are available. Since potentially significant inhalation exposures are likely only in workers, the occupational exposure criterion of 0.1 mg/m^3 proposed by American Conference of Governmental Industrial Hygienists is used. This value is a factor of 10 below the occupational criteria proposed by NIOSH and OSHA.

3.3.2. Acute Exposures

3.3.2.1. Acute Oral – As summarized in Section 3.1.4, the U.S. EPA (2000a) bases the acute oral RfD for DDVP on the study by Bast et al. (1997) in which no effects, including assays for alterations in behavior, were noted at 0.5 mg/kg but neurological effects related to AChE inhibition were noted at 35 mg/kg. In deriving the acute RfD, the U.S. EPA (2000a, p. 18) used an uncertainty factor of 300 and recommended an acute RfD of 0.0017 mg/kg/day [0.5 mg/kg ÷ 300 = 0.0017 mg/kg]. ATSDR (1997) has recommended a somewhat higher acute oral minimal risk level (MRL) – a value that is analogous to the RfD – of 0.004 mg/kg/day. This is based on a 14-day LOAEL of 4 mg/kg/day in which brain AChE was inhibited by 44%. The MRL was calculated using an uncertainty factor of 1000 (ATSDR 1997, pp. 83-84).

As also discussed in Section 3.1.4, the study by Stanton et al. (1979) suggests that DDVP in a PVC formulation will be much less toxic than unformulated DDVP. The extent of the difference in toxicity, however, is difficult to quantify. For unformulated DDVP, the LD_{50} value was 157 (113–227) mg/kg with no mortality observed at 56 mg/kg. For the DDVP-PVC formulation, no deaths occurred at doses of up to 1000 mg/kg, although signs of toxicity consistent with AChE

inhibition were observed at doses of 320 mg/kg and 1000 mg/kg using the DDVP-PVC formulation. No tremors or salivation were observed at doses of 240 or 180 mg/kg of the DDVP-PVC formulation. Stanton et al. (1979) do not provide comparative data the extent of AChE inhibition in unformulated DDVP and the DDVP-PVC formulation.

As detailed in Section 3.2.3.3, estimates of acute oral exposure for a small child sucking on a pest strip are far above the acute RfD of 0.0017 mg/kg. Thus, the potential for more severe effects must be considered. Based on the recent study by Gledhill (1997), no changes in AChE activity and no signs of toxicity were seen in a group of 6 men administered DDVP in a gelatin capsule at an approximate dose of 1 mg/kg. This is a factor of about 600 above the acute oral RfD. This study is unpublished and was submitted to the U.S. EPA by a registrant. In the U.S. EPA (2000a) human health risk assessment, the MRID number for this study is cited but the results of the study are not discussed specifically. For the current risk assessment, a dose of 1 mg/kg from the Gledhill (1997) study is used qualitatively to characterize the risks of exposures that are not likely to produce clinically significant effects.

For many pesticides, exposures that would be associated with severe and possibly fatal effects often can be estimated from poisoning reports. Most reports of fatal exposures to DDVP, however, do not provide sufficient information to estimate a lethal dose in humans. An approximate lethal dose, however, can be estimated from the study by Shimizu et al. (1996), which reports a fatal exposure of a 62.5 kg woman who intentionally consumed a pesticide formulation containing 75% DDVP and 25% xylene. While xylene is also a toxic agent, the oral LD_{50} for xylene in rodents is in the range of 3,500 to 8,600 mg/kg (ATSDR, 1995, p. 59). This is much greater than the reported LD_{50} values for DDVP in rodents – i.e., in the range of 25 to 300 mg/kg as summarized in Section 3.14. The amount of DDVP that the woman ingested is unclear. About 300 grams (300,000 mg) of DDVP were found in the stomach and Shimizu et al. (1996, p. 65) estimate that the woman probably absorbed about 1,000 mg/kg. Taking the estimated absorbed dose, a lethal dose for humans can be estimated at about 16 mg/kg [1,000 mg ÷ 62.5 kg]. This is not necessarily a minimum lethal dose – i.e., the individual might have died after ingesting a lesser amount of DDVP. Other reported poisoning cases involving DDVP (e.g., ATSDR 1997; WHO 1988) do not have sufficient information to estimate a minimum lethal dose for humans.

3.3.2.2. Acute Dermal – For short-term dermal exposure, the U.S. EPA (2000a) recommends an oral NOAEL of 0.1 mg/kg with a margin of exposure of 300 for residential exposure and 100 for occupational exposure. This would correspond to an acute RfD of 0.00033 mg/kg for residential exposures and 0.001 mg/kg for occupational exposures. The U.S. EPA (2000a) recommends using this value with dermal deposition data and an assumed dermal absorption fraction of 11%.

These values will not be used in the current risk assessment. Following the general approach used in other risk assessments prepared for USDA (SERA 2001), the absorbed doses estimated in Section 3.2.2.3 for workers and Section 3.2.3.2 for the general public will be used with the acute oral RfD of 0.0017 mg/kg/day. The general rationale for this approach is given in SERA (2001).

For DDVP in particular, the standard approach used in USDA risk assessments is necessary because the incidental or accidental handling of VaporTape strips does lead to estimates of dermal deposition.

3.3.2.3. Acute Inhalation – For short-term inhalation exposures, the U.S. EPA (2000a) recommends the same acute toxicity value used for dermal exposures. Given the extensive inhalation toxicity data available for DDVP, the rationale for this approach is unclear. The U.S. EPA (1994) has derived an inhalation RfC for DDVP of 0.0005 mg/m^3. This is based on an animal NOAEL of 0.05 mg/m^3 with a corresponding LOAEL of 0.48 mg/m^3 from a two year exposure study in rats. As noted below, this chronic RfD is not relevant to the current risk assessment because no chronic exposures are anticipated. In addition to this value recommended by EPA, ATSDR (1997) has recommended an acute minimum risk level (MRL) of 0.002 ppm for DDVP which corresponds to a concentration of about 0.018 mg/m^3 – i.e., 1 ppm = 9.04 mg/m^3. This value is intended to be applied to exposure periods of up to 14 days.

As detailed in Section 3.2.2.2, all exposures for workers are short-term. OSHA and NIOSH share responsibility for proposing exposure criteria to protect workers. OSHA provides regulatory enforcement (exposure standards) and NIOSH provides science based exposure criteria (NIOSH 2002). For DDVP, NIOSH recommends a time-weighted average exposure limit of 1 mg/m^3 and this value has been adopted by OSHA (NIOSH 2002). Another group involved in recommending criteria for occupational exposure is ACGIH (2004), which recommended a lower occupational exposure limit of 0.1 mg/m^3 (ACGIH 1991). This lower value appears to have been selected by ACGIH (1991) based on an unpublished report to the TLV committee that exposures to 1 mg/m^3 over the course of a workday resulted in an inhibition of plasma AChE of 20%-25% in a group of workers (ACGIH 1991, p. 446). The documentation for the TLV, however, does not suggest that any adverse health effects were observed. The lower and more protective value of 0.1 mg/m^3 is adopted in the current risk assessment for the protection of workers during inhalation exposures.

3.3.3. Chronic Exposures

The U.S. EPA (2002), ATSDR (1997), and WHO (1998) have all recommended various criteria for chronic exposure to DDVP by oral, dermal, and/or inhalation routes. Because none of the exposure scenarios in this risk assessment involve chronic or subchronic exposures, these recommendations are not considered in the current risk assessment. While the previous USDA risk assessment (USDA 1995a) considered the potential cancer risks associated with exposure to DDVP, this approach is not adopted in the current risk assessment. As discussed in Section 3.1.10, the recent re-evaluation of the cancer data on DDVP (U.S. EPA 2000a,b) has concluded that the data available on the carcinogenicity of DDVP is not sufficient for quantitative risk assessment.

3.4. RISK CHARACTERIZATION

3.4.1. Overview

The quantitative risk characterizations for workers and members of the general public are summarized in Table 3-3. This table is taken directly from Worksheet C02 and is included in the body of the risk assessment only for convenience.

In most cases, exposures to both workers and members of the general public should be negligible. If workers take prudent steps to limit both dermal and inhalation exposures, the likelihood of exposures to DDVP reaching a level of concern appears to be very low. Similarly, members of the general public should not be exposed to substantial amounts of DDVP. The DDVP is contained within a PVC strip to insure that the active ingredient is slowly released over a long period of time. The strip, in turn, is placed within a trap and the trap is placed in areas that will not be generally accessed except in the case of intentional tampering or trap monitoring.

Nonetheless, this risk assessment develops exposure scenarios for both workers and members of the general pubic that are intended to illustrate the potential effects of mishandling or tampering with DDVP strips. For workers, the greatest risks are associated with inhalation exposures from assembling the traps in enclosed and poorly ventilated spaces or transporting the traps in the passenger compartments of vehicles. These risks can be readily avoided. Dermal exposures can also lead to lesser but sill undesirable levels of exposure. For members of the general public, all of the exposure scenarios are accidental and some are extreme. The most likely of these is the accidental contamination of a small body of water. This scenario leads to exposures that are below the level of concern by a factor of about 25. If a child were to come into contact with a DDVP strip, however, both dermal and oral exposures could substantially exceed a level of concern. While such exposures should clearly be avoided, it does not seem likely that frank signs of toxicity would be observed. This is consistent with human experience in the use of DDVP resin strips.

3.4.2. Workers

The risk characterization for workers is highly dependant on how the worker handles the DDVP strip during assembly of the milk carton trap. If the trap is assembled outdoors and if the worker wears protective gloves during the assembly of the trap, both dermal and inhalation exposures as well as consequent risk should be negligible. Whether or not this is common practice is unclear. The MSDS states that gloves (vinyl, latex, or rubber) should be worn if the strip is handled for prolonged periods of time (Hercon 1993). The product label (Hercon 2004) indicates that hands should be washed thoroughly after handling the pest strip. In addition, the Gypsy Moth Program Manual (USDA 2001, p. E-6) recommends that workers "*use the outer package or rubber gloves to handle the insecticide strip. Handle the insecticide strip as little as possible*". If these recommendations are followed, direct dermal exposure to DDVP should be negligible.

If workers assemble traps in enclosed areas or do not use protective gloves during the assembly of traps or take other measures to prevent dermal exposure, it is plausible that exposures will exceed a level of concern. As summarized in Table 3-3, the potential for undesirable inhalation

exposures is substantial – i.e., risk quotients up to 18 – if the traps are assembled or transported in areas with poor or no ventilation. As discussed in Section 3.2.2.2 and detailed further in Appendix 1, these exposure assessments are based on a large number of site and situation specific factors – i.e., the volume of the room or area in which the strips are assembled or transported, the number of strips that are involved, and the ventilation rates of the area in which exposure occurs. Thus, if the pest strips are assembled indoors, it would be prudent to modify Worksheet A03a and ensure that the local conditions would likely lead to air concentrations that are below the ACGIH (1991) TLV of 0.1 mg/m^3.

It should be noted that the risk quotients associated with transport of the pest strips in the passenger compartment of a vehicle are substantially higher than risk quotients during assembly of the traps in a room. High ventilation rates – i.e., 3000 air turnovers per day or about 2 air turnovers per minute as detailed in Worksheet A03b – could probably be achieved in a vehicle by rolling down the window and this would reduce the inhalation exposure to below the level of concern. Nonetheless, transporting DDVP or any volatile neurotoxic agent in the passenger compartment of a vehicle is clearly imprudent and should be avoided.

Dermal exposure is of lesser and only modest concern based on the exposure assessments. As noted in Table 3-3, the acute RfD is modestly exceeded – i.e., a hazard quotient of 3 – at the upper range of estimated exposures if workers do not wear gloves . This risk quotient is associated with a dose of about 0.005 mg/kg bw. It seems unlikely that any adverse effects would be experienced at this dose level, which is a factor of 200 below the human NOAEL of 1 mg/kg [1 mg/kg ÷ 0.005 mg/kg = 200] and a factor of 3,200 below the lowest reported lethal dose in humans [16 mg/kg ÷ 0.005 mg/kg = 3200]. While there are uncertainties with the exposure assessment on which the risk quotient of 3 is based, contamination of the skin in workers not wearing gloves seems to be highly likely. As noted in the product label for the VaporTape II strip: "*After prolonged storage, a small amount of liquid may form on the strip*" (Hercon 2004). This liquid would presumably contain DDVP which would contaminate the surface of the exposed skin. It is also worth noting that the exposure assessment assumes that only the tips of the fingers are contaminated and that the duration of exposure is only 15 minutes to 1 hour. If the worker were to contaminate a greater area of the skin or to spend a longer period of time assembling the traps, the estimated doses would be greater.

3.4.3. General Public

The nature of risks to the general public is substantially different from those to workers. As detailed in the previous section, undesirable levels of exposure are plausible for workers if sensible measures are not taken to limit exposure. For members of the general public, essentially no significant exposures are plausible. The accidental contamination of a small pond with a pest strip (Worksheet B02) is probably the most likely exposure scenario. As indicated in Table 3-3, this exposure scenario leads to levels of risk that a very low – i.e., the highest hazard quotient is 0.04, below the level of concern by a factor of 25.

The probability of a child tampering with a trap is low because the traps will not generally be placed in areas that the general public will frequent and will be placed so that the traps are not easily accessible to children. Thus, the exposure scenarios involving a child either tampering with a trap or otherwise coming into direct contact with a DDVP strip appear to be highly unlikely. As illustrated in Table 3-3, dermal exposures would lead to risk quotients of up to 60. These exposures would be associated with doses of up to about 0.1 mg/kg (Worksheet B01b). This dose is below the lowest reported lethal dose in humans by a factor of about 160 [16 mg/kg ÷ 0.1 mg/kg], below the acute human NOAEL of 1 mg/kg by a factor of 10, and below the acute animal NOAEL of 0.5 mg/kg by a factor 5. Thus, while this type of exposure would be considered unacceptable, the plausibility of observing toxic effects seems remote.

The plausibility and consequences of oral exposures for a child tampering with a DDVP strip are very difficult to assess. The unpleasant taste and smell of the pest strip should help to decrease the amount of exposure; however, there are reported cases of child poisoning by pest strips containing DDVP, although none of the exposures have been fatal. Nonetheless, the oral exposure scenarios developed in this risk assessment lead to the highest risk quotients for DDVP, a central estimate of 97 with a range of 24 to 380 (Table 3-3 and Worksheet C02). These risk quotients are associated with doses of about 0.2 mg/kg with a range of about 0.04 mg/k to 0.6 mg/kg. As with the dermal exposures for a small child, these exposures should be clearly regarded as unacceptable. Nonetheless, it is not clear that any significant adverse effects would be observed since the dose estimates are below the human NOAEL of 1 mg/kg and the upper range of exposure is below the lowest reported lethal dose by a factor of over 25 [16 mg/kg ÷ 0.6 = 26.7]. Thus, while these exposure scenarios may be considered extreme and could warrant prompt medical attention as a precautionary measure, it is possible that no serious adverse effects would be observed. This risk characterization is consistent with the assessment of incidents involving exposures to DDVP resin strips – *"exposure to resin strips usually do not involve any significant acute symptoms that would require medical treatment"* (U.S. EPA 2000a, p. 26).

