METHIDATHION
(SUPRACIDE)

RISK CHARACTERIZATION DOCUMENT

(REVISION 1)

Volume I

Health Risk Assessment

Medical Toxicology Branch

DEPARTMENT OF PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

February 2007

Contributors and Acknowledgments

Principal Author:	Carolyn M. Lewis, M.S., D.A.B.T.
	Associate Toxicologist
	Health Assessment Section
	Medical Toxicology Branch

Toxicology Reviews: Marilyn H. Silva, Ph.D., D.A.B.T.
                                 Staff Toxicologist
                                 SB 950 Data Review Section
                                 Medical Toxicology Branch

Dietary Exposure Assessment: Carolyn M. Lewis, M.S., D.A.B.T.
                                 Associate Toxicologist
                                 Health Assessment Section
                                 Medical Toxicology Branch

                                 Wesley C. Carr, Jr., M.S.
                                 Associate Pesticide Review Scientist
                                 Health Assessment Section
                                 Medical Toxicology Branch

Occupational and Ambient   Sheryl Beauvais, Ph.D.
Air Exposure Assessment: Staff Toxicologist
                                 Worker Health and Safety Branch

Peer Reviewed By: Keith F. Pfeifer, Ph.D., D.A.B.T.
                                 Joyce F. Gee, Ph.D.
                                 Senior Toxicologists
                                 Health Assessment Section
                                 Medical Toxicology Branch

                                 Jay P. Schreider, Ph.D.
                                 Primary State Toxicologist
                                 Medical Toxicology Branch

TABLE OF CONTENTS

METHIDATHION

SUMMARY

Methidathion (O,O-dimethyl-phosphorodithioate, S-ester with 4-(mercaptomethyl)-2-methoxy-Δ-1,3,4-thiadiazolin-5-one) was first registered in 1974 by Ciba Geigy Corporation (U.S. EPA, 1989). The Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency placed methidathion on the high-priority list for risk assessment based on possible adverse effects identified in chronic toxicity, carcinogenicity and chromosomal aberrations studies submitted under the Birth Defect Prevention Act (SB 950). In 1989, the California Assembly passed AB2161 which requires DPR to conduct dietary risk assessments for all pesticides with food crop uses. The Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency completed a Risk Characterization Document (RCD) for methidathion in 2001 that addressed dietary and drinking water exposure. No mitigation was needed for either dietary or drinking water exposure; however, an acute tolerance assessment suggested that the tolerances for citrus fruit and apples should be reduced to be health protective. The purpose of this revision to the Risk Characterization Document for methidathion is to add the occupational and ambient air exposure to dietary and drinking water exposure, evaluating them separately and in combination.

Toxicity

The pharmacokinetic and toxicology studies were reviewed and presented in the Toxicology Profile section. Included in the Toxicology Profile are guideline studies submitted to the Department of Pesticide Regulation (DPR) and studies from open literature with the greatest weight generally given to guideline studies that met the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) guidelines. From the treatment-related effects identified in the studies, the highest dose, which did not cause any toxicological effect, known as No-Observed-Effect Level (NOEL), was established for each study. In the Hazard Identification section, the NOELs and effects at the Lowest-Observed-Effect Level (LOEL) from the available toxicity studies were then evaluated to determine what would be the most appropriate NOEL, referred to as a critical NOEL, to evaluate particular exposure scenarios. The toxicity studies can be categorized as acute (< 7 days), subchronic (> 7 days to < 6 months), and chronic (1 or more years) in duration. For methidathion, critical NOELs were identified for acute, subchronic, and chronic exposure scenarios. In addition, a potency factor was estimated for carcinogenicity. The critical NOELs were adjusted to absorbed doses because human exposures were expressed as absorbed doses. Since all the critical NOELs were derived from oral studies and the oral absorption rate was assumed to be 100%, no adjustment for oral absorption was necessary.

Methidathion and its oxygen analog produce their toxic reaction primarily through their inhibition of cholinesterase (ChE) enzymes, including acetylcholinesterase (AChE). AChE is responsible for the termination of nerve impulses across synaptic clefts of certain types of nerves in the central and peripheral nervous systems. The effects observed in laboratory animals after acute exposure to methidathion were various neurological signs typical of ChE inhibitors, including ataxia, muscle fasciculations, convulsions, excessive salivation and lacrimation, difficulty in breathing and death. The most sensitive endpoint in the acute neurotoxicity study in rats was ChE inhibition in the cerebral cortex of males, but a NOEL was not established in this

study.   After 2 weeks of exposure in the 90-day neurotoxicity study in rats, a NOEL was established for the same endpoint. Therefore, the critical NOEL selected for evaluating the acute dietary, drinking water, occupational and ambient air exposure to methidathion was 0.18 mg/kg/day based on a significant reduction of ChE activity in the cerebral cortex of male rats after 2 weeks of exposure in the 90-day neurotoxicity study. The selection of this 2-week NOEL for the acute NOEL was supported by the benchmark dose analysis.

        Brain ChE inhibition and cholinergic signs similar to those observed with acute exposure were also observed in laboratory animals after subchronic exposure. In addition, reduced body temperatures, reduced body weights and food consumption, hematological changes suggestive of anemia, changes in serum enzyme levels suggestive of liver toxicity, and lesions in the liver, gallbladder, stomach, kidney and heart were seen. The lowest subchronic NOEL was 0.18 mg/kg/day that was observed in a 90-day neurotoxicity study in rats based reduced ChE activity in RBCs and various brain regions in both sexes. ChE inhibition in RBCs was considered a surrogate for ChE inhibition in the peripheral nervous system which was not measured in this study. Dietary and drinking water exposure to methidathion did not vary significantly with season; however, seasonal occupational and ambient air exposure to methidathion is anticipated. Therefore, the subchronic neurotoxicity study in rats was selected as the definitive study for evaluating seasonal occupational and ambient air exposure to methidathion.

        Several developmental and reproductive effects were seen in studies including reduced pup weights, signs of maternal neglect, and reduced maternal index. The NOELs for fetal or pup effects were equal to or higher than the maternal or parental NOELs, suggesting there is no increased pre- or post-natal sensitivity to methidathion. However, in one direct-dosing study where the LD_{50} was determined in both weanling and adult rats, the weanling rats appear to be slightly more sensitive.

        The effects observed in laboratory animals with chronic exposure to methidathion were similar to those observed with subchronic exposure, except that evidence of hepatotoxicity was more common. Although both the neurotoxicity and hepatoxicity were seen in most species, there appeared to be some species differences in the pharmacokinetics of methidathion. Cholinesterase inhibition appeared to be the more sensitive endpoint in rats while the hepatotoxicity was a more sensitive endpoint in dogs. The lowest NOEL in a chronic study of acceptable quality was 0.15 mg/kg/day based on elevated liver enzymes in the serum and microscopic lesions in the liver of dogs exposed to methidathion in the diet for 1 year.

        An increase in liver tumors was also observed in male mice in two different carcinogenicity studies with chronic exposure. The tumors were only observed at dose levels that produced significant increases in other non-neoplastic lesions in the livers of mice suggesting that they maybe secondary to these non-neoplastic lesions. Most of the genetic toxicity tests for methidathion were negative. However, direct DNA interaction could not be eliminated since its genetic toxicity potential has not been thoroughly tested in well-conducted, sensitive assays with mammalian cells and a few genetic toxicity tests were positive (a gene conversion/forward mutation assay with yeast and an *in vitro* sister chromatid exchange assay with mammalian cells).   Furthermore, no mechanistic data was submitted to support a threshold mechanism. Therefore, it was assumed that a non-threshold mechanism was involved and the

carcinogenic potential of methidathion was evaluated using a linear approach based on the increase in liver tumors in male mice. The cancer potency was estimated to range from 0.34 $(mg/kg/day)^{-1}$ for the maximum likelihood estimate to 0.53 $(mg/kg/day)^{-1}$ for the 95% upper bound estimate.

The following table summarizes the critical NOELs and cancer potency factor used for evaluating methidathion exposure along with their respective reference doses and concentrations:

Exposure Scenario	NOEL	Effects on LOEL	RfD	RfC	
				Infants	Adults
Acute	0.18 mg/kg	Reduced ChE activity in cerebral cortex of male rats	1.8 µg/kg	3.1 µg/m^3 (0.25 ppb)	6.4 µg/m^3 (0.52 ppb)
Seasonal	0.18 mg/kg/day	Reduced ChE activity in RBCs, cerebral cortex (M), striatum (F) and hippocampus (F) of rats	1.8 µg/kg/day	3.1 µg/m^3 (0.25 ppb)	6.4 µg/m^3 (0.52 ppb)
Chronic	0.15 mg/kg/day	Elevated liver enzymes in serum and liver histopathology in dogs	1.5 µg/kg/day	2.5 µg/m^3 (0.21 ppb)	5.4 µg/m^3 (0.43 ppb)
Lifetime	Potency 0.53 $(mg/kg/day)^{-1}$	Liver tumors in male mice	1.9 ng/kg/day	-----	6.8 ng/m^3 (0.6 ppt)

The oxygen analog or oxon is the presumed active metabolite of methidathion for the neurological effects, although the pharmacokinetics studies suggest that it may be a minor metabolite. There were no toxicity studies for methidaoxon, therefore, it was assumed that the oxon was equivalent in toxicity to the parent compound for all endpoints. Most likely the NOELs for methidaoxon would have been lower since the oxon is usually the active metabolite for organophosphorothioates, at least for neurological effects. Consequently, the health risks from exposure to methidathion are probably underestimated.

Exposure

Dietary

A tiered approach was used in the dietary exposure analysis. A tier 3 analysis was conducted for both acute and chronic exposure using primarily U.S. Department of Agriculture's (USDA's) Pesticide Data Program (PDP) monitoring data from 2000-2003 and adjustments for percent crop treated. Dietary consumption of commodities with methidathion residues by various population subgroups was based on USDA's Continuing Survey of Food Intakes by Individuals (CSFII) from 1994 to 1998. The estimated acute dietary exposure dosages at the

99.9th percentile for users ranged from 0.175 to 0.780 µg/kg/day. The population subgroup with the highest acute dietary exposure was children 1 to 2 years old.   The estimated chronic dietary exposure dosages ranged from 0.001 to 0.019 µg/kg/day. Non-nursing infants less than 1 year old had the highest estimated chronic dietary exposure.

Drinking Water

Methidathion residues have been detected in DPR's surface water monitoring in California. However, it is uncertain if any of the surface water sampled represented drinking water sources. No methidathion residues have been detected in well water monitored by DPR. In addition, no methidathion residues were detected in the PDP drinking water samples from 2001 to 2003 including California. Surface water was the source of most of the PDP drinking water sampled. Since the PDP data represent finished drinking water, the data from California was selected for evaluating drinking water exposure to methidathion. The estimated acute drinking water exposure to methidathion at the 99.9th percentile for users ranged from 0.002 to 0.012 µg/kg/day. Non-nursing infants had the highest estimated acute exposure to methidathion in drinking water. The estimated chronic drinking water exposure was less than 0.001 µg/kg/day for all population subgroups, except non-nursing infants less than 1 year old whose chronic exposure was approximately 0.001 µg/kg/day.

When dietary and drinking water exposure to methidathion were combined, the acute exposure at the 99.9th percentile for users ranged from 0.172 to 0.777 µg/kg. Children 1 to 2 years old had the highest combined acute exposure. Acute estimates for combined dietary and drinking water exposure at the 99.9th percentile of users were less than dietary exposure alone at the 99.9th percentile of users, because they represented different populations. The number of users increased with the addition of water, but the exposure only increased slightly. The combined chronic exposure to methidathion ranged from 0.002 to 0.020 µg/kg/day. Non-nursing infants had the highest combined chronic exposure to methidathion.

Occupational

There were no acceptable chemical-specific occupational exposure studies for methidathion, so handler exposure was estimated using the Pesticide Handler Exposure Database (PHED). Daily, seasonal, chronic and lifetime exposure dosages were estimated for 9 handler exposure scenarios covering aerial, airblast, groundboom, backpack sprayer and low-pressure handwand application. The Absorbed Daily Dosage (ADD) represented the upper confidence limit on the 95th percentile after adjusting for dermal and inhalation absorption using default values of 50 and 100%, respectively. The ADDs for handlers ranged from 0.0034 to 5.86 mg/kg/day. The Seasonal Average Daily Dosage (SADD) was the upper confidence limit on the mean daily exposure during the high-end use months. The seasonal and annual exposures for handlers were estimated to occur over 1 to 2 months. The SADDs for handlers ranged from 0.044 to 1.55 mg/kg/day. The Annual Average Daily Dosage (AADD) was calculated by multiplying the SADD by the annual use months per year and dividing by 12 months. The AADDs for handlers ranged from 0.004 to 0.129 mg/kg/day. The Lifetime Average Daily Dosage (LADD) was estimated by multiplying the AADD by 40 years of work in a lifetime and dividing by 75 years in a lifetime. The LADDs for handlers ranged from 0.002 to 0.069 mg/kg/day.   Mixer/loader/applicators (M/L/As) using low-pressure handwands had the lowest

acute exposure dosages while airblast and aerial applicators had the highest acute exposure dosages. The M/L/As using backpack sprayers and low-pressure handwands were not considered to have seasonal and chronic exposures, so the lowest seasonal and chronic exposures among handlers were for airblast mixer/loaders and groundboom applicators. Aerial and airblast applicators continued to have the highest seasonal and chronic exposures.

The exposure dosages were calculated for 3 field worker exposure scenarios using dislodgeable foliar residues (DFRs) and transfer factors (TFs). The exposure scenarios for field workers covered scouting, thinning and harvesting crops treated with methidathion. The DFRs for the ADDs and SADDs were those anticipated at the end of the restricted entry interval (REI) and REI plus 7 days, respectively, for most activities. The default dermal absorption of 50% was applied to the field worker exposure calculations. The ADDs for field workers ranged from 0.007 to 0.093 mg/kg/day. The SADDs for field workers were between 0.0007 and 0.0045 mg/kg/day. The seasonal and annual exposures for field workers were estimated to occur over 2 to 4 months. The AADDs ranged from 0.0001 to 0.0011 mg/kg/day for field workers. The LADDs were between 0.00006 and 0.0006 mg/kg/day for field workers.

Ambient Air

Application site and ambient air were monitored in Tulare County during June and July of 1991. Tulare County had the highest use of methidathion in 1991, primarily in June and July. The air was monitored for both methidathion and methidaoxon. The application site monitoring study for methidathion was conducted following an application to an orange grove, but it was not used because no samplers were downwind due to an unanticipated wind direction. Instead a methyl parathion application to a walnut orchard in San Joaquin county in July of 2003 was used as a surrogate study. In this study, samplers were placed all around the field and the downwind samplers were used to estimate exposure. The methyl parathion study was considered an appropriate surrogate study for methidathion because of similarities in equipment used, timing of applications and vapor pressure. Exposure estimates were adjusted upward to account for differences in application rate in the methyl parathion study (2 lbs/acre) and the maximum application rate for methidathion on citrus (5 lbs/acre). In the methyl parathion study, the air was monitored for methyl paraoxon in addition to methyl parathion. The exposure estimates represent the sum of the parent and oxon exposure. The 1-hr acute exposure estimates (i.e., ADDs) for application site air were 4.62 and 0.832 µg/kg for infants and adults, respectively, using the highest measured concentration in the surrogate study, assuming heavy activity and assuming a default inhalation absorption of 100%. The 24-hr ADDs were 8.04 µg/kg for infants and 3.82 µg/kg for adults. Seasonal and chronic exposure estimates were calculated for people living or working near artichoke fields since up to 8 applications can occur in a year with a minimum of 2 weeks between applications. The SADDs for the application site were 0.936 and 0.444 µg/kg/day for infants and adults, respectively, assuming the high use months to be 2 months. The AADDs were 0.157 µg/kg/day for infants and 0.074 µg/kg/day for adults. The exposure estimates for ambient air were initially calculated for the Jefferson Elementary School in Lindsay since it had the highest daily and average air concentrations. An acute exposure estimate was not calculated since it would clearly be less than at the application site. The SADDs for ambient air at the Jefferson site were 0.060 µg/kg/day for infants and 0.028 µg/kg/day for adults based on the average air concentration during the monitoring period. The AADDs for ambient air at the Jefferson site were 0.045 and 0.021 µg/kg/day for infants and

adults, respectively, assuming the season of potential exposure is 9 months per year. Due to their higher respiratory rate relative to their body weight, infants consistently had the highest exposure.

Risk Characterization

The risk for non-carcinogenic health effects is expressed as a margin of exposure (MOE) which is the ratio of the NOEL from the animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower distribution of the overall human population and the sensitive subgroup. The negligible carcinogenic risk level is generally considered 1 excess cancer case in a million people.

Dietary

The MOEs for acute dietary exposure to methidathion in the various population subgroups ranged from 230 to 1,000. The MOEs for chronic dietary exposure ranged from 8,000 to 110,000. The MOEs for dietary exposure were sufficiently large (> 100) not to be of concern. The estimated cancer risk from dietary exposure to methidathion ranged from 0.7 to 1.1 excess cancer cases in a million people. The cancer risks from dietary exposure were also sufficiently low (~1 excess cancer case in a million people) not to be of concern. However, the health risks from dietary exposure were probably underestimated since commodities were not analyzed for the oxon in either the PDP or DPR monitoring programs.

Drinking Water

The MOEs for acute drinking water exposure to methidathion ranged from 15,000 to 120,000. The MOEs from chronic drinking water exposure ranged from 160,000 to 900,000. The MOEs from drinking water exposure were large enough that they were not of concern. The estimated cancer risk from drinking water exposure to methidathion ranged from 0.9 to 1.4 excess cancers in 10 million people. The cancer risks from drinking water exposure were also low enough not to be of concern.

The MOEs for combined acute dietary and drinking water exposure to methidathion ranged from 230 to 1,000. The MOEs for combined chronic exposure ranged from 7,700 to 92,000. The estimated cancer risk from combined dietary and drinking water exposure to methidathion ranged from 0.8 to 1.2 excess cancer cases in a million people. Even considering the combined dietary and drinking water exposure, the health risks from these exposure scenarios were not of concern.

Occupational

Occupational exposure to methidathion is of particular concern since the MOEs for acute, seasonal and chronic occupational exposure were less than 100 for all worker exposure scenarios, except seasonal exposure for thinning of artichokes and chronic exposure for all field worker scenarios. The MOEs were less than 10 for most handler scenarios and less than 1 for some handler scenarios (aerial handlers and airblast applicators), suggesting mitigation is needed

especially for handlers.   The cancer risk estimates for occupational exposure to methidathion all exceeded the negligible risk level, ranging from 2.0 excess cancer cases in 100,000 to 3.7 excess cancer cases in 100. The cancer risk estimates from occupational exposure are extremely high and are of concern, especially for handlers.   Aerial applicators had the highest estimated cancer risk.

Ambient Air

The MOEs for acute air exposure at the application site were less than 100 for both infants and adults, not only meeting the criteria for listing methidathion as a toxic air contaminant, but suggesting mitigation may be needed. The MOEs for seasonal and chronic air exposure at the application site were greater than 100 for both infants and adults, but less than 1,000 (except for chronic exposure in adults) which also meets the criteria for identifying methidathion as a toxic air contaminant. The cancer risk estimates for the application site air ranged from 2.5 to 3.9 excess cancer cases in 100,000 which are low enough not only to meet the criteria for listing, but also to suggest mitigation is needed. The seasonal and chronic MOEs for ambient air were greater than 1,000 for infants and adults; however, the cancer risk estimates for ambient air exceeded the negligible risk level, ranging from 0.71 to 1.1 excess cancer cases in 100,000. These cancer risk estimates not only meet the criteria for listing methidathion as a toxic air contaminant, they also suggest mitigation may be needed.

Aggregate

Aggregate exposure for agricultural workers and the general public were evaluated. The MOEs for most agricultural workers were already significantly less than 100 from occupational exposure alone without adding in additional exposure from diet, drinking water and ambient air. Therefore, the aggregate MOEs for most agricultural workers was not significantly lower than their occupational MOEs. Similarly, the air exposure was a major contributor to the aggregate exposure for the general population. Consequently, the aggregate MOEs for the general public were only slightly lower than the MOEs for air exposure alone.

Tolerance Assessment

A tolerance assessment for methidathion 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 citrus fruit and apples. Based on these estimates, the tolerances for citrus fruit and apples do not appear to be health protective and DPR recommends that U.S. EPA reevaluate these tolerances.

Conclusions

The potential health risks from dietary and drinking water exposure to methidathion appear to be low, although dietary risks may have been underestimated since DPR and PDP monitoring did analyze commodities for the methidaoxon. On the other hand, the potential health risks from occupational exposure to methidathion appear to be quite high for most exposure scenarios, especially for handlers, suggesting mitigation is needed. The potential health risks for bystanders from acute exposure to air at the application site are also high, not

only meeting the criteria for listing methidathion as a toxic air contaminant, but suggesting mitigation is needed. Cancer risk estimates for both the application site and ambient air were also high enough to suggest mitigation is needed.   The potential health risks from exposure to methidathion may be underestimated since methidaoxon was assumed to be equally toxic as methidathion due to the lack of toxicity data for the oxon. Furthermore, the health risk estimates for methidathion were probably underestimated since they did not take into consideration cumulative exposure from other organophosphates. Mitigation of the occupational and air exposures to methidathion is not addressed in this document due to the separation of risk assessment from risk management. Mitigation of these exposures will be addressed in a separate document during the risk management phase.

I. INTRODUCTION

I.A. REGULATORY BACKGROUND

Methidathion (O,O-dimethyl-phosphorodithioate, S-ester with 4-(mercaptomethyl)-2-methoxy-Δ-1,3,4-thiadiazolin-5-one) was first registered in 1974 by Ciba Geigy Corporation (U.S. EPA, 1989). The Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency placed methidathion on the high-priority list for risk assessment based on possible adverse effects identified in chronic toxicity, carcinogenicity and chromosomal aberrations studies submitted under the Birth Defect Prevention Act (SB 950). Methidathion 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.

Methidathion was placed in reevaluation in 1989 along with chlorpyrifos, diazinon, and ethyl parathion which were used as dormant sprays to control scale and other pests on almond trees (DPR, 1996). Reevaluation of these organophosphates was based on a study conducted by the California Department of Fish and Game (CDFG) which identified possible adverse effects in resident and migratory red-tailed hawks. The registrants were then asked to submit additional data to further evaluate this potential wildlife problem. During the course of these field studies, the use of ethyl parathion as a dormant spray was canceled. Field and laboratory studies indicated that methidathion had the greatest effect on cholinesterase inhibition of these four organophosphate pesticides with the exception of ethyl parathion. The principle route of exposure to these chemicals for raptors (birds of prey, such as hawks) appears to be the dermal route from perching on sprayed trees. DPR concluded that no mitigation was needed because the elimination of ethyl parathion resulted in a significant reduction in the raptors identified with lowered cholinesterase levels and, therefore, continued use of the other three organophosphates did not pose a significant hazard. CDFG concurred with DPR's decision.

In 2001, DPR completed a Risk Characterization Document (RCD) for methidathion addressing dietary and drinking water exposure. No mitigation was needed for either the dietary or drinking water exposure, although the tolerance assessment suggested that the tolerances for citrus fruit and apples should be reduced to be health protective. This document has been revised to include additional occupational and ambient air exposure assessments for methidathion. DPR is also updating its use of ChE inhibition data in the risk assessment for ChE inhibitors. In anticipation of changes in the use of these endpoints in the risk assessments, NOELs for both blood and brain ChE inhibition were included in this document.

I.B. CHEMICAL IDENTIFICATION

Methidathion is an organophosphate insecticide and acaricide (U.S. EPA, 1988). Methidathion and its oxygen analog produce their toxic reaction primarily through their inhibition of cholinesterase (ChE) enzymes, including acetylcholinesterase (AChE) and butyryl-cholinesterase (BuChE). AChE is also called specific or true cholinesterase and is found near cholinergic synapses, in some organs (e.g., lung, spleen, gray matter) and in hematopoietic cells

9

(Lefkowitz *et al.*, 1990). Normally, AChE metabolizes acetylcholine to acetate and choline, which results in the termination of stimulation to dendritic nerve endings and motor endplates. Acetylcholine is the neurochemical transmitter at endings of postganglionic parasympathetic nerve fibers, somatic motor nerves to skeletal muscle, preganglionic fibers of both parasympathetic and sympathetic nerves, and certain synapses in the central nervous system (Murphy, 1986). The concentration at which methidathion inhibited 50% of the free AChE activity in electric eel and bovine red blood cells (RBCs) was reported to be 2.3×10^{-4} M and 4.6×10^{-4} M, respectively, compared to paraoxon which was 2.8×10^{-7} M and 9.6×10^{-8} M, respectively (Mionetto *et al.*, 1992). The bimolecular rate constant, Ka ($M^{-1}mm^{-1}$), of methidathion was 1.9×10^{2} and 9.3×10^{1} for the free AChE in electric eel and bovine RBCs, respectively, compared to paraoxon which was 4×10^{5} and 0.7×10^{6}. However, the active metabolite of methidathion, the oxygen analog, was not used, so the ability of methidathion to inhibit AChE was underestimated in this experiment.

The inhibition of AChE results in the accumulation of endogenous acetylcholine in nerve tissue and effector organs. In acutely toxic episodes, muscarinic, nicotinic and central nervous system (CNS) receptors are stimulated with characteristic signs and symptoms occurring throughout the peripheral and central nervous systems (Ellenhorn and Barceloux, 1988; Murphy, 1986). Muscarinic effects can include increased intestinal motility, bronchial constriction and increased bronchial secretions, bladder contraction, miosis, secretory gland stimulation and bradycardia. Nicotinic effects include muscle weakness, twitching, cramps and general fasciculations. Accumulation of acetylcholine in the CNS can cause headache, restlessness, insomnia, anxiety and other non-specific symptoms. Severe poisoning results in slurred speech, tremors, ataxia, convulsions, depression of respiratory and circulatory centers and, eventually, coma.

Butyrylcholinesterase (BuChE), sometimes referred to as plasma ChE, pseudo-cholinesterase, or serum esterase, is also inhibited by methidathion. Any reference in this document to "cholinesterase", without specifically indicating that the enzyme is serum or plasma ChE, should be interpreted as AChE. BuChE only occurs to a limited extent in neuronal elements of the central and peripheral nervous systems in adults, but there is compelling evidence for a role of BuChE in the developing nervous system and in the co-regulation of acetylcholine (ACh) levels in the mature nervous system. The evidence for a role in the co-regulation of ACh is based on 1) substrate inhibition of AChE, but not BuChE, at high concentrations of ACh, 2) survival of AChE knockout ($AChE^{-/-}$) mice past birth, 3) an increase in BuChE levels in Alzheimer's patients while the AChE levels decrease (Giacobini, 2003; Li *et al.*, 2000; Ballard and Perry, 2003). Unlike AChE, BuChE occurs primarily in non-neuronal or non-synaptic sites in adults like the liver, lung, and plasma and has no known physiological function (Lefkowitz *et al.*, 1990; Brimijoin, 1992; U.S. EPA, 1993; Pantuck, 1993). An atypical genetic variant of plasma cholinesterase has been associated with an increased susceptibility to various drugs, such as succinylcholine and cocaine (Lockridge, 1990; Pantuck, 1993). However, it is unclear if this increased susceptibility to certain drugs in people with the atypical plasma ChE translates to a possible adverse effect when plasma ChE is inhibited by organophosphates. There is some evidence suggesting that BuChE does play a role in the metabolism of organophosphates in that administration of exogenous BuChE provided significant protection against organophosphate toxicity in several species tested including rats, mice, guinea pigs and non-human primates (Raveh et al., 1997; Allon et al., 1998).

The physiological role of AChE in RBCs is also unknown. Due to the expression of AChE in several types of hematopoietic cell lines, it has been proposed that circulating AChE may be important in erythropoiesis (Grisaru *et al.* 1999).   U.S. EPA does not consider RBC ChE inhibition an adverse effect in itself, but does use RBC ChE inhibition as a surrogate for peripheral ChE inhibition which is usually not measured (U.S. EPA, 2000a). Caution is needed when using RBC ChE as a surrogate since unlike nervous tissue, RBCs lack the ability to synthesize new AChE (Brimijoin, 1992).   Consequently, the recovery of RBC ChE activity is much slower than in the central and peripheral nervous system because it is dependent on the replacement of RBCs.

I.C. TECHNICAL AND PRODUCT FORMULATION

Currently, there are two products registered for use in California containing methidathion: Supracide® 25W and Supracide® 2E. Supracide® 25W is a wettable powder containing 25% methidathion. Supracide® 2E is an emulsifiable concentrate containing 24.4% methidathion. The registrant for both products is Gowan Company.

I.D. USAGE

Supracide® 25 W and 2E may be applied directly to the soil by injection, shank or chisel. It may also be applied as a spray by ground or aerial application. The application rate for most tree crops was 4 to12 lbs. of product (1 to 3 lbs. methidathion) per acre per application, except for citrus fruit which may be applied up to 20 lbs of product (5 lbs methidathion) per acre. For deciduous fruit and nut trees, the product is usually applied as a dormant spray and diluted in a minimum of 20 and 50 gallons of water per acre for aerial and ground application, respectively. For citrus and olives, the product is diluted in a minimum of 20 and 400 gallons of water per acre, respectively. Generally, only one application per season is made to deciduous fruit and nut trees and nursery stock. Up to 2 applications per season may be permitted with citrus at anytime, except during the bloom period or 2 weeks before harvest. Application rates for row and field crops ranged from 2 to 4 lbs. of product (0.5 to 1 lbs. methidathion) per acre per application. Three to 8 applications maybe applied to artichokes and safflower, respectively. The pre-harvest intervals (PHIs) ranged from 7 days for walnuts to 80 days for almonds. Applications to artichokes and almonds are prohibited after bud formation.

The use of methidathion has been decreasing since 1998 in which 178,451 lbs of methidathion were used in California. In 2004 (the most recent year use data is available), only 61,204 lbs of methidathion were used in California. The biggest decrease was seen between 1999 and 2000 when use decreased by 45% primarily due to decreased use on almond and citrus trees. Despite these reductions, 70% of the total use for methidathion in 2004 was still on tree crops. Use on nut trees, stone fruit trees, citrus trees, olive trees and pome fruit trees represented 21%, 21%, 19%, 5% and 4% of the total, respectively.

I.E. ILLNESS REPORTS

Dermatitis was associated with exposure to organophosphate insecticides in 202 patients in Japan either as a solitary compound or as multiple compounds (Matsushita *et al.*, 1985). None of the cases of dermatitis associated with a solitary compound involved methidathion. In another study, 84 tea growers in Japan were given a patch test for 11 pesticides including methidathion (Fujita, 1985). Thirteen percent (4 males and 7 females) had an unequivocal positive response for methidathion and another 23% (4 males and 15 females) had an equivocal response. Five female tea growers had contact dermatitis from occupational exposure, one of which had a positive patch test for methidathion.

Eleven greenhouse applicators in Hungary were examined for potential health effects on two occasions approximately three months apart (Desi *et al.*, 1986). These workers were exposed to a variety of pesticides including methidathion. The examination included urinalysis, hematology, immunoglobulin levels, whole blood ChE activity, serum γ-glutamyl transferase activity, lymphocyte chromosome aberrations, and electrocardiography. No differences in these measurements were seen, except a slight increase (2.7%) in the numerical chromosome aberrations rate which was within the reported normal range (4-7%) for the Hungarian population.

The lymphocytes of 55 male agricultural workers from Hungry were examined for chromosome aberrations (Nehéz *et al.*, 1988). These men worked with a variety of pesticides including methidathion. Plasma cholinesterase activity was normal in all workers. Chromosome aberrations were not observed in any of the 41 men working in closed spaces (green houses or plastic tents), but there was a significant increase in chromosome aberrations in 14 men working in open fields. The investigators suggested that the increased chromosome aberrations in men working in open fields may be due to exposure to larger volumes of pesticides and/or to a contaminant in the products.

In a prospective cohort study, 204 farmers in Indonesia were evaluated for pesticide exposure and signs and symptoms (Kishi *et al.*, 1995). Methidathion was one of many pesticides used by these farmers. Extensive exposure to pesticides was seen because protective clothing was too hot or costly, resulting in a significantly higher incidence of signs and symptoms during the spraying season. Twenty-one percent of the respondents had 3 or more neurological, intestinal or respiratory signs or symptoms per spray operation. There was a dose-response relationship between the use of multiple organophosphates and the neurobehavioral signs and symptoms.

Five case reports of individuals poisoned with methidathion were available. A 25-year-old farmer ingested an unknown quantity of a 40% methidathion formulation (Teitelman *et al.*, 1975). At admission to the hospital, he was semicomatose, sweating, miotic, and had rales. The serum cholinesterase activity was zero a few hours after admission. He was treated with gastric lavage, atropine, obidoxime chloride, and cortisol hemisuccinate. He later developed jaundice, a high fever and went into a deep coma. After the first week, there was a gradual improvement. He was reevaluated at 2 months and no abnormalities were found, including any evidence of delayed neurotoxicity.

A 50-year-old Italian man ingested 20 ml of 20% methidathion formulation in a suicide attempt (Zoppellari *et al.*, 1990). He exhibited lacrimation, salivation, sweating, miosis, bradycardia, muscle fasciculations and mental confusion. He was treated with hemoperfusion, gastric lavage, atropine and pralidoxime. The clinical course appeared to vary as methidathion was redistributed from the fat to the blood. Methidathion was present in plasma, urine and gastric juice until the 6th, 7th and 8th day, respectively. Significant plasma and red blood cell (RBC) ChE inhibition was seen through day 8. There was no evidence of delayed neuropathy or neuropathy target esterase (NTE) inhibition in the lymphocytes. He was fully recovered 45 days after exposure.

Three cases of methidathion poisoning in Crete were reported involving either intentional or accidental ingestion (Tsatsakis *et al.*, 1996). A 47-year old man developed miosis, sialorrhea, cyanosis and diffuse rales initially after ingesting 250 ml of a methidathion formulation (concentration not reported). His recovery was protracted and complicated by tonicoclonic spasms, fasciculations, atelectasis and arrhythmias despite treatment with gastric lavage, activated carbon, atropine and pralidoxime. The patient was fully recovered 45 days after exposure. A 74-year-old man did not recover after ingesting an unknown quantity of a 40% methidathion emulsifiable concentrate formulation. He had acute respiratory failure and was comatose on admission to the hospital. Despite treatment with atropine and pralidoxime, he developed pseudomonas sepsis and multiple organ failure. Progressively diffuse pulmonary fibrosis was the main cause of death. Another 70-year-old man died after ingesting 200 ml of a 40% methidathion emulsifiable concentrate. Although conscious and breathing normally, the patient was given gastric lavage, followed by activated carbon and atropine. He developed an episode of general seizures 6 hours after admission to the hospital. A second episode of seizures 28 hours later was fatal.

Between 1992 and 2003, 39 incidents of illness or injury associated with definite, probable or possible exposure to methidathion were reported to DPR's Pesticide Illness Surveillance Program (PISP) (Beauvais, 2006). Ten of these incidents were associated with exposure to methidathion alone while the rest were associated with exposure to methidathion in combination with other pesticides. Systemic effects were reported in 28 of the incidents (72% of the incidents) including nausea, vomiting, abdominal cramps, headache and dizziness. The other 11 incidents involved irritation or injuries to the eyes, skin or respiratory tract. Several of the systemic cases also involved injuries or irritation to the eyes, skin or respiratory tract. No deaths were associated with methidathion exposure. All but one incident were occupational exposures, mostly involving handlers (19 applicators and 7 mixer/loaders). The rest of the occupational exposures were field workers (5) who entered a field treated with methidathion. The one non-occupational exposure involved a drift incident of a person doing yard work.

I.F. PHYSICAL AND CHEMICAL PROPERTIES

1.	Common Name:	Methidathion
2.	Chemical Name:	O,O-dimethyl-phosphorodithioate, S-ester with 4-(mercaptomethyl)-2-methoxy-Δ-1,3,4-thiadiazolin-5-one

3.   Trade Names: Supracide®, Suprathion®, Medacide®, Ultracide®

4.   CAS Registry No.:   950-37-8

5.   Structural Formula:

6.   Empirical Formula: $C_6H_{11}N_2O_4PS_3$

7.   Molecular weight: 302.3 g

8.   Density: 1.445 g/ml (Newell, 1987)

9.   Solubility: Water (22°C) (Wyler, 1987): 220 mg/L
                                        Solvents (20°C) (Lail, 1991):
                                            Cyclohexane: 850 g/L
                                            Acetone: 690 g/L
                                            Xylene: 600 g/L
                                            Ethanol: 260 g/L
                                            n-Octanol   53 g/L

10.   Vapor pressure: 3.37×10^{-6} mmHg at 25°C (Rordorf, 1988)

11.   Octanol/water partition coefficient: 166 (log P_{ow} = 2.2) (Daly, 1987)

12.   Henry's law constant: 1.95×10^{-9} atm•m^3/mole at 22°C (Leffingwell, 1989)

I.G. ENVIRONMENTAL FATE

Water: Although the water solubility of methidathion is relatively low, it has been detected in surface water due to rain run off from fields treated with the winter dormant spray. Methidathion residues were detected in 20 of 967 samples collected during surface water monitoring in 14 counties in California between June 1999 and September 2003 (Starner, 2005). DPR collected most of these samples with the Sacramento Watershed Program collecting the remainder. The maximum residue level detected was 1.749 ppb. Methidathion oxon was not detected in any of the 740 surface water samples analyzed for it.

The hydrolysis of methidathion varies with temperature and pH with hydrolysis half-lives ranging from 0.05 days to 41.3 days (Burkhard, 1978). The hydrolysis increased primarily with temperature and to a lesser degree with pH. Methidathion also underwent photodegradation in an aqueous environment with photolysis half-lives between 8 and 11 days (Suter, 1983; Saxena, 1989a). The primary hydrolytic and photolytic degradate was 2-methoxy-1,3,4-

thiadiazole-5(4H)-one, the thiadiazole ring moiety (identified as the RH compound in Figure 1 in the Pharmacokinetics section).

Soil: The soil adsorption coefficients (K_{OC}) for methidathion range from 29 (sandy soil) to 859 (sandy loam) (Martinson, 1988). Although the adsorption and desorption coefficients for methidathion vary considerably, the K_{OC} values suggest considerable leaching potential. DPR has identified methidathion as a potential groundwater contaminant based on a combination of its water solubility (> 3 ppm or mg/L), soil adsorption ($K_{OC} < 1900$ cm^3/g), and hydrolysis half-life ($t_{1/2} > 14$ days) (DPR, 2003a). However, methidathion has not been detected in 271 wells monitored in 13 counties in California by DPR from 1986 to 2004 (DPR, 2003b & 2004).

Soil metabolism studies with methidathion indicate that it is rapidly degraded in soil under both aerobic and anaerobic conditions (Saxena, 1990). The estimated half-life under aerobic conditions was approximately 3 days. The degradation of methidathion was longer under anaerobic conditions with a half-life of 30 days. The field dissipation studies indicate that methidathion is not likely to migrate below 12" in the soil (Honeycutt, 1986a&b; Silvoy, 1991a&b).

Methidathion also undergoes photodegradation in soil in a biphasic pattern with a half-life of approximately 9 days for the first phase and 21 days for the second phase (Saxena, 1989b). The two metabolites isolated from the irradiated soil samples were the thiadiazole ring and the sulfoxide.

Air: The vapor pressure for methidathion is relatively low; however, it has been detected in air monitoring studies of application sites and ambient air conducted in Tulare County in 1991 which were contracted by the California Air Resources Board at the request of the California Department of Pesticide Regulation (Royce *et al.*, 1993). Aston and Seiber (1997) also detected methidathion in the ambient air in the Sierra Nevada. The Henry's Law Constant for methidathion is also low indicating that under evaporative conditions it will increase in concentration on the soil surface and volatilization will increase with time (Spencer, 1987). The vapor phase photodegradation of methidathion was very limited under laboratory conditions when exposed to natural sunlight with an estimated half-life of 1.5 years (Kieatiwong, 1992).

For more details on the environmental fate of methidathion see Volume III of the Risk Characterization Document for methidathion (Gurusinghe, 2006).

II. TOXICOLOGY PROFILE

All the available toxicity studies for methidathion are summarized in the Toxicology Profile including studies from the open literature and studies submitted to the Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency (Cal/EPA) for registration of pesticide products in California as required by the Birth Defects Prevention Act (SB-950). DPR reviews the studies submitted to fill data requirements for SB-950 and determines the acceptability of these toxicology studies based on study guidelines as required under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (U.S. EPA, 2006). For SB-950, literature studies are generally considered supplemental because they do not follow FIFRA guideline protocols and/or do not provide sufficient detail in their reports to determine if they were conducted properly. In the risk assessment, greater weight was given to guideline studies, especially if they were found acceptable based on FIFRA guidelines. However, literature studies are useful in the selection of the critical NOEL in the Hazard Identification section to support effects seen in the guideline studies and can be used for the critical NOEL if they evaluate an endpoint not examined in the guideline studies and they appear to be scientifically valid studies. Except for the Pharmacokinetics and Acute Toxicity sections, the studies are generally organized within each section by route and species with the older studies discussed first. When mechanistic studies are available they are discussed after the guideline studies under the appropriate route and species. The Pharmacokinetics section was organized by different phases in the disposition of xenobiotics in the body. The Acute Toxicity section was separated into data for the technical grade material and the various formulations.

As discussed in the Introduction, cholinesterase (ChE) in nervous tissue is one of the primary target sites for methidathion. ChE activity was measured in the brain, red blood cells (RBCs) and plasma in many of the toxicity studies for methidathion. ChE inhibition was one of the more sensitive endpoints with acute, subchronic and chronic exposure, therefore, when analyzed the ChE data were summarized in a table for each study. In general, DPR considers brain ChE inhibition to be indicative of overt toxicity since more subtle functional changes in the nervous system due to ChE inhibition, such as memory and learning losses, may not be easily detected in animals unless they are specifically tested for these effects. The toxicological significance of plasma and RBC ChE inhibition is less certain because the physiological function of ChEs in blood have not been clearly established, although several possible physiological functions have been proposed, which were discussed in the Introduction.

II.A. PHARMACOKINETICS

Summary: There are FIFRA guidelines for metabolism and pharmacokinetic studies, however, these studies are not required under SB-950 for older pesticides. However, DPR requires metabolism studies for newer pesticides when they are first registered for use in California. Although methidathion was registered before SB-950 was enacted, the registrants have submitted some metabolism studies for methidathion, none of which met FIFRA guidelines. Even if the studies did not meet guidelines or had non-guideline protocols, the information from them can be used in evaluating the other toxicity studies. The most useful information derived from the pharmacokinetic studies is that related to the amount of radioactive material excreted by various routes which is then used to estimate absorption rates depending on the route of

administration. These absorption rates can then be used to adjust NOELs to obtain an internal dose. Internal dosages are used when doing route-to-route extrapolation.

Methidathion is readily absorbed, metabolized and excreted in rats after oral exposure. The major routes of excretion were urine and CO_2. Fecal excretion represented a minor route. Based on the amount excreted in the urine, CO_2 and feces, the oral absorption was assumed to be 100%. Methidathion was also readily absorbed by the dermal route. Based on deficiencies in the available dermal absorption study in mice, a default value of 50% was assumed for dermal absorption. The pharmacokinetic studies usually include proposed metabolic pathways based on the metabolites identified which can help identify the active metabolite(s) and may help explain some of the toxic effects observed. Several urinary metabolites of methidathion were identified in the rat, including the cysteine conjugate, and the sulfide, sulfoxide, sulfone, RH, and desmonomethyl derivatives (Figure 1). The presumed active metabolite of methidathion is its oxygen analog (i.e., oxon). However, the pharmacokinetics studies suggest that the oxidative desulfuration of methidathion to the oxon is a minor metabolic pathway.

The guideline studies for metabolism and pharmacokinetics only recommend testing in adult male rats and, consequently, do not provide any information regarding differences due to species, gender, age, and pregnancy. There was also no information in the literature studies for methidathion regarding differences in metabolism or pharmacokinetics due to gender, age or pregnancy. This information would be useful in identifying subpopulations or life stages where people may be at greater risk.

II.A.1. Absorption

Oral: Groups of 5 rats/sex/dose were administered a single dose of ^{14}C-methidathion (labeled on the carbonyl carbon of the thiadiazole ring) by oral gavage at 0.314 or 2.985 mg/kg (Szolics, 1987). A third group was administered unlabeled methidathion by oral gavage at 0.25 mg/kg for 14 days and then given single dose of ^{14}C-methidathion by oral gavage at 0.309 mg/kg on day 15. Urine and feces was collected for 7 days following the final application. The CO_2 excretion was estimated in this study based on data from a non-guideline pilot study using 2 rats/sex/dose at 0.295 mg/kg and at 2.949 mg/kg (Simoneaux, 1987a). In this pilot study, 75-89% of the administered dose was excreted in the first 24 hours whereas in the main study 63-73% of the administered dose was excreted in the first 24 hours. However, there was a significant difference in the recoveries between the main study (76-93%) and the pilot study (99-102%). The author suggested that the low recoveries in the main study were due to losses during the storage of urine samples for three months prior to analysis. Since the CO_2 excretion was not actually monitored in the main study, it is uncertain if the recoveries were lower from the losses in the urinary samples or from the CO_2 excretion being higher than estimated from the pilot study. A comparison of these two studies is also difficult because different laboratories conducted these studies and different breeders provided the Sprague-Dawley rats used which could have slight genetic differences in their metabolism of methidathion. The main study conducted by Szolics (1987) did not meet FIFRA guidelines due to incomplete recovery of radiolabeled compound. Despite having fewer animals per dose group, the data from the non-guideline pilot study was used to estimate the percent oral absorption since the recoveries were better and the CO_2 excretion was measured. The combined urinary, fecal and CO_2 excretion in the pilot study ranged from 98 -102%. The radioactivity in the feces was assumed to be due

primarily to biliary excretion because of similar fecal excretion rates with dermal application (Simoneaux and Marco, 1984). Therefore, the oral absorption rate was assumed to be 100%.

