AZINPHOS-METHYL
(GUTHION)

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology and Worker Health and Safety Branches

DEPARTMENT OF PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

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AZINPHOS-METHYL

EXECUTIVE SUMMARY

Introduction

Azinphos-methyl (O,O-dimethyl-S-[(4-oxo-1,2,3-benzotriazin-3(4H)yl)methyl] phosphorodithioate) is a broad spectrum organophosphate insecticide, acaricide, and molluscacide that was first registered in 1959 by Mobay Chemical Corporation in the United States (U.S. EPA, 1986a). The Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency (Cal/EPA) placed azinphos-methyl on the high-priority list for risk assessment based on possible adverse effects identified in genetic toxicity and oncogenicity (carcinogenicity) studies submitted under the Birth Defect Prevention Act (SB 950) and due to its low no-observed-effect level (NOEL) for acute toxicity. Azinphos-methyl is a California restricted-use pesticide due to its acute toxicity. In 1993, the U.S. EPA issued an acute data call-in notice for illness reports from poison control centers for azinphos-methyl based on concerns about its potential acute human health risks. The purpose of this current risk assessment is to address the potential adverse health effects associated with both occupational and dietary exposure to azinphos-methyl.

The Risk Assessment Process

The risk assessment process consists of four aspects: hazard identification, dose-response assessment, exposure assessment, 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 result in 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 testing involves chemical levels many times higher than those to which people might be exposed.

The exposure assessment includes an estimation of the potential occupational and dietary exposure through the oral, dermal and inhalation routes on an acute (one time) and chronic (long-term) basis. Occupational exposure is based on the amount of pesticide residue in the air, on clothing, and on skin. The exposure is adjusted for the number of hours worked per day, body weight, dermal absorption rate and breathing rate. For dietary exposure, the levels of exposure are determined by the amount of pesticide residue on specific commodities and processed foods, and the consumption rate.

The risk characterization then 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 through agricultural work or in the diet. The potential for possible non-oncogenic adverse health effects in human populations is expressed as the margin of exposure (MOE), which is the ratio of the dosage which produced no effect in laboratory studies to the estimated occupational or dietary dosage. For oncogenic effects, the probability of risk is calculated as the product of the cancer potency of the pesticide and the estimated occupational or dietary exposure.

Toxicology

The acute effects of azinphos-methyl are due primarily to its inhibition of acetylcholinesterase (AChE) which is an enzyme in the nervous system responsible for terminating transmission of impulses across certain nerve synapses. Cholinergic signs (piloerection, ocular and nasal discharge, salivation, breathing difficulties, staggering gait, tremors, twitching, and/or convulsions) were the primary effects observed in laboratory animals with acutely toxic exposures to azinphos-methyl. The lowest established acute NOEL from an acceptable study was 1.0 mg/kg based on inactivity, reduced reflexes, and brain cholinesterase (ChE) inhibition in female rats. The effects observed in animals with subchronic or chronic exposure to azinphos-methyl included cholinergic signs, reduced body weights and food consumption, microscopic pathological changes in the uterus, reduced sperm production, decreased survival of pups following birth, and brain ChE inhibition. The lowest NOEL in a subchronic or chronic study was 0.28 mg/kg/day based on brain ChE inhibition in rats.

There was an increase in tumors of the pancreas, thyroid, and adrenal glands in male rats of one chronic study. However, there was no increase in tumor incidence in the females of this study or in either sex in two other chronic rat studies. Two mouse oncogenicity studies were also negative. Azinphos-methyl was positive in selected *in vitro* genotoxicity assays, but in none of the *in vivo* assays. DPR concluded that the limited evidence of an oncogenic effect was insufficient to warrant a low-dose extrapolation from animal data to humans.

Exposure Analysis

Azinphos-methyl is used on a variety of crops; however, its major use is on tree crops, including pome and stone fruit and nut crops. The estimated potential acute exposure for mixer/loader/applicators ranged from 31 to 69 µg/kg/day. For field workers, the acute exposure estimates ranged from 2.2 to 85.6 µg/kg/day with proppers (workers who prop up heavy, fruit laden branches) having significantly lower exposure than thinners and harvesters. It was estimated that mixer/loader/applicators work approximately two weeks per year while field workers work an average of 87 days per year. The estimated chronic exposure for mixer/loader/applicators was 0.8 to 1.9 µg/kg/day. For field workers, the estimated chronic exposure ranged from 0.5 to 20.4 µg/kg/day.

The estimated potential acute exposure to azinphos-methyl in the diet ranged from 1.5 to 12.4 µg/kg for various population subgroups. Infants and children had the highest exposure. The estimated chronic exposure to azinphos-methyl in the diet for the various population subgroups ranged from 0.10 to 0.52 µg/kg/day.

Risk Evaluation

The risk for acute and non-oncogenic chronic health effects in humans is expressed as a margin of exposure (MOE). The MOE is the ratio of the NOEL in animal studies to the potential human exposure dosage. The MOEs for acute effects were less than 35 for mixer/loader/applicators. The MOEs for acute effects were less than 25 for thinners and harvesters and greater than 200 for proppers. The MOEs for chronic effects in mixer/loader/applicators ranged from approximately 150 to 350. For thinners and harvesters, the chronic MOEs were less than 30. The MOEs for proppers were between 260 and 560. The addition of dietary exposure did not drastically reduce the MOEs for most pesticide workers whose occupational exposure was relatively high. However, the acute MOEs for combined occupational and dietary exposure were significantly lower for proppers, ranging from 170 to 270.

The MOEs for acute effects with dietary exposure among the various population subgroups ranged from approximately 81 to 680. Non-nursing infants less than one year old had the lowest MOE for acute dietary exposure. The MOEs for chronic effects with dietary exposure ranged from approximately 540 to 2,800. The chronic MOEs were also lowest for non-nursing infants less than one year old.

Tolerance Assessment

A tolerance assessment for azinphos-methyl was conducted assuming commodities were consumed at their tolerance level for acute exposure. The MOEs for potential acute effects were less than 100 for one or more population subgroups for various commodities including grapes, watermelon, apples, grapefruit, kiwi fruit, oranges, cantaloupe, honeydew melon, pears, plums, peaches, tomatoes, tangerines, broccoli, nectarines, and cabbage. Based on these estimates, the tolerances for these commodities should be reviewed.

Conclusions

Generally, a margin of exposure greater than 100 is desirable when the NOEL is based on animal data. The MOEs for acute effects from azinphos-methyl were less than 100 for all agricultural workers, except for proppers. The MOEs for chronic effects were greater than 100 for all agricultural workers, except harvesters and thinners. Mitigation should be considered for those occupational activities where MOEs were less than 100. The MOEs for acute effects from dietary exposure were less than 100 for nursing and non-nursing infants less than 1 year old. The acute dietary MOEs were greater than 100 for all other population subgroups. The MOEs for chronic effects from dietary exposure were greater than 100 for all population subgroups.

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I. SUMMARY

This Risk Characterization Document addresses potential occupational and dietary exposure to O,O-dimethyl-S-[(4-oxo-1,2,3-benzotriazin-3(4H)yl)methyl] phosphorodithioate (azinphos-methyl). Azinphos-methyl is a broad spectrum organophosphate insecticide, acaricide, and molluscacide whose primary use in California is on tree crops such as almonds, pears, walnut, apples, peaches, and pistachios. Azinphos-methyl and its oxygen analog produce their toxic reaction primarily through their inhibition of acetylcholinesterase (AChE) which is responsible for terminating transmission of impulses across certain nerve synapses.

The primary effects observed in laboratory animals from acute exposure to azinphos-methyl are cholinergic signs including piloerection, ocular and nasal discharge, salivation, breathing difficulties, staggering gait, tremors, twitching, and/or convulsions. The lowest established no-observed-effect level (NOEL) for acute effects in an acceptable study was 1.0 mg/kg based on reduced performance in the functional observational battery (sitting/lying in open field, reduced approach response, and uncoordinated righting response) and brain cholinesterase (ChE) inhibition in female rats. With subchronic and chronic exposure to azinphos-methyl, cholinergic signs, brain ChE inhibition, reduced body weights and food consumption, impaired spermatogenesis, decreased pup viability and lactation indices, and cystic endometrial hyperplasia were seen. The lowest subchronic or chronic NOEL was 0.28 mg/kg/day based on brain ChE inhibition in rats.

There was an increase in tumors of the pancreas, thyroid, and adrenal glands of male rats in one chronic study. However, there was no evidence of oncogenicity in the female rats or in either sex in two other chronic rat studies. Two mouse oncogenicity studies were also negative. Azinphos-methyl was positive in selected *in vitro* genotoxicity assays, but in none of the *in vivo* assays. DPR concluded that the limited evidence that azinphos-methyl was oncogenic was insufficient to warrant a low-dose extrapolation from the animal data to humans.

The absorbed daily dosages (ADDs) for mixer/loader/applicators ranged from 31 to 69 µg/kg/day. For field workers, the ADDs ranged from 2.2 to 85.6 µg/kg/day with proppers (workers who prop up heavy, fruit laden branches) having significantly lower exposure than thinners and harvesters. It was estimated that mixer/loader/applicators work approximately two weeks per year while field workers work an average of 87 days per year. The annual average daily dosages (AADDs) for mixer/ loader/applicators ranged from 0.8 to 1.9 µg/kg/day. The AADDs for field workers ranged from 0.5 to 20.4 µg/kg/day.

The estimated potential acute exposure to azinphos-methyl in the diet ranged from 1.5 to 12.4 µg/kg for various population subgroups. Infants and children had the highest potential exposure. The estimated potential chronic exposure to azinphos-methyl in the diet for the various population subgroups ranged from 0.10 to 0.52 µg/kg/day.

The risk for acute and non-oncogenic chronic health effects in humans is expressed as a margin of exposure (MOE). The MOE is the ratio of the NOEL in animal studies to the human exposure dosage. Generally, a MOE greater than 100 is desirable when the NOEL is based on animal data. The MOEs for acute effects ranged from 15 to 33 for mixer/loader/applicators. The MOEs for acute effects for thinners and harvesters ranged from 12 to 24, and for proppers between 220 and 460. The chronic MOEs ranged from 150 to 350 for mixer/loader/applicators and from 260 to 560 for proppers; however, the MOEs were less than 100 for harvesters and thinners, ranging from 14 to 28. Mitigation should be considered for agricultural activities where

MOEs were less than 100. The addition of dietary exposure did not drastically reduce the MOEs for most pesticide workers whose occupational exposure was relatively high. However, the acute MOEs for combined occupational and dietary exposure were significantly lower for proppers, ranging from 170 to 270.

The MOEs for acute effects from dietary exposure were less than 100 for nursing and non-nursing infants less than 1 year old, ranging from 81 to 88. The acute MOE was lowest for non-nursing infants less than one year old. The acute dietary MOEs were greater than 100 for all other population subgroups. The MOEs for chronic effects with dietary exposure ranged from 540 to 2,800. Non-nursing infants less than one year old also had the lowest MOE for chronic dietary exposure.

A tolerance assessment for azinphos-methyl was conducted assuming commodities were consumed at their tolerance level for acute exposure. The MOEs for potential acute effects were less than 100 for one or more population subgroups for various commodities including grapes, watermelon, apples, grapefruit, kiwi fruit, oranges, cantaloupe, honeydew melon, pears, plums, peaches, tomatoes, tangerines, broccoli, nectarines, and cabbage. Based on these estimates, the tolerances for these commodities should be reviewed.

II. INTRODUCTION

A. REGULATORY BACKGROUND

Azinphos-methyl was first registered in 1959 by Mobay Chemical Corporation in the United States (U.S. EPA, 1986a). In 1986, the U.S. EPA issued a reregistration standard for azinphos-methyl. The Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency placed azinphos-methyl on the high-priority list for risk assessment based on possible adverse effects identified in chromosomal aberrations and oncogenicity studies submitted under the Birth Defect Prevention Act (SB 950) and due to its low no-observed-effect level (NOEL) for acute toxicity. Azinphos-methyl is a restricted-use pesticide based on its acute toxicity. In 1993, the U.S. EPA issued an acute data call-in for illness reports from poison control centers because of concerns regarding acute risks to human health. Azinphos-methyl is also a high-priority pesticide for risk assessment under the California Toxic Air Contaminant Act (AB 1807). In 1989, the California Assembly passed AB2161 which requires DPR to conduct dietary risk assessments for all pesticides with food crop uses. The purpose of this current risk assessment is to address the potential adverse health effects for agricultural workers exposed to azinphos-methyl and for the general public exposed to azinphos-methyl through the foods they eat. A separate risk assessment document for AB1807 will address potential health effects in the general public from exposure to azinphos-methyl in ambient air.

B. CHEMICAL IDENTIFICATION

Azinphos-methyl (O,O-dimethyl-S-[(4-oxo-1,2,3-benzotriazin-3(4H)yl)methyl] phosphorodithioate) is a broad spectrum organophosphate insecticide, acaricide, and molluscacide (U.S. EPA, 1986a). Azinphos-methyl and its oxygen analog produce their toxic reaction primarily through their 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 overstimulation of the nerves followed by depression or paralysis of the cholinergic nerves throughout the central and peripheral nervous system. AChE is highly selective, although not exclusively, for acetyl esters as substrates (Brimijoin, 1992). Another form of cholinesterase, butyrylcholinesterase (BuChE), preferentially hydrolyzes 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 kidney. 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

B. CHEMICAL IDENTIFICATION (cont.)

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 fasciculations. 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.

At 0.1 mM, azinphos-methyl also inhibits the active transport of glucose in isolated mouse intestine (Guthrie *et al.*, 1974). The mechanism by which it inhibits glucose transport is unknown. It is also unknown if this *in vitro* biochemical effect has any relationship to clinical or pathological effects observed *in vivo*.

C. TECHNICAL AND PRODUCT FORMULATION

Currently there are 6 products containing azinphos-methyl as an active ingredient registered in California. Three formulations are wettable powders (50% azinphos-methyl) and 3 are emulsifiable concentrates (22% azinphos-methyl). Miles Inc. is the registrant for 3 of these formulations (1 wettable powder and 2 emulsifiable concentrates). Gowan Company is the registrant for the other 3 formulations (2 wettable powders and 1 emulsifiable concentrate).

D. USAGE

The azinphos-methyl formulations registered in California are all considered restricted use pesticides based on their acute toxicity. Azinphos-methyl may be applied by ground or aerial equipment by certified applicators or persons under their supervision. The maximum rate of application is 2 lbs of active ingredient/acre. The major uses for azinphos-methyl are on six fruit tree crops (almonds, walnuts, pears, pistachios, apples, and peaches in descending order of use) which constituted 96% of its use in 1995 (DPR, 1996a). In 1995, 434,098 pounds of azinphos-methyl were used on 40 different commodities.

Mixer/loader/applicators are required to wear a protective suit that covers all the body except the head, hands, and feet, chemical resistant gloves, chemical resistant shoes, shoe coverings or boots, chemical resistant apron, and goggles or face shield and a pesticide or organic vapor respirator when handling the concentrate. In California, a closed system is required for mixing Category I liquid formulations. If a closed system is used, no respirator is required, and a long sleeved shirt and long pants may be substituted for the protective suit; however, a chemical resistant apron and gloves are still required. During application, equipment repair, disposal of the pesticide or reentry into treated areas prior to expiration of the reentry interval, workers are required to wear all the protective equipment listed above except the chemical resistant apron, respirator and goggles. With airblast application, workers must

D. USAGE (cont.)

also wear a chemical resistant head covering. If application is made from an enclosed vehicle (e.g., tractor cab or airplane cockpit), then a long sleeved shirt and long pants are the only protective clothing required; however, chemical resistant gloves should be worn exiting the vehicle. With aerial application, the use of human flaggers is prohibited unless they are in an enclosed vehicle.

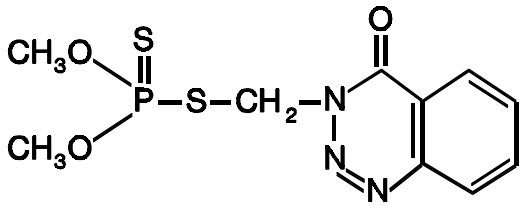
The reentry intervals are 30 days for citrus, 21 days for grapes, 14 days for apples, peaches, nectarines and other stone fruits (except almonds). When the total amount of azinphos-methyl applied per season is less than 1 lb/acre, thinning may be done to apples and stone fruit (except almonds) after 7 days. The reentry interval for all other crops, including almonds, is 24 hours.

E. ILLNESS REPORTS

In California, there were 119 cases of work related illnesses/injuries with azinphos-methyl between 1984 and 1990 (Appendix A). Azinphos-methyl was the only pesticide associated with 55 of these cases while several pesticides, including azinphos-methyl, were associated with the remaining 64 cases. In 81% of the cases, the symptoms were systemic. Severe eye and skin injuries were reported in the other 19% of the cases. There were no deaths associated with azinphos-methyl during this period.

F. PHYSICAL AND CHEMICAL PROPERTIES (U.S. EPA, 1986a)

1.	Common Name:	Azinphos-methyl
2.	Chemical Name:	O,O-dimethyl-s-[(4-oxo-1,2,3-benzotriazin-(4H)yl)-methyl] phosphorodithioate
3.	Trade Names:	Guthion, Gusathion, Gusathion-M, Crysthyron, Cotnion, Cotnion-methyl, Metriltrizotion, Carfene, Bay 9027, Bay 17147, R-1852
4.	CAS Registry No.:	86-50-0
5.	Structural Formula:	



6.	Empirical Formula:	$C_{10}H_{12}N_3O_3PS_2$
7.	Molecular weight:	317.3 (Bayer AG, 1981)

F. PHYSICAL AND CHEMICAL PROPERTIES (cont.)

8.	Specific Gravity:	1.44 at 20°C (Baird, 1987)
9.	Solubility:	Water - 28 mg/L at 20°C (Krohn, 1987) Solvents (20°C): (Bayer AG, 1981) n-Hexane - <1 g/L Dichloromethane - >1000 g/L 2-Propanol - 1 to 10 g/L Toluene - 100 to 1000 g/L
10.	Vapor pressure:	1.6×10^{-6} mmHg at 20°C. (Talbott and Mosier, 1987)
11.	Octanol/water partition coefficient:	360 at 20°C (Sandie, 1983)
12.	Henry's law constant:	2.55×10^{-8} atm-m^3/mol at 20°C (Talbott, 1987)

G. ENVIRONMENTAL FATE

Hydrolysis

Liang and Lichtenstein (1972) reported that azinphos-methyl was hydrolyzed in aqueous solutions at pH values from 6 to 11. The hydrolysis increased as the pH increased. At pH 11, 97% of the applied azinphos-methyl was converted to water soluble products. The hydrolytic products were identified as methyl benzazimide sulfide, anthranilic acid, benzazimide, and azinphos-methyl oxygen analog. Wilkes *et al.* (1979a) also studied the hydrolysis of azinphos-methyl at pH 4, 7, and 9, at 30 and 40°C, and at 1 and 10 ppm. The half-lives ranged from 1 to 42 days. The half-lives decreased as the pH and temperature increased. The azinphos-methyl was slightly more stable at 10 ppm than at 1 ppm at all pH values. The major metabolites were identified as benzazimide and/or hydroxymethyl benzazimide. Anthranilic acid, mercaptomethyl benzazimide and *bis*-(benzazimide-N-methyl) sulfide were identified as minor metabolites. No losses could be attributed to volatilization.

Photolysis

Rapid and extensive photodegradation of azinphos-methyl was observed when exposed to artificial UV light (254 nm), whereas no or little decomposition occurred in the dark (Liang and Lichtenstein, 1972). The photodegradation products identified were benzazimide, N-methyl benzazimide, anthranilic acid, methyl-benzazimide sulfide. Wilkes *et al.* (1979b) also reported rapid photodegradation of azinphos-methyl in a non-sterile, pH 4 aqueous solution under a high intensity mercury lamp. The half-life was 9.4 hrs. The photodegradation products identified were benzazimide and/or hydroxymethyl benzazimide, anthranilic acid, and methyl benzazimide. No volatile products were detected. Rapid photodegradation was also seen when azinphos-methyl was irradiated with natural sunlight in a sterile, pH 4 aqueous solution (Morgan, 1987a). The estimated half-life was 76.7 hrs. The photodegradation products identified were benzazimide, anthranilic acid, and methyl anthranilate.

G. ENVIRONMENTAL FATE (cont.)

Azinphos-methyl undergoes photodegradation more slowly when applied to soil. When azinphos-methyl was irradiated with a mercury lamp after application to sandy loam soil, the half-life was 220 hrs (Wilkes *et al.*, 1979c). The major photodegradation products were benzazimide and/or hydroxymethyl benzazimide, azinphos-methyl oxygen analog, methyl benzazimide, and bis-(benzazimide-N-methyl) sulfide. No volatile products were formed. The photodegradation of azinphos-methyl, applied to sandy loam soil (pH 5), was slower with exposure to natural sunlight (Morgan, 1987b). The estimated half-life was 99 days. In a subsequent study, the estimated half-life was 66 days when azinphos-methyl was applied to sterile sandy loam soil (pH 7) and exposed to natural sunlight (Gronberg, 1989). After correcting for non-photolytic degradation, the estimated half-life was 241 days. No degradation products were identified in either of these two experiments.

Soil Metabolism

The metabolism of azinphos-methyl in soils under laboratory and field conditions were studied by Schulz and coworkers (1970). In the laboratory study, azinphos-methyl was applied to silt loam and quartz sand soil and incubated at 30°C over a 10 week period. Approximately 95% of technical grade azinphos-methyl and emulsifiable concentrate (2 lb/gal) had degraded after 6 and 22 days, respectively. The metabolites detected were benzazimide, methyl benzazimide, and three other unknown compounds. In the field study, azinphos-methyl was applied to silt loam soil and its degradation followed for 4 years. The estimated half-life was 12 and 28 days for the emulsifiable concentrate and granular formulation, respectively. The major metabolites identified were mercaptomethyl benzazimide, N-methyl benzazimide, N-methyl benzazimide sulfide (disulfide), and benzazimide.

In a subsequent soil metabolism study, the estimated half-life of azinphos-methyl in a non-sterile soil was 21 days under aerobic conditions and 68 days under anaerobic conditions (Gronberg *et al.*, 1979). The degradation products included benzazimide, anthranilic acid, hydroxy-methylbenzazimide, methyl benzazimide sulfide, N-methyl benzazimide, and traces of mercaptomethyl benzazimide and the oxygen analogue of azinphos-methyl. Azinphos-methyl is stable in sterile soil conditions with a half-life of 355 days.

Field Dissipation

Azinphos-methyl was applied once or twice at 3 lb. a.i./acre (the highest single application rate) at two different locations in California, Fresno and Chualar (Grace and Cain, 1990). The first order dissipation constants from the single application plots were 0.063 at Chualar and 0.130 at Fresno with respective half-lives 10.9 and 5.3 days. In only one sample were residues of azinphos-methyl or its oxygen analog (0.09 ppm) detected at depths below 6". This was found in the soil layer 6-12" below the surface 28 days post-application.

Persistence and degradation of azinphos-methyl in soil are affected by formulation and mode of applications (Schulz *et al.*, 1970). The half-life of azinphos-methyl residues ranged from 6.5 to 168 days (average 67 days) using various formulations incorporated 6 inches into the soil. Azinphos-methyl applied as an emulsion on the soil surface had a half-life of 12 days, while azinphos-methyl applied in granular form, as well as rototilling into the soil to a depth of 4-5 inches, increased the half-life to 28 days. Degradation of azinphos-methyl was also affected by pH and temperature (Heuer *et al.*, 1974; Liang and Lichtenstein, 1976). At a pH of <9, the half-life of azinphos-methyl in water is approximately one month at a temperature of 6° or 25°C.

G. ENVIRONMENTAL FATE (cont.)

Increasing the pH to greater than 9.5 caused the half-life to fall to less than one week. Moisture content and temperature also significantly affect the persistence of azinphos-methyl in soil (Yaron *et al.*, 1974). Half-lives of 484, 88, and 32 days was observed in dry natural soil at temperatures of 6°, 25°, and 40°C ,respectively. In wet soil at identical temperatures, the half-lives were 64, 13, and 5 days respectively.

Soil Adsorption

Available data indicate that azinphos-methyl has a relatively low affinity for various types of soil. Ziegler and Hallenbeck (1987) reported adsorption coefficients (K_d) of 12.7, 4.0, 6.8, and 8.4 for silt loam, sandy loam, sand, and clay loam, respectively. The adsorption coefficients based on soil organic carbon (K_{oc}) were 829, 693, 1282, and 723 for silt loam, sandy loam, sand, and clay loam, respectively. Similar K_d values (3.3, 11.0, and 28.5 ml/g) were reported by Flint *et al.* (1970) for sandy loam, silt loam, and high organic silt loam, respectively.

Mobility

In a column leaching study, azinphos-methyl was incubated in silt loam soil for 28 days and then placed on top of a 30.5 x 1.5 cm silt loam soil column (Atwell and Close, 1976). Water was passed through the column at a rate of 0.5 inch/day for 45 days. Ninety percent of the azinphos-methyl remained in the upper 2 inches of soil, with only 4% reaching the leachate. In another column leaching study, azinphos-methyl was applied directly the top of 45 x 1.6 cm soil columns without a pre-incubation period (Flint *et al.*, 1970). An estimated 62, 195 and 186 inches of rainfall were required to leach azinphos-methyl one foot into sandy loam, silt loam, and high organic silt loam, respectively. Minimal leaching characteristics of aged residues of azinphos-methyl were also observed in field studies (Schulz et. al., 1970; Staiff *et al.*, 1975; Kuhr *et al.*, undated). The majority of the residual azinphos-methyl was detected in the upper 2 to 6 inches of the soil in fields treated with the chemical.

Pesticide Contamination Prevention Act

Pursuant to the Pesticide Contamination Prevention Act (AB 2021), DPR has identified azinphos-methyl as a potential groundwater contaminant based on its high water solubility (> 3 ppm), low soil adsorption (K_{oc} < 1900 cm^3/g), long hydrolysis half-life ($t_{1/2}$ > 14 days) and long anaerobic soil metabolism half-life ($t_{1/2}$ > 9 days) (DPR, 1996c). However, azinphos-methyl was not detected in the water from 1,180 wells sampled in California between 1983 and 1996 (DPR, 1992a, 1993a, 1994, & 1995a & 1996b).

Plant Metabolism

Azinphos-methyl is found primarily as a surface residue with slight to moderate absorption into plants. In lettuce, oranges, potatoes, apples, and cotton, 59-99% of the total residues remained on the surface 14-119 days after application (Magill and Everett, 1966; Gronberg *et al.*, 1975; Drager, 1987; Krolski, 1988a&b; Chopade and Bosnak, 1988). The absorption was slightly greater in kidney bean plants where 36-74% of the residues remained on the leaf surface 28 days after application of azinphos-methyl (Steffens and Wieneke, 1976). Azinphos-methyl has high affinity for the cuticle waxes and oils which may partially account for its poor absorption into plants (Anderson *et al.*, 1974).

G. ENVIRONMENTAL FATE (cont.)

The uptake and translocation of azinphos-methyl from a nutrient solution in young bean and barley plants was examined (Al-Adil *et al.*, 1973). The assimilation of azinphos-methyl by the roots and the translocation of the radiocarbon into the aerial parts of both plant species were most rapid during the first 24 hours period. On day 8, the majority of the residues (98%) was identified as the parent compound. Topical application to the stem and seed injection with azinphos-methyl also showed translocation of the residues throughout the plant system. After penetration into cotton, azinphos-methyl appears to translocate throughout the plant especially into the new growth and bolls (Chopade and Bosnak, 1988).

The major component of the residues in plants was the parent compound. In lettuce, kidney beans, potatoes, apples, and cotton, the parent compound was 56-99% of the total residues (Magill and Everett, 1966; Weineke and Steffens, 1976; Drager, 1987; Krolski, 1988a&b; Chopade and Bosnak, 1988). In sorghum and oranges, azinphos-methyl was also the predominant residue 28-30 days after treatment, but it represented only 12-25% of the total residues (Gronberg *et al.*, 1974 & 1975). Several metabolites common to sorghum, kidney bean plants, apples, and cotton were azinphos-methyl oxygen analog and benzazimide (Gronberg *et al.*, 1974; Weineke and Steffens, 1976; Krolski, 1988b; Chopade and Bosnak, 1988). Anthranilic acid was also identified in sorghum, oranges, potatoes, apples, and cotton (Gronberg *et al.*, 1974 & 1975; Krolski, 1988a&b; Chopade and Bosnak, 1988). Other minor metabolites included benzazimide (sorghum, oranges), methyl benzazimide (sorghum, kidney bean plant), bis-methyl benzazimide sulfide or disulfide (kidney bean plant), mercaptomethyl benzazimide (potatoes, cotton), cysteinylmethyl benzazimide, desmethyl isoazinphos-methyl, desmethyl azinphos-methyl oxygen analog, and desmethyl azinphos-methyl oxygen analog glucoside (cotton) (Gronberg *et al.*, 1974 & 1975; Weineke and Steffens, 1976; Krolski, 1988a; Chopade and Bosnak, 1988). The metabolic pathway appears to be similar in the various plant species, with the initial oxidation of azinphos-methyl to the oxygen analog, followed by hydrolysis and ultimately conjugation. The relative toxicity of these various plant metabolites is unknown except for benzazimide and methyl benzazimide which are discussed under the Acute Toxicity section of the Toxicology Profile in this document.