3.4.4. Sensitive Subgroups

Children are of primary concern to this risk assessment. As noted above, imprudent handling of a DDVP impregnated strip would most likely involve a child. In addition, very young children (that is, infants less than 6-months old) may be at special risk because they have incompletely developed AChE systems and immature livers (ATSDR 1993). Several other groups may be at special risk to all cholinesterase inhibiting compounds, including DDVP. A small proportion of the population has an atypical variant of plasma cholinesterase. This condition is known to make these individuals sensitive to succinylcholine and may make them more susceptible to exposure to DDVP and other AChE inhibitors. Other groups known to have low plasma AChE levels are long-distance runners, women in early stages of pregnancy, women using birth control pills, individuals with advanced liver disease, alcoholics, individuals with poor nutritional status, and individuals with skin diseases. Asthmatics may also be at special risk because DDVP may induce or exacerbate respiratory distress (ATSDR 1993).

3.4.5. Connected Actions

There are no data regarding the effects of exposure to DDVP combined with exposure to the other agents used to control the gypsy moth or the gypsy moth itself. Inhibition of AChE is the most sensitive effect of DDVP. This effect is not associated with exposure to the other control agents or exposure to the gypsy moth. Therefore, there is no plausible basis for assuming that the effects of exposure to DDVP and any or all of the other control agents or the gypsy moth will be additive.

Exposure to other compounds that inhibit AChE are likely to lead to an additive effect with DDVP. The most common examples include any other organophosphate or carbamate pesticides (ATSDR 1993; Gallo and Lawryk 1991). Thus, if members of the general public or workers use other organophosphate pesticides to the extent that AChE activity is substantially inhibited, they could be at increased risk if exposed to significant levels of DDVP.

No studies were located regarding toxicological interactions between Vaportape II and other chemicals. There are several studies regarding combined exposures to commercial grade DDVP and other chemicals, all of which involve animal exposure, and, in most cases, overtly neurotoxic doses of DDVP administered by acute injections. Of the few studies regarding oral or dermal exposure to DDVP, most involve acute durations of exposure and do not provide adequate evidence of toxicological interactions. Nevertheless, some of these studies are discussed here because they concern certain interactions that are generally associated with organophosphate insecticides as a class and because they are relevant to the issue of whether or not such interactions involving DDVP are plausible.

Phenothiazine-derived drugs such as chlorpromazine have been shown to enhance the toxicity of acutely administered organophosphate insecticides such as parathion (Calabrese 1991). The mechanism for this enhancement is not known and may involve altered metabolic activation or deactivation of the organophosphate. The interaction between topically applied DDVP/Crotoxyphos insecticide and orally administered phenothiazine anthelmintic has been studied to a limited extent in livestock, and no obvious interactions have been observed. A series of case studies were reported in which young cattle were treated with topical doses of various organophosphate insecticides at the end of a 30-day oral treatment with phenothiazine anthelmintic, followed by DDVP/Crotoxyphos insecticide 1 month later. There was no evidence of an interaction between the phenothiazine and DDVP/Crotoxyphos insecticide (Schlinke and Palmer 1973). In a more controlled study, lambs were treated orally with phenothiazine antihelmentic (12.5 g initially and 4 days later with 6.25 g every 3 days for nine treatments) or topical application of an emulsifiable mixture of 2.3% DDVP and 10% Crotoxyphos (1,550 mL of 0.25% emulsion sprayed every 2 weeks for three applications) or both. Erythrocyte acetylcholinesterase inhibition and clinical signs of acetylcholinesterase inhibition occurred within 40 minutes after each DDVP/Crotoxyphos mixture spray; the severity of the effects was not affected by the concurrent phenothiazine treatment (Mohammad and St. Omer 1983, 1985).

Because of their ability to inhibit acetylcholinesterase and thereby alter the metabolism and deactivation of acetylcholine, organophosphate insecticides are expected to interact with drugs that mimic the effect of acetylcholine (cholinergic drugs) or that block the effects of acetylcholine (anticholinergic drugs). In fact, the anticholinergic drug, atropine, is indicated for treatment of severe cholinergic symptoms of organophosphate insecticide toxicity. Because both cholinergic and anticholinergic drugs have many other uses, inadvertent interactions in which the organophosphate insecticide alters the effect of the drug also should be considered. Acute interactions of this type involving DDVP have been studied only to a limited extent in animal models of peripheral cholinergic control mechanisms. In one such study, the anticholinergic drug, atropine, was administered to dogs (0.022 mg/kg by intramuscular injection) 90 minutes after an acute oral dose of 60 mg/kg DDVP, and the heart rate was monitored for cholinergic (decreased rate) and anticholinergic (increased rate) effects. Although the DDVP dose alone had no effect on heart rate, it did attenuate the acceleration of the heart rate caused by atropine. The DDVP dose decreased plasma and erythrocyte cholinesterase by approximately 50% (Dellinger et al. 1987). This study suggests that interactions in which DDVP affects the actions of anticholinergic drugs (for example, atropine, scopolamine, belladonna alkaloids) are plausible; however, there is no evidence of such interactions in humans.

Chemicals that inhibit carboxyesterases such as the non-organophosphate insecticide, triorthotolyl phosphate (TOTP), have been shown to enhance the toxicity of certain organophosphate insecticides. Inhibition of carboxyesterases may be a mechanism by which certain organophosphate insecticides act synergistically (Calabrese 1991). The significance of this interaction mechanism to DDVP toxicity has not been thoroughly investigated. In a study using mice, an acute intraperitoneal dose of TOTP 3 days before DDVP treatment enhanced the toxicity of an acute intraperitoneal dose of either malaoxon or paraoxon but did not alter the toxicity of an intraperitoneal dose of DDVP. Dieldrin, administered orally 4 days before sacrifice, increased liver carboxyesterase activity but had no effect on the toxicity of subsequently administered DDVP (Ehrich and Cohen 1977). This study suggests that carboxyesterase inhibitors may have a more significant effect on malaoxon and paraoxon toxicity than on DDVP toxicity.

The interaction of DDVP with other commonly occurring chemicals in the environment has not been well studied. In rats, pretreatment with acetaminophen, a common analgesic, had no effect on the acute toxicity of DDVP (Costa and Murphy 1984).

Toxicological interactions of DDVP have not been studied extensively or well enough to be of use in quantitative risk assessment. The few studies described here suggest that certain interactions typical of the organophosphate insecticides as a class (for example, anticholinergic agents) are plausible for DDVP. Nevertheless, there is no evidence that such interactions actually occur in humans. Furthermore, the studies regarding those kinds of interactions in animals have examined single exposures and have focused only on the acute anticholinesterase activity as the toxic endpoint (usually assessed by measurements of plasma or blood cholinesterase or cholinergic symptoms). There need to be more complete interaction bioassays

that examine multiple dose levels and durations, and more complete assessments of toxicity if risks related to possible interactions are to be assessed.

3.4.6. Cumulative Effects

Cumulative effects associated with DDVP exposures might be associated with repeated exposures during a single season or repeated exposures over several seasons. For the general public, the only substantial exposures will occur from tampering with traps containing DDVP. Such incidents have not been reported despite the long use of DDVP in traps for the gypsy moth as well as other species. These scenarios are considered in this risk assessment as accidental exposures, which occur infrequently. Consequently, it does not seem reasonable to expect that the same person will be involved repeatedly in such unusual exposures.

Workers, on the other hand, may be exposed repeatedly to DDVP if they are involved in the assembly and placement of traps over a period of several weeks. Such exposures, however, are encompassed by the current risk assessment. For inhalation exposures, the risk is characterized using the TLV (ACGIH 1991). The TLV is intended to be protective of exposures that occur during a typical career (for example, 8 hours/day, 5 days/week, for 20 years).

For some organophosphates, concern about cumulative effects is diminished because studies have demonstrated tolerance to repeated exposures (Gallo and Lawryk 1991). This tolerance has not been demonstrated for exposure to DDVP. As is true for exposures involving the general public, concern for repeated exposures is diminished because, under normal handling conditions, substantial levels of exposure are not anticipated.

4. ECOLOGICAL RISK ASSESSMENT

4.1. HAZARD IDENTIFICATION

4.1.1. Overview

As described in Section 3.1.2., DDVP is an organophosphate insecticide. DDVP inhibits acetylcholinesterase (AChE) activity, resulting in overstimulation of cholinergic neurons. Inhibition of this enzyme in mammalian systems produces a variety of systemic effects, including salivation, urination, lacrimation, convulsions, increased bronchial secretions, respiratory depression, and even death. DDVP is readily absorbed by the oral, dermal, and inhalation routes of exposure. Because the target enzyme (cholinesterase) for DDVP is common to mammals, fish, fowl, and insects, toxicity due to DDVP exposure can result in all of these species. By contrast, DDVP exhibits low toxicity to plants.

The available data suggest that invertebrates are more sensitive to DDVP than other organisms. For example, the oral LD_{50} in honey bees is 0.29 µg/g bee, and the topical LD_{50} is 0.65 µg/g bee. DDVP is also toxic to birds with an oral LD_{50} value of < 10 mg/kg for the most sensitive species. Short-term repeat dose studies in mammals found that oral exposures to doses below about 0.5 mg/kg-day or inhalation exposures to 1–2 mg/m³ generally do not result in adverse effects.

Aquatic animals are also sensitive to DDVP and, as with terrestrial animals, invertebrates may be more sensitive than vertebrates. The lowest reported LC_{50} value in fish is approximately 0.2 mg/L. Some aquatic invertebrates are much more sensitive to DDVP than fish. For daphnids, the most sensitive group of invertebrate species, reported EC_{50} values range from 0.00007 mg/L to 0.00028 mg/L.

The majority of the toxicity data in ecological receptors is limited to free DDVP, rather than a slow-release formulation such as the Vaportape II product used in USDA programs for control of the gypsy moth. Hence, the toxicity values reported for indicator species will likely be conservative (i.e., suggest greater toxicity) as compared to Vaportape II. U.S. EPA has assessed the ecological effects of DDVP; however, the exposures assessed by U.S. EPA are not specific to formulations where DDVP is encapsulated in PVC resin. In general, aside from those organisms that enter the milk carton trap or those that remove the strip from the trap, toxicity resulting from exposure of ecological receptors to DDVP in Vaportape II milk carton traps is not likely.

4.1.2. Toxicity to Terrestrial Organisms.

4.1.2.1. Mammals – As summarized in Section 3.1, the database includes a number of toxicity studies in experimental mammals. The principal adverse effects of DDVP exposure are directly related to inhibition of cholinesterase (the mode of action for DDVP). Inhibition of this enzyme in mammalian systems produces a variety of systemic effects (Table 3-1). The nature and magnitude of the toxicity produced by a given exposure to DDVP by any route are directly related to the dose and rate at which the exposure occurs. In USDA programs for the control of the gypsy moth, the use of milk carton traps employing slow-release of DDVP from PVC strips essentially precludes rapid exposures to high doses of DDVP. As described in Section 3.1.4,

short-term animal studies have shown that oral exposures to free DDVP below about 0.5 mg/kg-day (or inhalation exposures to 1–2 mg/m³) do not result in meaningful reductions in cholinesterase activity. Experiments in laboratory mammals that were exposed to DDVP during pregnancy (by oral or inhalation route) did not show any effect on fertility or health of the offspring, even at levels that produced maternal toxicity (see Section 3.1.9).

Dietary administration of DDVP (free and encapsulated in PVC resin pellets) has been used as a veterinary anthelminthic agent in a variety of species, including dogs (Batte et al. 1966; Batte et al. 1967), pigs (Batte et al. 1965; Bris et al. 1968; Stanton et al. 1979; Todd 1967), horses (Himes et al. 1967), sheep (Bris et al. 1968), cattle (Bris et al. 1968), dromedary camels (Wallach and Frueh 1968), and non-human primates (Wallach and Frueh 1968). In general, oral administration of DDVP produced no signs of organophosphate poisoning at doses that were effective at reducing intestinal parasites (Wallach and Frueh 1968). For example, two consecutive days of dosing at 2.3 in camels or 1.7 mg/kg in non-human primates, respectively, was well tolerated by the animals despite debilitating intestinal infection (Wallach and Fueh 1968). In cows, Lloyd and Matthysse (1971) reported that diets containing DDVP (in PVC pellets) at doses 1.3, 1.8, or 2.3 mg/kg bw for 14 days produced no adverse effect on milk production (no other effects were reported). No DDVP was found in the milk at 1, 3, 7, 10 or 14 days. Free DDVP – i.e., not encapsulated in a PVC resin – produced severe inhibition of cholinesterase activity at a dose of 4.5 mg/kg (Tracey et al 1960).

As discussed in Section 3.1.4, the effect of PVC encapsulation on the toxicity of DDVP has been quantified in parallel assays (Stanton et al. 1979), in which DDVP (undiluted technical grade) and DDVP (impregnated in PVC) were administered to groups of young swine. For the technical grade liquid formulation, the LD_{50} was 157 (113–227) mg/kg and the NOAEL based on lethality was 56 mg/kg. For the PVC formulation, no deaths occurred at any doses including 1,000 mg/kg, the highest dose tested.

As discussed in Section 3.1.16, simultaneous exposure to DDVP and another cholinesterase inhibitor (e.g., organophosphate or carbamate insecticides) or a cholinomimetic agent (e.g., pilocarpine and carbachol) would likely enhance the cholinergic toxicity produced by DDVP. This is the major toxicologic interaction for DDVP. In addition, Short et al. (1971) also reported that DDVP exposure in combination with the muscle relaxant succinylcholine can produce cardiac arrythmias, apnea, and death in Shetland ponies depending on the degree of cholinesterase inhibition.

4.1.2.2. Birds – The acute oral LD_{50} in birds ranges from 6.5–24 mg/kg (WHO 1989, Hudson et al. 1984, Grimes and Aber 1988). As in mammals, the signs of DDVP intoxication in birds are typical of organophosphorus poisoning (e.g., tremors, and convulsions) and usually appear shortly after dosing. At lethal doses, death occurs within 1 hour, with survivors recovering completely within 24 h after dosing (WHO 1989). Tucker and Crabtree (1970) found various internal hemorrhages at autopsy in sacrificed pheasants and mallard ducks that survived acute high dose exposures.