Dermal: ^{14}C-Methidathion (labeled on the carbonyl carbon of the thiadiazole ring) was applied to shaved backs of 4 mice/sex in either an acetone solution or formulated product containing petroleum hydrocarbon with an emulsifier at 12 mg/kg over an 0.25 sq. inch area (Simoneaux and Marco, 1984). Urine, feces, and CO_2 excretion were monitored for 72 hours after application. With this route of application, CO_2 was the main route of excretion ranging from 51-56% with the formulated product to 61-64% with the acetone solution. Urinary excretion was significantly lower ranging from 14-15% with the acetone solution to 16-23% with the formulated product. The combined urinary, fecal, and CO_2 excretion after 72 hours ranged from 75.4% for females treated with the formulated product to 82.1% for males treated with the acetone solution. It is interesting that while the amount absorbed is not that different between the two formulations, the pathways by which they are metabolized changed slightly. Due to the use of organic solvents and the testing of only one dose level, DPR found this study unacceptable for estimating dermal absorption (Beauvais, 2006). Therefore, DPR assumed a default value of 50% for dermal absorption.

II.A.2. Distribution

In the pilot study conducted by Simoneaux (1987a), the total amount excreted within the first 24 hours ranged from 75% in females at 2.949 mg/kg to 89% in males at 0.295 mg/kg. In the main study conducted by Szolics (1987), the total amount excreted within the first 24 hours was estimated to be 63% in males at 0.295 mg/kg to 73% in females at 2.949 mg/kg assuming similar CO_2 excretion rates to the pilot study. Elimination half-lives were not calculated for the pilot study, but are obviously less than 24 hours. Using the CO_2 excretion data from the pilot study, the estimated elimination half-lives for the main rat metabolism study ranged from 7.4 hours in females at 0.295 mg/kg to 9.7 hours in males receiving 0.295 mg/kg/day for 14 days. In the pilot study, only carcass residue levels were measured 7 days after dosing, ranging from non-detectable in both sexes at 0.295 mg/kg to 0.93% of administered dose in females at 2.949 mg/kg. In the main study, tissue residue levels ranged from 0.53% of administered dose in the females at 2.949 mg/kg to 1.14% in males at 0.295 mg/kg 7 days after the last dose. The vast majority of the radioactivity (0.40-0.98% of administered dose) was found in the carcass. No other tissue levels exceeded 0.1% of the administered dose.

II.A.3. Biotransformation

One of the earliest metabolism studies was conducted by Bull (1968) in which male Wistar rats (number not reported) were administered methidathion (10 mg/kg [14]C- and 1.5 mg ^{32}P-labeled in propylene glycol) intraperitoneally. With the ^{14}C-label on the methoxy or carbonyl carbon of the thiadiazole ring, 22.4 and 25.8% of the dose was expired as radioactive CO_2, respectively, and 57.4 and 52.0% was excreted, respectively, within 48 hrs in the urine and feces. When the ^{14}C-label was on the methylene carbon, 17.7% was expired as CO_2 and 59.0% excreted in the urine and feces. No metabolites were identified in the urine and feces. With the ^{32}P-label, 80% of the applied dose was excreted within 48 hours, with only 7.1% of the applied dose excreted in the feces. The urinary metabolites identified dimethyl phosphate (33.6%), dimethyl

phosphorothioate (24.2%), desmethyl derivative (11.1%), methyl phosphate and phosphoric acid (both 1.5%). This was a non-guideline study and was considered supplemental.

Four male rats were administered 0.642 mg ^{14}C-labeled methidathion by oral gavage in a non-guideline study conducted by Cassidy *et al.* (1969). The ^{14}C-label was on the carbonyl carbon of the thiadiazole ring. Urine samples were collected during the first 24 hours after dosing and analyzed for metabolites. Six radioactive urinary metabolites were isolated, but only three were identified. The three identified urinary metabolites were the sulfoxide, the sulfone, and the desmethyl derivative which represented 52%, 13%, and 7% of the radioactivity in the urine, respectively. This non-guideline study was considered supplemental.

Prior to the main study conducted by Szolics (1987), three non-guideline studies were conducted in which methidathion was administered to rats with the ^{14}C-label on different carbons of the thiadiazole ring: the carbonyl carbon, the methoxy group carbon, and the methylene carbon adjacent to the methoxy group (Simoneaux, 1987a-c). The amount excreted in the respiratory gases was lowest with the ^{14}C-label on the methylene carbon (10-12%). Significantly higher amounts of radioactivity were found in the respiratory gases when the ^{14}C-label was on the carbonyl carbon (33-44%) or the methoxy group carbon (40-44%). With the ^{14}C-label on the methoxy group carbon, an additional unknown ^{14}C-labeled material other than CO_2 was found in the trapping solution. The investigators suggested it might be another volatile gas such as methane. Analysis of the urinary metabolites indicated that approximately two-thirds were organic soluble and one third aqueous soluble, regardless of the position of the ^{14}C-label. The sulfide, sulfoxide, sulfone, and RH derivatives were the major urinary metabolites in the organic soluble fraction. The cysteine conjugate and the desmonomethyl derivative were the major urinary metabolites in the aqueous soluble fraction. With the ^{14}C-label on the carbonyl carbon and the carbon adjacent to the methoxy group, the major urinary metabolite was the sulfide. With the ^{14}C-label on the methoxy carbon, the sulfoxide was the major urinary metabolite. The parent compound was found only with the ^{14}C-label on the carbonyl carbon (0.7%). The oxygen analog was found when the ^{14}C-label was on either the methoxy carbon or adjacent to the methoxy carbon (0.2-0.8%). These non-guideline studies were considered supplemental.

A recent study examined the excretion of dialkyl phosphate metabolites after oral and dermal exposure to methidathion in rats for biomonitoring application (Min *et al.*, 2005). Five Sprague-Dawley rats/dose were administered methidathion with a propylene glycol vehicle at 2.16 mg/rat orally or 66.5 mg/rat dermally to a clipped area of 6.25 cm^2 covered with semi-occlusive dressing for 96 hours.   Urine was collected up to 168 hours after exposure. Identification of urinary dialkyl phosphate metabolites was determined by GC/MS. With oral exposure, 6.5%, 6.0% and 2.9% of the dose was excreted as *O,O*-dimethyl phosphate (DMP), *O,O*-dimethylphosphorothioate (DMTP) and *O,O*-dimethylphosphorodithioate (DMDTP), respectively. With dermal exposure, 1.1%, 1.0% and 0.7% of the dose was excreted as DMP, DMTP, and DMDTP, respectively. All of the DMP and DMDTP and 94% of the DMTP were excreted within 24 hours after oral administration. Excretion was slower with dermal application where 100%, 75% and 87% of DMP, DMTP and DMDTP, respectively, were excreted within 48 hours. The parent compound was not detected in any of the samples. More research is needed to address species differences in excretion and effect of dose level on excretion. This non-guideline study from the open literature was also considered supplemental.

The *in vitro* metabolism of ^{14}C-methidathion (labeled on the carbonyl carbon) was examined in another non-guideline study using rat and mouse liver subcellular fractions (Chopade and Dauterman, 1981). Methidathion underwent *O*-demethylation via the glutathione *S*-transferases forming des(mono)methyl methidathion. Methidathion also underwent oxidative desulfuration via the mixed function oxidase system to form the oxygen analog. Methoxythiadiazolin (RH compound) was also formed by the mixed function oxidase system, but the exact mechanism is unknown. The P-S bond of methidathion and its oxygen analog were hydrolyzed forming a reactive mercaptomethyl intermediate which underwent *S*-methylation to form the sulfide. The sulfide was then oxidized to the sulfoxide by the FAD-dependent monooxygenase system; however, the sulfoxide was oxidized to the sulfone by the mixed function oxidase system. There did not appear to be any significant species differences in metabolism between rats and mice. This non-guideline study from the open literature was considered supplemental.

The possible metabolic pathways of the isolated urinary metabolites of methidathion is shown in Figure 1. These metabolic pathway are based primarily on metabolic pathway proposed for methidathion by Szolics (1987). The first step in the major metabolic pathway is the hydrolysis of the S-P bond to form the reactive mercaptomethyl intermediate which undergoes S-methylation to form the sulfide. The sulfide then undergoes oxidation to form the sulfoxide and sulfone. Szolics proposed a secondary metabolic pathway in which the mercaptomethyl intermediate undergoes conjugation with glutathione to form the glutathione conjugate and its derivatives such as the cysteine conjugate. Another proposed secondary metabolic pathway was the *O*-demethylation to form the des(mono)methyl derivative. The oxidative desulfuration of methidathion to the oxygen analog was considered a minor metabolic pathway. Szolics suggested that the RH metabolite could be derived from a variety of intermediates. The metabolic pathway proposed by Szolics (1987) for methidathion is similar to one proposed by Chopade and Dauterman (1981), although Chopade and Dauterman considered the *O*-demethylation of methidathion to the des(mono)methyl derivative to be the major pathway. Not shown in this metabolic pathway is the generation of CO_2. This occurred with the ^{14}C-label in all three locations (methoxy, carbonyl, and methylene) on the thiadiazole ring , although the amount was significantly lower with the methylene label. No intermediate metabolites were identified in this pathway. *O*-demethylation is probably involved in the generation of CO_2 from the methoxy carbon with formaldehyde as a likely intermediate. The generation of CO_2 from the carbonyl carbon and methylene carbon would involve breaking of the thiadiazole ring. In addition to the urinary metabolites identified with ^{14}C-label, Figure 1 includes the urinary metabolites identified with the ^{32}P-label (Bull, 1968; Min *et al.*, 2005).

II.A.4. Excretion

The two major routes of excretion appear to be the urine and CO_2 in both the main study conducted by Szolics (1987) and the pilot study conducted by Simoneaux (1987a). In the pilot study, the mean urinary excretion was essentially identical at both 0.295 and 2.949 mg/kg, but varied slightly between sexes (M: 57%; F: 54%). In the main study, the mean urinary excretion was significantly lower, ranging from 30% in males at 0.295 mg/kg to 42% in males at 2.949 mg/kg, except in females at 2.949 mg/kg which excreted 57%. As mentioned previously under the discussion for oral absorption, Szolics suggested the lower recoveries in the main study were
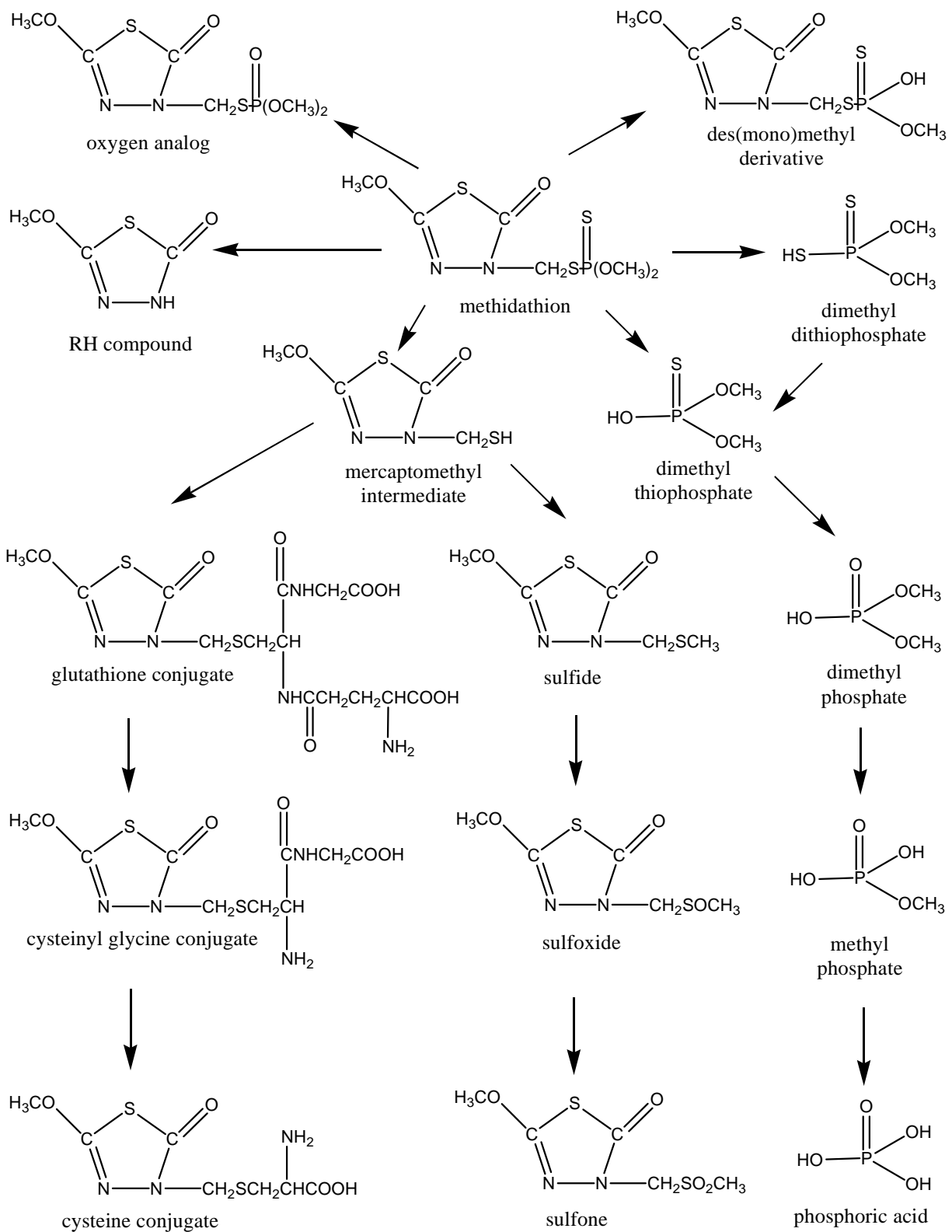
Figure 1. Possible Metabolic Pathways for Isolated Urinary Metabolites of Methidathion (Bull, 1968; Cassidy, 1969; Szolics, 1987; Min *et al.*, 2005)

due to losses in the urine during a 3-month storage period. However, another possible explanation may be slight genetic differences in the metabolism of methidathion due to different sources of Sprague-Dawley rats used in the two studies. In the pilot study, the mean CO_2 excretion was slightly higher at 0.295 mg/kg (M: 41%; F: 44%) than at 2.949 mg/kg (M: 34%; F:32%), whereas the mean fecal excretion was lower at 0.295 mg/kg (M: 5%; F: 3%) than at 2.949 mg/kg (M: 8%; F: 12%). Since the CO_2 excretion was not measured in the main study, it is unknown if the CO_2 excretion in this study also varied with dose level or with repeated exposure. The mean fecal excretion in the main study was relatively similar between dosing regimens, but it tended to be slightly higher in the males (0.78-1.14%) than the females (0.53-0.72%).

II.B.   ACUTE TOXICITY

Summary: A battery of six acute toxicity tests (acute oral, dermal and inhalation LD_{50}/LC_{50} tests, dermal and eye irritation tests, and a dermal sensitization test) are required for each pesticide formulation to be registered in California. Registrants are not required to submit these guideline acute toxicity studies for the technical material unless it is sold as a product. Consequently, only literature studies on the acute oral and dermal toxicity of technical grade methidathion were available and none of these met FIFRA guidelines. The clinical signs observed with the technical material were typical cholinergic signs including tremors, ataxia, fasciculations, difficulty in breathing, salivation, lacrimation and exophthalmos. There were insufficient information in any of these studies for establishing a No-Observed-Effect Level (NOEL) or Lowest-Observed-Effect Level (LOEL) for the technical grade material. Based on the limited data for the technical grade material, it appears to be a Category I pesticide. One study found weanling rats were more sensitive to methidathion than adult rats based on their oral LD_{50} values. Several other non-guideline mechanistic studies found evidence of lipid peroxidation in erythrocyte membranes and liver after a single oral dose of methidathion. More acute toxicity data were available for the methidathion formulations since they are required to register the formulations in California. Furthermore, these studies were acceptable based on FIFRA guidelines. The wettable powder formulation was a Category II pesticide based on its oral toxicity and inhalation toxicity. The emulsifiable concentrates were considered a Category I pesticide based on oral toxicity and severe eye irritation. Two non-guideline studies evaluated the relative sensitivity of young and adult turkeys to a single oral or dermal dose of a 25% wettable powder formulation with the young appearing more sensitive in one study and the adults more sensitive in the other. Another non-guideline study reported a synergistic increase in the toxicity of a 25% wettable powder formulation when administered simultaneously with 6 other organophosphate chemicals. Other guideline studies with acute or short-term exposure will be discussed separately under the Developmental Toxicity and Neurotoxicity sections in the Toxicology Profile. No acute toxicity data were available on the oxygen analog of methidathion which could have been used to develop a toxicity equivalency factor.

II.B.1. Technical Grade Methidathion

Table 1 summarizes the guideline type acute toxicity studies for technical grade methidathion. The data available on the technical material are limited to literature studies with brief summaries of the acute oral and dermal toxicity. The purity of the technical grade material

Table 1.   The Acute Toxicity of Technical Grade Methidathion

Species	Sex	Results	References[a]
Acute Oral LD$_{50}$			
Rat	NR	25-48 mg/kg	1
Mouse	NR	26-32 mg/kg	
Rabbit	NR	63-80 mg/kg	
Guinea Pig	NR	25 mg/kg	
Hamster	NR	30 mg/kg	
Rat, weanling adult	M M F	21 mg/kg 31 mg/kg 32 mg/kg	2
Pigeon	NR	30-40 mg/kg	3
Acute Dermal LD$_{50}$			
Rabbit	M/F	140-155 mg/kg	1
Rat	M F	94 mg/kg 85 mg/kg	2
Pigeon	NR	>59 mg/kg	3
Dermal Sensitization			
Guinea Pig	F	Moderate-Severe	4
a References: 1. Geigy, 1964; 2. Gaines and Linder, 1986; 3. Henderson *et al.*, 1994; 4. Matsushita and Aoyama, 1981.			

was not reported in any of these reports and none of these studies met FIFRA guidelines due to the limited information provided. The effects reported included dizziness, ataxia, irregular and increased respiration, dyspnea, fasciculations, trembling, salivation, exophthalmos, and death. Rabbits appear to be less sensitive to methidathion than rats, mice, guinea pigs and hamsters based on the LD$_{50}$ values reported for these species by Geigy (1964). Weanling rats appear to be more sensitive than adult rats to methidathion based on their oral LD$_{50}$ values in the study conducted by Gaines and Linder (1986). A study was conducted by Henderson *et al.* (1994) which compared the acute oral and dermal toxicity in pigeons of several organophosphates used as dormant sprays in orchards, including ethyl parathion, diazinon and methidathion. Methidathion was the least toxic of these three organophosphates based on its lethal oral dose range (30-40 mg/kg). The investigators also applied these three organophosphate pesticides to the feet of pigeons to simulate exposure in hawks from perching in orchards. With the dermal exposure, only birds given ethyl parathion at ≥ 59 mg/kg died. They found no significant plasma ChE inhibition at the highest dose tested of methidathion, 37 mg/kg, despite mild signs (not specified) of organophosphate poisoning. In another study, a significant reduction in plasma ChE activity (71% of controls) was seen in pigeons administered a single oral dose of methidathion at 10 mg/kg (Bartkowiak and Wilson, 1995). Plasma carboxylesterase activity was

not affected at this dose level. No other dose levels were tested nor were any other endpoints evaluated in this study. Insufficient information was provided in all of these acute toxicity studies for methidathion to establish a LOEL or NOEL for an acute, single dose exposure scenario.   No data were available on the ocular or dermal irritation potential of the technical grade methidathion. One dermal sensitization study was available that suggests that methidathion is a potential sensitizer (Matsushita *et al.*, 1985). These investigators also examined if exposure to methidathion during the induction phase causes a cross reaction when later challenged with benomyl, DDVP, and naled. There was some evidence of a cross reaction with DDVP and naled, but no cross reaction with benomyl.

Several non-guideline studies in the open literature evaluated the mechanism of toxicity for methidathion with acute exposure. The effect of methidathion on Na^+/K^+-ATPase, Ca^{2+}/Mg^{2+}-ATPase, cholesterol and phospholipid levels in RBC membranes was evaluated in rats administered 1, 3, 5 or 7 daily doses at 2 mg/kg (El-Dawy *et al.*, 1995). There was a significant reduction in the activity of both ATPases with 1 to 7 doses. The investigators suggested that this reduction in ATPase activity could result in the preservation of cell energy and ions. The cholesterol levels in the membranes were also elevated with one or more doses of methidathion. By contrast, the phospholipid levels decreased with 3 or more doses. The investigators suggested that these changes in cholesterol and phospholipid levels may be an adaptive response to increase the resistance of the RBCs to osmotic lysis.

Altuntas *et al.* (2002a) reported that a single oral dose of methidathion (8 mg/kg) to rats resulted in a significant increase in malondialdehyde (MDA) levels (a biomarker of membrane lipid peroxidation resulting from the interaction of reactive oxygen species and the cellular membrane) and a significant decrease in the anti-oxidant enzymes, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) activities in erythrocytes compared to control animals. Another group of rats was administered methidathion (8 mg/kg) plus vitamin E (150 mg/kg i.m.) and vitamin C (200 mg/kg i.p.) 30 minutes later. In this group (MD+Vit), the MDA levels were comparable to controls. The SOD and CAT were reduced to a similar degree as animals treated with methidathion only (MD). The GSH-Px activity was also reduced in the MD+Vit group, but less than in the MD group such that the mean activity was significantly different from the MD group, but not the controls.

Altuntas *et al.* (2002b) also examined the effect of methidathion on lipid peroxidation and liver enzymes in rats. Rats were assigned to three groups as before: controls, MD and MD+Vit. In this experiment, they measured the thiobarbituric acid reactive substances (TBARS, a endproduct of lipid peroxidation), ChE, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), and lactate dehydrogenase (LDH) in the serum. The AST, ALP, GGT and LDH levels were all significantly higher in the MD and MD+Vit groups. ChE and ALT were significantly lower in the MD and MD+Vit groups. TBARS were only significantly higher in the MD group. The addition of vitamins E and C moderated the effects of methidathion with significant differences between the MD and MD+Vit groups for TBARS, ChE and AST. This group also examined the effect of methidathion on these enzymes in human serum. They divided serum samples into four portions: controls, Vit (7.5 µg/ml vitamin E and 10 µg/ml vitamin C), MD (0.4 mg/ml methidathion) and MD+Vit (0.4 mg/ml methidathion, 7.5 µg/ml vitamin E and 10 µg/ml vitamin

C). Only significant decreases in ChE, ALT and LDH were observed in the MD and MD+Vit groups.

In another experiment from this same research group, investigators microscopically examined the livers of rats approximately 24 hours after a single oral dose of methidathion at 8 mg/kg (MD) or MD+Vit (8 mg/kg methidathion, 150 mg/kg vitamin E i.m., 200 mg/kg vitamin C i.p.) (Gokalp *et al*. 2003). They observed significant increases in mononuclear cells at parenchymal tissue, sinusoidal dilatation, focal necrotic areas, granular degeneration and picnotic nuclei in hepatocytes compared to controls in both the MD and MD+Vit groups; however, the severity of the granular degeneration and sinusoidal dilatation was less in the MD+Vit group.

II.B.2. Methidathion Formulations

The acute toxicity of the Supracide® wettable powder in FIFRA guideline studies is summarized in Table 2. The primary clinical signs observed with inhalation exposure included hypoactivity, piloerection, tremors, salivation, unsteady gait, exophthalmos, polyuria, nasal discharge, and lacrimation (Holbert, 1992). Gross necropsy findings included discoloration of the contents of the gastrointestinal tract, discoloration of the liver and lungs, lungs swollen, and small intestine distended with gas. Similar clinical and gross pathological observations were observed with oral exposure to the Supracide® wettable powder, except they were less pronounced (Kuhn, 1992a). With dermal exposure to the Supracide® wettable powder, the only effect observed was decreased defecation in one of five males (Kuhn, 1992b). No erythema or edema was observed with dermal exposure to the Supracide® wettable powder (Kuhn, 1992c). Slight corneal opacity was observed in one of six rabbits exposed to the Supracide® wettable powder (Kuhn, 1992d). No other ocular effects were seen. No sensitization response was observed in guinea pigs after exposure to the Supracide® wettable powder (Kuhn, 1992e).

Two non-guideline acute studies were conducted in which young (6-8 weeks) and adult (16-18 weeks) turkeys were administered the 25% wettable powder by the oral or dermal route (Schlinke and Palmer, 1971; Radeleff and Kunz, 1972). In the study conducted by Schlinke and Palmer (1971), 6-week-old turkeys appeared to be more sensitive to methidathion based on a lower acute oral NOEL (10 mg a.i./kg) for unspecified signs compared to 16-week-old turkeys (20 mg a.i./kg). However, in another study conducted by Radeleff and Kunz (1972), 18-week-old turkeys appeared more sensitive with an acute oral NOEL of 10 mg a.i./kg for unspecified signs compared to 15 mg a.i./kg in 8-week-old turkeys. A similar comparison of dermal NOELs was not possible in either of these studies because of the limited number of dose levels tested with dermal exposure.

The acute toxicity of Supracide® emulsifiable concentrate in the guideline studies was similar to the wettable powder with the exception of the ocular and dermal irritation (Table 3). The clinical signs observed with inhalation, oral and dermal exposure to the emulsifiable concentrate were similar to those observed with the wettable powder with similar LC_{50}/LD_{50} values (Holbert, 1989; Kuhn,1989a&b). Unlike the wettable powder, the Supracide® emulsifiable concentrate caused moderate dermal irritation including well-defined erythema lasting up to 21 days and slight edema lasting up to 14 days (Kuhn, 1989c). The Supracide® emulsifiable concentration also caused severe eye irritation including complete corneal opacity

Table 2.   The Acute Toxicity of Methidathion (25%) Wettable Powder

Species	Sex	Results	References[a]
Acute Inhalation LC$_{50}$			
Rat	M	0.57 mg/L (4-hr, whole body)	1*
	F	0.11 mg/L (4-hr, whole body)	
Acute Oral LD$_{50}$			
Rat	M	94 mg/kg	2*
	F	53 mg/kg	
Acute Dermal LD$_{50}$			
Rabbit	M/F	> 2,020 mg/kg	3*
Primary Dermal Irritation			
Rabbit	M/F	Non-Irritant	4*
Primary Eye Irritation			
Rabbit	M/F	Moderate Irritant	5*
Dermal Sensitization			
Guinea Pig	M	Non-Sensitizer	6*
a References: 1. Holbert, 1992; 2. Kuhn, 1992a; 3. Kuhn, 1992b; 4. Kuhn, 1992c; 5. Kuhn, 1992d; 6. Kuhn, 1992e. * Acceptable study based on the FIFRA guidelines.			

in some rabbits lasting up to 21 days, iritis that lasted up to 17 days and conjunctivitis that lasted up to 21 days (Kuhn, 1989d). Like the wettable powder, there was no evidence of dermal sensitization in guinea pigs with the Supracide® emulsifiable concentrate (Kuhn, 1989e).

II.B.3. Synergism

Synergism is sometimes observed when two organophosphate chemicals are given simultaneously. In a non-guideline study, the toxicity of a 25% methidathion wettable powder formulation was evaluated in rats when co-administered with one of 17 compounds (carbophenothion, demeton, coumaphos, diazinon, azinphos-methyl, dioxathion, EPN, ethion, malathion, mevinphos, methyl parathion, carbaryl, ethyl parathion, fenchlorphos, schradan, disulfoton and S,S,S-tributyl phosphorotrithioite) at 1/8, 1/4 and 1/2 of their LD$_{50}$ dose (Woodard Research, 1966a). A synergistic increase in the toxicity of methidathion was reported with 6 compounds (carbaryl, mevinphos, azinphos-methyl, methyl parathion, fenchlorphos and disulfoton). No details were provided on how the toxicity of methidathion was evaluated.

Table 3.   The Acute Toxicity of Methidathion (22.5%) Emulsifiable Concentrate

Species	Sex	Results	References[a]
Acute Inhalation LC$_{50}$			
Rat	M	0.575 mg/L (4-hr, whole body)	1*
	F	0.167 mg/L (4-hr, whole body)	
Acute Oral LD$_{50}$			
Rat	M	111 mg/kg	2*
	F	22 mg/kg	
Acute Dermal LD$_{50}$			
Rabbit	M	> 1,990 mg/kg	3*
	F	2,240 mg/kg	
Primary Dermal Irritation			
Rabbit	M/F	Moderate Irritant	4*
Primary Eye Irritation			
Rabbit	M/F	Severe Irritant	5*
Dermal Sensitization			
Guinea Pig	M	Non-Sensitizer	6*
a References: 1. Holbert, 1989; 2. Kuhn, 1989a; 3. Kuhn, 1989b; 4. Kuhn, 1989c; 5. Kuhn, 1989d; 6. Kuhn, 1989e. * Acceptable study based on the FIFRA guidelines.			

I.C. SUBCHRONIC TOXICITY

Summary: Twelve subchronic toxicity studies were available for methidathion, 6 oral studies in rats, mice and turkeys and 6 dermal studies in rats, rabbits and turkeys. Most of the subchronic studies were non-guideline studies, but did provide useful supplemental information regarding the adverse effects in different species and/or mechanism of toxicity with subchronic oral and dermal exposure. One 21-day dermal study in rabbit came close to meeting FIFRA guidelines, but was found unacceptable due to an incomplete histopathological examination. Clinical signs observed with subchronic exposure to methidathion included lethargy, anorexia, labored or rapid breathing, hunched posture, ataxia, tremors, soft feces, and low body temperature. Reductions in body weights and food consumption were also seen. Pathological findings included changes in hematological values suggesting anemia, changes in serum enzymes suggesting liver toxicity, reduced brain ChE activity, and lesions in the liver, gallbladder, stomach and heart. A few mechanistic studies found biochemical evidence of lipid peroxidation in the heart, aorta and kidneys along with histopathological lesions in these tissues after subchronic exposure to methidathion. ChE inhibition was one of the most sensitive endpoints with subchronic exposure. The lowest NOEL was 0.18 mg/kg/day based on a

reduction in plasma, RBC and brain ChE activity in rats in several studies of varying length from the same laboratory. Other guideline studies that involve short-term or subchronic exposure are discussed in detail in the Reproductive and Developmental Toxicity sections in the Toxicology Profile.

II.C.1. Gavage-Rat

Ten rats/dose (sex and strain not reported) were administered methidathion (purity not reported) at 0.25, 0.83, 2.5, 8.3, 16.6 or 33.2 mg/kg/day by oral gavage in propylene glycol daily for 4 weeks (Geigy, 1964). Five and 10 rats died within the first 4 days of exposure at 16.6 and 33.2 mg/kg/day, respectively. Consequently, all survivors at these dose levels were sacrificed at 2 weeks. No changes in body weights were observed at or below 8.3 mg/kg/day. Rats at 8.3 mg/kg/day and higher were reported to have clinical signs of toxicity, but no details were provided. Plasma ChE activity was only reduced at 8.3 mg/kg/day (Table 4). RBC ChE activity was reduced at 0.83, 2.5 and 8.3 mg/kg/day. There was no apparent statistical analysis of the ChE data. Based on the limited information provided, the NOEL for this study appears to be 0.25 mg/kg/day based on the reduced RBC ChE activity (62% and 77% of reported normal values at 2 and 4 weeks, respectively) at 0.83 mg/kg/day. This study had major deficiencies based on the FIFRA guidelines for subchronic studies; however, it was conducted before the guidelines existed. The deficiencies included no analysis of test article or dosing material, no control animals, inadequate number of animals per dose level, inadequate exposure duration, limited clinical chemistry analyses, no hematology or urinalysis, no pathological examination, no summary of body weights and clinical signs by treatment group, and no individual data.

Table 4. Blood Cholinesterase Activity Relative to Controls in Rats Administered Methidathion by Gavage for 4 Weeks[a]

Tissue	Dose Level (mg/kg/day)			
	0.25	0.83	2.5	8.3
Plasma, 2 wks	112[b]	99	94	76
4 wks	93	104	98	73
RBC[c], 2 wks	100	62	51	6
4 wks	90	77	46	16

a Geigy, 1964. This study did not meet FIFRA guidelines since it predated them. Not reported, but ChE activity was presumably measured in all 5 rats/sex/dose.
b Mean activity relative to mean control activity expressed as percentage. There was no apparent statistical analysis of these data.
c RBC = Red Blood Cell

Geigy (1964) conducted a second subchronic study in which groups of 5 rats (strain not specified)/sex/dose were administered technical grade methidathion (purity not reported) at 2.5, 5, 10 or 20 mg/kg/day by oral gavage in gum arabic on 6 days/week for 4 weeks. Thirteen animals died (sex not indicated) during the study, 4 at 10 mg/kg/day and 9 at 20 mg/kg/day. Animals at 5 mg/kg/day exhibited signs which were described as typical of cholinesterase

inhibition (no other details provided). Body weight reductions were seen although the severity was difficult to estimate from the figures provided. At 5 mg/kg/day and higher, centro-medio-lobular fatty deposits in liver cells were seen microscopically. Based on the limited information provided, the tentative NOEL for this study appears to be 2.5 mg/kg/day. This study had numerous major deficiencies including no analysis of test article or dosing material, no control animals, inadequate number of animals per dose level, inadequate exposure duration, no clinical pathology analyses, no summary of body weights, clinical signs, and pathological findings by treatment group, and no individual data.

The cardiotoxicity and vascular wall damage following subchronic oral exposure to methidathion was examined in two mechanistic studies (Yavuz *et al.*, 2004a&b). In both studies, three groups of approximately 7 male Wistar rats were administered the following by gavage 5 days/week for 4 weeks: corn oil (controls), 5 mg methidathion/kg/day (MD) or 5 mg methidathion/kg/day plus 50 mg vitamin E/kg (i.m.) and 20 mg vitamin C/kg/day (i.p.) (MD+Vit). In both studies, severe fasciculations and fatigue were observed 1-1.5 hours after dosing in the MD group. The signs were less severe in the MD+Vit group. In one study, Yavuz *et al*. (2004a) found significantly elevated levels of cardiac troponin I (TnI, a biomarker of myocardial damage) in the serum and of malondialdehyde (MDA, a biomoarker of membrane lipid peroxidation) in cardiac homogenates in the MD and MD+Vit groups compared to controls. Serum ChE activity was significantly reduced in both the MD (60% of controls) and MD+Vit groups (81% of controls). Both the increases in TnI and MDA and the reduction in ChE activity were moderated by the addition of vitamins E and C to the extent that the levels in MD+Vit group were significantly different from the MD group. Histopathological examination of the heart revealed diffuse loss of striation and myocytoloysis of the cardiomyocytes in the MD and MD+Vit with the severity much less in the MD+Vit group. In another study, Yavuz *et al.* (2004b) found significantly elevated MDA levels in the thoracic aorta in the MD group, but not the MD+Vit group. Histopathological examination revealed irregulation, prominent breaks and fragmentation of the elastic fibers located in the media of the aortic wall in the MD group. The aortic wall also had diffuse vacuolation. The irregulation and fragmentation were significantly reduced in the MD+Vit group. The diameter of the aorta lumen was significantly increased in the MD and MD+Vit groups compared to controls, but much less in the MD+Vit group to the extent that it was also significantly different from the MD group. A NOEL could not be established in either one of these non-guideline studies.

This same research group also examined the mechanism behind the nephrotoxicity of methidathion using the same treatment groups (controls, MD, and MD+Vit) and dosing regimen (5 mg methidathion/kg/day, 50 mg vitamin E/kg/day i.m., 20 mg vitamin C/kg/day i.p.) 5 days/wk for 4 weeks (Sulak *et al.*, 2005). Serum ChE activity was significantly reduced in both the MD (67% of controls) and MD+Vit (79% of controls) groups. The ChE activity in MD+Vit group was also significantly higher than the MD group. The MDA levels in the kidney homogenates was significantly higher in the MD and MD+Vit groups compared to controls, but significantly lower in the MD+Vit group compared to the MD group. Histopathological examination of the kidney revealed glomerular sclerosis, vascular congestion and fibrosis, focal tubular necrosis, hydropic degeneration of tubular epithelial cells and severe interstitial mononuclear cell infiltration in the MD group. MD+Vit group had a similar severity of the glomerular sclerosis and vascular congestion, but reduced severity of hydropic degeneration of the tubular epithelial cell, interstitial mononuclear cell infiltration and vascular fibrosis

compared to the MD group. Focal tubular necrosis was not observed at all in the MD+Vit. A NOEL was not establish in this non-guideline study.

II.C.2. Gavage-Turkey

The oral toxicity of a 25% methidathion wettable powder was evaluated in 5 6-week-old turkeys (sex not reported)/dose at 0, 2.5, 5, 10 and 20 mg a.i./kg/day for 10 days (Schlinke and Palmer, 1971). One bird died at 20 mg/kg/day. No other effects were reported. The NOEL in the 6-week-old turkeys appears to be 10 mg/kg/day. The 25% wettable powder was also administered to 5 16-week-old turkeys/dose at 0, 5, 10 and 20 mg a.i./kg/day for 10 days. Three deaths and unspecified signs in the other two birds were seen at 20 mg/kg/day. Signs of toxicity were also seen in one bird at 10 mg/kg. The NOEL in 16-week-old turkeys appears to be 5 mg/kg/day. These data suggest that the adults are more sensitive to methidathion with repeated exposure. This is in contrast with the findings of Schlinke and Palmer (1971) after acute exposure in turkeys which found young turkeys more sensitive, but is consistent with the findings of another acute study in turkeys by Radeleff and Kunz (1972) which found adult turkeys more sensitive. In all cases, the differences in NOELs or LD_{50} values were small and may be the result of random chance given the small number of animals tested rather than any real difference in sensitivity. This study had major deficiencies based on the FIFRA guidelines for subchronic studies including no analysis of test article and dosing material, inadequate exposure period, inadequate number of animals, inadequate summary of clinical signs, no pathological examination, and no individual data.

II.C.3. Diet-Rat

Methidathion (purity not reported) was administered to 24 rats (strain not reported)/sex/dose in the diet at 0, 1, 4, 16 or 64 ppm (0, 0.05, 0.2, 0.8 or 3.2 mg/kg/day, respectively[1]) for 4 to 22 weeks (Geigy, 1964). Animals in each group (numbers not reported) were sacrificed at different times (not specified) during the study for cholinesterase analyses. In addition, unspecified blood and urine analyses were performed on rats at 64 ppm during the 14th week. There was one death in each of the treatment groups at 4 ppm and higher. There were no reported effects on food intake, body weight, hematology, urine analysis, and pathological findings. There was no indication if there were any clinical signs. It was reported that there was no effect on ChE activity at 4 ppm, a moderate reduction (25-30%) at 16 ppm and strong reduction (70-80%) at 64 ppm. However, no details were provided about which ChE was reduced except that plasma ChE activity was reduced to a lesser extent than RBC or brain ChE activity. Based on the limited information provided, the NOEL was tentatively identified as 4 ppm (0.18 mg/kg/day) based on possible plasma, RBC and brain ChE inhibition at 16 ppm.   The study had numerous major deficiencies including no analysis of test article or dosing material, no clinical chemistry analyses, no summary of body weights, clinical signs, urinalysis, hematology, cholinesterase activity and pathological findings by treatment group, and no individual data.

---

[1]   Estimated assuming for a rat that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (FDA, 1959).

I.C.4. Diet-Rat

Twenty rats (strain not reported)/sex/dose were administered methidathion (purity not reported) dissolved in propylene glycol and mixed in the diet at 0 (two control groups with and without propylene glycol), 0.5, 2, 10, 50 or 250 ppm (0.05-0.06, 0.2-0.24, 1.1-1.2, 5.5-6.0 or 30 mg/kg/day, respectively) for 6 months (Geigy, 1964). Several males died during the study including 2 controls, 1 at 2 ppm, 2 at 20 ppm and 2 at 250 ppm. These deaths were all attributed to a severe chronic respiratory disease and was not considered treatment-related. The only clinical signs reported was fine fibrillation in the extremities and hyperexcitability at 250 ppm. A slight transient reduction in body weights (percentage or mean body weights not reported) was reported at 250 ppm. RBC ChE activity was reduced (percentage not reported) at 10 ppm and higher. Plasma, brain, muscles, liver and kidney ChE were reduced only at 250 ppm. No abnormal pathological lesions were reported, although the histopathological results were not available at the time of the report. Based on the limited data provided, the NOEL appears to be 2 ppm (0.18 mg/kg/day) based on the reduced RBC ChE activity (percentage not reported). The study had numerous major deficiencies including no analysis of test article or dosing material, limited clinical chemistry analyses, no hematology or urinalysis, no histopathology, no summary of body weights, clinical signs, cholinesterase activity, and pathological findings by treatment group, and no individual data.

II.C.5. Diet-Mice

Technical grade methidathion (93.8% purity) was administered to 5 Charles River strain albino mice/sex/dose in the diet at 0, 0.3, 1, 3, 10, 30, 100, 300, 1,000 or 3,000 ppm (M: 0, 0.059, 0.23, 0.60, 2.3, 6.5, 20, 62, 219 or 276 mg/kg/day; F: 0, 0.045, 0.17, 0.54, 1.8, 4.2, 18, 42, 330 or 574 mg/kg/day, respectively) for 28 days (Albanese, 1976). Five mice (2 males, 3 females) at 1,000 ppm and all the mice at 3,000 ppm died during the first few weeks of the study. Generalized weakness was observed in mice at 1,000 ppm and higher. No other clinical signs were reported. Surviving mice at 1,000 ppm had reduced mean body weights (M: 29%; F: 16%) after 28 days. Plasma ChE activity was only reduced at 300 ppm (Table 5). RBC and brain ChE activity was reduced at 100 and 300 ppm. There was no apparent statistical analysis of the body weight, food consumption or ChE data. No gross pathological lesions were seen. With the limited information provided, the tentative NOEL appears to be 30 ppm (4.2 mg/kg/day) based on reduced RBC ChE activity (F: 57% of controls) and brain ChE activity (M: 49%; F: 65% of controls) at 100 ppm. This study had major deficiencies including no analysis of dosing material, inadequate number of animals per treatment group, inadequate clinical chemistry, no hematology, urinalysis or histopathology, and no individual data.

II.C.6. Dermal-Rat

Methidathion technical material (purity not reported), 40% wettable powder and 40% emulsifiable concentrate were each applied in gum arabic to 20 cm^2 shaved dorsal skin of 3 rats (strain not reported)/sex/formulation at 1.50 mg/kg/day (technical material) or 54 mg/kg/day (formulations) for 5 successive days (Geigy, 1964). It does not appear any protective covering was used since the rats were restrained for 3 hours during exposure and then the skin was wiped with a damp sponge. Typical acute clinical signs (not described) were seen, but no mortalities or dermal irritation were reported. A NOEL could not be established for this study based on the

Table 5.   Cholinesterase Activity Relative to Controls in Mice Fed Methidathion in the Diet for
               28 Days[a]

Tissue	Dose Level (ppm)[b]						
	0.3	1	3	10	30	100	300
MALES							
Plasma	107[c]	107	99	114	95	118	73
RBC[d]	112	124	97	112	110	100	87
Brain	104	99	92	96	93	51	29
FEMALES							
Plasma	97	107	108	110	101	87	79
RBC	78	83	104	98	81	57	66
Brain	109	120	105	104	96	65	34

a   Albanese, 1976. This study did not meet FIFRA guidelines due to major deficiencies. ChE activity was measured in all
    survivors at the study termination.
b   Dose level of 0, 0.3, 1, 3, 10, 30, 100 or 300 ppm = 0, 0.059, 0.23, 0.60, 2.3, 6.5, 20, 62, 219 or 276 mg/kg/day,
    respectively, in males and 0, 0.045, 0.17, 0.54, 1.8, 4.2, 18, 42, 330 or 574 mg/kg/day, respectively, in females.
c   Mean activity relative to mean control activity expressed as percentage. There was no apparent statistical analysis of this
    data.
d   RBC = Red Blood Cell

limited information provided. The study had numerous major deficiencies including no analysis
of test article or dosing material, inadequate number of animals, inadequate number of treatment
groups, no controls, inadequate exposure duration, no body weight data, no pathology, no
summary of clinical signs by treatment group, and no individual data.

II.C.7. Dermal-Rat

        Technical grade methidathion (purity not reported) in gum arabic was applied to the
shaved skin of 5 rats(strain not specified)/sex/dose at 1.5, 3, 6 or 12 mg/kg/day on 5 days/week
for 4 weeks (Geigy, 1964). It does not appear any protective covering was used since the rats
were immobilized for 3 hours during exposure after which the skin was wiped with a damp
sponge. No deaths, clinical signs or dermal irritation was seen. Body weights were also normal.
Based on this limited information, the tentative NOEL appears to be 12 mg/kg/day.   The study
had numerous major deficiencies including no analysis of test article or dosing material,
inadequate number of animals, no controls, no pathology, no summary of body weights and
clinical signs by treatment group, and no individual data.

II.C.8. Dermal-Rabbit

Methidathion (purity not reported) was applied topically (non-occlusive exposure) to the clipped back and flanks of 5 New Zealand white rabbits/sex/dose at 0, 1, 5, or 20 mg/kg/day for 6 hr/day for 22 consecutive days (Folinusz *et al.*, 1986). A control male and a female at 5 mg/kg/day were injured during the study and were either sacrificed in moribund condition or died. Neither of these deaths were considered treatment-related. Diarrhea or soft feces was observed on more than one day in several treated animals (1 male at 1 mg/kg/day, 2 males at 5 mg/kg/day, 1 male and 1 female at 20 mg/kg/day). It is unclear if the diarrhea was treatment-related, although it is possible. A male at 20 mg/kg/day also had reduced activity on days 6-19. A papular rash was observed in several animals (1 male and 2 females at 1 mg/kg/day, 1 male at 5 mg/kg/day, 1 male and 1 female at 20 mg/kg/day) from days 16 to 24. Slight reductions in mean body weights (5%) were observed at 20 mg/kg/day, but were not statistically significant. No other treatment-related effect on food consumption, clinical chemistry, hematology or pathology were noted. The NOEL appears to be 20 mg/kg/day since the effects seen at this dose level were minor and not clearly treatment related. The study had a few deficiencies in that the purity of the methidathion was not reported and a maximum tolerated dose (MTD) was not clearly established.

