DICHLORVOS
(DDVP)

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology and Worker Health and Safety Branches

Department of Pesticide Regulation

California Environmental Protection Agency

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Executive Summary

INTRODUCTION

This Risk Characterization Document for dichlorvos (DDVP) addresses potential human exposures from its use in California. Oncogenic, genotoxic, and neurotoxic effects have been identified in animal studies. DDVP is listed under California Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986, as a chemical known to the State of California to cause cancer.

DDVP is an insecticide used for space spray treatment of food processing, handling, and storage plants; feedlots; stockyards; corrals; holding pens; animal buildings; poultry houses; as well as residential, commercial and institutional buildings. It is also used in flea collars for pets. The direct food uses are on vegetables grown in greenhouses, on livestock, and processed food items to control pests. Humans may be exposed to DDVP through inhalation, direct contact on the skin, and the diet.

THE RISK ASSESSMENT PROCESS

The risk assessment process consists of four aspects: hazard identification, dose response assessment, exposure evaluation, and risk characterization.

Hazard identification entails review and evaluation of the toxicological properties of each pesticide. The dose-response assessment then considers the toxicological properties and estimates the amount which could potentially cause an adverse effect. The amount which will not result in an observable or measurable effect is the no-observed-effect level, NOEL. A basic premise of toxicology is that at a high enough dose, virtually all substances will cause some toxic manifestation. Chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes. In reality, these terms describe chemicals which require low or high dosages, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental studies which define the types of toxic effects which can be caused, and the exposure levels (doses) at which effects may be seen. State and federal testing requirements mandate that substances be tested in laboratory animals at doses high enough to produce toxic effects, even if such levels are many times higher than those to which people might be exposed.

The exposure assessment includes an estimation of the potential exposure through the occupational, residential, and dietary routes on an acute (one time) and chronic (long-term and lifetime) basis. The levels of exposure are determined by the amount of pesticide residue in the air or on specific commodities and processed foods, and the exposure rates by inhalation or ingestion.

The risk characterization integrates the toxic effects observed in the laboratory studies, conducted with high dosages of pesticide, to potential human exposures to low dosages of pesticide residues in the air and diet. The potential for possible non-cancer adverse health effects in human population after acute and chronic exposures (long-term and lifetime) is generally expressed as the margin of safety, which is the ratio of the dosage which produced no effects in laboratory studies to the estimated exposure dosage. For cancer effects after potential lifetime exposures, the probability of risk is calculated as the product of the cancer potency of the pesticide and the estimated exposure dosage.

BACKGROUND INFORMATION

DDVP is currently in Special Review, a process by the U.S. Environmental Protection Agency (USEPA) to determine the risk and benefit for the use of the pesticide. The major concerns are the inhibition of cholinesterase (ChE) activity, cancer, and nerve damage effects observed in animal studies. Cholinesterase is an essential enzyme in the body for the degradation of acetylcholine, a

transmitter of signals from the nerve to another nerve or muscles. The inhibition of ChE results in cholinergic signs such as salivation, diarrhea, tremors, respiratory failure, and death due to the accumulation of acetylcholine and over-stimulation of nerves or muscles. USEPA has proposed the revocation of DDVP tolerances for processed commodities because of concerns on DDVP-induced cancer in experimental animals.

TOXICOLOGY

Cholinergic signs (tremors and diarrhea) and death in experimental animals were the most sensitive endpoints for the acute toxicity of DDVP after inhalation and oral exposures. The dose (the no-observed-effect level or NOEL) at which death and cholinergic signs did not occur was used to quantitate the hazard for potential one-time exposure to humans. The long-term (chronic) health hazard to humans from repeated exposures to DDVP was evaluated based on the inhibition of cholinesterase activity in the brain observed in both inhalation and oral studies. The cancer risk from lifetime exposure was evaluated based on the finding of leukemia in rats after chronic oral exposure.

EXPOSURE ANALYSIS

The potential exposure scenarios of humans to DDVP include the work place, home, and the food. Workers are exposed to DDVP in the work place due to warehouse fumigation, livestock applications, and structural applications. The general population is exposed to DDVP in the home from the uses as directed spray, fogger, flea collars, and no-pest strips; as well as in the diet from the use of DDVP on vegetables, livestock, and processed foods. The worker exposure was also assessed in combination with exposure at home (from home use and in the diet).

RISK EVALUATION

A margin of safety (MOS) of at least 100 is generally considered sufficient to be protective of human health. The following exposure groups have MOSs greater than 100: chronic exposure of residents after structural fumigation; acute and chronic exposures of pet owners to flea collars; acute dietary exposure of all population subgroups; and chronic dietary exposure of all subgroups, except children 1 to 6 years old.

The following exposure groups have MOSs less than 100 for non-oncogenic effects: acute, chronic, and lifetime exposures for all workers exposed to DDVP only at work and in combination with exposure at home; acute exposure of residents after structural fumigation; acute, chronic, and lifetime exposures of residents to home-use foggers; acute and chronic exposures of children to no-pest strips; and chronic dietary exposure of children 1 to 6 years old.

For oncogenic effects, the excess lifetime oncogenic risks of the workers, residents, and the general population exposed to DDVP at work, at home, or in the diet and in combinations were greater than the benchmark oncogenic risk level of 1×10^{-6} which is generally considered protective of human health.

The MOSs for the acute exposure to DDVP on vegetables and livestock products at tolerance levels are greater than 100.

CONCLUSIONS

The toxicological risk of potential exposure to DDVP was evaluated for occupational, residential, dietary and combined uses based on the inhibition of brain ChE activity, clinical signs, and the finding of mononuclear leukemia in animal studies. Using the conventional benchmark levels, a margin of safety of at least 100 for non-oncogenic effects and a risk level of 1×10^{-6} or less for oncogenic effects are generally considered sufficiently protective of human health. The exposure levels of only a few groups meet those benchmark levels. Groups which have exposure levels which do not meet the benchmark levels are: all people occupationally exposed to DDVP alone and in combination with home exposure on an acute, chronic, and lifetime basis; people exposed through residential use on an acute, chronic, and lifetime basis; and the general population exposed through the diet on a potentially lifetime basis.

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I. SUMMARY

A risk assessment has been conducted on dichlorvos (2,2-dichlorovinyl dimethyl phosphate, DDVP) because of possible adverse effects identified in rat and mouse oncogenicity, neurotoxicity, and genotoxicity studies. DDVP is listed under Proposition 65 as a chemical known to the State of California to cause cancer.

INTRODUCTION

Chemical Identification- DDVP is an organophosphate insecticide used for the control of pests in enclosed spaces such as buildings and residents, on pets, on vegetables in greenhouses, on commodities during post-harvest storage, and on livestock. From 1991 to 1993, approximately 4000-5000 pounds/year of DDVP were used primarily for structural and livestock pest control.

DDVP exerts its toxicological activity primarily through the inhibition of acetylcholinesterase activity. Signs and symptoms associated with its toxicity included salivation, diarrhea, tremors, and death.

Regulatory History- DDVP is currently under Special Review by the U.S. Environmental Protection Agency (USEPA). In 1989, the Scientific Advisory Panel of the USEPA recommended that DDVP oncogenicity classification be changed from a B2 carcinogen to a C carcinogen. Because of oncogenic risks, most of the food tolerances have been revoked. A revocation of tolerances for bagged or packaged nonperishable commodities has been proposed. In 1993, the registrations of DDVP in California for the use on fresh vegetables were voluntarily cancelled by the registrants.

Environmental Fate- DDVP is not likely to persist in the environment since it is volatile, does not bind to soil, and is hydrolyzed. The half-life of DDVP was 5.2 days in aqueous buffered solution at pH 7. The half-lives ranged from 9 to 20 days for DDVP in tap water with pH 7.5 to 8.1. DDVP was also degraded by soil microorganisms with a half-life of 10.2 hours. After foliar application, DDVP residues on the leaves may be volatilized, hydrolyzed, and absorbed into the plants.

TOXICOLOGY PROFILE

Pharmacokinetics- DDVP was rapidly absorbed by the oral, intravenous, intraperitoneal, and inhalation routes and slowly absorbed by the dermal route. After absorption, the radioactivity distributed to major organs including the liver and kidneys. DDVP was metabolized completely by ester hydrolysis and demethylation. Initial metabolites were mono- and dimethyl phosphates, and desmethyl DDVP. Once formed, they may be further metabolized. Final metabolites were either incorporated in tissues or excreted. Major routes of excretion were in the urine and in the exhaled air, while to a lesser extent in the feces and in the milk. Excretion routes, tissue distribution, and urinary metabolites in rats were similar following inhalation or oral exposures.

Acute Toxicity- DDVP was more toxic than its metabolites as determined by the magnitude of the 72 hour lethal dose after intraperitoneal administration. Human exposure of DDVP by ingestion and from the use of no-pest strips resulted in the inhibition of plasma cholinesterase (ChE) activity, but not erythrocyte ChE activity. Acute effects observed in laboratory animals from oral or inhalation exposures included diarrhea, irritability, salivation, lethargy, pupillary constriction, tremors, decreased neuromuscular functions, and death.

Subchronic Toxicity- Subchronic exposures to DDVP resulted in the inhibition of brain, erythrocyte, or/and plasma ChE activities in humans, rats, mice, dogs, and cows. Clinical signs observed in laboratory animals were tremors, diarrhea, decreased body weight gain, increased frequency of salivation and urine staining in rats, and increased activity and urination in dogs. Other effects included statistically significant decreases in red blood cell parameters (cell counts, hemoglobin, and

hematocrit) in rats. From studies with lactating rats and milk cows after oral subchronic dosing, ChE activity depression and cholinergic signs were noted in the dams, but not in the offspring.

Chronic Toxicity and Oncogenicity- DDVP caused the inhibition of plasma, erythrocyte, and brain ChE activities. Other non-oncogenic effects included hepatocellular lesions (vacuoles in the cytoplasm, cell swelling, prominence of cell membranes), reduced body weight, emesis, salivation, and ataxia. Oncogenic effects observed in rats and mice were pancreatic adenoma; mononuclear leukemia; mammary gland carcinoma, fibroadenoma, and adenoma; forestomach papillomas and carcinomas; and pituitary adenomas. DDVP also increased tumor growth rate in rats given leukemia transplant.

Genotoxicity- DDVP was genotoxic in some in vitro systems, including assays with Salmonella TA 100 strain and Schizosaccharomyces pombe, mouse lymphoma forward mutation assay, and unscheduled DNA synthesis assay using human epithelial cells. However, DDVP was not genotoxic in the micronucleus, dominant lethal, in vivo chromosomal aberrations, and in vivo sister chromatid exchange assays. Studies conducted in the presence and absence of a liver preparation (S-9 fraction) showed that the decrease in genotoxicity in the presence of the preparation may be due to the inactivation of DDVP by liver esterases. Methylated DNA was detected in tissues of mice given DDVP by intraperitoneal injection, but not in rat tissues when DDVP was given by inhalation.

Reproductive Toxicity- Exposure of rats to DDVP in the water during reproduction resulted in the inhibition of plasma, erythrocyte, and brain ChE. Clinical signs were observed in both parents and offsprings. Other toxicity included decreased body weights and decreased water consumption. Re-mating of the F_1 females after the F_2 generation showed that decreased estrous cycling and increased incidence of abnormal estrus cycling. Mice exposed to DDVP-containing resin strips showed only plasma ChE depression and no effect on reproduction.

Developmental Toxicity- DDVP, given by oral or inhalation routes, was not teratogenic in rats, mice, or rabbits. Cholinergic signs (tremors, ataxia, diarrhea, and other effects) were observed in the pregnant rats and rabbits.

Neurotoxicity- Possible adverse effects of nerve fiber degeneration and spinal cord degeneration were observed in chickens treated with DDVP. No acute delayed neurotoxicity in hens was reported, except at lethal doses. Acute neurotoxicity study in the rat given DDVP by gavage resulted in cholinergic effects which included gait alteration, constricted pupils, tremors, and salivation.

RISK ASSESSMENT

Hazard Identification- The no-observed-effects levels (NOELs) from both inhalation and oral studies, and oncogenic risk from an oral study were used to evaluate the health hazards from potential exposure by workers and the general population to DDVP. For non-oncogenic endpoints, acute and chronic inhalation and dietary exposures were considered. For oncogenic endpoints, inhalation and dietary exposures to DDVP were assessed.

For acute inhalation exposure, the definitive NOEL was 1.25 *u*g/L or 0.65 mg/kg-day (NOEL adjusted for exposure duration and respiration rate). The NOEL was based on death in pregnant rabbits after 2 days of inhalation exposure to a LOEL of 2 *u*g/L DDVP.

The NOEL for acute oral exposure was 0.5 mg/kg-day based on tremors, salivation, neuromuscular deficits, and other cholinergic signs observed in rats within 1 day after a single dose by gavage.

The NOELs for chronic toxicity were based on the inhibition of brain ChE activity in a one-year dog oral study and a two-year rat inhalation study. The adjusted NOELs for inhalation and oral routes were 0.025 mg/kg-day, and 0.05 mg/kg-day, respectively.

Oncogenic risk was determined based on the finding of mononuclear leukemia in rats given DDVP by gavage for 2 years. The human equivalent potency factors were 0.20 mg/kg-day^{-1} for q_1 and 0.35 mg/kg-day^{-1} for q_1*, the 95th percentile upper confidence limit.

Exposure Assessment- The potential health hazard associated with the use of DDVP was considered for occupational, residential, and dietary exposures under acute, chronic, and lifetime scenarios. The population subgroups exposed to DDVP in the work place were workers involved in warehouse fumigation, livestock applications, and structural applications. Residential exposures to DDVP were due to the use of liquid sprays, foggers, no-pest strips, and flea collars. Dietary exposures to DDVP were due to the use on raw agricultural commodities (RAC), livestock, and processed foods. Estimates for chronic dietary exposure by USEPA were also assessed.

RISK APPRAISAL

The margins of safety (MOSs) for non-oncogenic effects from acute, chronic, and lifetime occupational exposures were less than 100 for the workers involved in warehouse fumigation, livestock applications, and structural applications. The lifetime oncogenic risk for the workers was greater than 1×10^{-6}.

For residential exposure, the MOSs for non-oncogenic effects were greater than 100 only for structural residents (chronic and lifetime), and pet owners (acute, chronic, and lifetime). The MOSs were less than 100 for all other home uses under acute, chronic, and lifetime exposures. The lifetime oncogenic risk for the residents under all exposure scenarios was greater than 1×10^{-6}

For dietary exposure assessment using either USEPA or DPR exposure estimates, the MOSs for non-oncogenic effects were at or greater than 100 for all population subgroups for acute and chronic exposure. For lifetime exposure to all commodities, the oncogenic risk for the U.S. population was greater than 1×10^{-6} for both DPR and USEPA estimates.

For combined exposures in the work place and at home, the MOSs for non-oncogenic effects for all the workers were less than 100 and the lifetime oncogenic risk was greater than 1×10^{-6}.

TOLERANCE ASSESSMENT

The MOSs for the acute exposure based on individual tolerances on RACs and livestock products were greater than 100.

CONCLUSIONS

The toxicological risk of potential exposure to DDVP was evaluated for occupational, residential, dietary and combined uses based on the inhibition of brain ChE activity, clinical signs, and the finding of mononuclear leukemia in animal studies. Using the conventional benchmark levels, a margin of safety of at least 100 for non-oncogenic effects and a risk level of 1×10^{-6} or less for oncogenic effects are generally considered sufficiently protective of human health. The exposure levels of only a few groups meet those benchmark levels. Groups which have exposure levels which do not meet the benchmark levels are: all people occupationally exposed to DDVP alone and in combination with home exposure on an acute, chronic, and lifetime basis; people exposed through residential use on an acute, chronic, and lifetime basis; and the general population exposed through the diet on a potentially lifetime basis.

II. INTRODUCTION

The human health risk assessment has been conducted for the active ingredient dichlorvos (DDVP) because of adverse effects in oncogenicity, genotoxicity, and neurological studies. DDVP is listed under California Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986, as a chemical known to the State of California to cause cancer.

A. CHEMICAL IDENTIFICATION

Dichlorvos (2,2-dichlorovinyl dimethyl phosphate, DDVP) is an organophosphate pesticide. It is effective against aphids, spider mites, caterpillars, thrips, and white flies. The major use is for space treatment of food processing, handling, and storage plants; feedlots; stockyards; corrals; holding pens; animal buildings; poultry houses; as well as commercial and institutional buildings. The only "direct" food uses are on beef and dairy cattle skin to control insects, as post-harvest treatment of processed commodities, and in the greenhouses for tomatoes, radishes, lettuce, and cucumbers. DDVP is also used in homes for insect control. Tolerances are established for the use of DDVP in raw agricultural and processed commodities (Appendix A).

The primary biological activity for DDVP is through its inhibition of cholinesterase (ChE) enzymes. ChEs are a family of enzymes found throughout the body that hydrolyze choline esters. In the nervous system, acetylcholinesterase (AChE) is involved in the termination of impulses across nerve synapses including neuromuscular junctions by rapidly hydrolyzing the neural transmitter, acetylcholine. Inhibition of AChE leads to accumulation of acetylcholine in the synaptic cleft which results in over-stimulation of the nerves followed by depression or paralysis of the cholinergic nerves throughout the central and peripheral nervous systems. AChE is highly selective, although not exclusively, for acetyl esters as substrates (Brimijoin, 1992). Another form of cholinesterase, butyrylcholinesterase (BuChE), preferentially hydrolyses butyryl and proprionyl esters, depending on the species; however, it will hydrolyze a wider range of esters, including acetylcholine (Brimijoin, 1992). Unlike AChE, the physiological function of BuChE is not known. Although AChE and BuChE are found in most tissues, their ratio varies from one tissue to another and from one species to another. In rats, AChE is the predominant form of ChE in the central nervous system and in the neuromuscular junctions of peripheral tissues such as the diaphragm, skeletal muscle, heart, and spleen (Gupta *et al.*, 1991; Mendoza, 1976). AChE and BuChE are present in roughly equal proportions in the liver and kidneys of rats. Non-synaptic AChE is also present to a lesser extent in peripheral tissues; however, its function is not known (Brimijoin, 1992). Non-synaptic AChE is essentially the only ChE present in erythrocytes of higher animals. BuChE is the predominant form of ChE in the plasma of humans; however, the ratio of AChE to BuChE varies greatly from species to species and between sexes. For example, the AChE:BuChE ratio in human plasma is approximately 1:1000, but closer to 1:2 in female rats and 3:1 in male rats.

In acutely toxic episodes, muscarinic, and nicotinic receptors are stimulated by acetylcholine with characteristic signs and symptoms occurring throughout the peripheral and central nervous systems (Murphy, 1986). Peripheral muscarinic effects can include increased intestinal motility, bronchial constriction and increased bronchial secretions, bladder contraction, miosis, secretory gland stimulation and bradycardia. Peripheral nicotinic effects include muscle weakness, twitching, cramps and general fasciculation. Stimulation of muscarinic and nicotinic receptors in the central nervous system can cause headache, restlessness, insomnia, anxiety, slurred speech, tremors, ataxia, convulsions, depression of respiratory and circulatory centers, and coma. Death is usually due to respiratory failure from a combination of peripheral and central effects.

DDVP appears to be more selective for insects than for mammals (van Asperen an Dekhuijzen, 1958). The inhibition by DDVP of mouse brain ChE was reversible while the inhibition of fly head ChE was irreversible. DDVP also had higher affinity for fly head ChE than for mouse brain ChE. Sustained atmospheric DDVP concentration as low as 0.015 *u*g/liter (L) is effective for fly and mosquito control, but 0.15 *u*g/L is required for 100% kill in 30 minutes (WHO, 1967).

B. REGULATORY HISTORY

DDVP was first registered in 1954 for insecticidal use in the United States (USEPA, 1987). It was marketed by Shell Chemical Company under the trademark of Vapona™ in 1960, and No-Pest™ resin strips were available in 1963. In 1990, the State of California filed a Complaint for Civil Penalties, Injunctive and Declaratory Relief against Amvac Chemical Corporation and Bio-strip, Inc., on the sale of DDVP-containing no-pest strips without proper warning labels as required by Proposition 65. The case was settled out of court when Amvac Chemical Corporation agreed to place proper warning labels on the products and on the display shelves (State of California, 1992).

In 1980, the U.S. Environmental Protection Agency (USEPA) referred DDVP to the Special Review process because of studies which indicated that DDVP was mutagenic and may be oncogenic, neurotoxic, and teratogenic (USEPA, 1988). The result of the review issued in 1982 found DDVP to be carcinogenic and mutagenic, but not teratogenic. In addition, evaluation of the chronic and subchronic toxicity studies showed that DDVP was a hepatotoxin and a potent ChE inhibitor. In 1988, the USEPA initiated a formal Special Review (USEPA, 1988). Evidence from chronic studies showed that DDVP by the oral route was a potential human carcinogen, and was classified as a category B2 carcinogen. However, in 1989, the USEPA Scientific Advisory Panel recommended that DDVP should be classified as a category C carcinogen (Mennear, 1989). The Panel based their recommendation on the marginal dose-related increase in pancreatic tumors, the lack of oncogenicity in chronic inhalation studies in rats, the variability in the incidences of mononuclear cell leukemia in rats, and the difficulties in the interpretation of the forestomach papilloma and carcinoma in mice.

As part of Special Review, USEPA determined that the oncogenicity observed in the gavage study (Chan, 1989) was not applicable for the inhalation or dermal routes of exposure (Ghali, 1993). For oncogenicity by the oral route, the calculated oral slope factor (q_1*) for human was 0.122 mg/kg-day^{-1} derived from the geometric means of slope factors for forestomach tumors in mice, and mononuclear cell leukemia in rats from a NTP study (Fisher and Pettigrew, 1994). The International Agency for Research on Cancer (IARC) determined that there was sufficient evidence for DDVP carcinogenicity in experimental animals, but inadequate evidence for carcinogenicity in humans. The overall evaluation by IARC was possibly carcinogenic to humans (IARC, 1991). In 1993, a Data Call-In notice for illness data from DDVP registrants was required by the USEPA (Barolo, 1993).

In 1989, Amvac Chemical Corp. indicated that it would only support indoor uses and livestock feedyard uses, but not greenhouse uses, field uses, or lawn applications (Jellinek, 1989). In 1993, the registrations of DDVP (Flora-Fog and GH-19) in California for its use on RACs (cucumbers, tomatoes, lettuces, and radishes) in greenhouses were cancelled by the registrants.

While Special Review was in progress, USEPA revoked the tolerance for the residues of DDVP on figs, a use no longer registered (USEPA, 1989 and 1991a). A revocation of tolerances for DDVP on bagged or packaged nonperishable food was proposed because the carcinogenic risk (1×10^{-5}) exceeded the de minimis level (1×10^{-6}) (USEPA, 1991b and 1991c; USEPA, 1993b). However, USEPA has granted a stay on the revocation (USEPA, 1994). The tolerance for DDVP in non-perishable commodities in bulk form was not affected by the proposal.

In 1995, Amvac Chemical Corp. voluntarily cancelled the following uses: domestic dwellings (except for impregnated resin strips, total release fogger, and crack and crevice applications), rangeland grasses, greenhouses, tomatoes, tobacco and tobacco warehouses, food service establishments, certain food manufacturing establishments, all aerial applications, aircraft, and buses (USEPA, 1995a). However, USEPA in the Notice of Preliminary Determination (Position Document 2/3) from the Special Review proposed cancellation of most uses of DDVP (USEPA, 1995b). The proposed cancelled uses include: use on bulk, packaged or bagged non-perishable processed or raw agricultural commodities; all residential and homeowner uses (including commercial application in the home); use in warehouses (except for the use of impregnated strips not in contact with food); use in commercial, institutional, and industrial areas (including food manufacturing, food processing, and

food service facilities); hand-held application to farm livestock (except poultry); use on turf, ornamental lawns and plants; use in airplanes; pet flea collars; and use in trucks, shipholds, and railcars. Restrictions were placed on the use of DDVP in greenhouses and mushroom houses, passenger buses, kennels, feedlots, animal premises, livestock, manure, and garbage dumps.

The oral reference dose (RfD) of 0.0005 mg/kg-day previously set for DDVP has been withdrawn by the USEPA pending further review of the data (USEPA, 1993a). The World Health Organization (WHO) acceptable daily intake (ADI) is 0.004 mg/kg-day (WHO, 1993) based on the absence of erythrocyte ChE inhibition in human volunteers given DDVP 0.9 mg three times a day for 21 days (Boyer *et al.*, 1977). The Permissable Exposure Level (PEL) in the air for occupational exposure is 0.1 ppm (0.9 mg/m^3) set by the American Conference of Governmental Industrial Hygienists and required by the California Department of Occupational Health Administration (Barclays California Code of Regulations, 1991).

C. TECHNICAL AND PRODUCT FORMULATIONS

Amvac Chemical Corp. is the primary registrant for technical DDVP in the US (Farm Chemicals Handbook, 1991). In addition to technical DDVP, DDVP is found in liquid formulations, resin strips, flea collars, foggers, and pressurized sprays.

D. USAGE

In California, the reported use was 5900, 5700, and 3600 pounds for 1991, 1992, and 1993, respectively (DPR, 1993). The major uses are for pest control in structures and on livestock (cattle and poultry), each use accounting for 30-40% of total pounds. The only direct food uses were on cucumbers, nut crops, and processed commodities and were 10% or less of the total. Lesser amounts are used in landscape maintenance, in nursery (non-food), and other pest control sites.

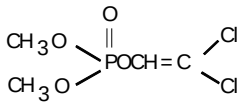
The use of DDVP on mushrooms and figs is no longer on the California registered labels. The only greenhouse use formulations were Flora-Fog™ for cucumbers, tomatoes, lettuce, and radishes and GH-19™ for tomatoes. The application rate was 1 ounce/3000 ft^3 (or 1 gm/1000 ft^3) and the preharvest interval for both products was 24 hours after application. There is no pre-slaughter interval for the use of DDVP directly on the skin of livestock. Label instructions include directions to use an approved cleaning solution to clean teats prior to milking.

E. ILLNESS REPORTS

From 1982 to 1990, 78 cases of human illness and/or injury were reported to the California Pesticide Illness Surveillance Program that were associated with exposure to DDVP (Mehler, 1993; Appendix B). The cases included 60 systemic illnesses, 12 eye injuries, and 6 skin injuries. No hospitalizations were reported and only 1-2 work day losses for 5 cases. A survey of poison control centers showed several reports of children who chewed on DDVP-containing resin strips, but without clinical symptoms (Gillette, 1972). Ingestion of 400 mg/kg DDVP was lethal to a man in a suicide, while 100 mg/kg was sublethal to a woman who survived after intensive treatment (Hayes, 1982).

F. PHYSICAL AND CHEMICAL PROPERTIES [a]

Chemical name:	2,2-dichlorovinyl dimethyl phosphate
CAS Registry number:	62-73-7
Common name:	dichlorvos, dichlorovos
Trade names:	Vapona, Elastrel, Flora-Fog, GH-19
Molecular formula:	$C_4H_7Cl_2O_4P$
Molecular weight:	220.98 g/mole
Chemical structure:	



Physical appearance:	Colorless to amber liquid
Solubility:	10 g/L - 15.7 g/L in water, 5 g/L in glycerol, miscible with alcohol and most nonpolar solvents
Boiling point:	35°C at 0.05 mm Hg
Vapor pressure:	0.012 mm Hg at 20°C
Octanol-water coefficient:	38.4 at 25°C
Henry's Law constant:	3.06×10^{-7} atm. m^3/g-mole
Additional source:	metabolic product of naled (Dibrom) and trichlorfon (Dipterex, Dylox, Proxol) (Appendix C)

[a/] Amvac Chemical Corp., 1987; Chan, 1989; Farm Chemicals Handbook, 1991; The Merck Index, 1989; and White, 1990.

G. ENVIRONMENTAL FATE

Summary: DDVP is not likely to persist in the environment since it is volatile, does not bind to soil, and is hydrolyzed. The half-life of DDVP was 5.2 days in aqueous buffered solution at pH 7. The half-lives ranged from 9 to 20 days for DDVP in tap water with a pH 7.5 to 8.1. DDVP was also degraded by soil microorganisms with a half-life of 10.2 hours. After foliar application, DDVP on the leaves may be volatilized, hydrolyzed, and absorbed into the plants.

Hydrolysis

The half-lives of DDVP (^{14}C, 95% purity, 9-12 ppm) were 12,5, 5.8, and 0.9 days, respectively, in aqueous buffered solution at pH 5, 7, and 9 after incubation in the dark at 25°C for 28 days (pH 5), 38 days (pH 7), or 3 days (pH 9) (Vithala, 1990a). The metabolites detected were 2,2-dichloroacetaldehyde, des-methyl DDVP, glyoxylic acid, and 2,2-dichloroacetic acid. However, the half-life of DDVP in tap water (pH 7.5-8.1) was longer at 9-20 days (Leafe and Feiler, 1988).

Microbial Degradation

DDVP (^{14}C, 97% purity, 12 ppm) was added to non-sterilized sandy loam soil and incubated in the dark at 25°C under aerobic conditions (Vithala, 1990b). The half-life for DDVP in the soil was 10.2 hours. After 96 hours, DDVP residue was not detectable. The non-volatile metabolites were 2,2-dichloroacetic acid (major metabolite), 2,2-dichloroacetaldehyde, and dichloroethanol. The only volatile metabolite detected was CO_2 which at 360 hours was 60% of the initial DDVP concentration.

Mobility (Soil, Air, Plants)

In a soil mobility study, DDVP (^{14}C, 87% purity) was mixed in soil and water (1:4). After 3 hours of incubation, DDVP residues remaining in sandy, silt, and clay soils were 8, 12, and 24% of the initial concentrations, respectively (Vithala, 1990c). Desorption experiments showed that DDVP was released from the soil.

DDVP was not found in well water samples from 17 California counties monitored from 1986 to 1992 (DPR, 1992). The minimum detection limit (MDL) for the studies ranged from 0.005 to 1 ppm with more than 50% of the samples analyzed at a MDL of 0.1 ppm.

Application of DDVP (0.5 g/1000 cubic ft) by aerosol in a warehouse experiment showed that DDVP was rapidly dissipated (Knight, 1985). The air concentration of DDVP declined from 17.1 mg/m^3 after 1 hour to 0.12 mg/m^3 after 16 hours.

The release of DDVP from resin strips to the ambient air was dependent on ventilation, air temperature, and humidity. Under conditions of domestic use, the air concentrations of DDVP increased rapidly with a highest mean concentration of 0.04 mg/m^3 at 1-2 weeks after placement (Elgar and Steer, 1972). Three months after placement, the mean concentration in the air declined to 0.01 *u*g/L.

Plant Residues/Metabolism

Multiple (1-5) applications of DDVP (Vaponite™, 4 pounds/acre) on figs showed that there was an accumulation of residues 5 days after treatment (Rutgers University, 1981). The range of residue levels in fresh figs was of <0.005 to 0.05 ppm. The residue levels in ground dried (air dried on the ground and then washed) figs (0.116-0.527 ppm) were higher than those in dehydrated (washed and then dried at 120°C for 48 hours) figs (<0.005-0.054 ppm).