The data from unpublished egg production and hatchability studies suggests that mallard ducks are more sensitive to DDVP than northern bobwhite quail. In mallard ducks, 20 weeks of dietary exposure identified a NOEC of 5 ppm and a LOAEL of 15 ppm based on number of eggs laid, eggshell thickness, number of viable embryos and number of live 3-week embryos (Redgrave and Mansell 1997). Cameron (1996) reported no effect on bobwhite quail reproduction following dietary exposure to DDVP at concentrations of 12 or 30 ppm for 20 weeks. At 100 ppm, however, statistically significant reductions in the number of eggs laid, viable embryos, live 3-week embryos, and survivors at 14 days. The short-term dietary LD_{50} in birds (5 days of exposure followed by three days of untreated diet) ranged from 300 ppm in Japanese quail to 5000 ppm in mallard ducks (Hill et al. 1975). Using chick and duck eggs, injections with DDVP at various incubation stages revealed that the LD_{50} values for these avian species at the mid-incubation stage were comparable to the rodent oral LD_{50} values (i.e., >50 mg/kg) (Khera and Lyon 1968).

Five days of continuous exposure of canaries, Indian finches, and budgerigars to DDVP vapor at 0.14 mg/m^3 reduced cholinesterase activity, but produced no overt signs of organophosphate intoxication (Brown et al. 1968, as cited by WHO 1989).

It is important to note that the LD_{50} values reported from these studies are derived from the active ingredient, DDVP, in free form. Encapsulation in PVC resin (such as Vaportape II used in milk carton traps) would be expected to slow the release of DDVP, thereby reducing the acute toxicity and increasing the LD_{50} values (Section 3.1.4). No published data are available concerning the acute toxicity of DDVP encased in PVC resin in birds.

4.1.2.3. Terrestrial Invertebrates – In general DDVP is highly toxic to invertebrates with effect levels for honey bees below 1 µg/g bee. In laboratory studies of honey bees, Atkins et al. (1973) found an LD_{50} of 0.495 µg/bee in 48 h (topical application of dust; 26.7 ˚C with a relative humidity 65%). Beran (1979) reported an oral LD_{50} of 0.29 µg/g body weight and a topical LD_{50} of 0.65 µg/g body weight.

A variety of other studies are available; however, they are not reported in sufficient detail to provide quantitative estimates of exposures. Nevertheless, these studies support the conclusion that invertebrates are highly susceptible to the toxic effects of DDVP. Following the exposure of honeycombs to DDVP vapor emanating from DDVP resin strips for 4 months, the combs absorbed the insecticide and were toxic to bees for approximately one month after exposure. Contamination of the bees appeared to be by inhalation rather than direct contact (Clinch 1970). Consumption of mulberry leaves sprayed with 1.56–6.25 mg/L DDVP produced 50% mortality in silkworm larvae after 4 hours of feeding (Aratake and Kayamura 1973). No adverse effects were observed on the hatchability and general condition of silkworm larvae hatched in the generation following feeding of mulberry leaves pre-treated with 3 mg/kg DDVP of leaf to adults (Yamanoi 1980).

4.1.2.4. Terrestrial Plants (Macrophytes) – Neither the published literature nor the review documents include data regarding the phytotoxicity of DDVP. Given the mode of action of DDVP, the U.S. EPA (1999a) has determined that toxicity testing in plants is not required for registration.

4.1.2.5. Terrestrial Microorganisms – WHO (1989) reported that the effect of DDVP on microorganisms is variable and species dependent. Certain microorganisms are able to metabolize DDVP, but DDVP may interfere with the endogenous oxidative metabolism of the organism. In certain organisms DDVP inhibits growth, while in others it has no influence or may stimulate growth. The above effects have been seen over a concentration range of 0.1–100 mg/L (Lieberman and Alexander 1981).

As noted earlier, the LD_{50} values reported from these studies are derived from the active ingredient, DDVP, in free form. Encapsulation in PVC resin (such as Vaportape II used by the Forest Service in milk carton traps) would be expected to slow the release of DDVP, thereby reducing the acute toxicity and increasing the LD_{50} values. No published data are available concerning the acute toxicity of DDVP encased in PVC resin in terrestrial microorganisms.

4.1.2.6. Terrestrial Field Studies – No terrestrial field studies on the effects of free DDVP or DDVP in PVC resin were located. Whitehead (1971) has advised caution in the use and handling of DDVP, where birds might be exposed because of their particular sensitivity to the toxic effects of organophosphate poisoning. In the case of the USDA programs involving the use of DDVP in traps, however, the probability of widespread contamination of soil or aquatic ecosystems is very low because a small amount of DDVP (590 mg) is used in the Vaportape II trap and because the DDVP is released slowly from the PVC resin.

4.1.3. Aquatic Organisms.

4.1.3.1. Fish – DDVP is classified as highly toxic to both freshwater and estuarine fish (U.S. EPA 1999a). In freshwater fish, reported 96-h LC_{50} values range from about 0.2 mg/L for lake trout or cutthroat trout and 12 mg/L for fathead minnows (U.S. EPA 1999a, p. 12). In estuarine fish, 96-h LC_{50} values range from 0.23–14.4 mg/L for striped mullet and mummichog, respectively (U.S. EPA 1999a, p. 12). Sublethal effects – i.e., brain and liver cholinesterase inhibition – have been reported in fish at doses of 0.25–1.25 mg/L, but cholinesterase activity recovered when the fish were returned to clean water (WHO 1989). The acute toxicity of DDVP in cutthroat trout or lake trout was not altered by variations in water hardness from 44 to 162 mg/L or at pH 6 to 9 (Johnson and Finley 1980).

Studies of sublethal effects in fish, most involving exposure periods of about 30 days, have demonstrated that exposure to ≤ 1 mg/L DDVP may produce changes in respiratory rates, serum and liver enzyme activity (aside from cholinesterase), lipid and carbohydrate metabolism, and hemoglobin and clotting time (WHO 1989). From these reports of adverse effects in fish, WHO (1989) derived an NOEC of 0.03 mg/L.

Only unpublished studies submitted to U.S. EPA were located regarding the chronic toxicity of DDVP in fish. These studies are all summarized in U.S. EPA (1999a). A NOEC of 0.0052 mg/L was reported for rainbow trout with a corresponding LOAEL of 0.0101 mg/L for a reduction in larval survival. Another study found that 0.96 mg/L produced no effects on fry of sheepshead minnow, whereas 1.84 mg/L produced statistically significant reductions in fry survival and length. As discussed in Section 3.1.7., *in vitro* studies on cells from embryonic renal tissue of carp demonstrated a dose-related decrease in lymphocyte proliferation and myeloid cell respiratory burst activities, both of which indicate immunosuppression; however, no effects on antibody production were noted in an *in vivo* study of carp cells (Dunier et al. 1991). The authors concluded that the results suggest that chronic exposure to DDVP may impair the immune system of fish.

4.1.3.2. Amphibians – Neither the published literature nor the review documents include data regarding the toxicity of DDVP to amphibians.

4.1.3.3. Aquatic Invertebrates – In general, invertebrates tend to be more sensitive to the toxic effects of DDVP than fish. Whereas the lowest reported LC_{50} value reported in fish is 0.183 mg/L (the value for lake trout reported by U.S. EPA 1999a, p. 12), the lowest comparable value reported for aquatic invertebrates is 0.00007 mg/L (the 48-hour EC_{50} value for *Daphnia pulex* reported by U.S. EPA 1999a, p. 13). Based on these measures, aquatic invertebrates appear to be more sensitive than fish by a factor of over 2500 [0.183 mg/L ÷ 0.00007 mg/L = 2614]. WHO (1989) reports that the acute toxicity of DDVP to aquatic insects (stone fly) and estuarine crustaceans (hermit crab) is also extremely high (96-hour LC_{50} values ranging from 0.0001–0.045 mg/L, respectively).

As with the data on fish, some of the more important studies are unpublished and have been submitted to U.S. EPA for the registration of various uses of DDVP (U.S. EPA 1999a). As summarized by U.S. EPA (1999a), the 48-hour EC_{50} values in two species of water flea range from 0.00007 mg/L to 0.00028 mg/L. In an unpublished 21-day study in daphnids, the NOEC and LOEC are 0.0000058 mg/L and 0.0000122 mg/L, respectively.

Not all species of aquatic invertebrates, however, are this sensitive. The most remarkable exception to the sensitivity of aquatic invertebrates to DDVP is the freshwater snail; Jonnalagadda and Rao (1996) reported a 96-hour LC_{50} of approximately 21 mg/L in this species. Exposure of prawns to DDVP concentrations of 0.31 or 0.62 mg/L for 96 hours produced a decrease in hepatic glycogen and an increase in the blood glucose level (Omkar and Shukla 1984).

Forget et al. (1998) report static 96-hour LC_{50} values for copepods ranging from 0.00092–0.0046 mg/L (different sensitivity depending on life stage). Treatment of eutrophic carp ponds with 0.325 mg/L DDVP killed *Cladocera* (predominantly *Bosmina* and *Daphnia* species) and decreased cyclopods (mainly *Cyclops*). These reductions were offset by increased development of rotifers (mainly *Polyarthra* and *Brachionus* species) and phytoplankton (mainly *Scenedesmus*

and *Pediastrum* species), so that the total plankton biomass changed only slightly (Grahl et al. 1981).

4.1.3.4. Aquatic Plants – The database for DDVP does not contain many reports of its toxicity in aquatic plants. In an unpublished report cited by U.S. EPA 1999a), EC_{50} values >100 ppm are reported for green algae, 14 ppm for algae (NOS), and 17-28 ppm for marine diatoms. Butler (1977) reported that 3.5 mg/L DDVP produces 50% growth inhibition of *Euglena gracilis* (algae).

4.1.3.5. Other Aquatic Microorganisms – Neither the published literature nor the review documents include data regarding the toxicity of DDVP to other aquatic microorganisms.

4.2. EXPOSURE ASSESSMENT

4.2.1. Overview

As in the human health risk assessment, exposure of terrestrial mammals to DDVP from the VaporTape strips used in milk carton traps is likely to be negligible under most circumstances. Nonetheless, it is conceivable that some mammals such as racoons or bears could easily access and tamper with the milk carton trap. Depending on the proportion of the DDVP strip that is consumed, doses (as DDVP in the PVC strip) are estimated to range from 10.5 mg/kg (10% of strip) to 105 mg/kg (100% of strip) and the central estimate is taken as 31.6 mg/kg (30% of strip). In addition, contamination of water with a pest strip is plausible, although probably rare, and is considered in a manner similar to the corresponding scenario in the human health risk assessment (Section 3.2.3.4). This scenario is based on the consumption of contaminated water by a small mammal and the dose to the animal is estimated at about 0.00003 mg/kg with a range of 0.000009 mg/kg to 0.00009 mg/kg. Other exposure scenarios for terrestrial vertebrates, while possible, seem far less plausible and are not considered quantitatively. No quantitative exposure assessments for terrestrial invertebrates are developed because the milk carton trap will attract only male gypsy moths because of the pheromone bait in the milk carton trap. Nontarget insects that incidentally enter the trap are likely to be killed by exposure to the DDVP vapor. Exposures to aquatic species are based on the same water concentrations used for terrestrial species: 0.000177 mg/L with a range of 0.000059 mg/L to 0.00059 mg/L.

4.2.2. Terrestrial Vertebrates

4.2.2.1. Oral Exposure to DDVP Strip – For the exposure of a young child discussed in Section 3.2.3.3, only sucking on the strip rather than ingestion of all or part of the strip is considered. Various species of wildlife, however, are probably capable of consuming all or part of a pest strip. For the current risk assessment, it will be assumed that a racoon tampers with a milk carton trap and consumes part or all of the strip – i.e., 590 mg of DDVP in the PVC formulation. Taking a body weight of about 5.6 kg for an adult racoon (the average of the values reported by U.S. EPA/ORD 1993, p. 2-236) and assuming that the animal consumes between 10% and 100% of the strip with a central value of 30%, the dose to the racoon would be about 31.6 mg/kg with a range of 10.5 mg/kg to 105 mg/kg (Worksheet D01).

4.2.2.2. Oral Exposure to Water Contaminated with DDVP – Estimated concentrations of DDVP in water are identical to those used in the human health risk assessment (Worksheet B02) and involve the accidental contamination of a small pond with a DDVP-PVC strip. The only major differences in this scenario compared to the scenario in the human health risk assessment involve the weight of the animal and the amount of water consumed. There are well-established relationships between body weight and water consumption across a wide range of mammalian species (e.g., U.S. EPA/ORD 1993). These relationships are used to estimate the amount of water that a 20 g mammal would consume in one day (Worksheet D02). Unlike the human health risk assessment, estimates of the variability of water consumption are not available. Thus, for this acute scenario, the only factor affecting the variability of the ingested dose estimates is the amount of DDVP that might be released in one day. These amounts are discussed in Section

3.2.3.4 and are used in Worksheet D02. As indicated in Worksheet D02, the central estimate of the dose is about 0.00003 mg/kg with a range of 0.000009 mg/kg to 0.00009 mg/kg.

4.2.3. Terrestrial Invertebrates

As in the previous risk assessment (USDA 1995b), quantitative exposure assessments for terrestrial invertebrates are not considered. The only terrestrial invertebrates that are likely to come into close contact with the DDVP strip are male gypsy moths, which will be attracted by the disparlure in the trap, or carnivorous wasps and hornets that may enter the trap to feed on dead and dying gypsy moths. Other insects and perhaps other invertebrates such as spiders might incidentally enter the milk carton traps. Because DDVP in a non-specific insecticide, nontarget invertebrates would likely be killed by exposure to the DDVP vapor within the trap.

4.2.4. Aquatic Species

The exposure assessment for aquatic species is based on concentrations of DDVP in water that are identical to the concentrations used in the human health risk assessment (Worksheet B02) and the exposure assessment for a small mammal drinking contaminated water (Worksheet D02). As indicated in these worksheets, the central estimate of the concentration of DDVP in the pond is 0.000177 mg/L with a range of 0.000059 mg/L to 0.00059 mg/L.

4.3. DOSE-RESPONSE ASSESSMENT

4.3.1. Overview

Given the limited nature of the use of DDVP in programs to control the gypsy moth and consequent limited number of exposure assessments, the dose-response assessment for DDVP is relatively simple. For terrestrial mammals, a value of 240 mg/kg from a study using DDVP in a PVC formulation is used for direct exposure to the DDVP-PVC strip – i.e., a raccoon tampering with a milk carton trap and consuming all or part of the DDVP strip. At the dose of 240 mg/kg, no mortality or frank signs of AChE inhibition were observed. For the contaminated water scenario, the NOAEL of 0.5 mg/kg from a study involving exposure to free or unformulated DDVP is used. This NOAEL is from the study that forms the basis for the acute RfD used in the human health risk assessment. Although DDVP is classified as highly toxic to fish, the estimated levels of acute exposure for fish are far below the 30-day NOEC of 0.03 mg/L. Thus, this value is used for all fish and no attempt is made to consider differences in sensitivity among fish. A somewhat different approach is taken with aquatic invertebrates, some of which are more sensitive to DDVP than fish by a factor of over 2500. Risks to sensitive species of aquatic invertebrates – i.e., daphnids and other small arthropods – are characterized based on the lowest reported LC_{50} value, 0.00007 mg/L from a 48-hour bioassay in *Daphnia pulex*. Some other groups of aquatic invertebrates, such as snails, appear to be much less sensitive than small arthropods. Risks to such tolerant species are based on a LC_{50} value of 21 mg/L in a freshwater snail.