II.C.9. Dermal-Rabbit

A range-finding study was conducted in which methidathion (95% purity) was applied to the clipped backs of 2 New Zealand White rabbits/sex/dose for 6 hours/day for 10 days at 0 (vehicle polyethylene glycol 400), 125, 250, 350, 500 or 740 mg/kg/day (Osherhoff, 1987a). The application site was covered with an occlusive binder during the 6-hr exposure period and then wiped clean after the binder was removed. The mortality rate was 25%, 50%, 50%, 75%, 100% and 100% of animals at 0, 125, 350, 250, 500, and 750 mg/kg/day, respectively. The onset of deaths was usually earlier at the higher dose levels.   Clinical signs were observed at all dose levels including anorexia, depression, labored or rapid breathing, hunched posture, ataxia, tremors, and prostration. A reduction in body weight, body weight gains, and food consumption were seen in the treatment groups relative to controls. Plasma, RBC and brain ChE activity were significantly reduced in survivors at 125 mg/kg/day (M: 16-22%; F: 15-17% of controls), 250 mg/kg/day (M: 9-17%; F: 7-16% of controls) and 350 mg/kg/day (F: 9-14% of controls) after 10 days. Interpretation of these reductions was difficult because of the small number of animals per group and the high mortality rate, so the data were not summarized in a table. No treatment-related changes in organ weights or gross pathological lesions were seen. A NOEL was not established in this study based on the mortalities at the lowest dose, 125 mg/kg/day. This study had several major deficiencies including inadequate number of animals per group, inadequate exposure duration, inadequate clinical chemistry, no hematology, and no histopathology.

II.C.10. Dermal-Rabbit

Five New Zealand White rabbits/sex/dose were administered methidathion (95% purity) dermally (rubber dam occlusion) to their clipped backs at 0 (vehicle propylene glycol 400), 1, 10, 40 or 80 mg/kg/day for 6 hours/day for 21 consecutive days (Osherhoff, 1987b). A dose-related increase in mortalities was seen in the treatment groups (2 males at 1 mg/kg/day, 2 males at 10 mg/kg/day, 3 males and 2 females at 40 mg/kg/day, 3 males and 4 females at 80

mg/kg/day). Clinical signs were observed in all of the treatment groups, including anorexia, lethargy, ataxia, hunch posture, labored respiration, soft feces, thin appearance, low body temperature and tremors. There were no significant differences in dermal irritation, body weights, food consumption, and ophthalmological findings. The surviving female at 80 mg/kg/day had reduced RBC count, hemoglobin, hematocrit, alkaline phosphatase, and gamma glutamyl transferase values and increased alanine aminotransferase, aspartate transferase and blood glucose values. Males at 80 mg/kg/day only had reduced lymphocyte values. The plasma, RBC and brain ChE activity was significantly reduced at 10, 40, and 80 mg/kg/day in one or both sexes (Table 6).

Table 6.   Cholinesterase Activity Relative to Controls in Rabbits Administered Methidathion Topically for 21 Consecutive Days[a]

Tissue	Dose Level (mg/kg/day)			
	1	10	40	80
MALES				
Plasma	93[b]	62*	27*	14*
RBC[c]	103	60*	22*	22*
Brain	101	58*	20*	12*
FEMALES				
Plasma	137	83	42*	25[d]
RBC	79	55*	20*	24[d]
Brain	109	63*	24*	12[d]

a   Osherhoff, 1987b. This study met FIFRA guidelines, except for an incomplete histopathological examination of the control and high-dose animals. ChE activity was measured in all survivors on day 22.
b   Mean activity relative to mean control activity expressed as percentage
c   RBC = Red Blood Cell
*   Significantly different from controls by the Dunnett's test at $p < 0.05$.
d   Statistical comparison with controls not possible since only one animal in this treatment group survived to the end.

Histological examination revealed lesions in the liver (capsular/subcapsular necrosis with acute inflammation, hepatocytic clearing, congestion, coagulation necrosis) at 10, 40 or 80 mg/kg/day, in the gallbladder (caseous necrosis, hemorrhage, chronic serosal inflammation, vasculitis, thrombosis, fibroid necrosis, granulation tissues) at 10, 40 and/or 80 mg/kg/day, in the stomach (erosion/ulceration, inflammation, hemorrhage, submucosal fibrin) in all groups, in the kidney (serous atrophy of fat) at 40 and 80 mg/kg and in the heart (degeneration of aortic media, inflammation of myocardium, myocardial degeneration) at 1, 40 and/or 80 mg/kg/day. The investigators considered the liver lesions to be compound-related; however, they suggested the gall bladder lesions were secondary to reflux of enteric bacteria into the bile duct due to episodes of hyperperistalsis. The investigators also suggested that the ulceration and inflammation in the stomach was stress-related due to the wrapping material and/or neck collar. Evidence of stress

was seen in all groups, including the controls based on poor weight gains and subnormal food consumption. The investigators also attributed the serous atrophy of fat in the kidneys to the weight loss.   However, the toxicological significance of the lesions in the stomach and heart were uncertain since only one stomach and no hearts from control animals were examined microscopically, apparently due to protocol stipulations and the lack of gross lesions. Consequently, DPR toxicologists assumed that the lesions in the stomach and heart were treatment-related. The NOEL appears to be less than 1 mg/kg/day based on the deaths and histological lesions in the heart and stomach. One major deficiency of this study was the incomplete histopathological examination of control and high dose animals.

II.C.11. Dermal-Turkey

Ten 8-week-old and 10 18-week-old turkeys (sex not reported) were exposed dermally to methidathion (purity not reported) by placing them in pens in which the soil had been sprayed at 0 and 64 lb a.i./acre (Radeleff and Kunz, 1972). The birds were observed for 28 days following the spraying. Signs were not observed in any of the birds, although the 8-week-old birds at 64 lb/acre had reduced plasma ChE activity (46% of normal). This study had major deficiencies based on the FIFRA guidelines for subchronic studies, including no analysis of test article, inadequate exposure duration, inadequate number of dose levels, no overt toxicity at highest dose tested, inadequate summary of clinical signs, no pathological examination, and no individual data.

II.D. CHRONIC TOXICITY/CARCINOGENICITY

Summary: Seven oral chronic toxicity studies were available for methidathion using four different species, including mice, rats, dogs and monkeys. Three of the 7 chronic toxicity studies met FIFRA guidelines and are discussed in more detail. However, the other older incomplete studies provide useful supplemental information, especially with regards to ChE inhibition. Effects seen with chronic exposure were similar to those observed with subchronic exposure, although hepatotoxicity was more prevalent. In addition, focal accumulation of foamy macrophages in the alveoli and ulceration and inflammation of the skin were seen in one chronic feeding study in rats. The lowest NOEL observed in an acceptable study was 0.15 mg/kg/day based on the elevated liver enzymes in the serum and histological lesions in the liver of dogs. There was an increase in hepatocellular adenomas and carcinomas in males in two mouse studies. There was no evidence of carcinogenicity in female mice or in either of the rat studies.

II.D.1. Diet-Mouse

Sixty CD-1 mice/sex/dose were administered methidathion (98.8% purity) in the feed at 0, 1, 10, or 100 ppm (0, 0.15, 1.5 or 15 mg/kg/day, respectively[2]) for 18 and 19 months for males and females, respectively (IBT, 1980). There was no treatment-related effect on clinical signs or body weights. A significant increase in several gross pathological lesions were seen in males at 100 ppm, including liver cysts, liver nodules, and spleen nodules. Histopathological

---

[2]   Estimated assuming for a mouse that 1 ppm in the diet is equivalent to 0.15 mg/kg/day (FDA, 1959).

examination revealed an increase in neoplastic lesions (hepatocellular adenomas and carcinomas) and non-neoplastic lesions (cystic bile ducts, chronic pericholangitis, intracanalicular pigment, bile duct hyperplasia, and focal necrosis) in the liver of males at 100 ppm (Table 7). There was no increase in neoplastic or non-neoplastic lesions in the liver of females. The NOEL for non-carcinogenic systemic toxicity appears to be 10 ppm (1.5 mg/kg/day) based on the gross and histopathological changes in the liver and spleen. The study had numerous major deficiencies including no food consumption data, control group mistakenly dosed with treated feed in month 14, apparent degradation of test material in the first 8 months, and no hematology data.

II.D.2. Diet-Mouse

Groups of 170 CD-1 mice/sex/dose were fed methidathion technical (purity not reported) in the diet at 0, 3, 10, 50 or 100 ppm (M: 0, 0.4, 1.4, 6.7 or 13.1 mg/kg/day; F: 0, 0.5, 1.6, 8.1 or 15.9 mg/kg/day, respectively) (Goldenthal, 1986). Fifty mice/sex/dose assigned to the carcinogenicity study were terminated at 23 months. The remaining 120 mice/sex/dose were assigned to the chronic toxicity study which terminated at 18 months with 4 interim sacrifices at 3, 6, 12 and 13 months. The mice sacrificed at 13 months were removed from treated feed at 12 months and then allowed to recover on the control diet for one month. An increase in mortality rate (68% versus 42% in controls) was observed in the males at 100 ppm in the carcinogenicity study. Discolored urine (dark yellow, orange or red) was observed in males at 50 and 100 ppm. The cause of the discoloration is unclear, although orange or red colored urine is clearly not normal. It could be due to blood in the urine or excretion of some orange to red colored product. No other treatment-related clinical signs were seen. There were no treatment-related differences in body weights, food consumption, water consumption, auditory response, ophthalmological findings, or hematology. Significant increases in several liver enzyme activities in the serum were seen which were suggestive of hepatotoxicity. The mean serum alkaline phosphatase (AKP) activity was significantly elevated in males at 100 ppm at 3, 6, 12, 18 and 23 months (12, 4, 10, 19, and 7 fold increase, respectively). Significant increases in the mean serum alanine aminotransferase (ALT) activity were observed in males at 50 ppm (200 and 122% at 12 and 23 months, respectively) and 100 ppm (146, 149, 274, 124 and 209% at 3, 6, 12, 18 and 23 months, respectively). The mean ALT values were significantly increased in females at 100 ppm (97 and 183% at 6 and 12 months, respectively). The mean aspartate aminotransferase (AST) activity was also increased in males at 100 ppm (64, 142 and 108% at 6, 12, and 23 months, respectively). The mean plasma ChE activity was increased significantly in males at 100 ppm (Table 8). In contrast, the mean RBC ChE activity was significantly reduced in males at 100 ppm. The RBC ChE activity in males also appears to be reduced at 50 ppm, but the reductions were never statistically significant. In females, the mean RBC ChE activity was reduced at 50 and 100 ppm. Brain ChE activity was significantly reduced at all time points at 100 ppm for both males and females. Brain ChE activity also was reduced at 50 ppm in both sexes, although the reductions were only significant on a few occasions (M: 6 mos.; F: 24 mos.).

Numerous gross pathological lesions in the liver were seen, primarily the males, including enlargement, foci, masses, nodules, cysts, discoloration, mottling, depressions, and granularity. Microscopic examination of the liver and gall bladder revealed a significant increase in numerous non-neoplastic lesions in males at 50 and 100 ppm and in females at 100

Table 7.   Non-neoplastic and Neoplastic Lesions in the Liver of Male Mice Fed Methidathion
in the Diet for 18 Months[a]

Lesion	Dose Level (ppm)			
	0	1	10	100
Hepatocellular adenoma	0/59[+++] (0%)	0/59 (0%)	0/57 (0%)	14/59*** (24%)
Hepatocellular carcinoma	2/59[+++] (3%)	1/59 (2%)	2/57 (4%)	10/59* (17%)
Cystic bile duct	1/59[+++] (2%)	1/59 (2%)	2/57 (4%)	17/59*** (29%)
Chronic pericholangitis	1/59[+++] (2%)	3/59 (5%)	1/57 (2%)	15/59*** (25%)
Intracanalicular pigment	0/59[+++] (0%)	1/59 (2%)	2/57 (4%)	57/59*** (97%)
Bile duct hyperplasia	0/59[+++] (0%)	0/59 (0%)	3/57 (5%)	34/59*** (58%)
Focal necrosis	1/59[+] (2%)	1/59 (2%)	1/57 (2%)	6/59 (10%)

a   IBT, 1980.
+,+++   Significant trend based on Cochran-Armitage trend test with p < 0.05 and 0.001, respectively.
*,***   Significantly different from controls based on the Fisher exact test with p < 0.05 and 0.001, respectively.

ppm (Table 9). The non-neoplastic changes included cholecystitis, hyperplasia of the gall
bladder and bile duct, bile stasis, cholangiofibrosis, and chronic hepatitis.

Neoplastic lesions of the liver were also observed in males which consisted of
hepatocellular adenomas and/or carcinomas (Table 10). The incidence of hepatocellular
adenomas and carcinomas exhibited a dose-related trend that was highly significant when the
tumors were analyzed separately or combined. In addition, 3 males at 100 ppm had multiple
liver tumors. The increase in hepatocellular adenomas was significant by pairwise comparison
to controls at all dose levels. The incidence of hepatocellular adenomas at 100 ppm exceeded
the historical control range for this tumor type in studies conducted at the test laboratory between
1978 and 1985 with this strain of mice (Table 11) (Quest *et al.*, 1990*)*. Based on these historical
control means, it appears that the incidence of adenomas in the control group in this study is
unusually low. The toxicological significance of the apparent increase in adenomas at 3, 10 and
50 ppm is uncertain since the incidences are all greater than the historical control means, but
within the historical control range. The increase in hepatocellular carcinomas was only
significantly different (p < 0.05) than controls at 100 ppm. However, the incidence of
carcinomas in the concurrent control group was greater than the historical control range. When

Table 8.   Cholinesterase Activity Relative to Controls in Mice Fed Methidathion in the Diet for 24 Months[a]

Tissue		Dose Level (ppm)[b]							
		3		10		50		100	
		M	F	M	F	M	F	M	F
Plasma,	3 mos.	92[c]	101	84	97	103	97	118	100
	6 mos.	106	103	102	103	108	106	127*	90
	12 mos.	94	111	99	95	95	106	117*	92
	18 mos.	101	97	111	105	172	108	144*	97
	24 mos.	107	108	107	105	122	109	154*	91
RBC[d],	3 mos.	104	105	95	105	77	70*	55**	55**
	6 mos.	97	94	88	97	85	64**	67	67**
	12 mos.	96	107	91	105	73	81	62*	57**
	18 mos.	85	100	91	100	73	73*	91	65**
	24 mos.	119	103	95	100	76	74*	81	71**
Brain,	3 mos.	109	102	107	98	85	96	61**	77**
	6 mos.	107	109	98	102	76*	104	66**	76*
	12 mos.	104	106	99	98	87	91	51**	74**
	18 mos.	100	109	107	103	90	90	66**	78**
	24 mos.	109	94	111*	92	85	84*	64**	66**

a   Goldenthal, 1986. This study met FIFRA guidelines. ChE activity was measured in 8-10 animals/sex/dose at each time point.
b   Dose level of 0, 3, 10, 50 or 100 ppm = 0, 0.4, 1.4, 6.7 or 13.1 mg/kg/day, respectively, in males and 0, 0.5, 1.6, 8.1 or 15.9 mg/kg/day, respectively, in females
c   Mean activity relative to mean control activity expressed as percentage
d   RBC = Red Blood Cell
*,**   Significantly different from controls by the Dunnett's Test at p < 0.05 and 0.01, respectively.

combined, the increase in hepatocellular adenomas and carcinomas was statistically significant (p < 0.05) at 50 and 100 ppm. The incidence of carcinomas and combined adenomas/carcinomas exceeded the historical control range at 50 and 100 ppm.

Although there were no treatment-related differences in body weights, an increase in the mean liver weights was observed in males at 50 (absolute: 35%; relative to body: 36% ; relative

Table 9. Non-neoplastic Lesions in the Liver and Gall Bladder of Mice Fed Methidathion in the Diet for 23 Months[a]

Lesion	Dose (ppm)[b]				
	0	**3**	**10**	**50**	**100**
MALES					
Gallbladder					
Cholecystitis	4/49[+++] (8%)	0/46 (0%)	1/47 (2%)	21/48*** (44%)	37/48*** (77%)
Hyperplasia	0/49[+++] (0%)	0/46 (0%)	0/47 (0%)	15/48*** (31%)	33/48*** (69%)
Liver					
Bile duct hyperplasia	0/50[+++] (0%)	1/47 (2%)	0/47 (0%)	21/49*** (43%)	42/48*** (88%)
Bile stasis	0/50[+++] (0%)	0/47 (0%)	0/47 (0%)	25/49*** (51%)	47/48*** (98%)
Cholangiofibrosis	1/50[+++] (2%)	0/47 (0%)	0/47 (0%)	18/49*** (37%)	45/48*** (94%)
Chronic hepatitis	3/50[+++] (6%)	1/47 (2%)	2/47 (4%)	24/49*** (49%)	47/48*** (98%)
FEMALES					
Gallbladder					
Cholecystitis	1/45[+++] (2%)	1/46 (2%)	0/46 (0%)	2/44 (5%)	11/46** (24%)
Hyperplasia	0/45[+++] (0%)	0/46 (0%)	0/46 (0%)	0/44 (0%)	5/46* (11%)
Liver					
Bile duct hyperplasia	0/46 (0%)	1/48 (2%)	2/47 (4%)	0/44 (0%)	3/46 (7%)
Bile stasis	0/46[+++] (0%)	1/48 (2%)	1/47 (2%)	0/44 (0%)	11/46*** (24%)
Cholangiofibrosis	0/46[+++] (0%)	0/48 (0%)	1/47 (2%)	0/44 (0%)	7/46** (15%)
Chronic hepatitis	3/46[++] (7%)	2/48 (4%)	2/47 (4%)	4/44 (9%)	8/46 (17%)

a　Goldenthal, 1986. This study met FIFRA guidelines.
b　Dose level of 0, 3, 10, 50 or 100 ppm = 0, 0.4, 1.4, 6.7 or 13.1 mg/kg/day, respectively, in males and 0, 0.5, 1.6, 8.1 or 15.9 mg/kg/day, respectively, in females
++,+++　Significant trend based on the Armitage-Cochran trend test at $p < 0.01$ and 0.001, respectively (Gart *et al.*, 1986).
*,**,***　Significantly different from the control group based on the Fisher's exact test at $p < 0.05$, 0.01 and 0.001, respectively.

Table 10. Neoplastic Lesions in the Liver of Male Mice Fed Methidathion in the Diet for 23 Months[a]

Lesion	Dose (ppm)[b]				
	0	**3**	**10**	**50**	**100**
Hepatocellular adenoma	1/46[c+++] (2%)	9/45** (20%)	7/47* (15%)	8/43* (19%)	24/45*** (53%)
Hepatocellular carcinoma	8/46[+++] (17%)	6/45 (13%)	4/47 (9%)	13/43 (30%)	17/45* (38%)
Combined[d]	9/46[+++] (20%)	15/45 (33%)	11/47 (23%)	21/43** (49%)	38/45*** (84%)

a   Goldenthal, 1986. This study met FIFRA guidelines.
b   Dose level of 0, 3, 10, 50 or 100 ppm = 0, 0.4, 1.4, 6.7 or 13.1 mg/kg/day; respectively
c   The denominator is the number of animals at risk (excluding those that died before the first tumor was observed on day 445); the number in parentheses represents the incidence in percentage.
d   Animals with both adenomas and carcinomas counted once under combined. There were 3 animals at 100 ppm with both adenomas and carcinomas.
+++   Significant trend based on the Armitage-Cochran trend test at $p < 0.001$ (Gart *et al.*, 1986).
*,**,***   Significantly different from the control group based on the Fisher's exact test at $p < 0.05, 0.01$ and 0.001, respectively.

Table 11. Historical Control Data on Liver Tumor in Male CD-1 Mice[a]

Type of Liver Tumor	Studies terminated between			
	1978 and 1983 (11 studies)		1984 and 1985 (3 studies)	
	Mean (%)	**Range (%)**	**Mean (%)**	**Range (%)**
Adenoma	11	0-26.7	14.8	8.0-24.0
Carcinoma	5.7	0-14.3	6.9	3.3-10.0
Combined	16.7	5.0-26.7	20.0	13.3-32.0

a   Data obtained from 11 studies conducted at the test laboratory and terminated between 1978 and 1983, and from 3 studies conducted at the test laboratory and terminated between 1984 and 1985 (Quest *et al.*, 1990). The carcinogenicity study of methidathion in CD-1 mice was terminated in 1984.

to brain: 36%) and 100 ppm (absolute: 122%; relative to body: 116%; relative to brain: 120%) at 23 months. There was also a significant increase in the mean spleen weights (absolute: 67%; relative to body: 67%; relative to brain: 75%) and a decrease in the mean testes weights (absolute: 26%; relative to body: 29%; relative to brain: 26%) in males at 100 ppm that were sacrificed at 23 months. The increased spleen weights were associated with macroscopic changes including enlargement, nodules, adhesions and mottling of the spleen. An increase in extramedullary hematopoiesis of the spleen were observed microscopically in males at 100 ppm. No macroscopic or microscopic changes in the testes were associated with the decrease in testes

weight. Significant changes in the kidney (3 ppm), brain (100 ppm) and adrenal gland weights (100 ppm) observed in females were of uncertain toxicological significance since they were not associated with pathological changes. The NOEL established for systemic non-neoplastic effects was 10 ppm (1.4 mg/kg/day) based on reduced RBC ChE activity (F: 64-74% of controls), discolored urine, elevated serum ALT values, and histopathological lesions in the liver and gall bladder of males. This study was considered acceptable by DPR toxicologists based on FIFRA guidelines.

II.D.3. Diet-Rat

Twenty-five albino rats (strain not reported)/sex/dose were fed a 40% methidathion wettable powder (actual purity not reported) in the diet at 0, 4, 16 or 64 ppm (as active ingredient; 0, 0.2, 0.8 or 3.2 mg/kg/day, respectively[3]) for 2 years (Johnston, 1967). The body weights were reduced (25% at terminal sacrifice) in males at 64 ppm throughout the study. There was no apparent statistical analysis of any of the data in this study. The mean hemoglobin level was reduced (21%) in males at week 100 due primarily to two males with very low hemoglobin values. There were no dose-related reductions in the mean plasma ChE activity, except for the females at 64 ppm which had consistently reduced activity from week 13 to 100 (Table 12). The mean RBC ChE activity was reduced primarily at 16 and 64 ppm from week 13 to 100, but was occasionally reduced at 4 ppm. A reduction in the mean brain ChE activity was seen at 4, 16, and 64 ppm at the terminal sacrifice. There was no effect on the absolute and relative organ weights, except for a reduction in the mean weights of the ovary in females at 64 ppm (absolute: 1%; relative: 26%) and of the adrenal glands in females at 16 ppm (absolute: 18%; relative: 13%) and 64 ppm (absolute: 32%; relative: 28%), respectively. No treatment-related differences in gross pathological findings were seen. A slightly higher incidence of degenerative changes in the liver were seen in the treatment groups than the controls; however, the study pathologist indicated that the high incidence of deaths due to pulmonary infections and subsequent autolysis made interpretation of the hepatic changes difficult. The NOEL was less than 4 ppm (0.18 mg/kg/day) based on reduced brain ChE activity (M: 86%; F: 92% of controls). The study had major deficiencies including high mortality due to pulmonary infections, insufficient hematological and clinical chemistry analysis, and incomplete histopathology and individual data.

II.D.4. Diet-Rat

Methidathion (97.3% purity) was administered in the feed to 80 Sprague-Dawley rats/sex/dose at 0, 4, 40 or 100 ppm (M: 0, 0.17, 1.77 or 4.95 mg/kg/day; F: 0, 0.23, 2.24 or 6.94 mg/kg/day, respectively) for 104 weeks (Yau *et al.*, 1986). There was no treatment-related effect on mortality and ophthalmological findings. An increased incidence of alopecia, chromorhinorrhea, hyperactivity, hypersensitivity to touch, skin lesions, and tremors were noted at 40 and 100 ppm. Most of the neurological signs subsided as the study progressed, suggesting tolerance since the mean brain ChE activity remained severely reduced at 40 and 100 ppm at the

---

[3]   Estimated assuming for a rat that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (FDA, 1959).

Table 12. Cholinesterase Activity Relative to Controls in Rats Fed Methidathion in the Diet for 2 Years[a]

Tissue	Dose Level (ppm)					
	4		**16**		**64**	
	M	**F**	**M**	**F**	**M**	**F**
Plasma, 13 wks	111[b]	87	100	92	135	79
26 wks	110	98	110	84	110	76
52 wks	60	96	71	96	67	83
80 wks	100	91	92	98	82	67
100 wks	106	107	86	112	98	87
RBC[c], 13 wks	111	106	81	81	37	25
26 wks	98	92	61	77	41	26
52 wks	90	97	74	76	32	35
80 wks	110	85	90	81	34	55
100 wks	83	97	49	55	37	11
Brain, 100 wks	86	92	77	90	37	33

a   Johnston, 1967. This study did not meet FIFRA guidelines since it predated them. Plasma and RBC ChE activity were measured in 3-5 rats/sex/dose at each time point. Brain ChE activity was measured in 6-14 rats/sex/dose.
b   Dose level of 0, 4, 16 or 64 ppm = 0, 0.2, 0.8 or 3.2 mg/kg/day, respectively.
c   Mean activity relative to mean control activity expressed as percentage. There was no apparent statistical analysis of this data.
d   RBC = Red Blood Cell

study termination (Table 13). Brain ChE activity was also significantly depressed (86% of controls) in females at 4 ppm at 52 weeks, but not at 93 and 104 weeks. Reductions in the mean RBC ChE activity was seen at 40 and 100 ppm at most time points during the study including the study termination. The mean serum ChE activity was also significantly reduced throughout the study at 40 and 100 ppm, but less frequently than seen with RBC ChE activity. Significant reductions in the mean body weight were noted at 40 ppm (M: 3-5% wks 1-5, 7, 9-10; F: 4-6% wks 1-3) and 100 ppm (M: 4-13% wks 1-16, 72-92; F: 12-21% wks 1-104). Significant increases in the mean feed consumption was seen at 40 ppm (M: 5-14% wks 40, 48, 76, 84, 88; F: 6-16% wks 4-12, 24, 36, 44-52, 64-80, 88) and 100 ppm (M: 5-22% wks 5-7, 16-40, 48-76, 84-100; F: 7-15% wks 24, 48, 68, 84, 88). The mean water consumption was significantly reduced at 40 ppm (F: 19-32% wks 28, 44, 84) and 100 ppm (M: 15-16% wks 9, 11; F: 14-54% wks 2-3, 6, 9, 11, 20, 28-48, 56-72, 84-92).

Table 13. Cholinesterase Activity Relative to Controls in Rats Fed Methidathion in the Diet for 104 Weeks[a]

Tissue		Dose Level (ppm)[b]					
		4		40		100	
		M	F	M	F	M	F
Serum,	26 wks	77[b]	118	59*	81	70*	60**
	52 wks	105	108	74*	78**	72**	65**
	78 wks	93	108	77	76	44**	60**
	93 wks	65	110	56	77	34	98
	104 wks	80	99	88	75	72	54**
RBC[c],	26 wks	107	107	92	63**	86**	62**
	52 wks	100	98	86**	97	76**	84**
	78 wks	105	108	94	85**	81**	77**
	93 wks	100	106	106	89	86	98
	104 wks	96	102	78**	82*	77**	81*
Brain,	52 wks	113*	86**	58**	34**	45**	31**
	93 wks	97	94	56**	54**	54**	39**
	104 wks	92	95	49**	48**	34**	26**

a   Yau *et al.*, 1986. This study met FIFRA guidelines. ChE activity was measured in 9-10 rats/sex/dose at each time point, except at 52 weeks where blood ChE activity was measured in 19-20 rats/sex/dose and at 93 week s where all ChE activity was measured in 5 rats/sex/dose.
b   Dose level of 0, 4, 40 or 100 ppm = 0, 0.17, 1.77 or 4.95 mg/kg/day, respectively in males and 0, 0.23, 2.24 or 6.94 mg/kg/day, respectively, in females.
c   Mean activity relative to mean control activity expressed as percentage
d   RBC = Red Blood Cell
*,**   Significantly different from controls by the Dunnett's Test at $p < 0.05$ and 0.01, respectively.

Significant reductions in erythrocytic parameters (hemoglobin, red blood cell counts, hematocrits, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) were seen primarily in females at 100 ppm, but the reductions were usually transient and less than 10%. A significant increase in the percent neutrophils and a corresponding significant reduction in the percent lymphocytes were seen in both sexes at 100 ppm. Transient increases in granulocytes, such as neutrophils, have been observed after administration of some drugs and endotoxins, but are not believed to be of any physiological consequence (Smith, 1996). An increase in granulocytes has also been associated with chronic leukemia; however, the total white blood cell counts were not significantly different at 100 ppm even though the differential counts were affected. In addition, a significant increase in the

platelet counts was seen in both sexes at 100 ppm; however, an increase in platelets has not been associated with any chemical exposure (Smith, 1996). Significant differences in various serum clinical chemistry values (aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, glucose, blood urea nitrogen, total bilirubin, cholesterol, total protein, calcium, sodium, potassium, chloride, inorganic phosphorus) were seen in both sexes primarily at 100 ppm, but occasionally at 40 ppm. These changes were usually transient and often in a direction opposite of what is normally considered toxicologically significant. However, a few clinical chemistry changes of toxicological concern were still present at the study termination in females at 100 ppm, including an increase in serum aspartate aminotransferase (71%) and serum lactate dehydrogenase (63%). Transient reductions in urine volume and increases in urinary specific gravity were seen during the first year at 40 ppm (females) and 100 ppm (both sexes), and were not considered toxicologically significant. A significant reduction in the mean liver weights were seen in females at 40 ppm (relative to body: 14%) and in both sexes at 100 ppm (males - relative to body: 17%, relative to brain: 13%; females - absolute: 31%, relative to brain: 34%) at day 364. At study termination, only the females still had significantly reduced liver weights at 40 ppm (relative to body: 27%) and 100 ppm (absolute: 18%; relative to brain: 20%). Although no histological lesions were seen in the liver, the increase in liver enzymes in the serum and the reduction in liver weights were assumed to be due to mild hepatotoxicity. Ulceration and inflammation of the skin was observed microscopically at 100 ppm which correlated with the clinical observations of skin lesions. An increased incidence of focal accumulation of foamy macrophages in the alveoli was seen at 100 ppm. No dose-related increase in tumors was seen in this study. The systemic NOEL for this study was established at 4 ppm (M: 0.17 mg/kg/day; F: 0.23 mg/kg/day) based on the clinical signs, reduced body weights and food and water consumption, reduced RBC and brain ChE activity, reduced liver weights, and skin lesions at 40 ppm. DPR toxicologists found this study to be acceptable based on FIFRA guidelines.

II.D.5. Diet-Dog

Three beagle dogs/sex/dose were fed a 40% wettable powder (actual purity not stated) in their diet at 0, 4, 16 or 64 ppm (as active ingredient; 0, 0.1, 0.4 or 1.6 mg/kg/day, respectively)[4] for 105 weeks (Johnston, 1967). There was no effect on clinical signs, body weights, electrocardiograms, heart rates, blood pressure, ophthalmology, and hematology. The mean serum AKP activity was increased 1 to 2-fold in dogs at 16 and 64 ppm. The mean serum AST activity was not affected, but the mean serum ALT activity was increased in a dose-related manner at 4, 16 and 64 ppm from approximately 2 to 10 fold. There was no treatment-related effect on plasma and brain ChE activity. The mean RBC ChE activity was reduced throughout the study in dogs at 64 ppm (M&F: 67-89% of controls). Dark pigmentation of the liver was seen microscopically in a few dogs at 4 ppm and all dogs at 16 and 64 ppm. Increased pigmentation of the upper nephron tubular cells of the kidney was also noted in dogs at 64 ppm. Increased extramedullary hematopoiesis of the spleen was also seen at 16 and 64 ppm. The NOEL was 4 ppm (0.1 mg/kg/day) based on the histological changes in the liver and spleen and the elevated liver enzyme activities in the serum. This study had several major deficiencies

---

[4]   Estimated assuming for a dog that 1 ppm in the diet is equivalent to 0.025 mg/kg/day (FDA, 1959).

including inadequate number of animals per group, missing electrolyte balance data, inadequate histopathological examination, and no food consumption data.

II.D.6. Diet-Dog

Methidathion (96% purity) was administered in the feed to 4 beagle dogs/sex/dose at 0, 0.5, 2, 4, 40 or 140 ppm (M: 0, 0.02, 0.07, 0.15, 1.33 or 4.51 mg/kg/day; F: 0, 0.02, 0.07, 0.15, 1.39 or 4.90 mg/kg/day, respectively) for 1 year (Chang and Walberg, 1991). An increased incidence of salivation and wet coat on forefoot were noted at 2 ppm and higher. However, the toxicological significance of these signs is uncertain since there was no clear dose-response relationship and no significant ChE inhibition except at 140 ppm. Serum ChE activity was not affected at any dose level at any time point (Table 14). The mean RBC activity was significantly reduced at 140 ppm at 3, 6 and 12 months. The mean brain ChE activity was also significantly reduced at 140 ppm in the vermis of the cerebellum and the right hemisphere minus the vermis at the study termination. There was no treatment-related effect on body weights or body weight gains in either sex, but there was a reduction in food consumption (17-37%) in males at 140 ppm from weeks 7 through 45. A reduction in the percent neutrophils and a corresponding increase in the percent lymphocytes was seen at 40 and 140 ppm at 3 months. In addition, there was a decrease in mean corpuscular volume at 2 and 40 ppm at the study termination. These hematological changes are of uncertain toxicological significance, either because of their transient nature or lack of dose-response relationship. Moderate to marked increases in several serum liver enzyme activities, including AKP, AST, ALT, and sorbitol dehydrogenase, were seen at 40 and 140 ppm at all time points tested (Table 14). The mean γ-glutamyl transferase activity was elevated in females at 40 (40%) and 140 ppm (40-80%) at 3 and 6 months. Increases in the mean total bilirubin (100-200%) were seen in both sexes at 40 and 140 ppm at 3 months and in males at 12 months. Reductions in the mean total serum protein (8% at 6 months) and serum albumin (9-15% at 3, 6 and 12 months) were seen in females at 40 and 140 ppm. No treatment-related effects were seen in the urinalysis, fecal analysis, ophthalmological findings or organ weights. An increase in livers with generally dark red discoloration were observed macroscopically in both sexes at 40 and 140 ppm (Table 15). Moderate to marked cholestasis was observed microscopically in all dogs of both sexes at 40 and 140 ppm. Mild chronic inflammation of the liver was also observed at 40 ppm (M: 1/4; F: 3/4) and 140 ppm (F: 1/4). Although the incidence of liver inflammation did not show a dose-response relationship or correlate with the severity of cholestasis, the investigators considered it a treatment-related effect. The NOEL was established at 4 ppm (0.15 mg/kg/day) based on the elevated serum liver enzymes and liver pathology. This study was found acceptable by DPR toxicologists based on FIFRA guidelines.

II.D.7. Gavage-Monkey

Five to 7 rhesus monkeys/sex/dose were administered methidathion (purity not reported) by oral gavage at 0, 0.25 and 1 mg/kg/day 6 days/week for 23 months (Coulston and Golberg, 1971). There was no effect on clinical signs, body weights or food consumption, although there was no apparent statistical analysis of any of the data in the study. Hematological and clinical chemistry values were normal, except for an elevated alanine aminotransferase activity level in one male in the 1 mg/kg/day group at 22 months. A reduction in the mean plasma ChE activity was seen in the 1 mg/kg/day group at 22 months (Table 16). The mean RBC ChE activity was

Table 14. Cholinesterase Activity Relative to Controls in Dogs Fed Methidathion in the Diet for 1 Year[a]

Tissue		Dose Level (ppm)[b]				
		0.5	2	4	40	140
MALES						
Serum,	3 mos.	103[c]	95	99	102	101
	6 mos.	90	76	83	87	79
	12 mos.	102	92	100	103	99
RBC[d],	3 mos.	111	85	109	70	13**
	6 mos.	107	91	106	73	18**
	12 mos.	116	95	113	80	23**
Brain[e],	12 mos.	89	109	97	95	73**
Brain[f],	12 mos.	98	103	105	99	84
FEMALES						
Serum,	3 mos.	119	111	121	126	120
	6 mos.	134	120	129	135	136
	12 mos.	121	109	130	129	138
RBC,	3 mos.	105	114	131	86	17**
	6 mos.	118	126	137	96	24*
	12 mos.	109	125	133	95	24**
Brain,	12 mos.	101	100	107	96	78*
Brain,	12 mos.	99	101	103	101	83

a   Chang and Walberg, 1991. This study met FIFRA guidelines. ChE activity was measured in 4 dogs/sex/dose at each time point.
b   Dose level of 0, 0.5, 2, 4, 40 or 140 ppm = 0, 0.02, 0.07, 0.15, 1.33 or 4.51 mg/kg/day, respectively, in males and 0, 0.02, 0.07, 0.15, 1.39 or 4.90 mg/kg/day, respectively, in females
c   Mean activity relative to mean control activity expressed as percentage
d   RBC = Red Blood Cell
e   ChE activity in the vermis of the cerebellulm
f   ChE activity in the right hemisphere minus vermis
*,** Significantly different from controls by the Dunnett's Test at $p < 0.05$ and 0.01, respectively.

Table 15. Dose-Related Effects on Serum Liver Enzyme Activity and Liver Pathology in Dogs Fed Methidathion for One Year[a]

	Dose Level (ppm)[b]					
	0	**0.5**	**2**	**4**	**40**	**140**
MALES						
Alkaline Phosphatase (U/L)	126 ± 46	122 ± 101	103 ± 41	99 ± 34	297* ± 38	371** ± 152
Asp. Aminotransferase (U/L)	23 ± 3	23 ± 3	21 ± 2	23 ± 3	29 ± 7	32* ± 4
Ala. Aminotransferase (U/L)	15 ± 4	21 ± 3	21 ± 4	40 ± 16	134** ± 37	140** ± 70
Sorbitol Dehydrogenase (U/L)	4 ± 1	6 ± 1	3 ± 1	6 ± 3	11** ± 3	13** ± 5
Liver Discoloration	0/4[++]	0/4	0/4	0/4	1/4	2/4
Cholestasis	0/4[+++]	0/4	0/4	0/4	4/4*	4/4*
FEMALES						
Alkaline Phosphatase (U/L)	152 ± 81	133 ± 66	114 ± 60	190 ± 40	353 ± 120	623* ± 467
Asp. Aminotransferase (U/L)	24 ± 2	25 ± 6	21 ± 3	22 ± 3	28 ± 6	35* ± 7
Ala. Aminotransferase (U/L)	17 ± 5	15 ± 1	15 ± 4	26 ± 7	126** ± 42	134** ± 58
Sorbitol Dehydrogenase (U/L)	5 ± 1	6 ± 2	6 ± 1	6 ± 1	13** ± 4	10* ± 3
Liver Discoloration	0/4[+++]	0/4	0/4	0/4	2/4	3/4
Cholestasis	0/4[+++]	0/4	0/4	0/4	4/4*	4/4*

a   Chang and Walberg, 1991.   This study met FIFRA guidelines.
b   Dose level of 0, 0.5, 2, 4, 40 or 140 ppm = 0, 0.02, 0.07, 0.15, 1.33 or 4.51 mg/kg/day, respectively, in males and 0, 0.02, 0.07, 0.15, 1.39 or 4.90 mg/kg/day, respectively, in females
*,**   Significantly different from controls based on the Fisher's exact test at $p < 0.05$ and 0.01, respectively.
++,+++   Significant trend based on the Cochran-Armitage trend test at $p < 0.01$ and 0.001, respectively.

Table 16. Cholinesterase Activity Relative to Controls in Monkeys Administered Methidathion by Oral Gavage for 23 Months[a]

Tissue		Dose Level (mg/kg/day)	
		0.25	**1.0**
Plasma,	18 months	107[b]	105
	22 months	84	39
RBC[c],	6 months	81	76
	12 months	73	60
	18 months	83	63
	22 months	91	74
Brain,	12 months	112	98
	22 months	101	108

a Coulston and Golberg, 1971. This study did not meet FIFRA guidelines since it predated them. Plasma and RBC ChE activity were measured in 4-8 monkeys (M&F combined)/dose at each time point. Brain ChE activity was measured in 2-9 monkeys (M&F combined)/dose at each time point.
b Mean activity relative to mean control activity expressed as percentage. There was no apparent statistical analysis of this data.
c RBC = Red Blood Cell

reduced at 1 mg/kg/day from 6 to 22 months. There was no effect on brain ChE activity, or gross and histopathological findings. The NOEL was 0.25 mg/kg/day based on the reduction in plasma and RBC ChE activity. The study had major deficiencies including insufficient number of dose levels tested, lack of overt toxicity at the highest dose level, inadequate histopathological examination and no individual data.

II.E. GENOTOXICITY

Summary: Nine gene mutation studies for methidathion (5 reverse-mutation assays with *Salmonella typhimurium*, 1 reverse-mutation assay with *Escherichia coli*, and 3 host-mediated assays) were negative. Reverse mutation assays with *S. typhimurium* for 3 metabolites of methidathion were also negative.   Positive responses were reported in a gene conversion/forward mutation assay with *Saccharomyces cerevisiae*; however, this assay is considered a poor predictor of gene mutation in mammalian systems. None of the gene mutation studies met FIFRA guidelines; however, the negative results were reproduced in the reverse-mutation assays from several different laboratories over a range of doses with and without metabolic activation, presenting consistent and compelling evidence of the lack of mutagenicity. An *in vivo* micronucleus assay in Chinese hamster and a dominant lethal assay in mice were negative. The dominant lethal assay met FIFRA guidelines, but that assay is considered relatively insensitive. There was an equivocal response in an *in vivo* sister chromatid exchange

(SCE) assay with Chinese hamsters with an increase in SCEs at the mid-dose only and an unequivocal positive response in an *in vitro* SCE assay with Chinese hamster cell line V79. Neither of these studies met FIFRA guidelines; however, even if these findings had been in acceptable studies, the biological significance of SCEs has not been demonstrated. A chromosomal aberrations assay was not conducted for methidathion either *in vitro* or *in vivo*. An *in vivo* micronucleus assay for a metabolite of methidathion was negative. Based on the limited data, DPR concluded methidathion-induced chromosomal damage could not be ruled out. Six assays for DNA damage were available for methidathion, including 5 unscheduled DNA synthesis (UDS) assays and 1 rec assay. These studies were all negative. Two of the UDS assays met FIFRA guidelines; however, the UDS assay is not considered very sensitive. Overall, the evidence that methidathion is genotoxic is limited, but its potential to induce chromosomal damage cannot be ruled out.

II.E.1. Gene Mutation

Five reverse mutation assays for methidathion using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were submitted by the registrant. All five assays were negative, but none of the studies met FIFRA guidelines. The results for one assay were only presented in abstract form with no information about the levels tested, purity of test article or number of replicates (Lippens *et al.,* 1983). Two assays were conducted using methidathion (purity not stated) at 0, 25, 75, 225, 675 and 2025 µg/0.1 ml with and without metabolic activation in triplicate (Arni, 1980a&b). Both studies had major deficiencies including inadequate positive controls, no individual plate data, and inadequate test article characterization. Two other assays tested methidathion (99.95% purity in one study; purity not reported in other) at 0, 10, 50, 100, 500, 1000 and 5000 µg/plate with and without metabolic activation (Simon and Poole, 1977; Satou *et al.*, 1979). The study conducted by Simon and Poole (1977) had several major deficiencies including questionable positive controls for two strains, inadequate number of replicates and no individual plate data in the report. The Satou *et al.* (1979) study also had major deficiencies including no indication of the number of replicates, no statistics, no individual plate data, inadequate test article characterization, and inadequate positive controls for several strains. There was no evidence of mutagenicity in a reverse mutation assay using *Escherichia coli* strain WP2 Hcr- where methidathion (99.95% purity) was tested at 0, 10, 50, 100, 500, 1000 and 5000 µg/plate with and without activation (Satou *et al.*, 1979). This study also had several deficiencies including no confirmatory assay, inadequate number of replicates, and no individual plate data.

Positive results were reported in a gene conversion/forward mutation assay where *Saccharomyces cerevisiae* MP-1 were exposed to methidathion (93.4% purity) at 675, 1250, 2500, 5000 or 10,000 µg/ml (Arni and Muller, 1981). It was not possible to assess the quality of the study based on the limited information that was available.

No evidence of mutagenicity was found in several host-mediated assays. In a study conducted by Simmon and Poole (1977), 6-10 male Swiss Webster mice/dose were given methidathion (purity not reported) by oral gavage either in a single dose at 0, 10, 20 or 40 mg/kg/day or in five daily doses at 0, 5, 10, or 20 mg/kg/day. *S. typhimurium* strains TA1535 and 1538 were injected intraperitoneally at the time of dosing and then recovered from the peritoneal cavity four hours later. The study had several major deficiencies including no

evidence of actual exposure of bacteria to test material, no individual plate data, and insufficient test article characterization. In a study conducted by Arni (1980c), 6 male albino mice/dose were administered methidathion (purity not reported) by oral gavage at 0, 5, 10, or 20 mg/kg/hour at 2 hours, 1 hour and immediately before injection of *S. typhimurium* strains TA98, TA100 or TA1537 into the tail vein. One hour later the animals were sacrificed and the homogenized liver assayed for mutants. This study also had major deficiencies including no evidence for actual exposure of bacteria to test material, no positive controls, no testing with TA1535, excessive mortality, no individual plate data and insufficient test article characterization. In a third study conducted by Strasser (1980), methidathion (purity not stated) was administered to 4 DBA/Bom/SPF mice/dose at 0 or 15 mg/kg by oral gavage after intraperitoneal injection of mouse lymphoma cells. The cells were harvested from the peritoneal cavity 3 days later. This study had major deficiencies including no evidence of actual exposure of cells to the test material, no positive controls, inadequate detail on cell viability or replicates, and inadequate test article characterization.