Increasing relative humidity and rain increased the uptake and metabolism of azinphos-methyl from bean plants, although the rain often removed residues on the surface of leaves depending on the intensity and time of rainfall (Steffens and Wieneke, 1975). Residues in food products decreased with washing, heating, and other processes. There was a 63-96% reduction of the azinphos-methyl in lemon and orange rind by normal washing procedures (Gunther *et al.*, 1963). When citrus rind was converted into dried citrus pulp cattle feed, more than 80% of the residue was removed in the process. Juice pressed from grapes subjected to heating removed about 65% of the azinphos-methyl residues (Anderson *et al.*, 1974).

Accumulation of Residues in Fish

Catfish exposed to azinphos-methyl had a relatively low magnitude of accumulation with a rapid rate of uptake and excretion (Lamb and Roney, 1976). The accumulation factor was approximately 60 during the last 21 days of the 28-day exposure. Azinphos-methyl and the des-methyl oxygen analog were found. Approximately 67% and 85% of the residues were excreted within 5 hours and four days, respectively, after exposure was discontinued.

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Oral Absorption

Azinphos-methyl, administered to rats, cattle and chickens by the oral route, was rapidly absorbed (Anderson *et al.*, 1974; Patzschke *et al.*, 1976; Kao, 1988; Everett *et al.*, 1966; Scheele *et al.*, 1977). Oral absorption appears to be nearly complete 2-6 hours post-dosing in these three species at which time the maximal blood concentrations are reached. The oral absorption rate was estimated to be 90-100%.

Dermal Absorption

The dermal absorption rate of azinphos-methyl in humans was approximately 16% based on a study with male volunteers (Feldman and Maibach, 1974). Radiolabeled azinphos-methyl was applied unoccluded in a 0.25% acetone solution to the forearms of one group, while another group was given the compound intravenously. Approximately 70% of the dose was excreted in the urine within 5 days after intravenous administration of azinphos-methyl. Only 16% was excreted in the urine when applied topically after correcting for the incomplete urinary excretion when administered intravenously.

Distribution

Forty-eight to 72 hours after oral administration of azinphos-methyl, less than 5% of the total dose remained in the tissues of rats (Patzschke *et al.*, 1976; Kao, 1988). The highest residue levels were in liver and kidneys of rats, cattle, goats, and chickens (Patzschke *et al.*, 1976; Kao, 1988; Everett *et al.*, 1966; Gronberg *et al.* 1988; Ridlen and Pfankuche, 1988). The residue levels in these highly perfused tissues may be related to the apparent binding of azinphos-methyl to hemoglobin (Patzschke *et al.*, 1976). With the exception of erythrocytes, there was a 10-fold decrease in tissue levels of rats from 6 to 48 hrs after application. There was no difference in the disposition and metabolism of azinphos-methyl between sexes of rats (Kao, 1988).

Biotransformation

The first evidence to suggest that azinphos-methyl required metabolic activation to produce its cholinergic effects was the marked differences in its anticholinesterase activity *in vitro* and *in vivo* (DuBois *et al.*, 1957a; Murphy and DuBois, 1957; March *et al.*, 1957; Dahm *et al.*, 1962). These studies indicated that its activation is rapid and occurs primarily in the microsomal fraction of liver. The active metabolite was identified as the oxygen analog of azinphos-methyl. The concentration of the oxygen analog required to inhibit 50% of rat brain cholinesterase *in vitro* was several orders of magnitude lower than of the parent compound (Dahm *et al.*, 1962). Subsequently, *in vitro* and *in vivo* experiments with mice and rats have shown that the metabolism of azinphos-methyl is primarily due to mixed function oxidases (MFOs) and glutathione (GSH)-transferases in the liver (Motoyama and Dauterman, 1972; Lin *et al.*, 1980; Kao, 1988). Oxidation of azinphos-methyl by MFOs resulted in the formation of azinphos-methyl oxygen analog, benzazimide, and a possible intermediate metabolite, mercaptomethylbenzazimide (Kao, 1988). Further methylation and oxidation of mercapto-methylbenzazimide generated methylthiomethylbenzazimide and its corresponding sulfoxide and sulfone. Metabolism of azinphos-methyl by GSH transferases resulted in the formation of

A. PHARMACOKINETICS (cont.)

desmethyl isoazinphos-methyl and glutathionyl methylbenzazimide. Further hydrolysis and oxidation led to the formation of cysteinylmethylbenzazimide and its corresponding sulfoxide and sulfone. Piperonyl butoxide administered 1 hr prior to azinphos-methyl inhibited its oxidative desulfuration and oxidative cleavage (Levine and Murphy, 1976). Detoxification of azinphos-methyl by glutathione conjugation increased with the inhibition of oxidative metabolism; however, no significant detoxification of the oxygen analog occurred by glutathione conjugation. The metabolism in cattle, goats, and chickens appear to be similar to rats (Everett *et al.*, 1966; Gronberg *et al.*, 1988; Ridlen and Pfankuche, 1988). The toxicity of the various metabolites is unknown except for benzazimide and methyl benzazimide whose LD_{50} values are at least an order of magnitude larger than the parent compound (see Acute Toxicity section).

The major metabolites in tissues of goats and chickens were identified. In goats, the major metabolites identified in liver, kidney, muscle, fat and milk were (in decreasing order of prevalence) methylthiomethylbenzazimide sulfone, methylbenzazimide-type protein conjugates and methylthiomethylbenzazimide sulfoxide (Gronberg *et al.*, 1988). In chickens, the major metabolites in liver, kidney, muscle, fat, and eggs were (in decreasing order of prevalence) benzazimide, methylthiomethylbenzazimide and its sulfoxide and/or sulfone, azinphos-methyl, and mercaptomethylbenzazimide protein or glucuronide conjugate (Ridlen and Pfankuche, 1988). The difference in metabolite patterns between these two species may be partly due to the difference in the time between the last dose and their sacrifice. The chickens were sacrificed only 2 hrs after their last dose whereas the goats were sacrificed 17-18 hrs after their last dose. One would expect that within a few hours of dosing some of the parent compound would not have been metabolized and many of the metabolites would not have been conjugated.

Metabolites found in the urine after oral administration in rats were cysteinylmethyl-benzazimide sulfoxide and sulfone, methylsulfonylmethylbenzazimide, methylsulfinylmethyl-benzazimide, glutathionyl methylbenzazimide, desmethyl isoazinphos-methyl, benzazimide, and cysteinylmethylbenzazimide (Ecker, 1976; Kao, 1988). The metabolites identified in feces were desmethyl isoazinphos-methyl, azinphos-methyl oxygen analog, methylsulfonylmethyl-benzazimide, cysteinylmethylbenzazimide sulfoxide, and methylthiomethylbenzazimide. No parent compound or its glucuronic or sulfate conjugates were found in urine or feces.

Excretion

Within 48 hours after rats and chickens were administered azinphos-methyl by the oral route, more than 90% of the total dose was eliminated in the excreta (Ecker, 1976; Patzschke *et al.*, 1976; Kao, 1988; Scheele *et al.*, 1977). The excretion in cattle was slower with only 52% of the applied dose excreted by 48 hrs, 40% in urine and 12% in feces (Everett *et al.*, 1966). In rats, 60-80% and 15-35% of the total dose was excreted in urine and feces, respectively, irrespective of the route of administration (Ecker, 1976; Kao, 1988). Less than 0.1% was eliminated from the lungs. In lactating cows and goats, less than 1% of the applied dose was excreted in milk (Everett *et al.*, 1977; Gronberg *et al.*, 1988).

The excretion of azinphos-methyl appears to fit a two compartment model based on its disappearance from tissues in rats (Patzschke *et al.*, 1976). The elimination half-life was approximately 10 hrs for the alpha-phase and 10 days for the beta-phase. The slower elimination phase may be due to the apparent binding of azinphos-methyl and/or its metabolites to hemoglobin.

A. PHARMACOKINETICS (cont.)

Benzazimide Metabolite

Weber *et al.* (1980) studied the pharmacokinetic behavior of the plant and animal metabolite, benzazimide, in rats. Greater than 95% of benzazimide administered orally was absorbed. More than 99% of the amount administered was excreted in the urine (54-66%) and feces (33-45%) within 48 hours. The elimination half-life for all tissues was approximately 4 days with the slowest elimination in blood and erythrocytes ($t_{1/2}$ = 11 days). The identification of metabolites, if any, was not attempted.

B. ACUTE TOXICITY

Systemic Effects

Acute toxicity of azinphos-methyl varies depending on species, sex, route, and formulation (Table 1-3). In rats, females tended to be more sensitive than males for all routes of exposure. It is less clear if there were sex differences for other species. The acute inhalation toxicity of azinphos-methyl is summarized in Table 1. The 1-hour LC_{50} values for the technical grade material were within an order magnitude (38 to 385 mg/m^3) except in one study which reported an LC_{50} greater than 17,560 mg/m^3 after a 1-hour, whole body exposure (Harris, 1976a). In a 4-hour inhalation study (head-only), all of the female rats at the lowest dose tested (80 mg/m^3 or 14.4 mg/kg)[1] exhibited several cholinergic signs (ocular and nasal discharge, salivation, hypoactivity, tremors, and/or twitching) (Shiotsuka, 1987). No mortalities occurred at this dosage. Red turbinates and lungs were observed at necropsy in several high-dose animals that died. An acute inhalation NOEL of 23 mg/m^3 (4.1 mg/kg)[2] was established in male rats exposed (whole body) for 4 hours to azinphos-methyl (Kimmerle, 1966). All of the males at the LOEL (59 mg/m^3) exhibited unspecified signs of toxicity. The one-hour LC_{50} values for formulations varied from 245 mg/m^3 in female rats exposed (head only) to a 50% wettable powder (Shiotsuka, 1986) to greater than 20,000 mg/m^3 in female rats and mice exposed (whole body) to a 2% dust (Crawford and Nelson, 1970b).

By the oral route, rats and dogs appear to be more susceptible to the acute toxicity of azinphos-methyl than guinea pigs (Table 2). The oral LD_{50} values for technical grade azinphos-methyl ranged from 4.4 mg/kg to 26 mg/kg for rats. The clinical signs observed with the technical grade material included tremors, twitching, convulsions, staggering gait, prostration, salivation, breathing difficulties, lethargy, and piloerection, all typical of ChE inhibition. The onset of signs was 5 to 20 minutes after dosing and usually lasted 1-2 days. There were no compound-related abnormalities observed in the one study that reported necropsy findings (Mihail, 1978). A NOEL could not be established in most studies either due to the dose levels being too high or insufficient information, but in one study a NOEL was established for rats at 1 mg/kg/day (Mihail, 1978). All of the animals (males and females) at the LOEL (2.5 mg/kg)

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[1] Assuming a female Sprague-Dawley rat weighs 204 kg and breathes 0.037 m^3 in 4 hours (U.S. EPA, 1988).

[2] Assuming a male Wistar rat weighs 215 g and breathes 0.0383 m^3 in 4 hours (U.S. EPA, 1988).

B. ACUTE TOXICITY (cont.)

Table 1. Summary of Acute Inhalation Toxicity for Azinphos-methyl

Species	Sex	LC_{50} (mg/m^3)	References[a]
		Technical Grade (86 - 90%)	
Rat	M	385 (1-hr, whole body)	1
	F	107 (1-hr, whole body)	2
	M/F	>17,560 (1-hr, whole body)	3
	M	152 (4-hr, whole body)	1
	M	155 (4 hr, head only)	4
	F	132 (4-hr, head only)	
Mouse	F	38 (1-hr, whole body)	2
		Wettable Powders (25-62.5%)	
Rat	M	200 - >5,000 (1-hr, whole body)	5-7
	F	169 - 4,000 (1-hr, whole body)	5-8
	M/F	>17,560 (1-hr, whole body)	9
	M	198 - 596 (4-hr, head or nose only)	7,10
	F	170 - 422 (4-hr, head or nose only)	7,10
		Liquid Concentrates (12.1-24%)	
Rat	F	475 (30-min, whole body)	11
	M	820 - 3,000 (1-hr, whole body)	12-16
	F	590 - >2,600 (1-hr, whole body)	12-16
Mouse	F	190 (1-hr, whole body)	11
	M	<2,000 (1-hr, whole body)	12
		Dust (2%)	
Rat	F	>20,000 (1-hr, whole body)	17
Mouse	F	>20,000 (1-hr, whole body)	

[a] References: 1. Kimmerle, 1966; 2. Doull and DuBois, 1956; 3. Harris, 1976a; 4. Shiotsuka, 1987; 5. Crawford and Anderson, 1970; 6. Cannon and Taylor, 1978; 7. Shiotsuka, 1986; 8. Nelson and Doull, 1967; 9. Harris, 1976b; 10. Warren, 1990; 11. DuBois, 1967; 12. DuBois and Kleeburg, 1970; DuBois and Kinoshita, 1970; 14. DuBois, 1970b; 15. Nelson, 1978c; 16. Cannon and Taylor, 1979; 17. Crawford and Nelson, 1970b.

exhibited unspecified cholinergic signs. The oral LD_{50}'s for formulations ranged from 14.8-101 mg/kg depending on the percent active ingredient and species. In addition to the clinical signs observed with the technical grade material, lacrimation, exophthalmos, clear and red nasal discharge, anorexia, vomiting, diarrhea, perianal stains, and alopecia were also observed. These signs are typical of ChE inhibitors and are probably due to the active ingredient.

The acute dermal toxicity of technical grade azinphos-methyl and various formulations is summarized in Table 3. The LD_{50} values for the technical grade material were fairly similar (72-250 mg/kg) except for one study which reported an LD_{50} of 2,500 to 5,000 (Mihail, 1978). The clinical signs observed were similar to those observed with the oral route, except that erythema was noted at the site of application. A NOEL was not established for the technical grade material in any of the studies. A LOEL of 63 mg/kg in female rats was reported (Heimann, 1982). There were no mortalities at the LOEL, but all females at the LOEL exhibited

B. ACUTE TOXICITY (cont.)

Table 2. Summary of Acute Oral Toxicity for Azinphos-methyl

Species	Sex	LD_{50} (mg/kg)	References[a]
		Technical Grade (88.9 - 99.0%)	
Rat	M	4.6 - 26	1-7
	F	4.4 - 24	2-9
Guinea pig	M	80	8
Dog	M	10	6
		Wettable Powders (35-62.5%)	
Rat	M	23.6 - 58	10-13
	F	14.8 - 58	10-14
		Liquid Concentrates (12.1-24%)	
Rat	M	37 - 101	15-19
	F	21 - 85	18-23
	M/F	37	24
Mouse		NR[b]	825
		Dusts (2%)	
Rat	F	>50	26

[a] References: 1. Hecht, 1955; 2. Gaines, 1960; 3. Crawford and Anderson, 1974; 4. Lamb and Anderson, 1974; 5. Pasquet *et al.*, 1976; 6. Mihail, 1978; 7. Heimann, 1982; 8. DuBois *et al.*, 1957a; 9. Nelson, 1968; 10. DuBois, 1970a; 11. Cooper *et al.*, 1978; 12. Nelson, 1979b; 13. Sheets, 1990a; 14. Bauman and Nelson, 1969; 15. DuBois, 1962a; 16. DuBois and Kinoshita, 1965c; 17. DuBois and Kinoshita, 1970; 18. Nelson, 1978a; 19. Nelson, 1979a; 20. DuBois, 1963; 21. Nelson and Bauman, 1968; 22. Nelson and Bauman, 1969; 23. DuBois, 1970b; 24. Lightowler and Gardner, 1978a; 25. Sato, 1959; 26. Crawford and Nelson, 1970a.

[b] NR = Not Reported

unspecified cholinergic signs. Possible compound-related gross lesions observed at necropsy in these studies were pulmonary emphysema, enlarged adrenal glands, dark liver, pale spleen, reddened renal medulla, and ulcers (Mihail, 1978; Heimann, 1982). The LD_{50} values for the formulations varied from 65 mg/kg in mice exposed to a 20% emulsifiable concentrate (Sato, 1959) to greater than 2,000 mg/kg in rats exposed to a 2% dust (Crawford and Nelson, 1970a) or a 35% wettable powder (Sheets, 1990b).

There are several reports of biochemical/histochemical changes in the liver after a single dose of azinphos-methyl. The effect of azinphos-methyl on liver glycogen is unclear. Murphy and Porter (1966) reported that liver glycogen levels increased 8 to 15-fold in rats after an intraperitoneal injection of azinphos-methyl at 3 mg/kg. El-Banhawy and El-Ganzuri (1986) reported marked depletion of liver glycogen in rats administered a single dose of azinphos-methyl orally at 6.5 mg/kg. The glycogen depletion in this study was based on the loss of glycogen inclusions in liver cells examined histologically. One explanation for the different findings may be the difference in the time at which the animals were sacrificed. El-Banhawy and El-Ganzuri sacrificed their animals 24 hrs after dosing whereas Murphy and Porter sacrificed their animals 5 hrs after dosing. El-Banhawy and El-Ganzuri (1986) also reported a disintegration and subsequent loss of lipoid inclusions in liver cells of rats given a single dose of

B. ACUTE TOXICITY (cont.)

Table 3. Summary of Acute Dermal Toxicity for Azinphos-methyl

Species	Sex	LD_{50} (mg/kg)	References[a]
		Technical Grade (88.9 - 99.0%)	
Rat	M	200 - 5,000	1-4
	F	72 - 5,000	1,3-5
		Wettable Powders (35-62.5%)	
Rat	M	816 - >2,000	6-8
	F	300 - >2,000	7-9
Rabbit	M	1,137	10
	F	1,147	
	M/F	1,780	11
		Liquid Concentrates (12.1-25%)	
Rat	M	322 - 475	12-13
	F	150 - >1,500	14-17
	M/F	325	18
Mouse	NR[b]	65	19
Rabbit	M	504 - >1,500	14,20
	F	568	20
		Dusts (2%)	
Rat	F	>2,000 mg/kg	21

[a] References: 1. Gaines, 1960; 2. Pasquet *et al.*, 1976; 3. Mihail, 1978; 4. Heimann, 1982; 5. Nelson, 1968; 6. DuBois and Kinoshita, 1970; 7. Sheets, 1990b; 8. DuBois, 1970a; 9. Nelson, 1967a; 10. Nelson, 1979c; 11. Seaman and Imlay, 1978; 12. DuBois and Murphy, 1956; 13. DuBois and Kinoshita, 1965c; 14. DuBois, 1963; 15. Nelson, 1967b; 16. Nelson and Bauman, 1968.; 17. Nelson and Bauman, 1969; 18. Lightowler and Gardner, 1978b; 19. Sato, 1959; 20. Nelson, 1978b; 21. Crawford and Nelson, 1970a.

[b] NR = Not Reported

azinphos-methyl at 6.5 mg/kg. Murphy and Porter (1966) reported an increase in liver alkaline phosphatase and tyrosine transaminase activities in the rats given a single dose of azinphos-methyl at 3 mg/kg. The toxicological significance of these findings is uncertain.

Local Effects

Technical grade azinphos-methyl caused only slight conjunctival redness in rabbits which cleared by 48 hrs (Table 4). The various formulations were more severe ocular irritants causing slight to severe conjunctival redness, very slight to moderate chemosis, slight to severe ocular discharge, slight to moderate corneal opacity, and slight iritis which cleared by day 7.

No dermal irritation was observed in rabbits exposed to technical grade azinphos-methyl; however, slight erythema was observed in humans after a 24 hour exposure (Table 5). The inert ingredients appear to be responsible for the dermal irritation (slight to moderate erythema and very slight to slight edema) observed with several formulations.

B. ACUTE TOXICITY (cont.)

Table 4. Summary of Eye Irritation Potential of Azinphos-methyl

Species	Sex	Results	References[a]
		Technical Grade (~92%)	
Rabbit	M/F	Slight Irritation	1-2
		Wettable Powders (25-50%)	
Rabbit	M/F	Slight-Moderate Irritation	3-6
		Liquid Concentrates (22%)	
Rabbit	M/F	Slight-Moderate Irritation	7-8

[a] References: 1. Thyssen, 1981; 2. Harris, 1976a; 3. Hixson, 1979; 4. Sheets, 1990c; 5. Seaman, 1978a; 6. Harris, 1976b; 7. Nelson, 1978d; 8. Knapp and Doyle, 1979a.

Table 5. Summary of Dermal Irritation Potential of Azinphos-methyl

Species	Sex	Results	References[a]
		Technical Grade (~92%)	
Rabbits	M/F	No irritation	1-2
Humans	NR[b]	Slight Irritation	3
		Wettable Powder (25-50%)	
Rabbits	M/F	No to Slight Irritation	4-7
		Liquid Concentrates (22%)	
Rabbits	M/F	Slight Irritation	8-9

[a] References: 1. Thyssen, 1981; 2. Harris, 1976a; 3. Hecht, 1955; 4. Hixson, 1979; 5. Sheets, 1990d; 6. Seaman, 1978b; 7. Harris, 1976b; 8. Nelson, 1978d; 9. Knapp and Doyle, 1979b.
[b] NR = Not Reported

Technical grade azinphos-methyl appears to be a weak to moderate dermal sensitizer using the Buehler patch test (Table 6). The sensitization response was variable with the formulations being the same or weaker than the technical grade material. In a modified Buehler's patch test, a 12.5% solution of azinphos-methyl was applied topically to male guinea pigs once a week for 3 weeks during the induction phase (Heiman, 1987). Two weeks later, they were challenged with a 6% solution. Six of 12 animals tested reacted positively to the challenge. Two weeks following the first challenge, the same animals were challenged a second time with a 0.6% solution. None of the animals reacted to the second challenge. This finding suggests that there may be a threshold for this response. The time between exposures may be another factor.

B. ACUTE TOXICITY (cont.)

Table 6. Summary of Dermal Sensitization Potential of Azinphos-methyl

Species	Sex	Results	References[a]
		Technical Grade (89-92%)	
Guinea Pig	M	Weak to Moderate Sensitization	1-2
		Wettable Powders (35-50%)	
Guinea Pig	M	No to Moderate Sensitization	3-4
		Liquid Concentrates (22%)	
Guinea Pig	M	No Sensitization	5

[a] References: 1. Porter *et al.*, 1987a; 2. Heimann, 1987; 3. Rosenfeld, 1984a; 4. Porter *et al.*, 1987b; 5. Rosenfeld, 1984b.

Metabolites - Benzazimide and Methyl Benzazimide

The acute toxicity of two metabolites of azinphos-methyl, benzazimide and methyl benzazimide, was evaluated (Crawford and Anderson, 1974; Lamb and Anderson, 1974). These metabolites are common in both plants and animals. The oral LD_{50} values for benzazimide ranged from 269 to 576 mg/kg in rats with females being slightly more susceptible than males. The oral LD_{50} for methyl benzazimide ranged from 330 to 524 mg/kg in rats with males and females being equally sensitive. The clinical signs observed with both metabolites were sedative in nature, including lethargy, sedation, dyspnea, and comatose. These signs and death were observed at doses as low as 200 mg/kg of benzazimide in female rats. The LOEL for methyl benzazimide was 250 mg/kg. A NOEL was not established for either benzazimide or methyl benzazimide.

Synergism

Synergism is sometimes observed when two organophosphate chemicals are given simultaneously. The combined acute toxicity of azinphos-methyl and certain organophosphates was additive, including EPN, methyl parathion, methiocarb, fenitrothion, and trichloronate (DuBois, 1956a; DuBois *et al.*, 1957b; DuBois and Raymund, 1961; DuBois and Kinoshita, 1963a & 1965a). The acute toxicity was less than additive when azinphos-methyl was combined with other organophosphates, such as malathion, demeton, parathion, fensulfothion and naftalofos (DuBois, 1956b&c; DuBois and Kinoshita, 1963b and 1965b). DuBois (1956c) suggested that the less than additive response was due to significantly different rates in the conversion of the chemicals to the active metabolite or the detoxification resulting in different times of peak cholinesterase inhibition. Evidence of a synergistic effect were found with several other organophosphates and azinphos-methyl, including ethion, crufomate, and trichlorfon (DuBois, 1962b; DuBois, 1958; McCollister *et al.*, 1968). For these combinations, the acute toxicity was 1.5 to 2.2 greater than expected. There was also evidence of synergism with another study in which azinphos-methyl was tested in combination with 21 other chemicals (Witherup and Schlecht, 1963). Interpretation of the findings from this finding was more difficult since the chemicals were only tested in combination at the LD_{01} level. Factorial analysis was used to determine if there were significant interactions between the chemicals. Seven

B. ACUTE TOXICITY (cont.)

chemicals, coumaphos, crotoxyphos, DDVP, diazinon, dicrotophos, disulfoton and ronnel, had significant interactions with azinphos-methyl indicating synergism. It was not possible with this method of analysis to determine the degree of synergism other than the level of significance. It was also not possible to determine if the interaction between the other chemicals (carbaryl, demeton, dimethoate, dioxathion, EPN, ethion, malathion, methyl parathion, mevinphos, OPMA, naled, parathion, phosphamidon, and trithion) was additive or less than additive.

Pretreatment with diethyl maleate, which depletes glutathione levels by conjugating with glutathione, enhanced the acute toxicity of azinphos-methyl in mice (Sultatos and Woods, 1988). On the other hand, these same investigators found that buthionine sulfoximine, a selective inhibitor of glutathione synthesis, did not affect the acute toxicity of azinphos-methyl. They concluded that glutathione conjugation is of minor importance in the detoxification of azinphos-methyl because these two chemicals had different effects on the acute toxicity. The investigators suggested that diethyl maleate may be enhancing the acute toxicity of azinphos-methyl through some other metabolic pathway.

C. SUBCHRONIC TOXICITY

Inhalation-Rat

Bayer AG, 1976: Ten SPF Wistar rats/sex/dose were exposed (whole body) to technical grade azinphos-methyl (purity not reported) at 0, 0.195, 1.24 or 4.72 mg/m^3 (0, 0.05, 0.32 or 1.26 mg/kg/day)[3] for 6 hrs/day, 5 days/wk for 12 weeks (Kimmerle, 1976). There was no effect on appearance, behavior, clinical chemistry, hematology, organ weights, gross pathological or histological findings. The mean body weights were reduced slightly (~8%) in males at 4.72 mg/m^3. The mean plasma and erythrocyte ChE were also reduced (52-93% of control activity) at 4.72 mg/m^3 in both sexes. There was no effect on brain ChE activity in either sex. In general, DPR does not consider plasma and erythrocyte ChE inhibition in the absence of clinical signs or symptoms an adverse effect because the ChEs in blood have no known physiological function. However, plasma and erythrocyte ChE inhibition are considered an indication of exposure. Based on the lack of significant findings, the NOEL was greater than or equal to 4.72 mg/m^3 (1.26 mg/kg/day), the highest dose tested. This study was unacceptable based on several major deficiencies including incomplete clinical chemistry and histopathological examination and no individual data.

Dietary-Rat

University of Chicago, 1956: Thirteen Sprague-Dawley rats/sex/dose were fed azinphos-methyl (25% wettable powder) in the diet at 0, 2, 5, or 20 ppm active ingredient (0, 0.2, 0.5 or 1.9 mg/kg/day)[4] for 16 weeks (Doull and Rehfuss, 1956). There was no effect on food consumption or gross and microscopic lesions. Male rats receiving 20 ppm had up to 20%

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[3] Using the average body weight from the study and assuming a Wistar rat breathes 0.05 m^3 in 6 hours (U.S. EPA, 1988).

[4] Estimated assuming a 235 g Sprague Dawley rat consumes 22 g of feed per day (U.S. EPA, 1988).

reduction in weight gain. After 16 weeks of treatment at 20 ppm, the mean ChE activity in brain, serum, and red blood cells was reduced (90, 70 and 60% of control activity, respectively). No ChE inhibition was observed in the 2 ppm or 5 ppm groups. Recovery of the ChE activity was observed in serum, brain and erythrocytes by 4, 10, and 20 days after the treatment was discontinued. The NOEL was determined to be 5 ppm (0.5 mg/kg/day) based on brain ChE inhibition and reduced weight gain. This study had major deficiencies including no analysis of the test article or diet, no hematology, no individual data and incomplete clinical chemistry and histopathology.

University of Chicago, 1957: In a subsequent study, 18 male Sprague-Dawley rats/dose were fed azinphos-methyl (25% wettable powder) in the diet at 0, 50 or 100 ppm active ingredient (0, 4.7 or 9.4 mg/kg/day)[4] for 16 weeks (Doull and Anido, 1957b). Marked symptoms of cholinergic stimulation including diarrhea, salivation, lacrimation, and muscular fasciculations were observed at both 50 and 100 ppm during the first 4 weeks of exposure (time of onset not reported). There were 8 and 10 deaths at 50 and 100 ppm, respectively. The first death occurred during week 4 at 100 ppm and week 6 at 50 ppm. A decrease in the mean weight gain (10-18%) was observed in both treatment groups. The mean ChE activity of the plasma, erythrocyte, and brains of rats at 50 and 100 ppm was reduced (37-61%, 27-29%, and 25-52% of control activity, respectively). There was no treatment-related changes in the macroscopic and microscopic findings. The NOEL was less than 50 ppm (4.7 mg/kg/day) based on the cholinergic signs, brain ChE inhibition and reduced weight gain. This study was also unacceptable due to major deficiencies (no females, no analysis of the test article or diet, no hematology, no individual data, and incomplete clinical chemistry and histopathology).