4.3.2. Toxicity to Terrestrial Organisms

Two different types of exposure assessments are given for terrestrial vertebrates: direct consumption of all or part of the DDVP-PVC stip (Section 4.2.2.1) and consumption of water contaminated with DDVP (4.2.2.2). The former scenario involves exposure to the formulated DDVP and the latter exposure scenario involves exposure to unformulated or free DDVP. For the exposure assessment involving direct consumption of the DDVP-PVC strip, the dose of 240 mg/kg for neurotoxicity from the study by Stanton et al. (1979) will be used to characterize risk. No mortality or frank signs of AChE inhibition were observed at this dose. For exposure to free DDVP in water, the NOAEL of 0.5 mg/kg for changes in AChE activity and other signs of neurotoxicity will be used to characterize risk. This is the NOAEL selected by the U.S. EPA (2000a) as the basis for the acute oral RfD for DDVP. As indicated in Section 4.4., these two NOAEL values are substantially below the corresponding exposure levels. Thus, elaboration of the dose-response assessment is not necessary.

4.3.3. Aquatic Organisms

4.3.3.1. Fish – The U.S. EPA typically uses LC_{50} values as benchmark doses for developing acute hazard quotients and the most sensitive LC_{50} of 0.183 mg/L was used by U.S. EPA in it's ecological risk assessment for DDVP (U.S. EPA 1999a, p. 29). USDA risk assessments typically prefer to use NOEC (no observed effect concentrations) when such data are available. As discussed in Section 4.1.3.1, WHO (1989) has identified an NOEC of 0.03 mg/L from studies involving exposure periods of about 30 days. This NOEC will be adopted in the current risk assessment. While the application of a 30-day NOEC to the acute and much shorter term

exposures considered in this risk assessment is likely to be over-protective, this has no impact on the characterization of risk because the anticipated levels of acute exposure are substantially below this NOEC. Also because this conservative NOEC value is below a level of concern, separate assessments are not made for sensitive and tolerant species of fish. This is discussed further in Section 4.4.

4.3.3.2. Aquatic Invertebrates **–** As noted in Section 4.1.3.3, some aquatic invertebrates are much more sensitive to DDVP than fish. Based on the lowest reported LC_{50} values in fish and invertebrates, some aquatic invertebrates are more sensitive than fish by a factor of over 2500. There is, however, a very wide range of tolerances in aquatic invertebrates. The lowest reported LC_{50} value is 0.00007 mg/L. This is a 48-hour LC_{50} value in *Daphnia pulex* reported by U.S. EPA (1999a, p. 13). A NOEC value is not reported by U.S. EPA (1999a). Thus, the LC_{50} 0.00007 mg/L is used directly in the risk characterization for sensitive aquatic invertebrates. As also noted in Section 4.1.3.3, the sensitivity of aquatic invertebrates to DDVP is highly variable. The least sensitive group of species appears to be aquatic snails, with a reported 96-hour LC_{50} of 21 mg/L (Jonnalagadda and Rao 1996). This value will be used to characterize risks in tolerant aquatic invertebrates.

4.4. RISK CHARACTERIZATION

4.4.1. Overview

As with the human health risk assessment, it is anticipated that typical exposures and consequent risks to nontarget species should be negligible. As with the human health risk assessment, it is anticipated that typical exposures and consequent risks to most nontarget species should be negligible. The containment of the DDVP within a slow release PVC strip combined with the target specific nature of pheromone baited traps should reduce the risks of inadvertent effects in non-target species. Other insects and arthropods that may inadvertently enter the trap will probably be killed by DDVP vapor. While such inadvertent contact may occur, it is not likely to impact substantial numbers of nontarget insects or arthropods.

Because of the limited use of DDVP, a relatively small number of exposure scenarios – all of which might be considered accidental or incidental – are developed. For terrestrial mammals, contact with the pest strip could occur by an animal directly tampering with a trap or by an animal consuming water that had been accidentally contaminated with a DDVP strip. Adverse effects would not be expected in either case. In the case of accidental contamination of a small body of water with a DDVP strip, concentrations of DDVP in the water would be below the level of concern for fish by factors of about 50 to 500. Some aquatic invertebrates, however, might be affected. For the most sensitive species of aquatic invertebrates – i.e., small aquatic arthropods such as daphnids – exposures could substantially exceed laboratory LC_{50} values by factors of up to about 8. Exposures to tolerant aquatic invertebrates – such as snails – would be below a level of concern by a substantial margin – i.e., factors of about 30,000 to 300,000. The exposure assessments that serve as the bases for these risk characterizations are highly dependent on specific conditions – i.e., how much DDVP was in the strip at the time that the contamination occurred and the size of the body of water that was contaminated.

4.4.2. Terrestrial Organisms

There is no indication that adverse effects in terrestrial vertebrates are likely. This assessment is based on the exposure scenarios for a relatively small mammal – i.e., a raccoon – consuming all or part of a DDVP-PVC strip as well as a very small mammal consuming water that had been contaminated with a pest strip.

The former scenario, direct consumption, may be plausible but is clearly extreme. The upper range of the exposure assessment assumes that the animal consumes the entire strip with a resulting dose of about 100 mg/kg (Section 4.2.2.1). The assessment of risk is based on a controlled laboratory study using a DDVP-PVC formulation in which no mortality was observed at 1,000 mg/kg and no signs of AChE inhibition were apparent at 240 mg/kg (Section 4.3.2). The dose of 100 mg/kg associated with upper range of the hazard quotient, 0.4, is below the the NOAEL by a factor 2.5.

The scenario for the consumption of contaminated water is based the assumption that a fresh DDVP strip inadvertently contaminates a small pond and, at the upper range of the estimated dose, the further assumption that all of the DDVP in the strip leaches into the water (Section

4.2.2.2 and Worksheets D02). The estimated dose is probably higher and perhaps much higher than what might actually occur because degradation of the DDVP in water is not considered. Even with these highly protective assumptions, the upper range of the risk quotient is only 0.0002 – i.e., below the level of concern (1) by a factor of 5,000. Thus, there is no plausible basis for asserting that adverse effects are likely.

No quantitative risk characterization is presented for terrestrial invertebrates. This approach is taken because there is no reason to anticipate that significant exposures to nontarget invertebrates are likely. It is possible that some insects and perhaps other arthropods could inadvertently enter a milk carton trap. In such a case, it is likely that the nontarget organisms would be killed by the DDVP vapor. While this is the intended effect in the target species, the gypsy moth, the efficacy of the traps is dependant on the use of another agent, disparlure, that serves as an attractant to male gypsy moths. As discussed in the risk assessment for disparlure, this attractant is highly specific to the gypsy moth and will not attract other species. Thus, the numbers of nontarget species that might be killed by inadvertently entering the traps is likely to be small and inconsequential.

4.4.3. Aquatic Organisms

4.4.3.1. Fish – There is no indication that fish are likely to be adversely affected by the use of DDVP in PVC strips. The exposure assessment for fish (Section 4.2.4) is based on the same very conservative exposure assessment used for mammals – i.e., the concentrations in water are likely to be over-estimated. The dose-response assessment is based on a 30-day NOEC for sublethal effects. The resulting risk quotients – i.e., 0.002 to 0.2 – are below the level of concern by factors of 50 to 500.

4.4.3.2. Aquatic Invertebrates – As discussed in Section 4.3.3.2, some aquatic invertebrates are much more sensitive to DDVP than fish and this difference in sensitivity impacts the characterization of risk. Based on the same conservative exposure assessment used for both fish and terrestrial vertebrates, some sensitive aquatic invertebrates could be adversely affected by DDVP contamination of water. As in the other exposure assessments involving contaminated water, this exposure scenario should be regarded as accidental rather than routine. In other words, under normal circumstances, water contamination from DDVP strips will be negligible and this is consistent with the conclusions reached by U.S. EPA (1999a, p. 25). Nonetheless, based on the modeled concentrations in the event of the accidental deposition of a strip containing 590 mg of DDVP into a small pond, concentrations of DDVP in the water would reach or substantially exceed the LC_{50} value for sensitive invertebrates and substantial mortality in sensitive invertebrates could occur.

The actual extent of mortality would depend on the rate at which DDVP is released from the strip, the degree of mixing that occurs in the water, and the rate of breakdown and dissipation of DDVP. These processes cannot be generically modeled but the conservative exposure assessment used to estimate concentrations in water suggests that adverse effects in sensitive aquatic invertebrates are plausible. No effects are likely in less sensitive aquatic invertebrates

such as aquatic snails. As discussed in Section 3.2.3.4, the hydrolysis of DDVP in water is rapid and it is likely that the estimates of adverse effects in some aquatic invertebrates would apply to only a very limited area near the pest strip rather than to the larger area of the body of water that is contaminated.

5. REFERENCES

Abdelsalam EB. 1999. Neurotoxic potential of six organophosphorus compounds in adult hens. Vet Hum Toxicol. 41(5):290-292.

ACGIH (American Conference of Governmental Industrial Hygienists). 1991. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Dichlorvos. Cincinnati, OH: American Conference of Governmental Industrial Hygienists; 446-448.

ACGIH (American Conference of Governmental Industrial Hygienists). 2004. TLV/BEI Development Process: An Overview. http://www.acgih.org/TLV/DevProcess.htm.

Aratake Y; Kayamura T. 1973. [Toxicity of insecticides to silkworm larvae.] Sanshi Kenkyu (Acta serol.). 87: 68-78 (in Japanese). (As cited by WHO 1989).

Arimatsu S; Hoshiro Y; Nomura T. 1977. [Studies on primary irritation test of pesticides in rabbits.] Nippon Noson Igakkai Zasshi. 26572-573. (In Japanese) As cited by WHO 1989.

ARS (USDA/Agricultural Research Station). 1995. ARS Pesticide Properties Database. http://www.arsusda.gov/ppdb.html. Last updated May 1995

Atkins EL; Greywood EA; Macdonald RL. 1973. Toxicity of pesticides and other agricultural chemicals to honey bees. University of California (Agricultural Extension Report No. M-16 Rev. 9/73). (As cited by WHO 1989).

ATSDR (Agency for Toxic Substances and Disease Registry). 1993. Case Studies in Environmental Medicine No. 22: Cholinesterase Inhibiting Pesticide Toxicity. U.S. Department of Health and Human Services, Public Health Service. September, 1993. Available at: http://books.nap.edu/books/0309051401/html/584.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1995. Toxicological Profile for Xylene. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Division of Toxicology, Toxicology Information Branch, Atlanta, Ga. August, 1995. Available at: http://www.atsdr.cdc.gov/toxprofiles/

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Dichlorvos. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Division of Toxicology, Toxicology Information Branch, Atlanta, Ga. Sep. 1997. Available at: http://www.atsdr.cdc.gov/toxprofiles/

Bast CB; Milanez S; Forsyth CS. 1997. Data Evaluation Report: Dichlorvos, Study Type, Subchronic Oral Neurotoxicy. MRID No. 42958101, 42655301, 41593101, 41951501, and 40299401, CHEG-000155.

Bisby JA; Simpson GR. 1975. An unusual presentation of systemic organophosphate poisoning. Med J Aust. 2:394-395.

Blair D; Hoadley EC; Hutson DH. 1975. The distribution of dichlorvos in the tissues of mammals after its inhalation or intravenous administration. Toxicol Appl Pharmacol. 31(2):243-253.

Blair D; Dix KM; Hunt PF; Thorpe E; Stevenson DE; Walker AIR. 1976. Dichlorvos – a 2-year inhalation carcinogenesis study in rats. Arch Toxicol (Berlin). 35:281-294.

Braun WG; Killeen JC Jr. 1975. Acute Oral Toxicity in Rats: Compound No. L-65-39: Project No. 2564-75. MRID 00029130.

Brown VKH; Blair D; Holmes DL; Pickering RG. 1968. The toxicity of low concentrations of dichlorvos by inhalation in rodent and avian species. Sittingbourne, Shell Research Ltd (Unpublished Report No. TLGR.0015.68). (As cited by WHO 1989).

Bryant D.H. 1985. Asthma due to insecticide sensitivity. Aust NZ J Med. 15:66-68. As cited by Vial et al. 1996.

Budavari S. (Ed). 1989. The Merck Index: An Encyclopedia of Chemicals, Drugs,and Biologicals, 11th ed. Merck & Co., Inc., Rahway, New Jersey.

Butler GL. 1977. Algae and pesticides. Residue Rev. 66: 40. (As cited by WHO 1989).

Calabrese EJ. 1991. Multiple chemical interactions. Chelsea, Michigan: Lewis Publishers; 355-385.

Casale GP; Cohen SD; DiCapua RA. 1983. The effects of organophosphate-induced cholinergic stimulation on the antibody response to sheep erythrocytes in inbred mice. Toxicol Appl Pharmacol. 68:198-205.

Cavegna G; Locati G; Vigliani EC. 1969. Clinical effects of exposure to DDVP (Vapona) insecticide in hospital wards. Arch Environ Health. 19:112-123.

Cervoni WA; Oliver-Gonzales J; Kaye S; Slomka MB. 1969. Dichlorvos as a single-dose intestinal anthelmintic therapy for man. Am J Trop Med Hyg 18:912.

Charles KE; Veitch JA. 2002. Outdoor Ventilation Rates in Offices and Occupant Satisfaction. National Research Council Canada, Institute for Research in Construction. Report IRC-RR-160. Available at: http://irc.nrc-cnrc.gc.ca/ircpubs.

Civen M; Leep JE; Wishnow RM; Wolfsen A; Morin RJ. 1980. Effects of low level administration of dichlorvos on adrenocorticotrophic hormone secretion, adrenal cholesteryl ester and steroid metabolism. Biochem Pharmacol (Oxford). 29:635-641.

Clements RG; Nabholz JV; Zeeman M. 1996. Estimating Toxicity of Industrial Chemicals to Aquatic Organisms Using Structure-activity Relationships. Available at: http://www.epa.gov/oppt/newchems/sarman.pdf .

Clinch PG. 1970. Effect on honey bees of combs exposed to vapour from dichlorvos slow-release strips. NZ J Agric Res. 13(2): 448-452.