Direct applications of DDVP (^{32}P, 67-78% purity) to cotton seedlings showed that 50% of the dose volatilized within the first 5 minutes (Casida *et al.*, 1962). The half-life of DDVP in the seedling was 1.2 hours, and DDVP was metabolized by hydrolysis. In an absorption study with peas, cotton, and corn seedlings, DDVP was transported into the plants and subsequently hydrolyzed. The hydrolysis rates follow first order kinetics with half-lives of 3, 9, and 9 hours, respectively for the three plants studied.

DDVP, used as a fogger in greenhouses, was released as a 10% aerosol (1 gram DDVP/1000 ft^3) in greenhouses with tomatoes, lettuce, cucumbers, and radishes (Beroza and Hill, 1968). Air samples showed that DDVP concentrations decreased rapidly. Within 15 minutes, the air concentration decreased from the initial 35 *u*g/L to 1.5 *u*g/L. After 135 minutes, the average air level was 0.12 *u*g/L. Samples for each vegetable were collected after the release of DDVP into the air. The highest residue for tomatoes was 0.023 ppm after 88 hours, for lettuce was 0.026 ppm after 160 hours, for cucumbers was 0.055 ppm after 160 hours, and for radishes was 0.003 ppm (MDL= 0.003 ppm). Because of the limited number of samples analyzed per time period after application and because the levels were similar, all the residue values for each commodity were averaged, and the results from this study were used for the dietary exposure assessment.

III. TOXICOLOGY PROFILE

Pharmacokinetics and toxicological studies of DDVP are summarized in this section. Studies involving cattle and other farm animals are included since DDVP is used directly on livestock. Acceptability of the studies (except for genotoxicity studies) where noted, is determined by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies by the Department of Pesticide Regulation (DPR) is based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). The toxicology summary for studies reviewed for SB 950, The Birth Defect Prevention Act of 1984, is available upon request to the Registration Branch. DDVP is also the metabolite of the pesticides naled and trichlorfon. A summary of the toxicology of naled and trichlorfon is presented in Appendix C.

The animal inhalation toxicity studies reviewed in this document were conducted with whole-body exposure (except where noted). Therefore, the internal dose under these exposure conditions may be higher than that calculated based on the air concentration. Additional exposure to DDVP by oral ingestion due to licking of the fur, dermal absorption, and contamination of food and water are possible. Blair *et al.* (1976) estimated that the retained dose by all routes was 2 times that for nose-only inhalation exposure. However, the estimate could not be verified because data were not presented in the report.

Equations in Appendix D are used for the conversion of nominal concentrations in the inhalation studies and diet studies to "adjusted dosages" by accounting for respiration and dosing regimen such that the dosages are expressed in mg/kg-day units and averaged for 24 hours and 7 days of exposure. An example of the calculation is also provided in Appendix D. The dosages listed in the summary tables (Tables 2, 3, 9, 12, and 13) are adjusted dosages to allow comparisons of the no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) between studies.

A. PHARMACOKINETICS

Summary: DDVP was rapidly absorbed by the oral, intravenous, intraperitoneal, and inhalation routes and slowly absorbed by the dermal route. After absorption, radioactivity distributed to major organs including the liver and kidneys. DDVP was metabolized completely by ester hydrolysis and demethylation. Initial metabolites were mono- and dimethyl- phosphates, and desmethyl DDVP. Once formed, they may be further metabolized with final metabolites either incorporated into tissues or excreted. Major routes of excretion were in the urine and in the exhaled air, while to a lesser extent in the feces and milk. Excretion routes, tissue distribution, and urinary metabolites in rats were similar following inhalation or oral exposures to DDVP. The biotransformation pathways of DDVP in rats are presented in Figure 1.

DDVP

Oral - Rat

DDVP (^{14}C- and ^{32}P-labelled, 10 mg/kg, 78 and 67-78% purity, respectively) was rapidly absorbed following gavage administration to albino rats (strain not specified) (Casida *et al.*, 1962). After absorption, the primary site of metabolism was the liver, and the metabolism of DDVP was rapid. At 0.25 hour after treatment, the tissues (liver, kidneys, and blood) contained primarily hydrolysis products and less than 5% as DDVP. Radioactivity was also found in the bone which is likely due to the deposition of phosphoric acid in the bone. Routes of excretion for DDVP were exhaled air, urine, and feces. After 24 hours, the percentage of radioactivity in the exhaled air as CO_2 was 16%. Urinary metabolites included desmethyl DDVP, mono- and dimethyl phosphates, inorganic phosphate, and dichloroethyl glucuronide. Over 80% of the radioactivity in the urine collected 3 hours after treatment were mono- and dimethyl phosphates. Only about 10% of the dose excreted in the feces was water-

soluble DDVP derivatives. Other metabolites included inorganic phosphate, two-carbon fragments (glycine and serine), phosphate ions, and chloride ions.

Rats (strain not specified) were given DDVP (^{14}C and ^{36}Cl, purity not specified; 0.99 mg/male rat and 0.72 mg/female rat) by gavage (Hutson *et al.*, 1971). Urine, feces, and exhaled air were collected every day for 4 days. Radioactivity in tissues was also determined. Additional female rats were used for the determination of metabolites in the urine and the liver. There was no difference in the excretion patterns between sexes. After 4 days (daily result not given), the percentages of administered doses in the urine, feces, and exhaled air were 12.8-18.2%, 3.4-4.8%, 36.8-38.8%, respectively. The identified urinary metabolites included hippuric acid (8.3% of total urinary radioactivity), desmethyl-DDVP (10.9%), and 2,2-dichloroethyl-*B*-d-glucopyranosiduronic acid (27%), while no unmetabolized DDVP, dichloroacetaldehyde or dichloroacetic acid was found. Of the tissues examined, the highest level of radioactivity (4.4-5.0% of dose) was in the liver. Analysis of the liver tissue showed that 75% of the radioactivity was associated with glycine, serine, and cystine in the protein hydrolysate fraction.

Rats (Crl:CD (SD) BR) were given DDVP (^{14}C, purity not specified) either as a single intravenous dose (1 mg/kg), by gavage as a single dose (0.8 mg/kg or 21 mg/kg), or by gavage as multiple doses (0.8 mg/kg) for 16 days (Cheng, 1989 and 1991). Radioactivity in the tissues and carcasses was determined 7 days after dosing. Urine, feces, and exhaled air as CO_2 were monitored for 7 days after dosing. Clinical signs, such as tremors and salivation, were observed 2.5 hours after gavage dosing in the 21 mg/kg group. There were no differences in the tissue distribution and excretion patterns between the dosing regiment or sexes. Consistent with the earlier studies, the liver and kidneys contained higher levels of radioactivity than other organs (lung, spleen, uterus, and bone). For both routes of administration, the percent of total dose excreted ranged from 40 to 58% in the exhaled air, 10-17% in the urine, and 4-7% in the feces. The majority of the radioactivity in the exhaled air and excreta was eliminated within 24 hours after dosing. The major metabolites in the urine and feces were hippuric acid and urea. Glucuronide conjugates and other dehalogenated products were not positively identified.

Intravenous - Rat

Rats (Carworth Farm strain E) were given DDVP (purity not specified, 0.83 mg/kg) by intravenous injection (Blair *et al.*, 1975). DDVP was distributed primarily in the kidneys. Levels in the other tissues (blood, liver, fat, testes, and brain) were 0.01 to 0.1 *u*g/g, at the limits of detection for the analysis method used. DDVP degradation in the kidneys was rapid as the levels decreased from 1.44-2.25 *u*g/g at 10 minutes to 0.15-0.80 *u*g/g at 30 minutes after dosing.

The kinetics after intravenous administration to rats (Crl:CD (SD) BR) was similar to those for gavage dosing (Cheng, 1989 and 1991) (see discussion under **Oral - Rat** section).

Intraperitoneal - Rat

The kinetics of DDVP in the rat (strain not specified) after intraperitoneal administration followed similar kinetics as those for the oral route (Casida *et al.*, 1962). However in the study conducted by Hutson *et al.* (1971), the amount of radioactivity in the urine (35.0% of dose) was higher than that for exhaled air (18.6%). The major metabolite in the urine was dichloroethanol glucuronide, with hippuric acid and desmethyl DDVP as minor metabolites.

Inhalation - Rat

Carworth Farm strain E rats were exposed to DDVP (purity not specified; at nominal concentrations of 0, 10, 50, or 90 *u*g/L) for 2-4 hours (Blair *et al.*, 1975). The half-life of DDVP in the kidneys was 13.5 minutes. After exposure to 90 *u*g/L, the levels of DDVP in the lungs (<0.01-0.04 *u*g/g) were less than those in the kidneys (<0.01-2.39 *u*g/g).

In a comparison study with the oral route of exposure, rats (male, strain not given) were exposed to DDVP (0.71-1.07 mg in vapor) for 1 hour by nose-only inhalation (Hutson *et al.*, 1971). Urine, feces, exhaled air, and tissues were collected following the same protocol as the oral route. The actual administered dose was unknown since DDVP adsorbed to the apparatus. Therefore, results were expressed as the percentage of the total recovered yield of carbon dioxide, the major metabolite. The amount of radioactivity retained in the tissues was similar to those for the oral route with the highest radioactivity level in the liver. The rates and routes of excretion, and urinary metabolites by the inhalation route were considered similar to those after oral administration and summarized below:

% of total carbon dioxide in 4 days

	0-24 hr		24-48 hr		48-72 hr		72-96 hr	
	Inhale	Oral	Inhale	Oral	Inhale	Oral	Inhale	Oral
Air	78.7	74.2	12.9	14.3	*	7.0	8.4*	4.5
Urine	34.5	28.3	2.6	2.1	0.5	1.4	0.9	1.2
Feces	3.2	4.5	2.3	2.1	1.1	1.0	3.2	1.3

* 48-96 hour collection

Dermal - Rat

DDVP (^{14}C, 93% purity; 0, 0.3, 3.0, or 30 *u*g/cm^2) was applied dermally on rats (Jeffcoat, 1990). After 10 hours of exposure, the percent of dermal absorption (determined by radioactivity in the carcass, blood, exhaled air, urine, feces, and cage rinses) ranged from 7.3 to 13.3% for all doses. There was no further absorption after 10 hours and up to 120 hours. The majority of the applied dose (37.7-51.6%) was lost to evaporation and trapped by a charcoal impregnated covering placed over the area. Washing of the exposed skin with soapy water removed 8.4-14.7% of the administered dose. Based on the results of this study, the DPR Worker Health and Safety Branch recommended a dermal absorption factor of 13% for the estimation of potential human exposure.

Oral - Human

A male subject was given DDVP (purity not specified, 5 mg ^{14}C-DDVP) in 100 ml of orange juice, and urine and exhaled air samples were collected (Hutson and Hoadley, 1972). The total percentages of the administered dose detected as CO_2 in the exhaled air were 27% after 8 hours. Between 0 and 48 hours, only 9% of the administered dose was excreted in the urine. Urinary metabolites included hippuric acid, desmethyl dichlorvos, and urea.

Inhalation - Human

Two male subjects were exposed to DDVP (purity not specified, a nominal concentration of 0.25 *u*g/L for 10 hours or 0.7 *u*g/L for 20 hours) by inhalation (Blair *et al.*, 1975). DDVP was not detected in the blood samples taken immediately after exposure, and the MDL was 0.1 *u*g/g. An in vitro study with the blood from these subjects showed that the half-life for DDVP hydrolysis by plasma esterases was 7 to 12 minutes.

Dichloroethanol was detected in the urine of a volunteer after inhalation exposure of DDVP (purity not specified, a nominal concentration of 38 *u*g/L) for 105 minutes (Hutson and Hoadley, 1972).

Other Studies

Metabolism in other species (mice, hamsters, and pigs) proceeded at different rates compared to those for rats, but the metabolites were similar (Hutson and Hoadley, 1972; Page *et al.*, 1971; Potter *et al.*, 1973a; Potter *et al.*, 1973b; Loeffler *et al.*, 1976).

In vitro studies using rat subcellular fractions showed that DDVP was metabolized by the liver enzymes in the soluble and mitochondrial fractions (Hodgson and Casida, 1962). Desmethyl DDVP was found in both rat liver microsomal and cytosolic fractions indicated that demethylation occurred in both fractions (Hutson *et al.*, 1971). Using rat liver supernatant fraction, Dicowsky and Morello (1971) showed that the metabolism of DDVP to desmethyl DDVP was glutathione dependent. The hydrolysis of DDVP to dimethyl phosphate and dichloroacetaldehyde, as well as the metabolism of desmethyl DDVP to dichloroacetaldehyde and monomethyl phosphate, were glutathione independent.

In a recent study, Holstein cows (3/group) were given DDVP (0, 2, 6, or 20 ppm based on dry matter in the feed) in capsules by gavage twice daily for 28 days (March *et al.*, 1993). The estimated dosage based on average amount of DDVP in the capsules for each group and a body weight of 650 kg were 0.062, 0.17, and 0.63 mg/kg-day. Milk samples, as a composite of evening and morning samples when possible, were collected periodically from days 1 to 28 of the treatment period. Cows were sacrificed at the end of the experiment and tissues (muscles, fat, liver, and kidneys) were collected. All milk and tissue samples showed DDVP residue levels at below the limit of quantitation (0.01 ppm).

Cows and goats were treated with DDVP (^{32}P, 67-78% purity) by three routes of exposure (Casida *et al.*, 1962). Cows were exposed to DDVP by intravenous (1 mg/kg), subcutaneous (1 mg/kg), and oral (1 or 20 mg/kg) administrations. Goats were exposed to DDVP by subcutaneous (1.52 mg/kg) injections only. For both species and all routes of exposure, DDVP was hydrolyzed into mono- and dimethyl phosphates, and to a lesser extent desmethyl DDVP and inorganic phosphate. Unmetabolized DDVP (recovered in the organosoluble fraction) was found in the milk in the first 2 hours after administration. After 8 hours, the amount of organosoluble products in the milk was below detection limit as the majority of the radioactivity was due to hydrolysis products. Over 80% of the dose was excreted in the urine and feces after 96 hours.

Studies conducted on farm animals showed no detected residues in the milk, meat, or meat by products of cows, goats, and steers sacrificed 1 or more days after single or multiple dermal applications of DDVP (Shell Chemical Co., 1968). Cows were treated with DDVP after milking. When hogs were given DDVP (9495 ppm) daily in the diet for 90 days, no residues were found in the tissues except for the large intestines. Immediately after dosing, the mean residue level in the large intestines was 0.36 ppm. After 24 hours, the level declined to 0.16 ppm (MDL= 0.02 ppm).

DIMETHYL PHOSPHATE

Oral - Rat

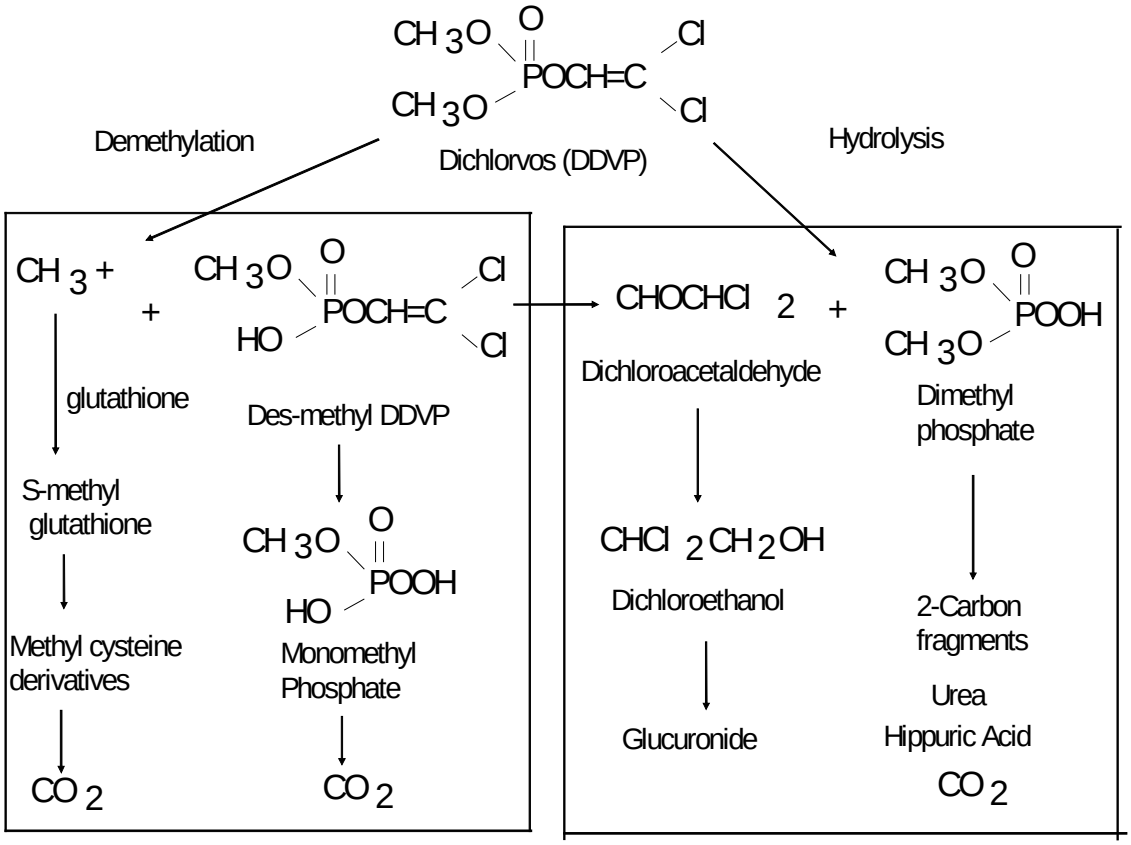
Rats (strain not specified) were given dimethyl phosphate (^{32}P, 500 mg/kg, purity not specified) by gavage (Casida *et al.*, 1962). Radioactivity was completely eliminated by 90 hours. About half of the dose was excreted in the urine as the parent compound.

DES-METHYL DDVP

Oral - Rat

Rats (strain not specified) were given des-methyl DDVP (^{32}P, 500 mg/kg, purity not specified) by gavage (Casida *et al.*, 1962). A majority (86%) of the urinary metabolites was phosphoric acid, and the remaining was des-methyl DDVP at 90 hours after treatment. Phosphoric acid was found deposited in the bone.

Figure 1. Metabolic pathways of DDVP in laboratory animals[a].



[a/] Reference: Wright *et al.*, 1979.

B. ACUTE TOXICITY

Summary: The acute toxicities of technical grade DDVP, selected formulations, and metabolites are presented in Tables 1 and 2. The LD_{50} of DDVP was at least 9 times more toxic than its metabolites (LD_{50} of 250 mg/kg for dichloracetic acid) as determined by the magnitude of the 72 hour lethal dose after intraperitoneal administration. Human exposure of DDVP by ingestion and from the use of no-pest strips resulted in the inhibition of plasma ChE activity, but not erythrocyte ChE activity. Acute effects observed in laboratory animals from oral or inhalation exposures included diarrhea, irritability, salivation, lethargy, pupillary constriction, tremors, decreased neuromuscular functions, and death.

TECHNICAL

Gavage - Rat

In a range finding study, rats (Sprague-Dawley Crl:CD.BR, 1/sex/group) were exposed to a single dose of DDVP (97.87% purity; 0, 0.1, 0.5, 1, 10, 20, 30, 40, 60, 70, or 80 mg/kg) in water by gavage and observed for 24 hours (Lamb, 1992). No clinical effects were observed at 0.1 and 0.5 mg/kg. There was a dose-related increase in the number and severity of the cholinergic effects at 1 mg/kg and higher concentrations. Gait alterations (rocking, lurching, swaying, and prostration) and pupil constriction were observed in the 1, 10, and 20 mg/kg groups. Tremors and reduced forelimb/hindlimb grasp were additional effects found in the 30 mg/kg group. At 40 mg/kg and higher concentrations, rats were also severely affected with labored respiration and salivation. One male rat of the 80 mg/kg group died.

Based on the results of the range finding study, the full study on neurotoxicity was conducted in rats (Sprague-Dawley Crl:CD.BR, 12/sex/group) with DDVP (97.87% purity) at 0.5, 35, and 70 mg/kg given by a single gavage dose (Lamb, 1993a). At 35 and 70 mg/kg, the effects observed in both groups (except when noted) included altered posture, clonic convulsions, whole body tremors, constricted pupils (males only), salivation, increased eye prominence, decreased muscle tone, altered respiration, pale skin, poor grooming, increased mean time to first step, impaired mobility and gait, decreased arousal, decreased rearing, absence of approach response (except for 35 mg/kg females), absence of touch response, absence of tail pinch response, lack of response to olfactory stimuli (70 mg/kg only), absence of pupil response, impaired air righting reflex, reduced hindlimb resistance, reduced grip strength (70 mg/kg), impaired rotarod performance, increased hindlimb foot splay (70 mg/kg only), increased duration of catalepsy, decrease in body temperature, and reduced motor activity. Recovery of functional observational battery parameters and locomotor activity was evident by day 7 for all animals. Six rats of the 70 mg/kg group died. Consistent with the observations in the range finding study, the NOEL was 0.5 mg/kg based on treatment-related cholinergic signs at 35 and 70 mg/kg.

Intraperitoneal - Rat

Adult male Long Evans rats (12-28/group) were exposed to a single dose of DDVP (96% purity) at 0, 5, 10, or 30 mg/kg by intraperitoneal injection for the determination of delayed neuropathy using a functional observational battery (Ehrich *et al.*, 1993). Atropine was given before treatment, 1 hour after treatment to those with cholinergic signs, and 2-3 hours after treatment to all animals. At 4 hours after treatment, four rats from each group were sacrificed in order to determine brain and spinal cord acetylcholinesterase and neurotoxic esterase activities. Spinal cord ChE as well as brain and spinal cord neurotoxic esterase activities were significantly ($p \leq 0.05$) reduced by $\geq$ 30% in a dose-related manner for all doses. Brain ChE activity was significantly ($p \leq 0.05$) depressed by $\geq$ 20% only in the 10 and 30 mg/kg groups. There was no treatment-related effect on the body weights. Functional observational battery showed alterations in the response to approach and activity after 7 to 21 days of

treatment. No neuropathologic lesions were observed. The LOEL was 5 mg/kg based on reduction of spinal cord ChE, and brain and spinal cord neurotoxic esterase activities.

Inhalation - Rat

Male rats (strain not specified, number of rats used unspecified) were exposed to DDVP (purity not specified; at nominal concentrations of 0.05 to 90 *u*g/L) for 4 hours (Blair *et al.*, 1975). Mild signs of intoxication (lethargy and pupillary constriction) were observed in the 90 *u*g/L group. The NOEL for cholinergic signs was 50 *u*g/L (adjusted dosage of 8 mg/kg-day).

Inhalation - Monkey

Two experiments were conducted with rhesus and cynomolgus monkeys exposed to warehouses treated with DDVP applied as an aerosol (Durham *et al.*, 1959). In the first experiments, monkeys (2/dose) were exposed to DDVP-treated warehouses (0, 0.5, 1.0, or 2.0 mg/ft^3) 24 hours after treatment. The measured air concentrations showed that DDVP levels declined with time. For 2.0 mg/ft^3, the peak level was 2.2 mg/ft^3 and declined to 0.14 mg/ft^3 and 0.07 mg/ft^3 after 24 and 72 hours, respectively. In the second experiment, monkeys (2/dose) were placed in warehouses to be treated with DDVP at 1.0 or 2.0 mg/ft^3 twice a week for 6 weeks. The monkeys were removed from the treatment area prior to application and returned 12 hours after application. In the first experiment, because the baseline levels of plasma and erythrocyte ChE were variable for each monkey and between monkeys, no treatment related effects were detected. In the second experiment with multiple applications and longer duration of exposure, a dose-related decrease in the plasma and erythrocyte ChE activities was observed after 50 days of exposure (data were presented only in graphs). After removal from exposure, the activities of both plasma and erythrocyte ChE recovered toward baseline levels.

Inhalation - Human

In several human studies, brief continuous exposures to DDVP aerosol up to 10 mg/ft^3 (3.5 mg/L) either generated by no-pest strips or solution left for evaporation did not result in statistically significant inhibition of plasma or erythrocyte ChE activities (Durham *et al.*, 1959; Shell Chemical Co., 1965).

In a study conducted with DDVP resin strips (1 strip/30 m^3, Vapona™ Strips) in a hospital, the effects of DDVP exposure on 125 patients (men with and without liver disease, women during labor and postpartum, and sick children) were studied (Cavagna *et al.*, 1969). After 24 hours of exposure, plasma ChE activity of the women was not affected while the activity for the other groups were inhibited. The extent of the inhibition, expressed as percent of control values, for DDVP air concentrations of 0.1-0.28 mg/m^3 were 28-65% for men without liver disease, 35-67% for men with liver disease, and 55-92% for children. For DDVP air concentrations of 0.02-0.1 mg/m^3 after 16 hours of exposure, only the plasma ChE activity of the men with liver disease was lowered (35-57% of control values). Based on the estimated DDVP intake per day from the report and the DPR default body weights of 55 kg for adults and 10 kg for children, the NOEL for plasma ChE inhibition was 0.014 mg/kg-day for children, 0.02 mg/kg-day for men without liver disease, and 0.026 mg/kg-day for women. Since men with liver disease were affected by both levels of DDVP, the LOEL was 0.006 mg/kg-day. There was no effect on erythrocyte ChE activity.

In another hospital study, new-born babies (22) were exposed to DDVP (1 strip/30 to 40 m^3, Vapona™ Strips) released from resin strips with a time-weighted average air concentration of 0.15 *u*g/L for 18 hours per day for 5 days (Cavagna *et al.*, 1970). No significant depression of plasma and erythrocyte ChE activities was found. The estimated daily dose was 0.07 mg/kg-day assuming a respiratory rate of 0.46 m^3/kg-day.

Oral - Human

One hundred and eight patients with infections were treated with DDVP in a granular-resin formulation as a broad-spectrum anthelmintic agent (Pena Chavarria *et al.*, 1969). The patients were divided into 2 groups: 24 subjects (14 males and 10 females) at the low dose of 6 mg/kg-day and 84 subjects (37 males and 47 females) at the high dose of 12 mg/kg-day. The only clinical sign reported was brief mild headaches in a few subjects; no details were provided. Both plasma and erythrocyte ChE activities were inhibited to varying extent according to the data (presented in graphs). The significance of the data was difficult to determine as no raw data were presented, and the extent of the inhibition was presented in 25% intervals.

Human subjects (6/group, average body weight of 81 kg) were fed DDVP (0.9 mg) in either gelatin salad or a premeal capsule containing cottonseed oil three times a day for 21 days (Boyer *et al.*, 1977). No clinical signs or erythrocyte ChE inhibition were reported. Plasma ChE activity decreased continuously with dosing. After 21 days, the plasma ChE activities were about (estimated from graph) 40% and 28% of pre-treatment activities for cottonseed and gelatin formulations, respectively. After termination of exposure, the plasma ChE activity returned to pre-treatment level and the half-life for the regeneration was calculated to be 13.7 days. The no-observed-adverse effect level (NOAEL) was reportedly 0.04 mg/kg-day for the calculation of Acceptable Daily Intake by WHO (1993).

Special studies

Additional studies for the consideration of acute toxicity are described in the **III.C. SUBCHRONIC TOXICITY**, **III.G. DEVELOPMENTAL TOXICITY**, and **III.H. NEUROTOXICITY** sections. The following are brief descriptions of the studies.

DDVP (100% purity; 0 to 40 mg/kg) was administered to lactating rats by gavage every 2-4 days for 3 weeks (Tracy *et al.*, 1960). The adjusted dosages based on 3 days per week were 4.5, 9, 13, and 17 mg/kg-day. Cholinergic signs of varying severity were observed 10 to 20 minutes after ingestion and included irritability, salivation, nasal twitching or scratching, sialorrhea, pronounced exophthalmus with excessive lacrimation, diarrhea, muscle fasciculation, violent tremors, convulsions, and death. The NOEL was 9 mg/kg-day.

DDVP (0 to 21.0 mg/kg-day) was given to pregnant Sprague-Dawley rats by gavage once daily from gestational days 6 to 15 (Tyl *et al.*, 1991a). Tremors were observed in the dams of the 21.0 mg/kg-day group with onset within 10-60 minutes after each daily dosing. Other signs of toxicity included prone positioning, hindlimb splay, circling, vocalization, hypoactivity, labored respiration, ear shaking, and coprophagia. The NOEL was 3.0 mg/kg-day for cholinergic signs in the dams.

Acute delayed neurotoxicity of DDVP was studied in atropinized chickens after oral administration of 16.5 mg/kg DDVP on day 1 and again on day 22 (Beavers *et al.*, 1988). At sacrifice on day 43, nerve fiber degeneration and axonal swelling were noted in one of 10 treated chickens.

Two experiments were conducted in the Tunstall Laboratory with rabbits exposed to DDVP by inhalation. In the first experiment, female Dutch rabbits were exposed to DDVP by inhalation from day 1 of mating

to gestation day 28 (Thorpe *et al.*, 1971b). Severe toxicity and mortality were observed after the 6th day of exposure in the 6.25 *u*g/L (3.25 mg/kg-day) group. Cholinergic signs observed included anorexia, lethargy, muscular tremors, mucous nasal discharges, and diarrhea. Severely affected rabbits were prone with heads turned to one side. Sixteen of 20 does died or were killed because of intoxication.

In the second experiment by Thorpe *et al.* (1971b), Dutch rabbits (20/group) were exposed to DDVP (0 to 4 *u*g/L, equivalent to 0 to 2.0 mg/kg-day) by inhalation. One doe in the 2 *u*g/L (1.0 mg/kg-day) group died after 2-3 days of exposure. Six does of the 4 *u*g/L group died or were killed because severe cholinergic signs.

Table 1. The acute toxicity of DDVP.

Species	Sex	Results	References[a]
		TECHNICAL GRADE	
Oral LD_{50}			
Rat	M/F	56-80 mg/kg	1
Mouse	na[b]	184 mg/kg	2
Dog	na	100-316 mg/kg	2
Intraperitoneal LD_{50}			
Rat	M/F	6 mg/kg	2
Mouse	F	28 mg/kg	3
Dermal LD_{50}			
Rat	M/F	75-107 mg/kg	1
Inhalation LC_{50}			
Rat	M	14.8 *u*g/L (4 hrs)	2
Mouse	M	13.2 *u*g/L (4 hrs)	2
Ocular Irritation			
Rabbit	na	mild	4
Dermal Irritation			
Rabbit	na	mild	4
		LIQUID CONCENTRATE (1.0-23.25%)	
Oral LD_{50}			
Rat	M/F	3200-10,000 mg/kg	5
Dermal LD_{50}			
Rabbit	M	1800 mg/kg	6
Rabbit	na	< 200 mg/kg	7
Ocular Irritation			
Rabbit	na	mild	8
Dermal Irritation			
Rabbit	na	moderate	9

a/ 1. Gaines, 1960; 2. Denka Chemie BV, 1982; 3. Casida *et al.*, 1962; 4. USEPA, 1987; 5. The Hine Lab., 1973a; 6. The Hine Lab., 1973b; 7. Unilab Research Inc., 1981; 8. Product Safety Lab., 1982a; 9. Product Safety Lab., 1982b.

b/ na=not available

Table 1. The acute toxicity of DDVP (Continued).