Capsule-Human

Franklin Hospital Foundation, 1972: Five male human volunteers/dose were given azinphos-methyl in capsules (corn oil vehicle) at doses between 1 and 20 mg/day (14 to 286 µg/kg/day for 70 kg person) for 30 days (Rider *et al.*, 1972). ChE activity was measured twice weekly during the exposure period. No plasma ChE inhibition was observed at doses up to 20 mg/day. No erythrocyte ChE inhibition was seen at doses up to 18 mg/day, but erratic inhibition was seen at 20 mg/day. However, the investigators did not consider the erythrocyte ChE inhibition at 20 mg/day sufficient to be an adverse effect. There was also no effect on clinical signs, hematology, prothrombin time, and urinalysis. Therefore, the NOEL was determined to be greater than or equal to 20 mg/day (286 µg/kg/day) based on plasma and erythrocyte ChE inhibition. Although there are no FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act) guidelines for conducting human studies, this study had several obvious deficiencies (insufficient information including no summary tables or individual data and inadequate exposure period).

Dermal-Rabbit

Bayer AG, 1980: Azinphos-methyl (94.1% purity) was applied with a Cremophor EL and water vehicle to the shaved backs and flanks of 6 New Zealand rabbits/sex/dose at 0, 2 or 20 mg/kg and left uncovered in place for 6 hrs/day, 5 days/wk for 3 weeks (Flucke and Schilde, 1980). An additional 3 rabbits/sex/dose had their skin abraded before being exposed. No significant differences in clinical signs, body weights, clinical chemistry, hematology, urinalysis, organ weights, gross pathological or histological findings (including local effects) were found. A slight to moderate reduction in the mean erythrocyte ChE activity (62-77% of control activity)

C. SUBCHRONIC TOXICITY (cont.)

was seen at study termination. There was no effect on plasma or brain ChE activity. The NOEL was greater than or equal to 20 mg/kg, the highest dose tested. This study had several major deficiencies, including too few dose levels and no overt toxicity at the highest dose, and incomplete individual data.

D. CHRONIC TOXICITY/ONCOGENICITY

Dietary-Mouse

Gulf South Research Institute, 1978: Azinphos-methyl (90%) was administered to 50 male B6C3F1 mice/dose at 31.3 or 62.5 ppm (5.4 and 10.8 mg/kg/day)[5] and to 50 female B6C3F1 mice/dose at 62.5 and 125 ppm (10.8 and 21.5 mg/kg/day) for 80 weeks (NCI, 1978). Ten mice/sex were used as controls. The animals were observed for another 12-13 weeks after dosing stopped, then sacrificed. The body weights were reduced in females at 125 ppm. Several treatment-related clinical signs were observed intermittently during the second year of the study including rough hair coat (males at 31.3 and 62.5 ppm), hyperactivity (females at 62.5 and 125 ppm), and convulsions (one male at 62.5 ppm and one female 125 ppm). The only apparent dose-related increase in non-neoplastic lesions was in the incidence of cystic endometrial hyperplasia in females (2/7, 32/48, 32/48 or 29%, 67%, 67%, respectively). There was a increase in the combined incidence of hepatocellular adenomas and carcinomas in male mice at 62.5 ppm (2/8, 11/49, 19/50 or 25%, 22%, 38%, respectively). The NOEL was less than 31.3 ppm (5.4 mg/kg/day) based on the clinical signs in both sexes and cystic endometrial hyperplasia in females. This study was unacceptable to DPR due to major deficiencies (no individual data, inadequate number of concurrent control animals, and too few dose levels).

Mobay Chemical Corp., 1985: An oncogenicity study was conducted in which 50 CD1 mice/sex/dose were fed azinphos-methyl (86.7%) in the diet at 0 (corn oil), 5, 20, or 40 ppm (0, 0.9, 3.8 or 12.8 mg/kg/day) for 104 weeks (Hayes, 1985). No significant compound-related effects were seen in feed consumption, body weight, organ weight, clinical signs, mortality, hematology, and incidence of gross and histopathological lesions. At the study termination, the mean plasma, erythrocyte, and brain ChE activity were markedly reduced (33-44, 37-41 and 33-37% of control activity, respectively) in the 40 ppm animals. In the 20 ppm mice, the mean plasma, erythrocyte, and brain ChE activity were also slightly reduced (69-76, 51-57% or 74-85% of control activity, respectively). There was only very slight reduction in the mean plasma, erythrocyte, and brain ChE activity at 5 ppm (84-91%, 84-99%, and 88-89% of controls, respectively). No statistical analysis was performed on the cholinesterase data; however, the investigators concluded that the ChE inhibition at 5 ppm was not biologically significant. Therefore, the NOEL was established at 5 ppm (0.9 mg/kg/day) based on the brain ChE inhibition. DPR considered this study acceptable based on FIFRA guidelines.

Dietary-Rat

Huntington Research Centre, 1966: In a study conducted by Lorke (1966a) azinphos-methyl (purity not reported) was administered to 40 Wistar derived rats/sex/dose at 0, 5, 20, or

[5] Estimated assuming a 36 g B6C3F1 mouse consumes 6.2 g feed per day (U.S. EPA, 1988).

D. CHRONIC TOXICITY/ONCOGENICITY (cont.)

50 ppm (increased to 100 ppm at 45 weeks) (0, 0.2, 1.0 or 3.6 mg/kg/day) in the diet for 97 weeks. A low dose of 2.5 ppm (0.1 mg/kg/day) was started 6 months into the study with its own controls. At 50→100 ppm convulsions were observed in several females 7 weeks after the dose level was increased to 100 ppm. There was no effect on growth, food consumption, food utilization, hematology, urinalysis, macroscopic or microscopic findings at any dose level. At the end of the study, the mean plasma ChE activities was slightly depressed (82-90% of control activity) in the 20 ppm group. In the 50→100 ppm animals, the mean plasma, erythrocyte and brain ChE activity were reduced (70-76%, 67%, and 51-81% of control activity, respectively). The NOEL was 20 ppm (1.0 mg/kg/day) based on the convulsions and brain ChE inhibition. DPR found this study unacceptable due to major deficiencies including no analysis of the test article or diet, limited pathology and clinical chemistry, and high mortality rate in all groups (55-85%).

Gulf South Research Institute, 1978: Azinphos-methyl (90%) was administered to 50 Osborne-Mendel rats/sex in the diet at 78 or 156 ppm (5.7 or 11.4 mg/kg/day)[6] to males and at 62.5 or 125 ppm (4.6 or 9.2 mg/kg/day) to females for 80 weeks (NCI, 1978). Ten rats/sex were used as concurrent controls. The animals were observed for another 34-35 weeks after dosing stopped, then sacrificed. Reduced body weights were observed in males at 78 and 156 ppm and in females only at 125 ppm. Tremors were observed in males at 156 ppm and in females at 125 ppm after the first week. At week 34, exophthalmos (which progressed to unilateral or bilateral blindness) was observed in 15 females at 125 ppm.

There were no treatment-related increases in non-neoplastic lesions; however, the incidence of pancreatic tumors (islet cell adenoma or adenocarcinoma), thyroid follicular cell tumors (adenoma, adenocarcinoma, follicular cell adenoma, cystadenoma, cystadeno-carcinoma, papillary cystadenocarcinoma), and adrenal tumors (cortical adenoma or adenocarcinoma) in males was increased at 156 ppm (Table 7). Because there were so few animals in the concurrent control group, the investigators "pooled" control rats of the same strain from several other bioassays from this laboratory to perform their statistical analysis of the tumor incidence. When compared to concurrent controls, the incidence of these tumors were not statistically significant by the Fisher's exact test. However, when compared to "pooled" or historical controls, the incidence of these tumors was significantly higher. Using concurrent controls, slightly significant trends were found only with the combined incidence of pancreatic islet-cell tumors and with the incidence of thyroid cystadenoma. With pooled controls, highly significant trends were found with the combined incidences of pancreas tumors, thyroid follicular-cell tumors, and adrenal tumors. The investigators reported that the historical control range for thyroid follicular-cell tumors was between 0 and 43% with a mean of 7% for male Osborne-Mendel rats at this laboratory. Therefore, they concluded that the increase in thyroid tumors was not clearly treatment-related. The apparent NOEL for this study was less than 78 ppm (5.7 mg/kg/day) based on the reduced body weights in males. DPR found this study unacceptable due to the lack of individual data, use of pooled control data, and the exposure for only 80 weeks at two dose levels.

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[6] Estimated assuming a 450 g Osborne-Mendel rat consumes 33 g of feed per day (U.S. EPA, 1988).

Table 7. Incidence of Neoplastic Lesions in Male Rats Fed Azinphos-Methyl for 80 Weeks[a]

	Dose Level (ppm)[b]			
	Pooled Controls	Concurrent Controls	78	156
Pancreas				
Islet-cell adenoma	2/92^{+} (2%)	0/9 (0%)	1/47 (2%)	4/45 (9%)
Islet-cell carcinoma		0/9 (0%)	0/47 (0%)	2/45 (4%)
Combined	2/92^{++} (2%)	0/9^{+} (0%)	1/47 (2%)	6/45* (13%)
Thyroid				
Cystadenoma		0/9^{+} (0%)	7/44 (16%)	10/43 (23%)
Combined - cystadenoma, follicular-cell adenoma or adenoma	7/86^{++} (8%)	1/9 (11%)	10/44* (23%)	12/43** (28%)
Adenocarcinoma		0/9 (0%)	3/44 (7%)	3/43 (7%)
Combined - adenocarcinoma, cystadenocarcinoma or papillary cystadenocarcinoma	0/86^{++} (0%)	0/9 (0%)	4/44* (9%)	4/43* (9%)
Combined - all follicular-cell tumors	7/86^{+++} (8%)	1/9 (11%)	14/44*** (32%)	14/43*** (33%)
Adrenal Glands				
Adenocarcinoma	0/95^{++} (0%)	0/9 (0%)	1/45 (2%)	3/46* (7%)
Cortical adenoma		1/9 (11%)	3/45 (7%)	7/46 (15%)
Combined	3/95^{+++} (3%)	1/9 (11%)	4/45 (9%)	10/46*** (22%)

[a] The denominator is the number of animals examined; the number in parentheses represents the incidence in percentage.

[b] The test compound intake was estimated to be 5.7 and 11.4 mg/kg/day for 78 and 156 ppm, respectively, assuming a 450 g Osborne-Mendel rat consumes 33 g of feed per day (U.S. EPA, 1988).

$^{+}$, $^{++}$, $^{+++}$ Significant trend based on a dose-weighted chi-square test at $p < 0.05$, 0.01 and 0.001, respectively (Peto *et al.*, 1980).

*, **, *** Significantly different from the pooled control group based on the Fisher's exact test at $p < 0.05$, 0.01, 0.001, respectively.

D. CHRONIC TOXICITY/ONCOGENICITY (cont.)

Bayer AG, 1984: Groups of 60 SPF Wistar rats/sex/group were fed azinphos-methyl (87.2%) in the diet at 0 (vehicle = 1% peanut oil), 5, 15 or 45 ppm (0, 0.28, 0.86 or 2.72 mg/kg/day) for 104 weeks (Schmidt and Chevalier, 1984). Ten rats/sex/group were sacrificed at 12 months. The only compound-related clinical sign was an increased incidence of alopecia at 45 ppm after 4 weeks (M: 8, 4, 5, 15; F: 18, 22, 26, 49). The mean body weights of males at 45 ppm were significantly reduced (up to 10%). Feed consumption was slightly increased in the females at 45 ppm (~10%). There were no treatment-related effects on survival rate, clinical chemistry, hematology, urinalysis, gross pathology, and histopathology. At week 104, the mean plasma ChE activity was reduced (81-88 and 38-51% of control activity, respectively) at 15 and 45 ppm. The mean erythrocyte ChE activity was also reduced to approximately 78-84 and 63-71% of control activity, respectively, at 15 and 45 ppm. The mean brain ChE activity was reduced to 45-68% of control activity in both sexes at 45 ppm and to 79% of control activity in females at 15 ppm. The NOEL was 5 ppm (0.28 mg/kg/day) based on the brain ChE inhibition in females. This study was acceptable to DPR.

Dietary-Dog

Huntington Research Centre, 1966: Four cocker spaniel dogs/sex/dose were fed azinphos-methyl (purity not reported) in the diet at 0, 5, 20, 50 ppm for two years (Lorke, 1966b). The high dose level was raised from 50 to 300 ppm in 4 steps (time-weighted average ~ 4.3 mg/kg/day). The intermediate dose level was raised from 20 to 50 ppm in 2 steps (time-weighted average ~ 1.3 mg/kg/day) and the lowest dose level was kept at 5 ppm (~ 0.2 mg/kg/day). Within one week after increasing the high dose level to 300 ppm, the dogs in this group exhibited tremors, muscular weakness, inactivity, and abnormal sitting posture. One male died during week 94 after receiving 300 ppm in the diet for 9 weeks. This dog had ataxia, lacrimation, increased respiratory rate, labored breathing, myosis, vomiting, and jaundice the week before it died. The necropsy of this dog revealed that the gallbladder and common bile duct were grossly distended, but not obstructed. The liver was congested, but otherwise normal in appearance. Although the death of this dog was attributed to cholangitis, investigators did not consider the cholangitis treatment-related since the only other hepatic abnormalities in the other dogs were an occasional focus of cellular infiltration. There was a slight reduction in the mean body weights (~5-15%) at 300 ppm and in the mean food consumption (6-10%) at 150→300 ppm. The mean plasma and erythrocyte ChE activities were significantly reduced (52-84% and 17-71% of control activity, respectively) at 20→50 ppm and 50→300 ppm. Brain ChE activity was not measured. There were no treatment-related changes in the hematology, clinical chemistry, urinalysis, macroscopic or microscopic lesions. The apparent NOEL was 20→50 ppm (~1.3 mg/kg/day) based on the death, clinical signs, and reduced body weight and food consumption. DPR found this study unacceptable due to major deficiencies including incomplete reporting of data, no analysis of test article and diet, and frequent dose level changes.

Research and Consulting Company AG, 1990: In another chronic study, 4 beagle dogs/sex/group were fed azinphos-methyl (91.9%) in the diet at 0, 5, 25 or 125 ppm (0, 0.2, 0.7 or 4.1 mg/kg/day) for 52 weeks (Allen, 1990). There was no dose-related difference in the number of dogs exhibiting clinical signs during the study. Although the number of dogs with diarrhea and mucus in feces did not exhibit a clear dose-relationship, the frequency of these signs appeared to be dose-related (Table 8). The frequency of diarrhea increased noticeably after the first month, especially in the females at 125 ppm, and remained fairly constant through

Table 8. Frequency of Diarrhea and Mucus in the Feces in Dogs Fed Azinphos-Methyl for 52 Weeks

	Dose Level (ppm)[b]			
	0	5	25	125
	MALES			
Diarrhea	9[b+] (4/4)[c]	5 (3/4)	71*** (4/4)	30*** (3/4)
Mucus in Feces	1[+++] (1/4)	0 (0/4)	22*** (4/4)	32*** (3/4)
	FEMALES			
Diarrhea	58[+++] (3/4)	40 (4/4)	44 (4/4)	268*** (4/4)
Mucus in Feces	75[+] (4/4)	9 (4/4)	18 (2/4)	56 (4/4)

[a] Actual average test compound intake 0.2, 0.7 and 4.1 for 5, 25, and 25 ppm, respectively.
[b] Total number occurrences of this sign during a total possible 1460 observations (4 dogs x 365 days).
[c] Number of dogs exhibiting this sign at any time during the study.
[+], [+++] Significant trend based on a dose-weighted chi-square test at $p < 0.05$ and 0.001, respectively.
*** Significantly difference from the control group based on the Fisher's exact test at $p < 0.001$.

the remainder of the study with some periodic decreases. The frequency of diarrhea in males at 25 ppm and in both sexes at 125 ppm was highly significant by pair-wise comparison with controls; however, the trend in males was only slightly significant because the frequency decreased from 25 to 125 ppm. At week 52, the mean plasma, erythrocyte, and brain ChE activity were significantly reduced in both sexes at 125 ppm (47, 14%, and 73-80% of control activity, respectively). The mean erythrocyte ChE activity was also lower (65-73% of control activity) in both sexes at 25 ppm, although the reduction was only statistically significant for females. Based on only a slight ChE inhibition in erythrocytes at 25 ppm in males and the erratic dose-response in males, it is unclear if the diarrhea and mucus in the feces are cholinergic signs, especially at 25 ppm. On the other hand, the sharp increase in the frequency of diarrhea in the females at 125 ppm suggests that it is treatment-related at this dose level, especially considering the significant brain ChE inhibition. The toxicological significance of the diarrhea at 125 ppm is also supported by a range-finding study where more overt cholinergic signs (muscle spasms and tremors) were seen in dogs fed azinphos-methyl at 100 ppm for 19 weeks (Löser and Lorke, 1967). The mean activity of liver cytochrome P-450 was significantly higher (39%) at 125 ppm in the males. The mean activities of N-demethylase were also higher (30-34%) in both sexes at 125 ppm, but the differences were not statistically significant. Males at 125 ppm had slightly lower mean plasma albumin levels (7-13%). The mean liver and spleen weights were lower in males at all dose levels (14-21% and 30-65%, respectively). The mean kidney weights were lower in males at 125 ppm (17%). The toxicological significance of the

D. CHRONIC TOXICITY/ONCOGENICITY (cont.)

changes in enzyme activities and organ weights is uncertain given there were no accompanying histological changes. Furthermore, the liver and kidney weights were not significantly different from the controls when compared relative to their body weights. There was no compound-related effect on mortality, body weight, food consumption, hearing, ophthalmology, hematology, urinalysis, macroscopic or microscopic observations. The NOEL was 25 ppm (0.7 mg/kg/day) based on the diarrhea and brain ChE inhibition. This was considered an acceptable study by DPR.

E. GENOTOXICITY

Gene Mutation

The results from only one *in vivo* gene mutation assay for azinphos-methyl was available for evaluation (Table 9). This study, a sex-linked recessive lethal assay with *Drosophila melanogaster*, was conducted for the U.S. EPA under contract (Valencia, 1981). There was no evidence of a mutagenic effect based on the percentage of cultures in the F_2 generation without wild-type males.

Numerous *in vitro* gene mutation assays have been conducted for azinphos-methyl including both forward and reverse mutation assays (Table 9). No significant increase in the mutation frequency was observed in a reverse mutation assay (Ames assay) in which *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to azinphos-methyl (92.3%) at concentrations up to 2,500 µg/plate (Herbold, 1978). This assay was unacceptable to DPR due to several deficiencies, including no individual data, no positive controls that did not require metabolic activation, and no justification of dose levels. Similar results were obtained when this same investigator repeated this assay with the same strains exposed to azinphos-methyl (92.5%) up to 9,600 µg/plate with and without metabolic activation (Herbold, 1988). This assay was considered acceptable by DPR. In another acceptable Ames assay, azinphos-methyl (88.8%) was tested at concentrations up to 4,000 µg/plate using TA98, TA100, TA1535, TA1537, and TA1538 strains with and without metabolic activation (Lawlor, 1987). No mutagenic response was clearly identified, although an equivocal response was observed for TA100. This study was acceptable to DPR. The results were also negative in three published reports of Ames assays for azinphos-methyl (Simmon, 1976: TA100, TA1535, TA1537, TA1538; Garrett *et al.*, 1986: TA1537, TA98, TA100; Carere *et al.*, 1978: TA1535, TA1536, TA1537, TA1538). There was one published report of a weak mutagenic response using TA98 with activation (Zeiger *et al.*, 1987). However, the increase in mutation frequency was only observed at 3,333 µg/plate and above where precipitation occurred, confounding the results. A registrant also submitted a reverse mutation assay using *Saccharomyces cerevisiae* strains S128 and S211a (Hoorn, 1983). The results from this assay were negative, but this study was unacceptable to DPR based on an inadequate description of methods and materials.

There are also several published reports of forward mutation assays for azinphos-methyl. The results from the L5178Y TK+/- mouse lymphoma forward mutation assay were positive without metabolic activation (Garrett *et al.*, 1986). Azinphos-methyl was not tested in this system with metabolic activation. A forward mutation assay with *Streptomyces coelicolor* was negative (Carere *et al.*, 1978). The findings in two reports from the same laboratory using a forward mutation assay with *Schizosaccharomyces pombe* ade6 were inconsistent. Degraeve and coworkers (1980) reported negative results; however, Gilot-Delhalle and

Table 9. The Effects of Azinphos-methyl on Gene Mutation

Test Type/System	Strain	Dose	S9	Results	Comments/Reference
		In Vivo			
Sex-linked recessive lethal	*Drosophila melanogaster*	0, 0.25, 0.5, 1.0 ppm	NA	Neg	U.S. EPA document (Valencia, 1981)
		In Vitro - Reverse Mutation			
S. typhimurium	TA98, TA100, TA1535, TA1537	0, 75, 150, 300, 600, 1200, 2400, 4800, 9600 µg/plate	±	Neg	Acceptable (Herbold, 1988)
S. typhimurium	TA98, TA100, TA1535, TA1537, TA1538	0, 33, 100, 333, 1000, 2000, 4000 µg/plate	±	Neg	Acceptable; Equivocal effect with TA100±S9 (Lawlor, 1987)
S. typhimurium	TA100, TA1535, TA1537, TA1538	**Not Reported**	±	Neg	Published article (Simmon, 1976)
S. typhimurium	TA98, TA100, TA1537	Up to 1000 µg/plate	±	Neg	Published article (Garrett *et al.*, 1986)
S. typhimurium	TA1535, TA1536, TA1537, TA1538	**Not reported**	**NR**	Neg	Published article (Carere *et al.*, 1978)
S. typhimurium	TA98, TA100, TA1535, TA1537	0, 100, 333, 1000, 3333, 10000 µg/plate	±	Pos	Published article; weakly positive with TA98+S9 (Zeiger *et al.*, 1987
Saccharomyces cerevisiae	S128, S211a	0, 33, 100, 333, 1000, 3333, 10000 µg/plate	±	Neg	Unacceptable (Hoorn, 1983)

S9 = Supernatant from rat liver homogenates centrifuged at 9,000 x g which contain enzymes for metabolic activation.
NA = Not applicable
NR = Not reported

Table 9 (cont.). The Effects of Azinphos-methyl on Gene Mutation

Test Type/System	Strain	Dose	S9	Results	Comments/Reference
		In Vitro - Forward Mutation			
Mouse lymphoma	L5178Y Tk+/-	Up to 1,000 µg/ml	-	Pos	Published article (Garrett et al., 1986)
Streptomyces coelicolor	A3(2), hisAI	**Not reported**	**NR**	Neg	Published article (Carere *et al.*, 1978)
Schizosacchromyces pombe	ade6	**Not reported**	±	Neg	Published abstract (Degraeve *et al.*, 1980)
S. pombe	ade6	3-95 mM	±	Pos	Published article; positive response without S9 only (Gilot-Delhalle *et al.*, 1983)

S9 = Supernatant from rat liver homogenates centrifuged at 9,000 x g which contain enzymes for metabolic activation.
NR = Not reported

E. GENOTOXICITY (cont.)

coworkers (1983) reported positive results without metabolic activation. The differences in the findings are difficult to interpret since few details were given in the earlier report. Both appear to have tested azinphos-methyl with and without metabolic activation. The concentrations tested were not reported in the earlier study.

Structural Chromosome Aberrations

All the *in vivo* tests for structural chromosome aberrations were negative (Table 10a). In one of two dominant lethal assays submitted by registrants, 12 male albino mice/dose were administered azinphos-methyl (purity not reported) intraperitoneally at 0, 125 or 250 µg/kg (Arnold, 1971). This study was considered invalid by the registrant and unacceptable to DPR due to insufficient information. In the second dominant lethal assay, 50 male NMRI mice were administered azinphos-methyl (92.3%) by oral gavage at 0 and 4 mg/kg (Herbold, 1979a). DPR also found this study unacceptable due to insufficient information, only one dose level tested, and no positive control tested. Published reports of two dominant lethal assays for azinphos-methyl in mice were also negative (Degraeve *et al.*, 1986; Garrett *et al.*, 1986). In a micronucleus assay, 5 NMRI mice/sex/dose were administered azinphos-methyl (92.3%) by gavage at 0, 1.25, 2.5 or 5 mg/kg in 2 doses 24 hrs apart and sacrificed 6 hours later (Herbold, 1979b). This study was unacceptable to DPR due to major deficiencies (no pilot study data, no clinical observations or pathology on the animal that died, no signs of toxicity at the high dose). A published report of micronucleus assay in mouse bone marrow was also negative (Garrett *et al.*, 1986). In addition, two other published *in vivo* tests for structural chromosome aberrations were negative, including a cytogenetics test using mice (Q strain) spermatocytes and bone marrow cells (Degraeve *et al.*, 1986) and a sister chromatid exchange assay using central mudminnows, *Umbra limi* (Vigfusson *et al.*, 1983).

There are several reports of positive results for structural chromosome aberrations *in vitro* (Table 10b). In a study submitted by a registrant, an increase in chromosome aberrations (except gaps) was observed in human lymphocytes exposed to azinphos-methyl (91.9%) at 500 µg/ml with activation (Herbold, 1986). There was no increase in aberrations at any concentration without activation. This study was acceptable to DPR. There are three published reports of cytogenetic tests which were also positive. In one study conducted by Alam and coworkers (1974), Chinese hamster cells (CHO-Kl) were exposed to azinphos-methyl (90%) at concentrations of 60 to 120 µg/ml. In another study from the same laboratory, two human cell lines (WI-38 and HEp-2) were exposed to azinphos-methyl (90%) at 120 to 160 µg/ml (Alam and Kasatiya, 1976). Trépanier and coworkers (1977) exposed cells from a human lymphoblastoid cell line (L-MOORE) at 60 µg/ml. In all three studies, the most common chromosome aberrations were chromatid breaks and exchanges. The four published reports of *in vitro* sister chromatid exchange assays were all negative including one using Chinese hamster ovary cells (Garrett *et al.*, 1986) and three using in Chinese hamster V79 cells (Chen *et al.*, 1982a&b; Nicholas and Van Den Berghe, 1982).

Degraeve and coworkers (1985) investigated the synergism of chromosomal damage by azinphos-methyl when given in combination with trichlorfon. Twenty-five male mice (Q strain) were given two consecutive intraperitoneal injections of trichlorfon at 50 mg/kg and azinphos-methyl at 0.5 mg/kg. No increase in chromosomal damage was observed in bone marrow cells, spermatogonia or primary spermatocytes. The frequency of post-implantation losses was also not increased in a dominant lethal assay using 5 of the 25 treated male mice; however, there

Table 10a. The Effects of Azinphos-methyl on Chromosomal Aberrations - In Vivo Assays

Test Type/System	Strain	Dose	S9	Results	Comments/Reference
Dominant lethal	Albino mice	0, 125, 250 µg/kg	NA	Neg	Unacceptable (Arnold, 1971)
Dominant lethal	NMRI mice	0, 4 mg/kg	NA	Neg	Unacceptable (Herbold, 1979a)
Dominant lethal	Q strain mice	1 mg/kg	NA	Neg	Published article (Degraeve *et al.*, 1986)
Dominant lethal	Mice, strain not reported	Up to 100 mg/kg	NA	Neg	Published article (Garrett *et al.*, 1986)
Micronucleus	NMRI mice, bone marrow	0, 1.25, 2.5, 5 mg/kg	NA	Neg	Unacceptable (Herbold, 1979b)
Micronucleus	Mice, bone marrow	Up to 10 mg/kg	NA	Neg	Published article (Garrett *et al.*, 1986)
Cytogenetic	Q strain mice, spermatocytes and bone marrow	1 mg/kg	NA	Neg	Published article (Degraeve *et al.*, 1986)
Sister chromatid exchange	Central mudminnows, *Umbra limi*	0, 0.54 & 5.4 x 10^{-10} M	NA	Neg	Published article (Vigfusson *et al.*, 1983)

S9 = Supernatant from rat liver homogenates centrifuged at 9,000 x g which contain enzymes for metabolic activation.
NA = Not applicable

Table 10b. The Effects of Azinphos-methyl on Chromosomal Aberrations - In Vitro Assays

Test Type/System	Strain	Dose	S9	Results	Comments/Reference
Cytogenetic	Human lymphocytes	500 µg/ml	±	Pos	Acceptable; positive with S9 only (Herbold, 1986)
Cytogenetic	CHO-K1 cell line	60, 80, 100, 120 µg/ml	**NR**	Pos	Published article (Alam *et al.*, 1974)
Cytogenetic	Human WI-38 & HEp-2 cell lines	120, 140, 160 µg/ml	**NR**	Pos	Published article (Alam & Kasatiya, 1976)
Cytogenetic	Human lymphoblastoid cell line (L-MOORE)	60 µg/ml	**NR**	Pos	Published abstract (Trépanier *et al.*, 1977)
Sister chromatid exchange	Chinese hamster ovary cells	Up to 100 µg/ml	±	Neg	Published article (Garrett *et al.*, 1986)
Sister chromatid exchange	Chinese hamster V79 cell line	0, 2.5, 5, 10, 20 µg/ml	-	Neg	Published article (Chen *et al.*, 1982a)
Sister chromatid exchange	Chinese hamster V79 cell line	0, 5, 10, 20, 25 µg/ml	+	Neg	Published article (Chen *et al.*, 1982b)
Sister chromatid exchange	Chinese hamster V79 cell line	Up to 60 µM	**NR**	Neg	Published article (Nicholas & Van Den Berghe, 1982)

S9 = Supernatant from rat liver homogenates centrifuged at 9,000 x g which contain enzymes for metabolic activation.
NR = Not reported

E. GENOTOXICITY (cont.)

was an increase in pre-implantation losses during the fourth week of mating which the investigators attributed to the toxic effects of the compounds on the male germ cells.