Collins RD; DeVries DM. 1973. Air concentration and food residues from use of Shell's No-Pest Insecticide Strip. Bull Environ Toxicol. 9(4):227-233.

Collins JA; Schooley MA; Singh VK. 1977. The effect of dietary dichlorvos on swine reproduction and viability of their offspring. Toxicol Appl Pharm. 19:377.

Colosio C; Corsini E; Barcellini W; Maroni M. 1999. Immune parameters in biological monitoring of pesticide exposure: Current knowledge and perspectives. Toxicol Lett (Shannon). 108(2-3):285-295.

Costa LG; Murphy SD. 1984. Interaction between acetaminophen and organophosphates in mice. Chem Pathol Pharmacol. 44(3):389-400.

Cunningham ML; Matthews HB. 1995. Cell proliferation as a determining factor for the carcinogenicity of chemicals: Studies with mutagenic carcinogens and mutagenic noncarcinogens. Toxicol Lett. 82-83:9-14.

Dambska M; Iwanowski L; Kozlowski P. 1979. The effect of transplacental intoxication with dichlorvos on the development of cerebral cortex in newborn rabbits. Neuropatologia Polska (Warszawa) 17:571-576.

Das YT; Taskar PK; Brown HD; Chattopadhyay SK. 1983. Exposure of professional pest control operator to dichlorvos (DDVP) on house structures. Tox Letters. 17:95-99.

Davis, J.R.; Brownson, R.C.; Garcia, R. 1992. Family pesticide use in the home, garden orchard, and yard. Arch Environ Contam Toxicol. 22:260-266.

Davis, J.F.; Brownson, R.C.; Garcia, R.; Bentz, B; Turner, A. 1993. Family pesticide use and childhood brain cancer. Arch Environ Contam Toxicol. 24:87-92.

Dean BJ, Thorpe E. 1972. Studies with dichlorvos vapor in dominant lethal mutation tests on mice. Arch Toxicol. 30(1):5l-59.

Dellinger JA; McKiernan BC; Koritz GD; Richardson BC. 1987. Latent dichlorvos neurotoxicity detected by vagal tone monitoring in dogs. Neurotoxicol Teratol. 9:197-201.

Desi I; Varga L; Farkas I. 1978. Studies on the immunosuppressive effect of organochlorine and organophosphoric pesticides in subacute experiments. J Hyg Epidemiol Microbiol Immunol (Praha). 22:115-122.

Desi I; Varga L; Farkas I. 1980. The effect of DDVP, an organophosphorus pesticide, on the humoral and cell-mediated immunity of rabbits. Arch Toxicol Supp (Berlin). 4:171-174.

Desi I; Nagymajtenyi L; Schulz H; Nehez M. 1998. Epidemiological investigations and experimental model studies on exposure of pesticides. Toxicol Lett (Shannon). 96-97(Spec. Issue):351-359.

Dunier M; Siwicki AK; Demael A. 1991. Effects of organophosphorus insecticides: Effects of trichlorfon and dichlorvos on the immune response of carp (*Cyprinus carpio*), III. *In vitro* effects on lymphocyte proliferation and phagocytosis and *in vivo* effects on humoral response. Ecotoxicol Environ Saf. 22:79-87.

Durham WF; Gaines TB; McCauley RH; Sedlak VA; Mattson AM; Hayes WJ. 1957. Studies on the toxicity of O,O,-Dimethyl-2,2-dichlorovinyl phosphate (DDVP). AMA Arch Indus Health. 15:340- 349.

Durkin PR; Diamond G. 2002. Neurotoxicity, Immunotoxicity, and Endocrine Disruption with Specific Commentary on Glyphosate, Triclopyr, and Hexazinone: Final Report. SERA TR 01-43-08-04a dated January 30, 2002. Available at www.fs.fed.us/foresthealth/pesticide/risk.htm.

Ecobichon DJ. 2001. Toxic Effects of Pesticides. In: Klaassen, C.D., ed. Casarett and Doull's Toxicology: The Basic Science of Poisons, Sixth Edition. New York: McGraw-Hill; 774-784.

Ehrich M; Cohen SD. 1977. DDVP (Dichlorvos) detoxification by binding and interactions with DDT, dieldrin, and malaoxon. J Toxicol Environ Health. 3:491-500.

Eisler R. 1970. Acute toxicities of organochlorine and organophosphorus insecticides to estuarine fish. Washington DC, US Department of the Interior, Fish and Wildlife Service, Bureau of Sport Fisheries and Wildlife (Technical Paper No. 46). (As cited by WHO 1989).

England DC; Knight AD; Day PE; Kennick WH; Oldfield JE. 1969. Influence of dichlorvos on blood sugar, ovulation rate, and early embryo mortality in gilts. Proc West Sec Amer Soc Anim Sci. 20:73-78.

Fedoruk MJ; Kerger BD. 2003. Measurement of volatile organic compounds inside automobiles. Journal of Exposure Analysis and Environmental Epidemiology. 13: 31- 41.

Fernandes MD; Queiroz M LS. 1999. Measurement of the respiratory burst and chemotaxis in polymorphonuclear leukocytes from Anti-ChE insecticides-exposed workers. Immunopharmacol Immunotoxicol. 21(3):621-633.

Fernandez G; Diaz Gomez MI; Castro JA. 1975. Cholinesterase inhibition by phenothiazine and nonphenothiazine antihistaminics: Analysis of its postulated role in synergizing organophosphate toxicity. Tox Appl Pharmacol. 31:179-190.

Forget J; Pavillon JF; Menasria MR; Bocquene G. 1998. Mortality and LC_{50} values for several stages of the marine copepod *Tigriopus brevicornis* (Muller) exposed to the metals arsenic and cadmium and the pesticides atrazine, carbofuran, dichlorvos, and malathion. Ecotoxicol Environ Saf. 40(3):239-244.

Fujita K; Matsushima S; Abe E; Sasaki K; Kurosawa, K. 1977. [Examination of the effects of dichlorvos on the testis.] Nippon Noson Igakkai Zasshi. 26(3)328-329. (In Japanese)

Fukami J. 1980. Metabolism of several insecticides by glutathione-S-transferases. Pharmacol Ther. 10:437-514. As cited by Costa and Murphy 1984.

Gage JC. 1967. The significance of blood cholinesterase activity measurements. Residue Reviews. 18:159-173.

Gaines TB. 1969. Acute toxicity of pesticides. Toxicol Appl Pharmacol. 14:513-534.

Gallo MA; Lawryk NJ. 1991. Organic phoshporus pesticides. In: Hayes, W.J.; Laws, E.R., eds. Handbook of pesticide toxicology, Volume 2, Classes of pesticides. San Diego: Academic Press, Inc.; 917-1123.

Garcia-Repetto R; Martinez D; Repetto M. 1995. Malathion and dichlorvos toxicokinetics after the oral administration of malathion and trichlorfon. Vet Human Toxicol. 37(4):306-309.

Gillett JW; Harr JR; Lindstrom FT; Mount DA; St. Clair AD; Weber LJ. 1972a. Evaluation of human health hazards on use of dichlorvos (DDVP), especially in resin strips. Residue Reviews 44:115-159.

Gillett JW; Harr JR; St. Clair AD; Weber LJ. 1972b. Comment on the distinction between hazard and safety in evaluation of human health hazards on use of dichlorvos, especially in resin strips. Residue Reviews 44:161-184.

Gledhill A. 1997. Dichlorvos: A study to investigate the effect of a single oral dose on erythrocyte cholinesterase inhibition in healthy male volunteers: Lab Project Number: CTL/P/5393: XH6064. Unpublished study prepared by Zeneca Central Toxicology Lab. 44 p. MRID No. 44248802. Available from U.S. EPA/OPP/CBI Office.

Gold RE; Holcslaw T; Tupy D; Ballard JB. 1984. Dermal and respiratory exposure to applicators and occupants of residences treated with dichlorvos (DDVP). J Econ Entomol. 77(2):430-436.

Goldstein A; Aronow L; Kaman SM. 1974. Principles of Drug Action: The Basis of Pharmacology. 2nd ed. John Wiley and Sons, New York, NY. 854 p.

Grahl K; Horn H; Hallebach R. 1981. [Effect of butonate, trichlorfon, and dichlorvos on plankton populations.] Acta hydrochim. Hydrobiol., 9(2): 147-161 (in German). (As cited by WHO 1989).

Hass DK; Collins JA; Kodamma JK. 1971. Effects of orally administered dichlorvos in rhesus monkeys. J Amer Vet Med Assoc. 161(6):714-719.

Hattori K; Sato H; Tsuchiya K; Yamamoto N; Ogawa E. 1974. [Toxicological studies on the influences of chemicals to the birds. I. Oral acute toxicity and cholinesterase inhibition of three organophosphate insecticides in Japanese quail.] Hokkaidoritsu Eisei Kenkyusho Ho. 24: 35-38 (in Japanese, with English summary). (As cited by WHO 1989).

Health-Chem Corporation. 19??. Hercon Vaportape II Insecticidal Strips for Use as Toxicant in Insect Traps. MRID 00084822.

Hercon (Hercon Environmental Company). 1978. Application for pesticide registration: Hercon Disparlure dispenser. Located at: U.S. Department of Agriculture, Forest Service, Radnor, PA.

Hercon (Hercon Environmental Company) [Label for Vaportape II and memo to Noel Schneeberger]. 1993 April 20. Located at: U.S. Department of Agriculture, Forest Service, Radnor, PA.

Hercon (Hercon Environmental Company) [Facsimilie to Patrick Durkin]. 1994 April 13. Hercon Vaportape II: Release rate study, Rep 1 - Lot No. 0061V; Study date: October 9, 1991. Located at: U.S. Department of Agriculture, Forest Service, Radnor, PA.

Hercon (Hercon Environmental Company). 2004. VaporTape II label. Downloaded on May 29, 2004 from: http://www.herconenviron.com/pdf/hercon_vaportape.pdf

Hercon Products Group. 19??. DDVP Toxicity to Mammals. (Unpublished study received Oct 16, 1981 under 8730-32; submitted by Herculite Products, Inc., New York, N.Y.; CDL:246081-D) MRID 00084824.

Herculite Products Incorporated. 19??a. Hercon Vaportape II Insecticidal Strips. MRID 00084825.

Herculite Products Incorporated. 19??b. Study of the Chemical Hercon Vaportape. Includes undated method entitled: DDVP analysis in Hercon dispensers. MRID 00084823.

Hill EF; Heath RG; Spann JW; Williams JD. 1975. Lethal dietary toxicities of environmental pollutants to birds. Washington DC, US Department of the Interior, Fish and Wildlife Service, pp. 1-51 (Special Scientific Report: Wildlife No. 191). (As cited by WHO 1989).

Hine CH; Slomka MB. 1968. Human tolerance of the acute and subacute oral administration of a polyvinylchloride formulation of dichlorvos (V-3 and V-12). Pharmacologist. 10222. Cited by WHO 1989.

Hine CH; Slomka MB. 1970. Human toxicity studies on polyvinyl chloride formulation of dichlorvos. Toxicol Appl Pharmacol. 17:304.

Hour TC; Chen L; Lin JK. 1998. Comparative investigation on the mutagenicities of organophosphate, phthalimide, pyrethroid and carbamate insecticides by the ames and lactam tests. Mutagenesis. 13(2):157-66.

IARC (International Agency for Research on Cancer). 1979. Dichlorvos. In: IARC monographs on the evaluation of carcinogenic risks to humans: Some halogenated hydrocarbons. Volume 20; 97-127.

IARC (International Agency for Research on Cancer). 1991. Dichlorvos. In: IARC monographs on the evaluation of carcinogenic risks to humans: Occupational exposures in insecticide application, and some pesticides. 53:267-307.

ICRP (International Commission on Radiologic Protection). 1975. Report of the Task Group on Reference Man. Recommendations of the International Commission on Radiological Protection (ICRP) Publ. No. 23. Pergamon Press, New York, NY.

Institäoris L; Siroki O; Fekete K; Däesi I. 1995. Immunotoxicological investigation of repeated small doses of dichlorvos (DDVP) in three generations of rats. Int J Environ Health Res. 5(3):239-45.

Institoris L; Nagymajtenyi L; Siroki O; Desi I. 1997. Comparison of the immuno- and neurotoxicological effects of repeated small doses of an organophosphate pesticide, ddvp, in three generations of rats. Neurotoxicol. 18(3):898.

Jacobs DE. 1968. Experiences with a broad-spectrum anthelmintic, Dichlorvos, in the adult pig. Vet Rec. 83:160-164.

Jakubowska B; Nowak A. 1973. [The effect of organophosphorus and carbamate insecticides on the development of soil fungi.] Zesz. Nauk. Akad. Roln. Szczecinie, 39(10): 141-150 (in Polish). (As cited by WHO 1989).

Jeffcoat A. 1990. Dermal absorption of dichlorvos in rats: Lab Project Number: 4615. Unpublished study prepared by Research Triangle Institute. 196 p. MRID No. 41435201.

Jian T; Zhiying F. 1990. Chronotoxicologic studies on dichlorphos in mice and humans. Chronobiology: Its Role in Clinical Medicine, General Biology, and Agriculture. Part A. pp. 503-510.

Johnson, M.K. 1978. The anomalous behaviour of dimethyl phosphates in the biochemical test for delayed neurotoxicity. Arch Toxicol. 41:107-110.

Johnson MK. 1981. Delayed neurotoxicity: Do trichlorphon and/or dichlorvos cause delayed neuropathy in man or in test animals? Acta Pharmacol Toxicol (Copenhagen). 49(Suppl. 5):87-98.

Johnson WW; Finley MT. 1980. Handbook of acute toxicity of chemicals to fish and aquatic invertebrates, Washington DC, US Department of the Interior, Fish and Wildlife Service (Resource Publication No. 137). (As cited by WHO 1989).

Jokanovic M; Kosanovic M; Maksimovic M. 1996. Interaction of organophosphorus compounds with carboxylesterases in the rat. Arch Toxicol. 70(7):444-450.

Jones KH; Sanderson DM; Noakes DN. 1968. Acute toxicity data for pesticides. World Review of Pest Control. l 7:135-143.

Jonnalagadda PR; Rao BP. 1996. Histopathological changes induced by specific pesticides on some tissues of the fresh water snail *Bellamya dissimilis*. Bull Environ Contam Toxicol. 57(4):648-654.

Julka D; Pal R; Gill KD. 1992. Neurotoxicity of dichlorvoseffect on antioxidant defense system in the rat central nervous system. Exp Mol Patho1. 56(2):144-152.

Khera KS; Lyon DA. 1968. Chick and duck embryos in the evaluation of pesticide toxicity. Toxicol Appl Pharmacol. 13:1-15.

Kimbrough RD; Gaines TB. 1969. Effect of organic phosphorus compounds and alkylating agents on the rat fetus. Arch Environ Health. 16: 805-808.