Species	Sex	Results	References[a]
		PRESSURIZED LIQUID (0.186-6.51%)	
Oral LD_{50}			
Rat	M/F	2.5-> 50 mg/kg	9, 10
Dermal LD_{50}			
Rabbit	M/F	> 200 mg/kg	10
Inhalation LC_{50}			
Rat	M/F	> 5 mg/L (4 hrs)	10
Rat	na[b]	> 200 mg/L (1 hr)	11
Ocular Irritation			
Rabbit	na	non-irritant	10, 12
Dermal Irritation			
Rabbit	na	severe/moderate	10, 13
		IMPREGNATED RESIN (20%, strips)	
Oral LD_{50}			
Rat	na	400-1,200 mg/kg	14
Dermal LD_{50}			
Rabbit	na	24,000-50,000 mg/kg	14
		IMPREGNATED RESIN (20%, controlled release aerosol)	
Oral LD_{50}			
Rat	M/F	180-593 mg/kg	15, 16
Dermal LD_{50}			
Rabbit	M/F	> 2000 mg/kg	17
Ocular Irritation			
Rabbit	M/F	mild	18
Dermal Irritation			
Rabbit	na	mild	19

a/ 9. Warf Institute Inc., 1977a; 10. Pet Chemicals Inc., 1983; 11. Warf Institute Inc., 1977b; 12. Warf Institute Inc., 1977c; 13. Warf Institute Inc., 1977d; 14. Shell Chemical Co., 1965; 15. Pharmakon Research International, 1987; 16. Springborn Institute, 1987; 17. Pharmakon Research International, 1985; 18. Pharmakon Research International, 1989; 19. Pharmakon Research International, 1984.

b/ na=not available

Table 1. The acute toxicity of DDVP (Continued).

Species	Sex	Results	References[a]
FOGGER (DDVP 0.47%, Propoxur 1.0%, Methoprene 0.15%)			
Oral LD_{50}			
Rat	M/F	2.16 g/kg	20
Dermal LD_{50}			
Rabbit	na[b]	7.4 g/kg	21
Inhalation LC_{50}			
Rat	na	> 5.83 mg/L	22
Ocular irritation			
Rabbit	na	mild	23
Dermal irritation			
Rabbit	na	mild	24
FOGGER (DDVP 0.5%, Pyrethrum 0.25%)			
Oral LD_{50}			
Rat	M/F	> 5 g/kg	25
Dermal LD_{50}			
Rabbit	M/F	> 2 g/kg	25
Inhalation LC_{50}			
Rat	M/F	> 20.3 mg/L	25
Ocular irritation			
Rabbit	na	mild	25
Dermal irritation			
Rabbit	na	mild	25

a/ 20. Elars Bioresearch Lab., 1980a; 21. Elars Bioresearch Lab., 1980b; 22. Hazleton Lab., 1980; 23. Elars Bioresearch Lab., 1980c; 24. Elars Bioresearch Lab., 1980d; 25. S.C. Johnson & Sons, 1980.

b/ na=not available

Table 1. The acute toxicity of DDVP (Continued).

Species	Sex	Results	References[a]
		DESMETHYL DDVP	
Intraperitoneal LD_{50} Mouse	F	1500 mg/kg	3
		DICHLOROACETALDEHYDE	
Intraperitoneal LD_{50} Mouse	F	440 mg/kg	3
		DICHLOROETHANOL	
Intraperitoneal LD_{50} Mouse	F	890 mg/kg	3
		DICHLOROACETIC ACID	
Intraperitoneal LD_{50} Mouse	F	250 mg/kg	3

[a] 3. Casida *et al.*, 1962

Table 2. Selected no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of DDVP for sublethal acute effects from acute studies.

Species	Route	Duration[a]	Plasma ChE[a] NOEL (mg/kg-day)	Plasma ChE[a] LOEL (mg/kg-day)	Plasma ChE[a] % C	RBC ChE[a] NOEL (mg/kg-day)	RBC ChE[a] LOEL (mg/kg-day)	RBC ChE[a] % C	Brain ChE[a] NOEL (mg/kg-day)	Brain ChE[a] LOEL (mg/kg-day)	Brain ChE[a] % C	Other Effects NOEL (mg/kg-day)	Other Effects LOEL (mg/kg-day)	Effects	Ref.[b]
Rat[c]	gavage	1 dose	>30		no effect	-	30[d]	47-91%	-	-	-	9	13	irritability, salivation, diarrhea, tremors	1
Rat	gavage	1 dose	-		-	-		-	-	-	-	0.5	1.0	gait alteration	2
Rat	gavage	1 dose	-		-	-		-	-	-	-	0.5	35	gait alteration, pupillary constriction, tremors, and others	3
Rat[e]	gavage	d6-15 gestation	-		-	-		-	-	-	-	3	21	tremors after each dosing	4*
Chicken[f]	oral	1 dose	-		-	-		-	-	-	-	-	16.5[d]	nerve fiber degeneration, axonal swelling	5
Rat	inhal	4 h	-		-	-		-	-	-	-	8	14	lethargy, pupillary constriction	6
Rabbit[e]	inhal	d1-28	-		-	-		-	-	-	-	0.65	1.0	death in 2-3 days	7
Human new born	inhal	18h/dx5d	>0.07		no effect	>0.07		no effect	-	-	-	>0.07		no effect	8
Human	inhal	24h/dx1-5d													9
men without liver disease			0.02	0.031	28-65%	>0.031		no effect	-	-	-	>0.031		no effect	
men with liver disease			-	0.006	35-67%	>0.006		no effect	-	-	-	>0.006		no effect	
women (labor and postpartum)			>0.026		no effect	>0.026		no effect	-	-	-	>0.026		no effect	
sick children			0.014	0.02	55-92%	>0.02		no effect	-	-	-	>0.02		no effect	

a/ Abbreviations: ChE=cholinesterase, RBC=erythrocyte, inhal=inhalation, h=hours, d=days, % C=% of control values at the LOEL, -=data not available.

b/ * after the reference number indicates the study was acceptable according to FIFRA guidelines. References: 1. Tracy *et al.*, 1960; 2. Lamb, 1992; 3. Lamb, 1993a; 4. Tyl *et al.*, 1991a; 5. Beavers *et al.*, 1988; 6. Blair *et al.*, 1975; 7. Thorpe *et al.*, 1971b; 8. Cavagna *et al.*, 1970; and 9. Cavagna *et al.*, 1969.

c/ The study is described in III.C. SUBCHRONIC TOXICITY.

d/ The only concentration tested, not necessarily the LOEL.

e/ The study is described in III.G. DEVELOPMENTAL TOXICITY.

f/ The study is described in III.H. NEUROTOXICITY.

C. SUBCHRONIC TOXICITY

Summary: Subchronic exposures to DDVP resulted in the inhibition of brain, erythrocyte, or/and plasma ChE activities in humans, rats, mice, dogs, and cows. Clinical signs observed in laboratory animals were tremors, diarrhea, decreased body weight gain, increased frequency of salivation and urine staining in rats, and increased activity and urination in dogs. Other effects included decreases in red blood cell parameters (cell counts, hemoglobin, and hematocrit) in rats. From studies with lactating rats and milk cows after oral subchronic dosing, ChE activity depression and cholinergic signs were noted in the dams, but not in the offspring. Only studies with adequate descriptions of procedures and results were used for the determination of a critical NOEL, and they are presented in Table 3.

Gavage - Rat

Sprague-Dawley rats (Crl:CD.BR, 15/sex/group) were given DDVP (97.87% purity; 0. 0.1, 7.5, or 15 mg/kg-day) by gavage 7 days per week for 13 weeks (Lamb, 1993b). Tremors, salivation, exophthalmus, lacrimation, clear material on forelimbs, rales, chromodacryorrhea and material around the mouth were observed in the 15 mg/kg-day group with most of the clinical signs observed shortly after dosing (about 15 minutes). Tremors, salivation, and exophthalmus were observed in the 7.5 mg/kg-day group starting at week 3. Body weights of the 15 mg/kg-day females were significantly lower (91% of control value) by week 13. Plasma ChE activity of the 7.5 and 15 mg/kg-day groups was significantly ($p \leq 0.05$) inhibited at weeks 3, 7, and 13, and the activity ranged from 42% to 66% of control values. Erythrocyte ChE activity was not significantly inhibited, except for the 35% decrease (65% of control) in the 15 mg/kg-day group after 3 weeks of treatment. At week 13, brain stem and/or cerebral cortex ChE activity ranged from 88-89% of control values in the 7.5 mg/kg-day group, and 84-90% of control values in the 15 mg/kg-day groups. No adverse effects were observed in the functional observational battery, locomotor, brain weight, brain dimension or neuropathological parameters. The NOEL was determined to be 0.1 mg/kg-day based on cholinergic signs and cholinesterase inhibition.

Sprague-Dawley rats (Crl:CD (SD) BR, 10/sex/group) were given DDVP (98.3% purity; 0, 0.1, 1.5, or 15 mg/kg-day) by gavage 5 days per week for 13 weeks (Kleeman, 1988). The adjusted dosages were 0, 0.1, 1.1, or 10.7 mg/kg-day adjusted for 5 days/week dosing. Frequent salivation and urine staining on the fur were observed in the highest dose of 15 mg/kg-day after 6-12 weeks for males and 8-12 weeks for females. The NOEL for cholinergic signs was 1.5 mg/kg-day (adjusted 1.1 mg/kg-day). At week 14, erythrocyte ChE activity was significantly ($p \leq 0.05$) reduced to 75% of the control value in the 1.5 mg/kg-day treated males and to 92% of the control value in the 0.1 mg/kg-day treated females. The NOELs for erythrocyte ChE enzyme inhibition were determined to be 0.1 mg/kg-day in males, and < 0.1 mg/kg-day in females. The plasma ChE activity was significantly ($p \leq 0.05$) reduced to 65 and 53% of control values for the males and females, respectively, in the 15 mg/kg-day group. There was a significant ($p \leq 0.05$) decrease (nearly 50%) in brain ChE activity in the 15 mg/kg females, and a reduction of lesser magnitude was noted in the males. The NOEL for brain ChE inhibition was 1.5 mg/kg-day (adjusted 1.1 mg/kg-day). In addition at week 14, significant ($p \leq 0.05$) and dose-related decreases in the red blood cell parameters (cell count, hemoglobin, and hematocrit) were noted in both sexes at 15 mg/kg-day, as well as in the males at 1.5 mg/kg-day. For rats treated with 15 mg/kg-day, the decreases for cell count, hemoglobin, and hematocrit were 9-13%, 9-15%, and 7-10%, respectively, of control values. The decrease in hemoglobin and hematocrit were 10 and 8%, respectively, for the male rats at 1.5 mg/kg-day.

F344N rats (10/sex/group) were given DDVP (99% purity; 0, 2, 4, 8, or 16 mg/kg-day equivalent to 0, 1.4, 2.9, 5.7, or 11.4 mg/kg-day adjusted for 5 days/week dosing) for 1 month, and ChE activities were measured after 10, 24, and 32 days of treatment (Chan, 1989). No clinical signs were reported. Plasma ChE activities of all treatment groups in both sexes were significantly ($p \leq 0.05$) reduced in a

dose-related manner. At a dosage of 2 mg/kg-day, the plasma ChE activities in the females were 43% and 33% of control values after 10 and 32 days, respectively, of treatment. At 16 mg/kg-day, the plasma ChE activities were severely depressed at 13% and 7% of control values after 10 and 32 days, respectively, of treatment. The NOEL was < 2 mg/kg-day (adjusted < 1.4 mg/kg-day). The erythrocyte ChE activities of the male rats treated at 4 mg/kg and higher concentrations were significantly ($p \leq 0.05$) decreased to 86 and 82% of control values at 24 and 32 days, respectively, of administration. The erythrocyte ChE activity of the female rats was significantly ($p \leq 0.05$) decreased to 90% of control on day 32.

DDVP (100% purity; 0, 10, 20, 30, or 40 mg/kg-day) was administered to lactating rats (strain not specified, 11 dams and their litters with 2-11 pups/dam) by gavage every 2 to 4 days for 3 weeks (Tracy *et al.*, 1960). The adjusted dosages based on 3 days per week were 4.5, 9, 13, and 17 mg/kg-day. In the dams of the 13 and 17 mg/kg-day groups, cholinergic signs of varying severity included irritability, salivation, nasal twitching or scratching, sialorrhea, pronounced exophthalmus with excessive lacrimation, diarrhea, muscle fasciculation, violent tremors, convulsions, and death. The onset of signs was 10 to 20 minutes after ingestion and lasted for 30-90 minutes. Plasma and erythrocyte ChE activities were determined at the end of the exposure. The erythrocyte ChE activity of the rats decreased to 47-91% of the control values. The plasma ChE activity was affected to a lesser extent. The growth, and ChE activities of the plasma and erythrocytes of the neonates were not affected.

Dietary - Rat

Charles River rats (15/sex/group) were fed a diet containing DDVP (93% purity; 0, 0.1, 1.0, 10, 100, or 1000 ppm) for 15 weeks (Witherup *et al.*, 1964). The adjusted dosages were 0, 0.005, 0.05, 0.5, 5, and 50 mg/kg-day based on reported body weights and a DPR default consumption rate equivalent to 5% of body weight. There were no clinical signs and no differences in the body weight gain, food consumption rate, or gross pathology of the treated rats compared to the control groups. The plasma and erythrocyte ChE activities of the 100 ppm groups were depressed to 65-80% (male-female) and 63-73%, of control, respectively. The brain ChE activity was inhibited (37-39% of control values) only in the 1000 ppm group.

Gavage - Mouse

Mice (B6C3F1, 10/sex/group) were given DDVP (99% purity; 0, 5, 10, 20, or 40 mg/kg-day, equivalent to 0, 3.6, 7.1, 14.3, or 28.6 mg/kg-day adjusted for 5 days/week dosing) by gavage for 1 month and ChE activity was measured after 11, 25, and 33 days of treatment (Chan, 1989). Plasma ChE activity of all treatment groups in both sexes was significantly depressed ($p<0.01$) in a dose-related manner. The level of ChE inhibition was similar for both sexes. At 5 mg/kg-day, plasma ChE activity was 52%-54% of control values after 11 and 33 days, respectively, of treatment. At 40 mg/kg-day, the plasma ChE activity was 15%-11% of control values after 11 and 33 days, respectively, of treatment. The NOEL was < 5 mg/kg-day (adjusted < 3.6 mg/kg-day). The erythrocyte ChE activity of treated mice were either similar or slightly lower than control values.

Capsules - Dog

Beagle dogs (3/sex/group) were given DDVP (purity not specified; 0, 5, 15, or 25 ppm by volume in oil) in gelatin capsules daily for 90 days (The Hine Lab., 1962). After 21 days of treatment, the dose of the 5 ppm group was increased to 50 ppm. These concentrations were equivalent to 0.3, 1.0, 1.6, or 3.0 mg/kg-day based on mean initial weights of animals in each group and measured DDVP administered per day. The most significant finding was the depression (33% of control) of brain ChE activity of the high dose group (50 ppm) at the termination of the study. The NOEL for brain ChE inhibition was 25 ppm (1.6 mg/kg-day). There were moderate depressions of plasma, erythrocyte,

and total ChE activities intermittently during the study in all groups except for the 5 ppm group. After 50 days of treatment, plasma and erythrocyte ChE activities of the 15 ppm group were depressed to 87 and 57%, respectively of control values. After 70 days, the erythrocyte and plasma ChE activities of the 15 ppm group were 54% and 66% of control values. The NOEL for both plasma and erythrocyte ChE inhibition was 5 ppm (adjusted 0.3 mg/kg-day). The only clinical signs (time of onset was not specified) were increased activity and urinary output in the 25 ppm and 50 ppm groups. The NOEL for clinical signs was 15 ppm (adjusted 1.0 mg/kg-day).

Dietary - Cattle

Two dairy cows were fed increasing amounts of DDVP (100% purity) in the feed daily for 1 to 12 days (Tracy *et al.*, 1960). A newborn and a heifer were also exposed to DDVP from the cow milk or in the feed. When the milk cows were fed 200 ppm DDVP daily for 7 days, there was no effect on erythrocyte ChE activity. Increasing the diet concentration to 500 ppm (4.5 mg/kg) for 12 days resulted in greater than 75% depression of erythrocyte ChE activity. The oral shock dose (dose which caused cholinergic signs of salivation, diarrhea, tremors, and convulsions) determined for one of the cows was 3000 ppm (27 mg/kg). After 20 exposures, no detectable level (less than 0.17 *u*g/ml) of DDVP was found in the milk as determined by a bioassay with flies using death as the endpoint. Plasma and erythrocyte ChE activities in the suckling calves were not significantly affected by the treatment to the mothers.

Dermal - Cattle

The effect of DDVP on two cows after dermal application to the back, front shoulders, and upper back portions of the neck was studied using either a 1% DDVP aqueous solution, a 1% DDVP emulsion, or a 10% suspension (Tracy *et al.*, 1960). The solutions were applied on the skin daily for 10-11 days. No cholinergic signs were observed, and there was no inhibition of erythrocyte ChE activity.

Inhalation - Human

Human subjects (60 male inmates) were housed in Army barracks for at least 10 hours and exposed to DDVP aerosols released nightly every 30 minutes per hour for about 3 hours for either 14 days (phase I) or eight 30 minutes per night, 3 to 4 nights per week for 3 weeks (phase II) to simulate aircraft environments with DDVP applications (Rasmussen *et al.*, 1963). All the volunteers were given physical examinations, plasma and erythrocyte ChE measurements, airway resistance, and visual tests. The DDVP concentrations in the air were 0.14 to 0.33 *u*g/L during phase I, and 0.15 to 0.55 *u*g/L during phase II. No treatment-related findings were reported for phase I. The only significant finding in phase II was the inhibition of plasma ChE activity which returned to the pre-exposure level upon termination of the experiment (data as mean values were presented in a graph).

The plasma and erythrocyte ChE activities of 13 workers (both sexes), who were exposed to DDVP at an average air concentration of 0.7 mg/m^3 in the production of DDVP-releasing vaporizer, were monitored for 8 months (Menz *et al.*, 1974). The average plasma and erythrocyte ChE activities, measured weekly of the workers during production, were 35% and 60%, respectively, of the levels measured before production. The ChE activities had returned to the pre-production level one month after exposure ceased (data were presented in graphs). Medical examinations and blood chemistry performed during the study were within normal limits.

DDVP, in polyvinyl resin formulation pellets, was administered to male subjects in single doses up to 32 mg/kg and repeated doses up to 16 mg/kg-day for up to 3 weeks (Slomka and Hine, 1981). Of the 107 men who received DDVP in single doses of 0.1 mg/kg to 32 mg/kg, there was a dose-related inhibition of plasma and erythrocyte ChE activities as compared to pre-treatment values. At the highest dose (32 mg/kg), the inhibition was 20-30% and 55-75% for plasma and erythrocyte ChE, of

pretreatment levels, respectively. The plasma and erythrocyte ChE activities were also depressed (as low as 10% of pretreatment level) in men who were exposed continuously to DDVP. For both dosing regiments, side effects (diarrhea, nausea, stomach rumbling, lassitude, restlessness, and light-headedness) were reported by both placebo and treated men.

Additional Studies

Additional studies for the consideration of subchronic toxicity are described in the **III.D. CHRONIC TOXICITY**, **III.F. REPRODUCTIVE TOXICITY**, and **III.G. DEVELOPMENTAL TOXICITY** sections. The following is a brief discussion of the studies.

Osborne-Mendel rats were fed DDVP (0 to 1000 ppm) in the diet daily for 80 weeks (NCI, 1977a). After 3 weeks on the 1000 ppm (50 mg/kg-day) diet, the dosage of DDVP in this group was reduced to 300 ppm because of toxicity (tremors, rough coats, and diarrhea). The estimated dosages for 150 and 300 ppm were 7.5 and 15 mg/kg-day, respectively, based on the consumption rate of 5% body weight.

Sprague-Dawley rats were given DDVP (0 to 80 ppm) in the drinking water 24 hours daily (Tyl *et al.*, 1992). Rats of both sexes were treated for 10 and 11 weeks during the premating period, respectively, for the F0 and F1 animals and were then allowed to mate for 3 weeks. Selected F1 offspring were either necropsied or maintained to breed for the F2 generation. Cholinesterase activities of the plasma, erythrocyte, and brain were determined after mating for the males, and after lactation for the females. There were dose-related decreases in the plasma, erythrocyte, and brain ChE activities of all F0 and F1 adults, and the levels of inhibition at 20 and 80 ppm were statistically significant ($p \leq 0.05$). The NOAEL (No-Observed-Adverse-Effect Level) for plasma, erythrocyte, and brain ChE inhibition was 5 ppm (0.5 mg/kg-day for the males and 1.1 mg/kg-day for the females). The only significant ($p \leq 0.05$) effect observed in the pups was the reduction (91-92% of control values) in body weight of the 80 ppm F1 pups on postnatal days 14 and 21. After weaning the F2a litters, the F1 females were again exposed to DDVP and mated with untreated males for the F2b litters. There was a reduction (not statistically significant) of fertility at 80 ppm. The number of "abnormal" estrus cycles in the 80 ppm F1 females was significantly higher (68%) than in the controls (16%). The reproductive toxicity and parental NOEL for non-cholinergic endpoints was 20 ppm (2.7 mg/kg-day estimated from the premating dosage for females) based on the reduction of water consumption, body weight, fertility, and estrous cycling.

In the first experiment by Thorpe *et al.* (1971b), female Dutch rabbits were exposed to DDVP by inhalation from day 1 of mating to gestation day 28. The DDVP nominal concentrations were 0, 0.25, 1.25, or 6.25 *u*g/L for 23 hours per day (equivalent to 0, 0.13, 0.65, or 3.25 mg/kg-day). Severe toxicity and mortality were observed after the 6th day of exposure in the high dose 6.25 *u*g/L does. Cholinergic signs observed included anorexia, lethargy, muscular tremors, mucous nasal discharges, and diarrhea. Severely affected rabbits were prone with heads turned to one side. Sixteen of 20 does died or were killed because of intoxication. The NOEL for mortality and cholinergic signs was 1.25 *u*g/L (adjusted dosage of 0.65 mg/kg-day). The plasma, erythrocyte, and brain ChE activities were significantly inhibited for the 1.25 *u*g/L and 6.25 *u*g/L groups. The NOEL for ChE inhibition was 0.25 *u*g/L (adjusted 0.13 mg/kg-day)

New Zealand rabbits were given DDVP (0 to 7.0 mg/kg-day) by gavage from gestation days 7 to 19 and sacrificed on gestation day 30 (Tyl *et al.*, 1991b). Systemic toxicity included decreased weight gain (gestation days 7 to 19) as well as mortality (2 does of the 2.5 mg/kg-day group on gestation days 12 and 15, and 4 does of 7.0 mg/kg-day group on gestation days 17 and 19). In the high dose group, cholinergic signs (ataxia, salivation, diarrhea, breathing difficulties, tremors, and excitation) were observed with the first observation of ataxia made on gestation day 10. The NOEL was 0.1 mg/kg-day for maternal toxicity.

B6C3F1 mice were fed DDVP (94% purity) daily in the diet at 1000 and 2000 ppm for 2 weeks, and 300 and 600 ppm, respectively, from weeks 3 to 80 because of toxicity (tremors, rough coat, and diarrhea) with the initial doses (NCI, 1977b). The NOEL for cholinergic signs in 2 weeks was 1000 ppm (150 mg/kg-day).

Table 3. Selected no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of DDVP from subchronic studies.

Species	Route	Duration[a]	Plasma ChE[a] NOEL (mg/kg-day)	Plasma ChE[a] LOEL (mg/kg-day)	Plasma ChE[a] % C	RBC ChE[a] NOEL (mg/kg-day)	RBC ChE[a] LOEL (mg/kg-day)	RBC ChE[a] % C	Brain ChE[a] NOEL (mg/kg-day)	Brain ChE[a] LOEL (mg/kg-day)	Brain ChE[a] % C	Other Effects NOEL (mg/kg-day)	Other Effects LOEL (mg/kg-day)	Effects	Ref.[b]
Rat	gavage	5d/wx13w	1.1	10.7	53-65% at 14w	0.1 <0.1	1.1 0.1	75% (M)[a] 92% (F) at 14w	1.1	10.7	50% at 14w	1.1	10.7	salivation, urine stain after 6 weeks of dosing	1
Rat	gavage	5d/wx13w	0.1	7.5	42-44% at 13w	7.5	15	65% at 3w	0.1	7.5	89% at 13w	0.1	7.5	tremors, salivation	2*
Rat	diet	7d/wx15w	0.5	5	65-80%	0.5	5	63-73%	5	50	37-39%	> 50		no effects	3
Rat[c]	diet	7d/wx3w	-		-	-		-	-		-	15	50	tremors, diarrhea	4
Rat[d]	water	daily										2.7	9.5	parental -decreased fertility, increased abnormal cycles, reduced body weights	5*
		females F0	1.1	4.6	45%	<1.1	1.1	77%	1.1	4.6	74%				
		females F1	1.1	4.6	46%	<1.1	1.1	83%	1.1	4.6	68%				
		males F0	0.5	1.9	71%	0.5	1.9	71%	0.5	1.9	85%				
		males F1	0.5	1.9	74%	<0.5	0.5	86%	0.5	1.9	94%				
Mouse[c]	diet	7d/wx3w	-		-	-		-	-		-	-	150	tremors, diarrhea	6
Rabbit[e]	inhal	23h/d d1-28 gestation	0.13	0.65	65%	0.13	0.65	32%	0.13	0.65	44%	0.65	3.25	maternal-tremors, diarrhea after 6 days of dosing	7
Rabbit[e]	gavage	d7-19 gestation	-		-	-		-	-		-	0.1	2.5	maternal-lethality after 7-8 days	8
Dog	capsule	7d/wx90d	0.3	1.0	66% at 70d	0.3	1.0	54% at 70d	1.6	3.0	33% at 90d	1.0	1.6	increased urinary output and activity (time of onset not specified)	9

a/ Abbreviations: ChE=cholinesterase, RBC=erythrocyte, d=days, w=weeks, m=months, % C=% of control values at the LOEL, -=data not available.

b/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Kleeman, 1988; 2. Lamb, 1993b; 3. Witherup *et al.*, 1964; 4. NCI, 1977a; 5. Tyl *et al.*, 1992; 6. NCI, 1977b; 7. Thorpe *et al.*, 1971b; 8. Tyl *et al.*, 1991b; and 9. The Hine Lab., 1962.

c/ Studies are described in III.D. CHRONIC TOXICITY.

d/ Study is described in the III.F. REPRODUCTIVE TOXICITY.

e/ Studies are described in the III.G. DEVELOPMENTAL TOXICITY.

D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: DDVP caused the inhibition of plasma, erythrocyte, and brain ChE activities. Other non-oncogenic effects included hepatocellular lesions (vacuoles in the cytoplasm, cell swelling, prominence of cell membranes), reduced body weight, emesis, salivation, and ataxia. Oncogenic effects observed in rats and mice were pancreatic adenoma; mononuclear leukemia; mammary gland carcinomas, fibroadenomas, and adenomas; forestomach papillomas and carcinomas; and pituitary adenomas. DDVP also increased tumor growth rate in rats given leukemia transplant. The chronic toxicity of DDVP was studied in rats, mice, and dogs and is summarized in Table 9.

Dietary - Rat

Osborne-Mendel rats (10/sex/control, 50/sex/treated group) were fed DDVP (94% purity; 0, 150, or 1000 ppm) in the diet daily for 80 weeks (NCI, 1977a). After 3 weeks on the 1000 ppm diet, the dosage of DDVP in this group was reduced to 300 ppm because of toxicity (tremors, rough coats, and diarrhea). The estimated dosages for 150 and 300 ppm were 7.5 and 15 mg/kg-day, respectively, based on the assumed consumption rate of 5% body weight. In the second year of the study, clinical signs (rough coat, epistaxis, hematuria, alopecia, dark urine, palpable masses, bloating or abdominal distention) were observed in both the control and treated groups. The average body weights of the high-dose (300 ppm) rats were lower than those of the other groups, an approximate difference of 50 grams throughout the study (estimated from graphed data). The NOEL for reduced body weight was 150 ppm (7.5 mg/kg-day). The possible treatment-related findings were increased incidences of macrophage accumulation in the lungs, myocardial fibrosis, and thyroid follicular cell hyperplasia. There was no evidence of oncogenicity. This study was unacceptable to DPR according to FIFRA guidelines (no analysis of diet, no individual data, inadequate number of concurrent controls, and staggered start for low and high doses with 4-week interval). The EPA classification of this study was supplementary.

CD rats (25/sex/group) were fed DDVP (93% purity; 0, 0.1, 1, 10, 100 or 500 ppm) in the diet daily for 2 years (Witherup *et al.*, 1967). There was a 22-80% loss of the test material due to volatilization and hydrolysis. The average dosages were 0, 0.0013, 0.013, 0.13, 1.2, and 8.0 mg/kg-day based on the body weight and food consumption rates for both sexes at week 104, and the average concentrations of DDVP in the diet 12-16 hours after preparation of the diet. In the 100 ppm group, there were statistically significant ($p \leq 0.05$) decreases of 79% (of control values) for both plasma and erythrocyte ChE activities in the males, and of 95% for plasma and 82% for erythrocyte ChE in females. The reduction in brain ChE activity to 85% of control values in the 500 ppm group was not statistically significant. Histopathological examination of tissues from rats fed 500 ppm showed liver cells with diffused fine vacuoles in the cytoplasm, occasionally fat vacuoles, and swelling of the cell. The NOELs were 100 ppm (1.2 mg/kg-day) for liver effects and 10 ppm for plasma and erythrocyte ChE inhibition, and greater than 500 ppm (> 8.0 mg/kg-day) for brain ChE inhibition. This study was considered unacceptable to DPR according to FIFRA guidelines (inadequate numbers of animals at risk, weekly instead of daily preparation of diet, inadequate histopathology, as only major organs were examined, and blood chemistry). The EPA classification of the study was supplementary.

Gavage - Rat

In a study conducted by the National Toxicology Program (NTP), F344/N rats (50/sex/group) were dosed with DDVP (99% purity; 0, 4 or 8 mg/kg-day; or 0, 2.9, or 5.7 mg/kg-day adjusted for 5 days/week dosing) in corn oil by gavage for 24 months (Chan, 1989). There was no difference in the survival rate or body weight gain between the control and treated groups. Mild diarrhea was noted (frequency and treatment group were not specified) and was considered to be a compound-related clinical sign. There were dose-related increases in non-oncogenic lesions in the liver (cytoplasmic vacuolization), and adrenal glands (cortical cytoplasmic vacuolization). However, the effects in the liver and adrenal glands were considered minor and probably due to the use of corn oil as the vehicle rather than a direct effect of DDVP. Oncogenic effects observed were: increased multiplicity of pancreatic exocrine cell adenomas in the males and increased numbers of mononuclear cell leukemias in the males (Table 4). The increased incidences in the treated groups were significant with respect to pairwise comparison and trend. There were also minor increases, but not dose related or statistically significant, in the incidences of mammary gland combined tumors (adenomas, fibroadenomas, and carcinomas) in the females and alveolar/bronchiolar adenomas. This study was considered acceptable to DPR according to FIFRA guidelines.