Other Genotoxic Effects

Numerous tests for other genotoxic effects were also conducted for azinphos-methyl (Table 11). In a study submitted by a registrant, primary rat hepatocytes did not show an increase in the unscheduled DNA synthesis (UDS) when incubated with technical azinphos-methyl (91.1%) at up to 10.1 µg/ml (Myhr and Brusick, 1983). DPR found this study acceptable. Garret and coworkers (1986) also reported negative results from a UDS assay with human lung fibroblasts (WI-38).

There was no evidence of DNA damage in two differential toxicity tests. In a study submitted by the registrant, two *E. coli* pol strains, (K12)p 3478 (repair deficient) and W 3110 were exposed to azinphos-methyl (91.1%) at concentrations up to 10,000 µg/plate (Herbold, 1984). However, this study was unacceptable to DPR due to several deficiencies (no individual plate counts, inadequate description of protocol). In a published report by Garret and coworkers (1986), a differential toxicity test with *S. typhimurium* uvrB, rec was also negative.

The results for mitotic recombination, gene crossing-over, and gene non-disjunction from various published reports were inconsistent. Garrett and coworkers (1986) reported positive results for azinphos-methyl using the mitotic recombination assay with *S. cerevisiae* D3 at 10 mg/ml or higher. However, Riccio and coworkers (1981) reported negative results for mitotic recombination with *S. cerevisiae* D3. They also reported negative results for gene conversion, crossing-over, and reverse mutation with *S. cerevisiae* D7. There was no agreement in similar assays using *Aspergillus nidulans* D7. Morpurgo and coworkers (1977) reported negative results for point mutations, crossing-over, and non-disjunction. However, Vallini and coworkers (1983) reported positive results for crossing-over and non-disjunction at 30mM. There was a decrease in the response at the higher concentration which the investigators attributed to the growth stimulation effect of the phosphorus in azinphos-methyl on the fungi.

Summary

Azinphos-methyl appears to be genotoxic based on positive results in a mouse lymphoma assay and four *in vitro* cytogenetic assays with human cells or cell lines (primary lymphocytes, WI-38, HEp-2, and L-MOORE cell lines) or Chinese hamster cell line (CHO-K1). However, all of the *in vivo* cytogenetic assays (2 micronucleus assays and 1 cytogenetic assay in mice) were negative. All other tests for chromosomal aberrations, including sister chromatid exchange assays and dominant lethal assays, were negative. Furthermore, most of the reverse mutation assays with *Salmonella typhimurium* were negative except for an equivocal response with TA100 in one assay and a weak positive response in another assay with TA98. The weak positive response was only observed at concentrations (3,333 µg/plate and higher) where precipitation occurred, confounding the results. Negative results were reported for all of the other gene mutation tests and miscellaneous genotoxicity tests, except for a forward mutation assay with *Schizosaccharomyces pombe* ade6, a mitotic recombination assay in *Saccharomyces cerevisiae* D3, and an assay for gene conversion/crossing-over/non-disjunction in *Aspergillus nidulans* D7.

Table 11. Other Genotoxic Effects of Azinphos-methyl

Test Type/System	Strain	Dose	S9	Results	Comments/Reference
Unscheduled DNA synthesis (UDS)	Rat hepatocytes	0, 0.25, 0.5, 1, 2.5, 5, 10, 25, 50, 100 µg/ml	NA	Neg	Acceptable (Myhr and Brusick, 1983)
UDS	Human lung fibroblasts WI-38	Up to 100 µg/ml	±	Neg	Published article (Garrett *et al.*, 1986)
Differential toxicity (Pol A test)	*E. coli* W 3110 & (K12)p3478	0, 625, 1250, 2500, 5000, 10000 µg/plate	±	Neg	Unacceptable (Herbold, 1984)
Differential toxicity	*Salmonella typhimurium* uvrB,rec	Up to 1000 µg/ml	-	Neg	Published article (Garrett *et al.*, 1986)
Mitotic recombination	*Saccharomyces cerevisiae* D3	Up to 10 µg/ml	-	Pos	Published article (Garrett *et al.*, 1986)
Gene conversion and crossing-over	*S. cerevisiae* D7	Up to 10,000 µg/ml	±	Neg	Published article (Garrett *et al.*, 1986)
Mitotic recombination, gene conversion, crossing-over, and reverse mutation	*S. cerevisiae* D3 & D7	**Not reported**	±	Neg	Published abstract (Riccio *et al.*, 1981)
Gene conversion, crossing-over, and non-disjunction	*Aspergillus nidulans* D7	0, 30, 60 mM	±	Pos	Published article; positive for crossing-over and non-disjunction at 30 mM only (Vallini *et al.*, 1983)
Point mutations, crossing-over, and non-disjunction	*A. nidulans*	**Not reported**	**NR**	Neg	Published article (Morpurgo *et al.*, 1977)

S9 = Supernatant from rat liver homogenates centrifuged at 9,000 x g which contain enzymes for metabolic activation.
NA = Not applicable
NR = Not reported

F. REPRODUCTIVE TOXICITY

Dietary-Mouse

University of Chicago, 1965: In a 3-generation, 2-litter study, 24 female and 6 male CF1 mice/group were given azinphos-methyl (80%) in the diet at 0, 5, 10, 25 or 50 ppm (0, 0.075, 1.5, 3.75 or 7.5 mg/kg/day)[7] (Root *et al.*, 1965). The adults were fed the control or treated diet 30 days prior to mating. Thirty-day old F3b pups were sacrificed and submitted for macroscopic and microscopic examination. Nine and 15 pre-mating deaths occurred in the P0 females at 10 and 50 ppm, respectively. The deaths at 10 ppm were not considered compound-related by the investigators because the animals that died had severe diarrhea and other symptoms that were similar to other animals not on the study that had died and the deaths occurred in only two of six cages (the animals were group housed). The investigators concluded that the deaths at 50 ppm were compound-related because they occurred in all six cages of this group. Although fertility was not affected in the surviving mice at 50 ppm, this dose level was discontinued in the subsequent generations due to the high mortality rate. There was no compound-related effect on the fertility and gestation indices or the incidence of macroscopic and microscopic lesions. There was a decrease (66%) in the lactation index (percent of live pups from day 4 that survived until day 21) at 50 ppm. The apparent reproductive and parental NOEL was 25 ppm (3.75 mg/kg/day) based on the reduced survival of offspring and mortalities in adults, respectively. DPR found this study unacceptable due to major deficiencies including no individual data, no diet analysis, inadequate group size and inadequate exposure period prior to mating.

Dietary-Rat

Bayer AG, 1984: In a 2-generation, 2-litter study, azinphos-methyl (87.2%) was administered in the diet at 0, 5, 15, or 45 ppm (F0: 0, 0.4, 1.2 or 4.1 mg/kg/day; F1B: 0, 0.5, 1.6 or 8.8 mg/kg/day) to 12 male and 24 female Bor:WISW (SPF-Cpb) rats/group (Eiben and Janda, 1984). Alopecia (onset week 6), inflammation around eyes (onset week 3), convulsions (onset week 24) and mortality (20%, onset week 5) were observed at 45 ppm. The mean body weights were reduced (9%) in females at 45 ppm. The viability index (percent of pups born live that survived to day 4) and lactation index were reduced 60-68% and 53-72%, respectively, at 45 ppm in both the F1A and F1B generations. The viability and lactation indices were also slightly reduced (11 and 8%, respectively) at 15 ppm in one generation, but not both. ChE activity was not measured in this study, but based on other studies conducted in this laboratory using similar dose levels (Eiben *et al.*, 1983; Schmidt and Chevalier, 1984), the registrant suggested that the reproductive effects were due to significant ChE inhibition occurring at 15 ppm even though no cholinergic signs were observed (Van Goethem, 1987). The mean erythrocyte and brain ChE were reduced (63 and 82% of control activity, respectively) in females at 20 ppm in the 28-day range-finding study (Eiben *et al.*, 1983). Therefore, DPR lowered the parental NOEL from 15 to 5 ppm (0.4 mg/kg/day) based on the ChE inhibition data from these other studies. The reproductive NOEL is also 5 ppm (0.4 mg/kg/day) based on the decreased viability and lactation indices. This study was considered acceptable to DPR.

Bayer AG, 1990: Eighteen male and 46 female Wistar derived (Bor:WISW; SPF Cpb) rats/group were fed azinphos-methyl (91.7%) in the diet at 0, 5, 15 or 45 ppm (0, 0.5, 1.4 or 4.3 mg/kg/day during premating period) for one generation (Holzum, 1990). Ten additional

[7] Estimated assuming a 28 g mouse consumes 5 g of feed per day (U.S. EPA, 1988).

F. REPRODUCTIVE TOXICITY (cont.)

males/group were mated with 20 untreated females. The mean body weights were slightly reduced (<10%) in both sexes at 45 ppm of the F0 generation during several weeks of the mating period. Five females at 45 ppm died without clinical signs during the weeks 3 and 6 of mating. Two other 45 ppm females were sacrificed in a moribund condition in week 3 and 10 after exhibiting poor general condition, inertia, nasal discharge, and stumbling gait. Hyperemia and edema of the lungs and centrilobular hyperemia of the liver were observed histologically in the animals that died or were moribund. The investigators attributed these deaths to nonhomogeneous mixing of the diets which occurred weeks 3, 4 and 6 of mating. There was no effect on food consumption, insemination index, fertility index, gestation index, gestation period, lactation index, or clinical signs of pups. The viability index and pup body weights during the lactation period were significantly reduced (8-48% and 14-23%) at 15 and 45 ppm, respectively. At the end of the mating period, the mean plasma ChE activity was reduced at 15 and 45 ppm (54-86% and 34-57% of control activity, respectively) in both sexes of the F0 generation. The mean erythrocyte ChE activity was significantly depressed at 5, 15 and 45 ppm in the F0 generation (53-81%, 16-54%, and 6-29% of control activity, respectively). The mean parental brain ChE activity was also reduced (52-62% and 32-81% of control activity, respectively) at 15 and 45 ppm. The mean brain ChE activity in pups were reduced only at 45 ppm (54-83% of control activity). The parental NOEL was 5 ppm (0.5 mg/kg/day) based on the brain ChE inhibition. The reproductive NOEL was also 5 ppm based on the decreased viability index and pup weight. This study was considered supplemental by DPR, supporting the conclusions in the previous study that reduction in certain reproductive parameters occurs at the same dose level that significant ChE inhibition occurs. However, it does not establish a definitive link between the reproductive effects and the maternal toxicity.

Gavage-Rabbit

Alexandria and Mansoura Universities, Egypt, 1981: Spermatogenesis was examined in a study where 20 sexually mature male Buscat rabbits were administered azinphos-methyl orally by gavage at 1.5 mg/kg/day for 12 weeks (Soliman and El-Zalabani, 1981). An additional 10 male rabbits of comparable age served as controls. There was no effect on semen volume, but there was a significant decrease (42%) in mean sperm count and a significant increase (169%) in mean percent of abnormal spermatozoa. The testes in all treated rabbits exhibited varying degrees of impaired spermatogenesis when examined histologically. The histological changes included reduced size of seminiferous tubules with "a consequent increase in intertubular fibrous tissue stroma", a decrease in the number of all germ cells, degeneration and necrosis in the seminiferous tubules. Spermatogenesis was arrested primarily at the spermatid level. The Leydig and Sertoli cells appeared normal. Due to the limited endpoints examination, and only one dose level tested, a NOEL could not be established for this supplemental study.

G. DEVELOPMENTAL TOXICITY

Gavage-Mouse

Midwest Research Institute, 1978: Groups of 22-23 pregnant CD-1 mice were administered technical grade azinphos-methyl (purity not stated) in corn oil by gavage at 0, 1.25, 2.5, and 5 mg/kg/day from gestation day 6 to 15 and sacrificed on day 18 (Short *et al.*, 1978). Cholinergic signs (salivation, urination, tremors) and death were observed in the dams

at 5 mg/kg/day. The time of onset of these signs was not reported. There was no effect on litter size, incidence of resorptions, fetal body weights, external or soft tissue anomalies at any dose level. A significant increase in the incidence of malaligned sternebrae was observed at 5 mg/kg/day. The average percent of fetuses per litter with malaligned sternebrae were 6.4 and 24.3 at 0 and 5 mg/kg/day, respectively. The apparent maternal and developmental NOEL was 2.5 mg/kg/day based on cholinergic signs and malaligned sternebrae, respectively. However, DPR found this study unacceptable due to major deficiencies including no individual data, purity information or analyses of dosing solutions.

U.S. EPA, 1985: Azinphos-methyl (purity not reported) was administered to 15, 20 and 40 CD-1 pregnant female mice at 0, 16 and 20 mg/kg, respectively, by gavage in corn oil on day 8 of gestation (Kavlock et al., 1985). One dam at 16 mg/kg and 21 dams at 20 mg/kg died. The mean maternal weight gain was reduced by 6 and 20% at 16 and 20 mg/kg, respectively, but was not statistically significant at either dose level. A reduction in the mean fetal weight (11%) was observed at 20 mg/kg. A significant increase in supernumerary ribs (extra ribs) was observed at both dose levels. The investigators suggested that the increase in extra ribs was not treatment-related, but rather due to a reduced maternal weight gain based on a significant inverse relationship ($p < 0.001$) between maternal weight gain and extra ribs when they combined data for 10 unrelated chemicals (cacodylic acid, caffeine, deltamethrin, dinoseb, ethylene bisisothiocyanate sulfide, endrin, azinphos-methyl, kepone, sodium salicylate, and toxaphene). DPR did not concur with the investigators and assumed that the extra ribs were treatment-related. Therefore, the developmental NOEL was assumed to be less than 16 mg/kg based on the extra ribs. The maternal NOEL also was less than 16 mg/kg based on one mortality and slightly reduced weight gain. This study had major deficiencies including only one day exposure and no maternal clinical signs or gross pathology data.

Gavage-Rat

Midwest Research Institute, 1978: Charles River CD rats (21 pregnant rats/dose) were administered azinphos-methyl (purity not reported) in corn oil by gavage at 0, 1.25, 2.5 or 5 mg/kg/day during gestation days 6-15 (Short *et al.*, 1978). An additional 14-15 pregnant rats/dose were administered azinphos-methyl at the same dose levels from day 6 of gestation until the pups were weaned on day 21. Pups were sacrificed at 30 to 40 days of age. Cholinergic signs (tremors, salivation, urination) and death were observed in the dams at 5 mg/kg/day. The time of onset of these signs was not reported. A reduction in the mean maternal body weight gain and food consumption was also noted (52% and 24%, respectively, during the exposure period). There was no effect on litter size, incidence of resorptions, fetal body weight or external, visceral or skeletal anomalies. The developmental NOEL was equal to or greater than 5 mg/kg/day, the highest dose tested. The maternal NOEL was 2.5 mg/kg/day based on the cholinergic signs, reduced maternal weight gain, and reduced food consumption. This study was unacceptable to DPR due to major deficiencies including no individual data, purity information or analyses of dosing solutions.

Miles Inc., 1987: Azinphos-methyl (87.7%) was given in a 6% Emulphor emulsion by gavage to 33 pregnant Charles River Crl:CD BR rats/dose at 0, 0.5, 1.0, or 2.0 mg/kg on days 6-15 of gestation (Kowalski *et al.*, 1987). Five rats/dose were sacrificed on day 16 of gestation and 28 on day 20. The dams exhibited no clinical signs at any dose level, although the mean plasma, erythrocyte and brain ChE activity were significantly reduced in the 2.0 mg/kg/day dams on day 16 (63%, 77%, and 61% of control activity, respectively). By day 20, only the

mean brain ChE activity was still significantly reduced (73% of control activity). The brain ChE activity in the fetuses were not reduced even at 2.0 mg/kg/day. There was also no evidence for developmental toxicity at any dose. Therefore, the developmental NOEL was greater than or equal to 2.0 mg/kg/day, the highest dose tested. The maternal NOEL was 1.0 mg/kg/day based on the brain ChE inhibition. DPR found this study acceptable.

Gavage-Rabbit

University of Chicago, 1966: Ten pregnant New Zealand white female rabbits/group were administered azinphos-methyl (92.7%) in the diet at 0, 5 or 25 ppm (0, 0.15 or 0.75 mg/kg/day) on days 8-16 of gestation (Doull *et al.*, 1966). Five females/group were sacrificed on gestation day 29 and the fetuses removed, weighed, and examined for skeletal and visceral anomalies. The other 5 females in each group were allowed to deliver and nurse their pups until lactation day 30. The pups were then examined for gross pathological effects. There was no effect on the fertility index, litter size, survival of offspring, and gross pathological findings in the fetuses. The maternal and developmental NOELs appear to be equal to or greater than 25 ppm (0.75 mg/kg/day), the highest dose tested. DPR considered this study unacceptable due to numerous deficiencies including no diet analysis, inadequate group size, inadequate exposure period, body weight or food consumption data, and no individual data.

Bayer AG, 1975: Azinphos-methyl (92.4%) was administered in a 0.5% Cremophor emulsion by gavage to 9-11 pregnant female Himalayan rabbits/dose at 0, 0.3, 1 or 3 mg/kg/day on gestation days 6-18 (Machemer, 1975). There was no evidence of maternal toxicity (mortality, clinical signs, weight gain) or developmental toxicity (increased resorption, abortion, litter size, fetal weight, sex ratio, external, brain or skeletal malformations). The maternal and developmental NOEL were equal to or greater than 3 mg/kg/day, the highest dose tested. DPR found this study unacceptable due to major deficiencies including lack of maternal toxicity at the highest dose, and missing data on uterine weights, corpora lutea and resorptions.

Miles Inc., 1988: A teratology study was also performed in 20 artificially inseminated female rabbits given azinphos-methyl in a 7% Emulphor emulsion by gavage at 0, 1, 2.5 or 6 mg/kg/day on days 6-18 of gestation (Clemens *et al.*, 1988). Ataxia and tremors (onset day 16) were observed in 4 does at 6 mg/kg/day. The mean maternal plasma and red blood cell ChE activities on day 19 were significantly lower at 1.0 mg/kg/day (erythrocyte - 86% of control activity), 2.5 mg/kg/day (plasma - 87%; erythrocyte - 80% of control activity) and 6 mg/kg/day (plasma - 78%; erythrocyte - 50% of control activity). The mean maternal erythrocyte and brain ChE activity was also reduced at 6 mg/kg/day on day 28 (87% and 88% of control activity, respectively). There was a significant decrease in litter size at 6 ppm apparently due to pre- and post-implantation loss (Table 12). The median pre-implantation loss was significantly higher at 1, 2.5, and 6 mg/kg/day. However, the investigators indicated that the pre-implantation loss was within the historical control range (0-13.3%) at 1 and 2.5 mg/kg/day. There was also a slight increase in the mean post-implantation loss, but the difference was not statistically significant. The median weight of live fetuses and placentas were also significantly higher at 6 ppm, possibly due to the smaller litter size. The maternal NOEL was 2.5 based on the clinical signs and brain ChE inhibition. The developmental NOEL was also 2.5 mg/kg/day based on the increased pre- and post-implantation losses. This study was acceptable to DPR.

G. DEVELOPMENTAL TOXICITY (cont.)

Table 12. Developmental Effects in Rabbits Exposed to Azinphos-methyl[a]

		Dose Level (mg/kg/day)			
		0	1	2.5	6
Litter size	mean	7.4	6.2	7.0	5.5
	median	7.0	7.0	7.0	6.0*
	(range)	(4-10)	(1-9)	(3-11)	(2-8)
% Pre-implantation loss	mean	1.5	23.0	14.8	28.0
	median	0.0	11.3**	12.5*	30.3**
	(range)	(0-13)	(0-78)	(0-50)	(0-60)
% Post-implantation loss	mean	2.4	3.0	4.3	7.2
	median	0.0	0.0	0.0	0.0
	(range)	(0-20)	(0-25)	(0-29)	(0-33)
Median weight of live fetuses	male	36.7	37.9	35.2	40.1**
(grams)	female	35.9	36.2	35.7	38.2
	(combined)	37.1	38.2	36.1	39.4**
Median weight of placentas	(grams)	5.4	5.4	5.1	6.0*

[a] Does exposed from days 6-18 of gestation

*, ** Significantly different from controls at $p < 0.05$ and 0.01, respectively, by the Kruskal Wallis test.

H. NEUROTOXICITY

ACUTE

Gavage-Hen

Bayer AG, 1974: White leghorn hens were administered a single dose of azinphos-methyl (purity not reported) at 1-250 mg/kg without delayed neurotoxic effects (Kimmerle and Löser, 1974). The NOEL for delayed neuropathy was equal to or greater than 250 mg/kg, the highest dose tested. This published report was not submitted to DPR for review.

Hazleton Laboratories, 1988: Thirty white leghorn hens were administered azinphos-methyl (85%) by gavage at 330 mg/kg with atropine (15 mg/kg) administered intramuscularly 15 minutes prior to dosing (Glaza, 1988). This treatment was repeated 21 days later. No clear evidence of delayed neuropathy was observed during the 44 day observation period. DPR found this study acceptable.

H. NEUROTOXICITY (cont.)

Gavage-Rat

Miles Inc., 1994: Groups of 18 Fischer 344 rats/sex/dose were evaluated for neurotoxic effects after receiving a single dose of azinphos-methyl (92.2-92.8% purity) by oral gavage at 0, 2, 6 or 13 mg/kg for males and 0, 1, 3 or 6 mg/kg for females (Sheets, 1994). Twelve rats/sex/dose were assigned to the main study and 6 rats/sex/dose were assigned to a satellite group for ChE determination. Five males at 13 mg/kg and 15 females at 6 mg/kg died on the day of dosing. Most of these animals died before clinical observations were done. One surviving female at 6 mg/kg had oral and urine stains. Surviving males at 13 mg/kg had muscle fasciculations, tremors, gait incoordination, and oral/nasal/urine stains. No compound-related signs were observed in females at 3 mg/kg; however, males at 2 mg/kg had muscle fasciculations and oral stains. The onset of these signs was on day 0, and they were resolved by day 3. The functional observational battery (FOB) was conducted 30 minutes to 1 hour after dosing. Due to the early deaths, only 11 males and 3 females were available for the FOB. In the FOB, males at 6 and 13 mg/kg and females at 6 mg/kg exhibited gait incoordination, repetitive chewing, muscle fasciculations, tremors, lacrimation, salivation, sitting or lying (not standing) with minimal movement in the open field, reduced approach and touch responses, uncoordinated righting response, decreased body temperature, and reduced forelimb grip strength. Males at 13 mg/kg also had reduced hindlimb grip strength. Sitting and lying in the open field, reduced approach response, and uncoordinated righting response were observed in females at 3 mg/kg. The effects in females at 3 mg/kg were not statistically significant; however, given that the majority (15/18) of females at 6 mg/kg died before the FOB could be conducted these effects were considered biologically significant. Reductions of 43% and 77% were seen in males at 13 mg/kg in session motor activity and locomotor activity, respectively. Females at 6 mg/kg showed similar reductions (45% and 63%) in motor and locomotor activity. The reductions in motor and locomotor activity were not statistically significant in either sex at any dose level, due in part to the high mortality of females at 6 mg/kg and the variability in males at 6 and 13 mg/kg. The investigators suggested these reductions were biologically significant based on a general standard of 20% difference from control.

Blood and brain samples were collected for ChE measurements approximately 90 minutes after dosing. Due to the early death of all of the females in the satellite group at 6 mg/kg, no samples were collected from this group. Plasma ChE was reduced at 2, 6 and 13 mg/kg in the males (68%, 43%, and 50% of control activity, respectively) and at 3 mg/kg in females (64% of control activity). Erythrocyte ChE was also reduced at 2, 6, and 13 mg/kg in males (67%, 33%, and 37% of controls, respectively) and at 1 and 3 mg/kg in females (83% and 35% of controls, respectively). Brain ChE was significantly reduced only at 6 and 13 mg/kg in males (26% and 12% of control activity, respectively) and at 3 mg/kg in females (49% of control activity). No dose-related macroscopic, microscopic or organ weight changes were found. The NOEL for neurotoxic effects was 1 mg/kg based on the effects observed in the FOB (sitting or lying in open field, reduced approach response and uncoordinated righting response) and brain ChE inhibition (49% of controls) in females. This study was acceptable to DPR.

SUBCHRONIC

Dietary-Hen

Bayer AG, 1964: Eight HNL chickens/dose were fed azinphos-methyl (80%) in the diet at 0, 75, 150, 300 or 600 ppm for 30 days followed by a 4-week observation period (Kimmerle,

1964). A slight reduction in the mean whole blood ChE activity (73-84% of control activity) was observed in animals at 300 and 600 ppm at the end of the exposure period. No clinical signs and only a slight weight reduction were observed in the chickens at 600 ppm. DPR found the study unacceptable due to insufficient information regarding adverse effects, missing data on clinical observations and histopathology, no positive control and inappropriate route of administration.

Harris Laboratories, Inc., 1965: Groups of 6 Leghorn hens/dose were fed azinphos-methyl (purity not stated) in the diet at 0, 10, 50 or 100 ppm for 30 days and observed for additional 30 days (Tayler, 1965). No abnormal clinical signs or histologic evidence of demyelination were observed. This study was unacceptable to DPR due to the lack of individual data, no positive control and inappropriate route of administration.

Bayer AG, 1965: In a repeat experiment, 8 HNL chickens/dose were fed azinphos-methyl (80%) in the diet at 0, 900, 1200, 1500 or 1800 ppm for 30 days followed by a 4-week observation period (Kimmerle, 1965). No whole blood ChE inhibition was observed at any dose level. There was a slight reduction in the mean body weights in all treatment groups (4-15%) during the exposure period. No other overt signs of toxicity were noted. DPR found this study unacceptable due to major deficiencies (no individual data for clinical signs and histological observations, no positive control, inappropriate route of administration).

Dietary-Rat

Miles Inc., 1995: Azinphos-methyl (92.2% purity) was fed to 18 rats/sex/dose in the diet at 0, 15, 45 or 120 ppm for males (0, 0.91, 2.81 or 7.87 mg/kg/day) and at 0, 15, 45 or 90 ppm for females (0, 1.05, 3.23 or 6.99 mg/kg/day) for 13 weeks (Sheets and Hamilton, 1995). Twelve rats/sex/dose were used for neurobehavioral observation with half also undergoing neuropathological examination. The remaining 6 rats/sex/dose were used for ChE determinations only. Increased reactivity, perianal stain, red lacrimation, and oral stain were observed in males at 120 ppm and in females at 45 and 90 ppm. In addition, females at 90 ppm had uncoordinated gait and tremors. These clinical signs were observed within the first few weeks of exposure and persisted with continued exposure. The body weights and food consumption were reduced in males at 120 ppm (9-10%) and in females at 90 ppm (15-45%). The food consumption was reduced only during the first few weeks. In the FOB, perianal stain was the only sign observed in males at 120 ppm and in females at 45 ppm. Perianal stain, increased reactivity, decreased forelimb grip strength, impaired righting reflex, and tremor were observed in the females at 90 ppm. Motor and locomotor activity were significantly reduced (33-60%) in males at 120 ppm at weeks 4, 8 and 12 and in females at 90 ppm at week 4. ChE activity was significantly reduced at all dose levels for both sexes (19-87%, 5-63%, and 15-92% of control activity in plasma, erythrocyte, and brain, respectively). The slight reduction in brain ChE activity (85-92% of control activity) at 15 ppm was not considered toxicologically significant since no neurobehavioral effects were seen at this dose and the only effects seen at 45 ppm were brain ChE inhibition (28-54% of controls) in both sexes and increased reactivity and perianal stain in females. There was no treatment-related effect on mortalities, ophthalmic findings, macroscopic or microscopic lesions, or brain weights. The NOEL was 15 ppm (1 mg/kg/day) based on the brain ChE inhibition in both sexes and the increased reactivity and perianal stains in females. DPR found this study acceptable.