Kodama JK. 1960. Technical DDVP. Acute oral administration dogs, Vienna, Virginia, Hazleton Laboratories (Unpublished Report, 20 January). As cited by WHO 1989.

Korninger HC; Lenz K. 1978. Poisoning in childhood – an information center report. Wiener Klinische Wochenschrift (Wien). 90:1-7.

Lal R. 1982. Accumulation, metabolism, and effects of organophosphorus insecticides on microorganisms. Adv. Appl. Microbiol. 28: 149-200. (As cited by WHO 1989).

Lamoreaux RJ; Newland LW. 1978. The fate of dichlorvos in soil. Chemosphere. 10:807-814.

Laws ER. 1966. Route of absorption of DDVP after oral administration to rats. Toxicol Appl Pharmacol. 8:193-196.

Leary JS; Keane WT; Fontenot C; Feichtmeir E; Schultz D; Koos B; Hirsch L; Lavor EM; Roan CR; Hine CH. 1974. Safety evaluation in the home of polyvinyl chloride resin strip containing dichlorvos (DDVP). Arch Environ Health. 29:308-314.

Leonard D. 2004. Review comments on SERA TR 04-43-05-05a, Control/Eradication Agents for the Gypsy Moth – Human Health and Ecological Risk Assessment for DDVP (Dichlorvos), Peer Review Draft dated July 8, 2004. Comments by Donna Leonard, USDA Forest Service, Forest Health Protection, Asheville, NC. Comments received via email from dleonard@fs.fed.us.

Lieberman MT; Alexander M. 1981. Effects of pesticides on decomposition of organic matter nitrification in sewage. Bull Environ Contam Toxicol. 26: 554-560.

Liess; Savitz. 1995. Home pesticide use and childhood cancer: A case-control study. Am J Public Health. 85:249-252.

Lloyd JE; Matthysse JG. 1971. Residues of dichlorvos, diazinon, and dimetilan in milk of cows fed PVC-insecticide feed additives. J Econ Entomol. 64(4):821-822.

Liebhold AM; McManus M. 1999. The evolving use of insecticides in gypsy moth management. J For. 97(3): 20-23.

Lopez JD. 1998. Evaluation of various operational aspects for sex pheromone trapping of beet armyworm. Southwest Entomol. 23(4):301-307.

Maddy KT; Goh KS; Meinders DD; Edmiston S; Margetich S. 1984. Dissipation of dislodgeable residue of chlorpyrifos and DDVP on turf. California Department of Food and Agriculture, Division of Pest Management, Environmental Protection and Worker Safety, Worker Safety and Health Unit, Sacramento, CA. As cited by USDA 1995b.

Manley A, Brown WR, Mennear J. 1997. Dichlorvos and mononuclear cell leukemia in Fischer 344 rats: Lack of effect of chronic administration on progression of the disease. Int J Toxicol. 16(1):1-7.

Mason HJ. 2000. The recovery of plasma cholinesterase and erythrocyte acetylcholinesterase activity in workers after over-exposure to dichlorvos. Occup Med (Lond). 50(5): 343-7.

Mathias CGT. 1983. Persistent contact dermatitis from the insecticide dichlorvos. Contact Dermatitis. 9:217-218.

Mennear JH. 1994. Dichlorvos carcinogenicity: An assessment of the weight of experimental evidence. Regul. Toxicol. Pharmacol. 20354-361. As cited by Mennear 1998.

Mennear JH. 1998. Dichlorvos a regulatory conundrum. Regul Toxicol Pharmacol. 27(3):265-272.

Meylan W; Howard P. 2000. DDVP Output from EPI-SUITE – Estimation Program Interface, Version 3.11. Syracuse Research Corporation, Syracuse, N.Y. For: U.S. Environmental Protection Agency, Office of Pollution prevention and Toxics, Washington, D.C.

Michalek H; Stavinoha WB. 1978. Effect of chlorpromazine pre-treatment on the inhibition of total cholinesterases and butyryl-cholinesterase in brain of rats poisoned by physostigmine or dichlorvos. Toxicology. 9:205-218.

Mohammad FK; St. Omer VE. 1983. Interaction of dichlorvos-crotoxyphos insecticide with phenothiazine anthelmintic in sheep with or without *Haemonchus* and *Trichostrongylus* infections. Am J Vet Res. 44:1949-1953.

Mohammad FK; St Omer VE. 1985. Toxicity and interaction of topical organophosphate insecticide dichlorvos crotoxyphos and phenothiazine anthelmintic in sheep previously exposed to both drugs. Vet Hum Toxicol. 27:181-184.

Moriya M; Ohta T; Watanabe K; Miyazawa T; Kato K; Shirasu Y. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mut Res. 116:185-206.

Muller GH. 1970. Flea collar dermatitis in animals. J Am Vet Med Assoc. 157(11):1616-1626.

Murphy SD. 1980. Assessment of the potential for toxic interactions among environmental pollutants. In: The Principles and Methods in Modern Toxicology. Galli CL; Murphy SD; Paoletti R (eds.). pp. 277-294.

Naidu NV; Reddy KS; Janardhan A; Murthy MK. 1978. Toxicological investigation of dichlorvos in chicks. Indian J. Pharmacol. 10(14): 323-326. (As cited by WHO 1989).

NRC (National Research Council). 1983. Risk assessment in the Federal government: managing the process. Washington, DC: National Academy Press; 176 p. + app.

NCI (National Cancer Institute). 1977. Bioassay of Dichlorvos for Possible Carcinogenicity. Washington, DC: U.S. Department of Health Education and Welfare. Available from NTIS, Springfield, VA: PB 270 937.

NIOSH (National Institute for Occupational Safety and Health). 2002. Pocket Guide to Guide to Chemical Hazards: Dichlorvos. U.S. Department of Health and Human Services. Available at: http://www.cdc.gov/niosh/npg/npg.html.

NTP. 1989. Toxicology and Carcinogenesis Studies of Dichlorvos (CAS No. 62-73-7) in F344/N rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program. Washington, DC: U.S. Department of Health and Human Services. Technical Report Series No. 342.

Omkar; Shukla GS. 1984. Alteration in carbohydrate metabolism of fresh-water prawn *Macrobianchium lamarrei* after dichlorvos exposure. Ind. Health. 22: 133-136. (As cited by WHO 1989).

Pena-Chavarria A; Swartzwelder JC; Villarejos VM; Kotcher E; Arguedas J. 1969. Dichlorvos, an effective broad-spectrum anthelmintic. Am J Trop Med Hyg. 18:907.

Potter JC; Boyer AC; Marxmiller RL; Young R; Loeffler JE. 1973. Radioisotope residues and residues of dichlorvos and its metabolites in pregnant sows and their progeny dosed with dichlorvos-^{14}C or dichlorvos-^{36}Cl formulated as PVC pellets. J Agric Food Chem. 21(4):734-738.

Purshottam T; Kaveeshwar U. 1982. Effect of phenobarbital pretreatment on regeneration of plasma cholinesterase activity inhibited by parathion or dichlorvos. Arch Environ Health. 37(1):53-58.

Qiao CL; Sun ZQ; Liu JE. 1999. New esterase enzymes involved in organophosphate resistance in *Culex pipiens* (Diptera: Culicidae) from Guang Zhou, China. J Med Entomol. 36(6):666-670.

Queiroz MLS; Fernandes MD; Valadares MC. 1999. Neutrophil function in workers exposed to organophosphate and carbamate insecticides. Int J Immunopharmacol. 21(4):263-270.

Radeleff RD; Woodard GT. 1957. The toxicity of organic phosphorus insecticides to livestock. J. Am. Vet. Med. Assoc. 130: 215-216. (As cited by WHO 1989).

Ramel C; Drake J; Sugimura T. 1980. An evaluation of the genetic toxicity of Dichlorvos. Mut Res (Amsterdam). 76:297-309.

Rath S; Misra BN. 1979. Sub-lethal effects of dichlorvos (DDVP) on respiratory metabolism of *Tilapia mossambica* of 3 age groups. Exp. Gerontol. 14: 37-41. (As cited by WHO 1989).

Rath S; Misra BN. 1980. Pigment disperson in *Tilapia mossambica* Peters exposed to dichlorvos (DDVP). Curr. Sci. 49(23): 907-909. (As cited by WHO 1989).

Rath S; Misra BN. 1981. Toxicological effects of dichlorvos (DDVP) on brain and liver acetylcholinesterase (AChE) activity of *Tilapia mossambica* Peters. Toxicology. 19: 239-245. (As cited by WHO 1989).

Reeves, J.D.; Driggers, D.A.; Kiley, V.A. 1981. Household insecticide associated aplastic anaemia and acute leukaemia in children. Lancet (London). August 8: 300-301.

Sakaguchi K; Nagayama M; Masaoka T; Nishimura A; Kageyama K; Shirai M; Akahori F. 1997. Effects of fenthion, isoxathion, dichlorvos and propaphos on the serum cholinesterase isoenzyme patterns of dogs. Vet Hum Toxicol. 39(1):1-5.

Sarin S; Gill KD. 1997. *In vitro* and *in vivo* interaction of dichlorvos with neuropathy target esterase in rat brain. FASEB Journal. 11(9):A1228.

Sarin S; Gill KD. 1998. Biochemical and behavioral deficits in adult rat following chronic dichlorvos exposure. Pharmacol Biochem Behav. 59(4):1081-1086.

Sarin S; Gill KD. 2000. Biochemical characterization of dichlorvos-induced delayed neurotoxicity in rat. IUBMB Life. 49(2):125-130.

Schafer EW. 1972. The acute oral toxicity of 369 pesticidal, pharmaceutical, and other chemicals to wild birds. Toxicol. Appl. Pharmacol. 21: 315-330. (As cited by WHO 1989).

Schafer EW; Brunton RB. 1979. Indicator bird species for toxicity determinations: Is the technique usable in test method development? In: Beck, J.R; ed. Vertebrate Pest Control and Management Materials. Philadelphia, Pennsylvania, American Society for Testing and Materials, pp. 157-168 (ASTM STP 680). (As cited by WHO 1989).

Schulz H; Nagymajtenyi L; Desi I. 1995. Life-time exposure to dichlorvos affects behaviour of mature rats. Hum Exp Toxicol. 14(9):721-726.

Schwetz BA; Ioset HD; Leong BKJ; Staples RE. 1979. Teratogenic potential of dichlorvos given by inhalation and gavage to mice and rabbits. Teratology. 20:383-388.

Schlinke JC; Palmer JS. 1973. Combined effects of phenothiazine and organophosphate insecticides in cattle. J Amer Vet Med Assoc. 163:756-758.

Schwetz, B.A.; Ioset, H.D.; Leong, B.K.J.; Staples, R.E. 1979. Teratogenic potential of dichlorvos given by inhalation and gavage to mice and rabbits. Teratology. 20:383-388.

SERA (Syracuse Environmental Research Associates, Inc.). 2001. Preparation of Environmental Documentation and Risk Assessments, SERA MD 2001-01a, draft dated July 2001. Syracuse Environmental Research Associates, Inc., Fayetteville, NY.

SERA (Syracuse Environmental Research Associates, Inc.). 2004. Documentation for the Use EXCEL Worksheets in Forest Service Risk Assessments (Version 3.01), SERA TD 2004-03.01a, dated March 13, 2004.

Shell Chemical Company. 1972. Summary of Basic Data for Vapona Insecticide. Rev. San Ramon, Calif.: Shell. MRID 00049640.

Shimizu K; Shiono H; Fukushima T; Sasaki M; Akutsu H; Sakata M. 1996. Tissue distribution of DDVP after fatal ingestion. Forensic Sci Int. 83(1): 61-66.

Shimizu K; Sasaki M; Fukushima T; Shiono H. 1997. A fatal case of DDVP poisoning: Biochemical and toxicological findings. Res Pract Forensic Med. 40(0):183-187.

Shinkaji N; Adachi T. 1978. [The effect of certain pesticides on the predaceous mite *Amblyseius longispinosus* (Evans) (Acarina: Phytoseiidae).] Akitsu. 2: 99-108 (in Japanese, with English tables). (As cited by WHO 1989).

Short CE; Cuneio J; Cupp D. 1971. Organophosphate-induced complications during anesthetic management in the horse. J Amer Vet Med Assoc. 159(11):1319-1327.

Siers DG; DeKay DE; Mersmann HJ; Brown LJ. 1976. Late gestation feeding of dichlorvos: A physiological characterization of the neonate and a growth-survival response. J Anim Sci. 42(2):381-392.

Siers DG; Danielson DM; Chai EY; Keasling HH. 1977. Late gestation feeding of dichlorvos: The response in artificially and dam-reared litters. J Anim Sci. 44(1):1-7.

Singh VK; Perkins CT; Schooley MA. 1968. Effects of dichlorvos fed to gravid sows on performance of their offspring to weaning. Midwestern Section Abstracts. pp. 1779-1780.

Slomka MB. 1970. Facts about No-Pest DDVP strips. Shell Chemical Co.; 18 p. As cited by Gillett et al. 1972a.

Slomka MB; Hine CH. 1981. Clinical pharmacology of Dichlorvos. Acta Pharmacol Toxicol (Copenhagen). 49(Suppl. V):105-108.

Starner N. 1993. Stability Study of dichlorvos in Hercon Vaportape II. Unpublished study prepared by Hercon Environmental Co. 123 p. MRID 43109301.

Stanton HC; Albert JR; Mersman HJ. 1979. Studies on the pharmacology and safety of dichlorvos in pigs and pregnant sows. Am J Vet Res. 40:315-320.

Stewart TB; Hale OM; Marti OG. 1975. Efficacy of two dichlorvos formulations against larval and adult *Hyostrongylus rubidus* in swine. Am J Vet Res. 36(6):771-772.

Sturm A; Hansen PD. 1999. Altered cholinesterase and monooxygenase levels in *Daphnia magna* and *Chironomus riparius* exposed to environmental pollutants. Ecotoxicol Environ Saf. 42(1):9-15.

Taylor P. 1996. Anticholinesterase agents. In: Hardman, J.G. and Limbird, L.E., eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition. New York: McGraw-Hill. 162-174.

Terayama K; Honma H; Kawarabayashi T. 1978. Toxicity of heavy metals and insecticides on slime mold *Physarum polycephalum*. J Toxicol Sci. 3: 293-304. (As cited by WHO 1989).

Thorpe E; Wilson AB; Dix KM; Blair D. 1972. Teratological studies with dichlorvos vapour in rabbits and rats. Arch Toxicol. 30:29-38.

Timmons EH; Chaklos RJ; Bannister TM; Kaplan HM. 1975. Dichlorvos effects on estrous cycle onset in the rat. Lab Anim Sci. 25(1):45-47.