Table 4. The incidences of tumors in rats treated with DDVP by gavage for 2 years[a]

	Dosage (mg/kg-day)[b]		
Tumor types	0	2.9	5.7
Pancreatic adenoma, males	16/50^{++} (32%)	25/49* (51%)	30/50* (60%)
Pancreatic adenoma, females	1/50 (2%)	1/46 (2%)	4/50 (8%)
Mononuclear leukemia, males	11/50^{+} (22%)	20/50* (40%)	21/50* (42%)
Mononuclear leukemia, females	17/50 (34%)	21/48 (44%)	23/50 (46%)
Mammary gland tumors, females (carcinoma, fibroadenoma, and adenoma)	11/50 (22%)	20/48* (42%)	17/49 (35%)

a/ Data were from Chan (1989). Incidences were expressed as the number of animals bearing tumors per animals at risk. All animals with at least 52 weeks of exposure or alive when the first tumor was detected, whichever occurs first, were considered at risk. Level of statistical significance, $p \leq 0.05$ (* or $^{+}$) or $p \leq 0.01$ ($^{++}$), is indicated after each incidence. Significance at the control value is based on a dose-weighted chi-square trend test, and significance at the dosed groups is for the Fisher's Exact Test.

b/ Dosages adjusted for 5 days per week dosing.

Male Fischer 344 rats with leukemia transplants were used to develop a short-term assay for leukemogenic effects induced by DDVP and other chemicals in chronic toxicity studies (Dieter *et al.*, 1989). These rats (16/group) were given DDVP (purity not stated; 8 or 16 mg/kg-day) by gavage for 5 days per week for 70 days. Control groups included: untreated, transplant only, and DDVP only. At 70 days, clinical chemistry, body weight, spleen weight, and liver weight were determined. Death occurred only in the DDVP and transplant group where 3/16 rats died during the last week of dosing. An acceleration of tumor growth rate as shown by significant increases ($p \leq 0.05$; data presented in graphs only) in the spleen/body weight ratios and white blood cell counts, as well as decreases in red blood cell indices and platelet counts was observed in rats of both treatment levels. The changes were of similar magnitude for both levels. Saturation of metabolic processes was suggested as the reason for the lack of a dose-response relationship. Histological examination of the spleen and liver showed increased expression of the mononuclear cell leukemia in rats treated with DDVP. This was a published study and not reviewed for acceptability.

BD IX/Bln rats (70-100/sex/group; body weight not given) were given DDVP (97% purity; 0.1 mg/rat) by gavage twice (low dose) or 3 times (high dose) per week for 60 weeks (Horn *et al.*, 1988; WHO, 1993). A control group (60/sex) were gavaged with water 3 times per week. In the high dose males, there was a statistically significant ($p \leq 0.05$) increase (53% compared to 30% for controls) in the incidence of bile duct cells and liver oval cells hyperplasia. In females of both DDVP groups, there was a statistically significant ($p \leq 0.05$) reduction in the incidence of urinary bladder hyperplasia (24-27% compared to 29% for controls), adrenal gland tumors (37-40% compared to 82% in controls), and mammary gland tumors (32% compared to 46% in controls). No DDVP-induced neoplasia was observed. This was a published study and not reviewed for acceptability.

Drinking Water - Rat

F344 rats (60/sex/group) were forced to drink DDVP (purity not specified; 0, 140, or 280 ppm equivalent to 0, 14 and 28 mg/kg-day) in 10 ml of water daily for 104 weeks (Enomoto, 1978). A slight reduction in the body weight in the 280 ppm males was observed (estimated from graphed data). The NOELs for body weight reduction were 140 ppm for the males and 280 ppm for the females. There was a slight increase in the incidence of mononuclear cell leukemias in the males though the increase was not statistically significant ($p \leq 0.05$) by pair-wise comparison using the Fisher's Exact test. The incidences (number of animals affected/examined) were 2/51, 6/48, and 6/48 for the control, 140, and 280 ppm groups, respectively. This study was not acceptable to DPR according to FIFRA guidelines (inadequate histopathology protocol as not all organs were examined in all animals, dosing procedure unclear, purity of the test article not given, clinical hematology not performed, quality assurance program not reported).

Inhalation - Rat

Rats (Carworth Farm E strain, 50/sex/group) were exposed to DDVP (purity not specified; at nominal concentrations of 0, 0.05, 0.5 or 5.0 *u*g/L) for 23 hours per day, 7 days per week for 2 years (Blair *et al.*, 1974). The animals were exposed to DDVP by whole body exposure which included oral ingestion of DDVP deposited on the fur, food, and water as well as dermal absorption.[1] Using the default respiration

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[1/] In the discussion of the published report (Blair *et al.*, 1976), the authors reported that the retained dose by nose-only exposure to 5.0 *u*g/L was 5.0 mg/day. The total retained dose from all routes of exposure was 2 times that by nose-only exposure. However, data were not presented for evaluation.

rate (Appendix D) and the assumptions that the internal dose could be determined from the nominal air concentration and no accumulation of DDVP under chronic administration, the equivalent dosages were 0. 0.05, 0.5, and 4.6 mg/kg-day. The survival of the control groups was lower than that for the treated groups. At 104 weeks, the survival was 64 and 72% for males and females, respectively, of the high dose groups, compared to 22 and 47% for males and females, respectively, for the control groups. The body weights of the 5.0 *u*g/L group were consistently lower than those of the control groups (Table 5). As an example, the decrease in the mean body weights for weeks 28, 56, 80, and 100 ranged from 13-19% for the males and 9-11% for the females, and were statistically significant ($p \leq 0.05$). The NOEL for decreased body weight in the males was 0.5 *u*g/L (0.5 mg/kg-day). The food consumption rates of the treated groups were either the same or slightly higher than those for the controls.

In this study (Blair *et al.*, 1974), no cholinergic signs were observed. Cholinesterase activities of plasma, erythrocyte, and brain were measured only for animals exposed to DDVP for 2 years, and were depressed in the 0.5 and 5.0 *u*g/L groups of both sexes. The decreases in plasma ChE activities were 76-84% (both sexes) and 22-38% of control values for the 0.5 and 5.0 *u*g/L groups, respectively. For erythrocyte ChE, the activities were 69-72% and 4-5% of control values for the 0.5 and 5.0 *u*g/L groups, respectively. There was a dose-related inhibition of brain ChE activity; the decreases were 90% and 19-21% of control values for 0.5 and 5.0 *u*g/L, respectively (Table 6). The NOEL for ChE inhibition was 0.05 *u*g/L (0.05 mg/kg-day).

Histopathological examination of the tissues from rats that died before scheduled sacrifice was limited in some animals because of tissue autolysis. Autolysis of all or some of the organs was noted for 14-38% of males and 2-16% of females. Therefore, only those animals without tissue autolysis were considered at risk for oncogenicity, as instructed by the authors. There was an increase in the incidence of pituitary adenoma in treated groups. The incidences (animals affected/animals examined) of pituitary adenomas in males were 4/31, 10/32, 6/31, and 10/42 for the control, 0.05, 0.5 and 5 *u*g/L groups, respectively. The increase in the incidences of pituitary adenomas in females were 7/43, 5/44, 12/39, and 16/45 for control to 5 *u*g/L. The increased incidence in females was statistically significant by the trend test ($p \leq 0.01$) and by pair-wise comparison at the high dose ($p \leq 0.03$). Since there was a difference in survival, the data for female rats were adjusted for survival (McKnight, 1991) and re-analyzed. The adjusted incidences were 11.9/43, 7.4/44, 15.1/39, and 20.4/45, with statistical significance only for the trend test ($p \leq 0.05$). For mammary and thyroid tumors, the incidences decreased with increasing doses. This study was unacceptable to DPR according to FIFRA guidelines (only one-half of each brain was examined histologically; low survival of the control group, and lack of optimal high dose exposure).

Table 5. The mean body weights of rats treated with DDVP by inhalation for 2 years[a].

Sex	Dosage (mg/kg-day)[b]	Mean body weights as % of control[c] Week 28	Week 56	Week 80	Week 100
males	0	100	100	100	100
	0.05	97 **	98	100	93
	0.5	94 **	95 **	97	96
	4.6	82 **	81 **	85 **	87 **
females	0	100	100	100	100
	0.05	98	100	95	97
	0.5	97	98	93 **	95
	4.6	91 **	91 **	89 **	91 *

a/ Data were from Blair *et al.*, 1974.
b/ Calculated from nominal concentrations of 0, 0.05, 0.5, and 5 *u*g/L.
c/ Values expressed are percent of control values. Statistically significant (** for $p<0.01$, and * for $p \leq 0.05$) from control values.

Table 6. Brain cholinesterase inhibition in rats treated with DDVP by inhalation for 2 years[a].

Sex	Dosage (mg/kg-day)[b]	Number of animals	Mean[c] ± standard error of mean	% of Control
males	0	8	12.1 ± 0.26 unit/g/min	100
	0.05	18	11.6 ± 0.17	96
	0.5	12	10.9 ± 0.21 **	90
	4.6	29	2.5 ± 0.14 **	21
females	0	18	11.3 ± 0.21	100
	0.05	24	10.9 ± 0.19	97
	0.5	23	10.1 ± 0.19 **	90
	4.6	31	2.1 ± 0.17 **	19

a/ Data were from Blair *et al.*, 1974.
b/ Calculated from nominal concentrations of 0, 0.05, 0.5, and 5 *u*g/L.
c/ Statistically significant (** $p<0.01$) from control values.

Gavage - Mouse

In a study conducted by the NTP, B6C3F1 mice (50/sex/group) were given DDVP (99% purity) by gavage 5 days per week for 2 years (Chan, 1989). The doses selected were 10 and 20 mg/kg-day for the males and 20 and 40 mg/kg-day for the females. The highest dose for the males was limited to 20 mg/kg-day because of high mortality (50%) observed in mice treated with 80 mg/kg-day in a 13 week study. The adjusted dosages to account for 5 days per week dosing were 7.1, 14.3, and 28.6 mg/kg-day for 10, 20, and 40 mg/kg-day, respectively. No compound related clinical signs were reported. There were also no differences in the body weight gain and survival rate between the control and treated groups. Lesions in the forestomach were detected in both sexes with a significant positive trend in the incidences of squamous papilloma in both sexes (Table 7). The incidence for the high dose females was statistically significantly higher than that for the controls. In the high dose group, there were also squamous cell carcinomas in the forestomach of females and carcinoid tumor, a neuroendocrine type tumor, in the stomach of one male. These results were considered by the NTP to be clear evidence and some evidence, respectively for female and male mice, for oncogenicity. This study was considered acceptable to DPR according to FIFRA guidelines.

C57BI/6/Bln mice (100/sex/group; body weight not given) were given DDVP (97% purity, 0.2 mg/mouse) either twice (low dose) or 3 times (high dose) per week for 50 weeks (Horn *et al.*, 1987; WHO, 1993). Control groups were: water only (50/sex/group), and no treatment (35/sex/group). A slight increase in the incidence of focal hyperplasia (transitional cell hyperplasia) of the urinary bladder was observed in both sexes of both DDVP groups (incidence rates of 5-12% compared to 0-9% for control groups). Mixed lymphomas were observed in all groups as this strain of mice was reportedly known to have spontaneous occurrence of this type of tumors. The incidences of mixed lymphomas were increased in the males (28-31% compared to 17% of water controls), but decreased in females (23-30% compared to 36% in water controls). However the highest rate (55-61%) of mixed lymphomas was that for the non-treated controls. No neoplastic lesions were reported. This was a published study and not reviewed for acceptability.

Dietary - Mouse

B6C3F1 mice (50/sex/treated group, 5/sex/matched control group) were fed DDVP (94% purity) in the diet daily at 1000 and 2000 ppm for 2 weeks, and 300 and 600 ppm, respectively, from weeks 3 to 80 because of toxicity (tremors, rough coat, and diarrhea) with the initial 2 doses (NCI, 1977b). In addition to the matched control group, control mice from other experiments were used to form the pooled control group. The estimated dosages were 45 mg/kg and 90 mg/kg for 300 and 600 ppm, respectively (Bremmer *et al.*, 1988). The systemic NOEL was 300 ppm (45 mg/kg-day) based on decreased body weight. The treated body weights were 3 grams (estimated from graphed data) less than controls after 40 weeks of exposure. The evidence for oncogenicity based on esophageal tumors (carcinoma and papilloma) was considered equivocal due to the inadequacy of control data. The incidence rates (number of animals with tumors/number of animals examined) were 0/27, 0/10, 1/47, 0/46 in the males for pooled control, matched controls, 300 ppm, and 600 ppm, respectively. In the female mice, the respective rates were 0/16, 0/8, 0/45, and 2/41. This study was unacceptable to DPR according to FIFRA guidelines (no individual data, inadequate number of animals in concurrent control, no analysis of diets, two doses only). USEPA classification of the study was supplementary.

Table 7. The incidences of forestomach tumors in mice treated with DDVP by gavage for 2 years[a].

	Dosage (mg/kg-day)[b]			
Tumor types	0	7.1	14.3	28.6
Males				
Squamous papilloma	1/46^{+} (2%)	1/50 (2%)	5/48 (10%)	ND
Females				
Squamous papilloma	5/44^{++} (11%)	ND	6/44 (14%)	18/48** (38%)
Squamous cell carcinoma	0/44^{+} (0%)	ND	0/44 (0%)	2/48 (4%)
Papilloma or carcinoma	5/44^{++} (11%)	ND	6/44 (14%)	19/48** (40%)

a/ Data were from Chan (1989). Incidence rates were expressed as the number of animals bearing tumors per animals at risk. All animals with at least 52 weeks of exposure or alive when the first tumor was detected, whichever occurs first, were considered at risk. Level of statistical significance, $p \leq 0.05$ ($^{+}$) or $p \leq 0.01$ (** or $^{++}$), is indicated after each incidence. Significance at the control value is based on a dose-weighted chi-square trend test, and significance at the dosed groups is for the Fisher's Exact Test. ND is not determined.

b/ Dosages adjusted for 5 days per week dosing.

Capsules - Dog

DDVP (97.3-99.5% purity) was administered orally in gelatin capsules at 0 (gelatin capsules), 0.05 (0.1 for the first 3 weeks of study), 1.0, or 3.0 mg/kg-day to purebred beagle dogs (4/sex/group) daily for 52 weeks (Markiewicz, 1990). The dosage of the 0.1 mg/kg-day group was lowered to 0.05 mg/kg-day because of plasma ChE inhibition (21-26%) observed after 2 weeks of dosing. There were no treatment-related changes in the mean food consumption, ophthalmology, necropsy, or histopathology. Cholinergic signs (soft stools, lacrimation, emesis, salivation, ataxia, and dyspnea) were intermittently observed at low incidences with no increase in the frequency of the observations with continued exposure (Table 8). The occurrences (at least one observation noted per week) of emesis of food, soft stools, and salivation were dose-related. DDVP capsules were found in the emesis of 1 male and 3 females of the 3 mg/kg-day groups. However, only 7 occurrences were reported throughout the 1 year study. There was no apparent dose-related effect on lacrimation as it was observed more frequently in the lower doses. The earliest observation, reported on week 1, was soft stools in the 1.0 and 3.0 mg/kg-day males and emesis in the 3.0 mg/kg-day males. The NOEL for combined cholinergic signs was 1.0 mg/kg-day.

Plasma and erythrocyte ChE activities were determined on weeks 2, 6, 13, 26, 39, and 52. Brain ChE activity was measured only at the end of the experiment. From week 13 to week 52, the plasma and erythrocyte ChE activities were significantly ($p \leq 0.05$) depressed in the 1.0 and 3.0 mg/kg-day groups. At 52 weeks, the decreases in ChE activities (plasma-erythrocyte) were similar for both sexes and were 46-54% of the pretreatment values for the 1.0 mg/kg-day group and 15-35% for the 3 mg/kg-day group. The NOEL for both plasma and erythrocyte ChE inhibition was 0.05 mg/kg-day. The brain ChE activities were inhibited in the 1.0 and 3.0 mg/kg-day males (78 and 53% of control values respectively), and in the 3.0 mg/kg-day females (71% of control value) (Table 8). The NOELs for brain ChE inhibition were 0.05 and 1.0 for males and females, respectively. This study was considered acceptable to DPR according to FIFRA guidelines.

Dietary - Dog

DDVP (93% purity; 0, 0.1, 1.0, 10.0, 100, or 500 ppm) was given to beagle dogs (3/sex/group) in the diet for 2 years (Jolley *et al.*, 1967). When corrected for DDVP degradation (loss of 65% due to volatility) and adjusted for food intake and body weight, the calculated average DDVP doses for both sexes were 0, 0.003, 0.01, 0.09, 0.9, and 8.9 mg/kg-day. Erythrocyte ChE and plasma ChE activities were inhibited at 10 ppm and higher concentrations only at the beginning of the experiment. For 1 month to 6 months of exposure, erythrocyte ChE activities of the 10 ppm group were 49-60% of the control values. Plasma ChE was inhibited to a lesser extent as the inhibition was 64-86% of control values after 0.25 month to 3 months. For both erythrocyte and plasma ChE, the activities were not significantly different from controls for the rest of the study. The NOEL for plasma and erythrocyte ChE inhibition was 1.0 ppm (0.01 mg/kg-day). Brain ChE activity was not affected in this study. Hepatocytes from the females showed histological changes which were described as rarefaction of cytoplasmic substance (increased transparency), enlargement of cells, and prominence of cell membranes. The severity of the changes increased from 10.0 to 500 ppm; however, no concurrent changes in the level of serum glutamic-oxalacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), or alkaline phosphatase. The NOEL based on liver histological changes was 10.0 ppm (0.09 mg/kg-day). This study was unacceptable to DPR according to FIFRA guidelines (limited hematology and clinical chemistry, dose levels not adequately defined for actual exposure, inadequate tissues for histopathology, inadequate number of animals per group).

Table 8. Clinical signs and brain cholinesterase inhibition in dogs treated with DDVP in capsules for 1 year[a].

Cholinergic signs

Sex	Dosage (mg/kg-day)	Occurrences[b] soft stools	emesis	salivation	ataxia	dyspnea
Males and Females	0	18 +	2 +	0 +	0	0
	0.05	36 **	4	0	0	0
	1.0	42 **	13 **	2	0	0
	3.0	40 **	34 **	8	1	1

Brain ChE inhibition

Sex	Dosage (mg/kg-day)	% of Control[c]
Males	0	100
	0.05	89
	1.0	78 *
	3.0	53 *
Females	0	100
	0.05	106
	1.0	93
	3.0	71 *

a/ Data were from Markiewicz (1990).

b/ Values are occurrences reported during the study. An occurrence is at least one observation per week in any animal with a total possible occurrences of 416 (52 weeks x 8 animals per group). Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance at the control value is based on a dose-weighted chi-square trend test, and significance at the dosed groups is for the Fisher's Exact Test.

c/ Statistically significant (* $p \leq 0.05$) from control values determined by the analysis of variance (ANOVA) in the report.

Table 9. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of DDVP from chronic studies.

Species	Route[a]	Duration[a]	Plasma ChE[a] NOEL (mg/kg-day)	Plasma ChE[a] LOEL (mg/kg-day)	Plasma ChE[a] % C	RBC ChE[a] NOEL (mg/kg-day)	RBC ChE[a] LOEL (mg/kg-day)	RBC ChE[a] % C	Brain ChE[a] NOEL (mg/kg-day)	Brain ChE[a] LOEL (mg/kg-day)	Brain ChE[a] % C	Other Effects NOEL (mg/kg-day)	Other Effects LOEL (mg/kg-day)	Effects	Ref.[b]
Rat	diet	7d/wx80w	-	-	-	-		-	-		-	7.5	15	reduced body weight	1
Rat	diet	7d/wx2y	0.13	1.2	79-95% at 2y	0.13	1.2	78-92% at 2y	>8.0	-	1.2	8.0		hepatocyte degeneration	2
Rat	gavage	5d/wx2y	-		-	-		-	-		-	oncogenic risk[c]		mononuclear leukemia and other tumors	3*
Rat	water	7d/wx2y	-		-	-		-	-		-	14	28	reduced body weight in males	4
Mouse	gavage	5d/wx2y	-		-	-		-	-		-	oncogenic risk		forestomach tumors	3*
Mouse	diet	7d/wx80w	-		-	-		-	-		-	45	90	reduced body weight	5
Dog	capsule	7d/wx1y	0.05	1.0	46% at 52w	0.05	1.0	54% at 52w	0.05	1.0	78% at 52w	1.0	3.0	emesis, salivation, ataxia	6*
Dog	diet	7d/wx2y	0.01	0.09	64-86% at 1-12w	0.01	0.09	49-60% at 4-24w	>8.9	-	no effects	0.09	0.9	hepatocyte degeneration	7
Rat	inhal	23h/d x7d/wx2y	0.05	0.5	76-84% at 104w	0.05	0.5	69-72% at 104w	0.05	0.5	90% at 104w	0.5	4.6	reduced body weight	8

a/ Abbreviations: ChE= cholinesterase, RBC= erythrocyte, inhal= inhalation, h= hours, d= days, w= weeks, y= years, % C= % of control values at the LOEL, -= data not available.

b/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. NCI, 1977a; 2. Witherup *et al.*, 1967; 3. Chan, 1989; 4. Enomoto, 1978; 5. NCI, 1977b; 6. Markiewicz, 1990; 7. Jolley *et al.*, 1967; 8. Blair *et al.*, 1974.

c/ Oncogenic effects are assumed to have no threshold levels, and they are evaluated by the calculation of potency factors.

E. GENOTOXICITY

Summary: DDVP was genotoxic in some in vitro systems, including assays with Salmonella TA 100 strain and Schizosaccharomyces pombe, mouse lymphoma forward mutation assay, and unscheduled DNA synthesis assay using human epithelial cells. However, DDVP was not genotoxic in the micronucleus, dominant lethal, in vivo chromosomal aberrations, and in vivo sister chromatid exchange assays. Studies conducted in the presence and absence of a liver preparation (S-9 fraction) showed that the decrease in genotoxicity in the presence of the preparation may be due to the inactivation of DDVP by liver esterases. Methylated DNA was detected in tissues of mice given DDVP by intraperitoneal injection, but not in rat tissues when DDVP was given by inhalation.

Gene Mutation

Data from mutagenicity assays of DDVP in microbial systems showed mutagenic effects (Gilot-Delhalle *et al.*, 1983; and Braun *et al.*, 1982). DDVP at 5 *u*M or more per plate was positive in only TA100, one of five strains of Salmonella, in the absence of liver enzymes from the NMRI mouse (Braun *et al.*, 1982). DDVP (99% purity; 1.5, 4, or 14 mM) was mutagenic to Schizosaccharomyces pombe only in the absence of S9 fraction from mice pretreated with phenobarbital (Gilot-Delhalle *et al.*, 1983). These studies were considered unacceptable to DPR because of inadequate protocol description and/or results. The only negative mutagenicity study was in E. coli B/r WP2 (Dean, 1971). This study was unacceptable to DPR because no data or dose levels were stated.

Positive mutagenic response in the mammalian system was observed in two studies (Ford *et al.*, 1986; and NTP, 1985). The mutagenic effect of DDVP (97.5% purity, 0.004 to 0.5 *u*l/ml) in L5178Y TK +/- mouse lymphoma cells was examined in the presence and absence of Aroclor 1242 and 1254-induced rat liver S-9 preparation (Ford *et al.*, 1986). A dose-related increase in the mutation frequency was observed in cells treated with DDVP (0.043 to 0.24 *u*l/ml) in the absence of liver preparation. The results from experiments in the presence of the liver preparation showed the increase in mutation frequency was lower than those obtained in the absence of the preparation. The decrease in response may have been due to the rapid degradation of DDVP by the liver enzymes. This study was acceptable to DPR.

In the National Toxicology Program (NTP) study, DDVP (purity not specified) was tested at 0, 6.25, 12.5, 25, 50, 100, 200, or 250 nl/ml in mouse lymphoma L5178Y TK +/- cells (NTP, 1985). In the absence of the liver S-9 preparation, there was a concentration-related increase in the mutation frequency at the three lowest exposures (6.25 to 25 nl/ml). Cytotoxicity was observed at concentrations equal to and greater than 50 nl/ml. The effect of S-9 preparation on mutation was not tested. This study was unacceptable to DPR because metabolic activation was not studied and DDVP purity was not reported.

Structural Chromosomal Aberration

There was no evidence of micronucleus formation when DDVP (98.4% purity; 0, 4, 13, or 40 mg/kg) was given to mice by intraperitoneal injection twice at 24 hour interval and sacrificed at 30, 48, or 72 hours (SDS Biotech Corp. 1985). This study was acceptable to DPR.

DDVP has not been shown to induce dominant lethal effects. In the only acceptable study, DDVP (97.% purity; 0. 8, 16, or 32 mg/kg-day) were administered by intraperitoneal injection to male CD-1 mice for 5 days and mated weekly for 8 weeks (Ford and Killeen, 1987). In two unacceptable studies of similar protocols, no dominant lethal effects were observed when CD-1 mice were exposed to DDVP (>97% purity; up to 10 mg/kg-day) by intraperitoneal injection for 5 consecutive days (Ford *et al.*, 1985; Putman, 1985). These studies were unacceptable because of inadequacies in the protocols and/or report of the data.

Mice exposed to DDVP by inhalation also did not show dominant lethal effects. CF-1 mice were exposed to DDVP (>97% purity; 30 or 55 *u*g/L) by inhalation for 16 hours (Dean and Thorpe, 1971a). There was a significant ($p \leq 0.05$) increase in early fetal death only on week 6 of 8 matings of the 30 *u*g/L group. This effect was not considered to be compound-related since it was not observed in the other matings, and no other indications of dominant lethal effects were observed. Multiple exposures to DDVP (>97% purity; 0, 2.1, or 5.8 *u*g/L) by inhalation at 23 hours per day for 4 weeks also did not cause any effects (Dean and Thorpe, 1971b). Both of the studies were unacceptable to DPR because of inadequacies in the protocol and/or report of the data.

ICR male mice (10/group) was given DDVP (98.09% purity; 0, 12.5, 25, or 50 mg/kg-day) by gavage for 5 consecutive days (Putman and Shadley, 1992). Bone marrow cells and spermatogonial cells were collected 24 hours after the last dosing. Cyclophosphamide was the positive control. There was no increase in the number of aberrations in either the bone marrow or spermatogonial cells of DDVP treated animals. This study was unacceptable to DPR because bone marrow from only one sex was examined.

DDVP (purity not specified, 10 mg/kg) was given to male mice (Q strain) by a single intraperitoneal injection (Degraeve *et al.*, 1984a). After a recovery period of 10 to 15 days, there was no increase in the number of aberrations in the primary spermatocytes. This study was unacceptable to DPR because the report was incomplete.

DDVP (99% purity, 2 ppm) was given in the drinking water to male mice for 7 weeks (Degraeve *et al.*, 1984b). No increase in bone marrow or sperm chromosomal aberrations was detected. This study was unacceptable to DPR because the report was incomplete.

Other Genotoxic Effects

In an in vivo study, B6C3F1 mice were given DDVP (98.4% purity; 0, 3, 10, or 30 mg/kg-day) by intraperitoneal injection (Microbiological Associates, Inc. 1985). Sister chromatid exchanges were scored in cells collected 24 hours after treatment. There was no significant increase in the number of sister chromatid exchanges in cells treated with DDVP compared to the untreated controls. This study was acceptable to DPR.

DDVP (purity not specified; 0, 6.5, 65, or 650 mM) was added to human epithelial cells in the absence of rat liver preparation (Aquilina *et al.*, 1984). A positive, concentration-dependent effect for unscheduled DNA synthesis was detected for all doses. There was also no induction by DDVP (0, 1.25, 2.5, or 5.0 mM) of ouabain resistant mutations in Chinese hamster cells. This study was unacceptable to DPR because of inadequacies in the protocol and in the report of data.

Mice were exposed to DDVP resin strips for 80 days before mating (Selby *et al.*, 1982). No fetal skeletal malformation was observed. This study was unacceptable to DPR because of protocol inadequacies.

No methylation of tissue DNA, an indicator of mutation, was found from rats exposed to DDVP (^{14}C, 92.5% purity, 0.064 *u*g/L or equivalent to 31 *u*g/kg) for 12 hours by nose-only inhalation exposure (Wooder *et al.*, 1977). However, low levels (8×10^{-13} mole methyl/g DNA) of alkylation of guanine-N-7 were detected in the DNA of pooled organs (liver, kidney, spleen, heart, brain, lung and testes) from mice given DDVP (^{14}C, 99% purity, 420 *u*g/kg) by intraperitoneal administration (Segerback, 1981).

Table 10. Selected genotoxicity studies of DDVP.

Test types	Route/Duration[a]	Dose[b]	Effects/Comments	Ref.[c]
I. Gene Mutation				
Bacterial mutagenicity tests				
S. typhimurium, TA 1535	plate, 24 h	> 40 *u*M/plate	–	1
S. typhimurium, TA 1537	plate, 24 h	> 40 *u*M/plate	–	1
S. typhimurium, TA 1538	plate, 24 h	> 40 *u*M/plate	–	1
S. typhimurium, TA 98	plate, 24 h	> 40 *u*M/plate	–	1
S. typhimurium, TA 100	plate, 24 h	≥ 5 *u*M/plate	+, dose-related increase in revertants	1
S. pombe	plate, 1 h	≥ 1.5 mM	+, dose-related increase in mutants	2
Forward mutation test				
Mouse lymphoma L5178Y				
TK locus	solution, 4 h	≥ 0.043 *u*l/ml	+, without liver S9 fraction	3*
TK locus	solution, 4 h	≥ 6.25 nl/ml	+, without liver S9 fraction	4
II. Structural Chromosomal Aberrations				
Micronucleus test				
Mouse	ip, 2 dosesx1d > 40 mg/kg		–	5*
Dominant lethal test				
Mouse	ip, 5d	> 32 mg/kg-day	–	6*
Mouse	ip, 5d	> 10 mg/kg-day	–	7, 8
Mouse	inhale, 16h	> 55 *u*g/L	–	9
Mouse	inhale, 23hx4w	> 5.8 *u*g/L	–	10
Chromosomal aberrations				
Mouse	gavage, 5d	> 50 mg/kg-day	–	11
Mouse	ip, 1 dose	> 10 mg/kg	–	12
Mouse	water, 7w	> 2 ppm	–	13
III. Other Genotoxic Effects				
Unscheduled DNA synthesis				
Human epithelial cells	plate, 1 h	≥ 6.5 mM	+, dose-related increase	14
Chinese hamster cells	plate, 1 h	> 5.0 mM	–	14
Sister chromatid exchange				
Mouse	ip, 1 dose	> 30 mg/kg	–	15*
DNA alkylation				
Rat	inhale, 12 h	> 0.064 *u*g/L	–, no DNA alkylation	16
Mouse	ip, 1 dose	420 *u*g/kg	+, DNA alkylation	17

a/ Abbreviations are: h=hours, d=day, w=week, ip=intraperitoneal, inhale=inhalation

b/ Dose which resulted in a positive response or the highest dose tested with a negative response.

c/ * after the reference number indicates the study was acceptable to DPR. References: 1. Braun *et al.*, 1982; 2. Gilot-Delhalle *et al.*, 1983; 3. Ford *et al.*, 1986; 4. NTP, 1985; 5. SDS Biotech Corp., 1985; 6. Ford and Killeen, 1987; 7. Ford *et al.*, 1985; 8. Putman, 1985; 9. Dean and Thorpe, 1971a; 10. Dean and Thorpe, 1971b; 11. Putman and Shadley, 1992; 12. Degraeve *et al.*, 1984a; 13. Degraeve *et al.*, 1984b; 14. Aquilina *et al.*, 1984; 15. Microbiological Associates Inc., 1985; 16. Wooder *et al.*, 1977; 17. Segerback, 1981.