I. IMMUNOTOXICITY

Dietary-Rat

National Institute of Public Health, The Netherlands, 1983: Six male weanling Wistar-derived rats per group were administered azinphos-methyl (85%) in the diet at 0, 5, 25, or 125 mg/kg/day for 3 weeks (Vos *et al.*, 1983). Several general toxicological and immunological changes were observed at 125 mg/kg/day including increased mortality rate, decreased body weight, decreased relative spleen, pituitary, and mesenteric lymph node weights, and unspecified histopathological changes in the thymus, pituitary, adrenal glands, and testes. It is unclear if the immunological changes are due to azinphos-methyl acting directly on the tissue or indirectly through "stress" (Pruett *et al.*, 1993; Vogel, 1993). Since only a few endpoints were examined, a NOEL could not be established for this study.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

Acute Toxicity

The adverse effects observed with the acute studies are summarized in Table 13. In general, the effects that are considered adverse include clinical signs, reductions in body weight and food consumption greater than 10%, and increases in gross and histopathological lesions. Changes in clinical chemistry and hematology values and organ weights without accompanying functional or structural changes are generally not considered adverse. Some subtle neurological effects, such as memory and learning losses, may not be easily detected in animals unless they are specifically tested for these effects. Consequently, statistically significant brain ChE inhibition is considered an adverse effect even in the absence of clinical signs. Unlike brain ChE, there is no known physiological function of ChE in plasma and erythrocyte. Therefore, ChE inhibition in these tissues, in the absence of other effects, was not considered toxicologically significant.

For acute exposure, some effects observed in the developmental toxicity studies were also included. These include maternal effects observed within the first few days of exposure and all fetal effects. Fetal effects were observed in several developmental toxicity studies for azinphos-methyl including extra ribs in fetal mice at 16 mg/kg, malaligned sternebrae in fetal rats at 5 mg/kg and embryotoxicity (increased pre- and post-implantation losses) in rabbits at 6 mg/kg (Kavlock *et al.*, 1985; Short *et al.*, 1978; Clemens *et al.*, 1988). These effects were seen at doses that produced maternal toxicity, although sometimes the maternal effects were not considered acute effects based on their onset. Among the developmental toxicity studies, only one rat and one rabbit study did not have major deficiencies.

Cholinergic signs were the primary effects observed in adult animals in the acute studies for azinphos-methyl with the LOELs generally between 2-6 mg/kg. The lowest acute LOELs, 2.0 and 2.5 mg/kg, were observed in oral LD_{50} studies (Crawford and Anderson, 1974; Mihail, 1978). However, these studies, like most of the acute LD_{50}/LC_{50} studies, had major deficiencies such as an inadequate description of clinical signs observed at each dose level and no individual data. A LOEL of 3 mg/kg was established in an acceptable acute neurotoxicity study in rats based on effects observed in females in the functional observational battery (sitting/lying in open field, reduced approach response and uncoordinated righting response) and brain ChE inhibition (49% of controls) (Sheets, 1994). The dose response curve for azinphos-methyl appears to be very steep since the majority of females (15/18) at 6 mg/kg died in this study.

In a human study, azinphos-methyl was administered in capsules up to 20 mg/day (0.29 mg/kg/day) for 30 days with no significant plasma ChE inhibition and only erratic erythrocyte inhibition (Table 14, Rider *et al.*, 1972). Theoretically, this study could be used for an acute NOEL since no significant effects occurred after only 1 day of exposure if they did not occur after 30 days. Generally, it is preferable to use human data when available; however, this study had several deficiencies (in particular, insufficient information) which precluded its use. The data were presented at a scientific meeting, but actual data points were not included in a transcript of the presentation and the data were never later reported in a peer-reviewed journal article. Therefore, the NOEL of 1 mg/kg from the acute neurotoxicity study in rats was selected for evaluating the acute exposure in humans.

Table 13. Acute Effects of Azinphos-Methyl and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg)	LOEL (mg/kg)	Ref.[a]
		Inhalation			
Rat[b]	Single, 1-hr	Unspecified signs of toxicity	2.7[c]	8.9	1
	Single, 4-hr	Unspecified signs of toxicity	4.1	10.5	
Rat[b]	Single, 4-hr	Cholinergic signs	-----	17.8[d](M) 14.4 (F)	2*
		Oral			
Rat[b]	Single, gavage	Unspecified signs of toxicity	2.5	5.0	3
Rat[b]	Single, gavage	Cholinergic signs	-----	2.0	4
Rat[b]	Single, gavage	Cholinergic signs	-----	4.0	5
Rat[b]	Single, gavage	Cholinergic signs	1.0	2.5	6
Rat[b]	Single, gavage	Cholinergic signs	-----	5.0	7
Rat[e]	Single, gavage	Inactivity, reduced reflexes, brain ChE inhibition (49%)	1.0	3.0	8[f]*
Mouse[g]	Single, gavage	Maternal: Death, reduced weight gain	-----	16.0	9
		Fetal: Extra ribs	-----	16.0	
Mouse[g]	9 Days, gavage	Maternal: Cholinergic signs, death[h]	2.5	5.0	10
		Fetal: Malaligned sternebrae	2.5	5.0	
Rat[g]	9 Days, gavage	Maternal: Cholinergic signs, death[h]	2.5	5.0	
Rabbit[g]	12 Days, gavage	Fetal: Increased pre- and post- implantation losses	2.5	6.0	11*
		Dermal			
Rat[b]	Single, 24 hrs	Cholinergic signs	-----	100	6
Rat[b]	Single, 24 hrs	Cholinergic signs	----- -----	100 (M) 63 (F)	7

[a] References: 1. Kimmerle, 1966; 2. Shiotsuka, 1987; 3. Hecht, 1955; 4. Crawford and Anderson, 1974; 5. Lamb and Anderson, 1974; 6. Mihail, 1978; 7. Heimann, 1982; 8. Sheets, 1994; 9. Kavlock *et al.*, 1985; 10. Short *et al.*, 1978; 11. Clemens *et al.*, 1988.

[b] LD_{50}/LC_{50} study

[c] Assuming a male Wistar rat weighs 215 g and breathes 0.0096 liters per hour (U.S. EPA, 1988)

[d] Assuming a male Sprague Dawley rat weighs 265 g and breathes 0.045 m^3 in 4 hours; a female Sprague Dawley rat weighs 204 g and breathes 0.037 m^3 in 4 hours (U.S. EPA, 1988)

[e] Neurobehavioral study

[f] This study was selected for calculating the margin of exposure for acute effects.

[g] Developmental toxicity study: All fetal effects were considered acute effects; however, only maternal effects observed within the first few days of exposure were considered acute exposure.

[h] The time of onset of the maternal effects was not reported; therefore, it was assumed they occurred within the first few days.

* Acceptable study based on FIFRA guidelines

A. HAZARD IDENTIFICATION (cont.)

Pre- and Post-natal Sensitivity

Developmental toxicity studies in rats and rabbits and reproductive toxicity studies in rats were considered in assessing the potential for higher sensitivity in infants and children than adults. Two developmental toxicity studies were conducted for azinphos-methyl which met FIFRA guidelines, one in rats and the other in rabbits (Kowalski *et al.*, 1987; Clemens *et al.*, 1988. No treatment-related increases in embryotoxicity, fetal malformations or variations were observed in rats and rabbits. Maternal effects were primarily brain ChE inhibition. In rats, the maternal brain ChE activity was reduced (73% of controls) at 2.0 mg/kg/day on day 20 of gestation; however, fetal brain ChE activity was unaffected. In rabbits, brain ChE activity was reduced to 88% of controls in does at 6 mg/kg/day on day 28. Ataxia and tremors were also observed in the does at 6 mg/kg/day. A slight increase in pre- and post-implantation losses was seen at 6 mg/kg/day; however, brain ChE activity was not measured in fetuses. These findings in rats and rabbits suggest there is no increased prenatal sensitivity to azinphos-methyl.

An acceptable reproductive toxicity study was available in which azinphos-methyl was administered in the feed to rats (Eiben and Janda, 1984). Several signs were observed in adults at 45 ppm, including alopecia, inflammation of the eyes, convulsions, and death. Four of the 5 deaths occurred in females during lactation. The convulsions were also seen primarily in females. The investigators attributed the increased convulsions and death in females to increased consumption of feed during gestation and lactation. Brain ChE activity was not measured in this study; however, in a 28-day range-finding study conducted in the same laboratory, brain ChE activity was reduced at 20 ppm (82% of controls) at the study termination (Eiben *et al.*, 1983). Based on range-finding study, DPR concluded the NOEL for the reproductive toxicity study was 5 ppm (0.4 mg/kg/day). There was a slight reduction in pup survival to day 4 and day 21 (11% and 8%, respectively) at 15 ppm in one generation, but not both. Based on the reduced pup survival, DPR concluded the reproductive NOEL was also 5 ppm. Although brain ChE activity was not measured in pups, these data suggests there is no increased postnatal sensitivity to azinphos-methyl.

Chronic Toxicity

The effects observed in laboratory animals with subchronic and chronic exposure to azinphos-methyl were considered in evaluating the chronic exposure for humans (Tables 14 and 15). In addition to cholinergic signs, brain ChE inhibition, decreased weight gain and food consumption, impaired spermatogenesis, decreased viability and lactation indices, and cystic endometrial hyperplasia were seen. Cystic endometrial hyperplasia was only observed in one mouse study (NCI, 1978). As mentioned under the acute toxicity section, a NOEL of 0.29 mg/kg/day was established in a human study in which no significant plasma or consistent erythrocyte ChE inhibition were observed after 30 days of exposure (Rider *et al.*, 1972). It is generally preferable to use human data when available; however, the NOEL from this study was also not used for the chronic NOEL because of insufficient information and an inadequate exposure period. Brain ChE inhibition appeared to be the most sensitive endpoint. The lowest LOEL with either subchronic or chronic exposure was 0.86 mg/kg/day based on reduced brain ChE activity (79% of control activity) in females in an acceptable two-year rat study (Schmidt and Chevalier, 1984). The NOEL for this study (0.28 mg/kg/day) was selected for evaluating chronic exposure to azinphos-methyl in humans.

Table 14. Subchronic Effects of Azinphos-Methyl and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Ref.[a]
		Inhalation			
Rat	6 hrs/day, 5 days/wk, 12 wks	None	≥1.26[b]	-----	1
		Oral			
Rat[c]	9 days, gavage	Reduced weight gain and food consumption	2.5	5.0	2
Rat[c]	9 days, gavage	Brain ChE[d] inhibition (61%[e])	1.0	2.0	3*
Rabbit[c]	12 days, gavage	Cholinergic signs, brain ChE inhibition (88%)	2.5	6.0	4*
Mouse[f]	3-gen., 4-10 wks premating, diet	Mortality and decreased lactation index	3.75	7.5	5
Rat[f]	2-gen., 14 wks premating, diet	Decreased viability and lactation indices	0.4	1.2	6*
Rat[f]	1-gen., 14 wks premating, diet	Brain ChE inhibition (54-83%) and decreased viability index	0.5	1.4	7
Rabbit	12 weeks, gavage	Impaired spermatogenesis	-----	1.5	8
Rat	16 weeks, diet	Brain ChE inhibition (90%) and decreased weight gain	0.5	1.9	9
Rat	16 weeks, diet	Cholinergic signs, reduced weight gain, and brain ChE inhibition (25-52%)	-----	4.7	10
Rat	13 weeks, diet	Cholinergic signs, brain ChE inhibition (28-54%)	1.0	3.0	11*
Human	30 days, capsule	Plasma ChE inhibition	0.29	-----	12
		Dermal			
Rabbit	6 hrs/day, 5 days/wk, 3 wks	None	20	-----	13

[a] References: 1. Kimmerle, 1976; 2. Short *et al.*, 1978; 3. Kowalski *et al.*, 1987; 4. Clemens, 1988; 5. Root *et al.*, 1965; 6. Eiben and Janda, 1984; 7. Holzum, 1990; 8. Soliman and El-Zalabani, 1981; 9. Doull and Rehfuss, 1956; 10. Doull and Anido, 1957b; 11. Sheets and Hamilton, 1995; 12. Rider *et al.*, 1972; 13. Flucke and Schilde, 1980.

[b] Estimated assuming a Wistar rat weighs 235 g and breathes 0.05 m^3 in 6 hours (U.S. EPA, 1988).

[c] Developmental toxicity study: Only maternal effects observed after the first few days were included.

[d] ChE = Cholinesterase

[e] Percent of control activity

[f] Reproductive toxicity study

* Acceptable study based on FIFRA guidelines

Table 15. Chronic Effects of Azinphos-Methyl and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Ref.[a]
Mouse	80 weeks, diet	Hyperactivity, rough hair coat, cystic endometrial hyperplasia	-----	5.4	1
Mouse	104 weeks, diet	Brain ChE[b] inhibition (74-85%[c])	0.9	3.8	2*
Rat	97 weeks, diet	Convulsions, brain ChE inhibition (51-81%)	1.0	3.6	3
Rat	80 weeks, diet	Reduced body weights	-----	5.7	1
Rat	104 weeks, diet	Brain ChE inhibition (F: 79%)	0.28	0.86	4[d]*
Dog	2 years, diet	Mortality, cholinergic signs, reduced body weight and food consumption	1.3	4.3	5
Dog	52 weeks, diet	Diarrhea, brain ChE inhibition (73-80%)	0.7	4.1	6*

[a] References: 1. NCI, 1978; 2. Hayes, 1985; 3. Lorke, 1966a; 4. Schmidt and Chevalier, 1984; 5. Lorke, 1966b; 6. Allen, 1990.
[b] ChE = cholinesterase
[c] Percent of control activity
[d] This study was selected to calculate the margin of exposure for chronic exposure.
* Acceptable study based on FIFRA guidelines

Oncogenicity/Genotoxicity

The only evidence to suggest that azinphos-methyl is oncogenic came from a rat oncogenicity study. In this study, an increase in tumors of the pancreas, thyroid and adrenal glands were observed in male rats, but the increases were only significant when compared to pooled controls, not concurrent controls (NCI, 1978). This study had major deficiencies (too few concurrent controls, inadequate exposure period, no individual data) which made interpretation of these findings difficult. No increase in tumor incidence was seen in two other chronic rat studies, one of which was acceptable based on FIFRA guidelines (Lorke, 1966a; Schmidt and Chevalier, 1984). There was no evidence of an oncogenic effect in either of the mouse studies, one of which was acceptable (NCI, 1978; Hayes, 1985).

Azinphos-methyl appears to be genotoxic based on positive results with a mouse lymphoma assay (Garret *et al.*, 1986) and several *in vitro* cytogenetic assays using different human cell lines and a hamster cell line (Herbold, 1989; Alam *et al.,* 1974; Alam and Kasatiya, 1976; Trépanier *et al.*, 1977). However, all the *in vivo* cytogenetic assays were negative. In addition, all the other tests for chromosomal aberrations were negative, including sister chromatid exchange assays and dominant lethal assays. Most of the reverse mutation assays with *Salmonella typhimurium* were also negative except for an equivocal response with the

A. HAZARD IDENTIFICATION (cont.)

TA100 strain in one study and a weak positive response with the TA98 strain in another study (Lawlor, 1987; Zeiger *et al.*, 1987). The weak positive response was only observed at concentrations where precipitation occurred, confounding the results. All of the other gene mutation assays and miscellaneous genotoxicity tests were negative, except for positive results in a forward mutation assay with *Schizosacchromyces pombe* ade6 (Gilot-Delhalle *et al.*, 1983), a mitotic recombination assay with *Saccharomyces cerevisiae* D3 and a gene conversion/cross-over/non-disjunction assay with *Aspergillus nidulans* D7.

In analyzing the structural activity relationship of 301 chemicals tested under the U.S. NTP program, Ashby and Tennant (1991) considered chemicals containing an alkyl phosphate ester, such as azinphos-methyl, to be potential alkylating agents. However, they recognized the potential problem alkyl phosphate esters pose in predicting carcinogenicity since 6 of 15 alkyl phosphate esters examined were non-carcinogens and 3 were equivocal carcinogens. Furthermore, 3 alkyl phosphate esters that were considered carcinogens were negative for the *Salmonella* assay. Ashby and Tennant (1991) classified azinphos-methyl as an equivocal carcinogen based on the carcinogenicity study from NCI (1978). They also classified azinphos-methyl as positive for the *Salmonella* assay based on data reported by Zeiger *et al.* (1987) despite the confounding of the results due to the presence of precipitation. They did recommend confirming the mutagenic potential of these alkyl phosphate esters with a chemical alkylating test. The metabolite, benzazimide, did not contain any structural alerts identified by Ashby and Tennant (1991).

The available genotoxicity data for the structurally similar pesticide, azinphos-ethyl, also suggests that it is genotoxic. Azinphos-ethyl was mutagenic in a reverse mutation assay with *Salmonella typhimurium* TA100 strain without metabolic activation, but only weakly mutagenic with activation (Diril *et al.*, 1990). It was not mutagenic with the TA98 strain. Azinphos-ethyl was positive in an *in vitro* micronucleus assay with Chinese hamster lung cells, but negative in an *in vivo* micronucleus assay in mice (Ni *et al.*, 1993). Azinphos-ethyl was also negative for cytogenetic effects in bone marrow cells and spermatogonia from mice exposed *in vivo* and in a dominant lethal assay in mice (Degraeve *et al.*, 1986). Degraeve *et al.* (1986) noted that the high toxicity of azinphos-methyl and azinphos-ethyl may be a limiting factor in demonstrating a cytogenetic effect *in vivo*. Another explanation for the lack of concordance in response between the *in vivo* and *in vitro* cytogenetic assays may be that azinphos-methyl and azinphos-ethyl are quickly metabolized *in vivo* before they can exert any genotoxic effect. No genotoxicity data was available for the metabolite, benzazimide.

DPR concluded that the limited evidence that azinphos-methyl was oncogenic (one sex, one species, one laboratory) was insufficient to warrant a low-dose extrapolation from the animal data to humans. The U.S. EPA has classified azinphos-methyl as a Group E carcinogen (i.e., no evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies) (U.S. EPA, 1994).

B. EXPOSURE ASSESSMENT

Occupational Exposure Assessment

The estimated potential daily exposure to azinphos-methyl for mixer/loader/applicators is summarized in Table 16. A more detailed discussion of worker exposure is presented in

Table 16. Mean Potential Exposure to Azinphos-methyl for Mixer/Loader/Applicators[a]

Type of Sprayer	Additional Clothing[b]	n	Acute (µg/kg)		Chronic (µg/kg/day)	
			ADD[c]	Combined[d]	AADD[e]	Combined
Electrostatic[f]	None	2	30.7	32.2	0.8	0.9
Airblast[f]	None	1	44.1	45.6	1.2	1.3
Airblast[g]	None	8	62.1	63.6	1.7	1.8
Airblast[g]	Rubber suit	4	57.7	59.2	1.6	1.7
Airblast[g]	Rubber coat	4	68.5	70.0	1.9	2.0

[a] Potential exposure normalized based on a maximum application rate of 2 lb/acre
[b] Standard protective clothing included long-sleeved shirt, long pants, gloves, hat, and shoes
[c] ADD = Absorbed Daily Dosage from both dermal and inhalation exposure (see Appendix B)
[d] Combined = combined occupational and dietary exposure. Acute dietary exposure = 1.5 µg/kg/day based on the 95th percentile of user-day exposure for males and females 16 years and older. Chronic dietary exposure = 0.14 g/kg/day based on the mean annual consumption of the U.S. population subgroup.
[e] AADD = Average Annual Daily Dosage assuming workers are exposed at the ADD for 10 days out of 365 days (see Appendix B)
[f] Schneider *et al.*, 1987
[g] Franklin *et al.*, 1981

Appendix A. The exposure estimates are based on two studies in which different types of applicators were compared and different types of personal protective equipment (PPE) were compared (Franklin *et al.*, 1981; Schneider *et al.*, 1987). In both studies, the applicators also did mixing and loading. A closed system was used for mixing in the study conducted by Schneider *et al.* (1987). It was assumed that a closed system was also used in the study conducted by Franklin *et al.* (1981), although it is not certain. In the study conducted by Schneider *et al.* (1987), dermal exposure was estimated in 3 workers using hand washes and pads on the inside and outside of clothing on the arms, legs, chest, and back. Inhalation exposure was estimated with personal air sampling pumps. Two workers applied azinphos-methyl to almond trees using electrostatic sprayers while the other worker applied it with an airblast sprayer. Normalizing exposure for the maximum application rate, the estimated absorbed daily dosages (ADDs) for these workers ranged from 30.7 to 44.1 µg/kg/day. Azinphos-methyl is used on peaches in some regions of California for 9 out of 12 months (DPR, 1992c). Consequently, a seasonal exposure dosage was not estimated. The annual average daily dosages (AADDs) ranged from 0.8 to 1.2 µg/kg/day. Franklin *et al.* (1981) estimated the dermal exposure in 16 workers using pads and urinary metabolite recoveries. The urinary metabolites were considered a more accurate estimate of exposure. Since the workers wore respirators, inhalation exposure was estimated from the residues in air samples, assuming a breathing rate of 1.74 m^3/hr and a 50% respiratory uptake. Eight workers wore only short sleeve shirts, long pants, gloves, coveralls, and boots. In addition, 8 other workers wore either a rubber coat or a rubber suit. The estimated ADDs for these workers ranged from 57.7 to 68.5 µg/kg/day after normalizing for maximum application rate. The AADDs ranged from 1.6 to 1.9 µg/kg/day.

B. EXPOSURE ASSESSMENT (cont.)

The estimated daily exposure for field workers is summarized in Table 17. Exposure estimates were limited to a few tree crops for which dislodgeable foliar residue (DFR) data and transfer factors were available. DFRs are obtained by rinsing leaf discs taken from the fields when workers are performing various tasks. Transfer factors are estimated by dividing residues on skin and clothing by the DFRs. The DFRs came from studies conducted by the Worker Health and Safety Branch of DPR and studies submitted by the registrants. The arithmetic mean of the DFRs from all the sources was used to estimate exposure. The transfer factors were obtained from published reports and studies conducted by the Worker Health and Safety Branch. The ADDs were lowest for proppers (workers who prop up heavy, fruit laden branches) ranging from 2.2 to 4.5 µg/kg/day. The ADDs for thinners and harvesters were fairly similar ranging from 42.4 to 85.6 µg/kg/day. Exposure was highest for thinners and harvesters of peaches and nectarines. The AADDs ranged from 0.5 to 1.1 µg/kg/day for proppers and from 10.1 to 20.4 µg/kg/day for thinners and harvesters.

Table 17. Mean Potential Exposure to Azinphos-methyl for Field Workers[a]

Job Type	Crop	DFR[b] (µg/cm^2)	Transfer Factor (cm^2/hr)	Acute (µg/day)		Chronic (µg/kg/day)	
				ADD[c]	Combined[d]	AADD[e]	Combined
Harvester	peach/ nectarine	1.12	4,180	85.6	87.1	20.4	20.5
Harvester	apple	0.70	4,180	53.5	55.0	12.7	12.8
Harvester	orange	0.61	4,180	46.6	48.1	11.1	11.2
Thinner	peach/ nectarine	1.34	3,315	81.2	82.7	19.4	19.5
Thinner	apple	0.70	3,315	42.4	43.9	10.1	10.2
Propper[f]	peach/ nectarine	1.34	174	4.5	6.0	1.1	1.2
Propper	apple	0.70	174	2.2	3.7	0.5	0.6

[a] Potential exposure normalized based on a maximum application rate of 2 lb/acre. Assumed a dermal absorption rate of 16%, body weight of 70 kg, 8-hour workday, and work clothes included long-sleeved shirt, long-legged pants and shoes.

[b] DFR = Dislodgeable foliar residue at the end of the 14-day reentry interval. The DFR at the end of preharvest interval (21 days for peach/nectarine; 30 days for oranges) was used for harvesters.

[c] ADD = Absorbed Daily Dosage = DFR x transfer factor x 8 hrs/day x 16% ÷ 70 kg (see Appendix B)

[d] Combined = combined occupational and dietary exposure. Acute dietary exposure = 1.5 µg/kg/day based on the 95th percentile of user-day exposure for males and females 16 years and older. Chronic dietary exposure = 0.14 µg/kg/day based on the mean annual consumption of the U.S. population subgroup.

[e] AADD = Annual Average Daily Dosage assuming workers are exposed at the ADD for 87 days out of 365 days (see Appendix B)

[f] Propper = Worker who props up heavy, fruit laden branches

Although azinphos-methyl may be applied aerially, most of its use is in orchards (93% of use in 1991) where it is applied almost exclusively with ground equipment. Therefore, exposure to workers involved in aerial application (pilots, flaggers, and mixer/loaders) was not addressed in this exposure assessment.

B. EXPOSURE ASSESSMENT (cont.)

Dietary Exposure Assessment

DPR evaluates the risk of human exposure to an active ingredient in the diet using two processes: (1) use of residue levels detected in foods to evaluate the risk from total exposure, and (2) use of tolerance levels to evaluate the risk from exposure to individual commodities (see Section VI. Tolerance Assessment of this document). For evaluation of risk to detected residue levels, the total exposure in the diet is determined for all label-approved raw agricultural commodities, processed forms, and animal products (meat and milk) that have established U.S. EPA tolerances. The potential exposure from residues in the water and certain commodities without tolerances are also assessed in some cases. Tolerances may be established for the parent compound and associated metabolites. DPR considers these metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

Residue Data

The sources of residue data for dietary exposure assessment include DPR and federal monitoring programs, field trials, and survey studies. In absence of data, surrogate data from the same crop group as defined by U.S. EPA or theoretical residues equal to U.S. EPA tolerances are used. Residue levels that exceed established tolerances are not utilized in the dietary exposure assessment because over-tolerance incidents are investigated by DPR Pesticide Enforcement Branch and are relatively infrequent. DPR evaluates the potential risk from consuming commodities with residues over tolerance levels using an expedited acute risk assessment process.

DPR had two major sampling programs: priority pesticide and marketplace surveillance. The priority pesticide program focuses on pesticides of health concern as determined by DPR Enforcement and Medical Toxicology branches. Samples are collected from fields known to have been treated with the specific pesticides. For the marketplace surveillance program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods. The sampling strategies for both priority pesticide and marketplace surveillance are similar and are weighted toward such factors as pattern 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. DPR had two additional monitoring programs prior to 1991. The preharvest monitoring program routinely examined the levels of pesticides on raw agricultural commodities in the field at any time during the growth cycle. Commodities destined for processing were collected in the field no more than 3 days prior to harvest, at harvest, or post-harvest before processing.

The U.S. Food and Drug Administration (FDA) has three programs for examining residues in food: (1) regulatory monitoring, (2) total diet study, and (3) incidence/level monitoring. 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 the form that a commodity is commonly eaten or found in prepared meal. The incidence/level monitoring program is designed to address specific concerns about pesticide residues in particular foods.

B. EXPOSURE ASSESSMENT (cont.)

The U.S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program (PDP), a nationwide cooperative monitoring program. The PDP is designed to collect objective, comprehensive pesticide residue data for risk assessments. Several states, including California, collect samples at produce markets and chain store distribution centers close to the consumer level. The pesticide and produce combinations are selected based on the toxicity of the pesticide as well as the need for residue data to determine exposure. In addition, USDA is responsible for the National Residue Program that 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.

Primary Residues

Most of the residue values for RACs came from DPR's monitoring programs from 1990 to 1994 (DPR, 1991, 1992c,1993b, 1995b &1996d). DPR's multi-residue screen can detect both azinphos-methyl and its oxygen analog. The high and mean residue levels found during this period are summarized in Table 18. For the acute dietary assessment, the assumption was made that all commodities are consumed at the high residue value. The high value was either the highest measured residue level at or below the tolerance for a commodity or the 95th percentile, if there were more than 400 samples for a commodity. For the chronic dietary assessment, the assumption was made that all commodities are consumed at the mean or average residue level everyday on an annual basis. Other assumptions that were used in estimating both the acute and chronic dietary exposure include: a) the residue level does not change over time, b) residue concentrations are not decreased when the RAC is washed, and c) processing of raw agricultural commodity residue level that may be multiplied by an adjustment factor.

For some commodities that had only one or two samples analyzed during this time period, residues from a surrogate crop were used instead. Residues from apples, walnuts, chili peppers and green peppers were substituted for crabapples, pecans, paprika, and pimentos, respectively. The one loganberry sample analyzed during this time was combined with the data for boysenberries (to which it is related). The combined results were used for both boysenberries and loganberries. For a few commodities (cottonseed oil and meal, filberts, rye, cane sugar and molasses) where no residue monitoring data were available, residue data from field trials conducted by the registrant were used instead (Chemagro Corp., 1963 & 1967a&b; Grace, 1990a; Loeffler, 1964). In general, azinphos-methyl had been applied at or above the maximum application rate in these studies and the commodity was harvested at or before the specified pre-harvest interval. However, in the residue study for processed cottonseed commodities the application rate was 5 times greater than the maximum seasonal rate (Graces, 1990a). The assumption was made that the residues in cottonseed were directly proportional to amount and number of applications; therefore, the residues found in cottonseed oil and meal were divided by 5 for the dietary exposure assessment. Only one sample was analyzed for some of these commodities, including cottonseed oil and meal and rye, so the same residue levels (0.10, 0.05, and 0.01, respectively) were used for both acute and chronic exposure. In the other field trials for filberts and processed cane sugar commodities, no residues were detected, so the MDL (0.10 ppm) was used for acute exposure and 1/2 the MDL was used for chronic exposure.