Reverse mutation assays using *S. typhimurium* for 3 metabolites of methidathion were all negative. The RH metabolite of methidathion, GS 12956 (purity not stated), was tested at 0, 10, 30, 90, 270 and 810 mg/0.1 ml with and without metabolic activation using strains TA98, TA100, TA 1535 and TA1537 (Arni, 1980d). The sulfoxide of methidathion, GS 28370 (purity not stated), was tested at 0, 25, 225, 675, and 2025 μg/0.1 ml with and without metabolic activation using strains TA98, TA100, TA1535 and TA1537 (Arni, 1980e). The sulfone of methidathion, GS 28369 (purity not stated), was also tested at 0, 15, 30, 60, 120, 240, 480, and 960 μg/0.1 ml with and without metabolic activation with strains TA98 and TA100 (Arni, 1980f).

II.E.2. Chromosome Mutation

No evidence of a dominant lethal effect was seen in a study conducted by Fritz (1976a) in which 20 male NMRI mice/dose were administered methidathion (98.4% purity) by oral gavage at 0, 15 or 45 mg/kg and subsequently mated over 6 weekly periods with 2 females per week. Signs of toxicity (deaths, ataxia, diarrhea, somnolence, and convulsions) were seen at the high dose. DPR toxicologists found this study acceptable based on FIFRA guidelines. An increase in sister chromatid exchanges was observed at 34 mg/kg in a study conducted by Hool (1980a) in which 4 Chinese hamsters/sex/dose were given methidathion (93.4% purity) by oral gavage at 0, 17, 34 or 68 mg/kg and sacrificed 24 hours later. The toxicological significance of this finding is unclear since an increase in sister chromatid exchanges was not seen at 68 mg/kg. This study had an inadequate number of animals/cells scored. In another study using the Chinese hamster cell line V79, an increase in sister chromatid exchanges and cell cycle delay was seen at the highest dose levels, 40 and 80 μg/ml (Chen *et al.,* 1981). This study was only available as a published report and as a result it is unclear if the study met FIFRA guidelines. No increase in micronuclei formation were seen when methidathion (96.9% purity) was administered to 6 Chinese hamsters/sex/dose at 0, 17, 34 or 68 mg/kg twice 24 hours apart (Hool, 1980b). The hamsters were sacrificed 24 hours after the second dose. The slides from only 3 animals/sex/dose were scored. This study was also unacceptable to DPR toxicologists based on an inadequate number of animals examined and no data supporting the sacrifice time.

Hool (1980c) also conducted a micronucleus assay with the methidathion RH metabolite, GS 12956 (purity not stated), in which 3 Chinese hamsters/sex/dose were administered the test compound by oral gavage at 0, 121, 242, or 484 mg/kg/day twice 24 hours apart. The hamsters were sacrificed 24 hours after the second dose. No increase in micronuclei was found; however, DPR toxicologists found the study unacceptable due to insufficient information.

II.E.3. Other Genotoxic Effects

There was no evidence of genotoxicity in a rec assay in which *Bacillus subtilis* strains H17 and M45 were exposed to methidathion (99.95% purity) at 0, 250, 500, 1250, 2500, 5000 or 10000 μg/well without activation (Satou *et al.*, 1979). This study was unacceptable to DPR toxicologists based on no metabolic activation and insufficient information. Two acceptable autoradiographic DNA repair tests using primary hepatocytes from adult male Tif.FAIf(SPF) rats were negative for methidathion. In one test, cells were exposed to methidathion (97.2% purity) at 0, 0.128, 0.64, 3.2, and 16 mg/ml for 5 hours (Hertner, 1988). In the second test, cells were exposed to methidathion (96.0% purity) at 0, 1.85, 5.56, 16.67, 50, 100, and 200 mg/ml for 16-18 hours (Hertner, 1990). An autoradiographic DNA repair test was also conducted using human fibroblasts (Ciba-Geigy, 1982). Cells were exposed to methidathion (purity not stated) at 0, 1.024, 5.12, 25.6 or 128 μg/ml for 5 hours. No significant difference in the number of silver grains per nucleus were seen. This study had major deficiencies including no metabolic activation, no background grain counts, inadequate protocol information, inadequate test material information, and inadequate data summary. Two unscheduled DNA synthesis (UDS) assays were also negative for methidathion (purity not stated) using mouse and rat primary hepatocytes (Tong, 1982a&b). Hepatocytes were exposed at concentrations from 5×10^{-7}% to 1% (mouse) and 5×10^{-9}% to 1% (rat). Both were unacceptable based on insufficient information regarding the purity of the test article and number of cells examined.

Two *in vivo* studies were available in which liver DNA damage was evaluated in rats exposed to pesticide mixtures containing methidathion. In one study, the pesticide mixture induced free radical DNA damage based on an increase in the levels of 8-OH-2-deoxyguanosine in liver DNA at low doses, but not at high doses (Lodovici *et al.*, 1994). The investigators suggested the lack of free radical damage at high doses was due to a depression of cellular metabolism based on reductions in benzo(*a*)pyrene hydroxylase, *N*-demethylase activities, glutathione peroxidase, glutathione reductase, glutathione *S*-transferase and thiol transferase activities. In a medium-term liver bioassay, a significant increase in placental glutathione *S*-transferase (GST-P) positive foci was seen in the liver of rats fed a pesticide mixture containing 20 pesticides after an initial induction of hepatic carcinogenesis with diethylnitrosamine (Ito *et al.*, 1995). It is unclear if the effects seen in these studies are due to a single chemical or multiple chemicals acting either additively or synergistically. Methidathion has been shown to induce liver tumors in male mice, but not in rats.

II.F. REPRODUCTIVE TOXICITY

Summary: Four reproductive toxicity studies in rats were available for methidathion. More weight was given to the more recent two-generation study which met FIFRA guidelines; however, the two pre-FIFRA studies and one pilot study did provide useful supplemental

information. The purpose of the guideline reproductive toxicity studies is to provide information on the effects of a chemical on the integrity and performance of the male and female reproductive systems and preliminary information on pre- and postnatal developmental toxicity. The effects in the parental generations can also be used for identifying critical NOELs to evaluate subchronic exposure to methidathion. The effects observed in the parents included tremors, alopecia, reductions in food consumption and body weights, reduced mating index and poor maternal care. Some of these maternal effects, like the tremors, were only observed in lactating females and were probably due to their higher food consumption during this period. The effects observed in pups included tremors, signs of maternal neglect (cool to touch, starving, weak or lethargic), reduced pup weights and reduced survival. Pregnant females, fetuses and developing animals may be more susceptible to the toxicity of methidathion due to differences in their pharmacokinetics during these life stages; however, there was also no information available for methidathion regarding differences in metabolism or pharmacokinetics due to age or pregnancy. In the one acceptable study, the parental NOEL of 5 ppm (0.4 mg/kg/day) was based on alopecia and tremors (females), reduced mating index, and poor maternal care. The reproductive NOEL in this study was also 5 ppm (0.4 mg/kg/day) based on reduced pup weights and signs of maternal neglect. There was no evidence of increased postnatal sensitivity since the parental and reproductive NOELs were the same in the two studies where both were established.

II.F.1. Diet-Rat

Methidathion (purity not reported) was fed to 8 male and 4 female rats (strain not reported) per dose in the diet at 0 or 50 ppm (mg/kg/day) for 3 months and then mated (FPCL, 1965). The mean litter size was smaller in the treated group, but the difference was not statistically significant. The RBC ChE activity was reduced to about 20-40% of normal. It was unclear if plasma or brain ChE activity had been measured. A NOEL could not be established for this study based on this limited information. This study was unacceptable to DPR toxicologists since it did not follow standard FIFRA protocol for this type of study and the information provided was only a summary of findings; however, it was conducted before the FIFRA guidelines existed.

II.F.2. Diet-Rat

A 40% wettable powder methidathion formulation was fed to 10 male and 20 female rats in the diet at 0, 4 or 32 ppm (0, 0.2 or 1.6 mg/kg/day, respectively[5]) for 3 generations (Woodard Research, 1966b). The parental generation was maintained on their assigned diet for 27-28 weeks during which time the females were mated twice to different males within their treatment group. A reduction in survival of pups at 32 ppm was the only effect reported. A tentative reproductive NOEL of 4 ppm (0.2 mg/kg/day) was identified based on the reduced survival of pups. A parental NOEL could not be identified based on insufficient information. This study had major deficiencies including no analysis of test article and diet, inadequate number of dose levels tested, inadequate number of animals per dose level, no summary of clinical signs, body

---

[5]   Estimated assuming for a rat that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (FDA, 1959).

weights, and food consumption, inadequate summary of reproductive parameters, inadequate pathological examination, and no individual data.

II.F.3. Diet-Rat

As a pilot study, a one-generation, two-litter reproductive toxicity study was conducted in which methidathion technical (purity not reported) was fed to 15 male and 30 female Charles River CD® Sprague-Dawley rats/dose at 0, 5, 50 or 100 ppm (M: 0, 0.4, 4.4 or 9.1 mg/kg/day; F: 0, 0.5, 4.9 or 10.6 mg/kg/day, respectively) for 12 weeks prior to mating (Salamon, 1986). After weaning the first litter, the females were rested two weeks and then mated again. No deaths or clinical signs were observed during the premating period. During F_{1a} lactation, dams at 50 and 100 ppm exhibited muscle tremors possibly due to their higher compound intake (0, 0.6, 5.9 or 11.4 mg/kg/day) during this period. In general, the tremors occurred early in the lactation period at 100 ppm and later in the lactation period at 50 ppm. There was a significant reduction in the mean body weights at 100 ppm in both sexes during premating (M: 8-9%; F: 8-14%) and in females during F_{1a} gestation (11-12%) and lactation (10-18%). The mean food consumption was also significantly reduced at 100 ppm in males during premating week 2 and 3 (12%) and in females during premating week 2 (12%) and F_{1a} lactation weeks 1 and 2 (26-34%). There was a significant reduction in the mean food consumption in females at 50 ppm during lactation week 2 (20%). The F_{1a} mating index was significantly reduced at 100 ppm (25%). A significant reduction was seen in the percentage of F_{1a} pups surviving to days 4, 7, 14 and 21 (20.8-42.6%) at 100 ppm. The mean body weights of F_{1a} pups were significantly reduced at 50 ppm (5-25%) and 100 ppm (11-41%). Muscle tremors were also observed in 3 different litters of F_{1a} pups at 100 ppm. No structural anomalies or gross pathological lesions were seen in pups at the end of lactation. Based on the tremors and poor survival of pups at 100 ppm, this dose level was reduced to 25 ppm after the F_{1a} pups were weaned. However, because the reproductive performance of the animals at 25 ppm was significantly depressed during the F_{1b} mating period (14 of 22 mated with only 10 pregnancies; only 6 of the 10 delivered litters), the study was terminated. The parental NOEL appears to be 5 ppm (0.5 mg/kg/day) based on the tremors in dams at 50 ppm during lactation. The reproductive NOEL was also 5 ppm (0.5 mg/kg/day) based on the reduced pup weights. This study had several deficiencies, including no analysis of test article, changes in dose levels and only one generation was exposed due to early termination of study.

II.F.4. Diet-Rat

In the main reproductive toxicity study, 15 male and 30 female CR1:CD BR rats/dose were fed methidathion (95% purity) in the diet at 0, 5, 25 or 50 ppm (M: 0, 0.4, 2.2 or 4.3 mg/kg/day; F: 0, 0.5, 2.5 or 5.0 mg/kg/day, respectively) for two generations (Salamon, 1987). F_1 males at 50 ppm had significantly reduced mean body weights (15%) during weeks 1-8 of the premating period. The mean body weights for the F_0 and F_1 dams were significantly reduced (8-12%) at 50 ppm on lactation days 14 and 21. The mean food consumption was reduced in F_1 males at 25 ppm during week 2 (10%) and at 50 ppm during week 1-3 (11-14%). Significant reductions in the mean food consumption were also seen in F_0 dams at 50 ppm on lactation day 14 (15%) and F_1 dams at 50 ppm on lactation days 7 and 14 (19-28%). Significant increases in food consumption were also noted in F_0 dams at 50 ppm on gestation day 7 (23%) and at 25 ppm on gestation days 7 and 14 (14-19%) and lactation day 21 (42%). Tremors were observed in

dams during lactation, usually the second or third week, in both generations at 25 and 50 ppm. It is not surprising that signs of maternal toxicity were only seen during lactation since feed intake was higher during this period. The average compound consumption of methidathion was nearly doubled during lactation (0, 0.75, 3.84 and 7.16 mg/kg/day) compared to the average compound consumption during premating and gestation (0, 0.45, 2.22 and 4.62 mg/kg/day, respectively). There was also evidence in the pups suggesting poor maternal care, including being cool to the touch, starving, weak or lethargic. It is also possible these effects are due to consumption of methidathion in the milk by the pups rather than neglect by the dams. However, without cross-fostering studies it is uncertain if the effects are from maternal neglect or direct consumption of the methidathion in the diet. Other effects were seen in the pups including a significant reduction in the mean number of viable pups per litter (F_2: 30%) at 50 ppm, a significant reduction in the mean pup body weights at 25 ppm (F_1: 8-15%; F_2: 3-20%) and 50 ppm (F_1: 9-30%; F_2: 3-40%) during lactation, a significant reduction in survival of pups to day 21 at 50 ppm (F_2: 34%), and a reduction in the mean absolute brain (F_2: 7-8%) and liver weights (F_2: 23-27%) at 50 ppm. Adult males had reduced mating indices at 25 ppm (F_1: 18.9%) and 50 ppm (F_1: 22%). Adult females had an increased incidence of alopecia at 25 and 50 ppm (F_0) and reduced mean relative liver weight (F_1: 9%) at 50 ppm and reduced mean absolute and relative ovary weights (F_0&F_1: 20-22%) at 50 ppm. The parental NOEL was established at 5 ppm (0.4 mg/kg/day) based on a reduction in the mating index in males and alopecia, poor maternal care and tremors in females. The reproductive NOEL was also 5 ppm (0.4 mg/kg/day) based on reduced pup weights and signs of maternal neglect in pups (cool to touch, starving, weak or lethargic). This study had some minor deviations from FIFRA guidelines (age at start of treatment, number of animals/sex/dose, time intervals for body weights, males sacrificed at the same time as females), but none invalidated the study. Therefore, DPR toxicologists found this study acceptable for fulfilling the data requirement for reproductive toxicity.

II.G. DEVELOPMENTAL TOXICITY

Summary: Five developmental toxicity studies were available for methidathion (3 rat studies and 2 rabbit studies). Although more weight was given to the studies that met FIFRA guidelines, the 3 studies (2 rat and 1 rabbit) that did not meet FIFRA guidelines provided useful supplemental information. The purpose of the guideline developmental toxicity studies is to provide general information regarding the effects of exposure of the pregnant test animals on the developing organism. The signs observed in pregnant females in the first few days of exposure and most of the effects observed in the fetuses could be due to a single exposure and were considered in selecting a critical NOEL for evaluating acute exposure to methidathion. Some of the maternal signs that were not observed until the latter part of gestation are probably the result of repeated exposure and were considered in selecting a NOEL for evaluating subchronic exposure to methidathion. Systemic maternal effects included death, tremors, salivation, lacrimation, convulsions, ataxia, labored or raspy respiration, exophthalmia, miosis, chromodacryorrhea, crust around eyes, vaginal bleeding, unthriftiness, lethargy, stool alterations, loss of righting reflex, reduced food consumption and body weights. Pregnant females and fetuses may be more susceptible to the toxicity of methidathion due to differences in their pharmacokinetics during these life stages; however, there was also no information available for methidathion regarding differences in metabolism or pharmacokinetics during development or pregnancy. The lowest maternal NOEL in an acceptable study was 1.0 mg/kg/day based on the

mortality, clinical signs, and a reduction in food consumption and body weights in pregnant rats. Fetal effects included reduced ossification of the sternabrae and reduced body weights. The lowest developmental NOEL in an acceptable study was equal to or greater than 2.5 mg/kg/day, the highest dose tested in rats. There was no evidence of increased prenatal sensitivity in any of these studies, based on the developmental NOEL being equal to or greater than the maternal NOEL.

II.G.1. Gavage-Rat

Methidathion (technical, purity not reported) was administered by gavage in an aqueous solution of 2% carboxymethylcellulose to 24, 28, 23 and 21 pregnant female Sprague-Dawley rats at 0, 1, 2.5, and 5.0, respectively, on gestation days 6-15 (Fritz, 1976b). Dams at 5.0 mg/kg/day had tremors after each dosing beginning on treatment day 4.   A reduction in food intake and body weights were observed in dams at 2.5 and 5.0 mg/kg/day (no means or individual data provided). Incompletely ossified 5th sternabrae were observed at 5.0 mg/kg/day. The maternal NOEL was 1 mg/kg/day based on the reduction in body weights and food consumption. The developmental NOEL was 2.5 mg/kg/day based on the reduced ossification of the sternabrae. This study had major deficiencies including no analysis of test material or dosing solution, no summary tables for body weights, food consumption, uterine weights, fetal sex, and number of corpora lutea, no gross pathological examination of dams, and no individual data.

II.G.2. Gavage-Rat

In a range-finding study, 24 pregnant female Crl:COBS CD (SD) BR rats/dose were administered methidathion (technical, purity not reported) by oral gavage at 0 (vehicle = 3% cornstarch with 0.5% Tween 80), 0.1, 1.0 or 7.5 mg/kg/day on gestation days 6-15 (Marcsinsin *et al.*, 1986). Eighteen animals at 7.5 mg/kg/day died before the end of the study. Numerous clinical signs were seen at 7.5 mg/kg/day including ataxia, chromodacryorrhea, crust around eyes, labored respiration, lacrimation, salivation, tremors, convulsions, vaginal bleeding and unthriftiness. The onset of most of these signs (except ataxia, crust around eyes, vaginal bleeding and unthriftiness) was between gestation days 6 and 9 (treatment days 1 and 4) and, therefore, these signs were considered acute effects. Significant reductions in the mean food consumption (18-70%) and body weights (15-23%) were seen in females at 7.5 mg/kg/day during treatment. There was no significant effect on reproductive parameters including the number of corpora lutea, implantation sites, resorptions or dead fetuses. A significant reduction in the mean fetal weights was seen (M:18%; F: 19%). No significant increase in gross (external) malformations was observed in the fetuses. The maternal NOEL for this study was established at 1.0 mg/kg/day based on the mortalities, clinical signs and reduction in food consumption and body weights. The developmental NOEL was also 1.0 mg/kg/day based on the reduced fetal body weights. This study had several major deficiencies including no analysis of test article or dosing material, and no microscopic examination of fetuses for skeletal or visceral malformations.

II.G.3. Gavage-Rat

Methidathion (95% purity) was administered by oral gavage to 25 pregnant female Crl:COBS CD (SD) BR rats/dose at 0 (vehicle = 3% cornstarch with 0.5% Tween 80), 0.25, 1.0

or 2.5 mg/kg/day on gestation days 6-15 (Mainiero *et al.*, 1987). One animal at 2.5 mg/kg/day died on gestation day 12. Clinical signs were observed in dams at 2.5 mg/kg including lethargy, tremors, salivation, lacrimation, exophthalmia, raspy respiration, vaginal bleeding, and chromodacryorrhea. The onset of some of these signs (lethargy, tremors, salivation and raspy respiration) was between gestation days 6 and 9 (treatment days 1 and 4) and, therefore, the signs were considered acute effects. Significant reductions in the mean food consumption (9-16%) and body weights (5%) were seen at 2.5 mg/kg/day. There was no treatment-related effect on pregnancy rate, number of corpora lutea, resorptions, or stillbirths, sex ratio, fetal weights or fetal malformations (gross, visceral or skeletal). The maternal NOEL was established at 1.0 mg/kg/day based on the mortality, clinical signs, and reduction in food consumption and body weights. The developmental NOEL was equal to or greater than 2.5 mg/kg/day, the highest dose tested. DPR toxicologists found this study acceptable based on FIFRA guidelines.

II.G.4. Gavage-Rabbit

In a range-finding study, 6 pregnant New Zealand White were administered methidathion (purity not reported) by oral gavage at 0 (vehicle = 3% cornstarch solution with 0.5% Tween 80), 10, 30 and 50 mg/kg/day on gestation days 7-19 (Wallace, 1986). All animals at 30 and 50 mg/kg/day died during the treatment period. One doe died at 10 mg/kg/day on gestation day 15. Prior to dying, the females exhibited various signs including tremors, ataxia, salivation, miosis, lethargy, stool alterations (decreased/no/soft stools), loss of righting reflex, rales and convulsions. The only clinical sign exhibited in females at 10 mg/kg/day was decreased or soft stools. There was insufficient information on the onset of any of these signs to determine if they could be considered an acute effect. The food consumption was unaffected in animals at 10 mg/kg/day, but their mean body weight gains were reduced (38%) compared to controls. There was no treatment related effect on reproductive parameters (pregnancy rate, number of corpora lutea, implantations, resorptions or still births) or fetal weights. The maternal NOEL was less than 10 mg/kg/day based on the death, reduced body weight gains, and decreased or soft stools. The developmental NOEL could not be established since fetuses were not examined for malformations (gross, visceral or skeletal). This study had major deficiencies primarily due to it being a dose range-finding study and, consequently, there was limited data collected and/or reported.

II.G.5. Gavage-Rabbit

Methidathion (95% purity) was administered by oral gavage to 19 pregnant New Zealand White rabbits/dose at 0 (vehicle = 3% cornstarch with 0.5% Tween 80), 2, 6 or 12 mg/kg/day on gestation days 7 to 19 (Hummel *et al.*, 1987). One animal at 6 mg/kg/day died on day 17 after a mis-dosing and another animal at 12 mg/kg/day was sacrificed after a back injury. Three other does (one each at 2, 6 and 12 mg/kg/day) were sacrificed early because they aborted (on gestation days 20, 23 and 26, respectively). Clinical signs were observed at 12 mg/kg/day including ataxia, salivation, tremors, miosis, and blood in the cage pan. The onset for all of the neurological signs was gestation day 15 (exposure day 8) and for the blood in the cage pan was gestation day 26 (post exposure). These signs occurred after at least 8 consecutive daily doses and, therefore, were not considered acute signs. There were no treatment-related changes in the maternal food consumption, maternal body weights, pregnancy rate, number of corpora lutea, implantation sites or resorptions, sex ratio of fetuses, fetal body weights or fetal malformations

(gross, visceral or skeletal). The maternal NOEL was established at 6 mg/kg/day based on the neurological signs. The developmental NOEL was equal to or greater than 12 mg/kg/day, the highest dose tested. This study was acceptable based on FIFRA guidelines.

II.H. NEUROTOXICITY

Summary: Eight neurotoxicity studies were available for methidathion (5 acute studies in hens, 2 acute studies in rats and a 90-day study in rats). Although only 3 of these studies met FIFRA guidelines, including 1 hen study, 1 acute study in rats, and the 90-day study in rats, the other studies (4 pre-FIFRA hen studies and one pilot rat study) provided useful supplemental information. The purpose of the guideline neurotoxicity studies in hens was to evaluate the potential of organophosphate (OP) chemicals to induce delayed neuropathy. Design of these studies is generally not useful for deriving a NOEL. The hen is used instead of the rat for this type of study since rats are less sensitive to OP-induced delayed neuropathy (OPIDN). There was no evidence of delayed neuropathy in any of the hen studies. The purpose of the acute and subchronic neurotoxicity studies in rats is as a screen for gross neurological functional deficits and histopathological changes in the central and peripheral nervous system and are not intended to be a complete evaluation of the neurotoxic potential of a chemical. NOELs from these studies were considered in selecting critical NOELs for evaluating acute and subchronic exposure to methidathion. In the acute and subchronic neurotoxicity studies in rats, signs of neurotoxicity were observed in the functional observational battery, including changes in autonomic signs, CNS signs, sensorimotor effects, impaired neuromuscular functions and reduced body temperature. A reduction in maze activity was also observed. A reduction in ChE activity in four different regions of the brain (cerebellum, cerebral cortex, hippocampus, and striatum) and the spinal cord were seen. The acute NOEL was less than 1 mg/kg based on reduced ChE activity in the cerebral cortex of males (59% of controls) at the time of peak effect. The subchronic NOEL was 3 ppm (M: 0.182 mg/kg/day; F: 0.198 mg/kg/day) based on the reduced ChE activity in RBCs (M: 74-81%: F: 56-75% of controls - wks 4-13), cerebral cortex (M: 74% of controls - wks 2-4) and striatum (F: 63% of controls - wk 13).

II.H.1. Acute

II.H.1.a. Gavage-Hen

Methidathion (technical, purity not reported) was administered by gavage in 2% carboxymethylcellulose at 0 mg/kg to 10 hens (White Leghorn), 43.75 mg/kg to 15 hens, 87.5 mg/kg to 15 hens, 175 mg/kg to 30 hens and 350 mg/kg to 30 hens twice with a 21 day interval between dosing (Ullman, no date). Hens at 350 mg/kg were pretreated with atropine before dosing. Deaths occurred primarily at 175 and 350 mg/kg, but one death occurred at both 43.75 and 87.5 mg/kg. Clinical signs were seen at all treatment levels during the 42-day observation period including ataxia, convulsions, curved position, and sedation. There was no evidence of delayed neuropathy when the spinal cord and peripheral nerve were examined microscopically. This study had several major deficiencies including no forced motor activity, no body weight data, and no histopathological examination of the thoracic spinal cord or medulla oblongata.

II.H.1.b. Gavage-Hen

Four hens (Rhode Island/Light Sussex and White Leghorn/Light Sussex hybrids) were administered 4 weekly subcutaneous injections of methidathion (purity not reported) in glycerol formal at 50 mg/kg (Geigy, 1964). Signs of acute toxicity (no details provided) were seen, but no evidence of delayed neurotoxicity (ataxia, paralysis, loss of weight) was observed. This study had numerous major deficiencies including inadequate description of methods, no analysis of test article, inadequate number of animals, no dose justification, no positive or negative control groups, no data summaries or individual data.

II.H.1.c. Gavage-Hen

Four hens (strain not reported) were given four weekly subcutaneous injections of methidathion (technical, purity not reported) in glycerol formal at 0 or 50 mg/kg (FPCL, 1965). No hens developed signs of delayed neuropathy during the 8 weeks of observation. This study had numerous major deficiencies including inadequate description of methods, no analysis of test article, inadequate number of animals, no dose justification, no positive or negative control groups, no data summaries or individual data.

II.H.1.d. Gavage-Hen

Sixty production red breed hens were administered methidathion (96.5% purity) in corn oil by gavage at 145 mg/kg twice with a 21-day interval between doses (Kuhn, 1989f). The hens were given atropine at 5, 20.5, 25.5 and 29 hours after dosing. A negative control group containing 10 hens received corn oil only. A positive control group containing 8 hens was given tri-*O*-tolyl phosphate (TOTP) at 500 mg/ml once. Twenty-eight hens receiving methidathion died, 22 after the first dose and 6 after the second dose. Eight hens receiving methidathion exhibited signs of unsteadiness after the first dose, but only one was persistent. No signs of delayed neurotoxicity were seen after the second dose. Histopathological examination of the nervous tissue did not reveal any lesions in hens receiving methidathion that were consistent with organophosphate-induced delayed neuropathy. All hens receiving TOTP exhibited ataxia by day 16 and had some degree of degeneration and swelling of the axons of some portion of the nervous tissue examined microscopically. DPR toxicologists found this study acceptable based on FIFRA guidelines.

II.H.1.e. Diet-Hen

Methidathion in a 40% wettable powder was fed in the diet to 10 hens/dose at 0, 16, 52, or 160 ppm (as active ingredient) for 45 days (Woodard Research, 1965). Hens at 160 ppm had reduced food consumption (no data provided). Discolored livers were noted in all hens receiving methidathion with a higher frequency at 160 ppm. Two hens at 160 ppm had equivocal histopathological lesion in the nerves (no details provided). This study had major deficiencies including inadequate description of methods, no analysis of test article, no data summaries or individual data.

II.H.1.f. Gavage-Rat

        In a range-finding study, 3 male Sprague-Dawley Crl:CD® BR rats/dose were
administered a single dose of methidathion (94.3% purity) by oral gavage at 0, 4, 8, 12, 16 or 20
mg/kg (Leahy, 1993). Three females/dose were administered methidathion at 0, 4, 16, 20 (6
females) or 30 mg/kg. An additional 5 males and 6 females were also administered methidathion
at 25 mg/kg and observed for mortality for 2 days. Animals were evaluated in an abbreviated
functional observational battery (FOB) at 1, 2, 3, 4, 6, and 8 hours. The effects seen included
cholinergic signs (lacrimation, salivation, diarrhea, tremors, ataxia, and muscle fasciculations),
central nervous system (CNS) signs, autonomic signs, neuromuscular signs, and disturbances in
equilibrium at $\geq$ 8 mg/kg in males and $\geq$ 16 mg/kg in females. The onset of signs was as early as
1 hour after dosing. Deaths occurred at $\geq$ 20 mg/kg in males and $\geq$ 25 mg/kg in females. The
NOEL was 4 mg/kg in both sexes based on the effects seen in the FOB. As a range finding
study, this study was not designed to meet FIFRA guidelines and, therefore, it had several
deficiencies including an inadequate number of animals per dose level, inadequate FOB and no
pathological examination of rats.

II.H.1.g. Gavage-Rat

        Methidathion (93.2%) was administered to 20 Crl:CD® Sprague-Dawley rats/sex/dose at
0, 1, 4, 8 and 16 mg/kg after an 18-hour fast (Chang and Richter, 1994). The first 10
rat/sex/dose were subjected to a battery of tests to evaluate neurological function while the
remaining animals were divided into two satellite groups of 5 animals/sex/dose for
cholinesterase measurements at the time of peak effect (1.5 hours after dosing) and the study
termination (2 weeks). A positive control group of 10 rats/sex was administered carbaryl at 30
mg/kg by gavage. No deaths occurred; however, clinical signs (muscle fasciculations, pallor,
reduced activity, salivation and tremors) were observed at 8 and 16 mg/kg on the day of dosing.
One female at 1 mg/kg also exhibited clinical signs, but was considered improperly dosed.
There was a significant reduction in the mean cumulative body weight gain (15%) in males at 16
mg/kg. The mean food consumption was also reduced at 16 mg/kg (M: 15%; F: 11%) the first
week after dosing. Significant differences were observed in both sexes in the functional
observational battery (FOB) at 8 and/or 16 mg/kg (Table 17) at the time of peak effect (1.5 hours
after exposure). These differences included changes in autonomic signs, CNS signs,
sensorimotor effects, impaired neuromuscular functions and reduced body temperature. Some
CNS signs and impaired neuromuscular function were seen in females at 1 and 4 mg/kg, but the
incidence was not statistically significant. There was a significant reduction in the mean total
session activity for both sexes in the figure-8 maze at 8 mg/kg (M: 62%; F: 63%) and 16 mg/kg
(M: 84%; F: 83%) at the time of peak effect. There was also a significant reduction in the mean
activity for females at 4 mg/kg during the first 5 minutes of measurement which the investigators
considered treatment-related.

        The mean serum ChE activity was reduced in males at 8 mg/kg and 16 mg/kg at the time
of peak effect, but had returned to control levels two weeks after dosing (Table 18). Reductions
in the mean serum ChE activity between 71% and 77% of control activity was seen in the
females at all dose levels at the time of peak effect, but the reductions were not statistically
significant. The mean RBC ChE activity was significantly reduced at 4, 8, and 16 mg/kg at the

Table 17. Neurological Effects in Rats Administered a Single Oral Dose of Methidathion[a]

Functional Domain/ Observations	Dose Level (mg/kg)									
	MALES					FEMALES				
	0	1	4	8	16	0	1	4	8	16
Autonomic Respiration	0[b]	0	0	2	7**	0	0	0	4**	10**
Lacrimation	0	0	0	1	3	0	0	0	1	3
Salivation	0	0	0	1	2	0	0	0	0	4*
CNS Excitability Tremors (Home Cage) (Open Field)	0 0	0 0	0 0	3 7**	7** 7**	0 0	0 0	0 0	6** 7**	10** 10**
Tonic Convulsions (Home Cage) Clonic Convulsions (Open Field)	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	0 3
Ease of Handling (In Hand) Ease of Removal (From Cage)	0 0	0 0	0 0	0 0	3 0	0 0	0 1	0 1	1 1	3 5*
Lowered Arousal	0	0	0	4	7**	0	1	0	3	10**
Bizarre Behavior (Home Cage) (Open Field)	0 0	0 0	0 0	4* 7**	7** 7**	0 0	1 1	1 2	5* 6**	10** 10**
CNS Activity Home Cage Posture	0	0	0	2	4	0	0	0	1	5
Mean No. Rears/2 minutes	9	7	11	2**	2**	12	10	8	5**	1**
Sensorimotor Touch Response	0	0	0	0	4**	0	0	0	2	5**
Pupil Response	0	0	1	2	1	0	0	1	0	3
Tail Pinch Response	0	0	0	2	3	0	0	0	1	5**
Neuromuscular Ataxic Gait	0	0	0	8**	5**	0	2	1	8**	10**
Abnormal Gait	0	0	0	8**	7**	1	2	2	7**	10**
Righting Reflex	0	0	0	5**	6**	0	2	3	4	9**
Hindlimb Extensor Strength	0	0	0	1	2	0	1	1	2	7**
Hindlimb Position	0	0	0	2	4*	0	0	1	3	8**
Hindlimb Splay (% Control)	100	105	112	118	125*	100	119	121	128	124
Forelimb Grip Strength (% Control)	100	98	97	74*	37**	100	85	87	53**	21**
Hindlimb Grip Strength (% Control)	100	115	101	95	78	100	93	95	81	70
Physiological Temperature (% Control)	100	100	100	96**	96**	100	99	99	94**	92**

a   Chang and Richter, 1994. This study met FIFRA guidelines.
b   Behavioral effects observed at peak time to effect, 1.5 hours after dosing.   Ten animals/sex/dose at all doses except at 16 mg/kg (8 males, 9 females).
*, **   Significantly different at $p < 0.05$ & 0.01, respectively, when compared to control based on Fisher's exact test (categorical or incidence data) or Dunnett's test (quantitative or ranked data).

Table 18. Cholinesterase Activity Relative to Controls in Blood and Nervous Tissue of Rats Administered a Single Dose of Methidathion by Oral Gavage[a]

Tissue	Time	Dose Level (mg/kg)			
		1	**4**	**8**	**16**
MALES					
Serum	1.5 hrs	101[b]	81	70**	59**
	2 wks	116	111	129	110
Red Blood Cell	1.5 hrs	97	42**	26**	16**
	2 wks	102	65*	82	73
Cerebellum	1.5 hrs	88	47**	32**	22**
	2 wks	97	98	93	84
Cerebral Cortex w/ Hippocampus	1.5 hrs	59**	32**	12**	6**
	2 wks	129	130	104	95
Striatum	1.5 hrs	107	28**	16**	9**
	2 wks	110	135	68	64
FEMALES					
Serum	1.5 hrs	77	76	77	71
	2 wks	92	101	112	108
Red Blood Cell	1.5 hrs	91	33**	18**	14**
	2 wks	94	93	78	81
Cerebellum	1.5 hrs	87	39**	25**	17**
	2 wks	95	95	92	91
Cerebral Cortex w/ Hippocampus	1.5 hrs	87	29**	11**	6**
	2 wks	98	102	91	85
Striatum	1.5 hrs	92	27**	8**	5**
	2 wks	233	117	187	140

a   Chang and Richter, 1994. This study met FIFRA guidelines.
b   Percent of control activity. Five different animals/sex/dose tested at each time point.
*, **   The mean activity was significantly different from controls by Dunnett's test at $p < 0.05$ and 0.01, respectively.

time of peak effect. Two weeks later, only the males at 4 mg/kg had a significant reduction in RBC ChE activity. ChE activity was measured in three different regions of the brain: cerebellum, cerebral cortex with hippocampus, and striatum. The mean ChE activity in the cerebellum was significantly reduced at 4, 8, and 16 mg/kg. Significant reductions in the mean ChE activity in the cerebral cortex were seen at 1.5 hours after dosing at 1 (males only), 4, 8 and 16 mg/kg. The mean ChE activity in the striatum was also significantly reduced at the time to peak effect at 4, 8, and 16 mg/kg. The mean ChE activity in all three brain regions had returned

to control levels by two weeks, except for the striatum where reductions in the mean activity were still present in males at 8 and 16 mg/kg. However, the reductions in the ChE activity in the striatum at 2 weeks were not statistically significant. There is some uncertainty about the toxicological significance of the ChE inhibition in the cerebral cortex of males at 1 mg/kg since the females appear to be more sensitive to methidathion based on the higher incidence of effects in the FOB and the more severe reduction in ChE activity in all three regions of the brain at higher dose levels. Furthermore, the cerebral cortex does not appear to be uniquely sensitive to ChE inhibition when compared to the striatum at 4 mg/kg and higher. It is also unusual to see significant brain ChE inhibition without either serum or RBC ChE inhibition. However, the reduction in cortex ChE activity at 1 mg/kg does not appear to be a statistical aberration based on similar reduction in ChE activity in this brain region of males at 10 ppm (0.6 mg/kg/day) in a 90-day neurotoxicity study (Chow and Turnier, 1995). Therefore, DPR toxicologists made a health protective assumption that the ChE inhibition in the cerebral cortex of males at 1 mg/kg was of toxicological significance. No treatment-related gross or histopathological lesions were found. The study LOEL was 1 mg/kg/day based on the reduced ChE activity (59% of controls) in the cerebral cortex of males at 1.5 hours after exposure and, therefore, the NOEL was less than 1 mg/kg/day. DPR toxicologists found this study acceptable based on FIFRA guidelines.

II.H.2. Subchronic

II.H.2.a. Diet-Rat

Groups of 30 Crl:CD® Sprague-Dawley rats/sex/dose were fed methidathion (94.9% purity) at 0, 3, 10, 30 or 100 ppm (M: 0, 0.182, 0.608, 1.86 or 6.36 mg/kg/day; F: 0, 0.198, 0.659, 2.01 or 7.19 mg/kg/day, respectively) for 90 days (Chow and Turnier, 1995). The first 10 rats/sex/dose were subjected to a battery of tests to evaluate neurological function while the remaining animals served as four satellite groups of 5 rats/sex/dose for cholinesterase measurements at weeks 2, 4, 8 and 13. Ten additional rats/sex were administered acrylamide at 16 mg/kg by oral gavage as a positive control group. Two males at 10 ppm and 1 male at 30 ppm died during the study; however, the investigators did not consider any of these deaths to be treatment-related. Treatment-related clinical signs were seen in females at 100 ppm, including infrequent stools, transient tremors, and chromorhinorrhea. Females at 100 ppm had a dramatic reduction in body weight gains during the first two weeks of the study (67% and 36%, respectively) which resulted in the mean cumulative body weight gain to be significantly reduced until the near end of the study (16% at week 12). There was no significant reduction in the food consumption in females to account for the dramatic reduction in body weights during the first two weeks. The only treatment-related effects seen in the FOB were in females at 100 ppm. These effects included neuromuscular effects (abnormal gait and reduced forelimb and hindlimb grip strength), CNS signs (tremors, stereotypy, bizarre behavior), and sensorimotor effects (increased response to touch, sound and tail pinch). There was no significant difference in the figure-8 maze activity in either sex at any dose level.

The mean serum ChE activity was significantly reduced at 30 (females only) and 100 ppm (Tables 19 and 20). Significant reductions in the mean RBC ChE activity were seen at 10, 30, and 100 ppm. ChE activity was measured in the spinal cord and four regions of the brain: cerebellum, cerebral cortex, striatum, and hippocampus. The mean ChE activity in the cerebellum was significantly reduced at 30 and 100 ppm. In the cerebral cortex, significant

Table 19. Cholinesterase Activity Relative to Controls in Blood and Nervous Tissue of Male
Rats Fed Methidathion in the Diet for 90 Days[a]

Tissue	Time	Dose Level (ppm)			
		3	**10**	**30**	**100**
Serum	2 wks	89[b]	76	84	65*
	4 wks	94	105	95	66
	8 wks	92	79	95	70
	13 wks	92	90	106	68*
Red Blood Cell	2 wks	99	86	66**	19**
	4 wks	93	81*	40**	10**
	8 wks	85	74**	37**	17**
	13 wks	89	80*	41**	12**
Cerebellum	2 wks	93	93	90	58**
	4 wks	96	96	87**	47**
	8 wks	102	100	88	49**
	13 wks	99	86	86	48**
Cerebral Cortex	2 wks	89	74*	78	32**
	4 wks	86	74**	56**	15**
	8 wks	115	74	66	23**
	13 wks	81	75	59*	19**
Striatum	2 wks	104	113	91	35**
	4 wks	89	98	84	16**
	8 wks	114	90	61**	17**
	13 wks	93	90	59**	13**
Hippocampus	2 wks	97	101	108	41**
	4 wks	96	97	81**	23**
	8 wks	89	97	68**	21**
	13 wks	105	96	76**	26**
Spinal Cord	2 wks	103	90	88	48**
	4 wks	123	116	98	36**
	8 wks	104	94	80	35**
	13 wks	86	87	77*	23**

   a   Chow and Turnier, 1995. This study met FIFRA guidelines.
   b   Dose level of 0, 3, 10, 30 or 100 ppm = 0, 0.182, 0.608, 1.86 or 6.36 mg/kg/day, respectively
   c   Percent of control activity. Five different animals/sex/dose tested at each time point.
*, **   The mean activity was significantly different from controls by Dunnett's test at $p < 0.05$ and 0.01, respectively.

Table 20. Cholinesterase Activity Relative to Controls in Blood and Nervous Tissue of Female Rats Fed Methidathion in the Diet for 90 Days[a]

Tissue	Time	Dose Level (ppm)[b]			
		3	10	30	100
Serum	2 wks	138*[c]	103	136*	77
	4 wks	87	75	59**	44**
	8 wks	99	141	87	71
	13 wks	76	93	91	55*
Red Blood Cell	2 wks	95	92	54**	15**
	4 wks	87	75**	24**	9**
	8 wks	106	56**	20**	14**
	13 wks	98	68**	28**	9**
Cerebellum	2 wks	98	94	79**	41**
	4 wks	103	100	68**	34**
	8 wks	102	82	80	20**
	13 wks	92	81	64**	32**
Cerebral Cortex	2 wks	97	99	60**	18**
	4 wks	88	86	41**	11**
	8 wks	104	102	37**	11**
	13 wks	95	85	34**	8**
Striatum	2 wks	92	91	56**	9**
	4 wks	105	96	34**	6**
	8 wks	100	88	31**	3**
	13 wks	95	63**	34**	4**
Hippocampus	2 wks	97	89	60**	17**
	4 wks	105	97	71**	13**
	8 wks	102	83	32**	7**
	13 wks	103	76**	44**	9**
Spinal Cord	2 wks	102	103	72**	30**
	4 wks	116	93	52**	19**
	8 wks	102	86	47**	18**
	13 wks	108	99	64**	17**

a   Chow and Turnier, 1995. This study met FIFRA guidelines.
b   Dose Level of 0, 3, 10, 30 or 100 ppm = 0, 0.198, 0.659, 2.01 or 7.19 mg/kg/day, respectively
c   Percent of control activity. Five different animals/sex/dose tested at each time point.
*, **   The mean activity was significantly different from controls by Dunnett's test at $p < 0.05$ and 0.01, respectively.

reductions in the mean ChE activity were observed at 10 (males only), 30 and 100 ppm. There was some uncertainty about the toxicological significance of the reduced ChE activity in the cerebral cortex of males at 10 ppm because females had more pronounced inhibition of ChE in this region at higher doses. Furthermore, males did not exhibit any abnormal behavior in the FOB or maze even at 100 ppm. However, the cortex ChE activity in males at 10 ppm was consistently reduced to about 75% of control activity throughout the study (although it was not always statistically significant). Therefore, DPR toxicologists made the health protective assumption that the ChE inhibition in males at 10 ppm was of toxicological significance. The mean ChE activity in the striatum was reduced at 10 (females only), 30, and 100 ppm. Significant reductions in the mean ChE activity were seen in the hippocampus at 30 and 100 ppm. The mean ChE activity in the spinal cord was also significantly reduced at 30 and 100 ppm. No treatment-related gross or histopathological lesions were found. The NOEL for this study was established at 3 ppm (M: 0.182 mg/kg/day; F: 0.198 mg/kg/day) based on the reduced ChE activity in RBCs (M: 74-81%; F: 56-75% of controls - wks 4-13), cerebral cortex (M: 74% of controls - wks 2-4), striatum (F: 63% of controls - wk 13), and hippocampus (F: 76% of controls - wk 13). DPR toxicologists found this study acceptable based on FIFRA guidelines.