F. REPRODUCTIVE TOXICITY

Summary: Exposure of rats to DDVP during reproduction resulted in the inhibition of plasma, erythrocyte, and brain ChE. Clinical signs were observed in both parents and offsprings. Other toxicity included decreased body weights and decreased water consumption. Re-mating of the F_1 females after the F_2 generation showed decreased estrous cycling and increased incidence of abnormal estrus cycling. Mice exposed to DDVP containing resin strips showed only plasma ChE depression and no effect on reproduction. A summary of selected studies reviewed is listed in Table 12.

Dietary - Rat

DDVP (93% purity; 0, 0.1, 1.0, 10, 100, or 500 ppm) in the diet was fed daily to CD rats (15/sex/group) for 3 generations (Witherup *et al.*, 1965). The progenitor rats were dosed for 6 weeks before the first mating. No compound related effects in fertility, relative number of the progeny in each generation, or anatomical abnormalities were observed. The NOEL was greater than or equal to 500 ppm. The dosages were not estimated and body weight data were not included in the report. This study was unacceptable to DPR according to FIFRA guidelines (the diet was prepared once a week instead of daily, no individual data or histopathology data).

Drinking water - Rat

In a range-finding study for a two-generation reproductive toxicity study, Sprague-Dawley rats (10/sex/group) were given DDVP (purity not specified; 0, 20, 80, 200, or 400 ppm) in the drinking water (Tyl, 1990). The reported mean dosages were 0, 3, 12, 24, and 41 mg/kg-day from days 0 to 14 for both sexes during premating period. During gestation (days 0-20), the reported mean dosages were 0, 3, 11.3, 22.1, and 47.9 mg/kg-day. During lactation (days 0-21), the mean dosages were 5.2, 17.4, 44.4, and 77.3 mg/kg-day. Cholinergic signs were observed during all stages of reproduction in the parents and F_1 off-spring. At 400 ppm (48 mg/kg-day), tremors were first observed in the F_0 females on day 7 of premating. At 200 ppm, tremors, rough coat, and lethargy were first observed in the F_1 off-spring on postnatal day 26. No observations were reported for the 400 ppm pups due to early sacrifices of moribund pups and high mortality. The plasma, erythrocyte, and brain ChE activities measured after pre-mating and mating exposure were reduced in a dose-related manner for all treated groups. At 20 ppm, the plasma, erythrocyte, and brain ChE activities for male-female were 48-66%, 58-61%, and 54-93% of control values, respectively. Body weights, water intake, and food consumption when measured from premating to lactation were reduced, frequently statistically significant ($p \leq 0.05$) for the dams in the 200 and 400 ppm groups and the NOEL was 80 ppm (11-17 mg/kg-day for premating to lactation dosages). In addition to cholinergic signs, the food and water consumption, and average body weights were reduced in the 200 ppm pups. The fetal NOEL was 80 ppm (11 mg/kg-day based on gestation dosages). The recommended doses for the definitive study were 0, 5, 20, and 80 ppm.

In the definitive study, Sprague-Dawley rats (30/sex/group) were given DDVP (98.1% purity; 0, 5, 20, or 80 ppm) in the drinking water 24 hours daily (Tyl *et al.*, 1992). The reported dosages for each group are listed in Table 11. Rats of both sexes were treated for 10 and 11 weeks during the premating period, respectively, for the F_0 and F_1 animals and were then allowed to mate for 3 weeks. Selected F_1 offspring were either necropsied or maintained to breed for the F_2 generation. Cholinesterase activities of the plasma, erythrocyte, and brain were determined after mating for the males, and after lactation for the females. Because of low reproductive performance, F_1 males were subjected to detailed reproductive assessment, and the F_1 females were studied for estrous cyclicity as well as mated with untreated males for the F_2b generation. Decreased water consumption in both generations and reduced body weight in the F_1 parents were observed in the 80 ppm group.

No clinical signs were reported; however, Tyl *et al.* (1992) suggested that the signs could have been missed because rats were nocturnal animals and the consumption of DDVP in the water was highest at night. There were dose-related decreases in the plasma, erythrocyte, and brain ChE activities of all F_0 and F_1 adults, and the levels of inhibition at 20 and 80 ppm were statistically significant ($p \leq 0.05$) (Table 11). The inhibition of ChE activity was greater in the females than in the males because the females were exposed to DDVP for a longer time (during gestation and lactation also) and their dosages were higher. The NOAEL for plasma, erythrocyte, and brain ChE inhibition was 5 ppm (0.5 mg/kg-day for the males and 1.1 mg/kg-day for the females). It should be noted that a LOEL of 5 ppm may be established for the inhibition of erythrocyte ChE activity of the F_0 females and F_1 both sexes as well as plasma ChE activity for the F_1 males.

There was no evidence of pathological effects in the reproductive organs. The only significant effect observed in the pups was the reduction in the body weights of the 80 ppm F_1 pups on postnatal days 14 and 21. After weaning the F_2a litters, the F_1 females were exposed to DDVP again and mated with untreated males for the F_2b litters. There was a reduction (not statistically significant) of fertility at 80 ppm. The number of "abnormal" cycles in the 80 ppm F_1 females was significantly higher (68%) than in the controls (16%). The NOEL for reproductive toxicity and non-cholinergic endpoints was 20 ppm (2.7 mg/kg-day estimated from the premating dosage for females) based on the reduction of water consumption, body weight, fertility, and estrous cycling. This study was considered acceptable to DPR according to FIFRA guidelines.

Inhalation - Mouse

Crl:CD-1 mice (number of mice used not specified) were exposed to DDVP by inhalation during breeding (Casebolt *et al.*, 1990). Resin strips (1 by 2.5 inch, 2 by 2.5 inch, and 4 by 2.5 inch) were placed in the food hopper 4 days prior to mating and continued throughout pregnancy. The air concentrations measured on day 1 were 1.9 ± 1.2, 3 ± 2.2, and 4.6 ± 2.0 mg/m^3 for the three sizes of strips, respectively, but were not maintained throughout the experiment. The estimated dosages for the three air concentrations of day 1 were 3.4, 5.7, and 8.3 mg/kg-day. There were no effects on the reproductive performances as determined by litter frequency and mean litter size. No clinical signs were observed. Plasma ChE activity of the treated dams were depressed on days 4 and 7, but not on day 14. The plasma ChE activity was maximally inhibited on day 4 to 10%, 7%, and 6% of control values for 1.9, 3, and 4.6 mg/m^3 groups, respectively.

Table 11. The dosages and the inhibition of cholinesterase activity in rats treated with DDVP[a].

Dosages

mg/kg-day

ppm	premating F_0 and F_1 males	premating F_0 and F_1 females	gestation females	lactation females
5.0	0.48-0.5	0.65-0.66	0.56-0.59	0.93-1.1
20.0	1.92-1.95	2.43-2.67	2.12-2.42	4.3-4.6
80.0	6.90-7.53	9.37-9.47	7.04-8.15	13.2-17.5

Cholinesterase inhibition

F_0 generation

ChE activity as % of Control[b]

ppm	mg/kg-day[c]		Brain ChE		Plasma ChE		Erythrocyte ChE	
	M	F	M	F	M	F	M	F
5	0.5	1.1	99	94	96	88	93	77*
20	1.9	4.6	85*	74*	71*	45*	71*	61*
80	7.5	17.5	47*	41*	59*	17*	43*	40*

F_1 generation

ChE activity as % of Control[b]

ppm	mg/kg-day[c]		Brain ChE		Plasma ChE		Erythrocyte ChE	
	M	F	M	F	M	F	M	F
5	0.5	1.1	101	98	85*	91	86*	83*
20	1.9	4.6	94*	68*	74*	46*	68*	58*
80	7.5	17.5	60*	40*	42*	19*	45*	42*

a/ Data were from Tyl *et al.* (1992).

b/ Values are expressed as the mean % of control values. The values for female and males are presented as M or F, respectively. Statistical significance (*, $p \leq 0.05$) was determined by the analysis of variance by ANOVA or Dunnett's test as reported.

c/ The dosages were based on the highest value of the range during premating for males, and during lactation for females.

Table 12. Selected no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of DDVP from reproductive toxicity studies.

Species	Route	Duration	Plasma ChE[a] NOEL (mg/kg-day)	Plasma ChE[a] LOEL (mg/kg-day)	Plasma ChE[a] % C	RBC ChE[a] NOEL (mg/kg-day)	RBC ChE[a] LOEL (mg/kg-day)	RBC ChE[a] % C	Brain ChE[a] NOEL (mg/kg-day)	Brain ChE[a] LOEL (mg/kg-day)	Brain ChE[a] % C	Other Effects NOEL (mg/kg-day)	Other Effects LOEL (mg/kg-day)	Effects	Ref.[b]
Rat (range finding)	water	daily[c] females and males F_0	-	3	48-66%	-	3	58-61%	-	3	54-93%	-			1
		females F_0	-		-	-		-	-		-	11-17	22-44	maternal-reduced body weight gain, food consumption	
		females F_0	-		-	-		-	-		-	24	41	maternal- tremors (first on day 7)	
		fetal F_1	-		-	-		-	-		-	11	22	fetal-cholinergic signs	
Rat	water	daily[c,d]										2.7	9.5	parental -decreased fertility, increased abnormal cycles, reduced body weights	2*
		females F_0	1.1	4.6	45%	<1.1	1.1	77%	1.1	4.6	74%				
		females F_1	1.1	4.6	46%	<1.1	1.1	83%	1.1	4.6	68%				
		males F_0	0.5	1.9	71%	0.5	1.9	71%	0.5	1.9	85%				
		males F_1	0.5	1.9	74%	<0.5	0.5	86%	0.5	1.9	94%				

a/ Abbreviations: ChE= cholinesterase, RBC= erythrocyte, w= weeks, % C= % of control values at the LOEL, -= data not available.

b/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Tyl, 1990; and 2. Tyl *et al.*, 1992.

c/ Refer to text for durations of exposure.

d/ The dosages for ChE inhibition were from Table 11.

G. DEVELOPMENTAL TOXICITY

Summary: DDVP, given by oral or inhalation routes, was not teratogenic in rats, mice, or rabbits. Cholinergic signs (tremors, ataxia, diarrhea, and other effects) were observed in the pregnant rats and rabbits. Selected studies are presented in Table 13.

Gavage - Rat

DDVP (97% purity; 0, 0.1, 3.0, or 21.0 mg/kg-day) was given to Sprague-Dawley pregnant rats (25/group) by gavage once daily from gestational days 6 to 15 (Tyl *et al.*, 1991a). Systemic toxicity was observed only in the high dose group. There was a significant ($p \leq 0.05$) reduction in the maternal body weight as the mean maternal weight gain was 66% of control value during the treatment period. Cholinergic signs observed were tremors and excitability. Tremors were observed in the 21.0 mg/kg-day group with the onset within 10-60 minutes after each daily dosing. Other signs of toxicity included prone positioning, hindlimb splay, circling, vocalization, hypoactivity, labored respiration, ear shaking, and coprophagia. Examination of the fetuses showed no significant increases in the incidence of gestational parameters and of individual or pooled external, visceral, skeletal, or total fetal malformations or variations. The incidence (18 fetuses/8 litters) of enlarged lateral ventricles of the cerebrum in the fetuses of the 21.0 mg/kg-day was slightly higher, though not statistically significant, than that (9 fetuses/5 litters) for the control group. The NOELs were 3.0 mg/kg-day for maternal toxicity and greater than 21.0 mg/kg-day for developmental toxicity. This study was considered acceptable to DPR according to FIFRA guidelines.

Intraperitoneal - Rat

Pregnant Sherman rats (6/group) were given a single dose of DDVP (purity not stated, 15 mg/kg) by intraperitoneal injection on day 11 after insemination (Kimbrough and Gaines, 1968). On day 20 of pregnancy, the fetuses were examined. Of the 41 fetuses examined, omphalocele was noted in 3 fetuses. There were no significant differences in the average weight gain of the dams, average number of fetuses per litter, average number of resorptions, average weight of fetuses, and average weight of placenta. The report noted that a dose of 20 mg/kg DDVP was lethal to pregnant rats. Except for lethality and dam body weights, the report did not include clinical observations.

Inhalation - Rat

Female rats (Carworth Farm E strain, 9-10/treated group) were exposed to DDVP (>97% purity; at nominal concentrations of 0, 0.25, 1.25, or 6.25 *u*g/L equivalent to 0, 0.23, 1.15, or 5.75 mg/kg-day) for 23 hours daily by inhalation (Thorpe *et al.*, 1971a). They were treated from day 1 of insemination (pregnancy) to gestation day 20. At the end of the experiment, plasma, erythrocyte, and brain ChE activities of the 1.25 *u*g/L group were significantly ($p<0.01$) depressed to 67, 61, and 72 % of control values, respectively. The plasma, erythrocyte, and brain ChE activities of the 6.25 *u*g/L group were further reduced to 27, 12, and 17% of control values, respectively. The only clinical sign observed was lethargy in some animals in the 6.25 *u*g/L group. No fetal toxicity was observed. This study was unacceptable to DPR according to FIFRA guidelines (too few litters per group, experimental details not adequately described, and no individual data).

Gavage - Mouse

DDVP (96% purity, 60 mg/kg) was given to female CF-1 mice (number of mice used not specified) by gavage from gestation days 6 to 15 (Schwetz *et al.*, 1979a). The dose given was stated as the maximally tolerated dose (MTD). The only significant finding was reduced mean body weights (actual data not presented) of dams on day 16 of gestation. No developmental toxicity was reported. This study was unacceptable to DPR according to FIFRA guidelines (only 1 dose was tested and no individual data).

Inhalation - Mouse

Female CF-1 mice (number of mice used not specified) were exposed to DDVP (96% purity, at nominal concentration of 4 *u*g/L or equivalent to 2.1 mg/kg-day) by inhalation 7 hours per day from gestation days 6 to 15 (Schwetz *et al.*, 1979a). No significant findings were reported. This study was considered unacceptable to DPR according to FIFRA guidelines (single dose testing, no individual data, and MTD not reached).

Gavage - Rabbit

New Zealand rabbits (16/group) were given DDVP (97% purity; 0, 0.1, 2.5, or 7.0 mg/kg-day) by gavage from gestation days 7 to 19 and sacrificed on gestation day 30 (Tyl *et al.*, 1991b). Systemic toxicity included decreased weight gain (gestation days 7 to 19) as well as mortality (2 does of the 2.5 mg/kg-day group died on gestation days 12 and 15, and 4 does of 7.0 mg/kg-day group on gestation days 17 and 19). In the high dose group, there were significant ($p \leq 0.05$) decreases in food consumption (82% of control value) and cholinergic signs (ataxia, salivation, diarrhea, breathing difficulties, tremors, and excitation). The first observation of ataxia was made on gestation day 10. There were no increased incidences in the gestational parameters examined and of external, visceral, skeletal, or total fetal malformations or variations. The NOELs were 0.1 mg/kg-day for maternal toxicity and greater than 7.0 mg/kg-day for developmental toxicity. This study was considered acceptable to DPR according to FIFRA guidelines.

DDVP (96% purity, 5 mg/kg-day) was given to New Zealand rabbits (number of rabbits used not specified) by gavage from gestation days 6 to 18 (Schwetz *et al.*, 1979b). No adverse effects were observed. This study was considered unacceptable to DPR according to FIFRA guidelines (no individual data, and MTD not reached).

Capsules - Rabbit

DDVP (purity not specified) was incorporated onto polyvinyl chloride resin and was given orally to New Zealand female rabbits (15/group) at doses of 3, 12, 36, or 60 mg/kg-day on gestation days 6 to 16 (Vogin, 1969). Because of maternal toxicity, the 60 mg/kg-day group dose was reduced to 24 mg/kg-day after 7 days of treatment. At 24 and 36 mg/kg-day doses, increased incidences of mortality and toxicity (incontinence and disorientation) were observed in the does. The time of onset of the clinical signs was not specified in the study. No developmental toxicity was observed. This study was unacceptable to DPR according to FIFRA guidelines (too few pregnant does, test article not described adequately). A NOEL could not be determined for this study.

New Zealand female rabbits (15-26/group) were given DDVP (>97% purity; 0, 18, 54, or 93 mg) twice a day from gestation days 6 to 18 (Carson, 1969). The dosing duration for the high dose group was modified to only 3 consecutive days (day 6 to 8 or day 9 to 11) due to toxicity (incontinence, anorexia, lethargy, and death) when dosed consecutively from gestation days 6 to 13. In all treatment groups, the increase of in utero and neonatal toxicity was not significantly different from the vehicle control groups. This study was considered unacceptable to DPR according to FIFRA guidelines (actual test

levels not verified, too few pregnant rabbits, high mortality, exposure for only part of organogenesis). A NOEL could not be determined for this study.

Inhalation - Rabbit

Two experiments were conducted in the Tunstall Laboratory with rabbits exposed to DDVP by inhalation. In the first experiment, female Dutch rabbits (19-20/group) were exposed to DDVP (>97% purity) from day 1 of mating to gestation day 28 (Thorpe *et al.*, 1971b). The DDVP nominal air concentrations were 0, 0.25, 1.25, or 6.25 *u*g/L for 23 hours per day (equivalent to 0, 0.13, 0.65, or 3.25 mg/kg-day). Cholinesterase activities of the plasma, erythrocyte, and brain were measured at the end of the experiment. Severe toxicity and mortality were observed after the 6th day of exposure in the 6.25 *u*g/L group. Cholinergic signs observed included anorexia, lethargy, muscular tremors, mucous nasal discharges, and diarrhea. Severely affected rabbits were prone with heads turned to one side. Sixteen of 20 does died or were killed because of intoxication. There were no observations reported for earlier time periods. Plasma, erythrocyte, and brain ChE activities were significantly ($p \leq 0.05$) inhibited to 65, 32, and 44%, respectively, of control values for the 1.25 *u*g/L group; and 27, 7, and 15%, respectively, of control values for the 6.25 *u*g/L group. The NOELs were 0.25 *u*g/L (0.13 mg/kg-day) for ChE inhibition and 1.25 *u*g/L (0.65 mg/kg-day) for cholinergic signs and death. No developmental toxicity was reported.

In the second experiment, Dutch rabbits (20/group) were exposed to DDVP (0, 2, and 4 *u*g/L, equivalent to 0, 1.0, and 2.0 mg/kg-day) by inhalation using the same protocol (Thorpe *et al.*, 1971b). One doe in the 2 *u*g/L group died after 2-3 days of exposure. Six does of the 4 *u*g/L died or were killed because of intoxication with signs as noted in the first study. Five of the six does in the 4 *u*g/L group were affected in the week when the DDVP concentration reached as high as 6.6 *u*g/L due to a blockage of the chamber filter. There was apparent increase in late gestational fetal death in the 4 *u*g/L group. The NOEL was less than 2 *u*g/L (1.0 mg/kg-day) based on mortality in the 2 *u*g/L group. Both of the experiments were considered unacceptable to DPR according to FIFRA guidelines (inadequate number of fetuses, inadequate examination).

New Zealand rabbits (number of rabbits used not specified) were exposed to DDVP (96% purity, at a nominal concentration of 4 *u*g/L) for 7 hours per day from gestation days 6 to 18 (Schwetz *et al.*, 1979b). Even though the MTD was supposedly used, no maternal or fetal toxicity was observed. This study was considered unacceptable to DPR according to FIFRA guidelines (MTD not reached). A NOEL could not be determined for this study.

Table 13. Selected no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of DDVP from developmental toxicity studies.

Species	Route[a]	Duration[a]	Plasma ChE[a] NOEL (mg/kg-day)	Plasma ChE[a] LOEL (mg/kg-day)	Plasma ChE[a] % C	RBC ChE[a] NOEL (mg/kg-day)	RBC ChE[a] LOEL (mg/kg-day)	RBC ChE[a] % C	Brain ChE[a] NOEL (mg/kg-day)	Brain ChE[a] LOEL (mg/kg-day)	Brain ChE[a] % C	Other Effects NOEL (mg/kg-day)	Other Effects LOEL (mg/kg-day)	Effects	Ref.[b]
Rat	gavage	d6-15 gestation	-		-	-		-	-		-	3.0 >21	21.0	maternal-reduced body weight gain, tremors after each dosing no fetal effects	1*
Rabbit	gavage	d7-19 gestation	-		-	-		-	-		-	0.1 >7.0	2.5	maternal-decreased weight gain, lethality no fetal effects	2*
Rat	inhal	23h/d d1-20 gestation	0.23	1.15	67%	0.23	1.15	61%	0.23	1.15	72%	1.15 >5.75	5.75	maternal-lethargy no fetal effects	3
Rabbit	inhal	23h/d d1-28 gestation	0.13	0.65	65%	0.13	0.65	32%	0.13	0.65	44%	0.65 >3.25	3.25	maternal-cholinergic signs and death after 6 days no fetal effects	4
Rabbit	inhal	23h/d d1-28 gestation	-		-	-		-	-		-	<1.0	1.0	maternal-death in 2-3 days	5

a/ Abbreviations: ChE= cholinesterase, RBC= erythrocyte, inhal= inhalation, h= hours, d= days, % C= % of control values at the LOEL, -= data not available.

b/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Tyl *et al.*, 1991a; 2. Tyl *et al.*, 1991b; 3. Thorpe *et al.*, 1971a; 4. Thorpe *et al.*, 1971b (first experiment); and 5. Thorpe *et al.*, 1971b (second experiment).

c/ Dose at which the effect was observed at the specified duration or the only dose studied, not necessarily the LOEL.

H. NEUROTOXICITY

Summary: Possible adverse effects of nerve fiber degeneration and spinal cord degeneration were observed in chickens treated with DDVP. No acute delayed neurotoxicity in hens was reported, except at lethal doses. An acute neurotoxicity study in the rat given DDVP by gavage resulted in cholinergic effects which included gait alteration, constricted pupils, tremors, and salivation.

Gavage - Chicken

DDVP (97.87% pure; 0, 0.3, 1.0, or 3.0 mg/kg-day) was given to domestic hens (21/group) by gavage for 28 days (Huntingdon Research Centre Ltd., 1994). Hens were observed for a total of 49 or 77 days after the onset of dosing. There was an overall trend for decreased body weight gain from days 1-28 ($\leq$ 7%); however, recovery of body weigh gain occurred from days 28-77. Clinical signs of neurotoxicity was observed at 1.0 mg/kg (unsteady gait and an inability to stand), and 3.0 mg/kg (wings outstretched, being pecked, limping, inability to stand, quiet/subdued, unsteadiness, and death). Histological examination showed axonal degeneration in the cerebellum, spinal cord, sciatic nerve and tibial nerve, as well as splitting/thickened and/or densely staining material within the myelin in all doses. The NOEL for neurotoxicity was $\leq$ 0.3 mg/kg based on clinical and histological findings. On day 4, brain ChE was inhibited 44% at 1.0 mg/kg and 65% at 3.0 mg/kg. By day 30, brain ChE activities were inhibited: 26, 34, and 54%, respectively, for 3.0, 1.5, and 0.3 mg/kg. However, brain neurotoxic esterase and spinal cord neurotoxic esterase were not affected. This study was considered acceptable according to FIFRA guidelines.

Acute delayed neurotoxicity of DDVP was studied in atropinized chickens (10/group) after oral administration of 16.5 mg/kg DDVP (96.5% purity, LD50 of 16.15 mg/kg) on day 1 and again on day 22 (Beavers *et al.*, 1988). At sacrifice on day 43, a possible adverse effect was noted in one of 10 treated chickens. Histopathological examinations of the sciatic nerve showed nerve fiber degeneration in the proximal right sciatic nerve, and axonal swelling in proximal and distal parts of that nerve. This study was considered acceptable to DPR according to FIFRA guidelines.

No delayed neurotoxicity was observed in two studies where hens (15/group) were treated with 2.5 mg/kg DDVP (93% purity) daily, 5 days per week for 3 weeks (The Kettering Lab., 1964), and with 22.9 mg/kg (purity not specified) in a single administration (Shell Chemical Co., 1971). These studies were considered unacceptable to DPR according to FIFRA guidelines (protocol and results were not adequately described).

Delayed neurotoxicity at a dose in excess of the lethal dose was studied in hens (6/group) 2 weeks after being treated with a single dose of DDVP (purity not stated, 100 mg/kg) (Caroldi and Lotti, 1981). Fifteen minutes before DDVP dosing, hens were given eserine (0.1 mg), atropine sulfate (20 mg), and 2-PAM (100 mg/kg) to block the ChE effects of DDVP. At 24 hours after dosing, neurotoxic esterase activity (NTE) in the brain, spinal cord, and peripheral nerve was reduced more than 78% in the treated hens. The hens showed mild signs of ataxia at 12-14 days after exposure. This was a published study and not reviewed for acceptability.

Using a similar protocol as Caroldi and Lotti (1981), hens were not ataxic until a second dose was given 1-3 days after the first dose (Johnson, 1978). The investigator suggested that ataxia was associated with spinal cord NTE. The second dose resulted in significant level of spinal cord NTE inhibition to induce ataxia in the hens. This was a published study and not reviewed for acceptability.

Gavage - Rat

The acute neurotoxicity of DDVP in rats was studied (Lamb, 1992; Lamb, 1993a) and is described under **III.B. ACUTE TOXICITY**. In the range finding study, the NOEL was 0.5 mg/kg-day for cholinergic signs (gait alteration and pupil constriction) observed at 1.0 mg/kg-day and higher concentrations (Lamb, 1992). In the definitive study, the acute NOEL was 0.5 mg/kg with cholinergic effects (including alteration in posture, convulsions and tremors, and salivation) observed at 35 and 70 mg/kg.

I. IMMUNOTOXICITY

DDVP (purity not stated; 0, 0.31, 0.62, 1.25, and 2.5 mg/kg) in gelatin capsules was given 5 times weekly to male rabbits (strain not specified, 6/group) for 6 weeks (Desi *et al.*, 1978). To determine the humoral immune response, 0.5 ml of Salmonella typhi vaccine was given intravenously once a week. Based on the data presented (in graphic form), there was an apparent dose-related decrease in the titer levels. There was also an apparent decrease in the erythrocyte and brain ChE activities. The validity of the results can not be determined because of the inadequate description of the methods and the data.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

The risk assessment of DDVP has been conducted because of adverse effects found in oncogenicity, genotoxicity, and neurological studies in animals.

In this assessment, acute and chronic exposures as well as oncogenic risk for lifetime exposures to DDVP were considered. The non-oncogenic endpoints used were based on mortality, cholinergic signs, and brain ChE inhibition. While cholinergic signs are considered adverse effects, the biological significance of ChE inhibition is less certain. The inhibition of plasma and erythrocyte ChE activities is generally considered an indication of exposure and not necessarily of toxicity. Human studies with DDVP have shown that plasma and erythrocyte ChE inhibition were not accompanied by cholinergic signs (Cavagna *et al.*, 1969 and 1970; Slomka and Hine, 1981; Menz *et al.*, 1974; and Rasmussen *et al.*, 1963). Moreover, the ChE activities recovered to pre-exposure levels upon withdrawal from DDVP exposure (Menz *et al.*, 1974 and Rasmussen *et al.*, 1963). Plasma ChE inhibition is generally considered an indication of exposure rather than toxicity (USEPA, 1990; Brimijoin, 1992). On the other hand, the inhibition of brain ChE is considered an adverse effect (USEPA, 1990; Brimijoin, 1992). A published study showed a positive correlation between brain ChE inhibition and the severity of cholinergic signs induced by soman (pinacolylmethylphosphonofluoridate) (Jimmerson *et al.*, 1989). Both parameters were determined 30 minutes after dosing. For DDVP, several studies showed that the LOELs for the inhibition of brain, plasma, and erythrocyte ChE were within an order of magnitude (Tables 3, 9, 12, and 13). In addition to brain ChE inhibition, DDVP has also been shown to inhibit spinal cord ChE as well as brain and spinal cord neurotoxic esterase activities (Ehrich *et al.*, 1993). Because brain ChE inhibition was determined at the end of the studies and cholinergic signs were generally observed during the study or missed due to nocturnal activity by rodents, there was no clear association between DDVP-induced ChE inhibition and signs.

The inhibition of brain ChE activity by DDVP observed in subchronic and chronic studies was likely due to both a cumulative effect and an acute effect from the last dose. The relationship between the extent of inhibition and exposure duration was examined by comparing the effective doses for 75% or 50% of control levels of brain ChE activity from several studies (Table 14).[1] The effective doses for the oral route for short duration of exposure (2 weeks) were 3-fold higher than for longer (1 year) duration of exposure. However, for the inhalation route, there were no differences in the effective dose and the duration of exposure. The development of tolerance or the reversibility of inhibition may account for the small differences in the effective doses between the different durations of the studies. Reversibility of brain ChE inhibition has been shown with mouse in an in vitro study (van Asperen and Delhuijzen, 1958). Pharmacokinetics studies showed that DDVP was rapidly metabolized and excreted. The majority of the radioactivity was eliminated in the air and urine within 24 hours after dosing (Cheng 1989 and 1991).

[1/] The interpretation of this comparison is limited because there is no standard methodology for the determination of brain ChE activity.

Table 14. Comparison of brain cholinesterase inhibition under different durations of exposure.

Species/route	sex	Effective dose (mg/kg-day)[a] 75%	50%	Time	Ref.[b]
rat/water	male	8.3	17.7	2 weeks	1
	female	4.2	14.2	2 weeks	
rat/water	male	3.6	7.0	10-11 weeks	2
	female	6.0	14.0	10-11 weeks	
dog/capsule	male	1.4	3.1	1 year	3
	female	2.6	4.9	1 year	
rat/inhalation	female	1.6	3.3	3 weeks	4
rabbit/inhalation	female	0.57	1.4	4 weeks	5
rat/inhalation	male	1.4	2.9	2 years	6

a/ The effective dose for either 50% or 75% of control brain ChE activity was calculated from the linear regression analysis of the data for dosages and % of control activity.

b/ 1. Tyl, 1990; 2. Tyl *et al.*, 1992; 3. Markiewicz, 1990; 4. Thorpe *et al.*, 1971a; 5. Thorpe *et al.*, 1971b; and 6. Blair *et al.*, 1974.

Acute Toxicity

Inhalation

The critical NOEL for acute inhalation exposure was derived from the two experiments on the developmental toxicity of rabbits where the does were exposed to DDVP for 23 hours/day (Thorpe *et al.*, 1971b). The two experiments were considered together to derive the acute NOEL since they were conducted by the same laboratory with the same protocol. In the first experiment, mortality and cholinergic signs (16 of 20 does) occurred in the 6.25 *u*g/L (3.25 mg/kg-day) group after 6 days. The does were severely intoxicated. In the second experiment, 1 of 20 does in the 2 *u*g/L (the lowest dose tested, 1.0 mg/kg-day) group died after 2-3 days. No cholinergic signs were reported. Therefore, the no effect dose of 1.25 *u*g/L (0.65 mg/kg-day) from the first experiment may be used as the NOEL with the LOEL at 2.0 *u*g/L (1.0 mg/kg-day) determined by the second experiment. These studies were considered unacceptable to DPR as developmental toxicity studies, but do provide useful information on acute toxicity. Since there is insufficient information on the potential contribution to the exposure due to grooming and contamination of food and water by DDVP in the air, the air concentration provides the only estimate of actual exposure level by inhalation. The adjusted NOEL for risk assessment was 0.325 mg/kg-day (NOEL of 0.65 mg/kg-day x 0.5) based on a default inhalation absorption factor of 50% used for worker and residential exposures (Appendix B).