If there were no residues detected, then the high and mean residue levels were set at the MDL and 1/2 the MDL, respectively. Because the MDLs were not available from the DPR

Table 18. Residues in Raw Agricultural Commodities from DPR's Monitoring Programs from 1990-1994[a]

Raw Agricultural Commodity	No. of Samples	High Value[b]	Mean Value
Almonds	118	0.280	0.018
Apples	1447	0.399*	0.063
Apricots	275	1.500	0.027
Artichokes	243	0.030	0.015
Blackberries	32	0.030	0.015
Blueberries	118	0.160	0.018
Boysen/Loganberries	6	0.500	0.112
Broccoli	603	0.030	0.015
Brussel Sprouts	293	0.030	0.015
Cabbage, Green or Red	608	0.030	0.015
Cantaloupes	498	0.047*	0.016
Casabas	8	0.030	0.015
Cauliflower	332	0.030	0.015
Celery	541	0.038	0.015
Cherries	188	0.680	0.026
Cranberries	1315	0.030	0.015
Crenshaw Melons	18	0.030	0.015
Cucumbers	1400	0.045	0.015
Eggplant	494	0.030	0.015
Garlic	233	0.030	0.015
Grapefruit	496	0.077*	0.017
Grapes	1235	0.100*	0.017
Honeydew Melons	163	0.030	0.015
Kiwi Fruit	247	0.400	0.018
Kumquats	19	0.030	0.015
Lemons	487	0.078*	0.017
Limes	438	0.067*	0.016
Nectarines	505	0.231*	0.029
Melons, Other	79	0.030	0.015
Onions, Dry	767	0.030	0.015
Onions, Green	477	0.045*	0.016
Oranges	981	0.045*	0.015

[a] Residues from DPR's monitoring sampling programs 1 (priority pesticide), 3 (produce destined for processing), and 4 (marketplace surveillance). When no residues were detected in any of the samples for a commodity the high value was set at the minimum detection limit (MDL), 0.03 ppm, and the mean value at 1/2 of the MDL.

[b] The high value represents the highest residue level detected in any sample, except when there were more than 400 samples. In these cases (which are indicated by *), the high value is the 95th percentile of all the residues, assuming 0.03 ppm (MDL) for the samples with no detectable residues.

Table 18 (cont.). Residues in Raw Agricultural Commodities from DPR's Monitoring Program from 1990-1994[a]

Raw Agricultural Commodity	No. of Samples	High Value[b]	Mean Value
Peaches	668	0.607*	0.089
Pears	928	0.486*	0.079
Peppers, Chili	690	0.110*	0.023
Peppers, Green	1553	0.046*	0.015
Pistachio Nuts	12	0.200	0.015
Plums	550	0.129*	0.021
Pomegranates	37	0.030	0.015
Potatoes	1599	0.030	0.015
Quinces	25	0.600	0.107
Raspberries	74	0.030	0.015
Strawberries	667	0.030	0.015
Tangelos	44	0.080	0.015
Tangerines	242	0.110	0.021
Tomatoes	2015	0.079*	0.020
Walnuts	44	0.030	0.015
Watermelon	73	0.030	0.015

[a] Residues from DPR's monitoring sampling programs 1 (priority pesticide), 3 (produce destined for processing), and 4 (marketplace surveillance). When no residues were detected in any of the samples for a commodity the high value was set at the minimum detection limit (MDL), 0.03 ppm, and the mean value at 1/2 of the MDL.

[b] The high value represents the highest residue level detected in any sample, except when there were more than 400 samples. In these cases (which are indicated by *), the high value is the 95th percentile of all the residues, assuming 0.03 ppm (MDL) for the samples with no detectable residues.

monitoring programs, the lowest detected level was used as the surrogate MDL. The surrogate MDL used in the dietary assessment for azinphos-methyl residues below the detection limit in the commodities listed in Table 18 was 0.03 ppm.

Generally, residue data were not available for dried commodities or fruit juices. When no residue data were available, the residues in the dried commodities or juice were estimated from the fresh commodity by multiplying by the default adjustment factors for processed commodities that account for the loss of water. With some fruits (apple, pear, apricot, peach), the adjusted residue level in the dried commodity was higher than the tolerance for the RAC. Since other physical properties of azinphos-methyl would affect whether it concentrates in processed foods, these residue levels are only theoretical. Nonetheless, if the residues were higher than the tolerance for the RAC, they would be considered illegal since no food additive tolerances were established for these commodities. Therefore, the residue levels for the following processed commodities were set at the tolerance level for acute exposure: dried apples, dried pears, dried apricots, and dried peaches. Residue data in a few processed commodities were available indicating that the residues decreased rather than increased (Grace, 1990b-d). Based on these studies, the adjustment factor for apple juice, concentrated apple juice, orange juice, concentrated orange juice, tomato juice, tomato puree and tomato paste were changed from 1.3, 3.9, 1.8, 6.7, 1.5, 3.3, and 5.4 to 0.337, 0.876, 0.004, 0.020, 0.242, 0.020, and 0.007, respectively.

B. EXPOSURE ASSESSMENT (cont.)

In 1990, Mobay Corp. (now Miles Inc.) announced it was amending the labels for all Guthion products by deleting all uses and directions for 22 crops (U.S. EPA, 1990). These included apricots, barley, beans, blackberries, boysenberries, broccoli, brussels sprouts, cabbage, cauliflower, celery, clover, grass mixture, loganberries, oats, pasture grasses, peas, raspberries, rye, soybeans, spinach, tobacco, and wheat. Subsequently, the Interregional Project Number 4 (IR-4 Project) committed to U.S. EPA to develop residue data for 11 of these crops (apricots, blackberry, boysenberry, broccoli, brussels sprouts, cabbage, cauliflower, celery, loganberry, raspberry, and rye) (IR-4 Project, 1990). The IR-4 Project is funded by the USDA and develops analytical methods and residue data at various university laboratories on minor use crops for which there is no economic incentive for chemical companies to develop them. Therefore, residues for these 11 commodities were left in the dietary exposure analysis.

Secondary Residues

No residue monitoring data were available for meat or milk. A feeding study was conducted with dairy cattle in which azinphos-methyl was fed at 0, 11, 33 or 77 ppm in the diet for 28 days (Wargo, 1978). There was no effect on behavior, feed consumption, milk production or body weights; however, after 28 days whole blood ChE activity was depressed (50% and 25% of control activity) at 33 and 77 ppm, respectively. Residue levels were measured in tissue and milk after 28 days of exposure. There were no detectable residues of the parent compound or its oxygen analog in any tissue or milk. The minimum detection limits (MDLs) were 0.01 in tissue and 0.001 in milk.

The highest possible amount of azinphos-methyl that cattle might consume was estimated to be 10 ppm assuming that 100% of the feed came from almond hulls, the commodity with the highest tolerance. Although the actual consumption of azinphos-methyl would probably be less than 10 ppm, this dose level is still below the lowest dose level used in the cattle feeding study at which there were no ChE inhibition or detected residues in tissues and milk. The metabolism in rats, cattle, goats and chickens appear to similar; therefore, it was assumed that the residue levels in other livestock were similar to cattle (Kao, 1988; Everett *et al.*, 1977; Gronberg *et al.*, 1988; Ridlen and Pfankuche,1988).

Consumption Database

The USDA directs the Nationwide Food Consumption Survey (NFCS) and the Continuing Survey of Food Intakes by Individuals (CSFII) (USDA, 1989-91). The NFCS is a geographically stratified probability sampling of U.S. households and is conducted every 10 years (1977-78 and 1987-88). The CSFII is an annual survey which reflects the current consumption pattern and has a greater focus on consumption data for vulnerable population subgroups (e.g., infants and children).

Acute Dietary Exposure

The acute dietary exposure analyses were conducted using the Exposure-4™ software program developed by Technical Assessment Systems, Inc (TAS). The Exposure-4™ software program estimates the distribution of user-day (consumer-day) exposure for the overall U.S. population and specific subgroups (TAS, 1996a). 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 1989-91 USDA CSFII (USDA, 1989-91).

B. EXPOSURE ASSESSMENT (cont.)

Based on the 95th percentile of user-day exposure for all specific population subgroups, the potential acute dietary ingestion of azinphos-methyl from all labeled uses ranged from 1.5 to 12.4 µg/kg/day (Table 19). Non-nursing infants less than one year old had the highest potential acute dietary exposure.

Table 19. Potential Acute and Chronic Dietary Exposures to Primary and Secondary Azinphos-methyl Residues

Population Subgroup	Exposure Dosage (µg/kg/day)	
	Acute[a]	Chronic[b]
U.S. Population - All Seasons	2.5	0.14
Western Region	2.8	0.16
Nursing Infants (< 1 yr)	11.3	0.22
Non-nursing Infants (< 1 yr)	12.4	0.52
Children (1-6 yrs)	6.5	0.37
Children (7-12 yrs)	3.5	0.23
Females (13+ yrs/pregnant/not nursing)	1.5	0.11
Females (13+ yrs/nursing)	3.0	0.16
Females (13-19 yrs/not pregnant or nursing)	1.7	0.11
Females (20+ yrs/not pregnant or nursing)	1.6	0.10
Males (13-19 yrs)	1.5	0.12
Males (20+ yrs)	1.5	0.10
Seniors (55+ yrs)	1.8	0.11
Workers (16+ yrs)	1.5	NA

[a] Based on 95th exposure percentile for each user-day population subgroups.
[b] Based on the annual average daily dosage for each population subgroups.
NA Not available. The TAS Exposure-1™ program does not calculate an exposure estimate for customized population subgroups, such as, workers 16 years and older.

B. EXPOSURE ASSESSMENT (cont.)

Chronic Dietary Exposure

The potential chronic dietary exposure was calculated using the Exposure-1™ software developed by TAS (TAS, 1996b). The food consumption data for the chronic analysis were also calculated from the 1989-1991 USDA CSFII (USDA, 1989-91). The program estimates the annual average exposure for all members of a designated population subgroup.

The mean potential chronic dietary exposure for all population subgroups ranged from 0.10 to 0.52 µg/kg/day (Table 19). The population subgroup with the highest potential exposure was non-nursing infants less than one year old.

Combined Occupational and Dietary Exposure

The exposure to azinphos-methyl through the diet was also considered in the potential exposure for pesticide workers. The combined occupational and dietary exposure are summarized in Tables 16 and 17. The potential acute dietary exposure to azinphos-methyl for workers was estimated to be 1.5 µg/kg based on the 95th percentile of user-day exposure for workers (males and females 16 years and older). The combined acute exposure for mixer/loader/applicators ranged from 32.2 to 70.0 µg/kg/day. The combined acute exposure ranged from 3.7 to 6.0 µg/kg/day for proppers and from 43.9 to 87.1 µg/kg/day for thinners and harvesters. The potential chronic dietary exposure to azinphos-methyl for workers was estimated to be 0.14 µg/kg/day using the mean annual consumption for the U.S. population. The combined chronic exposure for mixer/loader/applicators ranged from 0.9 to 2.0 µg/kg/day. The combined chronic exposure ranged from 0.6 to 1.2 µg/kg/day for proppers and from 10.2 to 20.5 µg/kg/day for thinners and harvesters. The potential dietary contribution to the total exposure for workers was variable depending on the magnitude of their potential occupational exposure. The dietary contribution was greatest among proppers whose occupational exposure was lowest (25-40% of total acute exposure). The potential dietary contribution was lowest (2-5% of total acute exposure) among other agricultural workers whose occupational exposure was high.

C. RISK CHARACTERIZATION

The risk for human health effects is expressed as a margin of exposure (MOE). The MOE is the ratio of the NOEL from experimental animal studies to the human exposure dosage.

$$Margin\ of\ Exposure = \frac{NOEL}{Exposure\ Dosage}$$

Acute Toxicity

Occupational

The MOEs for acute occupational exposure were calculated using the ADD for the exposure dosage and the acute NOEL (1.0 mg/kg). The MOEs for mixer/loader/applicators are summarized in Table 20. The MOEs for acute toxicity ranged from 15 to 33 for occupational exposure alone. The MOEs for combined occupational and dietary exposure ranged from 14 to

C. RISK CHARACTERIZATION (cont.)

Table 20. Estimated Margins of Exposure for Potential Acute and Chronic Exposure to Azinphos-methyl for Mixer/Loader/Applicators[a]

	Acute		Chronic	
Type of Sprayer	Occupational	Combined[b]	Occupational	Combined
Electrostatic[c]	33	31	350	310
Airblast[c]	23	22	230	220
Airblast[d]	16	16	170	160
Airblast[d,e]	17	17	180	170
Airblast[d,f]	15	14	150	140

[a] Margin of exposure = NOEL / Exposure Dosage. Acute NOEL = 1.0 mg/kg (rats, inactivity, reduced reflexes, and brain ChE inhibition). Chronic NOEL = 0.28 mg/kg/day (rats, brain ChE inhibition). Exposure dosages from Table 15. Values were rounded to two significant figures.
[b] Combined = Combined occupational and dietary exposure
[c] Schneider *et al.*, 1987
[d] Franklin *et al.*, 1981
[e] A rubber suit was worn in addition to basic protective clothing
[f] A rubber coat was worn in addition to basic protective clothing

Table 21. Estimated Margins of Exposure for Potential Acute and Chronic Exposure to Azinphos-methyl for Field Workers[a]

		Acute		Chronic	
Job Type	Crop	Occupational	Combined[b]	Occupational	Combined
Harvester	peach/ nectarine	12	11	14	14
Harvester	apple	19	18	22	22
Harvester	orange	21	21	25	25
Thinner	peach/ nectarine	12	12	15	14
Thinner	apple	24	23	28	27
Propper[c]	peach/ nectarine	220	170	260	230
Propper	apple	460	270	560	470

[a] Margin of exposure = NOEL / Exposure Dosage. Acute NOEL = 1.0 mg/kg (rats, inactivity, reduced reflexes, and brain ChE inhibition). Chronic NOEL = 0.28 mg/kg/day (rats, brain ChE inhibition). Exposure dosages from Table 16. Values were rounded to two significant figures.
[b] Combined = Combined occupational and dietary exposure
[c] Propper = Worker who props up heavy, fruit laden branches

C. RISK CHARACTERIZATION (cont.)

31. The MOEs for field workers are summarized in Table 21. For occupational exposure alone, the MOEs for acute toxicity ranged from 12 to 24 for thinners and harvesters and from 220 to 460 for proppers. When dietary exposure was added, the MOEs ranged from 11 to 23 for thinners and harvesters and from 170 to 270 for proppers.

General Population

For dietary exposure alone, the MOEs were calculated for the various population subgroups using the NOEL for acute toxicity and the acute dietary exposure dosages (Table 22). The MOEs for acute toxicity ranged from 81 for non-nursing infants less than one year old to 680 for males 20 years and older.

Chronic Toxicity

Occupational

The MOEs for chronic occupational exposure were calculated using the AADD for the exposure dosage and the chronic NOEL (0.28 mg/kg/day). The MOEs for mixer/loader/ applicators ranged from 150 to 350 for occupational exposure alone (Table 20). With dietary exposure included, the MOEs ranged from 140 to 310. The MOEs for harvesters and thinners ranged from 14 to 28 for occupational exposure alone (Table 21). The MOEs were essentially unchanged after dietary exposure was added. For proppers, the MOEs ranged from 260 to 560 for occupational exposure alone. The MOEs for combined occupational and dietary exposure ranged from 230 to 470.

General Population

The MOEs for chronic dietary exposure to azinphos-methyl were calculated for the various population subgroups using the NOEL for chronic toxicity and the chronic dietary exposure dosages (Table 22). The MOEs ranged from 540 for non-nursing infants less than one year old to 2,800 for males 20 years and older.

Table 22. Estimated Margins of Exposure for Potential Acute and Chronic Dietary Exposure to Azinphos-methyl for Selected Population Subgroups[a]

Population Subgroup	Margin of Exposure	
	Acute	Chronic
U.S. Population	400	1,900
Western Region	350	1,800
Nursing Infants (<1 yr old)	88	1,300
Non-Nursing Infants (<1 yr old)	81	540
Children (1-6 yrs)	150	760
Children (7-12)	280	1,200
Females (13+ yrs/pregnant/not nursing)	660	2,500
Females (13+ yrs/nursing)	340	1,800
Females (13-19 yrs/not pregnant/not nursing)	600	2,700
Females (20+ yrs/not pregnant/not nursing)	620	2,700
Males (13-19 yrs)	660	2,400
Males (20+ yrs)	680	2,800
Seniors (55+ yrs)	540	2,400
Workers (16+ yrs)	650	NA

[a] Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 1.0 mg/kg (rats, inactivity, reduced reflexes, and brain ChE inhibition). Chronic NOEL = 0.28 mg/kg/day (rats, brain ChE inhibition). Exposure dosages from Table 17. Values rounded to two significant figures.

NA Not available. The TAS Exposure-1™ does not calculate an exposure estimated for customized population subgroups, such as, workers 16 years and older.

V. RISK APPRAISAL

Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects observed in toxicity studies with laboratory animals 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 azinphos-methyl are delineated in the following discussion.

Hazard Identification

Although the physiological role of AChE in the nervous system is well known, there is some uncertainty regarding the toxicological significance of brain ChE inhibition because of the poor correlation between the severity of cholinergic signs and the level of ChE inhibition in the brain (U.S. EPA, 1988b). Several factors probably contribute to the poor correlation. One of these factors is that ChE inhibitors produce different degrees of inhibition in the various regions of the brain (Nieminen *et al.*, 1990). Certain cholinergic signs may be due to inhibition in specific regions of the brain. The level of brain ChE inhibition required to produce these effects may not be representative if the activity is measured in the whole brain or regions of the brain that are insensitive to ChE inhibitors. Another factor is that some cholinergic signs may be due to peripheral rather than central inhibition of AChE (Murphy, 1986). For example, some of the respiratory effects may be due to peripheral inhibition of AChE in the diaphragm resulting in paralysis. In addition, brain ChE activity is usually measured at the end of the study whereas the cholinergic signs may be observed at various time points during the study. Often cholinergic signs are observed only at the beginning of the study and then the animals appear to develop a "tolerance" to the ChE inhibitor. This adaptation or "tolerance" may be due to several possible mechanisms including down-regulation of post-synaptic receptors (Costa *et al.*, 1982). Finally, clinical observation in animal studies is a very crude and subjective measurement. Some mild cholinergic signs, such as headaches and anxiety, cannot readily be detected in animals. The clinical signs can also be missed because of the timing of the observations, especially with reversible ChE inhibitors. Rodents are nocturnal and generally eat and drink at night. If a chemical is a reversible inhibitor, some of the cholinergic signs could be missed because the signs occurred shortly after the animals had eaten during the night. There may also be other subtle changes in neurological function that will only be detected if the animal is stressed or required to perform certain tasks (Nagymajtényi *et al.*, 1988; Raffaele and Rees, 1990). It is possible that some level of brain ChE inhibition can occur without any untoward effect on neurological function, overt or subtle. However, the only way to be certain of this is through rigorous behavioral and neurophysiological testing in animals or humans. Although some neurobehavioral testing was conducted (FOB and motor activity) with acute exposure to azinphos-methyl, no tests for memory or learning deficits were performed. Nor were there any tests for subtle neurological effects with subchronic or chronic exposure to azinphos-methyl. Therefore, the assumption was made that since there was a statistically significant inhibition of brain ChE inhibition, there was probably some deleterious effect to the neurological system.

A NOEL of 1 mg/kg from an acute rat neurotoxicity study was selected for evaluating acute exposure to azinphos-methyl in humans based on effects observed in a FOB (sitting or

lying in open field, reduced approach response and uncoordinated righting response) and brain ChE inhibition (49% of controls) in females (Sheets, 1994). Both of these endpoints are of uncertain toxicological significance. As mentioned above, the brain ChE inhibition was assumed to be toxicologically significant because of the lack of testing for learning and memory deficits. The performance in the FOB is also uncertain because the differences were not statistically significant, but they were assumed to be toxicologically significant because only 3 of 18 female survived at 6 mg/kg. Therefore, it is possible the NOEL is higher than assumed. However, the LOEL of 3 mg/kg in this study was similar to the LOELs observed in two rat LD_{50} studies, 2.0 and 2.5 mg/kg (Crawford and Anderson, 1974; Mihail, 1978). These studies were not used because the reports were so brief that the clinical signs were not described for each dose level and the studies did not meet FIFRA guidelines. Higher NOELs of 2.5 mg/kg were reported in several other acute oral toxicity studies; however, only one of these studies, a rabbit developmental toxicity study, did not have major deficiencies (Hecht, 1955; Short *et al.*, 1978; Clemens *et al.*, 1988). The NOEL in the rabbit study was based on an increase in pre- and post-implantation losses. The toxicological significance of this endpoint is also uncertain because they were not observed in two other range-finding studies where rabbits were administered azinphos-methyl at equal or higher dose levels. However, the number of animals per dose was too small (2-4 animals/dose) in both studies to allow meaningful statistical analysis.

While brain ChE inhibition was one of the more sensitive endpoints for azinphos-methyl, it was not the most sensitive with subchronic and chronic exposure. In a rat reproductive toxicity study, decreased viability and lactation indices were observed at a dose level which resulted in only a slight reduction in brain ChE activity (73% of control activity). In a one-year dog study, an increase in diarrhea and mucus in the feces was observed in males at a dose level which did not produce significant brain ChE inhibition. Because the increase in males did exhibit a clear dose-response, it is uncertain if this effect was treatment-related. It is possible that these clinical signs could be due to peripheral ChE inhibition, in which case, the chronic NOEL for azinphos-methyl may be lower than estimated.

The toxicity of azinphos-methyl may be underestimated if people are exposed simultaneously to other organophosphates, such as, DDVP, diazinon, disulfoton, etc., which have been shown to have a synergistic effect on the acute toxicity of azinphos-methyl in laboratory animals. Synergism between organophosphates is not uncommon, although the exact mechanism of this synergism is uncertain (Murphy, 1986). One possible mechanism is the inhibition the carboxylesterase enzymes that are involved in the detoxification of some organophosphates. Another mechanism could be competition for non-vital binding sites which may act as a buffer, thereby protecting AChE.

Exposure Assessment

In the study by Franklin *et al.* (1981), the exposure estimates for mixer/loader/ applicators were based on urinary metabolites of azinphos-methyl which are considered a more accurate method of estimating exposure than dermal patches. It is noteworthy, however, that the use of rubber suits and rubber coats did not reduce the exposure significantly. One possible explanation for this finding could be a "bellows effect" drawing pesticide through the openings of the rubber suit. The exposure estimates for field workers was based on DFRs and transfer factors. Consequently, these exposure estimates were more uncertain than if they had been based on residues on skin and clothing or urinary metabolites.

V. RISK APPRAISAL (cont.)

The acute and chronic exposure estimates for both mixer/loader/applicators and field workers were based on arithmetic means. The average exposure is acceptable for evaluating the risk of chronic effects since it is unlikely that someone will be continually exposed to high levels over a long period of time. On other hand, acute effects can occur with only a single exposure. In order to protect most workers, an upper bound estimate is generally considered an appropriate means for estimating acute exposure. Because of limitations in the data available for estimating exposure, a reliable upper bound estimate could not be calculated for acute exposure to azinphos-methyl.

Several factors may have resulted in an overestimation of the dietary exposure. The acute dietary exposure may have been overestimated since the high value was used for mixed commodities such as fruit juice which may be better represented by the average value. If average values have been used for mixed commodities, the MOEs for nursing and non-nursing infants would increase from 88 and 81 to 102 and 90, respectively. However, people may individually prepare fruit juices from just a few pieces of fruit, so the average was not used. Another factor which probably resulted in an overestimation of chronic dietary exposure was that exposure was not adjusted for percent of crop treated due to insufficient information. It is unlikely that all the commodities consumed on a single day or on average were treated.

The intake of azinphos-methyl residues may have also been overestimated since DPR's monitoring program measures residues in the whole commodity, not just the edible portion. Several metabolism and residue studies for apples and oranges found that greater than 85% of the residues remain on the surface or in the peel 21-28 days after treatment (Krolski, 1988b; Grace, 1990b&c; Gronberg *et al.*, 1975). Greater than 99% of the residues of azinphos-methyl remained on the foliage of potato plants 28 days after application (Krolski, 1988a). Since the MDL (0.03 ppm) and 50% of the MDL were used for acute and chronic dietary exposure, respectively, when no residues were detected, the dietary exposure for some commodities like potatoes may be exaggerated. Residues in whole potatoes were less than 0.01 ppm in a field study 7 days after the third application of azinphos-methyl at 60 oz of active ingredient/acre/ application which is over 5 times higher than maximum application rate (Grace, 1990e). Residues in orange juice were less than 0.02 ppm 7 days after the second application of azinphos-methyl at 48 oz of active ingredient/acre/application which is nearly twice the maximum application rate (Grace, 1990c).

The FDA's Total Diet Study from 1986 to 1991 estimated the mean dietary intake of azinphos-methyl was 0.0083 and 0.0311 µg/kg/day for infants 6-11 months old infants and children 2 years old, respectively (Gunderson, 1995). This residue monitoring program analyzes residues in foods prepared for "table-ready" consumption compared to DPR's monitoring program which analyzes residues in whole RACs (including inedible portions) that are usually collected at distribution centers. These estimates were less than 10% of the intakes DPR estimated from the residues in RACs. However, this report did not contain sufficient information about the MDL, the number and type of samples tested to be useful in this current risk assessment.

One factor that may have underestimated acute dietary exposure is that DPR's monitoring program analyzes composite samples rather than single serving samples. More variation would be expected with single serving samples and, therefore, the 95th percentile would probably be higher.

V. RISK APPRAISAL (cont.)

Risk Characterization

Generally, an MOE of at least 100 is considered sufficiently protective of human health when the NOEL is derived from an animal study. The MOE of 100 allows for humans being 10 times more sensitive than animals and for the most sensitive human being 10 times more sensitive than the average human. The MOEs for acute occupational exposure were below 100 for all pesticide workers, except for proppers. The MOEs for chronic occupational exposure were greater than 100. The MOEs for acute dietary exposure were less than 100 for infants, nursing and non-nursing. The MOEs for chronic dietary exposure were greater than 100 for all population subgroups.

The intraspecies differences for azinphos-methyl may be less than assumed based on the one human study. If the NOEL from the acute neurotoxicity study is compared with the NOEL from the 30-day human study, humans appear to be only 3.5 times as sensitive as rats (1 mg/kg vs. 0.29 mg/kg). The difference between species may be even less since the dose levels in the human study were never increased to a point where significant ChE inhibition was seen or other adverse effects. The NOEL in the human study probably would be higher, too, if only a single dose had been given.

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 (US EPA, 1991). The U.S. EPA 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 Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies (e.g. Pesticide Enforcement Branch of DPR).

The data requirements established by U.S. EPA 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 organism, (4) product performance such as efficacy, and (5) product chemistry which includes physical-chemical characteristics and analytical method (CFR, 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 (U.S. EPA, 1982).

Currently, the tolerances set by U.S. EPA 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 (U.S. EPA, 1991). U.S. EPA uses the Reference Dose for non-cancer risks, and negligible level (generally defined as a lifetime probability of excess 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.

Tolerances have been established for residues of azinphos-methyl in a variety of raw agricultural commodities in meat, fat and meat by-products, and in processed food and feed. Tolerance levels for food range from 0.04 ppm for milk up to 10 ppm for almond hulls and kiwi fruit. As discussed previously under the dietary exposure assessment section, Miles Inc. has dropped 11 uses from the azinphos-methyl label including barley, beans, clover, grass mixture, oats, pasture grass, peas, soybeans, spinach, tobacco, and wheat. For this reason tolerances for these uses were not analyzed. Specific tolerance values for various raw agricultural commodities and processed food and feed are presented in Appendix B.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance was conducted for each individual label-approved commodity. The TAS Exposure-4 software program and the 1989-1991 USDA CSFII data were 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 the tolerance decreases as the number of commodities included in the assessment increases. Since tolerances were established for azinphos-methyl on a number of RACs only the tolerances for the commodities on FDA's list of the 20 most frequently consumed fruits and vegetables consumed were examined. In addition, blueberries were examined because of the tolerance was high (5 ppm). The 95th percentile of users-days exposures for all specific population subgroups was used in evaluating the margins of exposure for the various population subgroups.

The acute MOEs for the 28 commodities analyzed are summarized in Table 22. There was no consumption reported in the 1989-1991 USDA CSFII data for some commodities by certain population subgroups. These population subgroups included nursing infants less than 1 year old, non-nursing infants less than 1 year old, pregnant females 13 years and older, and nursing females 13 years and older. However, the number of individuals surveyed in these population subgroups was small, so that it is uncertain if these commodities are consumed by these subgroups. The MOEs were less than 100 for one or more population subgroups for various commodities, including grapes, watermelon, apples, grapefruit, kiwi fruit, oranges, cantaloupe, honeydew melon, pears, plums, peaches, tomatoes, tangerines, broccoli, nectarines, and cabbage. Infants and children were the primary population subgroups with the MOEs below 100. The tolerances for blueberries, cauliflower, strawberries, limes, cucumbers, onions, celery, potatoes, green onions, cherries, lemons, and green peppers resulted in MOEs greater than 100 for all populations subgroups.

Based on these analyses, the tolerances for grapes, watermelon, apples, grapefruit, kiwi fruit, oranges, cantaloupe, honeydew melon, pears, plums, peaches, tomatoes, tangerines, broccoli, nectarines, and cabbage should be reviewed. In order to obtain MOEs of at least 100 for these commodities, the tolerances would need to be reduced to 1.0 ppm for kiwi fruit, honeydew melons, plums, tomatoes, tangerines, nectarines, and cabbage. The tolerances for grapefruit, cantaloupe, peaches, and broccoli would need to be lowered to 0.5 ppm. Grapes, watermelon, and pears would need their tolerances reduced to 0.2 ppm. The tolerances for apples and oranges would need to be reduced to 0.1 and 0.05 ppm, respectively, for the MOEs for nursing infants to be greater than 100.