III.   RISK ASSESSMENT

III.A. HAZARD IDENTIFICATION

III.A.1. Acute Toxicity

The NOELs and LOELs observed in the acute studies for methidathion are summarized in Table 21. The studies included in the table were all studies that have sufficient information to establish an acute NOEL or LOEL, regardless of whether they met FIFRA guidelines. This included LD_{50}/LC_{50} studies, mechanistic studies, acute neurotoxicity studies, and developmental toxicity studies. Table 21 also includes the acute effects that were observed at the LOEL. With acute, subchronic and chronic exposure, the effects that are generally considered adverse include clinical signs, reductions in body weight and food consumption greater than 10%, and increases in gross and histopathological lesions. Minimal changes in clinical chemistry and hematology values and organ weights without accompanying functional or structural changes are generally not considered adverse. The effects observed in the LD_{50}/LC_{50} studies included dizziness, ataxia, irregular and increased respiration, dyspnea, fasciculations, trembling, salivation, exophthalmos, and death. There was insufficient information available from the LD_{50}/LC_{50} studies to establish NOELs for these effects.

In general, DPR considers brain ChE inhibition to be indicative of overt toxicity since it is one of the primary functional target sites and more subtle central neurological signs, such as memory and learning losses, may not be easily detected in animals unless they are specifically tested for these effects. The toxicological significance of plasma and RBC ChE inhibition is less certain because the physiological function of ChEs in blood have not been clearly established, although several possible physiological functions have been proposed. Plasma ChE, or more specifically butyrylcholinesterase (BuChE), may be involved in the binding/metabolism of certain drugs, such as succinylcholine, which suggests that its inhibition may compromise an organism's ability to defend against subsequent toxic insults (Lockridge and Masson, 2000). BuChE is also the predominant form of ChE in the developing nervous system of birds and mammals (Brimijoin and Koenigsberger, 1999). Other evidence suggests that BuChE may also play a role in the co-regulation of ACh levels in the adult nervous system including 1) substrate inhibition of acetylcholinesterase (AChE) at high ACh concentrations, 2) the survival of AChE knockout mice, and 3) the increase in BuChE levels with Alzheimer's disease as AChE levels decrease (Giacobini, 2003; Li *et al.*, 2000; Ballard and Perry, 2003). Due to the expression of AChE in several types of hematopoietic cell lines, it has been proposed that circulating AChE may be important in erythropoiesis (Grisaru *et al.* 1999).   U.S. EPA does not consider plasma or RBC ChE inhibition an adverse effect in itself, but does use RBC ChE inhibition as a surrogate for peripheral ChE inhibition (U.S. EPA, 2000a). The Joint Meeting on Pesticide Residues of the FAO/WHO concluded that RBC ChE activity should only be used as a surrogate for peripheral ChE activity at the time of peak effect with acute exposure (JMPR, 1999) since RBCs lack the ability to synthesize new AChE (Brimijoin, 1992). Consequently, the recovery of RBC ChE activity is much slower than in neurological and neuromuscular tissue because it is dependent on the replacement of RBCs. DPR is reevaluating the use of ChE inhibition data in its risk assessments. In anticipation of changes in the use of these endpoints in the risk assessments, NOELs for blood and brain inhibition were identified in this document based on statistical significance.

66

Table 21. Acute Effects of Methidathion and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL	LOEL	Ref.[a]
			(mg/kg/day)		
Oral					
Rat[b]	Single, gavage	↓ ChE[c] activity in the cerebral cortex (M: 59%)[d]	---	1.0	1*
Rat	Single, gavage	↑MDA[e], ↓antioxidant enzymes in erythrocytes	---	8.0	2
Rat	Single, gavage	↑TBARS[f] & liver enzymes in serum	---	8.0	3
Rat	Single, gavage	Histopathological lesions in liver	---	8.0	4
Rat[g]	9 Days, gavage	Maternal: Tremors (onset day 4)	2.5	5.0	5
		Fetal: ↓Ossification	2.5	5.0	
Rat[g]	9 Days, gavage	Maternal: Tremors, salivation, lacrimation, convulsions, labored respiration, chromodacryorrhea (onset days 1-4)	1.0	7.5	6
		Fetal: ↓Birth weight	1.0	7.5	
Rat[g]	9 Days, gavage	Maternal: Lethargy, tremors, salivation, raspy respiration (onset days 1-4)	1.0	2.5	7*
Rat[b]	**14 Days, diet**	**↓ ChE activity in cerebral cortex (M: 74%)**	**0.18**	**0.61**	**8***

a   References: 1. Chang and Richter, 1994; 2. Altuntas *et al.*, 2002a; 3. Altuntas *et al.*, 2002b; 4. Gokalp *et al.*, 2003; 5. Fritz, 1976b; 6. Marcsinsin *et al.* 1986; 7. Mainiero *et al.*, 1987; 8. Chow and Turnier, 1995.
b   Neurotoxicity study
c   ChE = Cholinesterase
d   Percent of control activity
e   MDA = malondialdehyde, a biomarker of membrane lipid peroxidation
f   TBARS - thiobarbituric acid reactive substances, a endproduct of lipid peroxidation
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.
*   Acceptable study based on FIFRA guidelines

In two mechanistic studies, evidence of lipid peroxidation was observed in rats after a single oral dose at 8 mg/kg, including increased malondialdehyde (MDA) levels and reduced antioxidant enzyme levels (superoxide dismutase, glutathione peroxidase and catalase) in erythrocytes and increased thiobarbituric acid reactive substances (TBARS) in serum (Altuntas *et al.*, 2002a&b). The increase serum TBARS were also associated with an increase in liver enzymes (alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and lactate dehydrogenase) in the serum which were indicative of hepatotoxicity (Altuntas *et al.*, 2002b). In a subsequent study from the same research group, they found an increase in histopathological

lesions in the liver (mononuclear cells at parenchymal tissue, sinusoidal dilatation, focal necrotic areas, granular degeneration and picnotic nuclei in hepatocytes) in rats after a single oral dose at 8 mg/kg (Gokalp *et al.*, 2003). A NOEL was not established in any of these studies since only one dose level was tested.

Some effects observed in the developmental toxicity studies were considered acute including maternal signs observed within the first few days of exposure and any fetal effects assuming they were the result of a single exposure. Cholinergic signs (tremors, salivation, lacrimation, labored or raspy respiration, convulsions) were seen in dams in several rat developmental toxicity studies during the first few days of treatment. The NOELs in these studies ranged from 1 to 2.5 mg/kg/day. A NOEL of 1 mg/kg/day was established in an acceptable study conducted by Mainiero *et al.* (1986) where lethargy, tremors, salivation, and raspy respiration were observed in pregnant rats at 2.5 mg/kg/day on days 1 to 4 of treatment. Fetal effects were also observed in two of these developmental toxicity studies in rats, including reduced ossification and reduced body weights (Fritz, 1976b; Marcsinsin *et al.* 1986). The NOELs for the fetal effects were same as the maternal NOELs, 1 to 2.5 mg/kg/day. The onset of the neurological signs in the one rabbit developmental toxicity study which had sufficient information to determine this was after at least 8 consecutive daily doses and, therefore, was considered a subacute or subchronic effect rather than an acute effect (Hummel *et al.*, 1987). However, even if it had been considered an acute effect, the NOEL for these cholinergic signs in rabbits was higher (6 mg/kg/day) than the NOELs for similar signs in rats. No fetal effects were observed in the rabbit developmental toxicity studies.

In an acute neurotoxicity study in rats, treatment-related differences in clinical signs (muscle fasciculations, pallor, reduced activity, salivation and tremors), the functional observational battery (FOB) parameters and figure-8 maze activity were seen in both sexes at 8 and 16 mg/kg at the time of peak effect (Chang and Richter, 1994). The effects seen in the FOB included autonomic signs (impaired respiration, lacrimation, salivation), CNS signs (tremors, reduced arousal, decreased activity, convulsions, muscle fasciculations, repeated opening and closing of mouth), sensorimotor effects (reduced touch and tail pinch responses), impaired neuromuscular function (ataxic and/or abnormal gait, impaired righting reflex, reduced hind limb extensor strength, reduced forelimb and hindlimb grip strength) and reduced body temperature. Some signs indicative of CNS excitability and impaired neuromuscular function were seen in females at 1 and 4 mg/kg, but the incidence was not statistically significant. The toxicological significance of the low incidence of these signs at these lower dose levels is uncertain given that there was no significant ChE inhibition in the plasma, RBCs or brain of females at 1 mg/kg. Furthermore, the incidence of these signs were not significantly greater at 4 mg/kg where there was a marked reduction in brain and RBC ChE activity (25-40% of control activity).   There was a significant reduction in the mean ChE activity in the cerebral cortex of males (59% of controls) at 1 mg/kg at 1.5 hours after dosing even though there were no neurological signs observed in males at 1 or 4 mg/kg (except one male at 4 mg/kg with impaired pupil response).   The toxicological significance of the ChE inhibition in the cortex of males at 1 mg/kg is uncertain for several reasons. First, the females appear to be more sensitive to methidathion based on the ChE activity in all three regions of the brain at higher dose levels and the higher incidence of effects seen in the FOB. Second, the cerebral cortex does not appear to be uniquely sensitive to ChE inhibition when compared to the striatum at 4 mg/kg and higher dose levels. Third, it is unusual

to see significant brain ChE inhibition without either significant plasma or RBC ChE inhibition. However, the reduction in cortex ChE activity in males at 1 mg/kg does not appear to be a statistical aberration since a similar reduction in cortex ChE activity was seen in males at 10 ppm (0.61 mg/kg/day) at 2 weeks in an acceptable 90-day neurotoxicity study for methidathion (Chow and Turnier, 1995). Unlike the acute neurotoxicity study, a NOEL was observed for this endpoint at 2 weeks in the 90-day neurotoxicity study. It was assumed the NOEL with a single exposure would be equal to or greater than the NOEL after 2 weeks of repeated daily exposure. Therefore, the critical NOEL selected for evaluating acute dietary, drinking water, occupational and ambient air exposure to methidathion was 3 ppm (0.18 mg/kg/day) based on significantly reduced ChE activity in the cortex of males that was observed after 2 weeks in the 90-day neurotoxicity study. The use of the 2-week NOEL as a surrogate for the acute NOEL is supported by the benchmark dose analysis which showed that the dose response was the same for the ChE inhibition in cortex of males at 1.5 hrs in the acute study and at 2 weeks in the 90-day (see the Risk Appraisal section of this document for a detailed discussion). The 2-week NOEL of 0.18 mg/kg/day corresponded to the BMDL at 15%.

The methidathion oxon is the presumed active metabolite for the neurological effects, although the pharmacokinetics studies suggest that the oxidative desulfuration to the oxon is a minor metabolic pathway. Typically, the oxon is more toxic than the parent compound for organophosphorothioates. However, there were no acute toxicity studies for the oxon, not even an LD_{50} study, to derive a toxicity equivalency factor for the oxon. The registrant has cited the conclusion by U.S. EPA that the oxon was only a minor metabolite whose toxicity was accounted for in the toxicity studies for the parent as the reason why they never conducted any toxicity studies for oxon (U.S. EPA, 1995). In the 2006 update of the cumulative risk assessment for OPs, U.S. EPA became concerned about the contribution of methidaoxon to the drinking water cumulative risk assuming it was 10X or 100X as toxic as methidathion. Consequently, they have requested the registrant submit toxicity data for the oxon. In the absence of these data, DPR has assumed the acute toxicity of the oxon was equivalent to the parent compound. However, theoretical estimates of the risks from drinking water and air exposure have been calculated in the Risk Appraisal section of this document assuming the oxon was 10X or 100X as toxic as the parent. This exercise was not conducted for dietary and occupational exposure since the oxon was not included in these exposure estimates for different reasons.

III.A.2. Subchronic Toxicity

The NOELs and LOELs observed in laboratory animals after subacute (< 28 days) or subchronic (3 - 6 months) exposure to methidathion are summarized in Table 22. The studies included in the table were all studies with subacute or subchronic exposure that have sufficient information to establish a subchronic NOEL or LOEL, regardless of whether they met FIFRA guidelines. These include standard oral and dermal subchronic toxicity studies, subchronic neurotoxicity studies, developmental and reproductive toxicity studies, and mechanistic studies. Table 22 also includes the effects that are observed at the LOEL. Clinical signs observed in oral and dermal subchronic toxicity studies of varying length included lethargy, anorexia, labored or rapid breathing, hunched posture, ataxia, tremors, soft feces, and low body temperature. Reductions in body weights and food consumption were also seen. Pathological findings

Table 22. Subacute/Subchronic Effects of Methidathion and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL	LOEL	Ref.[a]
			(mg/kg/day)		
Oral					
Rat[b]	9 days, gavage	Maternal: ↓ Body weights & food consumption	1.0	2.5	1
Rat[b]	9 days, gavage	Maternal: Death, cholinergic signs, ↓ body weights & food consumption	1.0	7.5	2
Rat[b]	9 days, gavage	Maternal: Death, cholinergic signs, ↓ body weights & food consumption	1.0	2.5	3*
Rabbit[b]	13 days, gavage	Maternal: Decreased or soft stools, ↓ body weights	-----	10.0	4
Rabbit[b]	13 days, gavage	Maternal: Cholinergic signs	6.0	12.0	5*
Mouse	28 days, diet	↓ ChE[c] activity in RBCs (M&F: 57%[d]) & brain (M: 49%; F: 65%)	4.2	18.0	6
Rat	4 weeks, diet	↓ RBC ChE activity (M&F: 62%-77%)	0.25	0.83	7
Rat	4 weeks, diet	Unspecified cholinergic signs, fatty deposits in liver	2.5	5.0	7
Rat	4 week, 5 days/wk, gavage	↑ Cardiac TnI[e] in serum, ↑ MDA[f] & histopathological lesions in the heart	-----	5.0	8
Rat	4 week, 5 days/wk, gavage	↑ MDA & histopathological lesions in aorta, ↓ serum ChE activity (60%)	-----	5.0	9
Rat	4 week, 5 days/wk, gavage	↑ MDA & histopathological lesions in kidneys, ↓ serum ChE activity (67%)	-----	5.0	10
Rat[g]	2-gen., 10 wks premating, diet	Parental: Reduced mating index (M), alopecia (F), poor maternal care, tremor (F)	0.4	2.2	11*
		Fetal: Reduced pup weights and signs of maternal neglect	0.4	2.2	
Rat[h]	**90-days, diet**	**↓ ChE activity in RBCs (M: 74-81%; F: 56-75%), cerebral cortex (M: 74%), striatum (F: 63%), and hippocampus (F: 76%)**	**0.18**	**0.61**	**12***
Rat	22 weeks, diet	↓ ChE activity (70-75%, unclear if blood or brain)	0.2	0.8	7
Rat	6 months, diet	↓ RBC ChE activity (% not reported)	0.2	1.1	7

Table 22 (cont.). Subacute/Subchronic Effects of Methidathion and Their Respective NOELs and LOELs

Dermal					
Rat	3 hrs/day, 5 days/wk, 4 wks	None	12.0	-----	7
Rabbit	6 hrs/day, 22 days	None	20.0	-----	13
Rabbit	6 hrs/day, 21 days	Death, lesions in stomach and heart	-----	1.0	14

a	References: 1. Fritz, 1976b; 2. Marcsinsin *et al.*, 1986; 3. Mainiero *et al.*, 1987; 4. Wallace, 1986; 5. Hummel, 1987; 6. Albanese, 1976; 7. Geigy, 1964; 8. Yavuz *et al.*, 2004a; 9. Yavuz *et al.*, 2004b; 10. Sulak *et al.*, 2005; 11. Salamon, 1987; 12. Chow and Turnier, 1995; 13. Folinusz *et al.*, 1986; 14. Osherhoff, 1987b.
b	Developmental toxicity study: Only maternal effects observed after the first few days were included.
c	ChE = Cholinesterase
d	Percent of control activity
e	TnI = troponin I, a biomarker of myocardial damage
f	MDA = malondialdehyde, a biomarker of membrane lipid peroxidation
g	Reproductive toxicity study
h	Neurotoxicity study
*	Acceptable study based on FIFRA guidelines

included changes in hematological values suggesting anemia, changes in serum enzyme levels suggesting liver toxicity, reduced brain ChE activity, increased levels of a biomarker for lipid peroxidation in the heart, aorta and kidney, and histopathological lesions in the liver, gallbladder, stomach, kidney, aorta and heart. The lowest LOEL in a standard subchronic toxicity study was 1 mg/kg/day based on deaths and histological lesions in the stomach and heart in rabbits after a 21-day dermal exposure (Osherhoff, 1987). This study had one major deficiency in that there was an incomplete histopathological examination of the control and high-dose animals.

In addition to the standard subchronic toxicity studies, Table 22 includes several developmental toxicity studies where maternal effects were observed after subacute exposure for 1 to 2 weeks. Maternal signs observed after subacute exposure to methidathion included tremors, ataxia, salivation, lacrimation and other ocular discharge, exophthalmia, miosis, vaginal bleeding and unthriftiness. Reductions in food consumption and maternal body weights were also seen. The lowest maternal NOEL in an acceptable developmental toxicity study was 1 mg/kg/day based on death, lethargy, tremors, salivation, lacrimation, exophthalmia, raspy respiration, vaginal bleeding, chromodacryorrhea, and reduced food consumption and body weights in pregnant rats (Mainiero *et al.*, 1987). This study met FIFRA guidelines.

Any effects observed in reproductive toxicity studies were also included in Table 22. The effects observed in the parental generations of the reproductive toxicity studies for methidathion included tremors, alopecia, reductions in food consumption and body weights, reduced mating index and poor maternal care. The effects observed in pups included tremors, signs of maternal neglect (cool to touch, starving, weak or lethargic), reduced pup weights and reduced survival. In the one acceptable study, the parental NOEL of 5 ppm (0.4 mg/kg/day) was based on alopecia and tremors (females), reduced mating index, and poor maternal care (Salamon, 1987). The reproductive NOEL in this study was also 5 ppm (0.4 mg/kg/day) based on reduced pup weights and signs of maternal neglect.

In the acceptable 90-day neurotoxicity study in rats, females exhibited clinical signs (infrequent stools, transient tremors, chromorhinorrhea), changes in FOB parameters, and reductions in body weights at 100 ppm (Chow and Turnier, 1995). The changes in FOB parameters included neuromuscular effects (abnormal gait, reduced forelimb and hindlimb grip strength), CNS signs (tremors, stereotypy, bizarre behavior) and sensorimotor effects (increased response to touch, sound and tail pinch). Significant reductions in ChE activity in the cerebral cortex, cerebellum, hippocampus and striatum were also seen in both sexes. The NOEL for this study was 3 ppm (M: 0.18 mg/kg/day; F: 0.20 mg/kg/day) based on the reduced ChE activity in RBCs (M: 74-81%; F: 56-75% of controls - wks 4-13), cerebral cortex (M: 74% of controls - wks 2-4), striatum (F: 63% of controls - wk 13) and hippocampus (F: 76% of controls - wk 13). There was some uncertainty about the toxicological significance of the ChE inhibition in the cerebral cortex of males since females had more pronounced ChE inhibition in this region at higher dose levels and males did not exhibit any clinical signs, changes in FOB parameters or changes in maze activity at any dose level. However, the cortex ChE activity in males at 10 ppm was consistently reduced to about 75% of control activity throughout the study (although it was not always statistically significant). Therefore, DPR toxicologists made the health protective assumption that the reduced ChE activity in the cerebral cortex of males at 10 ppm (0.61 mg/kg/day) was of toxicological significance.

Reduced RBC and brain ChE activity appear to be the most sensitive endpoints with subchronic exposure to methidathion. ChE activity was not measured in any of the developmental or reproductive toxicity studies, so the NOELs for these studies might have been lower if ChE activity had been measured. There does not appear to be any significant seasonal variation in dietary or drinking water exposure to methidathion; however, the occupational and ambient air exposure to methidathion were seasonal. Therefore, the 90-day neurotoxicity study was selected as the definitive study for evaluating seasonal occupational and ambient air exposure to methidathion because it had the lowest subchronic NOEL and it met FIFRA guidelines. The critical NOEL was 0.18 mg/kg/day based on the reduced ChE activity in the RBCs of both sexes (56-81% of controls), in the cerebral cortex of male rats (74%) and in the striatum (63% of controls) and hippocampus (76% of controls) of female rats.

As with acute toxicity, there were no subchronic toxicity studies, including developmental and reproductive toxicity studies, for the methidathion oxon, the presumed active metabolite for the neurological effects. Therefore, it was assumed that the subchronic toxicity of the oxon was equivalent to the parent compound.

III.A.3. Chronic Toxicity

The NOELs and LOELs observed in laboratory animals with chronic exposure (> 1 year) to methidathion are summarized in Table 23. The studies included in the table were all studies that have sufficient information to establish a chronic NOEL or LOEL studies, regardless of whether they met FIFRA guidelines. This included the typical 1- to 2-year chronic feeding studies in mice, rats and dogs as well as an unusual 2-year gavage study in monkeys. Table 23 also includes the effects that are observed at the chronic LOEL. Effects seen in laboratory animals with chronic exposure to methidathion were similar to those seen with subchronic exposure, except hepatotoxicity was more common. In addition, ulceration and inflammation of the skin and focal accumulation of foamy macrophages in the alveoli were seen in a chronic

Table 23. Chronic Effects of Methidathion and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Ref.[a]
Mouse	18-19 months, diet	Histological lesions in the liver of males	1.5	15.0	1
Mouse	18-23 months, diet	Discolored urine, ↓ RBC ChE activity (F: 64-74%[c]), ↑ serum ALT levels, histological lesions in liver and gall bladder (M)	1.4	6.7	2*
Rat	2 years, diet	↓ Brain ChE activity (M: 86%; F: 92%)	-----	0.2	3
Rat	104 weeks, diet	Clinical signs, ↓ body weights, food & water consumption, ↓ ChE activity in RBCs (M: 78%; F: 82%) & brain (M: 49%; F: 48%), ↓liver weights, skin lesions	0.17	1.77	4*
Dog	105 weeks, diet	↑ Liver enzymes in serum, histological lesions in liver and spleen	0.12	0.48	3
Dog	**1 year, diet**	**↑ Liver enzymes in serum, histological lesions in the liver**	**0.15**	**1.33**	**5***
Monkey	23 months, gavage	↓ChE activity in plasma (M&F: 39%) and RBCs (M&F: 60-76%)	0.25	1.0	6

a   References: 1. IBT, 1980; 2. Goldenthal, 1986; 3. Johnston, 1967; 4. Yau *et al.*, 1984; 5. Chang and Walberg, 1991; 6. Coulston and Goldberg, 1971.
b   ChE = cholinesterase
c   Percent of control activity
*   Acceptable study based on FIFRA guidelines

feeding study with rats (Yau *et al.*, 1986).   Hepatotoxicity and brain ChE inhibition were the most common effects seen. Mice appear to be significantly less sensitive to the hepatotoxicity and brain ChE inhibition since the NOELs in mice were nearly an order of magnitude higher than in rats and dogs. The lowest LOEL (0.2 mg/kg/day) was observed in a 2-year rat chronic toxicity study based on slightly reduced brain ChE activity (M: 86%; F: 92%) (Johnston, 1967). There were multiple deficiencies in this older rat study including a high mortality rate due to pulmonary infections, no analysis of test compound or feed to verify purity or concentration, insufficient hematological and clinical chemistry analysis, incomplete histopathology and incomplete individual data. The findings from this older study were superceded by those from a more recent study conducted by Yau *et al.* (1985) which met FIFRA guidelines and established a NOEL of 0.17 mg/kg/day based on clinical signs, reduced body weights, reduced food and water consumption, reduced ChE activity in RBCs (M: 78%; F: 82% of controls) and brain (M: 49%;

F: 48% of controls), reduced liver weights, and skin lesions. A similar NOEL, 0.15 mg/kg/day, was seen in dogs based on elevated liver enzymes in the serum and histological lesions in the liver (Chang and Walberg, 1991). The rats appear to be slightly more sensitive to the neurotoxicity of methidathion whereas the dogs appear more sensitive to the hepatotoxicity. The different responses could be due to differences in metabolism (either in the rate or the major pathways) between dogs and rats. However, there are no metabolism or pharmacokinetic data to explain the apparent differences in sensitivity in the dog. Primates do not appear to be any more sensitive than rats to ChE inhibition in blood, although since the brain ChE activity was not analyzed in this study, it is unknown if this is also true for that endpoint. The monkey is a more relevant animal model for evaluating the risk for human health effects from methidathion; however, due to major deficiencies with this older study (including an insufficient number of dose levels tested, lack of overt toxicity at the highest dose level, inadequate histopathological examination and no individual data) less weight was given to this study. Instead, the dog study conducted by Chang and Walberg (1991) was selected as the definitive study for evaluating chronic exposure to methidathion since it had a slightly lower NOEL and it met FIFRA guidelines. The critical NOEL for chronic exposure was 0.15 mg/kg/day based on elevated liver enzymes in the serum and histological lesions in the liver.

As with acute and subchronic toxicity, there were no chronic toxicity studies for the methidathion oxon, the presumed active metabolite for the neurological effects. However, it is uncertain if the oxon is the active metabolite for the hepatotoxicity observed with chronic exposure to methidathion. Therefore, it was assumed that the chronic toxicity of the oxon was equivalent to the parent compound.

III.A.4. Carcinogenicity - Weight of Evidence

There is evidence that methidathion is carcinogenic based on a significant increase in the incidence of hepatocellular adenomas and carcinomas in male mice in two different carcinogenicity studies (IBT, 1980; Goldenthal, 1986). In one mouse study, an increase in hepatocellular adenomas and carcinomas was seen in males at 100 ppm (IBT, 1980). However, this study had numerous major deficiencies including no food consumption data, control group mistakenly dosed with treated feed in month 14, apparent degradation of the test material in the first 8 months, and no hematology data. In an acceptable mouse carcinogenicity study, there was also a significant increase in the incidence of hepatocellular adenomas and carcinomas at 50 and 100 ppm (Goldenthal, 1986). The incidence of both tumor types exhibited a dose-related trend that was highly significant when analyzed separately or combined (Table 10). In addition, 3 animals at 100 ppm had multiple liver tumors. The increase in hepatocellular adenomas was significant by pairwise comparison to controls at all dose levels. However, the incidence in the controls was unusually low and only the incidence at 100 ppm was clearly outside the historical control range for this laboratory (0-27%) (Table 11) (Quest *et al.*, 1990*)*. The increase in hepatocellular carcinomas was also significantly different than controls at 100 ppm. When combined, the increase in hepatocellular adenomas and carcinomas was significant at 50 and 100 ppm. The incidence of carcinomas and combined adenomas/carcinomas exceeded the historical control range (carcinomas: 0-10%; combined: 5-32%) at 50 and 100 ppm. The proportion of malignant tumors at 50 and 100 ppm (62 and 45%, respectively) was greater than historical controls (mean 34%), but not concurrent controls (89%).

There appeared to be a reduction in the time to tumor in males at 100 ppm since the proportion of tumor-bearing animals that died early was higher (76%) when compared to concurrent controls (33%). In fact, the shortest time to tumor (445 days) was seen in a male at 100 ppm. However, if the time to death of the liver tumor-bearing males that died early is compared, the means are similar for controls (618 days) and males at 100 ppm (608 days).   If only the males where liver tumors were considered the cause of death were included, the mean time to death was actually higher at 100 ppm (645 days) than controls (618 days). The liver tumors were considered the cause of death for only 11 of 29 male mice (38%) at 100 ppm that died early with liver tumors compared to 3 of 3 male mice (100%) in the control group.

It is noteworthy that the significant increases in neoplastic liver lesions in male mice occurred at dose levels that also caused significant increases in non-neoplastic liver lesions (Table 9). There was no increase in neoplastic liver lesions in females despite a slight increase in non-neoplastic lesions at 100 ppm. However, the incidence of non-neoplastic liver lesions in females at 100 ppm (bile stasis 24%, chronic hepatitis 17%) was considerably lower than in males at 50 ppm (bile stasis 51%, chronic hepatitis 49%). There was also no significant increase in neoplastic or non-neoplastic liver lesions in either sex of rats up to the highest dose level, 100 ppm (~ 5 mg/kg/day). The apparent association of the hepatotoxicity with the liver tumors suggests that an increase in cell proliferation or turnover may be responsible for the increase in tumors. The mechanism behind the liver toxicity is unknown, although research by Altuntas *et al.* (2002b) suggests the liver toxicity may be related to lipid peroxidation based on an increase in thiobarbituric acid reactive substances (TBARS, an end-product of lipid peroxidation) that was seen in the serum of rats along with increases in several liver enzymes after a single oral dose of methidathion at 8 mg/kg. The levels of TBARS and liver enzymes were reduced in rats treated with both methidathion and vitamins E and C. In a subsequent study, this same research group also observed histopathological lesions in the liver of rats after a single oral dose of methidathion at 8 mg/kg that was ameliorated by administration of vitamins E and C (Gokalp et al., 2003). However, if this mechanism is involved, there must be some species and gender differences in the formation or detoxification of the active metabolites, since the incidence of liver tumors and hepatotoxicity was much higher in male mice compared to female mice and rats of both sexes.

An argument could be made that the increase in mortalities (68% versus 42% in controls) and the high incidence of non-neoplastic lesions in the liver (bile stasis and chronic hepatitis - 98%) in male mice at 100 ppm indicate that this dose level was excessively toxic and the tumor response at this dose level should be disregarded in the evaluation of the carcinogenic potency of methidathion. It is less clear if the severity of hepatotoxicity at 50 ppm was sufficient to disregard the increase in tumors at this dose level. Furthermore, there is inadequate mechanistic data to demonstrate that the excessive toxicity at the high dose was solely responsible for the increase in tumors.

The evidence that methidathion is genotoxic is limited. All the gene mutation studies were negative (4 reverse-mutation assays with *Salmonella typhimurium*, 1 reverse-mutation assay with *Escherichia coli*, and 3 host-mediated assays with mice), except for a gene conversion/forward mutation assay with *Saccharomyces cerevisiae* (Simon and Poole, 1977; Satou *et al.*, 1979; Arni, 1980a,b&c; Strasser, 1980; Arni and Muller, 1981; Lippens *et al*., 1983). None of the gene mutation tests met FIFRA guidelines, however, the negative results

were reproduced in the reverse-mutation assays from several different laboratories over a range of doses with and without metabolic activation, presenting consistent and compelling evidence of the lack of mutagenicity. The reverse-mutation assay is considered a relatively sensitive test for evaluating mutagenic potential. The gene conversion/forward mutation assay is conducted in yeast and, therefore, is considered a poor indicator of mammalian genotoxicity. Furthermore, this positive finding was only available in summary form in a published report so there was insufficient information to evaluate the quality of the study. Two assays for chromosome damage (a dominant lethal assay in mice and an *in vivo* micronucleus assay in Chinese hamster) were negative (Fritz, 1976a and Hool, 1980b). Although the dominant lethal assay met FIFRA guidelines, this assay is considered relatively insensitive. The micronucleus assay is a useful test for evaluating the potential of chemicals to induce chromosomal anomalies. There is a high correlation between agents that induce chromosomal aberrations and micronuclei, however, this study was not of acceptable quality due to an inadequate number of animals scored and no data supporting the sacrifice time. The results were positive in an *in vitro* sister chromatid exchange (SCE) assay with Chinese hamster V79 cell line and equivocal in an *in vivo* SCE assay with Chinese hamsters (Chen *et al.*, 1981; Hool, 1980a). However, neither of these studies were of acceptable quality since the *in vitro* study had limited information provided in this published report and the *in vivo* study had an inadequate number of animals/cells scored. Even if these SCE studies had been of acceptable quality, the toxicological significance of SCEs has not been demonstrated. The six available assays for DNA damage/repair (5 unscheduled DNA synthesis (UDS) assays and 1 rec assay) were all negative (Lippens et al., 1983; Arni, 1980a,b&c; Simmon and Poole, 1977; Satou et al., 1979; Strasser, 1980; Fritz, 1976a; Hool, 1980b; Hertner, 1988 & 1990; Ciba-Geigy, 1982; Tong 1982a&b). Two of the UDS assays met FIFRA guidelines. The UDS assay, however, is not considered a very sensitive assay. Overall, the evidence that methidathion is genotoxic is limited, but its potential to induce chromosomal damage cannot be ruled out. It is noteworthy that chromosomal aberrations were observed in 14 out of 55 agricultural workers examined in Hungry who worked with various pesticides including methidathion (Nehéz *et al.*, 1988).

A few genotoxicity tests were available for several metabolites of methidathion including reverse-mutation assays for 3 metabolites and an *in vivo* micronucleus assay for one metabolite (Arni, 1980d-f; Hool, 1980c). These tests were all negative, but none of these were of acceptable quality. It is possible that there are some genotoxic metabolites of methidathion that have either not been isolated or not been tested thoroughly for genotoxicity. One example may be formaldehyde which is a likely intermediate in the metabolism of the methoxy carbon of the thiadiazole ring to CO_2. Formaldehyde is non-mutagenic to *Salmonella*, although mutagenic to *Drosophila* (Ashby *et al.*, 1985). Formaldehyde is thought to be a locally active carcinogen which could explain the liver tumors if methidathion is metabolized to formaldehyde in the liver (Ashby and Lefevre, 1982). If a genotoxic metabolite is responsible for the carcinogenicity of methidathion then there must be species and gender differences in the metabolism to explain why the liver tumors were only increased in male mice.

U.S. EPA performed a structure-activity relationship search for chemicals with structural similarity to methidathion (Quest *et al.*, 1990). Only two pesticides were identified as structurally similar, prothidathion and lythidathion. No toxicity data were available for these pesticides since they are not registered in the United States.

III.A.5. Quantitative Assessment of Carcinogenic Effects

There is little doubt that the increase in liver tumors in male mice is treatment-related. There was a clear dose-response relationship and an increase in these tumors was seen in male mice in two studies, although one study had major deficiencies (IBT, 1980; Goldenthal, 1986). Furthermore, in the study that met FIFRA guidelines, there was an increase in the multiplicity of tumors at the highest dose level, a possible increase in the proportion of malignant tumors, and a possible reduction in the time to tumor. On the other hand, the weight of evidence for carcinogenicity was limited because it involved a common tumor type in only one tissue site in only one sex of one species. There was no evidence of carcinogenicity in female mice or in two chronic rat studies for methidathion (IBT, 1980; Goldenthal, 1986; Johnston, 1967; Yau *et al.*, 1986). Moreover, there is only evidence of genotoxicity in two tests whose biological significance is uncertain. In addition, there appears to be an association between the incidence of hepatotoxicity and liver tumors.   The U.S. EPA has classified methidathion as a Group C carcinogen (i.e., possible human carcinogen), but did not consider the evidence sufficient to quantitate a carcinogenic potency factor (Quest *et al.*, 1990). The FAO/WHO Joint Meeting on Pesticide Residues (JMPR) also did not consider the evidence sufficient to warrant calculating a carcinogenic potency factor (Caris, 1992). Although DPR toxicologists agree that the weight of evidence is limited, the mode of action is uncertain. Direct DNA interaction could not be ruled out since its genotoxicity potential has not been thoroughly tested in well-conducted, sensitive assays with mammalian cells.   The association between the hepatotoxicity and the liver tumors suggests secondary DNA effects from a possible increase in cell proliferation; however, there were no mechanistic studies to support this possibility. An increase in lipid peroxidation may be another possible mechanism, but there were no studies demonstrating a connection between the lipid peroxidation and the liver tumors. The U.S. EPA Guidelines for Carcinogen Risk Assessment recommends that, when there is insufficient data on the mode of action, a linear approach be used as a default (U.S. EPA, 2005). Consequently, a linear approach was used to evaluate the carcinogenic potential of methidathion.

The combined incidence of hepatocellular adenomas and carcinomas in male mice in the carcinogenicity study conducted by Goldenthal (1986) was used to estimate carcinogenic potency. Due to the reduced survival of male mice at the highest dose tested, 100 ppm, the multistage-Weibull time-to-tumor model, MULTI-WEIB, was used to estimate the carcinogenicity potency. The dosages for male mice (0, 0.4, 1.4, 6.7 or 13.1 mg/kg/day) were first converted to human equivalent dosages (0, 0.06, 0.20, 0.97 or 1.90 mg/kg/day, respectively) by multiplying by an interspecies scaling factor of body weight to the 3/4 power $[(BWt_A/BWt_H)^{0.25} = (0.030 \text{ kg}/70 \text{ kg})^{0.25} = 0.144]$ (U.S. EPA, 2005). The estimated carcinogenic potency for methidathion ranged from 0.34 (mg/kg/day)$^{-1}$ (maximum likelihood estimate or MLE) to 0.53 (mg/kg/day)$^{-1}$ (95% upper bound or 95% UB).

The estimated carcinogenic potency for methidathion expressed as unit risk is shown in Table 24 relative to other chemicals for which there are carcinogenic potency estimates that have been approved by the Scientific Review Panel (SRP) for Toxic Air Contaminants (TACs). The unit risk estimate for methidathion was 1.5 x 10^{-4} (μg/m^3)$^{-1}$ at the 95% UB.

As with chronic toxicity, there were no carcinogenicity studies for the methidathion oxon, the presumed active metabolite for the neurological effects. However, it is uncertain if the oxon

Table 24. Carcinogenic Potency for Methidathion Relative to Other Carcinogenic Potencies Approved by the Scientific Review Panel for Toxic Air Contaminants[a]

Compound	Unit Risk $(\mu g/m^3)^{-1}$	Potency $(mg/kg/day)^{-1}$
Dioxins	3.8×10^1 to 3.8×10^0	1.3×10^4 to 1.3×10^5
Chromium IV	1.5×10^{-1}	5.1×10^2
Asbestos	6.3×10^{-2}	2.2×10^2
Dibenzo[a,h]pyrene	1.1×10^{-2}	3.9×10^1
1,6-Dinitropyrene	1.1×10^{-2}	3.9×10^1
6-Nitrochrysene	1.1×10^{-2}	3.9×10^1
Cadmium	4.2×10^{-3}	1.5×10^1
Inorganic Arsenic	3.3×10^{-3}	1.2×10^1
Benzo[a]pyrene	1.1×10^{-3}	3.9×10^0
Dibenzo[a,e]pyrene	1.1×10^{-3}	3.9×10^0
7H-Dibenzo[c,g]carbazole	1.1×10^{-3}	3.9×10^0
1,8-Dinitropyrene	1.1×10^{-3}	3.9×10^0
5-Methylchrysene	1.1×10^{-3}	3.9×10^0
Diesel Exhaust	3×10^{-4}	1.1×10^0
Nickel	2.6×10^{-4}	9.1×10^{-1}
1,3-Butadiene	1.7×10^{-4}	6.0×10^{-1}
Methidathion	**1.5×10^{-4}**	**5.3×10^{-1}**
Benz[a]anthracene	1.1×10^{-4}	3.9×10^{-1}
Benz[b]fluoranthrene	1.1×10^{-4}	3.9×10^{-1}
Indeno[1,2,3-cd]pyrene	1.1×10^{-4}	3.9×10^{-1}
Dibenzo[a,h]acridine	1.1×10^{-4}	3.9×10^{-1}
1-Nitropyrene	1.1×10^{-4}	3.9×10^{-1}
4-Nitropyrene	1.1×10^{-4}	3.9×10^{-1}
Ethylene Oxide	8.8×10^{-5}	3.1×10^{-1}
Vinyl Chloride	7.8×10^{-5}	2.7×10^{-1}
Ethylene Dibromide	7.1×10^{-5}	2.5×10^{-1}
Carbon Tetrachloride	4.2×10^{-5}	1.5×10^{-1}
Naphthalene	3.4×10^{-5}	1.2×10^{-1}
Benzene	2.9×10^{-5}	1.0×10^{-1}
Ethylene Dichloride	2.1×10^{-5}	7.2×10^{-2}
DEF	1.6×10^{-5}	5.9×10^{-2}
Inorganic Lead	1.2×10^{-5}	4.2×10^{-2}
Chrysene	1.1×10^{-5}	3.9×10^{-2}
2-Ntirofluorene	1.1×10^{-5}	3.9×10^{-2}
Perchloroethylene	5.9×10^{-6}	2.1×10^{-2}
Formaldehyde	6.0×10^{-6}	2.1×10^{-2}
Chloroform	5.3×10^{-6}	1.9×10^{-2}
Acetaldehyde	2.7×10^{-6}	1.0×10^{-2}
Trichloroethylene	2.0×10^{-6}	7.0×10^{-3}
Methylene Chloride	1.0×10^{-6}	3.5×10^{-3}
Methyl *tert*-butyl ether (MTBE)	2.6×10^{-7}	1.8×10^{-3}

a   Unit risk values from OEHHA (2005).

is the active metabolite for the carcinogenicity observed with chronic exposure to methidathion. Therefore, it was assumed that the carcinogenic potency of the oxon was equivalent to the parent compound.

III.B. EXPOSURE ASSESSMENT

III.B.1. Dietary Exposure

III.B.1.a. Introduction

The Department of Pesticide Regulation conducts acute and chronic dietary exposure assessments to evaluate the risk of human exposure to a pesticide in food (Bronzan and Jones, 1989). Two separate approaches are used to estimate the risk: (1) risk is determined for the total dietary exposure based on measured residue levels on all label-approved commodities and (2) risk is estimated for exposure to an individual commodity at the tolerance level (see Tolerance Assessment section).

Dietary exposure is a product of the amount of food that is consumed and the concentration of the pesticide residue in that food. The total exposure in an individual's diet during a defined period of time (e.g., a day) is the sum of exposure from all foods (in various forms and as ingredients in food items) consumed within that period:

$$Exposure = \sum_{i=1}^{n}\left(residue_i \; x \; consumption_i \; of \, foods\right)$$

where n is the number of food items in the diet.

Accordingly, two distinct pieces of information are required to assess the dietary exposure: (1) the amount of the pesticide residue on food and (2) the food consumption. For estimating the acute exposure, the highest residue values at or below the tolerance, or the distribution of residues are considered. In contrast, for chronic exposure, the mean residue values are appropriate. Finally, acute dietary exposure is calculated on a per-user basis (i.e., including in the distribution of exposure only the days of survey that at least one commodity with potential pesticide residues is consumed). Chronic dietary exposure to pesticides is generally calculated using per-capita mean consumption estimates to include the entire population.

III.B.1.b. Dietary Exposure

The acute and chronic dietary exposure analyses were conducted using the Dietary Exposure Evaluation Model- Food Commodity Ingredient Database (DEEM-FCID™, version 2.03) software developed by Exponent, Inc., in which the food translations are based on EPA/USDA FCID recipe set as of August 2002. DEEM-FCID™ calculates acute and chronic exposure estimates for 33 different population subgroups, including nursing or non-nursing infants less than 1 year old, children ages 1-2, 3-5 or 6-12 years old, youth 13-19 years old, pregnant or nursing women, and adults 50 years and older. The Acute Analysis module also allows for calculation of exposure for custom populations, such as workers, ages 16 years and older. The Acute Analysis module estimates the distribution of exposure per user-day (i.e., the

percentile exposure for only individuals that consume at least one commodity of concern on the day of survey). The Acute Analysis estimates exposure either using a deterministic approach (i.e., a single residue value or point estimate for each commodity) or a probabilistic approach (i.e., Monte Carlo method where residue and consumption values are randomly selected from different distribution curves for each commodity). In the deterministic approach, the distribution of exposure is calculated by multiplying the single residue value and the consumption distribution. In the probabilistic approach, the distribution of exposure is calculated by multiplying the distribution of residue and the distribution of consumption (Petersen *et al.*, 2001). Since the probabilistic approach is more time consuming, it is only used if the margins of exposure are inadequate using the deterministic approach and/or if there is sufficient residue data to describe the distributions. The Chronic Analysis estimates the annual average exposure per capita using point estimates that represent the average residue values. The chronic analysis estimates the average exposure of all surveyed individuals in a population subgroup at the average pesticide residue. The residue values for both acute and chronic exposure can be adjusted by percent crop treated; however, DPR generally only adjusts the acute residue values for percent crop treated when a probabilistic approach is used.

In the Acute Analysis, the Critical Exposure Commodity (CEC) analysis provides consumption records for individuals at the high end of dietary exposure (in the top 5% or less). The CEC analysis also identifies the commodities contributing to the high end of the dietary exposure. The records include the amount of food(s) consumed, body weight, age, residue values and the exposure estimate by food. The CEC analysis provides the means to identify high contributing commodities and any apparent error in the consumption database (e.g., unreasonable body weight at a given age). A detailed description on the CEC analysis is provided in the DEEM™ manual (Kidwell et al., 2001). In the Chronic Analysis, the Critical Commodity Contribution (CCC) analysis performs a similar analysis; however, with chronic exposure the contributing commodities identified are based on the average consumption of the population not the consumption at the high end.

III.B.1.c. Consumption Data

The United States Department of Agriculture (USDA) directs the Continuing Survey of Food Intakes by Individuals (CSFII), which analyzes the food intake and adequacy of the diets of various population subgroups.   The purpose of the CSFII is to analyze food intake every few years to provide up-to-date information on the adequacy of the diets of various population groups and early indications of dietary changes. Individual intake data are collected using both a 1-day recall and a 2-day record protocol. The surveys were conducted in all months of the year. In each year, approximately 5,500 participants in 62 geographical areas were surveyed. The consumption data used in this risk assessment were the CSFII 1994-98 data which were collected from January 1994 to February 1997 (referred to as 1994-96) and from December 1997 to December 1998 (referred to as 1998). This is the preferred consumption data since it is the most recent and representative consumption data. These data provide information on 2-day food intake by 20,607 individuals of all ages from 62 geographical areas. The 1994-96 data included 4,253 children, ages 0 to 9 years old. The 1998 CSFII data included an additional 5,559 children of the same age to increase the database for dietary patterns of infants and children in response to the Food Quality Protection Act of 1996.

III.B.1.d. Residue Data

The federal and state monitoring programs analyze food samples at produce markets and chain store distribution centers close to the consumer level. Recent, multi-year (3-5 years) residue data are preferred. The USDA Pesticide Data Program (PDP) is the most representative monitoring residue data because it is designed to obtain residue data for risk assessments. The PDP samples are collected in ten states, including California. When a sufficient number of samples (e.g., 30 or more) is analyzed in California, the California only data can be used instead of the nationwide data. Often the limit of detection (LOD) for the California laboratory is lower than the other USDA national contract laboratories.