Other acute studies (Table 2) showed rats with mild signs of toxicity (lethargy and pupillary constriction) after exposure to 90 *u*g/L for 4 hours (18 mg/kg-day), and the NOEL was 50 *u*g/L (10 mg/kg-day). Studies conducted with hospital patients showed that exposure to DDVP resin strips for 24 hours resulted in the inhibition of plasma ChE with a NOEL of 0.02 mg/kg-day for men without liver disease and of 0.014 mg/kg-day for sick children (Cavagna *et al.*, 1969). Since plasma ChE inhibition is considered an indication of exposure rather than toxicity (USEPA, 1990; Brimijoin, 1992), this study was not used to determine the critical acute NOEL.

Oral

The critical NOEL for the assessment of acute oral exposure was 0.5 mg/kg-day in the neurotoxicity studies in rats for cholinergic signs (tremors, salivation, neuromuscular deficits, and others) observed within 24 hours in both the range finding and definitive studies (Lamb, 1992; and Lamb, 1993a).

In the dog chronic study, soft stools were observed in the first week (Markiewicz, 1990). None were observed for the control and the 0.05 mg/kg-day group. However, this endpoint was not considered biologically significant as an acute effect because of the low incidences during the first week and lack of dose response relationship. In the rat developmental study, the NOEL was 3.0 mg/kg-day for tremors observed within 10-60 minutes in rats given 21 mg/kg-day by gavage (Tyl *et al.*, 1991a). Clinical signs were observed in rats 2.5 hours after an oral dose of 21 mg/kg by gavage with a NOEL of 0.8 mg/kg-day (Cheng 1989 and 1991) or 10-20 minutes after a single dose of 30 mg/kg (Tracy *et al.*, 1960).

Subchronic toxicity

Inhalation

The critical NOEL for subchronic inhalation toxicity of DDVP was 0.25 *u*g/L (0.13 mg/kg-day) based on brain ChE inhibition (Thorpe *et al.*, 1971b). There was a significant ($p \leq 0.05$) and dose-related inhibition of plasma, erythrocyte, and brain ChE activities in the 1.25 and 6.25 *u*g/L dams after 29 days of exposure. The inhibition of brain ChE activity was dose-related and statistically significant ($p \leq 0.05$); and was 44% and 15% of control values for the 1.25 *u*g/L (0.65 mg/kg-day) and 6.25 *u*g/L (3.25 mg/kg-day) groups, respectively. The adjusted NOEL for risk assessment was 0.065 mg/kg-day

(NOEL of 0.13 mg/kg-day x 0.5) based on brain ChE inhibition and a default inhalation absorption factor of 50%.

Oral

For subchronic exposure (more than 1 week), the critical NOEL was derived from subchronic and reproductive studies. The lowest NOEL was 0.1 mg/kg-day from a rat gavage study where tremors were observed after 3 weeks of exposure to DDVP at 7.5 mg/kg-day (Lamb, 1993b). The same NOEL (0.1 mg/kg-day) was determined for maternal mortality after 5 or more days of exposure in a rabbit developmental toxicity study (Tyl *et al.*, 1991b). For reproductive and parental effects, the NOEL was 20 ppm (2.7 mg/kg-day) for reduction of water consumption, body weight, fertility, and estrous cycling (Tyl *et al.*, 1992). Cholinergic signs were not reported in this study. However, the plasma, erythrocyte, and brain ChE activities of the F0 and F1 of both sexes (NOEL of 1.1 and 0.5 mg/kg-day for the females and males, respectively) were significantly decreased when compared to controls.

Chronic Toxicity

Inhalation

Only one chronic inhalation study was on file and it was considered unacceptable to DPR. The NOEL was 0.05 *u*g/L (0.05 mg/kg-day) based on brain ChE inhibition in the rat (Blair *et al.*, 1974). The brain ChE activities of the 0.5 and 5.0 *u*g/L groups were depressed significantly ($p<0.01$) to 90% and 19-21% of control values, respectively (Table 6); however, no cholinergic signs were observed. Reduced body weight in the 5.0 *u*g/L groups was observed throughout the study (Table 5). The NOEL for brain ChE inhibition in this study is of the same magnitude as for the chronic study by the oral route (Markiewicz, 1990). The NOEL for brain ChE inhibition was adjusted to 0.025 mg/kg-day (NOEL of 0.05 mg/kg-day x 0.5) for a default inhalation absorption factor of 50%.

Oral

The critical NOEL for chronic oral exposure was 0.05 mg/kg-day based on the inhibition of brain ChE activity in dogs fed DDVP in capsules for one year (Markiewicz, 1990) (Table 8). Brain ChE activity was depressed in a dose-related manner in both the males and females. The decrease was statistically significant ($p \leq 0.05$) for the males in the 1.0 and 3.0 mg/kg-day groups, and for the females in the 3.0 mg/kg-day group. The brain ChE activities for the 3.0 mg/kg-day males and females were 53% and 71% of control values, respectively. Clinical signs observed were soft stools, lacrimation, emesis, salivation, ataxia, and dyspnea, with a NOEL of 1.0 mg/kg-day.

Other chronic studies showed that DDVP affected the liver. Enlarged hepatocytes and increased liver weight were found in dogs fed DDVP 0.9 mg/kg-day in the diet for 2 years with a NOEL of 0.09 mg/kg-day (Jolley *et al.*, 1967). Alteration of hepatocytes (vacuolation and swelling) was also found in rats fed DDVP 8.0 mg/kg-day with the adjusted NOEL of 1.2 mg/kg-day (Witherup *et al.*, 1967).

Oncogenicity

Inhalation

Results from the only chronic inhalation study with rats to DDVP (Blair *et al.*, 1974) were inadequate to evaluate the oncogenicity by this route. The problems of decreased survival and tissue autolysis resulted in lower number of animals at risk, especially for the males, and limited the usefulness of data for oncogenicity assessment. There was a dose-related increase in the incidence of pituitary adenomas in female rats. The increase was considered marginal as the survival adjusted incidence

rates were not statistically significant at $p \leq 0.05$. While historical data for Carworth Farm rats are not available, historical data for other strains (Sprague-Dawley, F344, and Wistar) of rats showed that pituitary tumors are common in geriatric rats (Chandra *et al.*, 1992; Haseman *et al.*, 1985; Bomhard and Rinke, 1994).

USEPA has decided not to evaluate DDVP oncogenicity by the inhalation route because of uncertainties with the quality of the oral oncogenicity data and the level of DDVP achieved at the target site (Ghali, 1993). For the first point, USEPA stated that there was no dose response to the finding of mononuclear cell leukemia in rats from the gavage study (Chan, 1989). However, the trend test indicated statistical significance ($p \leq 0.05$). The small increase in incidence (40% and 42% for low and high doses versus 22% for control) between the low and high doses was not unexpected since there were only two doses with just a 2-fold difference. There was also a dose-related (not statistically significant) increase in the incidences of leukemia in female rats. The control incidence (34%) for the females was higher than that (22%) for the males, while the incidence for the treated females (44 and 46% for low and high doses) were similar to those for the treated males (40% and 42%).

Secondly, USEPA stated that an insufficient level of DDVP would be available to reach the target site for oncogenicity after inhalation exposure. This conclusion was based on the assumption that the oncogenicity observed in the gavage study was due to the saturation of the ester hydrolysis pathway at high DDVP levels after bolus administration and the predominance of the demethylation pathway. A reaction rate ratio for the demethylation pathway and hydrolysis pathway was estimated to be $1:3 \times 10^7$ and was based on the rate of DDVP alkylation of 4-(p-nitrobenzyl)pyridine and on the rate of DDVP hydrolysis in the presence of acetylcholinesterase *in vitro* (Aldridge and Johnson, 1977). Demethylation was assumed to lead to DNA alkylation and presumably the mechanism of oncogenicity. These assumptions were not supported by any appropriate data and therefore, should not be used as basis to dismiss the oncogenicity potential of DDVP. Pharmacokinetic studies showed metabolites from both pathways are present and there is no data on the level of DDVP required for saturation of ester hydrolysis. Since ester hydrolysis occurs in the blood and many tissues, it is unlikely that the doses used in the gavage study resulted in saturation of the pathway. In addition, the rates for the comparison of the two pathways may not be appropriate. The rates used to calculate the ratio of $1:3 \times 10^7$ were based on *in vitro* experiments under different experimental conditions (cited in Aldridge and Johnson, 1977). The result on DDVP alkylation to 4-(p-nitrobenzyl)pyridine only indicated that DDVP was a weak alkylating agent and does not measure the rate of dealkylation (Bedford and Robinson, 1972).

USEPA also suggested that there would be insufficient quantity of the dose absorbed by the inhalation route to get to the target site; therefore, oncogenicity by the inhalation route is not expected. The assumption was that DDVP would be metabolized much more rapidly by the inhalation route when compared with the oral bolus dosing. This assumption was based on the comparison of the half-life (13.5 mins) for DDVP in the kidney after a 4 hour inhalation exposure (Blair *et al.*, 1975) and the amount (57%) of an oral dose eliminated (in the urine, feces and expired air) with 24 hours from different studies. These parameters are not the same and therefore the comparison was not appropriate. Other pharmacokinetics studies showed that the disposition (tissue distribution, pattern of metabolites, and rates of excretion) of DDVP by the oral and inhalation routes were similar (Hutson *et al.*, 1971).

In addition, USEPA assumed that DNA alkylation which occurs at high doses is the mechanism for oncogenicity. The mechanism for leukemia or any of the other tumors observed in DDVP-treated animals is unknown. Furthermore, it is not known what type of tumors may be expected in humans. Alkylation of DNA after DDVP administration was demonstrated in tissues from mice (Segerback, 1981) but not from rats (Wooder *et al.*, 1977). It is also not known whether DDVP or a metabolite(s) is involved. Segerbeck (1981) suggested that dichloroacetaldehyde, a metabolite from ester hydrolysis,

may be involved in the alkylation of DNA. *In vitro* studies showed that dichloroacetaldehyde caused gene mutations in bacteria and dominant lethal mutations in mice (Aquilina *et al.*, 1984).

Therefore, in the absence of adequate data to evaluate the oncogenicity of DDVP by the inhalation route and in the presence of data from the gavage study (Chan, 1989) indicating potential oncogenicity, DDVP is assumed to be oncogenic by the inhalation route. The potency factor derived for mononuclear cell leukemia (a systemic effect) in rats (Chan, 1989) was used to assess human exposures.

Oral

Evidence of DDVP oncogenicity by the oral route was identified in rats and mice (Chan, 1989) (Tables 4 and 7). In 2.9 and 5.7 mg/kg-day male rats, there were dose-related increases in the incidences of pancreatic adenoma and mononuclear leukemia. The results showed positive trends and were considered significantly ($p \leq 0.05$) different from the concurrent controls based on Fisher's Exact test. In females, there were also dose-related increases in the incidences of pancreatic adenoma, mononuclear cell leukemia, and mammary gland tumors; even though the pair-wise comparison (except for mammary gland tumors found at 2.9 mg/kg-day) and trends were not statistically significant (at $p \leq 0.05$). The NTP considered the increased incidences of pancreatic adenoma and mononuclear cell leukemia in male rats as some evidence of carcinogenicity[1]. In female rats, the increased incidences of mammary gland and pancreatic tumors were considered to be equivocal evidence of carcinogenicity.

For pancreatic adenoma, there is evidence of progression to a malignant stage (McConnell *et al.*, 1986). The NTP proposed that pancreatic adenoma and carcinomas should be combined for the evaluation of oncogenicity. These results were, however, confounded by the use of corn oil as the vehicle, as high incidences of pancreatic adenomas were found in the controls. Corn oil has been shown to induce pancreatic tumors in F344/N male rats (Eustis and Boorman, 1985; Haseman *et al.*, 1985). In this study, DDVP may be a promoter rather than a direct carcinogen (Chan, 1989; Mennear, 1988). Consistent with the report by Haseman *et al.* (1985) for other compounds, corn oil did not have any effect in the females. Other studies have also shown an enhancement of toxicity and oncogenicity of organic compounds by corn oil (Condie *et al.*, 1986, and Bull *et al.*, 1986). However, a recent report by Huff and Hasemen (1991) showed that corn oil has little or no influence on the oncogenicity and that the previous finding may be due to a difference in body weight.

The control incidences (11/50 and 17/50 for males and females, respectively) of mononuclear cell leukemias were within the range (1/50 to 22/50) of historical controls for NTP carcinogenesis studies conducted during that period (Stefanski *et al.*, 1990). Comparison of concurrent control data with the historical control data confined to the testing period is appropriate because the background rate of certain tumor types, including leukemia, in F344 rats has been steadily increasing (Huff and Haseman, 1991). Possible reasons for the shift were: changes in histopathology diagnostic criteria over time, changes in the amount of tissue examined, intra- and interlaboratory variability, and dietary factors.

[1/] The descriptions of the evidence classification from the NTP are:

Clear evidence - there is a dose-related increase of malignant neoplasms, a combination of malignant and benign neoplasms, or marked increase of benign neoplasm if there is an indication that such tumors have the ability to progress to malignancy.

Some evidence - there is a chemically-related increase in the incidence of neoplasms (malignant, benign, or combined) but have less strength than clear evidence.

Equivocal evidence - there is a marginal increase of neoplasms that may be chemically related.

In mice, there were dose-related increases in the incidences of forestomach papilloma in the males, and of forestomach papilloma and carcinoma in the females (Chan, 1989; Table 7). The increased incidences of forestomach papilloma appeared to be due irritation from gavage administration (Benford *et al.*, 1994). No other DDVP-related lesions were observed in this study (Chan, 1989). The NTP considered the results for the male and female mice to be "some evidence" and "clear evidence", respectively, of oncogenicity.

Supporting evidence for the potential oncogenicity of DDVP was provided by studies with rats given DDVP in water (Enomoto, 1978), mice fed DDVP in the diet (NCI, 1977b), and DDVP increased growth rate of tumors in Fischer 344 rats with leukemia transplants (Dieter *et al.*, 1989). There were increased incidences of pituitary adenomas and mononuclear cell leukemia (Enomoto, 1978), and esophageal tumors (carcinoma and papilloma) (NCI, 1977b). There are limitations to the interpretation of these studies (as discussed in **III.D. CHRONIC TOXICITY** section) and the data are not appropriate for quantitative risk assessment.

Results from other chronic studies can not be used as weight of evidence because of various protocol deficiencies. For example, the dog studies (Markiewicz, 1990; Jolley *et al.*, 1967) were only for 1-2 years; therefore the duration of exposure was not a significant percentage of the lifetime. The exposure of rats and mice to DDVP was not continuous in the studies conducted by Horn *et al.* (1988). There were no individual data in the NCI (1977a) study with rats fed DDVP in the diet. An inadequate number (25 instead of 50) of animals was exposed to DDVP in the study by Witherup *et al.* (1967).

Results from the in vitro genotoxicity studies also indicated a potential for DDVP to induce DNA and gene damage in some systems including mammalian cells. Positive responses were detected in the mouse lymphoma forward mutation assay and in the unscheduled DNA synthesis assay. However, results from the micronucleus, dominant lethal, and in vivo sister chromatid exchange assays were negative for genotoxicity. Alkylation of tissue DNA was detected in mice exposed to DDVP by intraperitoneal injection, but not in rats exposed to DDVP by inhalation. The difference in results may be due to experimental design and species difference. DDVP is considered a weak alkylating agent as determined by its reaction with 4-(*p*-nitrobenzyl)pyridine *in vitro* (Bedford and Robinson, 1972).

Studies conducted in the presence and absence of liver activating system showed the genotoxicity of DDVP was reduced due to the inactivation of DDVP by liver enzymes. Pharmacokinetics studies with several species, including human, and using several routes of exposure, showed that DDVP was rapidly and completely metabolized (**III.A. PHARMACOKINETICS**). Toxicity studies by Casida *et al.* (1962) have shown that DDVP was more toxic than the metabolites. Dichloroacetaldehyde, a metabolite, when fed to mice has been reported to induce dominant lethal mutations (Fischer *et al.*, 1977). The significance of its formation in vivo and its mutagenic effect is unknown. Dichloroacetaldehyde was not detected in the rat urine (Hutson *et al.*, 1971).

Therefore, DDVP was considered by DPR to be potentially oncogenic in humans based on positive results in 2 animal species from the NTP study (Chan, 1989), supporting results from other studies, and evidence of potential genotoxic effects. The potential oncogenic risk for DDVP was evaluated using a quantitative approach. A non-threshold dose-response relationship was assumed to be linear at the low dose range. A linearized multistage model, Global 86, (Howe *et al.*, 1986) was used to extrapolate the dose-response relationship obtained from experimental animal data at high dose levels to low dose range which is generally more typical of human exposures . Both the maximum likelihood estimate (MLE, q_1) and the 95% upper confidence limit (q_1*) of the linear term of the multistage model were presented as estimates of the oncogenic potency. The human oncogenic risk at a low dose range was calculated by multiplying the potency by the potential exposure dosage.

Potency values were estimated by fitting the Global 86 model to the incidences of pancreatic adenoma, mononuclear leukemia, and forestomach papilloma or carcinoma identified in the NTP study (Chan, 1989) and are listed in Table 15 (Appendix E). The potency values estimated from experimental animals were extrapolated to humans assuming the interspecies dose equivalence based on the body weight to the 3/4 power (see Equation 4 in Appendix D). Using this assumption, a factor of 1/4 power of the human-to-animal body weight ratio was applied.

In this document, the theoretical cancer risk associated with the use of DDVP was assessed based on the incidence of mononuclear cell leukemias found in rats (Chan, 1989). This endpoint was chosen because it was a systemic effect and the result was statistically significant for both the Trend Test and the Fisher's Exact Test. The finding of pancreatic adenoma was not used because of the possible influence of corn oil in the induction and the lack of evidence for malignancy. The finding of forestomach tumors in mice was also not used in this assessment because the human equivalent potency factor was 5-fold lower than that for mononuclear cell leukemias in the rat. While there is no direct counterpart to the rodent forestomach, the human esophagus and possibly the squamous epithelium at the squamocolumnar junction of the cardiac portion of the stomach may be a site for either squamous cell carcinoma or adenocarcinoma (Huff, 1992).

Table 15. The maximum likelihood estimates and 95% upper confidence limit for tumors in rodents treated with DDVP[a].

Tumor type	Maximum likelihood estimate (q_1)		95% upper confidence limit (q_1*)	
	animal	human[b]	animal	human[b]
Pancreatic adenoma	0.097	0.33	0.15	0.52 mg/kg-day^{-1}
Mononuclear leukemia	0.058	0.20	0.10	0.35 mg/kg-day^{-1}
Forestomach papilloma or carcinoma	0.000	0.00	0.011	0.073 mg/kg-day^{-1}

[a/] Data were from Chan, 1989.
[b/] The human equivalent q_1 and q_1* were calculated by (**Appendix D Equation 4** for derivation):

$$q_1 \text{ human} = q_1 \text{ animal} \times (\text{human body weight}/\text{animal body weight})^{1/4}$$

where the human body weight = 70 kg, rat body weight = 0.5 kg, and
mouse body weight = 0.037 kg.
For example: for pancreatic adenoma: q_1 human = 0.097 x $(70/0.5)^{1/4}$ = 0.33

B. EXPOSURE ASSESSMENT

The exposure of the general population to DDVP is primarily associated with its use in space treatment of agricultural, commercial, and residential buildings. DDVP has limited use on RACs; however, it is used for post-harvest treatment for bulk and packaged commodities, and on livestock. Exposure estimates for various categories of occupational and residential exposures, were based on the information provided by the Worker Health and Safety Branch (Appendix B). There is no seasonal exposure.

Occupational Exposure

The absorbed daily dosages of DDVP in workers ranged from 9 *u*g/kg for structural pest control operators (PCOs) to 62 *u*g/kg for livestock applicators (Table 16). For chronic exposure, the livestock applicators had the highest exposure level at 4.6 *u*g/kg-day for annual average daily dosage (AADD) and 2.6 *u*g/kg-day for lifetime average daily dosage (LADD).

Residential Exposure

Residents were exposed to DDVP in the homes due to direct applications (referred to as structural residents) and from the release of DDVP from indoor foggers, no-pest strips, and flea collars. The absorbed daily dosages ranged from 0.3 *u*g/kg for pet-owners to 125 *u*g/kg for children from the use of foggers (Table 16). Children exposed to no-pest strips had the highest chronic exposure levels at 6.6 *u*g/kg-day for AADD and 3.1 *u*g/kg-day for LADD.

Table 16. Estimated occupational and residential exposures to DDVP[a].

Exposure type	Absorbed Daily Dosage (*u*g/kg-day)	Exposure (days/year)	AADD[b] (*u*g/kg-day)	LADD[b] (*u*g/kg-day)
Occupational				
Warehouse worker	12	17	0.6	0.3
Structural PCO	9	30	0.8	0.4
Livestock applicator	62	27	4.6	2.6
Residential				
Structural (Resident)	10	6	0.2	0.11
Home-use fogger (child)	125	6	2.05	0.88
Home-use fogger (adult)	74	6	1.22	0.70
Pet owner	0.3	60	0.05	0.03
Pest strip (child)	40	60	6.6	3.1
Pest strip (adult)	-	-	-	2.47[c]

a/ Data were adopted from Appendix B Table 3 (all except fogger exposure) and Table 4 for biological monitoring (fogger exposure).

b/ AADD=Annual average daily dosage, and LADD=Lifetime average daily dosage.

c/ Adult exposure level was estimated using the ratio of adult/child exposures for home-use fogger: 3.1 x (0.70/0.88) = 2.47 *u*g/kg-day. This estimate will be used for the calculation of lifetime exposure to pest strips.

Dietary Exposure

DPR evaluates the risk of exposure of an active ingredient in the diet using separate processes: (1) risk is determined for total exposure based on detected residue levels, and (2) risk is determined for exposure to an individual commodity at the tolerance level (**VI. TOLERANCE ASSESSMENT**). For the evaluation of risk from residues, the total exposure in the diet is determined for all label-approved crops (raw agricultural commodities) and their processed forms as well as any secondary residues in animal tissues. The degradation products and/or metabolites of the active ingredient which have established tolerances or whose toxicity is of concern are also considered in the assessment.

Chronic dietary exposure estimates calculated by DPR were compared to those determined by USEPA (Schaible 1994 and 1995). These estimates were considered because residue values used by USEPA were adjusted for percent of crop treatment and reduction due to processing; thus, they represented a more realistic estimate of dietary exposure compared to those by DPR.

Residue Data - general

The sources of residue data include surveillance programs conducted by the DPR and federal agencies, field trials, and survey studies by registrants. Residue data obtained from the monitoring programs are preferred for human dietary assessments since they are a more realistic estimate of potential exposure. When residues are at levels higher than established tolerances, they are not utilized in the dietary exposure assessments because incidents are investigated by the DPR Pesticide Enforcement Branch and are relatively infrequent (consistently less than 1 per cent incidence according to the DPR residue monitoring programs). DPR evaluates the potential risk of over-tolerance samples under a separate process referred to as an expedited acute risk assessment. In the absence of any measured residues, the DPR dietary exposure assessments utilize surrogate data from the same crop group as defined by USEPA or theoretical residues equal to USEPA tolerances.

There are two elements in the DPR residue testing program which are currently used for dietary exposure assessment: Marketplace Surveillance and Priority Pesticide. Marketplace Surveillance is designed to ensure that the pesticides are used according to the California laws and regulations. Sampling in this program is weighted toward such factors as patterns of pesticide use, relative number and volume of pesticides typically used to produce a commodity, relative dietary importance of the commodity, past monitoring results, and extent of local pesticide use. Priority Pesticide was instituted to target commodities known to have been treated with pesticides of toxicological concern.

The U. S. Food and Drug Administration (FDA) has three monitoring programs for determining residues in food: (1) regulatory monitoring, (2) total diet study, and (3) incidence/level monitoring. Depending on the program, raw agricultural commodities and/or processed foods are collected for analysis. For regulatory monitoring, surveillance samples are collected from individual lots of domestic and imported foods at the source of production or at the wholesale level. In contrast to the regulatory monitoring program, the total diet study monitors residue levels in foods in forms ready for consumption (Gunderson, 1988). The consumption patterns of 8 population subgroups are based on the USDA 1977-1978 Nationwide Food Consumption Survey and the 1976-1980 National Center for Health Statistics' Second National Health and Nutrition Examination. From these surveys, 234 food items were selected to represent the 5,000 foods identified. The individual food and necessary recipe ingredient items were collected from 4 broad geographic areas each year. The food items, after preparation, were analyzed by multi-residue analytical methods. The incidence/level monitoring program is designed to address specific concerns about pesticide residues in particular foods.

The U.S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program which is designed to collect objective, comprehensive pesticide residue data for fresh produce for risk assessments. The pesticides and produce to be sampled are selected based on the toxicity of the pesticide as well as the need for residue data to determine exposure. The samples are collected at produce markets and chain store distribution centers close to the consumer level in several states including California. The National Residue Program of USDA provides data for potential pesticide residues in meat and poultry. These residues in farm animals can occur from direct application, or consumption of commodities or by-products in their feed.

Residue Data - DDVP

The residue values used for dietary exposure assessment are in Table 17. From 1986 to 1990, DDVP residues were not detected in RACs sampled for the DPR Marketplace Surveillance Program. The MDLs varied from 0.02 ppm to 0.2 ppm; however, specific MDLs for each commodity were not available. The FDA monitoring data (1985 to 1990) showed no detectable DDVP residues in the RACs (Roy, 1991). Studies on the use of DDVP in greenhouses submitted by the registrant for the establishment of tolerances indicated relatively low residue levels (Beroza and Hill, 1968). The highest residue levels for each commodity ranged from 0.055 ppm in cucumbers to 0.003 ppm in radishes; and the MDL was 0.003 ppm (estimated from the lowest residue reported). The results from the greenhouse studies (**II.G. ENVIRONMENTAL FATE**) were used because they were generated from label-use conditions and residue values were available to estimate the MDL.

Secondary residues in meat products, including milk and eggs, may result from dermal applications of DDVP to cattle and other livestock. Pharmacokinetics studies showed that DDVP was rapidly metabolized and eliminated in farm animals. Both experimental studies and FDA monitoring data (1985-1990) showed that DDVP levels in the domestic animal tissues or in milk were below detection limits (MDL of at least 0.02 ppm). The tolerance for DDVP in the meat of goat, horses, poultry, and sheep was 0.02 ppm based on the MDL. Therefore, the tolerance values were used for the dietary assessment. A recent residue study showed that the residue levels in milk and cow tissues were below the limit of quantitation of 0.01 ppm (March *et al.*, 1993).

A recent market survey submitted by the registrant, Amvac Chemical Corp., showed post-harvest fumigation resulted in residues in packaged and bagged processed agricultural commodities (Williams, 1991). The residues were, in general, below the limit of quantitation (0.01 ppm). The commodity types and the range of residues were: spaghetti (<0.01 to 0.16 ppm), oats (<0.01 ppm), grits (0.64 ppm), rice (0.017 to 0.083 ppm), flour mixes (<0.01 to 0.072 ppm), sugar (<0.01 ppm), flour (0.014 to 0.082 ppm), hamburger helper (<0.01 to 0.015 ppm), chocolate chips (0.098 ppm), whole cocoa bean (0.025 ppm), cocoa bean nibs (<0.02 ppm), coconut (<0.02 to 0.025 ppm), dried potato entrees (<0.01 ppm), raisins (0.015 ppm), dried prunes (<0.01 ppm), cereals (<0.02 ppm), Shake 'n Bake™ (<0.02 ppm), and tea bags (1.3 ppm). Of the above commodities, chocolate chips, cocoa beans, coconut, flour, oats, prunes, raisins, sugar, and rice are included in the dietary assessment. Potato entrees, cereal, and grits were not assessed because the components can not be readily identified from the report. The tea sample was over the tolerance level; therefore, the tolerance level of 0.5 ppm was used.

The Total Diet Study conducted by the FDA showed that the amount of DDVP residues in foods prepared table-ready were $\leq$ 0.0001 *u*g/kg-day for all age groups (FDA, 1992).

Table 17. DDVP residue database.

Commodity	number of samples	Residue Levels highest (ppm)	Residue Levels mean[a] (ppm)
RAC[b]			
cucumbers	10	0.055	0.0103
lettuce	8	0.026	0.0035
radishes	7	0.003	0.0015
tomatoes	9	0.023	0.0065
Meat Products[c]			
cattle[d]	-	0.01	0.005
eggs	-	0.05	0.05
goats	-	0.02	0.02
horses	-	0.02	0.02
milk[d]	-	0.01	0.005
poultry	-	0.05	0.05
sheep	-	0.02	0.02
swine	-	0.10	0.10
Processed commodities[e]			
chocolate chips	2	0.098	0.098
cocoa beans	2	0.025	0.0175
coconut	2	0.025	0.0175
flour	2	0.082	0.048
oats	1	<0.01	0.005
dried prunes	1	<0.01	0.005
raisins	1	0.015	0.015
rice	4	0.083	0.0313
sugar	1	<0.01	0.005
tea[c]	-	0.5	0.5

a/ Calculated as the mean of levels of 1/2 of MDL for values below detection limits and actual values above MDL. The highest residue value and the mean values were used to evaluate acute and chronic exposures, respectively. When the tolerance level was used as the residue level, it was used for both acute and chronic exposure assessments.

b/ Data were from Beroza and Hill (1968).

c/ Values were based on USEPA tolerances (Appendix A), except for cattle and milk.

d/ Data were from March *et al.* (1993).

e/ Data were from Williams (1991).

Acute Exposure

Estimates of potential acute dietary exposure used the highest measured residue values at or below the tolerance levels for each commodity except for the use of tolerance levels for meat products (Table 17 and Appendix A). The following assumptions are used to estimate potential acute dietary exposure from measured residues: (1) the residue does not change over time, (2) the concentration of residue does not decrease when the RAC is washed or cooked, and (3) all foods that are consumed will contain the highest reported residue.

Chronic Exposure

Estimates of potential average annual chronic dietary exposure used the mean of measured and "below detection limit" residue values for each commodity. The default procedure assumed that "below detection limit" residues were equal to one-half (50%) of the MDL for each commodity. The following assumptions were used to estimate potential chronic dietary exposures from measured residues: (1) the residue level does not change over time, (2) residue are not reduced by washing or cooking, and (3) exposures to a commodity at all reported residue levels do occur, i.e. a commodity with the average calculated residue is consumed every day at an average annual level (dosage). The actual residue values used are presented in Table 17.

Lifetime Exposure

Estimate of potential lifetime dietary exposure used the result for the US general population from the chronic dietary analysis.

Dietary Assessment

Dietary assessment of DDVP was conducted for acute, chronic, and lifetime exposures. Copies of the exposure analyses are available upon request to the Medical Toxicology Branch.