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 chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from the FDA and DPR pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (DPR, 1991, 1992c, 1993, 1995 & 1996b).

Table 22. Margins of Exposure for Acute Dietary Exposure to Tolerance Levels of Azinphos-methyl on Selected Raw Agricultural Commodities[a]

Population Subgroup	Grapes	Watermelon	Apples	Grapefruit	Kiwi Fruit	Oranges	Cantaloupe	Honeydew Melon	Pears	Plums
U.S. Population	**39**	**35**	**39**	**66**	**24**	**74**	**82**	**73**	**75**	**94**
Western Region	**37**	**49**	**46**	**47**	**22**	**80**	**98**	**81**	**44**	99
Nursing Infants (<1 yr)	**7**	NC	**7**	NC	NC	**4**	NC	NC	**13**	169
Non-Nursing Infants (<1 yr)	**23**	IC	**13**	IC	NC	**32**	NC	NC	**20**	**69**
Children (1-6 yrs)	**17**	**23**	**19**	**70**	**18**	**34**	**31**	**51**	**43**	**66**
Children (7-12 yrs)	**43**	**36**	**40**	**41**	**25**	**63**	**74**	**93**	**94**	**64**
Females (13+ yrs/P/NN)	**91**	**63**	**64**	125	NC	**72**	107	IC	378	**69**
Females (13+ yrs/N)	**26**	115	**31**	**78**	NC	100	204	156	118	180
Females (13-19 yrs/NP/NN)	**46**	**62**	**75**	**52**	**70**	111	**77**	155	103	296
Females (20+ yrs/NP/NN)	**44**	**65**	110	**75**	**65**	113	**87**	**63**	153	102
Males (13-19 yrs)	**68**	**55**	**89**	150	107	**75**	146	151	192	143
Males (20+ yrs)	**49**	**67**	121	**64**	**38**	132	110	**86**	190	143
Seniors (55+ yrs)	**63**	**67**	125	**68**	**46**	130	**95**	**75**	176	118

a Based on 95th exposure percentile for all user-day population subgroups.
NC = There was no consumption of this commodity by this population subgroup in the 1989-1991 USDA Continuing Survey of Food Intakes by Individuals.
IC = Too few people in this population subgroup consumed this commodity to obtain an reliable estimate of the 95th percentile of exposure
P = Pregnant
NN = Not nursing
N = Nursing
NP = Not pregnant

Table 22 (cont.). Margins of Exposure for Acute Dietary Exposure to Tolerance Levels of Azinphos-methyl on Selected Raw Agricultural Commodities[a]

Population Subgroup	Peaches	Tomatoes	Tangerines	Broccoli	Nectarines	Cabbage	Blueberries	Cauliflower	Strawberries
U.S. Population	127	104	127	**99**	**91**	157	147	196	251
Western Region	132	106	**90**	114	**66**	178	221	187	322
Nursing Infants (<1 yr)	**49**	**61**	NC	130	NC	NC	164	NC	483
Non-Nursing Infants (<1 yr)	**31**	**78**	NC	131	NC	323	200	>2,000	>2,000
Children (1-6 yrs)	**66**	**59**	**85**	**40**	**55**	**65**	105	115	570
Children (7-12 yrs)	**97**	**81**	**92**	**54**	103	160	134	140	328
Females (13+ yrs/P/NN)	257	132	NC	241	131	141	627	324	248
Females (13+ yrs/N)	156	135	379	151	240	185	135	1,589	128
Females (13-19 yrs/NP/NN)	163	105	248	100	171	**72**	296	289	232
Females (20+ yrs/NP/NN)	195	137	204	133	96	149	212	217	208
Males (13-19 yrs)	214	121	195	128	168	183	127	129	429
Males (20+ yrs)	205	126	145	169	136	198	143	223	281
Seniors (55+ yrs)	188	144	349	138	126	162	140	219	232

a Based on 95th exposure percentile for all user-day population subgroups.
NC = No consumption of this commodity by this population subgroup in the 1989-1991 USDA Continuing Survey of Food Intakes by Individuals.
P = Pregnant
NN = Not nursing
N = Nursing
NP = Not pregnant

Table 22 (cont.). Margins of Exposure for Acute Dietary Exposure to Tolerance Levels of Azinphos-methyl on Selected Raw Agricultural Commodities[a]

Population Subgroup	Limes	Cucumbers	Onions	Celery	Potatoes	Green Onions	Sweet Cherries	Lemons	Bell Peppers
U.S. Population	314	337	470	592	634	769	842	1,356	>2,000
Western Region	369	485	473	519	603	694	830	1,320	>2,000
Nursing Infants (<1 yr)	NC	1,050	220	604	558	NC	287	NC	>2,000
Non-Nursing Infants (<1 yr)	>2,000	1,592	265	374	460	NC	152	>2,000	>2,000
Children (1-6 yrs)	172	190	302	285	381	638	602	820	>2,000
Children (7-12 yrs)	215	235	371	479	420	410	1,192	1,178	>2,000
Females (13+ yrs/P/NN)	>2,000	357	497	1,043	974	>2,000	1,716	1,281	>2,000
Females (13+ yrs/N)	NC	305	445	475	689	1,306	249	1,363	>2,000
Females (13-19 yrs/NP/NN)	240	231	552	600	700	932	>2,000	1,309	>2,000
Females (20+ yrs/NP/NN)	288	326	562	691	868	649	1,281	1,279	>2,000
Males (13-19 yrs)	1,243	607	542	742	466	1,008	1,744	1,793	>2,000
Males (20+ yrs)	460	413	515	703	778	1,009	716	1,660	>2,000
Seniors (55+ yrs)	672	335	503	721	844	717	922	1,468	>2,000

a Based on 95th exposure percentile for all user-day population subgroups.
NC = No consumption of this commodity by this population subgroup in the 1989-1991 USDA Continuing Survey of Food Intakes of Individuals.
P = Pregnant
NN = Not nursing
N = Nursing
NP = Not pregnant

VII. CONCLUSIONS

The risks of potential adverse human health effects for occupational and dietary exposure to azinphos-methyl were evaluated. Generally, a MOE greater than 100 is desirable to protect against adverse health effects in humans. The MOEs for acute effects were less than 100 for all pesticide workers, except proppers. The MOEs for chronic effects were less than 100 for harvesters and thinners, but between 100 and 600 for mixer/loader/applicators and proppers. Mitigation should be considered for those occupational activities where MOEs were less than 100. For acute dietary exposure in the general population, the MOEs were less than 100 for nursing and non-nursing infants less than one year old. The acute dietary MOEs ranged from 150 to 680 for the other population subgroups. The MOEs for chronic dietary exposure were between 540 and 2800 for all population subgroups. Non-nursing infants less than one year old had the lowest MOEs for both acute and chronic dietary exposure. The tolerances for a number of commodities (grapes, watermelon, apples, grapefruit, kiwi fruit, oranges, cantaloupe, honeydew melon, pears, plums, peaches, tomatoes, tangerines, broccoli, nectarines, and cabbage) should be reviewed based on MOEs of less than 100 for some population subgroups using the 95th percentile for acute exposure.

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IX. APPENDICES

APPENDIX A Worker Exposure Assessment

APPENDIX B U.S. EPA Tolerances for Azinphos-methyl

APPENDIX A

WORKER EXPOSURE ASSESSMENT

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO PESTICIDE PRODUCTS THAT CONTAIN AZINPHOS-METHYL

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ABSTRACT

Azinphos-methyl (AZM) is an organophosphate insecticide. AZM is a highly toxic pesticide that can cause cholinesterase depression. It is used on many crops, primarily on stone fruits. There were 119 illnesses/injuries associated with AZM exposure in California between 1984 and 1990. These cases were mostly systemic in nature. The human dermal absorption rate for AZM is 16%. AZM is metabolized and eliminated relatively rapidly, mostly in urine of human and animals. Mixer/loader/applicators' absorbed daily dosage (ADD) was estimated to be in the range of 20.6 to 68.5 ug/kg/day. Field workers' exposure varied greatly, depending on the amount of the dislodgeable foliar residues present at the time of field work and work activity. A set of transfer factors in cm^2/hour (leaf surface area over time) has been developed to estimate field workers' daily dermal exposure (DDE) from the dislodgeable foliar residue (DFR) values present at the time of work. Harvesters' ADD was estimated to range from 47 to 86 ug/kg/day.

This human exposure assessment was constructed to be incorporated in to the risk characterization document for AZM because of possible oncogenic effects noted in laboratory rats.

Department of Pesticide Regulation
Worker Health and Safety Branch

Human Exposure Assessment

AZINPHOS-METHYL

November 30, 1992
Revised April 30, 1993

GENERAL CHEMISTRY

Azinphos-methyl (O, O Dimethyl S-[(4-oxo- 1, 2, 3-benzotriazin-3 (4H)-yl) methyl] phosphorodithioate) is an organophosphate insecticide. Its trade name is Guthion^{R}. Azinphos- methyl's empirical formula is $C_{10}H_{12}N_3O_3PS_2$ and its molecular weight is 317.3 daltons. Pure azinphos-methyl (AZM) has a melting point of ~74^{o}C and a vapor pressure of 1.6 x 10^{-6} mmHg at 20^{o}C. It is rapidly hydrolyzed in alkali, forming anthranilic acid, and is also hydrolyzed in acid at a slower rate. It is slightly soluble in water (30 mg/liter at 25^{o}C) and readily soluble in organic solvents except aliphatics. AZM is an acetylcholinesterase inhibitor (1)(2)(3).

EPA STATUS

Upon review and evaluation of available data and relevant information on AZM, the U.S.EPA issued guidance in 1986 for the reregistration of pesticide products containing AZM as the active ingredient. The U.S.EPA did not place AZM into the Special Review process at that time. The guidance document listed numerous data gaps, including reentry protection and other exposure data. It also called for revised labeling, including additional protective clothing and work safety statements.

USAGE

Liquid formulations that contain greater than 13.5% AZM are classified as restricted use pesticides by U.S.EPA because of their acute toxicity. These formulations are for sale to and use only by certified applicators or persons under their supervision. AZM can be used by ground or aerial equipment. It can also be applied through irrigation systems (sprinkler, center-pivot or linear) to crops such as alfalfa, cotton and vegetables. The highest rate of application is 2 lb. of active ingredient (a.i.)/acre. The frequency of application varies with crop. The major uses of AZM in California, as reported by the 1990 Pesticide Use Report, are shown in Table 1 (4). In the category of "All other uses", the range of applied poundage is from plums (4,695 lb.) to eggplants (1.5 lb.).

Table 1

Reported Major Uses Greater Than 10,000 Pounds (lb.) of
Azinphos-methyl During 1990

CROP	LB. a.i. Applied	Percent of Total
Almonds	242,717	47
Pears	57,487	11
Walnut	54,986	11
Apples	52,217	10
Peaches	35,366	7
Pistachio	30,278	6
Cotton	13,242	2
SUBTOTAL	486,293	94
All other uses	31,251	6
TOTAL	517,544	100

Fong, WH&S, 1992

FORMULATIONS

There are nine products presently (11/19/92) registered in California that contain AZM as their active ingredient. Six products are wettable powders that contain 35% or 50% a.i. and the other three products are 22% emulsifiable concentrates that contain 2 lb. of a.i./gallon. Mobay Corporation and Gowan Company are the only two registrants in California for AZM.

LABEL PRECAUTION

All AZM-formulated products are toxicity category I (Danger, Poison) for their acute toxicities. AZM can be fatal if ingested. Hazards of ingestion, inhalation, and dermal and eye contact have been indicated on the product labels. Workers are required to wear protective clothing, natural rubber gloves, and goggles when loading the spray tank or handling the concentrate. A mechanical exhaust ventilation system must be provided if the product is handled indoors.

When handling the concentrate, workers must wear the following protective clothing and equipment:
1) A protective suit of one or two pieces that cover all parts of the body except the head, hands and feet.
2) Chemical resistant gloves.
3) Chemical resistant shoes, shoe coverings, or boots.
4) Chemical resistant apron.
5) Goggles or a face shield.
6) A Pesticide or organic vapor respirator approved by NIOSH.

Workers must handle the concentrate using a closed system, and long sleeved shirt and long pants may be substituted for the protective suit and the respirator requirement.

Workers must wear the following protective gear during the application, equipment repair or disposal of the pesticide:

1) A protective suit of one or two pieces that cover all parts of the body except the head, hands and feet.
2) Chemical resistant gloves.
3) Chemical resistant shoes, shoe coverings, or boots.

During airblast application, workers must also wear a chemical resistant head covering. If the application is made from an enclosed tractor cab, airplane cockpit, or other suitable enclosed vehicle in which windows are rolled up, a long sleeved shirt and long pants are considered adequate. Chemical resistant gloves must be available in the cab or cockpit and must be worn while exiting. Use of human flaggers is prohibited during aerial application, unless they are in totally enclosed vehicles.

REENTRY INTERVAL

Worker reentry intervals in California for AZM-treated crops are 30 days for citrus, 21 days for grapes, 14 days for apples, peaches, nectarines and other stone fruits except almonds. When a total of one lb./acre of AZM or less has been applied to apples, peaches, nectarines, and other stone fruits (except almonds) in the current calendar year, thinning may be done after 7 days (5). The reentry to all other crops is one day.

WORKER EXPOSURE ILLNESSES

From 1984 through 1990, there have been 119 illnesses/injuries associated with AZM exposure. Fifty-five of these cases were associated with AZM exposure only, while the remaining 64 were exposures to AZM in combination with other pesticides. Most of the illnesses were systemic in nature (96 total incidents accounting for 81% of the cases). Seven eye injuries and 16 skin effects constitute the balance of the illnesses. No deaths were associated with AZM exposure during this period.

DERMAL TOXICITY AND ABSORPTION

The acute dermal LD_{50} in rats has been reported to range from 80 to 220 mg/kg (2, 6), indicating substantial dermal absorption in rats.

Dermal penetration of AZM was studied by administering ^{14}C-AZM to the ventral forearms of six male human volunteers (7). The dose was dissolved in a small amount of acetone to prepare a 0.25% solution. The site of application was not occluded. Participants were asked not to wash the application site for 24 hours. In order to determine the extent of AZM metabolites eliminated in urine, another group of six human volunteers were administered a dose (1 uCi) of ^{14}C-AZM intravenously (IV). Urine samples from all participants were collected for five days following ^{14}C-AZM administration. Radioactivity of the samples was measured using a scintillation counter. Five-day urinary ^{14}C recovery was 69.5% $\pm$6.9 of the administered IV dose. The results of urinary excretion following dermal administration were corrected for incomplete urinary excretion that was observed in the IV study. The mean of five-day ^{1}^{14}C recovery was 15.9% $\pm$7.9 of the administered dermal dose. The rate of elimination in urine varied with time, both in dermal and IV studies.

Table 2

Percent Urinary Elimination of ^{14}C-AZM Administered Dose (Dermal) in Human

Hours after administration	% Elimination/hour *
0-4	0.044
4-8	0.202
8-12	0.294
12-24	0.276
24-48	0.207
48-72	0.125
72-96	0.059
96-120	0.040
Total	15.9 ± 7.9 (120 hours)

* Corrected for incomplete urinary elimination (69.5%).

Formoli, WH&S, 1992

A dermal absorption rate of 16% will be assumed for regulatory purposes to extrapolate absorbed doses from dermal exposure.

METABOLISM

AZM was absorbed extensively and eliminated relatively rapidly in rats administered carbonyl-^{14}C-AZM orally or intravenously (8) . Rats were dosed with 0.1 mg/kg and 2 mg/kg orally and intravenously, and 6 mg/kg orally. Recoveries were determined from the elimination of the activity in the exhaled air, urine, and feces. Only less than 0.1% of the administered dose was recovered in the exhaled air in 24 hours following oral or intravenous dosing of 2 mg/kg AZM. Rats excreted 60% to 70% of the administered dose in urine and 25% to 35% of the administered dose in feces within 48 hours of 0.1 mg/kg or 2 mg/kg administration of ^{14}C-AZM, regardless of the route of administration. These data indicate that oral bioavailability is virtually complete. Oral administration of a 6 mg/kg dose also showed similar recoveries in urine in 48 hours. The excretion of the radioactivity continued up to the last day of the observation (16 days) but at a very slow rate. Average recoveries were 97% to 100% of the administered dose. The amount of activity in the organs and tissues was 2% of the administered dose four days after the oral or intravenous administration. This amount decreased to less than 1% 16 days after the oral administration of 6 mg/kg.

In another study when rats were administered carbonyl-^{14}C-AZM intravenously, approximately 65% of the applied radioactivity was recovered in the urine (9). The activity was distributed among more than 10 spots in thin-layer chromatography. No parent compound was detected in urine. Only 10% of the activity in the urine was determined to be desmethyl-azinphosmethyl and 2% was identified as benzazimide (AZM metabolites). No other metabolites were identified in urine.

In a more recent study (1988), 72 hours after the administration of 0.125 mg/kg, 68 - 73% of the activity was recovered in urine and 21 - 26% of the activity was recovered in feces of rats dosed orally with (ring-UL-^{14}C)-AZM (10). The radioactivity was measured using a liquid scintillation counter. Metabolites were separated into peaks by a high performance liquid chromatograph (HPLC) radioactivity detector and characterized by different retention times in reference to the analytical standards. No mass spectral method was used to chemically identify these metabolites. A total of 12 radioactive peaks were separated by HPLC in urine samples. Eight of these metabolites

were characterized with reference standards and accounted for 59 to 68% of the total dose. The metabolites that were characterized are as follows:

Metabolite	% total dose		
	Lowest		Highest
Cysteinylmethylbenzazimide sulfone	13	-	30
Cysteinylmethylbenzazimide	0	-	2
Methylsulfinymethylbenzazimide	2	-	13
Benzazimide	0	-	4
Methylsulfonylmethylbenzazimide	14	-	20
Glutathionylmethylbenzazimide	0	-	14
Cysteinylmethylbenzazimide sulfoxide	0	-	12
Desmethyl isoazinphos-methyl	0	-	6

The proposed metabolic pathway of AZM in rats is shown in Figure 1.

The biokinetic behavior of benzazimide in rats was shown to be similar to that of the parent compound (AZM) (11). It was absorbed extensively (>95%) following oral administration and eliminated quickly. Only 1.3% of the administered dose was present in the animal, excluding the gastro-intestinal tract, 24 hours after the oral application. Recoveries reached 54% to 66% of the administered dose in urine and 33% to 45% of the administered dose in feces after 48 hours.

At least 10 metabolites were identified in tissues and/or milk of lactating goats dosed orally with [phenyl-UL-^{14}C]-AZM for 3 consecutive days (12). The goats (2) were sacrificed 17 to 18 hours after the last dose. No AZM oxygen analog was identified in tissues or milk samples. The identified metabolites were:

Azinphos-methyl	Desmethyl isoazinphos-methyl
Benzamide	Methylbenzazamide-type conjugates
Benzamide-type conjugate	Methylsulfinylmethylbenzazimide
Benzazimide	Methylsulfonylmethylbenzazamide
Desmethyl azinphos-methyl oxygen analog	Methylthiomethylbenzazimide

Two principal biochemical systems were suggested to be involved in metabolism of AZM in mice administered [P^{32}]-AZM, orally or intraperitoneally (13). These are: 1) The oxidation of the thiono sulfur moiety to produce the thiol analog of AZM, an extremely potent cholinesterase inhibitor and 2) The hydrolysis of AZM and its thiol analog, producing compounds of lower toxicity. An In vitro metabolism study of AZM by mouse liver has also shown the formation of AZM oxygen analog as a result of oxidative desulfuration of AZM (14). The further degradation of AZM oxygen analog was slower than that of AZM.

DISLODGEABLE FOLIAR RESIDUES

A great number of AZM dislodgeable foliar residue (DFR) studies are available in-house from Worker Health and Safety Branch's data collection efforts and submissions by the registrants. A number of DFR studies are also available in the open literature. Generally, the leaf disc samples were rinsed and dislodgeable residues were analyzed by gas chromatography. In some of these studies, the leaf samples were frozen prior to dislodging the residues. The results of these studies are not included here since overestimation of DFR values could be derived from the absorbed residues released in the damaged leaves. The mean predicted DFR values of the referenced studies for each crop are shown in Table 3. It appears that the foliar dissipation of AZM is relatively slow and crop dependent.

Table 3

Mean Predicted DFR Values (ug/cm^2) in Different Crops

Crop	Apples	Pears	Peaches	Oranges	Cotton
Reference #	15-17	18-19	20-23	24	25-26
Pre-application	ND-0.42	N/A	ND-0.67	N/A	N/A
Post (0 Day)	2.08 ±1.19	1.41 ±0.15	2.16 ±0.49	1.25	1.10 ±0.28
1	1.86 ±0.96	**1.33 ±0.14**	2.07 ±0.49	1.23	**0.60 ±0.07**
3	1.51 ±0.65	1.20 ±0.12	1.92 ±0.53	1.19	0.26 ±0.03
7	1.07 ±0.49	0.96 ±0.08	1.66 ±0.59	1.11	
14	**0.70 ±0.51**	0.66 ±0.03	**1.34 ±0.67**	1.00	
21	0.53 ±0.47	0.45 ±0.01	1.12 ±0.72	0.89	
30	0.40 ±0.39	0.28 ±0.01	0.94 ±0.76	**0.61**	
Formulation	W.P.	W.P.	W.P./E.C.	W.P.	E.C.
Application Rate (lb. a.i./acre)	0.75-2.00	0.75-2.00	1.00-2.25	3.75	0.50
Ave. Day-time Temperature (^{o}F)	72-88	80	89-95	N/A	89-100

ND - Not Detected N/A - Not Available
Bold - Reentry intervals and corresponding DFRs

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WORKER EXPOSURE

Mixer/Loader/Applicator Exposure:

Mixer/loader/applicator (M/L/A) exposure to AZM was monitored using two spray application systems (27). One worker applied a wettable powder formulation AZM to almond trees at a rate of 1.5 lb. a.i./100 gal water/acre, using a conventional air blast sprayer. Two other workers applied the same formulation of AZM to almond trees at a rate of 1.4 lb. a.i./25 gal water/acre, using electrostatic sprayers. Gauze pads were mounted on the outside and under standard uncoated Tyvek^R coveralls of each worker at arms, legs, chest, and back. A portable personal air sampling pump with glass fiber (0.3 um pore size) and XAD-4 sorbent was fastened to the belt and the filter was clipped on the collar (breathing zone) of each worker. Hand washes were taken using Sur-Ten^R solution to measure hand exposure.

Residues on pads at the back, chest, forearm, thigh, and shin of each worker were used to extrapolate exposure to the rest of the body regions. Body region surface areas recommended in the U.S.EPA Subdivision U were used for calculation. The coveralls were assumed as a layer of clothing (long sleeved shirts and long pants) and the residues on the pads located under the coveralls were considered as dermal exposure. The exposure to uncovered areas such as face, and neck were extrapolated from back and chest pads outside the coveralls. The exposure to hands was calculated based on residues found in the hand washes at the completion of the application.

Table 4

Exposure Estimate of Mixer/Loader/Applicators to AZM
Using Electrostatic or Air Blast Application Equipment

	Electrostatic Sprayers		Air Blast Sprayer
	Worker # 1	Worker # 2	Worker # 3
Spray duration (hrs)	2.6	7.0	7.0
Pounds a.i. sprayed	17.5	35.0	22.5
Body Region	ug	ug	ug
Head	1060	2455	6500
Neck	336	1464	2196
Hand	1226	463	246
Rest of Body	1440	1126	2472
Total Dermal Exposure	4,062	5,508	11,414
Dermal Exposure/lb. a.i.	232	157	507
Dermal Exposure/hr	1,562	787	1630
Daily Dermal Exposure	12,498	6,295	13,044
Potential Resp. Exp.	N/D	N/D	459
Absorbed Daily Dosage (ug/kg/day)	28.6	14.4	33.1

Assuming: An 8-hour work day, dermal absorption of 16%, inhalation rate of 29 liters/minute, 50% respiratory intake, body weight of 70 kg, and clothing consisting of a long sleeved shirt, long pants, gloves, hat, and shoes.
ND - Non-detectable

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The two M/L/As using electrostatic sprayers received lower dermal exposure/lb. a.i. sprayed when compared to the M/L/A using an air blast sprayer. The difference narrows when dermal exposure is presented per hour of work (Table 4).

In a separate worker exposure investigation, 16 applicators involved in mixing/loading and application were monitored for urinary dialkyl phosphate excretion, blood cholinesterase activity, and dermal exposure (28). The applicators sprayed Guthion^{R} 50 WP to orchards in British Columbia, at a rate of 0.625 lb. (0.28 kg) a.i./50-70 gal/acre using ultra-low volume air blast equipment. Each applicator was monitored for one day (2.5-9 hours). Ten area residents who were not involved in the spray operation were used as control. Their blood and urine samples were taken at the same time baseline and pre-exposure samples were collected from the applicators.

Each applicator wore a short sleeved cotton shirt, cotton pants, a long sleeved coverall, a respirator with organic vapor/dust cartridges, gloves (cotton, leather, or rubber), and boots (leather or rubber). In addition to these clothing, four applicators wore rubber suits (coat and pants), and another four applicators wore rubber coats. A fluorescent tracer was used to observe dermal exposure under rubber clothing.

Blood samples were taken each day after the end of work. Urine samples were taken 0-16, 16-24, 24-40, and 40-48 hours following initial exposure. Air samples were taken during work in the breathing zone of four applicators. Dermal exposure pads were pinned to the underside of the clothing in such a position that the plastic backing of the pads rested against the skin. Pads were located at the chest, back, upper arm, lower arm, upper leg, and lower leg of each applicator. The tracer was observed under ultraviolet light (UV). Urine and pad samples were analyzed using a gas chromatograph with a flame photometric detector. Blood samples were examined for serum and red blood cell (RBC) cholinesterase activities.

No tracer was seen under the respirator. Tracer deposition was intensive on the neck, hands, and parts of the face that were not covered by the respirator. Tracer was also observed on chest, shoulders, and lower arms under the rubber clothing, confirming the patch findings at these locations. AZM residues in the air samples taken from the breathing zone of the applicators ranged from 0.02 to 0.11 mg/m^3 with a mean of 0.05 mg/m^3. No serum or RBC cholinesterase depression greater than 15% from the baseline values was observed on the day of exposure. There were at least two individuals with 20% and 23% RBC cholinesterase depression from the baseline at post-exposure, but these were within the variation observed in the control group. No attempt was made to quantify dermal exposure to the face, neck, and hands where substantial exposure may have occurred based on observation of the tracer under UV light. AZM residue values on the pads under the clothing were used to measure dermal exposure to the rest of the body. One-half of the minimum detectable level (MDL) was assumed where non-detectable values were reported.

Table 5

Mean AZM Residues in Pads at Various Parts of the Body

# of Spray workers	Duration (hr)	Additional clothing	(ng AZM/cm^2/kg a.i. sprayed) Chest	Back	Upper arm	Lower arm	Upper leg	Lower leg
4	4.1	Rubber Suit	2.5	1.3	1.3	5.6	1.3	1.3
4	4.7	Rubber Coat	2.1	2.4	1.8	3.6	1.6	1.9
8	5.8	None	1.3	1.5	1.8	3.4	1.6	1.3

MDL = 2.5 ng/cm^2

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Body region surface areas as recommended in the U.S.EPA Subdivision U were used in Table 6 to calculate dermal exposure. The dermal exposure values were normalized for an 8-hour work day based on an average kg a.i. sprayed/hour.

Table 6

Mixer/Loader/Applicators' Estimated Daily Dermal Exposure
Excluding Head, Neck, and Hands

Spray duration (hrs)	kg a.i. sprayed	Additional clothing*	Dermal exposure ug/person/kg a.i.	Daily dermal exposure ug/person/day**
4.1	2.25	Rubber suit	33.2 ± 19.6	146
4.7	2.50	Rubber coat	38.8 ± 14.6	165
5.8	2.70	None	29.7 ± 5.9	113

* - Clothing in addition to a short sleeved shirt, long pants, gloves (cotton, leather, or rubber), coveralls, boots, and half-face respirator.

** - Assuming an 8-hour work day.

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AZM metabolites, expressed as AZM equivalents, in 48-hour urinary samples were reported as ug/kg a.i. sprayed. Since workers wore respirators and respirators are not required during application, respiratory exposure was calculated from the mean residues found in the breathing zones. These values were normalized for an 8-hour workday to calculate ADDs.

Table 7

Mixer/Loader/Applicators' Estimated AZM Absorbed Daily Dosage
Based on Urinary Metabolites Recoveries

Additional clothing*	48-hr urinary elimination ug/person/kg a.i.	Absorbed daily dosage ug/person/day**	Respiratory Exposure ug/person/day***	ADD ug/kg/day****
Rubber suit	135 ± 18.1	909	348	18.0
Rubber coat	176 ± 87.1	1152	348	21.4
None	176 ± 105	1008	348	19.4

* Clothing in addition to a short sleeved shirt, long pants, gloves (cotton, leather, or rubber), coveralls, and boots.