DPR has two major sampling programs: priority pesticide and marketplace surveillance. DPR monitoring programs may not be representative because they focus on commodities with known violations (DPR, 1994-2002). In addition, the residue LOD may be high. However, data from the DPR monitoring programs may be useful when PDP data are not available.

The U.S. Food and Drug Administration (FDA) Regulatory Residue Monitoring Program analyzes domestic and imported foods for pesticide residue to enforce the tolerances set by U.S. EPA. Thus, the residue data may not be representative. In addition, residue information may be incomplete for conducting a distribution (e.g., only a range of pesticide concentrations on a particular food is provided; LOD is not indicated, etc.). FDA data may be useful when PDP and DPR data are not available.

The monitoring studies may also be conducted by manufacturers or task force groups of a particular pesticide(s). In most cases, these food surveys are designed to determine the residues on specified commodities in response to the U.S. EPA Data Call-In Notices. Samples are usually collected at the produce markets, chain store distribution centers and/or at the farm gates. The task force studies most closely approximates the PDP sampling and may be representative in that they analyze a large number of samples of high consumption commodities and generally have a low LOD. However, the duration of task force studies is generally short (e.g., 1 year) unlike the multi-year analysis by the PDP.

Other sources for residue data include use of surrogate commodities, field trial studies, and tolerances. When residue data are not available from monitoring studies, residues reported for similar foods can be used as surrogates. The choice of the most appropriate surrogate commodity should be based on the classification or grouping of related raw agricultural commodities (RAC) into crop groups, established in 40 CFR 180.40, and according to the agricultural practices specified in the product label. The field trial studies are submitted to DPR by pesticide manufacturers for support in the setting of tolerances (U.S. EPA, 1982). These studies are usually conducted under the highest application rate permitted by the label conditions and, as a result, the residue data may likely consist entirely of upper-end pesticide concentrations. The residue levels are set at the tolerance level when no monitoring or field trial data are available and there is no suitable surrogate commodity. The tolerance is the legal maximum residue concentration of a pesticide on a RAC or processed food. The tolerances are established by the U.S. EPA at levels necessary to allow for the maximum application rate and frequency which most likely do not reflect the actual pesticide use pattern. Therefore, use of the tolerances for residue levels will most likely overestimate the residue levels.

Since dietary exposure assessments can be very labor intensive, DPR toxicologists use a tiered approach to the dietary exposure assessment with additional refinements when the risk for adverse health effects in humans is considered too high based on grossly overestimated exposure levels from a simplified approach. Some of the more common refinements to the dietary exposure estimate are: 1) use of residue monitoring data where commodities are analyzed closer to the point of consumption, 2) use of residue monitoring data with a lower LOD (which is important when no residues are detected), and 3) accounting for the percent of a crop that is treated with a pesticide. The initial dietary analysis for methidathion using the tolerances was considered as Tier 1. The tiered approach for acute dietary exposure begins with the point estimates, which are generally less time-consuming. Since the estimated acute and chronic dietary exposure appeared too high based on overestimated exposure (see criteria described in the Risk Characterization and Risk Appraisal sections), the dietary exposure was further refined.

In the Tier 2 analysis, the residue values from DPR's and PDP's market basket surveys were considered. PDP data were given preference over DPR data, when available, for the following reasons: 1) the commodities were analyzed closer to the point of consumption than DPR, 2) the commodities are usually washed and peeled if normally consumed that way, and 3) the LODs were usually lower. When sufficient data were available (i.e., > 100 samples), PDP data from California were used exclusively. The PDP data were limited in that most commodities were analyzed for only 1-3 years. The acute and chronic residue values used from the PDP data are summarized in Table 25. The acute residue value was the highest detected residue value if a point estimate was used. In 1995, U.S. EPA reviewed the metabolites of

Table 25. Methidathion Residues in Raw Agricultural Commodities from USDA's PDP Monitoring Programs

Raw Agricultural Commodity	N	Acute Value[a] (ppm)	Chronic Value[b] (ppm)	Years & Percent Crop Treated
Apple, whole	127	0.007	0.00035	2002, CA only, LOD = 0.007, PCT = 15% (acute), 10% (chronic)
Cherries	118	0.004	0.0001	2000 & 2001, CA only, LOD = 0.004, PCT = 10% (acute), 5% (chronic)
Nectarine	153	0.004	0.0001	2000 & 2001, CA only, LOD = 0.004, PCT = 10% (acute), 5% (chronic)
Orange, whole	333	0.007	0.000168	2000 & 2001, CA only, LOD = 0.004, PCT = 10% (acute), 5% (chronic)
Peach	254	0.004	0.000065	2001 & 2002, CA only, LOD = 0.001-2, PCT = 15% (acute), 10% (chronic)
Pear	187	0.004	0.0001	2003, National, LOD = 0.004, PCT = 10% (acute), 5% (chronic)

a   The acute value represents the highest residue level detected in any sample. When no residues were detected the acute value is the LOD. When a Monte Carlo analysis was done for a commodity, the PCT was used to set some of the non-detects to zero. The remaining non-detects were set at ½ of the LOD.
b   When no residue was detected, ½ of the LOD was used in calculating the chronic value for a commodity.
LOD   Limit of detection
PCT   Percent crop treated

methidathion that were identified in plant and livestock metabolism studies and found that the oxon was present in considerably lower concentrations than the parent (U.S. EPA, 1995). Furthermore, the toxicity of the metabolite could be accounted for in the toxicity studies with the parent. Therefore, the tolerance for methidathion included only the parent compound. The PDP data did not include the methidathion oxon in the analysis of these commodities for residues, presumably because it was not included in the tolerance.

Due to unacceptable exposures from the Tier 2 analysis, the acute exposure was further refined in a Tier 3 analysis by performing a Monte Carlo analysis on the commodities with high consumption.   This included all the commodities with PDP data and two commodities (apricots and plum) with DPR data. Instead of assuming that all commodities were 100% treated, the percent crop treated (PCT) was taken into consideration in the residue files for the Monte Carlo analysis by setting some of the samples with non-detectable residues to zero rather than ½ of LOD. The PCT estimates were calculated from data available from various state and federal regulatory agencies. The acreage treated in California with methidathion was obtained from DPR's Pesticide Use Report (DPR, 2000, 2002 & 2005). The acreage bearing or harvested in California was obtained from agricultural statistics available from the California Department of Food and Agriculture (CDFA) or U.S. Department of Agriculture (USDA) (CDFA, 2004 and USDA, 2000, 2002 & 2004). Generally, the years covered were 1999, 2001 and 2003 since reports for these crops were usually only generated every other year. The highest PCT in these 3 years was used for acute exposure while the average PCT for these 3 years was used for chronic exposure (see Table 25 for specific values used). PCT estimates were rounded up to the nearest 5% due to the uncertainty in these estimates.

Generally, PDP data were not available for processed commodities. There was one exception: pear juice. However, these data were not used because generally DPR does not adjust blended commodities like juice for PCT. Since there were no detections in either the whole pears or pear juice and their LODs were the same, using the pear juice data would result in a higher exposure estimate for pear juice since it is being determined entirely by the LOD. Therefore, the whole pear data was used to estimate exposure for pear juice. When no residue data were available for processed commodities, residues were estimated from the fresh commodity by multiplying by the adjustment factors that account for the loss of water. The following default adjustment factors from DEEM™ (version 7.87) were used in DEEM™-FCID (version 2.03): apple, dried - 8; apple, juice - 1.3; apricot, dried - 6; cherry, juice - 1.5; grapefruit - 2.1; lemon, juice - 2.0; lime, juice - 2.0; orange, juice - 1.8; peach, dried - 7; pear, dried - 6.25; plum/prune, dried - 5; plum/prune, juice - 1.4; tangerine, juice - 2.3. If the residues in processed commodities were higher than the tolerance for the RAC, they would be considered illegal since no tolerances were established for these commodities.   Therefore, if the resultant residue in the processed commodity was greater than the tolerance, the residue was set to the tolerance and the adjustment factor was set to 1.

There were several crops for which there were DPR monitoring data, but no PDP monitoring data. The residues for these commodities (apricots, artichokes, kiwifruit, mangos and plums) are summarized in Table 26. No residues were detected in any of the samples tested for all five commodities. The LODs for these five commodities were all 0.05 ppm which is an order of magnitude higher than the LODs for the PDP data. DPR also did not analyze these commodities for the methidathion oxon.

Table 26. Methidathion Residues in Raw Agricultural Commodities from DPR's Monitoring
Programs[a]

Raw Agricultural Commodity	N	Acute Value[b] (ppm)	Chronic Value[c] (ppm)	Years & Percent Crop Treated
Apricot	151	0.05	0.025	2000-2004, LOD = 0.05 PCT = 5% (acute and chronic)
Artichoke	131	0.05	0.025	2000-2004, LOD = 0.05 PCT = 100% (chronic only)
Kiwi fruit	108	0.05	0.025	2000-2004, LOD = 0.05 PCT = 10% (chronic only)
Mango	184	0.05	0.025	2000-2204, LOD = 0.05 PCT = 100% (chronic only)

Plum	329	0.05	0.025	2000-2004, LOD = 0.05
				  PCT = 15% plum (acute and chronic)
				     = 5% prune (acute and chronic)

a	Residues from DPR's monitoring sampling programs 1 (priority pesticide) and 4 (marketplace surveillance).
b	The acutevalue represents the highest residue level detected in any sample. When no residues were detected the acute value was set at the LOD.
c	When no residue was detected, ½ of the LOD was used in calculating the chronic value for a commodity.

For some commodities where there was no PDP monitoring data (grapefruit, lemons, limes, pummelos and tangerines), a surrogate crop (oranges) was used instead. The PCT for oranges (10% acute, 5% chronic) was used for these commodities. Apple data was used as surrogate for crabapple, quince and loquat data since they were also pome fruits. The PCT for apples (15% acute and 10% chronic) was also used for these other pome fruits.

For a few commodities where there was no monitoring data and no good surrogate crop, field trial data was used when available. This was done with safflower and sunflower residues because when ½ of the tolerance was used for the chronic residue value, the carcinogenic risk estimates were unacceptable. A commodity contribution analysis indicated that these commodities contributed to more than 75% of the chronic exposure estimate in the U.S. population when the residue was set at ½ of the tolerance. Field trial data for these commodities had been submitted to DPR. The residue for methidathion in safflower was less than the LOD, 0.01 ppm, in several studies where it was applied at the maximum label-approved application rate (0.5 lb/acre) and sampled after the minimum pre-harvest interval (28 days) (Ciba-Geigy, 1977). For sunflower, the average residue in the five residue studies was 0.11 ppm with a high value of 0.22 ppm at the maximum label-approved application rate (0.5 lb/acre) and sampled after the minimum pre-harvest interval (50 days) (Mattson and Kahrs, 1974). Processing data indicated that 55%, 20% and 20% of the residues were in the hulls, meal and oil of sunflower seeds. Assuming that the hulls are not normally consumed by humans, the residue in whole seeds was multiplied by a processing factor of 45%. A processing factor of 20% was multiplied by the residue in whole seeds to get the residue in oil. The residue in these crops could have been further refined by the PCT, but it was not possible to get an accurate estimate of the acres harvested in CA from CDFA's or USDA's agricultural statistics due to the small number of acres

planted. Consequently, the acres harvested in California were combined with other states or with other seed oil crops in California. It appears the PCT for sunflower is quite low since there was no reported use of methidathion on sunflowers in California in 4 of 5 years between 1999 and 2003. However, since there was insufficient information available to calculate a PCT for safflowers and sunflowers the PCT for these crops was assumed to be 100%.

If there were no monitoring data, appropriate surrogate data or field trial data, the residue levels were assumed to be at the tolerance level for acute exposure and ½ of the tolerance level for chronic exposure (CFR, 2004). The tolerance levels were used for the following commodities: nuts (0.05 ppm), cottonseed (0.2 ppm), olive (0.05 ppm), starfruit (0.1 ppm), sugar apple (0.2 ppm).   The PCT assumed for these commodities was 100% except for the following commodities with chronic exposure: almonds (5%), cottonseed (1%), olive (5%), pecan (10%), pistachio (10%), and walnut (5%) based on data from CDFA's agricultural statistics and DPR's PUR for these crops.

A Tier 3 analysis was performed for the chronic dietary exposure due to the unacceptable carcinogenic risk with a Tier 2 analysis. Point estimates are still used in the Tier 3 analysis with the chronic exposure analysis, but residues are refined by taking PCT into consideration as well as additional processing factors. Unlike acute exposure analysis, the point estimate in the chronic exposure analysis represents the average residue rather than the highest. The PCT is taken into consideration in the chronic residue values accordingly:

a.   When a default value was used (e.g., ½ tolerance or LOD) either due to no residue data or no detectable residues in all the samples, the default value was multiplied by the average PCT.

b.   When residues were detected, some of the non-detectable residues were replaced by zeros based on the average PCT according to the following formula:

$$AR = \frac{\sum R_{N1} + \left(\frac{LOD}{2} x N_2\right) + \left(0 x N_3\right)}{N} = \frac{\sum R_{N1} + \left[\frac{LOD}{2} x \left(N x PCT - N_1\right)\right]}{N}$$

where, AR = average residue, LOD= detection limit, R_{N1} = residue for the number of samples (N_1) in which residues were detected, N_2= the number of samples theoretically can contain residues with N_2=N x PCT – N_1 and residues assumed at ½ LOD, N_3= number of samples theoretically contain no residues with N_3=N x (1-PCT) and residue assumed at zero.

III.B.1.e. Acute Dietary Exposure Estimates

As mentioned, a tiered approach was used in the dietary exposure assessment. The results of the Tier 3 analysis are shown in Table 27. The 99.9[th] percentile of the user-day exposure for all specific population subgroups is presented. A user-day is any day in which at least one food form from the label-approved commodities is consumed. Based on the 99.9[th] percentile, the potential acute dietary ingestion of methidathion from all labeled uses ranged

from 0.175 µg/kg/day in adults 50 years and older to 0.780 µg/kg/day in children 1-2 years old (Table 27, Appendix B).

III.B.1.f. Chronic Dietary Exposure Estimates

A Tier 3 analysis was also performed for chronic dietary exposure assessment taking into consideration the PCT and processing factors in addition to the residue monitoring data.   A Tier 3 analysis was necessary with methidathion due to the carcinogenicity concern. The mean potential chronic dietary exposure ranged from 0.001 µg/kg/day for adults 20 years and older to 0.019 µg/kg/day for non-nursing infants less than 1 year old (Table 27, Appendix B). For estimating the lifetime exposure, these age-based exposures should be amortized over a lifetime of 70 years. With DEEM™-FCID, the amortized lifetime exposure was assumed to be the same as the chronic exposure output for the "U.S. population" which contains all the age-based population subgroups.

Table 27. Potential Acute and Chronic Dietary Exposures to Methidathion Residues

Population Subgroup	Exposure Dosage (µg/kg/day)	
	Acute[a]	Chronic[b]
U.S. Population	0.329	0.002
Western Region	0.351	0.003
Nursing Infants (< 1 yr)	0.275	0.005
Non-nursing Infants (< 1 yr)	0.504	0.019
Children (1-2 yrs)	0.780	0.007
Children (3-5 yrs)	0.603	0.005
Children (6-12 yrs)	0.474	0.003
Youth (13-19 yrs)	0.334	0.002
Adults (20-49)	0.214	0.001
Adults (50+ yrs)	0.175	0.001
Females (13-49 yrs)	0.215	0.002
Females (13+ yrs, pregnant/not nursing)	0.294	0.005
Females (13+ yrs, nursing)	0.298	0.004
Workers (16+ yrs)	0.196	NA

a   Based on 99.9[th] exposure percentile for each user-day population subgroups.
b   Based on the annual average daily dosage for each population subgroups.

III.B.2. Drinking Water Exposure

III.B.2.a. Drinking Water Residues

Although methidathion has been detected in 2% of surface water samples collected by DPR between June 1999 and September 2003 (Starner, 2005), it has not been detected by DPR in any wells tested between 1986 and 2004 (DPR, 2003b & 2004). It has also not been detected in drinking water sampled by PDP from 2001 to 2003 (USDA, 2003-2005). PDP did not begin testing drinking water until 2001. The PDP drinking water samples were collected at water treatment facilities. In 2001, samples were taken from 10 sites in California and 11 sites in New York representing major metropolitan areas, agricultural regions and highly protected

watersheds. In 2001, the LODs for methidathion and its oxon were 10 and 25 ppt, respectively, for the California sites. In 2002, 6 new sites (Kansas - 2, Colorado - 2, Texas - 1, California - 1) were added to the sites in New York and California tested in 2001. These same sites were tested again in 2003. Source waters for the PDP finished drinking water were primarily surface water. Although the range of the LODs for methidathion and its oxon increased with the addition of the new sites in 2002, the California LODs decreased to 0.009 ppb for the parent and 0.012 ppb for the oxon. Since PDP had the lowest LODs and the drinking water was from a mixture of sources, the California PDP data were selected to evaluate drinking water exposure to methidathion over DPR's surface water monitoring data which does not necessarily represent drinking water sources.

III.B.2.b. Drinking Water Exposure Estimates

        A Tier 2 analysis was done for both the acute and chronic drinking water exposure assessment using point estimates.   In the absence of any toxicity data for the oxon, it was assumed that the oxon was equivalent to the parent in toxicity. Since there were no detectable residues in any of the PDP drinking water samples, the California LODs for the parent (0.009 ppb) and the oxon (0.012 ppb) from the more recent years were added together for a combined worse case residue estimate of 0.021 ppb to evaluate acute drinking water exposure. To evaluate chronic drinking water exposure ½ of this LOD (0.011 ppb) was used. At the 99.9th percentile of user-day exposure, the potential acute exposure to methidathion and its oxon in drinking water ranged from 0.002 to 0.012 μg/kg/day with the highest exposure estimate for non-nursing infants less than 1 year old (Table 28). The mean potential chronic drinking water exposure for all population subgroups was less than 0.001 μg/kg/day for all population subgroups except non-nursing infants less than 1 year whose exposure estimate was 0.001 μg/kg/day (Table 28).

Table 28.   Potential Acute and Chronic Drinking Water Exposure to Methidathion for Selected Population Subgroups

Population Subgroup	Exposure Dosage (μg/kg/day)	
	Acute[a]	Chronic[a]
U.S. Population	0.004	< 0.001
Western Region	0.005	< 0.001
Nursing Infants (< 1 yr)	0.008	< 0.001
Non-nursing Infants (< 1 yr)	0.012	0.001
Children (1-2 yrs)	0.004	< 0.001
Children (3-5 yrs)	0.004	< 0.001
Children (6-12 yrs)	0.002	< 0.001
Youth (13-19 yrs)	0.003	< 0.001
Adults (20-49 yrs)	0.003	< 0.001
Adults (50+ yrs)	0.002	< 0.001
Females (13-49 yrs)	0.003	< 0.001
Females (13+ yrs/pregnant/not nursing)	0.002	< 0.001
Females (13+ yrs/nursing)	0.002	< 0.001
Workers (16+ yrs)	0.003	NA
a Based on 99.9th exposure percentile for each user-day population subgroups.		
b Based on the annual average daily dosage for each population subgroups.		

III.B.c. Combined Dietary and Drinking Water Exposure

The same dietary and drinking water residues used for the separate dietary and drinking water assessments were used for the combined assessment for acute and chronic exposures. The combined drinking water and dietary exposure estimates are summarized in Table 29. The combined exposure to methidathion in drinking water and food is not equal to the sum of the dietary and drinking water exposures because each of these estimates is based on a distribution among consumers which changes as commodities or water are added or removed.   In fact, the combined exposure estimates at the 99.9th percentile were lower than for food alone at the same percentile primarily because the drinking water component of the total exposure was very small and the number of users increased when drinking water was added. Based on the combined acute exposure to methidathion in drinking water and food ranged from 0.172 to 0.777 µg/kg/day. Children ages 1 to 2 years old had the highest potential combined acute exposure. The mean potential combined chronic exposure for all population subgroups ranged from 0.002 to 0.020 µg/kg/day. The population subgroup with the highest potential combined chronic exposure was non-nursing infants less than 1 year old.

Table 29. Potential Combined Acute and Chronic Dietary and Drinking Exposure to Methidathion for Selected Population Subgroups

Population Subgroup	Exposure Dosage (µg/kg/day)	
	Acute[a]	Chronic[b]
U.S. Population	0.321	0.002
Western Region	0.339	0.003
Nursing Infants (< 1 yr)	0.253	0.006
Non-nursing Infants (< 1 yr)	0.503	0.020
Children (1-2 yrs)	0.777	0.008
Children (3-5 yrs)	0.589	0.006
Children (6-12 yrs)	0.478	0.003
Youth (13-19 yrs)	0.335	0.002
Adults (20-49 yrs)	0.214	0.002
Adults (50+ yrs)	0.172	0.002
Females (13-49 yrs)	0.214	0.002
Females (13+ yrs/pregnant/not nursing)	0.295	0.006
Females (13+ yrs/nursing)	0.299	0.005
Workers (16+ yrs)	0.190	NA

a   Based on 99.9th exposure percentile for each user-day population subgroups.
b   Based on the annual average daily dosage for each population subgroups.

III.B.4. Occupational Exposure

There are no residential, industrial or institutional uses of methidathion. A number of studies were available in which agricultural worker exposure to methidathion was evaluated; however, none of these studies were acceptable for reasons explained in the Exposure Assessment Document (EAD) for methidathion (Beauvais, 2006). Therefore, exposure estimates

for handlers were derived using the Pesticide Handler Exposure Database (PHED) developed by U.S. EPA, Health Canada and the American Crop Protection Association. PHED provides mean exposure estimates, but does not provide sufficient information to allow calculation of an upper bound estimate. A method for approximating the upper bound from PHED data was developed by the Worker Health and Safety Branch which multiplied the mean by constants that increased as the number of observations decreased (Powell, 2002). The 95th percentile is used for acute exposure to estimate the highest exposure an individual may realistically experience while performing label-approved activities. When the acute exposure estimate is based on surrogate data (i.e., PHED), the 90% upper confidence limit on the 95th percentile is used to account for some added uncertainty with using surrogate data. The acute exposure estimate is referred to as the Absorbed Daily Dosage (ADD). Default assumptions of 50% dermal absorption, 100% inhalation absorption and 70 kg body weight were used in the calculation of the ADD. The default dermal absorption value is based on a review of dermal absorption of several chemicals (Donahue, 1996). The default inhalation absorption was used in the absence of any chemical specific data. The ADDs for handlers ranged from 0.0034 mg/kg/day for mixer/loader/-applicators (M/L/As) using low-pressure handwands to 5.86 mg/kg/day for airblast applicators (Table 30).

For seasonal and chronic exposure estimates, the 90% upper confidence limit on the arithmetic mean estimate was used to account for the uncertainty due to using surrogate data. The seasonal exposure estimate is referred to as the Seasonal Absorbed Daily Dosage (SADD). The SADD represents the mean daily exposure during the high-use season. The seasonal and annual exposures are estimated to occur over 1, 1 and 2 months for aerial, airblast and groundboom activities, respectively. No seasonal or annual exposures were anticipated for backpack sprayer and low-pressure handwand activities. The SADDs for handlers ranged from 0.044 mg/kg/day for groundboom applicators to 1.55 mg/kg/day for aerial applicators (Table 30). The chronic exposure estimate or Annual Average Daily Dosage (AADD) is the SADD multiplied by the annual use months per year divided by the number of months per year. The AADDs for handlers ranged from 0.004 mg/kg/day for airblast mixer/loaders (M/Ls) to 0.129 mg/kg/day for aerial applicators. The Lifetime Average Daily Dosage (LADD) was calculated to estimate carcinogenic risk for workers. The LADD is calculated by multiplying the AADD by 40 years of work in a lifetime and dividing it by 75 years in a lifetime. The LADDs for handlers ranged from 0.002 mg/kg/day for airblast M/Ls to 0.069 mg/kg/day for aerial applicators.

The ADDs for field workers were calculated from dislodgeable foliar residues (DFRs) and transfer factors (TFs) using Equation 3 described in the EAD for methidathion (Beauvais, 2006). The default assumptions of 50% dermal absorption, an 8 hr workday and a 70 kg body weight were used in this equation. The ADDs were calculated using DFRs that corresponded to the expiration of the REIs (REI = 48 hrs, except for harvesting and thinning of citrus which was 30 days). The ADDs ranged from 0.0007 mg/kg/day for harvesting/thinning of citrus to 0.093 mg/kg/day for scouting in cotton and safflower fields (Table 30). The DFRs used in calculating the SADDs corresponded to the REI plus 7 days for most activities (i.e., DFRs for 9 days), except for thinning and harvesting of citrus in which the DFRs corresponded to the REI plus 10 days (i.e, DFRs for 40 days). The SADDs for field workers ranged from 0.0007 mg/kg/day for thinning of artichokes to 0.0045 mg/kg/day for scouting in cotton and safflower fields. The AADDs for field workers were calculated as they were for handlers by amortizing the SADDs

Table 30. Estimated Exposure Dosages for Methidathion in Agricultural Workers[a]

Exposure Scenarios	Acute ADD[b] mg/kg/day	SADD[c] mg/kg/day	AADD[d] mg/kg/day	LADD[e] mg/kg/day
Handlers[f]				
Aerial				
M/L[g]	1.15	0.460	0.038	0.020
Applicator	4.65	1.55	0.129	0.069
Flagger	1.90	0.475	0.040	0.021
Airblast				
M/L	0.131	0.053	0.004	0.002
Applicator	5.86	1.46	0.122	0.065
Groundboom				
M/L	0.158	0.063	0.011	0.006
Applicator	0.177	0.044	0.007	0.004
Backpack sprayer				
M/L/A[h]	0.191	NA	NA	NA
Low-pressure handwand				
M/L/A	0.0034	NA	NA	NA
Field Workers[i]				
Scouting in cotton/safflower	0.093	0.0045	0.0011	0.0006
Harvesting/thinning citrus	0.007	0.0024	0.0008	0.0004
Thinning artichokes	0.014	0.0007	0.0001	0.00006

a   Exposure estimates from Table 10-12 in the Exposure Assessment Document (EAD) for methidathion by Beauvais (2006).
b   ADD = Acute Absorbed Daily Dosage. For handlers, acute ADD = [(short-term exposure) x (acres/day) x (rate lb AI/acre)] / (70 kg body weight) fro handlers. The short-term exposure is derived from Pesticide Handlers Exposure Database (PHED, 1995) using the 90% upper confidence limit on the 95th percentile. Acres treated per day assumptions differed for each application method. The acres applied per day were 350, 40 and 80 for aerial, airblast and groundboom scenarios, respectively. The application rates were 5, 5 and 3 lbs/acre for aerial, airblast and groundboom scenarios, respectively.   The application rate and acres applied are not applicable to backpack sprayer and low-pressure handwand scenarios. For field workers, acute ADD (μg/kg/day) = [dermal absorption x dislodgeable foliar residues (μg/cm^2) x transfer factor (cm^2/hr) x exposure duration (hrs/day)]/body weight (kg).
c   SADD = Seasonal Absorbed Daily Dosage which is the 90% upper confidence limit on the mean estimate of the total absorbed dosage from PHED during high-end use season for handlers. For field workers, the SADDs were calculated using DFRs from corresponded to the REI plus 7 days for most activities (i.e., DFRs for 9 days), except for thinning and harvesting of citrus in which the DFRs corresponded to the REI plus 10 days (i.e, DFRs for 40 days)
d   AADD = Annual Average Daily Dosage which is the SADD x (annual use months per year) / 12 months.
e   LADD = Lifetime Average Daily Dosage which is the AADD x (40 years of work in a lifetime) / (75 years in a lifetime).
f   The seasonal and annual exposures are estimated to occur over 1, 1, and 2 months for aerial, airblast, and groundboom activities, respectively. Seasonal and annual exposures were not anticipated for backpack sprayer and low-pressure handwand activities.
g   M/L = Mixer/Loader
h   M/L/A = Mixer/Loader/Applicator
i   The estimated seasonal exposure for field workers was assumed to be 3, 3 and 2 months for scouting in cotton/safflower, harvesting/thinning citrus, and thinning artichokes, respectively. The estimated annual exposure for field workers was assumed to be 3, 4 and 2 months for scouting in cotton/safflower, harvesting/thinning citrus, and thinning artichokes, respectively.

over a year (i.e., multiplying the SADD by the annual use months per year and dividing by 12 months). The estimated seasonal exposure for field workers was assumed to be 3, 3 and 2 months for scouting in cotton/safflower, harvesting/thinning citrus, and thinning artichokes, respectively. The estimated annual exposure for field workers was assumed to be 3, 4 and 2 months for scouting in cotton/safflower, harvesting/thinning citrus, and thinning artichokes, respectively. The AADDs for field workers were between 0.0001 and 0.0011 mg/kg/day. The LADDs for field workers ranged from 0.00006 to 0.0006 mg/kg/day.

III.B.5. Application Site and Ambient Air Exposure

III.B.5.a. Application Site Air Exposure

Individuals might be exposed to methidathion if they are working or standing adjacent to fields that are being treated or have recently been treated (i.e., bystander exposure). Air monitoring for methidathion was conducted following an application to an orange grove in Tulare County in July 1991 (Royce *et al.*, 1993). Only three monitoring stations were setup based on the prevailing wind direction (from the northwest), but during the application the winds were primarily from the southwest. Consequently, no samplers were located downwind where the highest air concentrations were expected. Therefore, surrogate data from an application site monitoring study for methyl parathion were used to estimate exposure to methidathion (Beauvais, 2006). The methyl parathion application monitoring study was conducted in July of 2003 following a walnut orchard application in San Joaquin county. The air was monitored for 5 days following application. A downwind sampler with the highest peak and daily concentrations was selected to evaluate bystander exposure. The methyl parathion study was considered an appropriate surrogate for methidathion due to similarity in equipment used, timing of applications and vapor pressure. Both studies had summer, nighttime applications to tree crops using airblast applicators with low wind and little vertical mixing resulting in likely higher off-site concentrations. In addition, neither methidathion or methyl parathion were very volatile with vapor pressures less than 10^{-4} mmHg. The vapor pressure for methyl parathion (1.7×10^{-5} mmHg at 25°C; Spencer et al., 1979) was slightly higher than that for methidathion (3.37×10^{-6} mmHg at 25°C; Rordorf, 1988) suggesting the air concentrations in this study might be higher than they would be with methidathion. The exposure estimates were not adjusted downward based on the difference in vapor pressures because of the uncertainties associated with the other factors affecting air concentrations. However, the exposure estimates were adjusted upward since the application rate in the methyl parathion study (2 lbs/acre) was less than the maximum application rate for methidathion on citrus (5 lbs/acre). Although the methyl paraoxon was monitored in this study, it was only detected in a few samples during the first few sampling intervals. For all the samples in which no methyl paraoxon residues were detected, the air concentration was assumed to be at the reporting limit or (0.077 µg/m^3 - 24 hours; 0.155 µg/m^3 - 11 hours) for acute exposure and ½ of reporting limit for seasonal and chronic exposure. The exposure estimates below represent the sum of the methidathion and methidaoxon exposure. The maximum concentration detected was used to calculate 1-hour exposures, while the 21-hour time-weighted average (TWA) was used to estimate 24-hour exposure.

Table 31 summarizes the exposure estimates for methidathion at the application site. The 1-hr acute exposure estimates (ADDs) were 4.62 µg/kg for infants and 0.832 µg/kg for adults. The 24-hr ADDs at the application site were 8.04 and 3.82 for infants and adults, respectively.

91

Table 31. Estimated Exposure for the General Public to Methidathion in Application Site and Ambient Air

Exposure Dosages	Infants	Adults
Application Site[a]		
ADD[b] - 1 hr (µg/kg)	4.62	0.832
ADD - 24 hr (µg/kg)	8.04	3.82
SADD[d] (µg/kg/day)	0.936	0.444
AADD[e] (µg/kg/day)	0.157	0.074
Ambient[c]		
SADD[d] (µg/kg/day)	0.060	0.028
AADD[e] (µg/kg/day)	0.045	0.021

a Application site exposure dosages based on surrogate data from an application site monitoring study for methyl parathion conducted in a walnut orchard in San Joaquin county during July of 2003. The exposure estimates represent the sum of the methidathion and methidaoxon exposure after adjusting for the application rate.

b ADD = Absorbed Daily Dosage. The 1-hr exposure is based on the maximum 11-hr TWA concentration. The 24-hr exposure was based on the highest 21-hr TWA concentration. A default inhalation absorption of 100% was used. For more explanation of the calculations, see the exposure assessment document for methidathion prepared by Beauvais (2006).

c   Ambient exposure dosages based on air concentrations at the Jefferson site in a study in Tulare County conducted by ARB.

d SADD = Seasonal Average Daily Dosage using on the mean air concentration during the monitoring period. No adjustment was made for application rate with application site air.

e AADD = Annual Average Daily Dosage = SADD x annual use months/12 months. Annual use months were assumed to be 2 months per year for application site air and 9 months per year for ambient air.

Although seasonal and chronic exposure is unlikely around tree crops due to the limited number of applications (1-2) allowed per year, seasonal and chronic exposure could occur near artichoke fields since up to 8 applications per year are allowed with a minimum 2-week interval between applications. Therefore, seasonal and chronic exposure estimates were calculated for application site air assuming the high-use season for artichokes to be 2-months. The SADDs at the application site were 0.936 µg/kg/day for infants and 0.444 µg/kg/day for adults. The AADDs were 0.157 and 0.074 µg/kg/day for infants and adults, respectively.

III.B.5.b. Ambient Air Exposure

Ambient air monitoring data of methidathion and the oxon was also conducted in Tulare County at four sites all within 0.25 mile of citrus groves (Sunnyside Union Elementary School in Strathmore, Jefferson Elementary School in Lindsay, Exeter Union High School in Exeter and the University of California Lindcove Field Station in Exeter) (Royce *et al.*, 1993).   The background site was the ARB Ambient Air Monitoring Station in Visalia.   Samples were collected during a 4-week interval between June 27 and July 25 of 1991.   In 1991, Tulare County had the highest use of methidathion in California (75,582 lbs.) which occurred primarily in June and July.   The Jefferson Elementary School in Lindsay had the highest daily and average air concentration. Therefore, the risk estimates were initially calculated using the exposure estimates from this site, assuming that if they were acceptable at this location, they would be acceptable at the other three locations in Tulare County where the air concentrations were lower. As with application site monitoring the air concentrations of methidathion and its oxon were added together to derive the exposure dosages, assuming they were equally toxic. The exposure

estimates for ambient air are also summarized in Table 31.   The SADDs were estimated to be 0.060 and 0.028 µg/kg/day for infants and adults, respectively, using the mean ambient air concentration at the Jefferson site during the 4-week monitoring period. The AADD is the average air concentration for a year assuming the season of potential exposure is 9 months per year for methidathion. The AADDs for the Jefferson site were 0.045 and 0.021 µg/kg/day for infants and adults, respectively.

III.B.6. Aggregate Exposure

III.B.6.a. Agricultural Workers

The exposure to methidathion through the diet, drinking water and residential (ambient) air was also considered in the potential exposure for agricultural workers (Table 32). The acute dietary and drinking water exposure to methidathion for workers (males and females 16 years and older) was estimated to be 0.190 µg/kg/day based on the 95th percentile of user-day exposure.   The chronic dietary and drinking water exposure for workers was estimated to be 0.002 µg/kg/day based on the average exposure for the U.S. population (custom subpopulations

Table 32. Estimated Aggregate Exposure Dosages for Methidathion in Agricultural Workers[a]

Exposure Scenarios	Acute mg/kg/day	Seasonal mg/kg/day	Chronic mg/kg/day	Lifetime mg/kg/day
Handlers				
Aerial				
M/L[b]	1.15	0.460	0.038	0.020
Applicator	4.65	1.55	0.129	0.069
Flagger	1.90	0.475	0.040	0.021
Airblast				
M/L	0.134	0.053	0.004	0.002
Applicator	5.86	1.46	0.122	0.065
Groundboom				
M/L	0.161	0.063	0.011	0.006
Applicator	0.180	0.044	0.007	0.004
Backpack sprayer				
M/L/A[c]	0.194	NA	NA	NA
Low-pressure handwand				
M/L/A	0.006	NA	NA	NA
Field Workers				
Scouting in cotton/safflower	0.096	0.0048	0.0012	0.0007
Harvesting/thinning citrus	0.010	0.0027	0.0009	0.0005
Thinning artichokes	0.017	0.0010	0.00015	0.00011

a   Aggregate exposure estimates are the sum of the occupational exposure estimates from Table 30 and the dietary and drinking water estimates from Table 29 and ambient air estimates from Table 31. The acute dietary and drinking water estimates for workers was 0.190 µg/kg. The seasonal and chronic dietary and drinking water estimates for workers were 0.002 µg/kg/day based on the U.S. population. The ambient air exposure estimates were adjusted to 2.56, 0.297 and 0.050 µg/kg/day for acute, seasonal and chronic assuming workers are exposed to application site air for a maximum of 16 hours per day at home which was adjacent to the treated fields.
b   M/L = Mixer/Loader
c   M/L/A = Mixer/Loader/Applicator

could not be calculated for chronic exposure).   The application site air exposure estimates for adults were used to estimate aggregate exposure assuming workers lived adjacent to treated fields.   The application site air exposure estimates were adjusted to 2.56, 0.297 and 0.050 µg/kg/day for acute, seasonal and chronic exposure, respectively, assuming a maximum exposure of 16 hours per day to residential air for agricultural workers. The acute aggregate exposures for workers ranged from 0.006 mg/kg/day to 5.86 mg/kg/day. The seasonal aggregate exposure for ranged from 0.0010 mg/kg/day to 1.55 mg/kg/day The chronic aggregate exposure for workers ranged from 0.00015 mg/kg/day to 0.129 mg/kg/day. The lifetime aggregate exposure for workers ranged from 0.00011 mg/kg/day to 0.069 mg/kg/day.   The dietary, drinking water and ambient air exposure was less than 5% of the aggregate exposure for most workers. Consequently, its addition had little impact on the aggregate exposure. Only for work activities where the occupational exposure was low (M/L/As using low-pressure handwands, field workers harvesting/thinning citrus, thinning artichokes) did the dietary, drinking water and ambient air represent a significant contribution. For these activities, the dietary, drinking water and ambient air exposure combined represented 6%-46% of the aggregate exposure.

III.B.6.b. General Public

The aggregate exposure to methidathion through the diet, drinking water and residential (ambient) air was considered in the potential exposure for the general public (Table 33). The estimated acute combined dietary and drinking water exposure to methidathion was assumed to be 0.503 and 0.321 µg/kg/day for infants (non-nursing, less than 1 year old) and adults (U.S. population), respectively. Since no seasonal exposure was estimated for dietary and drinking

Table 33. Estimated Aggregate Exposure Dosages for Methidathion in the General Public

Exposure Dosages	Infants	Adults
Application Site[a]		
ADD[b] - 1 hr (µg/kg)	5.12	1.15
ADD - 24 hr (µg/kg)	8.54	4.14
SADD[d] (µg/kg/day)	0.956	0.446
AADD[e] (µg/kg/day)	0.177	0.076
Ambient[c]		
SADD[d] (µg/kg/day)	0.080	0.030
AADD[e] (µg/kg/day)	0.065	0.023

a   The aggregate exposure estimates are the sum of the combined dietary and drinking water exposure (Table 29) and the ambient air exposure (Table 31). The combined acute dietary and drinking water exposure was assumed to be 0.503 µg/kg/day for infants based on non-nursing infants less than 1 years old and 0.321 µg/kg/day for adults based on the U.S. population. The combined chronic dietary and drinking water exposure was assumed to be 0.020 µg/kg/day for infants (non-nursing infants less than 1 year old) and 0.002 µg/kg/day for adults (U.S. population).

b   ADD = Absorbed Daily Dosage. The 1-hr exposure is based on the maximum 11-hr TWA concentration. The 24-hr exposure was based on the highest 21-hr TWA concentration. A default inhalation absorption of 100% was used. For more explanation of the calculations, see the exposure assessment document for methidathion prepared by Beauvais (2006).

c   Ambient exposure dosages based on air concentrations at the Jefferson site in a study in Tulare County conducted by ARB.

d   SADD = Seasonal Average Daily Dosage using on the mean air concentration at the Jefferson site during the monitoring period.

e   AADD = Annual Average Daily Dosage = SADD x annual use months/12 months. Annual use months were assumed to be 2 months per year for application site air and 9 months per year for ambient air.

water exposure, the chronic dietary and drinking water exposures were used estimating seasonal aggregate exposure. The estimated chronic dietary and drinking water exposure was assumed to be 0.020 μg/kg/day for infants (non-nursing, less than 1 year old) and 0.002 μg/kg/day for adults (U.S. population), respectively. The application site air exposure from Table 31 was used for the residential air exposure in the acute aggregate exposure for infants and adults. The ambient air exposure from Table 31 was used for the residential air exposure in the seasonal and chronic aggregate exposure estimates. The 1-hr acute aggregate exposure at the application site for infants and adults was 5.12 and 1.15 μg/kg, respectively. The 24-hr acute aggregate exposure estimates increased to 8.54 and 4.14 μg/kg for infants and adults, respectively. The seasonal aggregate exposure at the application site for infants and adults was 0.956 and 0.446 μg/kg/day, respectively. The chronic aggregate exposure was 0.177 and 0.076 μg/kg/day for infants and adults , respectively. The seasonal and chronic exposure estimates for ambient air at the Jefferson school site were more than an order of magnitude lower. The seasonal aggregate exposure estimates to ambient air for infants and adults was 0.080 and 0.030 μg/kg/day, respectively. The chronic aggregate exposure to ambient air was 0.065 and 0.023 μg/kg/day for infants and adults , respectively.

III.C. RISK CHARACTERIZATION

The risk for non-carcinogenic 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.

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

The risk for carcinogenic effects was calculated by multiplying the carcinogenic potency by the exposure dosage.

$$Carcinogenic\,Risk\,=\,Carcinogenic\,Potency\,x\,Exposure\,Dosage$$

III.C.1. Dietary Exposure

The MOEs for dietary exposure to methidathion were calculated for the various population subgroups using the NOEL for acute toxicity (0.18 mg/kg/day) and the acute dietary exposure dosages from Table 27.   With the Tier 3 analysis, the MOEs for acute toxicity ranged from 230 for children 1-2 years old to 1,000 for adults 50 years and older (Table 34). The MOEs for chronic dietary exposure to methidathion were calculated for the various population subgroups using the NOEL for chronic toxicity (0.15 mg/kg/day) and the Tier 3 chronic dietary exposure dosages in Table 27. The chronic MOEs ranged from 8,000 for non-nursing infants less than 1 year old to 110,000 for adults 20 to 49 years old. The estimated carcinogenic risk from dietary exposure was calculated using the Tier 3 chronic exposure estimate for the U.S. population and the carcinogenic potency.   The estimated carcinogenic potency of methidathion based on the incidence of liver hepatocellular adenomas and carcinomas in male mice ranged from 0.34 (mg/kg/day)[-1] for the maximum likelihood estimate (MLE) to 0.53 (mg/kg/day)[-1] for

Table 34. Estimated Margins of Exposure for Potential Dietary Exposure to Methidathion for Selected Population Subgroups

Population Subgroup	Margins of Exposure[a]	
	Acute	Chronic
U.S. Population	550	69,000
Western Region	510	52,000
Nursing Infants (< 1 yr)	650	29,000
Non-nursing Infants (< 1 yr)	360	8,000
Children (1-2 yrs)	230	20,000
Children (3-5 yrs)	300	29,000
Children (6-12 yrs)	380	51,000
Youth (13-19 yrs)	540	90,000
Adults (20-49)	840	110,000
Adults (50+ yrs)	1,000	100,000
Females (13-49 yrs)	840	98,000
Females (13+ yrs, pregnant/not nursing)	610	28,000
Females (13+ yrs, nursing)	600	35,000
Workers (16+ yrs)	920	NA

a   Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 0.18 mg/kg (male rats, reduced ChE activity in cerebral cortex). Chronic NOEL = 0.15 mg/kg/day (dogs, elevated liver enzymes in serum and histological lesions in the liver). Exposure dosages from Table 27. Values rounded to two significant figures.

the 95% upper bound (95% UB). The carcinogenic risk estimates ranged from 7.3×10^{-7} (MLE) to 1.1×10^{-6} (UB).

III.C.2. Drinking Water Exposure

The MOEs for exposure to methidathion in drinking water were calculated for the various population subgroups using the NOEL for acute toxicity (0.18 mg/kg/day) and the acute drinking water exposure dosages in Table 28.   The MOEs for drinking water exposure to methidathion are summarized in Table 35. The acute MOEs ranged from 15,000 for non-nursing infants less than one year old to 120,000 for pregnant, non-nursing females 19 years and older. The chronic MOEs for drinking water ranged from 160,000 for non-nursing infants less than one year old to 900,000 for youth between 13 and 19 years old. The estimated carcinogenic risk from exposure to methidathion in drinking water was calculated using the chronic water exposure for the U.S. population and the carcinogenic potency. The estimated carcinogenic risk for drinking water exposure alone ranged from 7.9×10^{-8} (MLE) to 1.2×10^{-7} (95% UB).

III.C.3. Combined Dietary and Drinking Water Exposure

The MOEs for combined exposure to methidathion in the diet and drinking water were calculated for the various population subgroups using the NOEL for acute toxicity (0.18 mg/kg/day) and the combined exposure estimates in Table 29.   The MOEs for combined dietary and drinking water exposure are summarized in Table 36. The acute MOEs for combined exposure ranged from 230 for children 1 to 2 years old to 1,000 for adults 50 years and older.