Acute Exposure

Acute dietary exposure analyses were conducted using the Exposure-4™ software program developed by Technical Assessment Systems, Inc. (TAS). The Exposure-4™ program estimates the distribution of user-day (consumer-day) exposure for the overall U.S. population and specific population subgroups (TAS, 1992a). A user-day is any day in which at least one food from the specific commodity list is consumed. The consumption analysis uses individual food consumption data as reported in the 1987-88 USDA Nationwide Food Consumption Survey (USDA, 1987-88).

Based on the 95th percentile of user-days exposures for all specific population subgroups, the potential acute dietary exposure of DDVP from all labeled uses ranged from 0.50 to 1.65 *u*g/kg-day (Table 18). Children (1-6 years old) had the highest potential acute dietary exposure (1.65 *u*g/kg-day) to DDVP residues.

Chronic Exposure

The potential chronic dietary exposure was calculated using the Exposure-1 software program developed by TAS, Inc. (TAS, 1992b). The food consumption data for the chronic analysis were also based on the 1987-88 USDA Nationwide Food Consumption Survey (USDA, 1987-88). The program estimates the average annual exposure for all members of a designated population subgroup. The mean potential chronic dietary exposure for all population subgroups ranged from 0.06 to 0.53 *u*g/kg-day (Table 18). The population subgroup of children (1-6 years) had the highest potential exposure (0.53 *u*g/kg-day). This level is 5,300-fold higher than the level (0.0001 *u*g/kg-day) estimated by the

USDA 1991 Total Diet Study (FDA, 1992). USEPA estimates of chronic exposure are also in Table 18 and were 1/4 to 1/2 fold of those by DPR.

Commodity contribution analysis was conducted to determine the critical commodities in the determination of total exposure (Table 19). Residues in cereal grains (28.2-30.9% of total exposure) and dairy products (25.4 to 51.25) were the major contributors toward the exposure levels of U.S. population, non-nursing, and children population subgroups.

Lifetime Exposure

The potential lifetime exposure to DDVP was evaluated based on the chronic dietary DDVP level of 0.22 *u*g/kg-day (DPR) and 0.036 *u*g/kg-day (USEPA) for the US population (Table 18).

Table 18. Potential acute and chronic dietary exposures to DDVP[a].

Population subgroups	DPR Acute exposure 95th percentile of exposure (*u*g/kg-day)	DPR Chronic exposure annual average (*u*g/kg-day)	USEPA Chronic exposure annual average (*u*g/kg-day)
US Population, all seasons	0.91	0.22	0.036
Western Region	0.88	0.22	0.038
Hispanics	1.00	0.24	0.038
Non-Hispanic Whites	0.87	0.22	0.036
Non-Hispanic Blacks	1.04	0.26	0.031
Non-Hispanic Other	1.13	0.28	0.035
Infants (nursing, < 1 year)	0.62	0.06	0.019
Infants (non-nursing, < 1 year)	1.44	0.24	0.063
Children (1-6 years)	1.65	0.53	0.076
Children (7-12 years)	1.15	0.35	0.053
Females (13-19 years) (not pregnant, not nursing)	0.64	0.20	0.030
Females (13+ years) (pregnant, not nursing)	0.51	0.17	0.027
Females (13+ years) (nursing)	0.52	0.18	0.034
Females (20+ years) (not pregnant, not nursing)	0.50	0.16	0.026
Males (13-19 years)	0.69	0.24	0.036
Males (20+ years)	0.57	0.18	0.029
Seniors (55+ years)	0.49	NA[b]	NA[b]

a/ Exposure levels have been rounded off to 3 significant figures.
b/ Chronic exposure data for this age group alone are not available.
c/ Data from Schaible, 1995.

Table 19. Commodity contribution of chronic dietary exposure to DDVP.

Crop Groups	% of Total Exposure U.S. population	Non-nursing infants	Children 1-6 years	Children 7-12 years
Cereal grains	29.5	29.3	28.2	30.9
Red meat	23.9	6.1	20.3	19.6
Poultry	12.8	10.2	11.0	12.8
Dairy (milk and eggs)	25.4	51.2	34.2	28.5

Combined Exposure

The combined exposure levels from occupational and residential sources are applicable only for workers who may be exposed to DDVP at work and at home (Tables 20 and 21). For home use, the adult exposure level due to fogger applications was used (Table 16). For exposure in the diet under acute and chronic exposures, the adult subgroup with the highest exposure (males 13-19 years) was used. For exposure in the diet under lifetime exposure, the chronic exposure level for the U.S. population was used.

Acute Exposure

The range of exposure levels was from 84 to 137 *u*g/kg-day. The highest combined exposure of DDVP from work and at home was 137 *u*g/kg-day by livestock applicators (Table 20).

Chronic and Lifetime Exposures

Under chronic exposure conditions, livestock applicators were exposed to the highest average annual level of DDVP at 6.1 *u*g/kg-day (Table 21). The range of exposure was from 2.1 to 6.1 *u*g/kg-day.

The potential lifetime exposure to DDVP ranged from 1.22 *u*g/kg-day for warehouse workers to 3.52 *u*g/kg-day for livestock applicators.

Table 20. Potential acute combined occupational and residential exposures to DDVP.

Exposure type	Occupational Daily Dosage (*u*g/kg-day)[a]	Residential Exposure (*u*g/kg-day)[b]	Dietary Exposure (*u*g/kg-day)[c]	Total Exposure (*u*g/kg-day)
Warehouse worker	12	74	0.69	87
Structural PCO	9	74	0.69	84
Livestock applicator	62	74	0.69	137

a/ Exposure levels were derived from Table 16.
b/ Exposure level of adults exposed to foggers (Table 16).
c/ Exposure level of adult subgroups (males 13-19 years) from Table 18.

Table 21. Potential chronic and lifetime combined occupational and residential exposures to DDVP.

Exposure type	Chronic Exposure (*u*g/kg-day)[a]	Lifetime Exposure (*u*g/kg-day)[b]
Warehouse worker	2.1	1.22
Structural PCO	2.3	1.32
Livestock applicator	6.1	3.52

a/ Exposure levels were sum of AADD for workers and adults using home-use fogger (adult) (Table 16), and chronic dietary exposure levels for males (13-19 years) (Table 18).
b/ Exposure levels were sum of LADD for workers and adults using home-use fogger (adult) (Table 16), and chronic dietary exposure levels for U.S. population (Table 18).

C. RISK CHARACTERIZATION

The potential health hazard associated with the use of DDVP was considered for occupational and residential exposures. Non-oncogenic effects were characterized in terms of margins of safety (MOS), defined as the ratio of the NOEL to the potential exposure dosage. The risk of cancer was characterized in terms of theoretical probability of excess cancer risk in a lifetime, and is calculated by potency factor and exposure levels. The critical NOELs (in terms of adjusted dosages) and potency factors used to address the various exposure scenarios for humans are listed in Table 22.

Table 22. The critical no-observed-effects levels (NOELs) and potency factors for risk characterization.

Scenarios	Potential routes of human exposure	Adjusted NOEL[a] *u*g/kg-day	Corrected NOEL[b] *u*g/kg-day	Effects in animal studies	References[c]
Acute					
occupational residential combined	inhalation	650	325	death (2-3 days)	Thorpe *et al.*, 1971b
dietary	oral	500	500	cholinergic signs (within 1 day)	Lamb, 1992 and Lamb, 1993a
Chronic					
occupational residential combined	inhalation	50	25	brain ChE inhibition, reduced body weights	Blair *et al.*, 1974
dietary	oral	50	50	brain ChE inhibition and cholinergic signs	Markiewicz, 1990*
	Potency factors	rat mg/kg-day^{-1}	human mg/kg-day^{-1}		
Lifetime	oral inhalation	q_1=0.058 q_1*=0.10	q_1=0.20 q_1*=0.35	mononuclear leukemia	Chan, 1989*

a/ NOELs were adjusted by converting doses to mg/kg-day units using equations in Appendix D.

b/ The NOEL from inhalation studies were corrected for 50% absorption factor. The oral absorption is assumed to be 100%.

c/ * indicates study was acceptable to DPR according to FIFRA guidelines.

Occupational Exposure

The MOSs for the acute exposure of DDVP were 27, 36, and 5 for warehouse workers, PCOs, and livestock applicators, respectively (Table 23).

The MOSs for non-oncogenic effects from chronic and lifetime exposures were 83 or less for workers (Table 23).

The lifetime oncogenic risk for workers ranged from 6×10^{-5} to 9×10^{-4}.

Residential Exposure

The MOSs ranged from 3 to 8 for acute exposure to home fogger and no-pest strip uses (Table 23). The MOSs were 33 for adult residents after structural application and 1100 for owners of pets with flea collars.

The MOS for non-oncogenic effects from chronic exposure was 4 for children after no-pest strip use (Table 23). The MOSs were 12 and 20 for children and adults after fogger use. The MOSs for chronic exposures were 125 for structural applications and 500 for pet owners. The MOSs for non-oncogenic effects after lifetime exposure were 10 to 833 (Table 23).

The lifetime oncogenic risk for residents ranged from 6×10^{-6} to 1×10^{-3}.

Dietary Exposure

The MOSs for acute dietary exposure of all population subgroups were greater than 300 (Table 24).

Based on the DPR estimate, the MOSs for non-oncogenic effects from chronic exposure of all population subgroups, except for 1 subgroup, were greater than 100 (Table 24). The MOS was 95 for children (1-6 years). For the USEPA estimate, all MOSs were greater than 100 (Table 24).

Based on DPR exposure and potency factors, the oncogenic risks for the lifetime exposure level of 0.22 *u*g/kg-day for the U.S. population were 4×10^{-5} and 7.7×10^{-5} for q_1 and q_1*, respectively. Based on the USEPA exposure estimate of 0.036 *u*g/kg-day and DPR potency factors, the risks were 7×10^{-6} and 1.3×10^{-5} for q_1 and q_1*, respectively.

Combined Exposure

For workers exposed to DDVP acutely at work, at home, and in the diet, the MOSs were less than 10 (Table 25).

The MOSs for non-oncogenic effects from chronic exposure were 12 or less for all workers (Table 25). The MOSs for non-oncogenic effects after lifetime exposure were 7 to 20 (Table 25).

The lifetime oncogenic risk for residents ranged from 2×10^{-4} to 1×10^{-3}.

Table 23. The margins of safety for potential acute, chronic, and lifetime occupational and residential exposures to DDVP[a].

	Acute Exposure	Chronic Exposure	Lifetime Exposure	
Exposure type	MOS[b]	MOS[c]	MOS[c]	Risk[d]
Occupational				
Warehouse worker	27	42	83	6×10^{-5} - 1×10^{-4}
Structural PCO	36	31	63	8×10^{-5} - 1×10^{-4}
Livestock applicator	5	5	10	5×10^{-4} - 9×10^{-4}
Residential				
Structural (Resident)	33	125	227	2×10^{-5} - 4×10^{-5}
Home-use fogger (Child)	3	12	-	-
Home-use fogger (Adult)	4	20	36	1×10^{-4} - 2×10^{-4}
Pet owner	1100	500	833	6×10^{-6} - 1×10^{-5}
Pest strip (Child)	8	4	-	-
Pest strip (Adult)	-	-	10	5×10^{-4} - 9×10^{-4}

a/ Exposure levels were from Table 16. The absorbed daily dosages were used for acute exposures. The AADD and LADD levels were used for chronic and lifetime exposures, respectively.

b/ Margin of safety = $\frac{\text{NOEL (325 } u\text{g/kg-day)}}{\text{Daily dosage (}u\text{g/kg-day)}}$

based on death in a rabbit inhalation study (Thorpe *et al.*, 1971b).

c/ Margin of safety = $\frac{\text{NOEL (25 } u\text{g/kg-day)}}{\text{AADD (}u\text{g/kg-day)}}$ or $\frac{\text{NOEL (25 } u\text{g/kg-day)}}{\text{LADD (}u\text{g/kg-day)}}$

based on brain ChE inhibition in a rat inhalation study (Blair *et al.*, 1974).

d/ Range for risk was calculated using the q_1 of 0.20 and q_1^* of 0.35 ($mg/kg\text{-}day^{-1}$) for mononuclear leukemia in a rat gavage study (Chan, 1989) and the equation of risk = potency x exposure (LADD).

Table 24. The margins of safety of potential acute and chronic dietary exposures to DDVP.

Population subgroups	DPR Acute exposure MOS[a]	DPR Chronic exposure MOS[b]	USEPA Chronic exposure MOS[b]
US Population all seasons	550	223	1389
Western Region	568	233	1316
Hispanics	497	213	1316
Non-Hispanic Whites	577	232	1389
Non-Hispanic Blacks	481	190	1613
Non-Hispanic Other	441	178	1429
Infants (nursing)	802	861	2632
Infants (non-nursing)	348	205	794
Children (1-6 yrs)	303	95	658
Children (7-12 yrs)	435	142	943
Females (13-19 yrs) (not pregnant, not nursing)	778	254	1667
Females (13+ yrs) (pregnant, not nursing)	975	298	1852
Females (13+ yrs) (nursing)	957	274	1471
Females (20+ yrs) (not pregnant, not nursing)	993	315	1923
Males (13-19 yrs)	724	209	1389
Males (20+ yrs)	881	273	1724
Seniors (55+ yrs)	1027	NA[c]	NA[c]

a/ MOS = NOEL (500 *u*g/kg-day) / Exposure Dosage

based on cholinergic signs observed in rat oral studies (Lamb, 1992 and Lamb, 1993a).

b/ MOS = NOEL (50 *u*g/kg-day) / Exposure Dosage

based on brain ChE inhibition and cholinergic signs in a dog oral study (Markiewicz, 1990).

c/ Chronic exposure data for this age group alone are not available.

Table 25. The margins of safety of potential acute, chronic, and lifetime combined occupational, residential, and dietary exposures to DDVP[a].

Exposure type	Acute Exposure MOS[b]	Chronic Exposure MOS[c]	Lifetime Exposure MOS[c]	Lifetime Exposure Risk[d]
Occupational, home, and diet				
Warehouse worker	4	12	20	2×10^{-4} - 4×10^{-4}
Structural Pest Control Operator	4	11	19	3×10^{-4} - 5×10^{-4}
Livestock applicator	2	4	7	7×10^{-4} - 1×10^{-3}

a/ Total exposure levels were from Tables 20 (acute exposure) and 21 (chronic and lifetime exposures).

b/ MOS= NOEL (325 *u*g/kg-day) / Total Exposure

based on death in a rabbit inhalation study (Thorpe *et al.*, 1971b).

c/ MOS= NOEL (25 *u*g/kg-day) / Total Exposure

based on brain ChE inhibition in a rat inhalation study (Blair *et al.*, 1974).

d/ Range for risk was calculated using the q_1 of 0.20 and q_1* of 0.35 (mg/kg-day^{-1}) for mononuclear leukemia in a rat gavage study (Chan, 1989) and the equation of risk = potency x total exposure.

V. RISK APPRAISAL

The health risk assessment of DDVP was conducted for the exposures of workers through work activities and the general population. Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects of a substance will occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment for DDVP are delineated in this section.

Toxicology

Pharmacokinetic studies with rats and humans showed that DDVP was rapidly metabolized, and the exhaled air was the primary route of excretion in both species (Blair *et al.*, 1975; and studies cited in the **III.A. PHARMACOKINETICS**). Acute and subchronic toxicology studies in humans showed the inhibition of plasma or/and erythrocyte activities. In several studies, the inhibition of erythrocyte ChE activity was transient (Rasmussen *et al.*, 1963 and Menz *et al.*, 1974). None of the subjects in those studies reported cholinergic signs. Since there is insufficient information on the effects of DDVP on humans and uncertainty in the interpretation of the human data based on plasma and erythrocyte cholinesterase inhibition, results from animals studies were used in the risk assessment of DDVP.

There was sufficient information in the toxicology database of animal studies to show that DDVP by the oral (acute and chronic exposures) and inhalation routes (acute exposure) was a potent cholinesterase inhibitor as both ChE inhibition and cholinergic signs were observed. The inhalation study used for the acute NOEL was not acceptable to DPR according to FIFRA guidelines as a developmental toxicity study (Thorpe *et al.*, 1971b). The deficiencies (inadequate number of fetuses and inadequate examination of fetuses) of the study did not affect the usefulness of the observations on maternal toxicity.

Chronic toxicity of DDVP by the inhalation route is less certain as only one study was available (Blair *et al.*, 1974). Rats were exposed to DDVP by whole body exposure which included inhalation, and potential oral (from grooming) or dermal exposure. The study was unacceptable to DPR according to FIFRA guidelines because of only partial brain examination, higher survival in the high dose group compared to controls, and lack of optimal high dose exposure. However, these deficiencies should not affect the interpretation of the data used to establish the NOEL at the lowest dose studied.

Exposure Assessment

Exposures to DDVP by humans in the work place were determined for warehouse workers, structural PCOs, and livestock applicators. The workers in livestock and other farm buildings were not specifically addressed. However for risk assessment purposes, the exposure levels from the warehouse workers may be used as a surrogate to evaluate the exposure.

The use of DDVP on raw agricultural commodities, livestock products, and processed commodities may result in DDVP residues in the diet. Of all the food-related uses, potential exposure from residues in livestock products represents the most significant concern. The direct applications of DDVP on livestock (cattle and poultry) and secondary residues in the milk may result in residues because there are no "pre-slaughter" or "pre-milking" intervals (similar to a preharvest interval) on the

label between treatment and the availability of the meat or milk for consumption. DDVP residue may also accumulate in processed commodities, especially grains which are not stored in sealed containers or packages. Critical commodity contribution analysis showed that the majority of the total exposure was from the consumption of milk, meat, and flour by children 1 to 6 years old, as well as the general population, non-nursing infants, and children 7-12 years. Since the use of DDVP on vegetables is limited, and the registrants have voluntarily cancelled the registration in California, exposure to DDVP in vegetables is minimal.

The total dietary exposure levels for the population subgroups based on the reported residue or tolerance level of each use of DDVP determined by DPR were higher than those obtained from the FDA Total Diet Study (TDS) and USEPA. They are likely to be over-estimates because of the assumptions of no degradation by cooking and 100% crop treatment. While data were not available to quantitatively determine the amount of residues reduced by cooking/processing, DDVP has been found to be destroyed by cooking (Abbott *et al.*, 1970). In addition, it is unlikely that all crops with label-approved uses were treated with DDVP especially since the California Use Report showed annual use of 5000 or less pounds for all uses. For chronic exposure, USEPA used field trial data and adjusted for percent of crop treatment (1%) and a cooking reduction factor (0.001 to 0.92). Therefore, the dietary exposure assessment presented both DPR and USEPA estimates of dietary exposure to DDVP. The TDS data were not used because the exposure was based only on commodities in selected recipes.

Risk Characterization

MOSs for potential acute and chronic exposures were based on NOELs for mortality, cholinergic signs, brain ChE inhibition, and reduced body weights in animal studies. In general, when non-oncogenic effects are based on animal data, a MOS of at least 100 is considered to be protective of human health. The MOS of 100 represents a 10 fold factor for intraspecies variation in humans, and a 10 fold factor for interspecies extrapolation. The assumption is that humans are about 10 times more sensitive to a chemical than the experimental animal, and that a sensitive individual is as much as 10 times more susceptible than an average individual. The value of 100 is used as a default because scientific data are not available to derive an absolute value. In addition, a modifying factor of up to 10 may be considered
for occupational and residential exposures to address the severity, in this case mortality, of the endpoint used for acute inhalation exposure assessment.

For oncogenicity, the risk from lifetime exposures was based on the finding of mononuclear leukemia in a rat oral (gavage) oncogenicity study. A risk of 1×10^{-6} or less is generally considered to be protective of human health. For inhalation exposure, DDVP given by the oral and inhalation routes was assumed to be of same oncogenic potency.

Since DDVP is a metabolite of naled and trichlorfon, there is the potential for additional exposure through the use of these two pesticides. However, the assessment of potential exposures to DDVP did not include additional exposure from these pesticides because of use pattern and biotransformation considerations. It is unlikely that human exposure levels by inhalation, at home and at work, due to structural and home applications will be increased significantly since major uses of naled and trichlorfon are in raw agricultural commodities and landscape maintenance (Appendix C). The contribution of DDVP from naled and trichlorfon in the diet is likely to be minimal because DDVP once formed is further biotransformed (as discussed in **II.G. ENVIRONMENTAL FATE**). Acute and chronic toxicity of naled and trichlorfon are lower than those for DDVP as the active ingredient (Appendix C).

In addition, neither naled nor trichlorfon are considered oncogenic by DPR (Appendix C). Naled has not been shown to be oncogenic in mice or dogs. The "slight" increased incidence of mammary

adenocarcinoma in male rats (by gavage) was not statistically significant (the incidences were 0/44, 0/50, 1/49, and 2/48 for 0, 0.2, 2, and 10 mg/kg-day) (Batham *et al.*, 1984; Slagowski (1987). There was a dose-related decrease in mammary tumors in females. The highest dose tested (10 mg/kg-day) was almost 2 fold-higher than that (5.7 mg/kg-day) in the DDVP rat oncogenicity study. Naled has not been shown to be genotoxic. Trichlorfon is not oncogenic in mice, dogs, or monkeys. The oncogenicity data for dietary exposure in rats were considered equivocal. The study was conducted in two parts (within two years). The first study was conducted with 0, 92, 273, and 1500 ppm. There was no evidence of oncogenicity (Hayes, 1989). The second study was conducted with only 0 and 2500 ppm groups (Christenson, 1990). The 2500 ppm was determined to be the MTD based on body weight reduction and brain ChE inhibition (50%). The increase in the incidence of mononuclear cell leukemia (34%) was found only in females and was statistically significant ($p \leq 0.05$). However, the concurrent control incidence (16%) was lower than that (26%) for the first study. Using a default consumption rate of 5% body weight (0.4 kg), the 2500 ppm dose is equivalent to 125 mg/kg-day. Trichlorfon has been shown to be positive in some genotoxicity assays.

Occupational Exposure

The MOSs for acute, chronic, and lifetime occupational exposures for all workers were less than 100 (Table 23). The oncogenic risks for all workers were all higher than 1×10^{-6}.

Residential Exposure

Residential exposures to DDVP were due to the use of liquid sprays, foggers, no-pest strips, and flea collars. Because the daily dosage was relatively low from flea collars, MOSs of 1100, 500, and 833 for acute, chronic, and lifetime exposures, respectively, were determined for pet owners (Table 23). For other residents, the MOSs for acute, chronic, and lifetime exposures were less than 100, except for one group. The exception was structural residents after chronic and lifetime exposures where the MOSs were higher than 100. The oncogenic risks for all residents were higher than 1×10^{-6}.

Dietary Exposure

The MOSs for acute and chronic dietary exposures were greater than 100 for all population subgroups, except for the MOS of 95 for the chronic exposure of children 1 to 6 years old (Table 24). For lifetime dietary exposure, the oncogenic risks (4×10^{-5} to 7.7×10^{-5}) based on the average annual exposure level to all labeled uses were higher than 1×10^{-6}.

Using the USEPA dietary exposure estimates, the MOSs for the chronic exposure were greater than 100 for all population subgroups. For lifetime dietary exposure, the oncogenic risks ranged from 7×10^{-6} to 1.3×10^{-5}, and were also higher than 1×10^{-6}.

Combined Exposure

The MOSs of 2 to 20 for the acute, chronic, and lifetime combined exposure from work and at home were less than 100 for all 3 types of workers (Table 25). The oncogenic risks for all workers were higher than 1×10^{-6}.

VI. TOLERANCE ASSESSMENT

A. BACKGROUND

A tolerance is the maximum amount of pesticide residue that may remain in or on a food, or animal feed (USEPA, 1991d). The USEPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g. improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to unapproved commodities). Tolerances are enforced by the FDA, the USDA, and state enforcement agencies (e.g. Pesticide Enforcement Branch of DPR).

The data requirements established by USEPA for tolerances include: (1) residue chemistry which includes measured residue levels from field studies, (2) environmental fate studies, (3) toxicology studies which evaluate the hazards to humans, domestic animals, and non-target organisms, (4) product performance such as efficacy, and (5) product chemistry which includes physical-chemical characteristics and analytical method (Code of Federal Regulations, 1992). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications, and formulations proposed (USEPA, 1982).

Currently, the tolerances set by USEPA are at levels necessary for the maximum application rate and frequency, and not expected to produce deleterious health effects in humans from chronic dietary exposure (USEPA, 1991d). USEPA uses Reference Doses for non-cancer risks, and negligible levels (generally defined as a lifetime probability of tumor occurrence at one in a million) for cancer risks as guides to determine the appropriate levels for dietary exposure.

Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides". In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance.....". As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population subgroups can be calculated from the product of the tolerance and the daily consumption rate.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity. The TAS Exposure-4™ software program and the USDA National Food Consumption Survey (USDA, 1987-1988) are used in this assessment. The acute tolerance assessment does not routinely address multiple commodities at the tolerance levels since the probability of consuming multiple commodities at tolerance levels decreases as the number of commodities included in the assessment increases. A list of all the tolerances is in Appendix A. The printouts from the TAS program analysis are on file at the Medical Toxicology Branch and are available on request.

In this document, the tolerances of raw agricultural commodities, milk, eggs, and meats were evaluated. The tolerance for mushrooms was not evaluated since the use has been deleted from the labels. Based on the 95th percentile user-day exposures and the acute NOEL of 0.5 mg/kg-day for cholinergic signs observed in the rats (Lamb 1992; and Lamb 1993a), the MOSs were greater than 800 for all population subgroups for the tolerances of tomatoes, radishes, poultry, eggs, beef, veal, pork, and sheep. The MOSs were greater than 200 for all population subgroups, with one exception, for the tolerances of cucumber, lettuce, and milk. The MOS for children (1-6 years) was 160 for the tolerance of lettuce. The MOSs for all other tolerances were greater than the benchmark level of 100 considered sufficient for the protection of human health.

C. CHRONIC EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities has not been conducted because it is highly improbable, that an individual would habitually consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from FDA and DPR (formerly CDFA) pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA and DPR, 1989-1991).

VII. CONCLUSIONS

The toxicological risk of potential exposure to DDVP was evaluated for occupational, residential, dietary and combined uses based on the inhibition of brain ChE activity, clinical signs, and the finding of mononuclear leukemia in animal studies. Using the conventional benchmark levels, a margin of safety of at least 100 for non-oncogenic effects and a risk level of 1×10^{-6} or less for oncogenic effects are generally considered sufficiently protective of human health. The exposure levels of only a few groups meet those benchmark levels. The groups which have exposure levels which do not meet the benchmark levels are: all people occupationally exposed to DDVP alone and in combination with home exposure on an acute, chronic, and lifetime basis; people exposed through residential use on an acute, chronic, and lifetime basis; and the general population exposed through the diet on a potentially lifetime basis.

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IX. APPENDICES

A. U.S. Environmental Protection Agency Tolerances for DDVP

B. Occupational Exposure Assessment

C. Toxicology of Naled and Trichlorfon

D. Calculation Equations

E. Oncogenicity Potency Calculations

APPENDIX A

U.S. ENVIRONMENTAL PROTECTION AGENCY TOLERANCES FOR DDVP

Tolerances for residues of DDVP are established as follows:
(from 40 Code of Federal Regulations 180.235 and 21 CFR 556.180)

Commodity	Tolerance level (ppm)
cattle, fat	0.02
cattle, meat	0.02
cattle, mbyp*	0.02
cucumbers (residues expressed as naled)	0.5
eggs	0.05
goats, fat	0.02
goats, meat	0.02
goats, mbyp	0.02
horses, fat	0.02
horses, meat	0.02
horses, mbyp	0.02
lettuce (residues expressed as naled)	1
milk	0.02
mushrooms (residues expressed as naled)	0.5
poultry, fat	0.05
poultry, meat	0.05
poultry, mbyp	0.05
radishes	0.5
raw agricultural commodities, nonperishable,	
bulk stored regardless of fat content	0.5
packaged or bagged, containing 6 percent fat or less	0.5
packaged or bagged, containing > 6 percent fat	2
sheep, fat	0.02
sheep, meat	0.02
sheep, mbyp	0.02
swine, edible tissue	0.1 (anthelmintic in feed and/or direct application)
tomatoes (residues expressed as naled)	0.05

*mbyp= meat byproducts

APPENDIX B

OCCUPATIONAL EXPOSURE ASSESSMENT

APPENDIX B

Department of Pesticide Regulation
Worker Health and Safety Branch

Human Exposure Assessment

DDVP

August 1, 1991
Revised June 14, 1993

GENERAL CHEMISTRY

DDVP (2,2-dichlorovinyl dimethyl phosphate / VAPONA^{R} / dichlorvos) is a volatile insecticide of moderate toxicity. It has a vapor pressure of 1.2×10^{-2} Torr (20^{o}C) and a boiling point of 35^{o}C at 0.05 Torr. Its chemical formula is $C_4H_7Cl_2O_4P$ and the molecular weight is 221 g/mole. It is soluble to 1 percent in water and very soluble in alcohols and organic solvents.

FORMULATIONS

In June 1993, there were 59 DDVP-containing pesticides products registered in California. There were 4 pet collar products for control of fleas and ticks. The rest were foggers, pressurized sprays, and liquids that were labeled for control of nuisance insects, pests in or on structures (homes, apartments, warehouses, office buildings, etc.), and pests associated with livestock production and storage of agricultural commodities. Home-use materials (foggers, pet collars, pressurized sprays and liquids) are primarily marketed to the general public to be applied in residences by the occupants.

The home-use aerosols usually have less than one percent DDVP in their formulation and in many cases the DDVP is only one of several materials in the product. The collars have ~10 percent DDVP for dogs and ~5 percent for cats. Home-use foggers are 0.5 percent DDVP.

REPORTED USAGE

The major uses of DDVP as reported by the 1990 Pesticide Use Report are shown in Table 1.

TABLE 1: Reported Uses of DDVP During 1990 (DPR, 1992).

USE	LB APPLIED	PERCENT OF TOTAL LB. APPLIED
Struc. Pest Cont.	2,252	46%
Cattle, Beef and Dairy	826	17%
Poultry	715	15%
Rights-of-way	276	6%
Landscape and Ornamentals	256	5%
Vertebrate Pest Control	174	3%
Other Uses	398	8%
TOTAL	4,897	100%

Formoli, WH&S, 1992

The reported sale of DDVP in California, as shown in Figure I, has been in a sharp decline for last several years (DPR, 1984-1990). The reported sale for 1984 was 117,213 lbs DDVP and it was reduced to only 17,301 lbs for 1990. The discrepancy between pounds used and pounds sold in 1990 are in the home-use formulations which did not require use reporting.

Use of DDVP in agriculture has been in decline for a number of years. Livestock use has shown the material to not be adequately effective in controlling horn and face flies and has resulted in reduction of use. Poultry producers, as reported by the UC Agricultural Extension, have great concerns over egg and meat residues and potential intoxication of the poultry from the "tight- ventilation" conditions of the poultry house. Outside the production facility some formulations are still apparently used.

Structural pest control use has dwindled to a very small user base. Because of DDVP's volatility, it has good "penetrating power" and is used for crack-crevice or spot-type treatments.