** Urinary elimination was corrected for incomplete urinary recovery (65%) in 48 hours.

*** Based on inhalation rate of 1.74 m^3/hour, air residue of 0.05 mg/m^3, and 50% respiratory uptake.

**** Body weight 70 kg and 8-hour workday.

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Assuming a 16% dermal absorption rate, the estimated daily dermal exposure excluding head, neck, and hands in Table 6 greatly underestimates ADD when compared to those in Table 7. The estimated ADD values in this study (Table 7) are slightly lower than those of the previous study (Table 4). The lower rate of application (0.625 lb./acre) in this study may have contributed to the lower ADD values. When M/L/As' ADD values were normalized for the maximum rate of application, the ADD values in these two studies appear essentially the same (Table 8) .

Table 8

AZM Mixer/Loader/Applicators' Estimated Absorbed Daily Dosage

Reference #	Type of Sprayer	Crop	Protective clothing	ADD*** (ug/kg/day)	AADD**** (ug/kg/day)
28	Electrostatic	almonds	*	20.6 - 40.8	0.6-1.1
28	Air blast	almonds	*	44.1	1.2
27	Air blast	orchards	** and rubber suit	57.7	1.6
27	Air blast	orchards	**	62.1	1.7
27	Air blast	orchards	** and rubber coat	68.5	1.9

* - Long sleeved shirt, long pants, gloves, hat, and shoes.
** - Short sleeved shirt, long pants, gloves, coveralls, and boots.
***- Normalized for maximum application rate (2 lb. a.i./acre).
****- Annual Average Daily Dosage based on two weeks of application time in a year (29).

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The rubber suit or rubber coat did not provide additional protection to the applicators of this study. It is also interesting to note that clothing made of closely woven fabrics may not necessarily provide greater dermal protection against AZM sprays compared to some non-woven fabrics. When spray application of an AZM formulation in the field was simulated in the laboratory, it was observed that closely woven fabrics such as cotton chambray permitted the greatest amount of penetration compare to non-woven fabrics such as Tyvek^{R}, Gore Tex^{R}, and Crown Tex^{R} (30). The penetration to the gauze layers placed under the fabrics was 0.014 to 0.023 ug AZM/cm^2 for non-woven fabrics and 0.46 to 0.56 ug AZM/cm^2 for closely woven fabrics. Regardless of AZM penetration and retention, one home laundry cycle with a heavy duty liquid detergent generally removes greater than 94% of AZM from different fabrics usually worn by farm workers (31).

Field Worker Exposure:

In a citrus harvester exposure study, a group of 15 workers' baseline plasma and RBC cholinesterase values were determined at 7, 5, and 3 days prior to exposure (24). Orange trees were treated with a wettable powder formulation of AZM at the rate of 3.75 lb. a.i./acre. Workers entered the treated grove on the seventh day after the application. Workers spent approximately 7 hours picking oranges every day for 10 days. Plasma and RBC cholinesterase activity was determined after 2 and 5 days of work. Two workers wore new cotton gloves, skin patches, and air sampling devices each day for only one hour. Two skin patches were used, one on the forearm and one on the head. Leaf discs were also collected post-application at various intervals for DFR determination.

The average plasma cholinesterase activity levels at day 2 and day 5 of entry were 28% and 40% below the average baseline, respectively. The average RBC cholinesterase activity levels at day 2 and day 5 were 14% and 12% below the average baseline, respectively. Residues in the gloves following one hour of harvesting ranged from 12.6 to 88.0 ug/cm^2. DFR on the 7th, 9th, and 11th day after application were 0.74, 2.2, and 0.82 ug/cm^2, respectively.

A similar study by the same authors with spray concentrate formulation at a rate of 2.25 lb. a.i./acre indicated significant RBC cholinesterase depression (24). Workers entered the treated area 7 days following the application. RBC cholinesterase activities were 28 and 40% below the average baseline 7, and 10 days after entry, respectively.

Table 9

Citrus Harvesters' Potential Hand, Arm, Head, and Respiratory Exposure

Days after application at 3.75 lb.	DFR Values ug/cm^2	ug AZM/cm^2 of Pads Gloves	Arms (ug/cm^2/hr)	Head	Potential Exposure Inhalation ug/l	Dermal ug/hr	Transfer* Factor cm^2/hr a.i./acre
7	0.74	51.0	1.75	0.80	0.13	45,203	61,085
9	2.20	71.5	1.90	0.45	0.15	61,723	28,056
11	0.82	33.4	0.62	0.25	0.12	28,672	34,966
at 2.25 lb. a.i./acre							
7	0.26	14.3	0.24	0.17	0.05	12,237	47,065

Body part surface area as recommended in USEPA Subdivision U (Arms include forearms only).
*- Based on hand, arms, and head potential exposure only.

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Gloves may have over estimated hand exposure (35, 36). But the extent of exposure to trunk, which has been shown to contribute a substantial percentage of harvesters dermal exposure (32, 33, 34), was ignored. Therefore, the transfer factors derived for citrus harvesters in Table 9 may not be reliable.

A group of 28 harvesters entered a treated nectarine orchard 52 days following application of AZM at 0.7 lb. a.i./acre (32). The harvesters wore long sleeved shirts, long pants, socks, and shoes. Urine samples were taken each day for urinary metabolite analysis. Blood samples were taken on day five of the study and two weeks after the completion of the study for cholinesterase analysis. Dermal exposure was monitored using long sleeved T-shirts, face/neck wipes, and hand washes. Potential daily dermal exposure was estimated at 17.2 $\pm$ 5.7 mg AZM plus AZM oxon/person/day. Arm and trunk residues accounted for over 90% of the potential dermal exposure. DMTP was the only metabolite detected in 48-hour urine samples, and it was equivalent to 0.28 - 1.52 mg AZM/person /day with a mean of 0.75 $\pm$ 0.44 mg/person/day. ChE activity remained within the baseline range (-7% to + 14%). Mean DFR for the four days of monitoring was 0.31$\pm$ 0.03 ug/cm^2. A transfer factor of 6935 cm^2/hour was calculated for potential dermal exposure. It is important to note that because of the hot weather the workers did not wear any clothing over the T-shirts that were used as the dosimeters. This may have contributed to an under-estimation of potential dermal exposure because some residues may have penetrated the T-shirts, and resulted in an under-estimation of the transfer factor. From the same study, daily dermal exposure of 10.1 mg/person/day can be estimated from the reverse calculation of the highest (1.52 mg AZM equivalent/person/day) residues found in the urine and 16% dermal absorption (1.52 X 100/16). This provides a transfer factor of 4072 cm^2/hour for harvesters dermal exposure.

A similar study of apple harvesters, peach harvesters, peach thinners, and peach proppers was conducted in California in 1989 (33). The T-shirt (dosimeter) was worn under a long sleeved shirt. Hand exposure was monitored by collecting hand washes and wipes. Face and neck wipes were also taken. Apple harvesters wore nylon knit gloves and their hand exposure was monitored using ungloved hand wipes. Daily dermal exposure, urinary metabolites, and ChE activities were monitored. Mean daily dermal exposure was estimated at 1.7 mg for apple harvesters, 15.6 mg for peach harvesters, 13 mg for peach thinners, and 0.7 mg for peach proppers. Workers entered treated areas 43 days following application of AZM to apples and 31 and 52 days following AZM application to peach orchards. Urinary equivalent of AZM was measured at 1.0 mg for apple harvesters, 2.4 mg for peach harvesters, 1.9 mg for peach thinners, and 0.6 mg for peach proppers. Peach harvesters' mean RBC cholinesterase value declined significantly (19% in second draw and 15% in third draw) below the baseline. Transfer factors of 360 cm^2/hour and 3,038 - 3525 cm^2/hour were estimated based on dermal exposure of apple and peach harvesters, respectively. The low transfer factor for apple harvesters may be because of hedge-row pruning and the nylon gloves

worn by them. The transfer factors for peach thinners and proppers were 3315 cm^2/hour and 174 cm^2/hour, respectively.

An additional peach harvester exposure monitoring in California during 1989 estimated a transfer factor of 2850 to 7430 cm^2/hour based on harvesters' dermal exposure to AZM residues (34).

Ten cucumber harvesters' hand exposure was monitored by using light-weight cotton gloves or washing with ethanol (35). Cucumbers were treated with Guthion^R 50 WP at a rate of 0.5 lb. a.i./acre. Workers entered the treated area one day after the application. DFR and hand exposure samples were taken simultaneously. Dermal exposure to the rest of the body was not monitored. Air samples were taken from workers' breathing zone to determine inhalation exposure. Average hand and inhalation exposures for 10 workers were 2023 $\pm$ 447 ug/hr and 3.8 $\pm$ 1.4 ug/hr, respectively. Average hand exposure based on 5 workers' ethanol hand rinses was 179 ug/hr $\pm$ 36. The average of 8 DFR samples was 1.1 ug/cm^2 $\pm$ 0.3. The transfer factor based on residues found in gloves was 1839 cm^2/hour, and based on residues found in hand rinse is 163 cm^2/hr.

Potential head, forearm, hand, and respiratory exposure of apple thinners was monitored at 1, 2, 6, and 9 days following an air blast application of AZM at 2 lb. a.i./acre (36). Hand exposure was monitored by using gloves or an ethanol wash. Gloves showed AZM residues 4.5 fold greater than residues found in ethanol wash. Head and neck exposure was assumed to be 14% of forearm exposure. Apple thinners' exposure is shown in Table 10.

Table 10

Apple Thinners' Head, Forearm, hand, and Respiratory Exposure to AZM residues

Days After Application	DFR Value ug/cm^2	Exposure (ug/hour) Head, Neck	Forearm	Hand*	Respiratory	Total Dermal Exposure (ug/hr)	Trans.** Factor cm^2/hr
1	1.7	270	1900	1300	49	3470	2040
2	1.9	440	3100	1800	78	5340	2810
6	1.4	190	1300	830	31	2320	1660
9	1.4	140	980	960	18	2080	1490

* - Ethanol hand rinse.
**- Based on dermal exposure to head, neck, forearm, and hand.

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In a controlled trial, two groups of workers (thinners) were monitored for AZM exposure (37). One group (8 men) of workers entered a peach orchard that was treated with AZM wettable powder at a rate of 2.5 lb. a.i./100 gal/acre. Workers entered the treated orchard when mean DFR reached no greater than 2.58 $\pm$0.74 ug/cm^2, presumably 9 days after AZM application. But leaf disc samples taken for this purpose were frozen before analysis. The other group (7 men) started working in a peach orchard treated with a non-cholinesterase inhibitor (Galecron^R). RBC and plasma ChE activity, and urinary dialkyl phosphate metabolites of these workers were measured pre-exposure and during routine thinning operation. RBC and plasma ChE measurements were taken on three separate days before exposure for the baseline and each day during the exposure. Plasma or RBC ChE activity was no less than 83.4% of the mean three day baseline for workers in either group and during the five days of monitoring. Dimethylphosphate (DMP) and dimethylphosphorothionate (DMTP), the primary urinary metabolites of AZM, were not detected in pre-exposure or control urinary samples (MDL of 0.1 ug/mL). Five days' mean DMTP and DMP were 14.1 ppm $\pm$ 6.2 and 15.1 ppm $\pm$ 6.8 per day, respectively. Since a single urine sample was taken each day from each worker, and urinary inorganic phosphate interferes with the complete recovery of the dialkyl phosphates, no attempt was made to quantify daily DMP and DMTP excretion.

Hand exposure of workers limb propping a peach orchard 17 days after AZM application was 15.7 ± 4.0 ug/8-hour work for three workers with cloth gloves and 60.0 ug/8-hour work for one worker with no gloves (38). The orchard was treated at a rate of 1 lb. AZM/acre. The DFR on the day of monitoring was measured at 0.77 ug/cm^2. No AZM was detected (MDL = 0.2 ppb) in any air samples taken at workers breathing zone.

Table 11 is a summary of field worker exposure studies showing the daily dermal exposure and estimated transfer factors. The estimated dermal transfer factors, Absorbed Daily Dosages, and Annual Average Daily Dosages for field workers performing different tasks are shown in Table 12.

Table 11

Summary of AZM Field Worker Exposure Studies
and the Estimated Dermal Transfer Factors

Job Description	Crop	Entry After Application (Days)	DFR (ug/cm^2)	DDE (mg/day)	Transfer Factor (cm^2/hr)
Harvester*	Peach	32, 52	0.48, 0.64	13.0, 15.6	3525, 3038
Harvester*	Peach	50, 74	1.00, 0.37	22.8, 22.0	2850, 7430
Harvester*	Nectarine	52	0.31	10.1	4072
Harvester**	Apple	43	0.64	1.7	360
Harvester***	Cucumber	1	1.10	1.4	163
Thinner*	Peach	31	0.49	13.0	3315
Thinner****	Apple	1-9	1.4-1.9	16.6-42.7	1490-2810
Propper*	Peach	31	0.50	0.70	174
Propper***	Peach	17	0.77	0.06	10

DDE - Daily dermal exposure.
* - Clothing of long-sleeved shirt, long-legged pants, and shoes.
** - Gloves were worn, as a normal practice, in addition to clothing described in *.
*** - DDE based on hand exposure only.
****- DDE based on head, forearm, and hand exposure only.

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Table 12

Field Workers' Estimated AZM Absorbed Daily Dosage (ADD)

Job Description	Crop	DFR at Reentry (14 days) ug/cm^2	Transfer Factor cm^2/hr	ADD*** ug/kg/day	AADD**** ug/kg/day
Harvester	Peach/Nectarine	1.12*	4,180	85.6	20.4
Harvester	Apple	0.70	4,180	53.5	12.7
Harvester	Orange	0.61**	4,180	46.6	11.1
Thinner	Peach/Nectarine	1.34	3,315	81.2	19.4
Thinner	Apple	0.70	3,315	42.4	10.1
Propper	Peach/Nectarine	1.34	174	4.5	1.1
Propper	Apple	0.70	174	2.2	0.5

* - DFR at 21 days after application (preharvest interval for peach/nectarine)
* * - DFR at 30 days after application.
*** - Based on a dermal absorption of 16%, Body weight of 70 kg, 8-hour workday, and work clothing of long-sleeved shirt, long-legged pants and shoes.
**** - Based on 87 workdays in a year, picking peaches from May 18 to September 20 (39).

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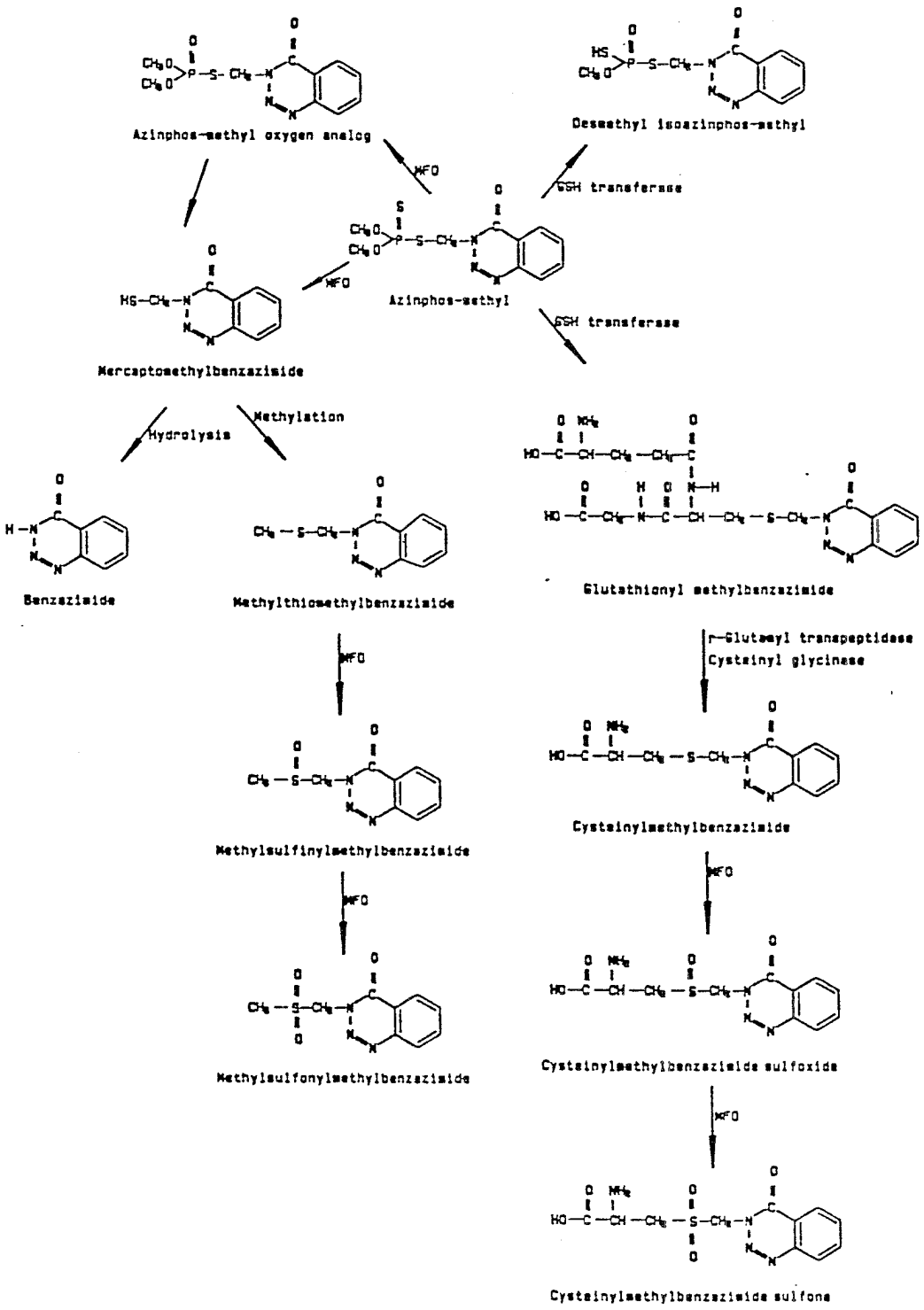
Figure 1

Proposed Metabolic Pathway of Azinphos-methyl in Rats (Reference 10)



APPENDIX B

U.S. EPA TOLERANCES FOR AZINPHOS-METHYL

TOLERANCES, GUIDELINES AND EXEMPTIONS

PESTICIDE RESIDUE TOLERANCES for raw agricultural products are listed in **Title 40, Code of Federal Regulations, Part 180.** Formal tolerances for pesticide residues as food additives permitted in food for human consumption are listed in **Title 40, Code of Federal Regulations, Part 185.** Formal tolerances for pesticides in animal feeds are listed in **Title 40, Code of Federal Regulations, Part 186.** Interim and time-limited tolerances are also found in these regulations. Temporary and time-limited tolerances also include the expiration date as it was reported in the ***Federal Register***. Temporary tolerances for pesticides that do not have an assigned 40 CFR number are found in the Temporary Tolerance Section of the GUIDE.

PROPOSED TOLERANCES for pesticides that do not have an assigned 40 CFR number or associated temporary tolerances are listed in the Tolerances Pending Section of the GUIDE. Temporary and Pending tolerances are not approved for general application and are limited by **Title 40, Code of Federal Regulations, Parts 180.7 and 180.31.** All pesticide applications are restricted to the conditions listed on the label.

FOOD/FEED ADDITIVE TOLERANCES, TEMPORARY TOLERANCES, and TOLERANCES PENDING are listed only in the section "Tolerances - Chemicals." When a pesticide is subject to an established food additive tolerance, its name is underlined in the "Tolerances - Crop" section. This indicates that the food additive tolerance for this pesticide can be found in the "Tolerances - Chemicals" section.

ADJUVANTS FOR PESTICIDES, 40 CFR 180.1001(c)(d)(e), are exempt from the requirements of a tolerance under section 409 of the FD&C Act.

ADMINISTRATIVE GUIDELINES OR LEGAL ACTION LEVELS have been established for some chemicals and products for which formal tolerances have not been promulgated. These guidelines are NOT tolerances. The criteria apply to objective samples. Legal action may be taken at residue levels lower than the Administrative Guideline if there is evidence of misuse of pesticides or if other factors appear to warrant action.

SECTION 18 CRISIS EXEMPTION notices may provide for interstate shipment of commodities where a formal tolerance has not been established for the pesticide residue. Permissible residue limits established by these notices are listed as "Administrative Guidelines/Section 18 Crisis Exemptions" or paragraph "B" in the reformatted pesticide and are found under their 40 CFR number in the "Tolerances - Chemicals" Section. The GUIDE will report these exemptions only when the *Federal Register* lists both the residue concentration level and an expiration date.

TOLERANCES REQUIRED BY MORE THAN ONE USAGE OR MORE THAN ONE FORM of a pesticide are designated by the letters matching those in the title preceding the chemical name in the "Tolerance - Chemicals" section.

INTERIM TOLERANCES are tolerances established for pesticide chemicals in or on raw agricultural commodities while petitions for tolerances for negligible residues are pending and until action is completed on these petitions. (See also 40 CFR 180.319)

TIME-LIMITED TOLERANCES are tolerances established for pesticide chemicals in or on raw agricultural commodities while petitions for tolerances are pending and until action is completed on these petitions.

(continued on next page)

Tolerances, Guidelines and Exemptions Continued:

NEGLIGIBLE RESIDUE TOLERANCES are any amount of a pesticide chemical remaining in or on a raw agricultural commodity or group of raw agricultural commodities that would result in a daily intake regarded as toxicologically insignificant on the basis of scientific judgment of adequate safety data. Ordinarily this will add to the diet an amount which will be less than 1/2000th of the amount that has been demonstrated to have no effect from feeding studies on the most sensitive animal species tested. Such toxicity studies shall usually include at least 90-day feeding studies in two species of mammals. Negligible residue tolerances are designated by an "N" in both the chemicals and crops sections of the GUIDE. Negligible residue tolerances are established by 40 CFR 180.1(L) in The Code of Federal Regulations.

REGIONAL REGISTRATION TOLERANCES are established for pesticide residues resulting from the use of the pesticide pursuant to a regional registration. Such a tolerance is supported by residue data from specific growing regions for a raw agricultural commodity. Individual tolerances with regional registrations are designated in separate subsections in 40 CFR 180.101 through 180.999, as appropriate. Regional registration tolerances are designated by an "R" in both the chemicals and crops sections of the GUIDE. However, the particular region affected is only listed in the "Tolerances - Chemicals" section of the GUIDE. Regional registration tolerances are established by 40 CFR 180.1(N) in The Code Federal Regulations.

GLOSSARY OF ABBREVIATIONS

APPLI	=	application
C-I MET	=	cholinesterase-inhibiting metabolite
CARB	=	carbamates
EPWRR	=	edible portion with rind removed
EXC	=	except
EXP	=	expires
FA	=	food and/or feed additive tolerance
I (in PPM column)	=	interim or time-limited tolerance
INC	=	including
K + CWHR	=	kernels plus cob with husk removed
MBYP	=	meat by products
MIN	=	minimum
N (in PPM column)	=	negligible residue tolerance
NMT	=	not more than
PPM	=	part(s) per million
POST-H	=	post-harvest application
PRE-H	=	pre-harvest application
R (in PPM column)	=	regional tolerance (state, geographic location)
RAC	=	raw agricultural commodity
T (in PPM column)	=	temporary tolerance

AZINPHOS-METHYL (INSECTICIDE)

GUTHION
O,O-DIMETHYL *S*-[(4-OXO-1,2,3-BENZOTRIAZIN-3(4*H*)-YL)METHYL] PHOSPHORODITHIOATE
CAS Reg. No. 86-50-0
CODEX 002

40 CFR 180.154; 180.3(e)(5); 185.2225; 186.2225

PPM	CROP
2.0	Alfalfa
5.0	Alfalfa Hay
0.3	Almonds
10.0	Almond Hulls
2.0	Apples
2.0	Apricots
2.0	Artichokes
0.2	Barley Grain
2.0	Barley Straw
0.3	Beans (Dry)
2	Birdsfoot Trefoil
5	Birdsfoot Trefoil Hay
2.0	Blackberries
0.3	Blackeyed Peas
5.0	Blueberries
2.0	Boysenberries
2.0	Broccoli
2.0	Brussels Sprouts
2.0	Cabbage
0.1	Cattle, Fat
0.1	Cattle, Meat
0.1	Cattle, MBYP
2.0	Cauliflower
2.0	Celery
2.0	Cherries
2.0	Citrus Fruits
5.0 FA	Citrus Pulp (Dried)
2.0	Clover
5.0	Clover Hay
0.5	Cottonseed
2.0	Crabapples
2.0	Cranberries
2.0	Cucumbers
0.3	Eggplants
0.3	Filberts
0.1	Goats, Fat
0.1	Goats, Meat
0.1	Goats, MBYP
5.0	Gooseberries
5.0	Grapes
2.0	Grass, Pasture, Green
5.0	Grass, Pasture, Hay
0.1	Horses, Fat
0.1	Horses, Meat
0.1	Horses, MBYP
10.0	Kiwi Fruit
2.0	Loganberries
2.0	Melons (Honeydew, Muskmelon, Cantaloupe, Watermelon, and other melons)
2.0	Nectarines
0.2	Oat Grain
2.0	Oat Straw
2.0	Onions
5	Parsley Leaves
2	Parsley Roots
2.0	Peaches
2.0	Pears
0.3	Pecans
0.3	Peppers
0.3	Pistachio Nuts
2.0	Plums (Fresh Prunes)
0.1(R)	Pomegranates (California)
0.3	Potatoes
2.0	Quinces
2.0	Raspberries
0.2	Rye Grain
2.0	Rye Straw
0.1	Sheep, Fat
0.1	Sheep, Meat
0.1	Sheep, MBYP
2.0	Snap Beans
1.0 FA	Soybean Oil
0.2	Soybeans
2.0	Spinach
2.0	Strawberries
0.3	Sugarcane
1.5FA	Sugarcane Bagasse
2.0**	Tomatoes
0.3	Walnuts
0.2	Wheat Grain
2.0	Wheat Straw

§180.154a Includes Residues of *O,O*-DIMETHYL *S*-[(4-OXO-1,2,3-BENZOTHRIAZIN-3(4*H*)-YL)METHYL] PHOSPHORODITHIOATE and/or its metabolites calculated as *O,O*-DIMETHYL *S*-[4-OXO-1,2,3-BENZOTRIAZIN-3 (4*H*)-YL-METHYL]PHOSPHORODITHIOATE:

PPM	CROP
0.04(N)	Milk

Administrative Guidelines: None
Tolerances Pending:

PPM	CROP
20	Almond Hulls 2/28/89
0.75	Cattle (Meat, Fat, Meat By-Products) Limited to 0.05 ppm O,O-DIMETHYL S-[(4-OXO-1,2,3-BENZO-TRIAZIN-3(4H)-YL)METHYL] PHOSPHORO-DITHIOATE AND/OR ITS OXYGEN ANALOGUE. 8/11/82
0.3	Corn Grain, Field, & Pop-corn 4/13/83
10	Corn Fodder & Forage 8/11/82, 4/13/83
0.05	Eggs 4/13/83
0.75	Goats (Meat, Fat, Meat By-Products) Limited to 0.05 ppm O,O-DIMETHYL S-[(4-OXO-1,2,3-BENZO-TRIAZIN-3(4H)-YL)METHYL] PHOSPHORO-DITHIOATE AND/OR ITS OXYGEN ANALOGUE. 8/11/82
0.75	Hogs (Meat, Fat, Meat By-Products) Limited to 0.05 ppm O,O-DIMETHYL S-[(4-OXO-1,2,3-BENZO-TRIAZIN-3(4H)-YL)METHYL] PHOSPHORO-DITHIOATE AND/OR ITS OXYGEN ANALOGUE. 8/11/82
0.75	Horses (Meat, Fat, Meat By-Products) Limited to 0.05 ppm O,O-DIMETHYL S-[(4-OXO-1,2,3-BENZO-TRIAZIN-3(4H)-YL)METHYL] PHOSPHORO-DITHIOATE AND/OR ITS OXYGEN ANALOGUE. 8/11/82
0.25	Milk Limited to 0.05 ppm O,O-DIMETHYL S-[(4-OXO-1,2,3-BENZO-TRIAZIN-3(4H)-YL)METHYL] PHOSPHORO-DITHIOATE AND/OR ITS OXYGEN ANALOGUE. 8/11/82
0.75	Poultry (Meat, Fat, Meat By-Products) Limited to 0.05 ppm O,O-DIMETHYL S-[(4-OXO-1,2,3-BENZO-TRIAZIN-3(4H)-YL)METHYL] PHOSPHORO-DITHIOATE AND/OR ITS OXYGEN ANALOGUE. 8/11/82
0.75	Sheep (Meat, Fat, Meat By-Products) Limited to 0.05 ppm O,O-DIMETHYL S-[(4-OXO-1,2,3-BENZO-TRIAZIN-3(4H)-YL)METHYL] PHOSPHORO-DITHIOATE AND/OR ITS OXYGEN ANALOGUE. 8/11/82
7	Sorghum Grain 12/12/74, 8/11/82
25.FA	Sorghum Mill Fractions (Except Flour) 8/11/82

** = Pre and Post Harvest Application
FA = Food and/or Feed Additive Tolerance
(N) = Negligible Residue Tolernce
(R) = Regional Tolerance