Table 35. Estimated Margins of Exposure for Potential Drinking Water Exposure to Methidathion for Selected Population Subgroups

Population Subgroup	Margins of Exposure[a]	
	Acute	Chronic
U.S. Population	43,000	650,000
Western Region	39,000	560,000
Nursing Infants (< 1 yr)	24,000	530,000
Non-nursing Infants (< 1 yr)	15,000	160,000
Children (1-2 yrs)	41,000	440,000
Children (3-5 yrs)	42,000	470,000
Children (6-12 yrs)	72,000	670,000
Youth (13-19 yrs)	67,000	900,000
Adults (20-49 yrs)	58,000	690,000
Adults (50+ yrs)	85,000	660,000
Females (13-49 yrs)	62,000	700,000
Females (13+ yrs/pregnant/not nursing)	120,000	670,000
Females (13+ yrs/nursing)	83,000	470,000
Workers (16+ yrs)	62,000	NA

a   Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 0.18 mg/kg (male rats, reduced ChE activity in cerebral cortex). Chronic NOEL = 0.15 mg/kg/day (dogs, elevated liver enzymes in serum and histological lesions in the liver). Exposure dosages from Table 28. Values rounded to two significant figures.

 The chronic MOEs for combined exposure ranged from 7,700 for non-nursing infants less than one year old to 92,000 for adults 20 to 49 years old. When drinking water exposure was combined with the dietary exposure, the estimated carcinogenic risk increased slightly ranging from 8.2×10^{-7} (MLE) to 1.3×10^{-6} (95% UB).

III.C.4. Occupational Exposure

The acute MOEs for occupational exposure to methidathion were calculated using the NOEL for acute toxicity (0.18 mg/kg/day) and the ADDs in Table 30.   The MOEs for acute exposure ranged from < 1 for aerial M/Ls to 53 for M/L/As using low-pressure hand wands (Table 37). The seasonal MOEs for occupational exposure to methidathion were calculated using the subchronic NOEL (0.18 mg/kg/day) and the SADDs in Table 30. The MOEs for seasonal exposure ranged from < 1 for aerial M/Ls to 260 for thinning of artichokes (Table 37). The MOEs for chronic occupational exposure to methidathion were calculated for the various exposure scenarios using the NOEL for chronic toxicity (0.15 mg/kg/day) and the AADDs in Table 30. The chronic MOEs ranged from 1 for aerial and airblast applicators to 1500 for thinning of artichokes (Table 37).

The carcinogenic risk for agricultural workers exposed to methidathion was calculated using the LADDs in Table 30. The estimated carcinogenic risk for agricultural workers using the MLE for carcinogenic potency ranged 2.0×10^{-5} to 2.3×10^{-2} (Table 38). When the 95% UB for carcinogenic potency was used, the estimated carcinogenic risk for workers ranged from 3.2×10^{-5} to 3.7×10^{-2}.

97

Table 36. Estimated Margins of Exposure for Potential Combined Dietary and Drinking Water Exposure to Methidathion for Selected Population Subgroups

Population Subgroup	Margins of Exposure[a]	
	Acute	Chronic
U.S. Population	560	63,000
Western Region	530	47,000
Nursing Infants (< 1 yr)	710	27,000
Non-nursing Infants (< 1 yr)	360	7,700
Children (1-2 yrs)	230	19,000
Children (3-5 yrs)	300	27,000
Children (6-12 yrs)	380	48,000
Youth (13-19 yrs)	540	82,000
Adults (20-49 yrs)	840	92,000
Adults (50+ yrs)	1,000	90,000
Females (13-49 yrs)	840	86,000
Females (13+ yrs/pregnant/not nursing)	610	27,000
Females (13+ yrs/nursing)	600	33,000
Workers (16+ yrs)	940	NA
a Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 0.18 mg/kg (male rats, reduced ChE activity in cerebral cortex). Chronic NOEL = 0.15 mg/kg/day (dogs, elevated liver enzymes in serum and histological lesions in the liver). Exposure dosages from Table 29. Values rounded to two significant figures.		

III.C.5. Application Site and Ambient Air Exposure

The MOEs for acute exposure to methidathion were calculated using the acute NOEL (0.18 mg/kg/day) and the ADDs for application site and ambient air in Table 31. The 1-hr acute MOEs for the application site were 39 for infants and 220 for adults (Table 39). The 24-hr acute MOEs for the application site ranged from 22 for infants to 47 for adults. The MOEs for seasonal exposure to methidathion were calculated using the NOEL from the 90-day neurotoxicity study in rats (0.18 mg/kg/day) and the SADDs from Table 31. The seasonal MOEs for the application site were 190 for infants and 400 for adults (Table 39).   The seasonal MOEs for ambient air at the Jefferson school site ranged from 3,000 for infants to 6,400 for adults (Table 39). The MOEs for chronic exposure to methidathion were calculated using the chronic NOEL of 0.15 mg/kg/day and the AADDs from Table 31. The chronic MOEs for the application site were 950 for infants and 2,000 for adults (Table 39). The MOEs for chronic exposure to methidathion in ambient air ranged from 3,300 for infants to 7,100 for adults. The carcinogenic risk was calculated using the AADDs for adults (Table 31) and the estimated carcinogenic potency based on liver hepatocellular adenomas and carcinomas in male mice (0.34 $(mg/kg/day)^{-1}$ for MLE or 0.53 $(mg/kg/day)^{-1}$ for 95% UB). For the application site, the carcinogenic risk estimates were between 2.5×10^{-5} (MLE) and 3.9×10^{-5} (95% UB). The estimated carcinogenic risk from lifetime exposure to ambient air at the Jefferson site ranged from 7.1×10^{-6} (MLE) to 1.1×10^{-5} (95% UB).

Table 37. Estimated Margins of Exposure for Agricultural Workers Exposed to Methidathion[a]

Exposure Scenarios	Acute	Seasonal	Chronic
Handlers			
Aerial			
M/L[a]	< 1	< 1	4
Applicator	< 1	< 1	1
Flagger	< 1	< 1	4
Airblast			
M/L	1	3	38
Applicator	< 1	< 1	1
Groundboom			
M/L	1	3	14
Applicator	1	4	21
Backpack sprayer			
M/L/A[c]	1	NA	NA
Low-pressure handwand			
M/L/A	53	NA	NA
Field Workers			
Scouting in cotton/safflower	2	40	140
Harvesting/thinning citrus	26	75	190
Thinning artichokes	13	260	1500

a   Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 0.18 mg/kg (male rats, cortex ChE inhibition).
    Seasonal NOEL = 0.18 mg/kg/day (rats, RBCs and regional brain ChE inhibition). Chronic NOEL = 0.15 mg/kg/day
    (dogs, elevated liver enzymes in serum and histological lesions in the lever). Exposure dosages from Table 30. Values
    rounded to two significant figures or the nearest whole number if less than 10.
b   M/L = Mixer/Loader
c   M/L/A = Mixer/Loader/Applicator

III.C.6. Aggregate Exposure

The acute aggregate MOEs for agricultural workers were calculated using the acute aggregate exposure estimates in Table 32 and the NOEL at 2-weeks in the 90-day neurotoxicity study in rats (0.18 mg/kg/day for ChE inhibition in cortex (M)). Since dietary, drinking water and residential air exposure contributed less than 5% to the aggregate exposure for most agricultural workers, the aggregate MOEs were not significantly different from the occupational MOEs for most workers (Table 40). The exceptions were MLAs using low-pressure handwands and field workers doing harvesting and thinning of citrus and thinning of artichokes. The acute aggregate MOEs were 30 for MLAs using low-pressure handwands, 18 for field workers harvesting/thinning citrus, and 11 for field workers thinning artichokes.   The MOEs for seasonal aggregate exposure were calculated using the aggregate seasonal exposure estimates in Table 32 and the subchronic NOEL from the subchronic neurotoxicity study in rats (0.18 mg/kg/day). Only the seasonal aggregate MOEs for field workers were quantitatively different from the MOEs for occupational exposure alone (Table 40). The MOEs for chronic aggregate exposure were calculated using the chronic exposure estimates in Table 32 and the chronic NOEL from the 1-year dog study (0.15 mg/kg/day). There was also no quantitative impact on the chronic MOEs when occupational exposure was aggregated with dietary, drinking water and ambient air exposure, except for field workers (Table 40).

Table 38. Estimated Carcinogenic Risk for Agricultural workers for Potential Lifetime Exposure to Methidathion[a]

Exposure Scenarios	Maximum Likelihood Estimate	95% Upper Bound
Handlers		
Aerial		
M/L	6.8×10^{-3}	1.1×10^{-2}
Applicator	2.3×10^{-2}	3.7×10^{-2}
Flagger	7.1×10^{-3}	1.1×10^{-2}
Airblast		
M/L	6.8×10^{-4}	1.1×10^{-3}
Applicator	2.2×10^{-2}	3.4×10^{-2}
Groundboom		
M/L	2.0×10^{-3}	3.2×10^{-3}
Applicator	1.4×10^{-3}	2.1×10^{-3}
Backpack sprayer		
M/L/A	NA	NA
Low-pressure handwand		
M/L/A	NA	NA
Field Workers		
Scouting in cotton/safflower	2.0×10^{-4}	3.2×10^{-4}
Harvesting/thinning citrus	1.4×10^{-4}	2.1×10^{-4}
Thinning of artichokes	2.0×10^{-5}	3.2×10^{-5}

a Carcinogenic Risk = Carcinogenic Potency x Exposure Dosage. The exposure dosage was the LADD in Table 30. The maximum likelihood estimate for carcinogenic potency was 0.34 (mg/kg/day)$^{-1}$. The 95% upper bound estimate for carcinogenic potency was 0.53 (mg/kg/day)$^{-1}$.

Table 39. Estimated Margins of Exposure for Potential Application Site and Ambient Air Exposure to Methidathion for the General Public[a]

Exposure Scenarios	Infants		Adults	
	MOE[b]	% RfC[c]	MOE	% RfC
Application Site				
Acute - 1 hr	39	250	220	46
Acute - 24 hr	22	440	47	210
Seasonal	190	51	400	25
Chronic	950	11	2,000	5
Ambient				
Seasonal	3,000	3	6,400	2
Chronic	3,300	3	7,100	1

a Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 0.18 mg/kg (male rats, cortex ChE inhibition). Seasonal NOEL = 0.18 mg/kg/day (rats, RBCs and regional brain ChE inhibition). Chronic NOEL = 0.15 mg/kg/day (dogs, elevated liver enzymes in serum and histological lesions in the lever). Exposure dosages from Table 31. Values rounded to two significant figures.

b MOE = Margin of Exposure

c % RfC = Percentage of Reference Concentration. The acute, seasonal and chronic reference concentration for methidathion are 3.1 μg/m^3 (0.25 ppb), 3.1 μg/m^3 (0.25 ppb) and 2.5 μg/m^3 (0.21 ppb). See section VI. Reference Doses/Concentrations for explanation of calculations. Values rounded to two significant figures.

Table 40. Estimated Margins of Exposure for Aggregate Exposure to Methidathion in Agricultural Workers[a]

Exposure Scenarios	Acute	Seasonal	Chronic
Handlers			
Aerial			
M/L[a]	< 1	< 1	4
Applicator	< 1	< 1	1
Flagger	< 1	< 1	4
Airblast			
M/L	1	3	38
Applicator	< 1	< 1	1
Groundboom			
M/L	1	3	14
Applicator	1	4	21
Backpack sprayer			
M/L/A[c]	1	NA	NA
Low-pressure handwand			
M/L/A	30	NA	NA
Field Workers			
Scouting in cotton/safflower	2	38	120
Harvesting/thinning citrus	18	67	170
Thinning artichokes	11	180	1000

a   Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 0.18 mg/kg (male rats, cortex ChE inhibition). Seasonal NOEL = 0.18 mg/kg/day (rats, RBC and regional brain ChE inhibition). Chronic NOEL = 0.15 mg/kg/day (dogs, elevated liver enzymes in serum and histological lesions in the lever). Exposure dosages from Table 32. Values rounded to two significant figures or the nearest whole number if less than 10.
b   M/L = Mixer/Loader
c   M/L/A = Mixer/Loader/Applicator

The aggregate carcinogenic risk for agricultural workers exposed to methidathion was calculated using the lifetime exposure estimates in Table 32. The estimated carcinogenic potency of methidathion based on the incidence of liver hepatocellular adenomas and carcinomas in male mice ranged from 0.34 (MLE) to 0.53 (95% UB) (mg/kg/day)$^{-1}$. The estimated aggregate carcinogenic risk for agricultural workers were not significantly different from the estimated carcinogenic risk from occupational exposure alone, except for field workers (Table 41).

The aggregate MOEs for the general public were calculated using the aggregate exposure estimates in Table 33 and the corresponding NOELs for acute, subchronic and chronic toxicity (0.18, 0.18 and 0.15 mg/kg/day, respectively). The 1-hr acute aggregate MOEs at the application site for infants and adults were 35 and 160, respectively (Table 42). The 24-hr acute aggregate MOEs were 21 for infants and 43 for adults. The seasonal aggregate MOEs at the application site were 190 for infants and 400 for adults. The chronic aggregate MOEs at the application site were 850 and 2,000 for infants and adults, respectively.   The seasonal aggregate MOEs for ambient air at the Jefferson site were 2,200 for infants and 6,000 for adults. The chronic aggregate MOEs for ambient air at the Jefferson site were 2,300 and 6,500 for infants and adults,

Table 41. Estimated Aggregate Carcinogenic Risk for Agricultural Workers for Potential Lifetime Exposure to Methidathion[a]

Exposure Scenarios	Maximum Likelihood Estimate	95% Upper Bound
Handlers		
Aerial		
M/L	6.8×10^{-3}	1.1×10^{-2}
Applicator	2.3×10^{-2}	3.7×10^{-2}
Flagger	7.1×10^{-3}	1.1×10^{-2}
Airblast		
M/L	6.8×10^{-4}	1.1×10^{-3}
Applicator	2.2×10^{-2}	3.4×10^{-2}
Groundboom		
M/L	2.0×10^{-3}	3.2×10^{-3}
Applicator	1.4×10^{-3}	2.1×10^{-3}
Backpack sprayer		
M/L/A	NA	NA
Low-pressure handwand		
M/L/A	NA	NA
Field Workers		
Scouting in cotton/safflower	2.4×10^{-4}	3.7×10^{-4}
Harvesting/thinning citrus	1.7×10^{-4}	2.6×10^{-4}
Thinning of artichokes	3.7×10^{-5}	5.8×10^{-5}

a Carcinogenic Risk = Carcinogenic Potency x Exposure Dosage. The exposure dosage was the LADD in Table 32. The maximum likelihood estimate for carcinogenic potency was 0.34 $(mg/kg/day)^{-1}$. The 95% upper bound estimate for carcinogenic potency was 0.53 $(mg/kg/day)^{-1}$.

Table 42. Estimated Margins of Exposure for Aggregate Exposure to Methidathion for the General Public[a]

Exposure Scenarios	Infants		Adults	
	MOE[b]	% RfC[c]	MOE	% RfC
Application Site				
Acute - 1 hr	35	280	160	64
Acute - 24 hr	21	470	43	230
Seasonal	190	52	400	25
Chronic	850	12	2,000	5
Ambient				
Seasonal	2,200	4	6,000	2
Chronic	2,300	4	6,500	2

a Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 0.18 mg/kg (male rats, cortex ChE inhibition). Seasonal NOEL = 0.18 mg/kg/day (rats, RBCs and regional brain ChE inhibition). Chronic NOEL = 0.15 mg/kg/day (dogs, elevated liver enzymes in serum and histological lesions in the lever). Exposure dosages from Table 33. Values rounded to two significant figures.

b MOE = Margin of Exposure

c % RfC = Percentage of Reference Concentration. The acute, seasonal and chronic reference concentration for methidathion are 3.1 $\mu g/m^3$ (0.25 ppb), 3.1 $\mu g/m^3$ (0.25 ppb) and 2.5 $\mu g/m^3$ (0.21 ppb). See section VI. Reference Doses/Concentrations for explanation of calculations. Values rounded to two significant figures.

respectively.   The aggregate carcinogenic risk for the general public was calculated using the chronic aggregate exposure estimate for adults and the estimated carcinogenic potency based on liver hepatocellular adenomas and carcinomas in male mice (0.34 $(mg/kg/day)^{-1}$ for MLE or 0.53 $(mg/kg/day)^{-1}$ for 95% UB). The aggregate carcinogenic risk at the application site ranged from 2.6×10^{-5} (MLE) to 4.0×10^{-5} (95% UB). For ambient air, the aggregate carcinogenic risk was estimated to be between 7.8×10^{-6} (MLE) and 1.2×10^{-5} (95% UB).

IV. 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. These, in turn, result 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 methidathion are delineated in the following discussion.

Following the discussion of the uncertainties related to the different components of DPR's risk assessment is a comparison with the endpoints and exposure estimates used in U.S. EPA's risk assessment for methidathion. In addition, there is a discussion of the information available for methidathion related to Food Quality Protection Act including potential increased pre- and post-natal sensitivity in infants and children, endocrine effects, cumulative toxicity and aggregate exposure. Both the uncertainties in the risk estimates and the information related to FQPA can be used in determining the adequacy of the MOEs for methidathion.

IV.A. HAZARD IDENTIFICATION

All the available toxicity studies for methidathion were summarized in the Toxicology Profile including studies from the open literature and studies submitted to DPR for registration of pesticide products in California. DPR determines the acceptability of the toxicology studies submitted for registration based on FIFRA study guidelines. DPR generally considers literature studies supplemental because they often do not follow FIFRA guideline protocols and/or do not provide sufficient detail in their reports to determine if they were conducted properly. In the risk assessment, DPR gives greater weight to guideline studies, especially if they were found acceptable. However, literature studies are useful in the selection of the critical NOEL in the Hazard Identification section for support of effects seen in the guideline studies and can be used for the critical NOEL if they evaluate an endpoint not examined in the guideline studies and they appear to be scientifically valid studies.

The studies considered in the selection of the NOELs for acute, subchronic and chronic exposure were any studies, regardless of whether they met FIFRA guidelines, that have sufficient information to establish an acute NOEL or LOEL. For the acute exposure, this included LD_{50}/LC_{50} studies, mechanistic studies, acute neurotoxicity studies, and developmental toxicity studies. The effects observed in the developmental toxicity studies which were considered acute included maternal signs observed within the first few days of exposure and any fetal effects assuming they were the result of a single exposure. For subchronic exposure, the studies considered included standard oral and dermal subchronic toxicity studies (> 7 days, but < 6 months), subchronic neurotoxicity studies, developmental and reproductive toxicity studies, and mechanistic studies. For chronic exposure, the studies included the typical chronic feeding

studies in mice, rats and dogs which lasted 1-2 years as well as an unusual 2-year gavage study in monkeys. The effects that are generally considered adverse with acute, subchronic and chronic exposure, include clinical signs, reductions in body weight and food consumption greater than 10%, and increases in gross and histopathological lesions. Minimal changes in clinical chemistry and hematology values and organ weights without accompanying functional or structural changes are generally not considered adverse.

The primary mechanism of toxicity for methidathion is the inhibition of AChE in the nervous system. In general, DPR considers brain ChE inhibition to be indicative of overt toxicity since more subtle functional changes in the nervous system due to ChE inhibition, such as memory and learning losses, may not be easily detected in animals unless they are specifically tested for these effects. The toxicological significance of plasma and RBC ChE inhibition is less certain because the physiological function of ChEs in blood have not been clearly established, although several possible physiological functions have been proposed, which were discussed in the Introduction. In an acute neurotoxicity study, reduced ChE activity was seen in the cerebral cortex of male rats (59% of control activity) at the time to peak effect at the lowest dose tested, 1 mg/kg (Chang and Richter, 1994). However, no clinical signs or changes in behavior were seen in the FOB until 8 mg/kg. At 8 mg/kg, clinical signs and behavioral signs were seen in both sexes, although they were more pronounced in females. The reduction in ChE activity in the different regions of the brain were also more pronounced in females (8-25% of controls) than males (16-32% of controls) at 8 mg/kg. A NOEL could have been estimated for this study by dividing the LOEL by a default uncertainty factor of 10. However, this would result in an estimated acute NOEL of 0.1 mg/kg which would be less than the observed NOEL of 0.18 mg/kg/day in 90-day neurotoxicity for the same endpoint. Consequently, the observed NOEL from the 90-day study was used for the acute NOEL.

An alternative to estimating a NOEL for the acute neurotoxicity study by dividing by an uncertainty factor was to estimate a benchmark dose (BMD). U.S. EPA's Benchmark Dose Software (BMDS, version 1.3.2) offers several models for estimating BMD values with continuous data; however, they all require that you select a benchmark response (BMR) level that is meaningful. The response level selected should depend on the normal variability found in the data. U.S. EPA used a BMR of 10% brain ChE inhibition in female rats when doing their evaluation of the cumulative toxicity of OPs (U.S. EPA, 2001). U.S. EPA selected this response level because it was at or near the limit of sensitivity for detecting a statistically significant decrease in ChE activity in blood or brain and is a response level close to background. Based on DPR's review of the coefficients of variation (CVs) for brain ChE activity in control animals in registrant data for OPs, a 10% response level appears to be a reasonable point of departure for whole brain data which had CVs usually between 5-10% (Lewis *et al.*, 2006). However, the normal variability in regional brain ChE activity was much greater with CVs usually between 10 and 20%. One contributing factor to this greater variability may be the difficulty in precisely excising various brain regions. Another possibility is that there may be an inherent variability in where the cholinergic neurons run through the different regions of the brain despite a small variability in the total number of cholinergic neurons in the whole brain. In the BMD analysis of the methidathion data presented here, the lower limit on the BMD (BMDL) was estimated for various brain regions in the acute and subchronic neurotoxicity where there was an apparent reduction in the mean activity at the lowest dose level, even if it was not statistically significant. The BMDL was estimated at the 10%, 15% and 20% response level. The results of this analysis

are shown in Table 43. Only the results from the Hill model are shown since it generally gave the best fit. It is interesting to note that the BMDLs at 10, 15 and 20% response levels were identical for ChE inhibition in the cortex of males in the acute study and at 2 weeks in the subchronic study, supporting that use of the 2-week NOEL from the subchronic neurotoxicity study as a surrogate for an acute NOEL. It also should be noted that the $BMDL_{15}$ for ChE inhibition in the cerebral cortex of males at 2 weeks was equivalent to the NOEL (0.18 mg/kg/day) that was established for this same endpoint and time based on statistical significance. The NOEL from the 90-day study is also similar to a $BMDL_{10}$ of 0.17 mg/kg/day for whole brain ChE inhibition in female rats in the chronic toxicity study that U.S. EPA used for methidathion in its cumulative risk assessment for OPs (U.S. EPA, 2006). However, if the BMDL at 10% or 20% response levels for the cortex in males had been used instead of the 2-week NOEL, the MOEs would be approximately 40% lower or higher than estimated, respectively.

The study selected for evaluating chronic dietary exposure to methidathion was a 1-year dog study (Chang and Walberg, 1991). The NOEL for this study was 4 ppm (0.15 mg/kg/day) ,

Table 43. Benchmark Dose Analysis of Regional Brain ChE Data in the Acute and Subchronic Neurotoxicity Studies for Methidathion[a]

	$BMDL_{10}$[b] (mg/kg/day)	$BMDL_{15}$ (mg/kg/day)	$BMDL_{20}$ (mg/kg/day)
ACUTE			
Males			
Cortex – 1.5 hrs	0.11	0.18	0.26
Cerebellum – 1.5 hrs	0.48	0.72	0.97
Females			
Cortex – 1.5 hrs	0.34	0.50	0.67
Cerebellum – 1.5 hrs	0.49	0.70	0.90
SUBCHRONIC			
Males			
Cortex – 2 wks[c]	0.11	0.18	0.26
4 wks	0.18	0.29	0.41
13 wks	0.12	0.20	0.28
Striatum – 4 wks[d]	0.63	0.95	1.28
13 wks	0.29	0.46	0.63
Hippocampus – 8 wks	0.60	0.89	1.18
13 wks	0.52	0.80	1.10
Spinal cord – 13 wks	0.75	1.12	1.50
Females			
Cortex – 4 wks	0.21	0.33	0.46
13 wks	0.29	0.40	0.51
Striatum – 13 wks	0.10	0.16	0.22
Hippocampus – 13 wks	0.21	0.32	0.43

a   Chang and Richter, 1994; Chow and Turnier, 1995.
b $BMDL_{10}$, $BMDL_{15}$ $BMDL_{20}$ = Lower limit of the benchmark dose at the 10, 15 and 20% response level. The Hill model from the U.S. EPA's Benchmark Dose Software (version 1.3.2) was used for the analysis.
b   Omitted 30 ppm (1.86 mg/kg/day) dose level due to poor fit when all dose levels included
c   Omitted 10 ppm (0.608 mg/kg/day) dose level due to poor fit when all dose levels included

based on elevated levels of liver enzymes (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase) in the serum, dark red liver discoloration cholestasis and mild chronic inflammation of the liver in both sexes at 40 ppm (M: 1.33 mg/kg/day; F: 1.39 mg/kg/day). A similar NOEL (0.17 mg/kg/day) was observed in a rat study based on clinical signs (alopecia, chromorhinorrhea, hyperactivity, hypersensitivity to touch, and tremors), reduced body weights, reduced food and water consumption, reduced ChE activity in RBCs (M: 78%; F: 82% of controls) and brain (F: 49%; M: 48% of controls), reduced liver weights, and skin lesions. Both studies were of acceptable quality, so this could not be used as the basis for selecting one study over the other. Differences in species sensitivity was also not clear. Rats were more sensitive to the neurotoxicity than dogs, but less sensitive to the hepatotoxicity. Therefore, the study with the lower NOEL was selected. However, the difference in the NOELs was minor and if the NOEL from the rat study had been used, the chronic MOEs would only be 13% higher than estimated. U.S. EPA also used the same dog study and NOEL for calculating the RfD for methidathion in their risk assessment for methidathion, although they included RBC ChE inhibition along with hepatotoxicity as the endpoints of concern (Travaglini, 1999). FAO/WHO JMPR identified a NOEL of 0.1 mg/kg/day in estimating the acceptable daily intake (ADI) for methidathion based on a one-year study in dogs (Caris, 1992).

The U.S. EPA Guidelines for Carcinogen Risk Assessment recommends using a linear approach when the mode of action is not known (U.S. EPA, 2005). They also recommend using a benchmark dose as a point of departure from the observed data to do a linear extrapolation to the origin.   If DPR had used this approach, the potency estimates would be similar to those obtained with the MULTI-WEIB model. The ED_{10} (benchmark dose with an estimated excess lifetime tumor incidence of 10%) and LED_{10} (lower limit on ED_{10}) were estimated to be 0.48 and 0.16 mg/kg/day, respectively, using Multi-stage model in the U.S. EPA's Benchmark Dose Software (BMDS, version 1.3.2). The slope or potency factors corresponding to the ED_{10} and LED_{10} were estimated to be 0.21 and 0.63 $(mg/kg/day)^{-1}$, respectively, by dividing the risk at these dose levels (10% or 0.1) by the dose.   If there had been sufficient evidence to support a threshold mechanism, a non-linear approach could have been used. In this case, the U.S. EPA guidelines recommend dividing the LED_{10} by the exposure dosage to calculate a margin of exposure for carcinogenicity. It is interesting to note that the LED_{10}, 0.16 mg/kg/day, is similar to chronic NOEL that was used to calculate the chronic MOEs, although the LED_{10} is based on the human equivalent dose. Consequently, the MOEs for carcinogenicity would be similar to chronic MOEs calculated based on hepatotoxicity. One problem with using the nonlinear approach for threshold mechanisms, as suggested by U.S. EPA's cancer guidelines, is that they have not suggested how large the MOE for carcinogenicity should be to be considered adequate. However, Gaylor et al. (1999) have proposed that the LED_{10}/10,000 or an MOE of 10,000 would be adequate for irreversible adverse health effects, including nongenotoxic carcinogenic effects. This proposal assumes the LED_{10} is equivalent to a LOAEL, so that an uncertainty factor of 10 is needed to extrapolate to a NOAEL. An additional uncertainty factor of 1,000 is recommended for interspecies extrapolation, intraspecies variation in susceptibility, and increased susceptibility for children. It should be noted that the chronic MOE for methidathion from combined dietary and drinking water exposure was greater than 7,000. The chronic MOEs for occupational exposure ranged from <1 to 1,500 with most less than 100. The chronic MOEs for air exposure ranged from 950 (infants, application site) to 7,100 (adults, ambient).

The methidathion oxon is the presumed active metabolite for the neurological effects, although the pharmacokinetics studies suggest that the oxidative desulfuration to the oxon may be a minor metabolic pathway. Typically, the oxon is more toxic than the parent compound for organophosphorothioates. However, there is no toxicity data for the oxon, not even an LD_{50} study, to derive a toxicity equivalency factor for the oxon. Therefore, the assumption was made that it was equivalent in toxicity to the parent. This assumption most likely underestimates the neurotoxicity of the oxon and, therefore, the risk for neurological effects. It is uncertain if the oxon is the active metabolite with regards to the hepatotoxicity and carcinogenicity of methidathion. Therefore, the risk for these endpoints may not have been underestimated.

In their recent update to the cumulative risk assessment for organophosphates, U.S. EPA calculated risks from drinking water exposure to methidathion and other OPs assuming the oxon was 10 times or 100 times as toxic as the parent for most OPs including methidathion (U.S. EPA, 2002a). If DPR made similar assumptions about the toxicity of methidaoxon, a combined MOE could have been calculated using the following calculation:

$$Hazard\ Index = \frac{ExposureDosage}{NOEL}$$

$$Margin\,of\ Exposure\,(MOE)_{combined} = \frac{1}{Hazard\ Index_{parent}\ +\ Hazard\ Index_{oxon}}$$

Some exposure estimates did not include the oxon for various reasons. With dietary exposure, the oxon was not monitored in food since the tolerance did not include the oxon. With occupational exposure, the oxon was not included in the exposure estimates since they were all theoretical estimates for the parent based on PHED database for handlers and DFRs and transfer factors for field workers. The methidaoxon was monitored in PDP drinking water samples; therefore, combined MOEs were calculated for drinking water assuming the oxon was 10X and 100X as toxic as methidathion (Table 44).   As might be expected, the MOEs decreased an order of magnitude as the toxicity of the methidaoxon was increased by 10-fold. However, these toxicity estimates for the oxon are only theoretical and, therefore, these combined MOEs presented here are highly speculative. It should be noted that for the two OPs that U.S. EPA had toxicity data for the oxon (chlorpyrifos and methyl parathion), the toxicity of the oxon was less than 10X as toxic as the parent compound.

Methidaoxon was also monitored in the air monitoring studies for methidathion; however, because of problems with location of samplers in relation to the wind direction surrogate data from a methyl parathion application site monitoring study were used to evaluate methidathion application site exposure. Using the formula above, the combined MOEs for air exposure were calculated assuming the methidaoxon is 10X or 100X more toxic than methidathion (Table 45). As with the drinking water MOEs, the MOEs for air exposure decreased nearly an order of magnitude for every 10-fold the toxicity of the oxon was increased. These MOEs are also highly speculative since the toxicity of the oxon is unknown.

Table 44. Estimated Combined Margins of Exposure for Potential Drinking Water Exposure Assuming Methidaoxon Is 10 or 100 Times as Toxic as Methidathion

Population Subgroup	Combined Margins of Exposure[a]			
	Acute		Chronic	
	10X[b]	100X[c]	10X	100X
U.S. Population	7,100	750	110,000	12,000
Western Region	6,300	680	96,000	10,000
Nursing Infants (< 1 yr)	3,800	410	90,000	9,700
Non-nursing Infants (< 1 yr)	2,500	260	27,000	2,900
Children (1-2 yrs)	6,700	710	74,000	7,900
Children (3-5 yrs)	6,900	730	79,000	8,500
Children (6-12 yrs)	12,000	1,300	110,000	12,000
Youth (13-19 yrs)	11,000	1,200	150,000	16,000
Adults (20-49 yrs)	9,500	1,000	120,000	13,000
Adults (50+ yrs)	14,000	1,500	110,000	12,000
Females (13-49 yrs)	10,000	1,100	120,000	13,000
Females (13+ yrs/pregnant/not nursing)	19,000	2,000	110,000	12,000
Females (13+ yrs/nursing)	14,000	1,400	79,000	8,500
Workers (16+ yrs)	10,000	1,100	NA	NA

a   Combined Margin of Exposure = 1/(Hazard Index$_{methidathion}$ + Hazard Index$_{methidaoxon}$) where the Hazard Index = Exposure Dosage/NOEL. The NOELs for methidathion were 0.18 and 0.15 mg/kg/day for acute and chronic exposure, respectively. Values rounded to two significant figures.
b   The NOELs for the methidaoxon were estimated by dividing the NOELs for methidathion by an uncertainty factor of 10X.
c   The NOELs for the methidaoxon were estimated by dividing the NOELs for methidathion by an uncertainty factor of 100X.

Table 45. Estimated Combined Margins of Exposure for Air Exposure Assuming Methidaoxon is 10 or 100 Times More Toxic Than Methidathion[a]

Exposure Scenarios	Infants		Adults	
	10X[b]	100X[c]	10X	100X
Application Site				
Acute - 1 hr	33	13	180	69
Acute - 24 hr	17	5	35	10
Seasonal	130	30	270	64
Chronic	750	140	1600	320
Ambient				
Seasonal	780	93	1,700	200
Chronic	920	100	1,900	210

a Combined Margin of Exposure = 1/(Hazard Index$_{methidathion}$ + Hazard Index$_{methidaoxon}$) where the Hazard Index = Exposure Dosage/NOEL. The NOELs for the methidathion were 0.18, 0.18, 0.15 mg/kg/day for acute, seasonal and chronic exposure, respectively. Values are rounded to two significant figures.
b The NOELs for the methidaoxon were estimated by dividing the NOELs for methidathion by 10.
c The NOELs for the methidaoxon were estimated by dividing the NOELs for methidathion by 100.

IV.B. EXPOSURE ASSESSMENT

The dietary exposure assessment was based primarily on PDP and DPR monitoring data . PDP monitoring data is more representative of the actual exposure because commodities are washed and peeled if normally consumed that way whereas DPR monitoring measures residue in the whole commodity, regardless of how it is normally consumed. Since the peel is not normally consumed for most citrus fruit, except for small quantities, the PDP orange data were used as surrogate for other citrus commodities even though there were some DPR data for some of these commodities. PDP apple data were used as a surrogate for several other pome fruits (crabapple, quinces and loquats) for which there were no monitoring data. Preference was also given to the PDP monitoring data since it tends to have lower LODs than the DPR monitoring program, which is important especially with chronic exposure where the mean residue value is used and there are a significant number of samples with non-detectable residues. When no residues are detected, ½ of the LOD is used. Even with these refinements, the dietary exposure was still probably overestimated since tolerance values were used for all the nut commodities because no monitoring data were available. Some other high contributing commodities such as safflower and sunflower were not adjusted for PCT, since agricultural statistics were not available for these crops. It seems very unlikely that 100% of sunflower seeds were treated, in particular, since there was no registered use in California on sunflowers for several of the more recent years for which use data are available. The acute dietary exposure assessment may have also been overestimated since probabilistic estimates were only used for the most highly consumed commodities (most citrus, pome and stone fruits).   Point estimates, including tolerance levels for most nut commodities, were used for the rest of the commodities. However, these conservative assumptions for acute exposure are counterbalanced to some degree by the fact that residues were monitored on composite samples which tends to eliminate the extreme values that might be found on single serving pieces of fruit or vegetables. The dietary exposure to methidathion was also probably underestimated since only the parent compound and not the oxon were analyzed in the PDP and DPR monitoring data. According to U.S. EPA's Human Health Risk Assessment, the HED Metabolism Assessment Review Committee (MARC) determined that the residue of concern in plants was the parent compound only (U.S. EPA, 1999). However, Simoneux (1991 & 1993) found that the oxygen analog was a major plant metabolite in cotton and artichokes. The metabolism in other rotational crops and citrus trees appears to be the same.

The revised drinking water exposure estimates for methidathion were considered fairly realistic since they were taken from the finished water at water treatment facilities in California from the three most recent years available from PDP (2001-2003). The previous estimate for drinking water exposure to methidathion by DPR was based entirely on surface water monitoring data which probably exaggerated the exposure since it is uncertain if the samples were collected from sites that were used for drinking water and if the residues would persist after standard water treatment. Furthermore, no methidathion residues have been found in DPR's well water monitoring. More recent surface water monitoring data by DPR indicates that the frequency and magnitude of the residues have dropped in surface water, probably due to significant reductions in the use of methidathion. DPR recognized in its previous drinking water exposure estimates that using DPR's surface water monitoring data probably overestimated the actual exposure, but at the time that risk assessment was conducted, there was only one year of PDP drinking water data available.

The uncertainties in the occupational exposure assessment are discussed in more detail in the Exposure Appraisal section of the EAD (Beauvais, 2006). In this assessment, PHED data were used to estimate exposure which results in more uncertainty in the estimates than if chemical-specific data were used. To compensate for this uncertainty, the 90% upper confidence limit on the mean and 95th percentile were used to estimate seasonal and acute exposure, respectively. This is a new approach used by DPR and one of the main reasons DPR's occupational exposure estimates were significantly higher than U.S. EPA's for the same scenarios.

Uncertainties associated with the ambient and application site air exposure estimates were also discussed in the Exposure Appraisal section of the EAD (Beauvais, 2006). The greatest uncertainties were in the estimates for the application site air exposure due to the use of surrogate data from a methyl parathion application to a walnut orchard in July of 2003 in San Joaquin Valley. There are also uncertainties associated with the ambient air monitoring that was conducted in Tulare County during June and July of 1991. These sites and time were selected based on their high use in this county during this time of year. It is unclear, however, how representative these sites were since applications of methidathion around these sites was not confirmed.

IV.C. RISK CHARACTERIZATION

Generally, an MOE of at least 100 is considered sufficiently protective of human health when the NOEL for an adverse effect is derived from an animal study. The MOE of 100 allows for humans being 10 times more sensitive than animals and for a 10-fold variation in sensitivity between the lower range of the normal distribution in the overall population and the sensitive subgroup (Dourson *et al.*, 2002). A carcinogenic risk level less than 10^{-6} is generally considered negligible.

The potential health risks from dietary exposure appear low. The acute MOEs for dietary exposure even at the 99.9th percentile were greater than 200 for all population subgroups. The chronic MOEs for dietary exposure were equal to or greater than 8,000 for all population subgroups. The upper bound estimate of carcinogenic risk from dietary exposure to methidathion in the U.S. population was just slightly greater than the negligible risk level at 1.1 x 10^{-6}. This risk level is probably acceptable given the limited evidence of a genotoxic mechanism for the carcinogenicity.

The potential health risks from drinking water exposure also appear low. The acute MOEs for drinking water at the 99.9th percentile were equal to or greater than 15,000 for all population subgroups. The chronic MOEs from drinking water exposure were greater than 150,000 for all population subgroups. The acute MOEs for combined dietary and drinking water exposure were still greater than 200 for all populations subgroups. The chronic MOEs for combined dietary and drinking water exposure were greater than 7,000. The estimated carcinogenic risk from exposure to methidathion in drinking water is clearly less than the negligible risk level at both the maximum likelihood estimate and the 95% upper bound estimate. The upper bound cancer risk estimate for combined dietary and drinking water exposure was slightly greater than the negligible risk level, but is probably acceptable given the limited

evidence of a genotoxic mechanism for carcinogenicity. A maximum contaminant level (MCL) has not been established for methidathion in water (U.S. EPA, 1999).

In contrast, the potential health risks from occupational exposure appear to be quite high for most exposure scenarios, suggesting mitigation is needed. The acute, seasonal and chronic MOEs were less than 100 for all scenarios, except seasonal MOEs for thinning artichokes and chronic MOEs for all field worker scenarios. The MOEs were less than 10 for most exposure scenarios and less than 1 for some scenarios (aerial handlers and airblast applicators). In addition, the carcinogenic risk estimates for occupational exposure to methidathion all exceeded the negligible risk level. The estimated carcinogenic risk based on the maximum likelihood estimate ranged from 2.0×10^{-5} to 2.3×10^{-2}. The upper bound estimates of carcinogenic risk were between 3.2×10^{-5} and 3.7×10^{-2}. Airblast applicators had the highest carcinogenic risk estimates.

Acute exposure to methidathion in application site air is of also concern since the MOEs were less than 100 for both infants and adults, suggesting mitigation is needed. The seasonal and chronic MOEs for application site air were greater than 100, but less than 1,000, still meeting the criteria for identifying methidathion as a toxic air contaminant since the MOEs are not 10-fold greater than the benchmark that is considered adequately protective of human health (California Code of Regulations, Title 3, Division 6, Section 6890). The MOEs for seasonal and chronic exposure to methidathion in ambient air were greater than 1,000 for both infants and adults. The carcinogenic risk estimates for both the application site air (2.5×10^{-5} to 3.9×10^{-5}) and ambient air (7.1×10^{-6} to 1.1×10^{-5}) were greater than the negligible risk level, also suggesting mitigation is needed.

The MOEs for most agricultural workers were already significantly less than 100 from occupational exposure alone, consequently, their aggregate MOEs were not significantly lower with the addition of dietary, drinking water and ambient air exposure. Similarly, air exposure was a major contributor to the aggregate exposure for the general population, so that their aggregate MOEs were only slightly lower than their MOEs for air exposure alone.

The health risks for methidathion were probably underestimated due to the lack of toxicity data for the oxygen analog which is the presumed active metabolite. In the absence of these toxicity data, the oxon was assumed to have equivalent in toxicity to the parent compound. Most likely the NOELs for the oxon would have been lower since the oxon is usually more toxic than the parent compound for organophosphorothioates, at least for neurological effects. In addition, the dietary exposure was probably underestimated since the oxon was not analyzed in either the PDP or DPR monitoring data.

IV.D. U.S. EPA'S REREGISTRATION ELIGIBILITY DOCUMENT FOR METHIDATHION

U.S. EPA completed a Human Health Risk Assessment for methidathion in December 1999 (Travaglini, 1999). U.S. EPA evaluated dietary, drinking water and occupational exposure to methidathion using route-specific NOELs whenever possible. U.S. EPA estimated acute dietary exposure to methidathion using PDP data and a Monte Carlo analysis in their recent Human Health Risk Assessment for methidathion (Travaglini, 1999). At the 99.9th percentile,

U.S. EPA's acute dietary estimates ranged from 0.281 µg/kg/day for females 13 years and older to 1.280 µg/kg/day for nursing infants less than 1 year old. These estimates were similar or slightly higher than the estimates DPR obtained for acute exposure with the Tier 3 analysis using the 99.9th percentile and PDP monitoring data. U.S. EPA estimated the chronic dietary exposure to range from 0.040 µg/kg/day for females 13 years and older to 0.338 µg/kg/day for children 1 to 6 years old with adjustment for percent crop treated. Unlike acute exposure, U.S. EPA's chronic dietary estimates are higher than DPR's chronic exposure estimates although it appears they only did a Tier 2 analysis whereas DPR did a Tier 3 analysis for chronic dietary exposure because of the carcinogenicity concern.

For acute dietary and drinking water exposure, U.S. EPA used a NOEL of 0.2 mg/kg/day from the 90-day neurotoxicity study based on brain ChE inhibition observed at 2 weeks (Chow and Turnier, 1995). DPR used the same study and NOEL for evaluating acute exposure. Using this acute NOEL, both U.S. EPA and DPR found the acute dietary MOEs did not exceed their level of concern even at the 99.9th percentile. For chronic dietary and drinking water exposure, U.S. EPA use a NOEL of 0.15 mg/kg/day from a 1-year chronic toxicity study in dogs based on RBC ChE inhibition, elevated liver enzymes and liver lesions (Chang and Walberg, 1991). DPR also used the same dog study and NOEL for evaluating chronic exposure to methidathion. Using this chronic NOEL, the MOEs for chronic dietary exposure also did not exceed the level of concern for either U.S. EPA or DPR, although the chronic MOEs from DPR's analysis were higher due to their more refined chronic dietary exposure analysis (Tier 3) compared to U.S. EPA's (Tier 2).

U.S. EPA calculated Estimated Environmental Concentrations (EECs) for methidathion in drinking water using the SCI-GROW model for ground water and the PRIZM-EXAMS model for surface water (Travaglini, 1999). The ground and surface water EECs were 0.4 and 6 ppb, respectively, for acute exposure. For chronic exposure, the EECs were 0.4 and 0.6 ppb for ground and surface water, respectively. Although DPR considers methidathion a potential groundwater contaminant based on environmental fate studies submitted, no methidathion residues have been detected in well water monitored by DPR between 1989 and 1996. Methidathion residues were detected in surface water monitoring by DPR and U.S. Geological Survey; however, no residues were detected in the PDP drinking water samples from California between 2001 and 2003 whose source waters were primarily surface water. Since it was uncertain if the surface water analyzed by DPR was used for drinking water or if the methidathion residues would remain after normal water treatment, the DPR used the PDP data in its drinking water exposure estimates. U.S. EPA's EECs were significantly higher than the residues used by DPR which were the LOD (0.021 ppb) and ½ of the LOD (0.011 ppb) for acute and chronic exposure, respectively.

U.S EPA used Drinking Water Levels of Comparison (DWLOCs) to evaluate risk for drinking water. A DWLOC is the concentration of pesticide that is acceptable as an upper limit taking into consideration the aggregate exposure from food, water and residential uses. A DWLOC may vary between population subgroups depending on water consumption patterns and body weights. They estimated the acute DWLOCs to vary from 7.2 to 59 ppb for various sensitive population subgroups. The estimated chronic DWLOCs ranged from 13 to 48 ppb for the sensitive population subgroups. In all subgroups, the EECs did not exceed the DWLOCs. DPR evaluated drinking water exposure by using PDP drinking water data from California

between 2001 and 2003. The acute and chronic drinking water exposure were evaluated separately and in combination with the dietary exposure for all population subgroups. The MOEs for drinking water exposure were all greater than 100, even when combined with dietary exposure.