DERMAL ABSORPTION

A dermal absorption study of DDVP technical in male rats was submitted by the registrant (Jeffcoat, 1990). Rats were divided into three dose groups. The fur on the back of each rat was clipped. ^{14}C-labeled DDVP was mixed with unlabeled DDVP and applied to the clipped back of rats at three dose levels (30, 3, and 0.3 ug/cm^2). The dosing solution was prepared with water. Each dose group was subdivided into three sacrifice times of 10, 24, and 120 hours. Exhaled $^{14}CO_2$, urine, and feces were collected at 10 hours, 24 hours and each subsequent 24-hour period until sacrifice.

The overall total radioactivity recovery of the administered dose ranged from 96.0 to 99.3 percent. Percent dermal absorption at each observation period and dose level is shown in Table 2. Dermal absorption of DDVP ranged from 10 to 13 percent of the applied dose in rats observed for 120 hours. A dermal absorption of 13 percent will be used in this document to estimate absorbed daily dosage.

TABLE 2: Percent DDVP Dermal Absorption in Rats.

Applied Dose (ug/cm^2)	Observation Period (hours) 10	24	120
30.0	13.3	11.4	12.9
3.0	10.7	11.0	12.7
0.3	7.3	10.8	9.8

Formoli, WH&S, 1992

METABOLIC DISPOSITION

DDVP is rapidly metabolized by mammals (Hudson, 1971). There is very little parent material found in tissues or biological media after exposure to DDVP. The metabolic products include dimethyl phosphate (DMP), dichloro-acetic acid, dichloro-ethanol glucuronide and carbon dioxide (Hudson, 1972). After oral or intraperitoneal administration of ^{14}C (vinyl)-DDVP, most of the radiolabel, 27 to 32 percent, was found in the urine, 16 percent in the expired CO_2 and 3 percent in the feces (24 hours post-application) (Shell, 1970).

An early multiphasic study of different carriers and radiolabels (Casida, 1962) used DDVP labeled at either the alpha-dichlorovinyl carbon (^{14}C) or the phosphorous (^{32}P). Rats were orally dosed with the test material in either water, corn oil, or propylene glycol at rates of 10 or 4 mg/kg. The data is reported in parts-per-million and is not convertible to ug or percentage. The results indicate that the ^{32}P label is retained in the bone, probably as incorporated phosphate. The ^{14}C label appears, even after 7 days, in the liver. But the radioactive residue was not DDVP and was most likely ^{14}C that was removed from DDVP, metabolized into the carbon-pool and utilized by the body for other functions.

DMP is an excellent indicator of total dermally absorbed doses of DDVP (McDonald, 1991). Six spare rats (4 dosed 2 controls) from the dermal absorption study (Jeffcoat, 1990) were dosed in the same manner. The urine of these rats was analyzed for DMP by British Columbia Research Corporation in Canada. The analyses were performed under a separate project from the dermal absorption study. No sample storage stability or spike recoveries were determined for DMP because of inadequate sample volumes. The amount of DMP found in urine was corrected for DDVP molecular weight and was reported as percentage of the applied dose. Total urinary DMP was equivalent to 37 to 45 percent, and in one rat to 82 percent, of DDVP applied dose.

WORKER ILLNESSES

From 1982 to 1990, there were 78 cases of human illness/injury reported by WH&S in its Pesticide Illness Surveillance Program that were associated with exposure to DDVP. These include 60 systemic illnesses, 12 eye injuries and 6 skin injuries. Many of these events also included a second or third pesticide material associated with the illness.

WORKER EXPOSURE

There are no studies available that could be considered standard agricultural worker exposure studies. This stems from the properties of the material and its primary mode of application. DDVP is usually applied in such a way as to maximize its fumigating properties. The 1990 ACGIH Threshold Limit Value (TLV^R) for DDVP is 0.9 mg/m^3 (0.9 ug/L, 0.1 ppm). The following summaries are from available DPR Registration Library files and WH&S data files for DDVP exposure. It is very difficult to approximate the degree of dermal contact and subsequent transfer of

DDVP from surfaces to skin. Additionally, there is no information available to estimate dermal exposure in the diverse scenarios indicated.

In one study a warehouse of ~95,000 ft^3 was fumigated with 236 grams of 20 percent DDVP. The maximum theoretical concentration would be 17.7 ug/L. Actual air concentration was 6.3 ug/L at 2 hours post application. Air concentration dropped rapidly over the monitored time period (21 hours). Workers re-entering the fumigated warehouse 12 hours after fumigation could be exposed to 0.21 ug/L. The calculated 8-hour Time Weighted Average (TWA) would be 0.124 ug/L. In a different warehouse using the same exposure parameters, surface residue was shown to be 1.43 mg/m^2 two hours after application and 0.19 mg/m^2 at 12 hours post-application (Knight, 1985).

A study reported in the public domain (Gold, 1985) investigated professional home-applicator exposure. This was not a registrant submitted document. Both dermal and inhalation exposure were measured, as were acetylcholinesterase (AChE) activity and urinary metabolites. The residents of the homes were also monitored. The applicators were equipped with interior and exterior clothing dosimeters. Washes measured hand exposure and air pumps connected to ethylene glycol-loaded impingers measured airborne DDVP levels. The applications took place in 20 residences, averaging 25.5 minutes per residence to apply 19.6 grams of DDVP (0.19 g/m^2) each. Applicators wore coveralls and rubber gloves.

Applicator dermal exposure was 2.35 mg/hr. The greatest exposure was to the face (20 percent of total), followed by the chest (17 percent) then the lower legs (16 percent). A 20 percent clothing penetration factor, empirically derived by the authors, is reflected in the 2.35 mg/hr dermal exposure. Hands accounted for less than 1 percent of the exposure, validating the use of rubber gloves as protective equipment. Airborne levels were 0.021 ug/L. Using 29 liters per minute (LPM) as the breathing rate over the 25.5 minutes, potential airborne exposure was 15 ug/application. The rate of inhalation exposure was 36.5 ug/hr. Total worker exposure was 2.39 mg/hr.

Analysis of urine samples from both applicators and residents failed to detect either DDVP or one of the metabolites, DCAA. Assay sensitivity was 1 ppb. Both applicators did show reduction in pseudo-acetylcholinesterase activity, up to 50 percent inhibition for one worker from baseline. Red blood cell (RBC) AChE results were inconclusive with one worker showing increased RBC AChE.

There are no DDVP exposure data for livestock applicators. The exposure data for cyromazine applicators were used as surrogate to estimate livestock applicator exposure to DDVP. Workers applied cyromazine (0.1% solution) to chicken manure using hand-held, backpack, or portable sprayers (Merricks, 1988). The applicators wore long-sleeved shirts, long pants, rubber gloves, socks, and shoes. Dermal exposure was monitored by attaching alpha-cellulose patches to the various parts of the body. Hand exposure was determined by wearing cotton gloves underneath the rubber gloves. A total of nine replications of mixing and applying were conducted at three locations. Dermal exposure was estimated at 1.44, 69.69, and 0.15 mg/kg active ingredient handled for applicators using hand-held, backpack, and portable sprayers, respectively.

DDVP is applied to livestock using hand application equipment. The maximum application rate is two ounces of a one percent solution (0.035 kg a.i./gal) per adult animal. An applicator could treat a maximum of 100 animals in an eight-hour workday. This is equivalent to 1.56 gallons of the spray solution or 0.05 kg of DDVP applied by an applicator during a workday. Using the worst case of the surrogate data (backpack), DDVP dermal exposure to livestock applicators is estimated at 3.83 mg/workday.

The rather high vapor pressure of DDVP discredits the use of inhalation exposure data from cyromazine or any other low vapor pressure chemicals. A study of mushroom house workers' exposure to DDVP found that the highest DDVP level in the air (0.55 ug/L) was during the application (Maddy, 1982). Inhalation exposure of livestock applicators in Table 3 was calculated assuming that they would be exposed to the same DDVP level as observed in the air during a mushroom house application.

RESIDENT EXPOSURES

Environmental monitoring of the homes treated by PCO's indicated that DDVP was present in the air for up to 24 hours post application (Gold, 1985). At two-hours post-application, air levels monitored by stationary air pumps were 0.55 ug/L. At 24 hours post-application air levels were 0.21 ug/L. Fallout dosimeters suggested an average deposition of 0.32 ug/cm^2/hour.

A second article not submitted by the registrant (Cavagna, 1969) investigated the AChE inhibition in patients admitted to a hospital. Of special concern were children, both babies (ages 7 to 21 months, mean 13 months) and children (ages 2 to 7, mean 4 years). Both RBC and pseudo-AChE were monitored every three days. Air levels of DDVP given off by the resin strips hanging in the children's rooms were also monitored. The older group of children, exposed an average of 22 days, showed no reduction in either RBC or pseudo-AChE, even when exposed for 16 hours a day to levels up to 0.21 ug/L. The younger group, exposed an average of 17 days (9 to 33 days), showed some reduction (9 to 45 percent, mean of 25 percent) in pseudo-AChE, none in their RBC AChE, when exposed for 24 hours/day to levels ranging between 0.10 ug/L and 0.21 ug/L. No one developed any cholinergic signs. There was no change in either parameter when the air levels were less than or equal to 0.10 ug/L.

Airborne levels for DDVP from the resin strips showed seasonal variation. In the winter, air levels peaked at 0.28 ug/L within the first 15 days of use and dropped to lower rates with increasing time. In the summer, with increased ventilation (open windows), the highest level reached was 0.18 ug/L, on day 4 to 6 post-introduction. Levels dropped below 0.100 ug/L in less than 10 days and had decreased to <0.020 ug/L in 20 to 30 days.

There are three DPR/Worker Health and Safety HS Reports dealing with DDVP exposure from home fogger use (Maddy, 1981, Maddy, 1984, and Goh, 1987). The earliest study (Maddy, 1981) was done using 0.5 percent DDVP foggers. Only air monitoring was conducted. Three rooms monitored showed a mean concentration of 0.41 $\pm$0.26 mg/m^3 at the time of allowed reentry (2.5 hours from the start of fogging). Only one room was followed for 24 hours or more. Its air residue level was 13.0 ug/m^3 at 24 hours, 10.0 ug/m^3 at 48 hours and below the limit of detection (unspecified) at 72 hours.

The second home-fogger study (Maddy, 1984) also addressed airborne DDVP levels. After use of a 0.5 percent DDVP fogger, air samples were taken at selected time intervals after the two hour treatment phase. Between 1 and 2 hours, the DDVP concentration averaged 0.4 $\pm$0.5 ug/L [n=10]; between 4 and 6 hours it was 0.100 $\pm$0.100 ug/L [n=11]; between 6 and 8 hours it was 0.040 $\pm$0.050 ug/L [n=8]; and at 24 hours the concentration had remained at 0.040 $\pm$0.030 ug/L [n=10]. Surface residue monitoring showed average residue levels of 1.2 $\pm$2.2 ug/cm^2 [n=10] at 2 hours post and 0.44 $\pm$0.62 ug/cm^2 [n=8] at 6 hours post, declining to 0.3 $\pm$0.4 ug/cm^2 [n=8] at 24 hours.

The third study (Goh, 1987) used the same percentage of a.i. in the fogger but only sampled surface residues. Both a theoretical and an actual measurement of DDVP deposits during fogging (first 15 minutes of application) were given. Three sites were sampled, each site having its own fogger. The mean theoretical maximum during fogging was 5.7 $\pm$1.0 ug/cm^2 and the mean actual maximum was 6.1 $\pm$0.6 ug/cm^2, indicating that a preponderance of the fogger's active ingredient initially impinge on the floor.

From the preceding studies, Average Annual Daily Dosages (AADD) and Lifetime Average Daily Dosages (LADD) were estimated. The following table displays the assumptions used in the AADD/LADD calculations. AADD was derived from Absorbed Daily Dosage multiplied by the Days Exposed per year. LADD was derived by multiplying AADD by Career Lifetime and dividing by Lifetime (except in case of Residents and Children, see footnotes).

TABLE 3: Annual Average and Lifetime Average Daily Dosage (AADD & LADD) for persons using or incidentally exposed to DDVP. Weight of adult male worker for dosage calculation is 70 kg. Dermal absorption is 13 percent (see dermal absorption section) and inhalation uptake is 50 percent (Raabe, 1988). Career lifetime for workers is 40 years. Lifetime is 70 years.

Exposure Type	TWA Air Levels [ug/L]	Air Exposure Time	Potential Dose Dermal/Inhal.[a] mg/day	Absorbed Daily Dosage ug/kg/day	Days Exposed	AADD[b]	LADD[c]
Warehouse							
12hr-post	0.12	8 hr.	ND / 1.67	12	17[d]	0.6	0.3
Struct. PCO	0.02	2 hr.	4.7 / 0.07	9	30	0.8	0.4
Livestock applicator	0.55	8 hr.	3.8 / 7.66	62	27	4.6	2.6
Resident[e]	0.10	16 hr.	NS / 0.71	5	6	0.1	0.06[f]
Resident[g]	0.20	16 hr.	NS / 1.42	10	6	0.2	0.11[f]
Child[h]	0.04	24 hr.	0.4 [i] / 0.24	16	6	0.3	0.10[j]
Child[k]	0.14	24 hr.	NS / 0.85	40	60[l]	6.6	3.1[j]
Child[m]	0.10	24 hr.	NS / 0.60	29	60[l]	4.8	2.2[j]
Pet Owner[n]	0.02	1 hr.	NS / 0.04	0.3	60[l]	0.05	0.03

a. inhalation dose = (air level)(exposure time)(29 LPM breathing rate, EPA, 1987).
b. ug/kg/day/year.
c. ug/kg/day/lifetime (Assuming children's body surface and weight increases are proportional to increases in the exposure).
d. application every 3 weeks.
e. exposed to home-use fogger air residue, breathing rate 7.4 LPM [resting (EPA, 1987)].
f. 40 years exposure.
g. exposed to SPCO application residue, breathing rate 7.4 LPM [resting].
h. child weighs 10.5 kg, body surface area of 3925 cm^2, breathing rate 4.2 LPM (Snyder, 1974), exposed to fogger residue at six hours post-ventilation and LADD calculated for 16 years.
i. DDVP transfer factor [McDonald, 1991]: (4 percent/hr)(6 hr contact/day) (0.4 ug/cm^2, Maddy, 1984).
j. 16 years as a child and 24 years as an adult in a 70-year lifetime.
k. from resin strip air-levels which caused inhibition in pseudo-AChE (Cavagna, 1969)
l. 10 days of high exposure/strip replaced every 2 months
m. from resin air-levels which did not cause inhibition in pseudo-AChE (Maddy, 1984)
n. collar is $1/10^{th}$ weight of resin strip, thus $1/10^{th}$ residue exposure from resin strip.

ND - no data
NS - not significant, material primarily airborne vapor or not available for dermal contact.

Fong, WH&S, 1993

A more recent DDVP indoor fogger exposure study was conducted in three phases in a hotel in British Columbia, Canada (McDonald, 1991). The first phase monitored residue fallout on the carpet, airborne residues, and carpet residue transfer to wipe fabrics at various intervals during 24 hours following treatment of rooms with a 0.5% DDVP fogger. The second phase monitored residue transfer from the carpet to the clothing (used as dosimeters) of four human volunteers performing Jazzercise^R routines and stretches at various times after the fogger treatment. The Jazzercise^R routines were used to conduct reproducible motions with extensive floor contact. Urine and blood samples were also collected in this phase for dimethyl phosphate (DMP) and cholinesterase (ChE) analysis, respectively. The third phase monitored urinary DMP and blood ChE activity of volunteers wearing shorts only and performing the same routines and stretches in DDVP treated rooms. The volunteers performed the routines for 20 minutes each time, for a total of 160 minutes in phase II and 80 minutes in phase III.

In phase II, DDVP airborne residues were 395, 234, and 50 ug/m^3 at three, nine, and 27 hours post-treatment, respectively. Clothing dosimeters contained 2010, 1506, and 1269 ug/person/20 minutes at three, six, and nine hours

post-treatment, respectively. Gloves contained 99 ug/person/20 minutes at three hours and 67 ug/person/20 minutes at nine hours post-treatment. Urinary DMP averaged 390 ug/person/hour of exposure in phase II and 432 ug/person/hour of exposure in phase III, suggesting that the tight-fitting clothing worn in phase II did not provide significant exposure protection. Blood acetyl-ChE activities of collected samples were within the normal range. The results for pseudo-ChE activities were inconclusive because of some missing or lost samples. Estimated absorbed daily dosages (ADD) for adult and child from dermal, inhalation, and non-dietary ingestion exposure to DDVP (Table 4) is based on average airborne residues and residues found in clothing dosimeters. ADDs based on urinary DMP are also shown in Table 4.

TABLE 4: DDVP Estimated Absorbed Daily Dosages from Clothing Dosimetry vs. Biological Monitoring Following DDVP Indoor Fogger Use for Resident Children and Adults.

	dermal	Inhalation	Ingestion	ADD (ug/kg/day)	AADD**	LADD
Clothing Dosimetry (C.D.):						
Adult	57.2	31.5	1.1	89.8	1.48	0.84
Child	84.6	33.3	16.6	134.5	2.21	1.01
Biological Monitoring (B.M.):						
Adult	73.0*		1.1	74.1	1.22	0.70
Child	107.9*		16.6	124.5	2.05	0.88

* - Dermal and inhalation for six hours of activity based on urinary DMP corrected for the ratio of DDVP/DMP molecular weights (1.754) plus inhalation for 18 hours of light activity and rest.

**- Six days in a year.

Based on: Six hours of activity and 18 hours of light activity and rest, dermal absorption of 13% (Jeffcoat, 1990), Inhalation uptake of 50% (Raabe, 1988), urinary DMP corrected for DDVP molecular weight and ratio of children body surface area over body weight to that of an adult.

	Adult	Child	Reference
Clothing (C.D./B.M.)	none/shorts	none/diaper	-
Body weight (kg)	70	10.5	Snyder, 1974
Body surface (cm^2)	17700	3925	Snyder, 1974
Inhalation rate (m^3/hr)	1.74 | 0.44	0.25 | 0.09	EPA, 1987
Hand residue ingestion (%)	5	50	Ross, 1992
Lifetime exposure (years)	40/70	16+24/70	-

Formoli, WH&S, 1992

The estimates of exposure based on clothing dosimetry and biological monitoring for home residents in Table 4 are very close. Biological monitoring is a more reliable indicator of exposure compared to passive dosimetry.

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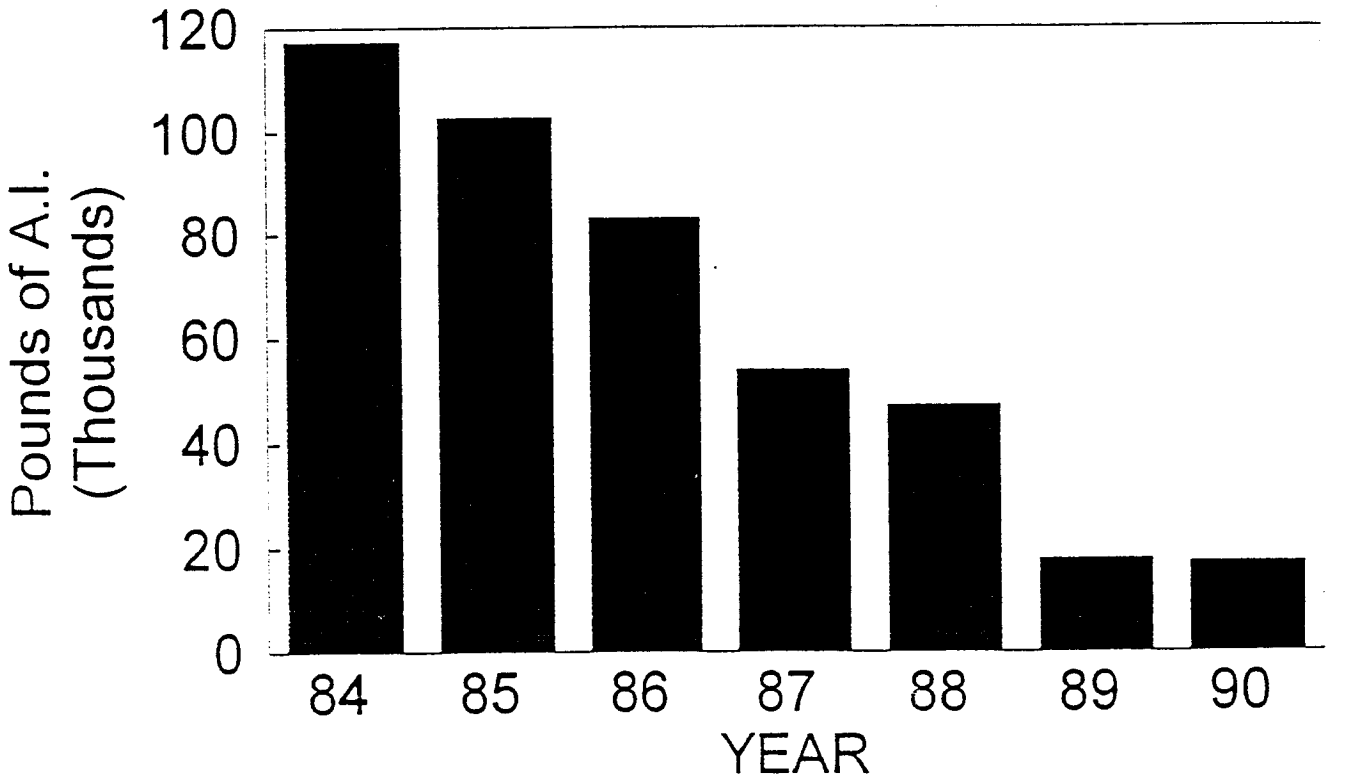
FIGURE I

DDVP SALES REPORT FOR 1984 TO 1990*



* - DPR, 1984-1990

APPENDIX C

TOXICOLOGY OF NALED AND TRICHLORFON

NALED

Naled, 1,2-dibromo-2,2-dichloroethyl dimethyl phosphate is an organophosphate with insecticidal activity. It is used on crops and in structures for insect control. In 1990, 450,000 pounds of naled applied in California and the distribution was 54% for lemons, 12% for oranges, 10% for fresh or processed grapes, 7% for safflower, and 3% for cotton (DPR, 1991).

Acute toxicity

Naled was acutely toxic to laboratory animals when administered by the oral, dermal, and inhalation routes. Cholinergic signs (such as salivation, convulsion, tremors, death) were observed in all the species tested. Pathological changes were observed in some tissues. Congested lungs and pale kidneys were observed in rats after oral exposure. The skin of rabbits exposed to naled dermally showed damage including necrosis, fibrosis, and ulceration. The lowest acute oral NOEL was 10 mg/kg-day for cholinergic signs in rats and rabbits.

Subchronic and chronic toxicity

The current Toxicology Summary (8/25/94) shows that there are no data gaps. All of the following studies were conducted by gavage administration. No adverse effects were found in the mouse oncogenicity, rat teratology, rabbit teratology, or neurotoxicity studies. Adverse effects were found in the dog chronic, rat chronic and oncogenicity, and rat reproductive toxicity studies. In the dog chronic study, the adverse effects (NOEL = 0.2 mg/kg-day) were the inhibition of brain, plasma, and erythrocyte ChE activities, degeneration of the testes, focal mineralization of the spinal cord, and mild siderosis in the spleen. In the rat chronic and oncogenicity study, the NOEL was also 0.2 mg/kg-day for the inhibition of brain, plasma, and erythrocyte ChE activities. There was a slight increase in the incidence of mammary adenocarcinoma in male rats (by gavage). In the two-generation reproductive toxicity study with naled, the only significant parental effect was a dose-related decrease in body weight in all treated F_1 males during both pre- and post-mating periods. The effects on the pups included decreased survival, body weight, and number of pups at birth with a NOEL of 2 mg/kg-day.

The only inhalation study reviewed showed corneal and nasal lesions in the rat exposed to naled ($\geq$ 3.4 *u*g/L) by inhalation for 3 weeks.

Genotoxicity

No adverse effects were found in the gene mutation (Ames assays), chromosomal aberration (bone marrow), and DNA damage (unscheduled DNA synthesis) studies.

TOXICOLOGY OF NALED AND TRICHLORFON

TRICHLORFON

Trichlorfon, dimethyl (2,2,2-trichloro-1-hydroxyethyl) phosphonate, is an organophosphate with insecticidal activity. It is used on crops, ornamentals, forests, and turf. It is also used for pest control of structures. In 1990 in California, 12,000 pounds of trichlorfon were applied primarily on alfalfa (43%) and on landscape maintenance (28%) (DPR, 1991).

Acute toxicity

The rat oral LD_{50} is approximately 250 mg/kg. The dermal LD_{50} in rats is > 5000 mg/kg, and in rabbits is >2100 mg/kg. No neurotoxicity was observed in chickens given a single dose of trichlorfon up to 300 mg/kg subcutaneously, or up to 200 mg/kg by oral administration.

Subchronic and chronic toxicity

The Toxicology Summary (June 11, 1993) shows a data gap for a reproductive toxicity study in the rat; the study was considered upgradeable. No adverse effects were observed in the monkey chronic, mouse oncogenicity, and neurotoxicity studies. Developmental effects (primarily skeletal malformations) were observed at maternally toxic doses. In the rat chronic and oncogenicity study, rats exposed to trichlorfon in the diet for 2 years showed small intestine hyperplasia, chronic nephropathy, cysts and calcification in the kidney, increased serum cholesterol, and increased specific gravity in the urine. The NOEL was 92.2 ppm. The NOEL was 273 ppm for the inhibition of brain and plasma ChE activities. The oncogenicity data for dietary exposure in rats were considered equivocal. The interpretation of the increased incidence of mononuclear cell leukemia in female rats was complicated by low concurrent control incidence. Exposure of rats to trichlorfon in the diet during reproduction resulted in decreased parental body weight, decreased number of live pups/litter, reduced fertility, and lowered body weight gain of parents and pups, and the NOEL was 300 ppm.

Genotoxicity

Trichlorfon was mutagenic in the microbial assays with Salmonella strain TA100, Saccharomyces cerevisiae, E. coli (WP2 uvrA) and (WP2 hcr), and in mouse lymphoma cells. Chromosomal damage was observed in the sister chromatid exchange assay with Chinese Hamster bone marrow cells, human lymphocytes, and Chinese Hamster ovary cells. No adverse effects were observed in the mouse dominant lethal and unscheduled DNA synthesis assays.

APPENDIX D

CALCULATION EQUATIONS

1. Dosage estimation for animals from an inhalation study (exposure level in ppm):

$$mg/kg\text{-}day = mg/m^3 \times respiration\ rate(m^3/kg\text{-}day) \times \frac{hours\ exposed}{24\ hours} \times \frac{days\ exposed/week}{7\ days} \times AF$$

For this equation, 1 *u*g/L in air is equivalent to 1 mg/m^3. The term for number of days exposed per week/7 days is used in the calculation only for studies when the animals were not dosed every day. The dosage was not corrected for absorption (absorption factor, AF). Only the dosages used in the calculation of MOS are corrected for 50% inhalation absorption rate.

The default respiration rates used are: 0.46 m^3/kg-day for children, 0.26 m^3/kg-day for human adults, 0.96 m^3/kg-day for rats, 0.54 m^3/kg-day for rabbits, and 1.80 m^3/kg-day for mice (Zielhuis and van der Kreek, 1979).

For example: Using the NOEL of 1.25 *u*g/L from Thorpe *et al.* (1971b) where rabbits were exposed to DDVP daily,

$$\frac{1.25\ mg}{m^3} \times \frac{0.54\ m^3}{kg\text{-}day} \times \frac{23\ hours}{24\ hours} = 0.65\ mg/kg\text{-}day$$

2. Dosage estimation for animals in a dietary study (exposure level expressed as ppm in the diet):

$$ug/kg\text{-}day = ppm\ (ug/g)\ x\ FR\ (g/day)\ x\ \frac{1}{body\ weight\ (kg)}\ x\ \frac{days\ exposed/week}{7days}$$

The food consumption rate (FR) is derived either from the reports or the standard default is used. The standard default is based on body weight, 15% for mouse, 5% for rat, and 3% for rabbit.

APPENDIX D (continued)

CALCULATION EQUATIONS

3. Margin of Safety:

$$Margin\ of\ Safety = \frac{NOEL}{exposure\ level}$$

4. Human equivalency in potency from animal data to human:

The equivalency in potency from animal to human is calculated based on the body weight to the 3/4 power (Davidson *et al.*, 1986; Travis and White, 1988).

$$\frac{Dose_A}{Dose_H} \times \frac{BW_H}{BW_A} = \frac{BW_A^{3/4}}{BW_H^{3/4}}$$

$$Dose_H = Dose_A \times \left(\frac{BW_A}{BW_H}\right)^{1/4}$$

Therefore,

$$q_1^*H = q_1^*A \times \left(\frac{BW_H}{BW_A}\right)^{1/4}$$

BW=body weight, A=animal, and H=human. Body weights used were: 70 kg for human, 0.50 kg for rat, and 0.037 kg for mouse.

APPENDIX E

ONCOGENICITY POTENCY CALCULATIONS

GLOBAL 86 (MAY 1986)

BY RICHARD B. HOWE AND CYNTHIA VAN LANDINGHAM
CLEMENT ASSOCIATES, 1201 GAINES STREET, RUSTON, LA 71270 (318) 255-4800

Pancreatic adenoma in male rats dosed DDVP by gavage for 2 years

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	0.00000	16/ 50	16.31
2	2.90000	25/ 49	24.06
3	5.70000	30/ 50	30.59

CHI-SQUARE GOODNESS OF FIT STATISTIC IS .11014

P-VALUE FOR THE MONTE CARLO TEST IS .4650000000

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .394703118704
Q(1) = 9.680185659774E-02
Q(2) = .000000000000

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -99.0030875953
CALCULATIONS ARE BASED UPON EXTRA RISK

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK
****

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-06	1.03304E-05	6.49111E-06	95.0%	Q(0) = .31574 Q(1) = .15406 Q(2) = .00000

ONCOGENICITY POTENCY CALCULATIONS

Mononuclear leukemia in male rats dosed DDVP by gavage for 2 years

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	0.00000	11/ 50	11.76
2	2.90000	20/ 50	17.67
3	5.70000	21/ 50	22.51

CHI-SQUARE GOODNESS OF FIT STATISTIC IS .72309

P-VALUE FOR THE MONTE CARLO TEST IS .2950000000

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .268176327600
Q(1) = 5.789349370575E-02
Q(2) = .000000000000

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -94.3688180916

CALCULATIONS ARE BASED UPON EXTRA RISK

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK
****

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-06	1.72731E-05	9.86160E-06	95.0%	Q(0) = .20214 Q(1) = .10140 Q(2) = .00000

ONCOGENICITY POTENCY CALCULATIONS

Combined forestomach papilloma and/or carcinoma in female mice dosed DDVP by gavage for 2 years

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	0.00000	5/ 44	4.67
2	14.3000	6/ 44	6.52
3	28.6000	19/ 48	18.83

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 7.76347E-02

P-VALUE FOR THE MONTE CARLO TEST IS .4450000000

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2 - Q3 * D^3)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .112255443366
Q(1) = .000000000000
Q(2) = .000000000000
Q(3) = 1.648741402970E-05

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -65.3646193952

CALCULATIONS ARE BASED UPON EXTRA RISK

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK
****

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-06	.39290	8.93870E-05	95.0%	Q(0) = 8.80886E-02 Q(1) = 1.11873E-02 Q(2) = 0.00000 Q(3) = 2.89517E-06