Tracy RL; Woodcock, JG; Chodroff S. 1960. Toxicological Aspects of 2,2'-dichlorovinyl dimethylphosphate (DDVP) in Cows, Horses, and White Rats. J Econ Entomol. 53(4): 593-601. (As cited by WHO 1989).

Tucker RK; Crabtree DG. 1970. Handbook of toxicity of pesticides to wildlife. Washington DC, U.S. Department of the Interior, Fish and Wildlife Service, 43 pp (Resource Publication No. 84). (As cited by WHO 1989).

Tumbleson ME; Wescott RB. 1969. Serum biochemic values in piglets from sows fed dichlorvos prior to farrowing. J Cop Lab Med. 3:67-70.

Ueda A, Aoyama K, Manda F, Ueda T, Kawahara Y. 1994. Delayed-type allergenicity of triforine (saprol). Contact Dermatitis. 31 (3):140-145.

U.S. EPA (U. S. Environmental Protection Agency). 1975. Summary of reported episodes involving the impregnated resin strip, (No-Pest, Pest Strip) from January 1967 to March 1975. Pesticide Episode Review System, Report No. 35. Washington, DC: Pesticide Use Analysis Branch, Operations Division, Office of Pesticides Program; report dated April, 1975; 5 pp.

U.S. EPA (U. S. Environmental Protection Agency). 1981. Summary of reported pesticide incidents involving dichlorvos. Pesticide Incident Monitoring System, Report No. 403. Washington, DC: Health Effects Branch, Hazard Evaluation Division, Office of Pesticides Program; report dated January, 1981; 6 p.

U.S. EPA (U.S. Environmental Protection Agency). 1989. Recommendations for and Documentation of Biological Values for use in Risk Assessment. U.S. EPA, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH. ECAO-CIN-554. [pagination not continuous].

U.S. EPA (U. S. Environmental Protection Agency). 1994. Integrated Risk Information System (IRIS). Washington, DC. Available online at: http://www.epa.gov/iris/.

U.S. EPA (U. S. Environmental Protection Agency). 1999a. Environmental Fate and Effects Division, Phase I Comments on Dichlorvos. Available at: http://www.epa.gov/pesticides/op/ddvp.htm.

U.S. EPA (U. S. Environmental Protection Agency). 1999b. Error in Resin Strip Exposure Assessment for Dichlorvos (DDVP), PC Code 084001, DP Code D257002. Memorandum from David Jaquith to Kimberly Lowe dated August 16, 1999. Available at: http://www.epa.gov/pesticides/op/ddvp/resin.pdf.

U.S. EPA (U. S. Environmental Protection Agency). 2000a. Revised Preliminary HED Risk Assessment for Dichlorvos. Available at: http://www.epa.gov/pesticides/op/ddvp.htm

U.S. EPA (U. S. Environmental Protection Agency). 2000b. Dichlorvos, Cancer Assessment Review Committee Final Report. Dated February 2, 2000. Available at: http://www.epa.gov/pesticides/op/ddvp.htm

U.S. EPA/ORD (U.S. Environmental Protection Agency/Office of Research and Development). 1992. Dermal Exposure Assessment: Principles and Applications. EPA/600/8-91/011B. Interim Report. Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, DC. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12188

U.S. EPA (U.S. Environmental Protection Agency, Office of Research and Development). 1993. Wildlife Exposure Factors Handbook. Volumes 1 and 2. EPA/600/R-93/187a,b. Pagination not continuous. Available NTIS: PB94-174778 and PB94-174779.

U.S. EPA (U.S. Environmental Protection Agency/Office of Research and Development). 1996. Exposure Factors Handbook. National Center for Environmental Assessment, U.S. EPA, Washington, DC. EPA/600/P-95/002Ba-c. Avail. NTIS: PB97-117683, 97-117691, PB97-117709.

USDA (U.S. Department of Agriculture). 1995a. Gypsy Moth Management in the United States: A Cooperative Approach. Final Environmental Impact Statement. Appendix F (Human Health Risk Assessment).

USDA (U.S. Department of Agriculture). 1995b. Gypsy Moth Management in the United States: A Cooperative Approach. Final Environmental Impact Statement. Appendix G (Risk Assessment).

USDA (U.S. Department of Agriculture). 2001. Gypsy Moth Program Manual. Prepared by Plant Protection and Quarantine, Animal and Plant Health Protection Service. Draft dated May, 2001. Available at: http://www.aphis.usda.gov/ppq/manuals/online_manuals.html.

Vadhva P; Hasan M. 1986. Organophosphate dichlorvos induced dose-related differential alterations in lipid levels and lipid peroxidation in various regions of the fish brain and spinal cord. J Environ Sci Health. B21(5): 413-424. (As cited by WHO 1989).

Venkat JA; Shami S; Davis K; Nayak M; Plimmer JR; Pfeil R; Nair PP. 1995. Relative Genotoxic activities of pesticides evaluated by a modified SOS microplate assay. Environ Mol Mut. 25 (1):67-76.

Vent-Axia Inc. 2004. Ventilation Requirements. http://www.vent-axia.com/sharing/requirements.asp

Verma SR; Tonk IP. 1984. Biomonitoring of the contamination of water by a sublethal concentration of pesticides. A system analysis approach. ACTA Hydrochim Hydrobiol. 12(4): 399-499. (As cited by WHO 1989).

Verma SR; Rani S; Bansal SK; Dalela RC. 1980. Effects of the pesticides thiotox, dichlorvos, and carbofuran on the test fish *Mystus vittatus*. Water Air Soil Pollut. 13(2): 229-234. (As cited by WHO 1989).

Verma SR; Rani S; Bansal SK; Dalela RC. 1981a. Evaluation of the comparative toxicity of thiotox, dichlorvos, and carbofuran to two fresh water teleosts, *Ophiocephalus punctatus* and *Mystus vittatus*. ACTA Hydrochem Hydrobiol. 9(2): 119-129. (As cited by WHO 1989).

Verma SR; Rani S; Dalela RC. 1981b. Isolated and combined effects of pesticides on serum transaminases in *Mystus vittatus* (African catfish). Toxicol Lett. 8: 67-71. (As cited by WHO 1989).

Verma SR; Rani S; Dalela RC. 1981c. Pesticide-induced physiological alterations in certain tissues of a fish, *Mystus vittatus*. Toxicol Lett. 9: 327-332. (As cited by WHO 1989).

Verma SR; Rani S; Dalela RC. 1981d. Determination of the maximum acceptable toxicant concentration (MATC) and the safe concentration for certain aquatic pollutants. ACTA Hydrochim Hydrobiol. 9(3): 247-254. (As cited by WHO 1989).

Verma S; Bansal S; Gupta A; Pal N; Tyagi A; Bhatnagar M; Kumar V; Dalela R. 1982a. Bioassay trials with twenty-three pesticides to a fresh water teleost, *Saccobranchus fossilis*. Water Res. 16: 525-529. (As cited by WHO 1989).

Verma SR; Rani S; Dalela RC. 1982b. Indicators of stress induced by pesticides in *Mystus vittatus*: haematological parameters. Indian J Environ Health. 24(1): 58-64. (As cited by WHO 1989).

Verma SR; Rani S; Tonk IP; Dalela RC. 1983. Pesticide-induced dysfunction in carbohydrate metabolism in three fresh water fishes. Environ Res. 32: 127-133. (As cited by WHO 1989).

Verma SR; Rani S; Dalela RC. 1984. Effects of pesticides and their combinations on three serum phosphatases of *Mystus vittatus*. Water Air Soil Pollut. 21: 9-14. (As cited by WHO 1989).

Vial T; Nicolas B; Descotes J. 1996. Clinical Immunotoxicity of Pesticides. J Toxicol Environ Health. 48 (3):215-229.

Vigliani EC. 1971. Exposure of newborn babies to VAPONA insecticide. Toxicol Appl Pharm. 19:379-380.

Voccia I; Blakley B; Brousseau P; Fournier M. 1999. Immunotoxicity of pesticides: A review. Toxicol Indus Health. 15(1-2):119-132.

Vogin EE; Carson S; Slomka MB. 1971. Teratology studies with dichlorvos in rabbits (Abstract No. 42). Toxicol Appl Pharmacol. 19:377-378.

Wagner JE; Johnson DR. 1970. Toxicity of dichlorvos for laboratory mice — LD_{50} and effect on serum cholinesterase. Lab Anim Care. 20:45.

Wallach JD; Frueh R. 1968. Pilot study of an organophosphate anthelmintic in camels and primates. J Am Vet Med Assoc. 153(7):798-799.

Weis N; Stolz P; Krooss J; Meierhenrich U. 1998. Dichlorvos insect strips indoors: Pollution and risk assessment. Gesundheitswesen. 60(7):445-9. (Publication is in German with an English abstract.)

WHO (World Health Organization). 1988. Dichlorvos Health and Safety Guide. Geneva, Switzerland: World Health Organization. Health and Safety Guide. 18:1-157.

WHO (World Health Organization). 1989. Environmental health criteria for dichlorvos. Geneva, Switzerland: World Health Organization. Environmental Health Criteria 79:1-157.

Wills JH. 1972. The measurement and significance of changes in cholinesterase activities of erythrocytes and plasma in man and animals. CRC Critical Reviews in Toxicology. March, pp. 153-202.

Wyrobek AJ, Bruce WR. 1975. Chemical induction of sperm abnormalities in mice. Proc Natl Acad Sci USA. 72(11):4425-4429.

Yamanoi F. 1980. [Effect of insecticides on the progeny in the silkworm *Bombyx mori*: I. Effect of organophosphorus insecticides on egg laying and their hatching.] Nippon Sanshigaku Zasshi. 49(5): 434-439 (in Japanese). (As cited by WHO 1989).

Yamashita M; Yamashita M; Tanaka J; Ando Y. 1997. Human mortality in organophosphate poisoning. Vet Human Toxicol. 39(2):84-85.

Zavon MR; Kindel EA. 1966. Potential hazard in using dichlorvos resin insecticide. Advances in Chemistry Series. 60:177-186.

Table 2-1: Selected physical and chemical properties of DDVP

Synonyms and trade names	SD 1750; Astrobot; Atgard; Canogard; Dedevap; Dichlorman; Dichlorophos; Dichlorvos; Divipan; Equigard; Equigel; Estrosol; Herkol; Nogos; Nuvan: Task; Vapona; Verdisol (Budavari 1989)
U.S. EPA Reg. No.	8730-50 (Hercon 2004)
CAS number	62-73-7 (ARS/PPD 1995; Meylan and Howard 2000)
Molecular weight	220.98 (Budavari 1989)
Molecular formula	$C_4H_7Cl_2O_4P$ (ARS/PPD 1995; Budavari 1989; Meylan and Howard 2000)
SMILES Notation	O=P(OC)(OC)OC=C(CL)CL (Meylan and Howard 2000)
Appearance/state, ambient	Liquid (ARS/PPD 1995; Budavari 1989)
mg/L to ppm conversion for air concentrations	1 ppm = 9.04 mg/m^3 (NOISH 2002) 1 mg/m^3 = 0.11 ppm
Boiling point	120°C at 14 mm Hg (ARS/PPD 1995) 251.76 °C (Meylan and Howard 2000)
Vapor pressure	1.2×10^{-2} mm Hg (Budavari 1989) 1,600 mPa (ARS/PPD 1995)
Water solubility (mg/L)	10,000 (Budavari 1989) 8,000 (ARS/PPD 1995)
Specific gravity	1.44 (Shell Chemical Company 1972)
log K_{ow}	1.40-2.29 (ARS/PPD 1995) [i.e., $K_{ow} = 10^{1.4} = 25.1$] 0.60 (estimated) (Meylan and Howard 2000) 1.47 (experimental) (Meylan and Howard 2000; U.S. EPA 1992)
Henry's law constant	0.044 Pa m ^{3}/mole at 20°C (ARS/PPD 1995) 8.58E-007 atm-m^3/mole (Meylan and Howard 2000)
Koc	40.2 (Meylan and Howard 2000)
BCF	0.4486 (Meylan and Howard 2000)
Hydrolysis half-time (days)	0.022 to 0.347 (ARS/PPD 1995)
Aqueous photolysis halftime (days)	2.295 (ARS/PPD 1995)

Table 3-1. Common effects of acetylcholinesterase inhibition [a]

System	Receptor Type	Organ	Action	Manifestation
Parasympathetic	Muscarinic	**Eye**		
		Iris muscle	Contraction	Miosis
		Ciliary muscle		Blurred vision
		Glands		
		Lacrimal	Secretion	Tearing
		Salivary		Salivation
		Respiratory		Bronchorrhea; rhinitis; pulmonary edema
		Gastrointestinal		Nausea; vomiting; diarrhea
		Sweat		Perspiration
Sympathetic (sympatholytic)		**Heart**		
		Sinus node	Slowing	Bradycardia
		Atrioventricular (AV) node	Increased refractory period	Dysrhythmia; heart block
		Smooth Muscle		
		Bronchial	Contraction	Broncho-constriction
		Gastrointestinal		Vomiting; cramps; diarrhea
		Sphincter	Relaxation	Fecal incontinence
		Bladder		
		Fundus	Contraction	Urination
		Sphincter	Relaxation	Urinary incontinence
Neuromuscular	nicotinic	**Skeletal**	Excitation	Fasciculations; cramps followed by weakness; pupillary dilation; loss of reflexes; paralysis
		Heart	Excitation	Tachycardia
Central nervous		**Brain/Brainstem**	Excitation (early)	Headache; malaise; dizziness; confusion; manic or bizarre behavior
			Depression (late)	Depression, then loss of consciousness; respiratory depression; respiratory (diaphragm) paralysis

[a] Modified from ATSDR 1993

Table 3-2: Parameters used in DDVP air model

Parameter	Value	Units	Description/Comment/Reference
γ	37.5	Unitless	Apparent adsorption coefficient based on optimization using relative errors. See Worksheet A02b and Section 3.2.2.2 for discussion.
λ	0.023	day^{-1}	First-order release rate from Shell No-Pest Strips from Gillett et al. (1972a). Used to estimate γ from the data reported by Slomka (1970).
	0.04	day^{-1}	First-order release rate from VaporTape II strips based on data from Hercon (1994). See Worksheet A01.
RH	0.4	Unitless	Relative humidity used by Gillett et al. (1972a) and used for model application in Worksheets A02a, A02b, A03a, and A03b. This is a sensitive parameter. See text for discussion.
k	109.3	$days^{-1}$	Hydrolysis rate constant from Gillett et al. (1972a)
At*/*Va	0, 60, and 625, and 6500	day^{-1}	Air turnover rate – i.e., the ratio of air flow to room volume. Values of 0 and 60 used by Gillett et al (1972a) for no ventilation and very poor ventilation, respectively. Values of 300 and 3000 are selected as adequate ventilation for a garage and vehicle, respectively – see Section 4.4 for discussion.

Table 3-3: Summary of Risk Characterization for Human Health Risk Assessment [1]

Group	Scenario	Hazard Quotients Central	Lower	Upper	Toxicity Value	Units	Section
Workers							
	Inhalation During Assembly	**3**	0.9	**5**	0.1	mg/m^3	3.3.2.3
	Inhalation During Transport	**15**	1.0	**18**	0.1	mg/m^3	3.3.2.3
	Dermal During Assembly	0.5	0.2	**3**	0.0017	mg/kg	3.3.2.2
Child							
	Incidental Dermal Contact	**10**	**1.8**	**60**	0.0017	mg/kg	3.3.2.2
	Oral Exposure from Strip	**97**	**24**	**380**	0.0017	mg/kg	3.3.2.1
	Oral Exposure from Water	0.008	0.002	0.04	0.0017	mg/kg	3.3.2.1

[1] All of the exposure assessments on which these hazard quotients are based should be regarded as atypical and most are extreme. As noted in Section 3.2, typical exposures for workers and members of the general public will typically be negligible.

Table 4-1: Summary of Exposure Assessments and Risk Characterization for Non-target Species

Exposure Assessments						
		Estimated Exposures				
Species	**Scenario**	**Central**	**Lower**	**Upper**	**Units**	**Worksheet**
Racoon	Consumption	3.16E+01	1.05E+01	1.05E+02	mg/kg	D01 as DDVP-PVC
Small mammal	Contaminated Water	2.59E-05	8.64E-06	8.64E-05	mg/kg	D02 as free DDVP
Aquatic Species	Contaminated Water	0.000177	0.000059	0.00059	mg/L	D02

Risk Characterization						
		Risk Quotients[1]			**Toxicity Value**	
Species	**Scenario**	**Central**	**Lower**	**Upper**	**Value**	**Units**
Racoon	Consumption	0.1	0.04	0.4	240	mg/kg as DDVP-PVC
Small mammal	Contaminated Water	0.0001	0.00002	0.0002	0.5	mg/kg as free DDVP
Aquatic Species						
	Fish	0.006	0.002	0.02	0.03	mg/L NOEC as free DDVP
	Sensitive Invertebrates	**3**	0.8	**8**	0.00007	mg/L LC_{50} as free DDVP
	Tolerant Invertebrates	0.00001	0.000003	0.00003	21	mg/L LC_{50} as free DDVP

[1] Risk quotients are calculated as the exposure value, given in the upper section of the table divided by the toxicity value specified for the non-target species. This ratio is rounded to one significant digit.

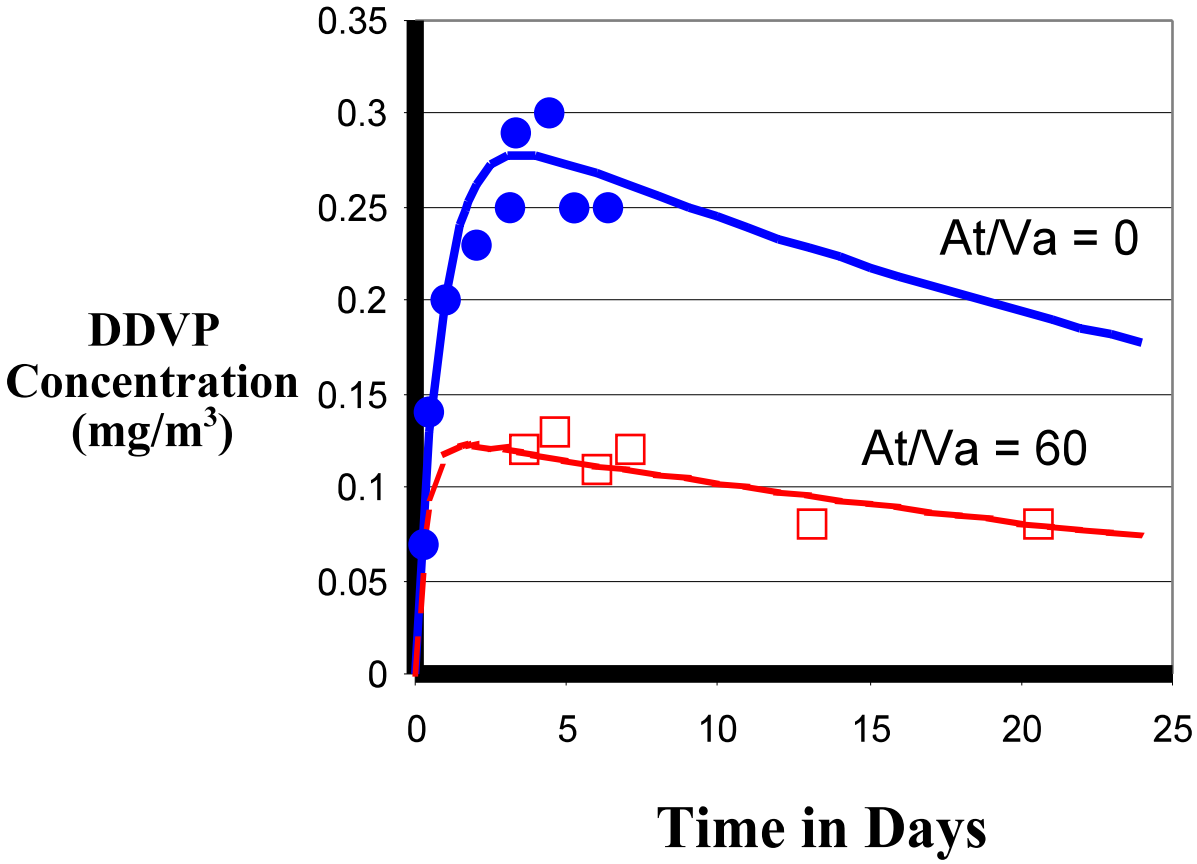


Figure 3-1: Concentration of DDVP in Air After the Placement of One Shell No-Pest Strip in an Unventilated Room (At/Va=0) and a Poorly Ventilated Room (At/Va=60)(data from Slomka 1970). See text for discussion and Worksheet A02b for details.

Appendix 1: Application and Optimization of DDVP Inhalation Exposure Model

Gillett et al. (1972a) proposed the following model for estimating concentrations of DDVP in air from the release of DDVP from PVC pest strips:

$$C_t = \frac{8}{\pi^2} \frac{M_0}{Va(1+\gamma)} \frac{\exp(-\lambda t) - \exp(\frac{-(kRH + \frac{At}{Va})}{1+\gamma} t)}{\frac{(kRH + \frac{At}{Va})}{\lambda (1+\gamma)} - 1} \qquad \text{(Eq. A-1)}$$

The terms in the above equation are defined as follows:

t	time after start of release
C_t	concentration of DDVP in air at time, *t* (days)
M_0	mass of DDVP in strip or strips at time zero (mg)
Va	volume of room or other space (m^3)
γ	apparent adsorption coefficient of DDVP on to surfaces
exp(***x***)	the exponential function, e^x, where is the constant 2.718 and ***x*** is any numeric expression
λ	first-order release rate constant ($days^{-1}$)
RH	relative humidity (proportion)
At	air flow rate (m^3/day)
k	first-order hydrolysis rate ($days^{-1}$)

and the parameters used in the model are summarized in Table 3-2.

The above equation is modified from Equation 3 in Gillett et al. (1972, p. 126). For simplicity, the term ***RH*** is used above rather than the term p/p_0 used by Gillett – i.e., the ratio of the ambient to the saturated vapor concentration of water. More significantly, the equation given in the Gillett publication – i.e., Equation 3, p. 126 – contains two typographical errors. Both errors are in the numerator to the second exponential function. The Gillett publication fails to note that the negative of the sum, ***k RH + At/Va***, must be used. These are essentially two first order processes – i.e., hydrolysis and dilution. If the negative of these values is not used, the equation models first-order growth rather than dissipation. Dissipation is clearly the intent of this term in the equation. The second more trivial error is that the ***k RH + At/Va*** term must be multiplied by ***t*** within the second exponential term. Otherwise, the units of the equation do not reduce to a concentration in air. This is analogous to the general equation for first-order absorption and first-

order elimination (e.g., Goldstein et al. 1974, p. 333). The discussion of the validation of this equation by Gillett et al. (1972a) and the implementation of this equation in the Worksheets uses the corrected form of the equation given above. Using the equation given by Gillett et al. (1972a) does not reproduce the results illustrated in Figure 4 of Gillett et al. (1972, p. 128) or in Worksheets A02a and A02b.]

Gillett et al. (1972a) applied this model to the data from Slomka (1970) in which a single Shell No-Pest Strip containing 20,000 mg of DDVP was placed rooms with a volume of 28.3 m^3 at 25°C and a relative humidity of 40%. Two different ventilation conditions were used, no ventilation and poor ventilation. No ventilation is characterized simply as a room with no air turnover – i.e., At/Va = 0. Poor ventilation is characterized as a room in which 20 air exchanges occurred per day – i.e., At/Va = 20. The apparent adsorption coefficient (γ) was treated as an empirical parameter and optimized to the data from Slomka (1970). All other model parameters were taken from the literature as specified in Table 3-2.

Gillett et al. (1972a) report an optimized value of 44.76 for the apparent adsorption coefficient (γ) but do not specify how this parameter was optimized. For the current risk assessment, the model given above was implemented in EXCEL and the data from Slomka (1970) was taken from Figure 4 in the publication of Gillett et al. (1972a). The apparent adsorption coefficient was then optimized using the EXCEL Solver function with the quasi-Newton method (with the tangent estimate and forward derivative options). Two sets of optimizations were conducted. The first was based on minimizing the standard square of error (Worksheet A02a) and the second was based on square of the relative error (Worksheet A02b). These optimizations yielded estimates of the apparent adsorption coefficient (γ) of 54.5 and 37.5, respectively, which bracket the estimate of 44.76 reported by Gillett et al. (1972a). As illustrated in Worksheets A02a and A02b, both of the optimized values fit the data from Slomka (1970) reasonably well. For the current risk assessment, the worker exposure estimates are based on the apparent adsorption coefficient (γ) 37.5, which leads to modestly higher estimates of exposure than do the higher estimates of the apparent adsorption coefficient. The fit of the Gillett et al. (1972a) model to the data from Slomka (1970) using the apparent adsorption coefficient (γ) of 37.5 is illustrated in Figure 3-1 (which is in turn taken from Worksheet A02b).

Appendix 2: Estimates of dermal absorption rates for DDVP

Table A2-1: Method for estimating the dermal permeability (K_p in cm/hr) and 95% confidence intervals.

Model parameters	ID	Value	
Coefficient for $k_{o/w}$	C_KOW	0.706648	
Coefficient for MW	C_MW	0.006151	
Model Constant	C	2.72576	
Number of data points	DP	90	
Degrees of Freedom (d.f.)	DF	87	
Critical value of $t_{0.025}$ with 87 d.f.[a]	CRIT	1.96	
Standard error of the estimate	SEE	45.9983	
Mean square error or model variance	MDLV	0.528716	
Standard deviation of model (s)	MSD	0.727129	$MDLV^{0.5}$
X′X, cross products matrix	0.0550931	-0.0000941546	-0.0103443
	-0.0000941546	0.0000005978	-0.0000222508
	-0.0103443	-0.0000222508	0.00740677

[a]Mendenhall and Scheaffer, 1973, Appendix 3, Table 4, p. A31.

NOTE: The data for this analysis are taken from U.S. EPA (1992), Dermal Exposure Assessment: Principles and Applications, EPA/600/8-91/011B, Table 5-4, pp. 5-15 through 5-19. The U.S. EPA report does not provide sufficient information for the calculation of confidence intervals. The synopsis of the above analysis was conducted in STATGRAPHICS Plus for Windows, Version 3.1 (Manugistics, 1995) as well as Mathematica, Version 3.0.1.1 (Wolfram Research, 1997). Although not explicitly stated in the U.S. EPA report, 3 of the 93 data points are censored from the analysis because they are statistical outliers: [Hydrocortisone-21-yl]-hemipimelate, n-nonanol, and n-propanol. The model parameters reported above are consistent with those reported by U.S. EPA but are carried out to a greater number of decimal places to reduce rounding errors when calculating the confidence intervals. See notes to Worksheet A07a for details of calculating maximum likelihood estimates and confidence intervals.

Table A2-2**:** Calculation of dermal permeability rate (K_p) in cm/hour for DDVP.								
Parameters	Value	Units	Reference					
Molecular weight	220.98	g/mole						
$K_{o/w}$ at pH 7	29.51	unitless						
$\log_{10} K_{o/w}$	1.47							
Column vector ***a*** for calculating confidence intervals (see Worksheet A07a for definitions.)								
a_1	1							
a_2	220.98							
a_3	1.47							
Calculation of $\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}$ - see Worksheet A07b for details of calculation.								
Term 1	0.0190806955							
Term 2	0.001157619							
Term 3	-0.006428795							
$\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}$	0.0138	calculation verified in Mathematica 3.0.1.1						
$\log_{10} k_p = 0.706648 \log_{10}(k_{o/w}) - 0.006151\ MW - 2.72576$							Worksheet A07b	
$\log_{10}$ of dermal permeability								
Central estimate	-3.04623542	±	$t_{0.025}$	×	s	×	$\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}^{0.5}$	
Lower limit	-3.21365532088	-	1.9600	×	0.727129	×	0.1174734012	
Upper limit	-2.87881551912	+	1.9600	×	0.727129	×	0.1174734012	
Dermal permeability								
Central estimate	0.00090	cm/hour						
Lower limit	0.00061	cm/hour						
Upper limit	0.0013	cm/hour						

Details of calculating $\mathbf{a'X'X\,a}$

The term $\mathbf{a'} \cdot (\mathbf{X'X})^{-1} \cdot \mathbf{a}$ requires matrix multiplication. While this is most easily accomplished using a program that does matrix arithmetic, the calculation can be done with a standard calculator. See details on following page.

Letting

$$\mathbf{a} = \{a\_1, a\_2, a\_3\}$$

and

$$(\mathbf{X'X})^{-1} = \{ \{b\_1, b\_2, b\_3\}, \{c\_1, c\_2, c\_3\}, \{d\_1, d\_2, d\_3\} \},$$

$\mathbf{a'}\cdot(\mathbf{X'X})^{-1}\cdot\mathbf{a}$ is equal to

Term 1: $\{a\_1 \times([a\_1\times b\_1] + [a\_2\times c\_1] + [a\_3\times d\_1])\} +$

Term 2: $\{a\_2 \times([a\_1\times b\_2] + [a\_2\times c\_2] + [a\_3\times d\_2])\} +$

Term 3: $\{a\_3 \times([a\_1\times b\_3] + [a\_2\times c\_3] + [a\_3\times d\_3])\}.$