U.S. EPA evaluated short-term dermal exposure in workers using a 21-day dermal toxicity study in rabbits conducted by Folinusz *et al.* (1986) with a NOEL of 20 mg/kg/day. DPR used the acute NOEL of 0.18 mg/kg/day based on ChE inhibition in the cerebral cortex of male rats at 2 weeks in the 90-day neurotoxicity study to evaluate acute dermal and inhalation occupational exposure to methidathion (Chow and Turnier, 1995). U.S. EPA selected the 90-day neurotoxicity study for evaluating intermediate-term dermal and short and intermediate-term inhalation exposure to methidathion in workers with an estimated NOEL of 0.2 mg/kg/day based on plasma, RBC and brain ChE inhibition. Because a route-specific NOEL was not used, U.S. EPA applied a dermal absorption factor of 30% or an inhalation absorption factor of 100% to the exposure dosage before calculating the MOEs. The dermal absorption was estimated by taking the ratio of the NOAELs from the oral developmental toxicity study in rabbits (6 mg/kg/day) and the 21-day dermal toxicity study in rabbits (20 mg/kg/day). DPR also used the same NOEL from the 90-day neurotoxicity study in rats for evaluating subchronic dermal and inhalation occupational exposure to methidathion. However, DPR assumed a default of 50% dermal absorption and 100% inhalation absorption.   U.S. EPA concluded that the current use pattern (1-2 applications/year) did not indicate a concern for potential long-term occupational exposure and, therefore, did not calculate any chronic MOEs. DPR concluded there was sufficient use throughout the year to calculate chronic MOEs for occupational exposure. U.S. EPA classified methidathion as a group C carcinogen (possible human carcinogen) based on the liver tumors in male mice, but did not consider the evidence strong enough to warrant a quantitative estimation of human risk. DPR did calculate carcinogenic risk estimates for occupational exposure.

U.S. EPA calculated the occupational exposure for handlers using their Pesticide Handlers Exposure Database (PHED). DPR also used PHED to calculate exposure dosages for handlers. The same assumptions were made regarding the application rates, average body weight, average workday, acres applied per day. Despite using the same general method for calculating exposure, the ADDs calculated by U.S. EPA were lower than those calculated by DPR, primarily because DPR used the 90th upper confidence limit on the 95th percentile for the ADD, and the 90th upper confidence limit on the arithmetic mean for the SADD. U.S. EPA used only the geometric mean estimates for their ADDs to evaluate both short-term and intermediate-term exposure. For post-application occupational exposure, U.S. EPA used a similar formula to DPR's for calculating dermal exposure dosages from dislodgeable foliar residues (DFRs) and transfer factors (TFs); however, different DFRs were used. The DFRs varied depending on the REI used and the data from which the DFRs were derived.   DPR preferred to use California-specific data whenever available due to the effect of weather on DFR dissipation. Consequently, different estimated dermal doses were calculated. U.S. EPA incorporated mitigation in their exposure assessment when MOEs were less than the target MOE of 100. However, in their 1999 risk assessment, U.S. EPA estimated the dermal MOEs were less than their target of 100 after mitigation for mixing/loading of the liquid formulation for aerial application. The combined dermal and inhalation MOEs were less than 100 for mixing and loading of water soluble packets (WSPs) for aerial application and liquid aerial application with

fixed-wing aircraft. U.S. EPA only considered changes in REIs in the mitigation for post-application exposure. The required REI that would result in an MOE greater than 100 varied from 1 day for early scouting in cotton fields to 24 days for citrus harvesting. DPR's exposure assessment only incorporated the protective equipment, engineering controls and REIs that are recommended in the current labels.

As part of the Food Quality Protection Act (FQPA), U.S. EPA evaluated the developmental and reproductive toxicity studies for methidathion and recommended the 10X uncertainty factor be reduced to 1X based on 1) completeness of the database, 2) no evidence of increased susceptibility in the developmental toxicity studies, 3) no evidence of increased susceptibility in the reproductive toxicity study, 4) no evidence for requiring a developmental neurotoxicity study in rats, 5) adequate residue data for evaluating dietary and drinking water exposure and 6) no residential use. DPR also concluded there was no evidence of increased pre- or post-natal sensitivity from the developmental and reproductive toxicity studies in rats and rabbits.

U.S. EPA completed an Interim Reregistration Eligibility Document (IRED) in March 2002 (U.S. EPA, 2002b). There were no changes in the dietary and drinking water assessment from the 1999 risk assessment. The toxicity studies selected for evaluating short-term and intermediate-term occupational exposure also did not change. There were some slight changes in the exposure estimates based on different MOEs reported for the same tasks compared to their risk assessment from 1999. It is unclear what the basis was for these changes in the exposure estimates since the discussion of the exposure estimates was more brief than in the 1999 risk assessment and the exposure estimates were not reported. Regardless, U.S. EPA remained concerned about mixing and loading of WSPs for aerial application and liquid aerial application by fixed-wing aircraft. U.S. EPA proposed mitigating these risks by limiting the use of WSPs to non-aerial application, addition of PPE, use of closed systems and the application of minimum of 500 gallons of water per acre to dilute methidathion products. U.S. EPA recognizes these measures will not increase the MOEs to above 100 in all cases, but considers the remaining risks reasonable given protective assumptions in the risk assessment and considering the benefits of methidathion use.

IV.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated U.S. EPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (U.S. EPA, 1997a and b). The improvements to risk assessment were based on the recommendations from the 1993 National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NAS, 1993). The Act required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, U.S. EPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

IV.E.1. Prenatal and Postnatal Sensitivity

Five developmental toxicity studies (3 with rats and 2 with rabbits) were available for methidathion. One rat and one rabbit study were acceptable based on FIFRA guidelines. Fetal effects included reduced ossification of the sternabrae and reduced body weights. The lowest developmental NOEL in an acceptable study was equal to or greater than 2.5 mg/kg/day, the highest dose tested in rats. There was no evidence of increased prenatal sensitivity to methidathion in any of these studies since the developmental NOELs were equal to or greater than the maternal NOELs. However, brain ChE activity was not measured in either adults or pups in any of the developmental toxicity studies.

Four reproductive toxicity studies in rats were available for methidathion with exposure ranging from one to three generations. Only one of these studies was found acceptable to DPR based on FIFRA guidelines. The effects observed in pups included tremors, signs of maternal neglect (cool to touch, starving, weak or lethargic), reduced pup weights and reduced survival. In the one acceptable study, the pup NOEL was the same as parental NOEL, 5 ppm (0.4 mg/kg/day). A comparison of the acute toxicity of methidathion in adult (> 90 days of age) and weanling (4-6 weeks of age) rats found weanling rats were slightly more sensitive to methidathion based on a slightly lower oral LD_{50} value (M: 21 mg/kg) than adults (M: 31 mg/kg; F: 32 mg/kg) (Gaines and Linder, 1986). Based on this evidence, there may be an increased postnatal sensitivity to methidathion. None of the reproductive toxicity studies nor the acute toxicity study conducted by Gaines and Linder (1986) measured brain ChE activity in either adults or pups.

IV.E.2. Endocrine Effects

The Food Quality Protection Act (FQPA) of 1996 required U.S. EPA to develop a screening program to determine the endocrine disruption potential of pesticides. In 1997, the Risk Assessment Forum of the U.S. EPA published a report that reviewed the current state of science relative to environmental endocrine disruption (U.S. EPA, 1997c). U.S. EPA formed the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to develop a strategy for screening and testing of pesticides for their potential to produce endocrine disruption. The EDSTAC members include various stakeholders and scientific experts. This screening and testing process was to be implemented by August of 1999 as required by FQPA.

Environmental chemicals can interact with the endocrine system, resulting in cancer, reproductive and/or developmental anomalies (EDSTAC, 1998). It may produce these effects by affecting hormonal production and synthesis, binding directly to hormone receptors or interfering with the breakdown of hormones (U.S. EPA, 1997c).   The interim science policy stated in U.S. EPA's 1997 report is that "*the Agency does not consider endocrine disruption to be an adverse endpoint per se, but rather to be a mode or mechanism of action leading to other outcomes*." The only possible endocrine related effects in the available animal studies for methidathion were reduced mating index and poor maternal care (Salamon 1986 & 1987). However, it is unclear from these data if either of these effects are mediated through endocrine disruption, ChE inhibition or some other mechanism.

IV.E.3. Cumulative Toxicity

There is a potential for cumulative toxicity between methidathion and other organophosphates (OPs) because they have a common mechanism of toxicity, inhibition of ChE. In fact, there is evidence that methidathion acted synergistically with at least 6 (carbaryl, mevinphos, azinphos-methyl, methyl parathion, fenchlorphos and disulfoton) out of 15 organophosphate compounds tested (Woodard Research, 1966a). Exposure to methidathion in the induction phase also resulted in a cross reaction when later challenged with DDVP and naled, but not benomyl (Matsushita *et al.*, 1985). However, until recently, a scientifically defensible approach to quantitatively evaluate the potential for cumulative toxicity was not available. An elaborate methodology was recently developed by U.S. EPA to assess the exposure to multiple chemicals with a common mechanism of action (U.S. EPA, 2002c). Because the OPs were assigned priority for tolerance reassessment, they were the first to be considered as a "common mechanism group" for cumulative risk assessments. In 2001, U.S. EPA completed a preliminary cumulative risk assessment for the OPs (U.S. EPA, 2001). The assessment estimated the potential risk from exposure to multiple OPs by multiple pathways. A total of 31 OP pesticides were included in the risk assessment. These OPs were selected based on their detection in the USDA's PDP, as well as their potential for human exposure through residential, non-occupational uses and drinking water. The assessment utilized data from three exposure pathways: food, drinking water and residential/non-occupational exposure to OPs (air, soil, grass, indoor surfaces). Methidathion was one of the evaluated OPs in the food and drinking water exposure pathways.

U.S. EPA employed the relative potency factor (RPF) method to determine the combined exposure to the OPs. RPF was defined as the ratio of the toxic potency of a compound to that of an index chemical. Methamidophos was selected as the index chemical, because of the quality and extensive availability of its dose-response data for all routes of exposure. The toxic potencies for the OPs were based on the common endpoint of the inhibition of the brain ChE activity in female rats for 21 days or longer. Both the point of comparison among the chemicals and the point of departure (POD) for the index chemical was based on the BMD_{10}, the benchmark response of 10% reduction of the ChE activity. In this analysis, U.S. EPA considered the exposure to OP residues in foods as uniform across the U.S. Twelve regional assessments were conducted for drinking water and residential exposures. The uniform food exposure estimate was combined with region-specific exposures from residential uses and drinking water. In Region 7, which included California, the use of methidathion on apples, pears, peaches, apricots, nectarines, plums, almonds, walnuts, oranges, tomatoes and alfalfa was considered in the drinking water exposure modeling for the north and/or south central valley.

The conclusions from the preliminary OP cumulative risk assessment were that the drinking water was not a major contributor to the total risk. The exposures from OPs in food at percentiles above the 95th percentile for all population subgroups were at least one order of magnitude higher than water. U.S. EPA indicated that additional sensitivity analysis is needed on the upper percentiles of the food exposure assessments before any risk management decisions can be made. Following this preliminary assessment, U.S. EPA began developing guidelines for the application of the FQPA factor for pre and post-natal sensitivity in the cumulative risk assessments for chemicals with a common mechanism of toxicity (U.S. EPA, 2002d).

117

U.S. EPA revised the preliminary cumulative risk assessment for OPs after considering public comment and additional scientific review (U.S. EPA, 2002a). One of the major additions was assignment of different FQPA factors to various OPs based on the available information regarding increased sensitivity in infants and children. They assigned an FQPA factor of 3X to most OPS including methidathion. This is in contrast to the FQPA factor that U.S. EPA has recommended in the separate risk assessments for methidathion conducted in 1999 and 2002 (U.S. EPA, 1999 & 2002b). This decision was based on missing comparative ChE inhibition data in young animals. They also included over-tolerance values into the dietary exposure assessment and added a 7-day rolling average exposure estimate. They reduced the number of regions for drinking water analysis down from 13 to 7. A sensitivity analysis was conducted to look at individual animal data, extreme outliers in the CSFII data (no outliers identified), use of 14- and 21-day rolling averages in dietary exposure, use of additional subpopulations in dietary and drinking water exposure assessments. They also identified pesticide/crop combinations that had significant roles in the risk estimates. Ranges of risks were identified at various percentiles of exposure. For most portions of the ranges, the MOEs did not represent levels of potential concern for dietary exposure. Drinking water still was not considered a significant source of exposure, even considering periods of high-volume runoff.

In 2006, U.S. EPA updated the cumulative risk assessment for OPs (U.S. EPA, 2006). This risk assessment took into consideration mitigation taken by the agency affecting food, drinking water and residential risk estimates for the various OPs. More OP-specific FQPA factors were used which were applied to RPF factor for each OP. However, a standard 10X FQPA factor was used for most OPs including methidathion which lacked two critical studies, a developmental neurotoxicity study and a comparative ChE study in juveniles and adults. In addition, inter- and intra-species extrapolation was evaluated, although a target MOE of 100 was still used. The MOEs for single-day dietary exposures were greater than 100 for all population subgroups at the 99th percentile, but not the 99.9th. The MOEs for 21-day dietary exposure were all greater than 100 at the 99.9th percentile, except for children 3-5 yrs old whose MOE was 99. The other change to the 2006 update was an evaluation of the drinking water risk estimates assuming the oxons of OPs that form them are 10X or 100X more toxic than the parent. When the oxon was assumed to be 10X as toxic methidathion became a major contributor to the risk for Region C (southwest and California central valley). Region C included the use of a number of oxon formers. When the oxon was assumed to be 100X as toxic, methidathion became the dominant contributor in Region C. However, the cumulative OP exposures from drinking water were generally orders of magnitude lower than exposures from food sources.

IV.E.4. Aggregate Exposure

The combined dietary, drinking water, occupational, and residential air exposure for agricultural workers has been addressed in this document. The dietary, drinking water and residential air exposure was less than 5% of the aggregate exposure for most workers. Consequently, its addition did not significantly impact the aggregate exposure. Only for work activities where the occupational exposure was low (e.g., M/L/As for low-pressure handwand, harvesting/thinning of citrus, and thinning of artichokes), did the dietary, drinking water and residential air represent a significant contribution. Even for these activities, the dietary, drinking water and residential air exposure represented 6-46% of the aggregate exposure.

The combined dietary, drinking water and ambient air exposure for the general public was also addressed in this document. The aggregate acute MOEs for the general public at the application site were all less than 100, except for the 1-hr MOE for adults. The aggregate carcinogenic risk estimates for the general public were higher than the negligible risk level for both the application site air (2.5×10^{-5} to 3.9×10^{-5}) and ambient air (7.1×10^{-6} to 1.1×10^{-5}). The air exposure appears to be the primary contributor since the carcinogenic risk estimates from air exposure alone were also significantly greater than negligible risk level. Dietary exposure was also a significant contributor since the carcinogenic risk estimates from dietary exposure alone were slightly greater than the negligible risk level. The drinking water exposure contributed the least to the aggregate exposure for the general population since drinking water exposure alone were slightly less than the negligible risk level.

V. TOLERANCE ASSESSMENT

V.A. INTRODUCTION

V.A.1. U.S. EPA

U.S. EPA is responsible under the Federal Food, Drug, and Cosmetic Act (FFDCA) for setting tolerances for pesticide residues in RACs (Section 408 of FFDCA) and processed commodities (Section 409 of FFDCA). A tolerance is the legal maximum residue concentration of a pesticide which is allowed on a raw agricultural commodity or processed food. The tolerances are established 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). The data requirements for tolerances include: (1) residue chemistry, (2) environmental fate, (3) toxicology, (4) product performance such as efficacy, and (5) product chemistry (Code of Federal Regulations, 1996). 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).

In 1996, the Food Quality Protection Act (FQPA) amended the overall regulation of pesticide residues under FIFRA and FFDCA (U.S. EPA, 1997a and b). One major change was the removal of the Delaney Clause that prohibited residues of cancer-causing pesticides in processed foods. The tolerances must be health-based and the same standards are used to establish tolerances for both the RACs and their processed forms. FQPA required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, the evaluations of the tolerance must take into account: (1) aggregate exposure from all non-occupational sources, (2) effects from cumulative exposure to the pesticide and other substances with common mechanisms of toxicity, (3) effects of *in utero* exposure; and (4) potential for endocrine disrupting effects.

Under FQPA, U.S. EPA is also required to reassess all existing tolerances and exemptions from tolerances for both active and inert ingredients by 2006 (U.S. EPA, 1997d). Previously, U.S. EPA reassessed tolerances as part of its reregistration and Special Review processes. In the evaluation of tolerances, the U.S. EPA uses a tiered approach and the assessment includes all label-use commodities.

V.A.2. California

In California, U.S. EPA established tolerances are evaluated under the mandate of Assembly Bill 2161, generally referred to as the Food Safety Act (Bronzan and Jones, 1989). The Act requires DPR to conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides. In these assessments, the tolerance for each specific commodity is evaluated individually and is discussed in the following sections. For a pesticide registered for use on a large number of commodities, tolerance assessments are conducted for only a group of selected fruits and vegetables. Generally, commodities are selected from all the uses based on the potential for high levels of exposure. For a number of

RACs, only the tolerances for the commodities on FDA's list of the 20 most frequently consumed fruits and vegetables were examined. These commodities were selected because of either their high consumption (oranges, apples, pears, peaches, plums, apricots, cherries, almonds, walnuts, sunflower seeds) and/or high tolerance (oranges, grapefruit, lemons, tangerines). For methidathion, the tolerances for the following commodities were evaluated: oranges (2.0 ppm), lemons (2.0 ppm), grapefruit (2.0 ppm), tangerines (6.0 ppm), apples (0.05 ppm), pears (0.05 ppm), peaches (0.05 ppm), apricots (0.05 ppm), cherries (0.05 ppm), plums (0.05 ppm), almonds (0.05 ppm), walnuts (0.05 ppm) and sunflower seeds (0.5 ppm). The tolerances for methidathion in these commodities do not include the oxygen analog.

V.B. ACUTE EXPOSURE

An acute exposure assessment is conducted for each individual label-approved commodity at the tolerance. The DEEM-FCID™ Acute Analysis software program and the 1994-98 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. The 95th percentile of user-day exposures for all specific population subgroups was used in evaluating the margins of exposure for the various population subgroups.

The acute MOEs for the 12 commodities analyzed are summarized in Table 45. The consumption of some commodities was sufficiently low in certain population subgroups, such as infants less than 1 year old and pregnant or nursing females (13 years and older), so that a calculation of the exposure and MOE was not considered reliable for these population subgroups. The exposure and MOE estimates were considered unreliable when there were less than 25 user-days for any population subgroup.

The MOEs were less than 100 for most population subgroups for oranges, grapefruit and tangerines. The MOEs were also less than 100 for a few infant or children population subgroups for lemons and apples. The MOEs were equal to or greater than 100 for all the population subgroups for pears, stone fruits, nuts and sunflower seeds. Based on these analyses, the tolerances for citrus fruit should be reevaluated by U.S. EPA. The tolerance for apples should also be reevaluated based on the low MOEs for infants and toddlers. In order to obtain MOEs of at least 100 at the 95th percentile, the tolerances for citrus fruit and apples would need to be reduced to 0.05 and 0.04 ppm, respectively.

V.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. This conclusion is supported by data from both PDP 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, 1994-2002).

Table 45.   Margins of Exposure for Acute Dietary Exposure to Tolerance Levels of Methidathion on Selected Raw Agricultural Commodities[a]

Population Subgroup	Oranges	Grapefruit	Tangerines	Lemons	Apples	Plums	Pears
U.S. Population	7	23	33	160	270	840	950
Western Region	7	23	33	160	270	750	780
Nursing Infants (<1 yr)	5	LC	LC	LC	100	LC	170
Non-Nursing Infants (<1 yr)	4	1	43	130	90	300	210
Children (1-2 yrs)	3	21	11	70	90	320	320
Children (3-5 yrs)	4	71	35	70	140	530	510
Children (6-12 yrs)	6	130	110	100	300	550	1,100
Youth (13-19 yrs)	7	20	110	120	470	LC	2,900
Adults (20-49 yrs)	10	19	33	160	730	1,300	1,400
Adults (50+ yrs)	16	21	21	280	880	960	1,400
Females (13-49 yrs)	9	20	25	150	640	970	1,400
Females (13+ yrs/P/NN)	11	LC	LC	110	310	LC	LC
Females (13+ yrs/N)	10	LC	LC	150	610	LC	LC

a   Based on 95th exposure percentile for all user-day population subgroups. Values rounded to two significant figures.
LC   There were less than 25 user-days for this population subgroup in the 1994-98 USDA Continuing Survey of Food Intakes by Individuals (CSFII), so the MOE was not considered reliable.
P   Pregnant
NN   Not nursing
N   Nursing

Table 45 (cont.).   Margins of Exposure for Acute Dietary Exposure to Tolerance Levels of
Methidathion on Selected Raw Agricultural Commodities[a]

Population Subgroup	Peaches	Apricots	Cherries	Almonds	Walnuts	Sunflower Seeds
U.S. Population	1,700	7,100	12,000	14,000	21,000	38,000
Western Region	1,600	3,700	11,000	12,000	18,000	10,000
Nursing Infants (<1 yr)	260	580	3,600	LC	LC	450
Non-Nursing Infants (<1 yr)	260	430	1,800	LC	LC	270
Children (1-2 yrs)	460	1,200	7,200	11,000	6,500	29,000
Children (3-5 yrs)	840	7,600	9,300	8,000	13,000	38,000
Children (6-12 yrs)	1,600	9,800	13,000	16,000	20,000	42,000
Youth (13-19 yrs)	2,300	19,000	20,000	17,000	21,000	85,000
Adults (20-49 yrs)	2,200	10,000	19,000	12,000	25,000	67,000
Adults (50+ yrs)	2,200	5,400	12,000	14,000	26,000	92,000
Females (13-49 yrs)	2,000	14,000	20,000	11,000	24,000	97,000
Females (13+ yrs/P/NN)	1,300	LC	76,000	LC	LC	140,000
Females (13+ yrs/N)	LC	LC	LC	LC	LC	66,000

  a   Based on 95th exposure percentile for all user-day population subgroups. Values rounded to two significant figures.
LC   There were less than 25 user-days for this population subgroup in the 1994-98 USDA Continuing Survey of Food
      Intakes by Individuals (CSFII), so the MOE was not considered reliable.
  P   Pregnant
NN   Not nursing
  N   Nursing

VI. REFERENCE DOSES/CONCENTRATIONS

The reference dose (RfD) or reference concentration (RfC) is the dose at which no adverse effects are expected to occur in humans. RfDs and RfCs were calculated for methidathion for acute, seasonal and chronic exposures.   Generally, the RfDs are calculated by dividing the NOELs by an uncertainty factor of 100 when the NOEL is from an animal study to account for interspecies and intraspecies variation in sensitivity. A NOEL of 0.18 mg/kg was selected for evaluating acute exposure based on depressed ChE activity in the cerebral cortex of male rats (74% of controls) after 2 weeks of exposure in the 90-day neurotoxicity study. Using this NOEL, the acute RfD for methidathion is 0.0018 mg/kg/day or 1.8 µg/kg/day. This acute RfD could be used for evaluating dietary exposure without adjustment for oral absorption since dietary exposure dosages are usually expressed as external dosages. For evaluating occupational exposure, the RfD may need to be converted to an absorbed dosage depending on how the exposure dosages for workers are calculated. The oral absorption for methidathion was assumed to be 100% based on the available pharmacokinetics data; therefore, no adjustment is needed. The acute RfD would be only protective for systemic effects with occupational exposure, although local effects such as dermal irritation are not a major concern with methidathion. An acute RfC was also calculated for evaluating acute inhalation exposure (ambient air) to methidathion using the acute oral NOEL. The oral NOEL was converted to an equivalent human inhalation NOEL by dividing it by the respiratory rate for humans.

$$ human\ inhalation\ NOEL\,(mg/m^3)\ \ =\ \frac{animal\ oral\ NOEL\,(mg/kg)}{respiratory\ rate_{human}\ (m^3/kg)} $$

The default respiratory rates assumed for infants and adults were 0.59 and 0.28 m^3/kg/day, respectively. The resulting equivalent acute human inhalation NOELs were 0.31 and 0.64 mg/m^3 for infants and adults, respectively. After dividing the equivalent human inhalation NOEL by an uncertainty factor of 100, the resultant acute RfCs (24 hrs) are 3.1 µg/m^3 (0.25 ppb) and 6.4 µg/m^3 (0.52 ppb) (Table 46).

$$ RfC\,(mg/m^3)\ \ =\ \frac{human\ inhalation\ NOEL\,(mg/m^3)}{uncerta\,inty\ factor\,(e.g.,100)} $$

$$ RfC\,(ppm)\ \ =\ \ RfC\,(mg/m^3)\,x\,\frac{M.Vol.\,(24.5L\ @\ 25^c\,C)}{M.Wt.\,(302g)} $$

The 24-hour time weighted average air concentration of methidathion in the first 24 hours with application site monitoring was 0.88 µg/m^3 (71 ppt). The 95th percent upper bound estimate of the ambient air concentrations at the Jefferson site was 0.66 µg/m^3 (54 ppt).

To evaluate seasonal exposure, the NOEL of 0.18 mg/kg/day from the oral 90-day neurotoxicity was selected in which depressed ChE activity in the RBCs of both sexes (56-81%), in the cerebral cortex of male rats (74% of controls) and in the striatum (63% of controls) and hippocampus (76'% of controls) of female rats was observed at the LOEL after 90 days.   Since the NOEL was the same for acute and seasonal exposure, the seasonal RfCs for infants and adults are the same as for acute RfCs. The mean air concentration at the Jefferson site during the one-month monitoring period was estimated to be 86 ng/m^3 (7.0 ppt).

Table 46. Reference Doses and Concentrations for Methidathion

Exposure Scenario	NOEL	Effects on LOEL	RfD	RfC	
				Infants	Adults
Acute	0.18 mg/kg	Reduced ChE activity in cerebral cortex of male rats	1.8 μg/kg	3.1 μg/m^3 (0.25 ppb)	6.4 μg/m^3 (0.52 ppb)
Seasonal	0.18 mg/kg/day	Reduced ChE activity in RBCs, cerebral cortex (M), striatum (F) and hippocampus (F) of rats	1.8 μg/kg/day	3.1 μg/m^3 (0.25 ppb)	6.4 μg/m^3 (0.52 ppb)
Chronic	0.15 mg/kg/day	Elevated liver enzymes in serum and liver histopathology in dogs	1.5 μg/kg/day	2.5 μg/m^3 (0.21 ppb)	5.4 μg/m^3 (0.43 ppb)
Lifetime	Potency 0.53 (mg/kg/day)$^{-1}$	Liver tumors in male mice	1.9 ng/kg/day	-----	6.8 ng/m^3 (0.6 ppt)

To evaluate chronic dietary and occupational exposure to methidathion, the NOEL of 0.15 mg/kg/day from the 1-year dog study was selected in which elevated liver enzymes in the serum and histological lesions in the liver were seen at the LOEL. Using this NOEL, the chronic RfD is 0.0015 mg/kg/day or 1.5 μg/kg/day. The equivalent chronic human inhalation NOELs were 0.25 and 0.54 mg/m^3 for infants and adults, respectively. The resultant chronic RfCs for methidathion are 2.5 μg/m^3 (0.21 ppb) for infants and 5.4 μg/m^3 (0.43 ppb) . Assuming the season for methidathion use lasts 9 months, the annual average air concentration at the Jefferson site would be 64 ng/m^3 (5.2 ppt).

Generally, RfDs/RfCs are not calculated for carcinogenicity since it is assumed there is no threshold for this endpoint. However, it is possible to calculate a dose or air concentration at which the carcinogenic risk is negligible. To do this, the negligible risk level (1×10^{-6}) is divided by the 95% UB estimate of carcinogenic potency (0.53 (mg/kg/day)$^{-1}$). For methidathion, the exposure dosage or RfD corresponding to a negligible carcinogenic risk is 1.9 ng/kg/day. The exposure dosage was converted to an air concentration by dividing by the estimated breathing rate for an adult male (0.28 m^3/kg/day). The air concentration below which there would be no regulatory concern for carcinogenic effects is 6.8 ng/m^3 (0.6 ppt).

VII. CONCLUSIONS

The risks for potential adverse human health effects with dietary, drinking water, occupational and ambient air exposure to methidathion were evaluated using margins of exposure (MOEs) estimates.   The MOEs for acute, subchronic and chronic exposure were calculated using no-observed-effect levels (NOELs) from the available guideline and literature toxicity studies for methidathion. In selecting the NOELs to evaluate exposure, the greatest weight was given to guideline studies which met FIFRA guidelines. Generally, an MOE greater than 100 is considered sufficiently protective of human health when the NOEL for an adverse effect is derived from an animal study. The MOE of 100 allows for humans being 10 times more sensitive than animals and for a 10-fold variation in sensitivity between the lower distribution of the overall human population and the sensitive subgroup. A carcinogenic risk level less than one in a million or 10^{-6} is generally considered negligible.

The potential health risks from dietary exposure to methidathion appear to be low. The MOEs for acute dietary exposure were greater than 200 for all population subgroups in a Tier 3 analysis which included a Monte Carlo analysis for high consumption fruit commodities for which there were PDP monitoring data. Percent crop treated was taken into consideration for the commodities in which the Monte Carlo analysis was performed. The MOEs for chronic dietary exposure to methidathion were equal to or greater than 8,000 with a Tier 3 analysis involving adjustment for percent crop treated for most commodities. The upper bound estimate of carcinogenic risk from dietary exposure to methidathion in the U.S. population was slightly greater than the negligible risk level of 10^{-6} even with use of PDP data and adjustment for percent crop treated. The acute dietary MOEs based on the tolerance for methidathion residues were greater than 100 for all population subgroups on various commodities, except for citrus fruit and apples. Based on these estimates, the tolerance levels for these commodities do not appear to be health protective and DPR recommends that U.S. EPA reevaluate these tolerances.

The potential health risks from methidathion in drinking water also appear to be low. The MOEs for acute exposure to methidathion in drinking water were greater than 15,000 for all population subgroups based on USDA's PDP drinking water data for California from 2001 to 2003. The MOEs for chronic drinking water exposure to methidathion were greater than 150,000. The estimated carcinogenic risk from exposure to methidathion in drinking water was less than the negligible risk level of 10^{-6}. When dietary and drinking water exposures were combined, the acute and chronic MOEs were still greater than 200 and 7,000, respectively, for all population subgroups. Addition of the drinking water exposure to dietary exposure increased the upper bound estimate for carcinogenic risk only slightly since the contribution from dietary exposure was so much greater.

The potential health risks from occupational exposure are of concern. The MOEs for acute, seasonal and chronic occupational exposure to methidathion were less than 100 for all exposure scenarios, except seasonal exposure for thinning artichokes and chronic exposure for all field worker scenarios. The MOEs were less than 10 for most handler scenarios and less than 1 for some handler scenarios (aerial handlers and airblast applicators). In addition, the carcinogenic risk estimates for occupational exposure to methidathion all exceeded the negligible risk level. The estimated carcinogenic risk based on the maximum likelihood estimate ranged from 2.0×10^{-5} to 2.3×10^{-2}. The upper bound estimates of carcinogenic risk were

between and 3.2×10^{-4} to 3.7×10^{-2}. Airblast applicators had the highest carcinogenic risk estimates.

The potential health risks from exposure to methidathion in application site and ambient air are also of concern. The MOEs for acute exposure to methidathion in application site air were less than 100 for both infants and adults, not only meeting the criteria for listing methidathion as a toxic air contaminant, but suggesting mitigation is needed. The seasonal and chronic MOEs for the application site were greater than 100, but less than 1,000 which are still low enough to meet the criteria for listing. The MOEs for seasonal and chronic exposure to methidathion in ambient air were greater than 1,000 for both infants and adults. The carcinogenic risk estimates for the application site (2.5×10^{-5} to 3.9×10^{-5}) and ambient air (7.1×10^{-6} to 1.1×10^{-5}) were above the negligible risk level not only meeting the listing criteria, but indicating mitigation may be needed.

The MOEs for most agricultural workers were already significantly less than 100 from occupational exposure alone, consequently, their aggregate MOEs were not significantly lower with the addition of dietary, drinking water and ambient air exposure. Similarly, air exposure was a major contributor to the aggregate exposure for the general population, so that their aggregate MOEs were only slightly lower than their MOEs for air exposure alone.

The health risks for methidathion were probably underestimated due to the lack of toxicity data for the oxygen analog which is the presumed active metabolite. In the absence of these toxicity data, the oxon was assumed to have equivalent in toxicity to the parent compound. Most likely the NOELs for the oxon would have been lower since the oxon is usually more toxic than the parent compound for organophosphorothioates, at least for neurological effects. Health risks may have also been underestimated from dietary exposure since neither the DPR or PDP monitoring programs analyzed commodities for the oxon. Furthermore, the health risk estimates for methidathion were probably underestimated since they did not take into consideration cumulative exposure from other organophosphates.

VIII. REFERENCES

Albanese, E.J. (Industrial Bio-Test Laboratories, Inc.), 1976. 28-Day range-finding study with Supracide® technical in albino mice. Ciba-Geigy Corp. DPR Vol. 298-016, Rec. No. 935983.

Allon, N., L. Raveh, E. Gilat, E. Cohen, J. Grunwald, and Y. Ashani, 1998. Prophylaxis against soman inhalation toxicity in guinea pigs by pretreatment alone with human serum butyrylcholinesterase. Toxicol. Sci. 43: 121-128.

Altuntas, I., N. Delibas, and R. Sutcu, 2002a. The effects of organophosphate insecticide methidathion on lipid peroxidation and anti-oxidant enzymes in rat erythrocytes: roles of vitamins E and C. Human Exper. Toxicol. 21: 681-685.

Altuntas, I., N. Delibas, M. Demirci, I. Kilinc and N Tamer, 2002b. The effects of methidathion on lipid peroxidation and some liver enzymes: role of vitamins E and C. Arch. Toxicol. 76: 470-473.

Arni, P., 1980a. Salmonella/mammalian-microsome mutagenicity test with GS 13005. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936024.

Arni, P., 1980b. Salmonella/mammalian-microsome mutagenicity test with GS 13005. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936025.

Arni, P., 1980c. Intrasanquine host-mediated assay with S. typhimurium with GS 13005. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936026.

Arni, P., 1980d. Salmonella/mammalian-microsome mutagenicity test with GS 12956. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936022.

Arni, P., 1980e. Salmonella/mammalian-microsome mutagenicity test with GS 28730. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936018.

Arni, P., 1980f. Salmonella/mammalian-microsome mutagenicity test with GS 28369. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936023.

Arni, P. and D. Muller, 1981. Mutagenicity test on *Saccharomyces cerevisiae* MP-1 in vitro with GS 13005 (Test for mutagenic properties in yeast cells). Ciba-Geigy Corp. Cited In: Caris, M. (Health and Welfare Canada), 1993. Methidathion (evaluation for acceptable daily intake). In: Pesticide Residues in Food - 1992. Toxicology Evaluations. World Health Organization, Geneva. pp. 233-265.

Ashby, J. and P.A. Lefevre, 1982. Formaldehyde generators: relationship between stability, lipophilicity and carcinogenic potency. Carcinogenesis 3(11): 1273-1276.

Ashby, J., R.D. Callander and F.L. Rose, 1985. Weak mutagenicity to Salmonella of the formaldehyde-releasing anti-tumor agent hexamethylmelamine. Mutat. Res. 142(3): 121-125.

Aston, L. and J. Seiber, 1997. The fate of summertime airborne organophosphate pesticide residues in the Sierra Nevada Mountains. J. Environ. Qual. 25: 1483-1492.

Ballard, C.G. and E.K. Perry, 2003. The role of butyrylcholinesterase in Alzheimer's disease. *In:* Butyrylcholinesterase: It's function and inhibitors (E. Giacobini, ed.). London: Martin Dunitz. pp. 123-134.

Bartkowiak, D.J. and B.W. Wilson, 1995. Avian plasma carboxylesterase activity as a potential biomarker of organophosphate pesticide exposure. Environ. Toxicol. Chem. 14(2): 2149-2153.

Beauvais, S., 2006 Estimation of Exposure of Persons in California to Pesticide Products That Contain Methidathion. Methidathion Risk Characterization Document, Vol. II. Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. HS-1805.

Bennett, K., 1997. Preliminary results of acute and chronic toxicity testing of surface water monitored in the San Joaquin River, winter 1996-1997. Memorandum to Don Weaver, Environmental Monitoring and Pest Management Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. June 6, 1997.

Brimijoin, S. 1992. Enzymology and biology of cholinesterases. Proceedings of the U.S. EPA Workshop on Cholinesterase Methodologies. Office of Pesticide Programs, U.S. Environmental Protection Agency.

Brimijoin, S. and C. Koenigsberger, 1999. Cholinesterases in neural development: New findings and toxicologic implications. Environ. Health Persp. 107(Suppl. 1): 59-64.

Bronzan and Jones, 1989. Assembly Bill 2161, Addition to the Food and Agriculture Code SEC 8 section 13060. California Food and Agriculture Code, Sacramento, CA.

Bull, D.L., 1968. Metabolism of *0,0*-dimethyl phosphordithioate *S* ester with 4-(mercaptomethyl)-2-methoxy-Δ^2-1,3,4-thiadiazolin-5-one (Geigy GS-13005) in plants and animals. J. Agr. Food Chem. 16(4): 610-615.

Burkhard, N., 1978. Hydrolysis of methidathion (Supracide®, Ultracide®) under laboratory conditions. Ciba-Geigy Corp. DPR Vol. 298-088, Rec. No. 52709.

Burnett, T.J. (Pan-Agricultural Laboratories, Inc.), 1992. Methidathion: Nature of the residues in citrus. Ciba-Geigy Corp. DPR Vol. 298-179, Rec. No. 138595.

Cassidy, J.E., N.F. Wood, and K. Lasker, 1969. Desmethyl GS-13005 and other metabolites in the urine of rats fed GS-13005-5-carbonyl-[14]C. Ciba-Geigy Corp. DPR Vol. 298-120, Rec. No. 92597.

Caris, M. (Health and Welfare Canada), 1992. Methidathion. *In*: Pesticide Residues in Food - 1992: Toxicology Evaluations. Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. World Health Organization, Geneva.

CDFA, 2004. California Agricultural Statistics - 2003. California Agricultural Statistics Service, Sacramento, CA. October 2004. (http://www.cdfa.ca.gov/card/card_new03.htm)

CFR, 2004. Methidathion, tolerances for residues. Code of Federal Regulations, Title 40, Section 180.298. U.S. Government Printing Office, Washington, D.C. July 1, 2004.

Chang, J.C.F. and A.G. Richter, 1994. Acute neurotoxicity study with methidathion technical in rats. Ciba-Geigy Corp. DPR Vol. 298-169, Rec. No. 138546.

Chang, J.C.F. and J.A. Walberg, 1991. 1-Year dietary toxicity study with GS-13005 in beagle dogs. Ciba-Geigy Corp. DPR Vol. 298-115, Rec. No. 89667. Also reported in: Chang, J.C.F., J.A. Walberg, and W.R. Campbell, 1992. One-year dietary toxicity study with methidathion in beagle dogs. Fund. Appl. Toxicol. 19: 307-314.

Chen, H.H., J.L. Hsueh, S.R. Sirianni and C.C. Huang, 1981. Induction of sister-chromatid exchanges and cell cycle delay in cultured mammalian cells treated with eight organophosphorus pesticides. Mut. Res. 88: 307-316.

Chopade, H.M. and W.C. Dauterman, 1981. Studies on the *in vitro* metabolism of methidathion by rat and mouse liver. Pest. Biochem. Physiol. 15: 105-119.

Chow, E. And J.C. Turnier, 1995. 90-Day subchronic neurotoxicity study with methidathion technical in rats. Ciba-Geigy Corp. DPR Vol. 298-207, Rec. No. 141663.

Ciba-Geigy, 1977. Results of tests concerning the amount of residues of methidathion remaining in or on safflower seeds, including a description of the analytical method used. Ciba-Geigy Corp. DPR Vol. 298-047, Rec. No. 21845.

Ciba-Geigy, 1982. Autoradiographic DNA repair test on human fibroblasts - GS 13005. Ciba-Geigy Corp. DPR Vol. 298-089, Rec. No. 53777.

Coulston, F. and L. Golberg (Institute of Experimental Pathology and Toxicology), 1971. Two-year safety evaluation study in rhesus monkeys with GS 13005. Ciba-Geigy Corp. DPR Vol. 298-014, Rec. No. 935999.

Daly, D. (ABC Laboratories, Inc.), 1987. Determination of octanol-water partition coefficient of ^{14}C-methidathion. Ciba-Geigy, Corp. DPR Vol. 298-102, Rec. No. 59677.

Desi, I., M. Palotas, G. Vetro, I. Csolle, M. Nehez, M. Zimanyi, A. Ferke, E. Huszta and L. Nagymajtenyi, 1986. Biological monitoring and health surveillance of a group of greenhouse pesticide sprayers. Toxicol. Letters 33: 91-105.

Donahue, J. (1996). Revised policy on dermal absorption default for pesticides. Memo No. HSM-96005. Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency .

Dourson, M., G. Charnley and R. Scheuplein, 2002. Differential sensitivity of children and adults to chemical toxicity. II. Risk and regulation. Regul. Toxicol. Pharmacol. 35: 448-467.

DPR, 1994-2004. Residues in Fresh Produce. Pesticide Enforcement Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. (http://www.cdpr.ca.gov/docs/pstrsmon/rsmonmnu.htm#resimon)

DPR, 1996. Semiannual Report Summarizing the Reevaluation Status of Pesticide Products During the Period of July 1, 1996 through December 31, 1996. California Environmental Protection Agency, Department of Pesticide Regulation.

DPR, 2000 Summary of Pesticide Use Report Data - 1999, Indexed by Chemical. Department of Pesticide Regulation, California Environmental Protection Agency. September (2000.http://www.cdpr.ca.gov/docs/pur/pur99rep/chmrpt99.pdf)

DPR, 2002. Summary of Pesticide Use Report Data - 2001, Indexed by Chemical. Department of Pesticide Regulation, California Environmental Protection Agency. October 2002. (http://www.cdpr.ca.gov/docs/pur/pur01rep/chmrpt01.pdf)

DPR, 2003a. 2003 Status Report Pesticide Contamination Prevention Act. Department of Pesticide Regulation, California Environmental Protection Agency. December 2003. EH03-07.

DPR, 2003b. Sampling for Pesticide Residues in California Well Water - 2003 Well Inventory Database, Cumulative Report 1986-2003. Department of Pesticide Regulation, California Environmental Protection Agency. December 2003. EH03-08

DPR, 2004. Sampling for Pesticide Residues in California Well Water - 2004 Update of Well Inventory Database. Department of Pesticide Regulation, California Environmental Protection Agency. December 2004. EH04-04.

DPR, 2005. Summary of Pesticide Use Report Data - 2003, Indexed by Chemical. Department of Pesticide Regulation, California Environmental Protection Agency. January 2005. (http://www.cdpr.ca.gov/docs/pur/pur03rep/chmrpt03.pdf)

EDSTAC, 1998. Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) - Final Report. August 1998.

El-Dawy, Kh., S.S. Abd El-Meged, M.F. Mahmoud, M.F. Dowidar, and A.A. Hassan, 1995.
    A biochemical study on the erythrocyte membrane in rats after exposure to some
    commonly used insecticides. Egypt. J. Biochem. 13(2): 329-337.

Ellenhorn, M.J. and D. G. Barceloux, eds., 1988. Pesticides. In: <u>Medical Toxicology:</u>
    <u>Diagnosis and Treatment of Human Poisoning</u>, pp. 1069-1108. Elsevier, New York.
    1512 pp.

Emrani, J., 1992. Methidathion - Metabolism of [2-^{14}C]-methidathion after multiple oral
    administration to lactating goats. Ciba-Geigy Corp. DPR Vol. 180, Rec. No. 138604.

**FDA (Division of Pharmacology, Food and Administration, Department of Health,
    Education and Welfare), 1959.** Appraisal of the Safety of Chemicals in Foods, Drugs
    and Cosmetics. The Association of Food and Drug Officials of the United States, Austin,
    Texas.

Folinusz, P., K. Huber, D.M. Schiavo, J.R. Hazelette, and J.D. Green, 1986. Methidathion -
    21-day dermal toxicity study in rabbits (MIN 852128). Ciba-Geigy Corp. DPR Vol.
    298-092, Rec. No. 55135.

FPCL (Fisons Pest Control Limited) , 1965a. Effect on reproduction. Ciba-Geigy Corp. DPR
    Vol. 298-076, Rec. No. 47484.

FPCL (Fisons Pest Control Limited) , 1965b. Neurotoxic effects in the hen. Ciba-Geigy
    Corp. DPR Vol. 298-076, Rec. No. 935971.

Fritz, H., 1976a. Dominant lethal study on GS 13005 technical - Mouse. Ciba-Geigy Corp.
    DPR Vol. 298-013, Rec. No. 936073.

Fritz, H., 1976b. Reproduction study GS 13005 tech. - Rat - Seg. II (Test for teratogenic or
    embryotoxic effects). Ciba-Geigy Corp. DPR Vol. 298-072, Rec. No. 1179.

Fujita, Y., 1985. Studies on contact dermatitis from pesticides in tea growers. Acta Med. Univ.
    Kagoshima., 27(1): 17-37.

Gaines, T.B. and R.E. Linder, 1986. Acute toxicity of pesticides in adult and weanling rats.
    Fund. Appl. Toxicol. 7: 299-308.

Ganapathy, C. 1999. Preliminary results of acute and chronic toxicity testing of surface water
    monitored in the San Joaquin River watershed, winter 1997-1998. Memorandum to Don
    Weaver, Environmental Monitoring and Pest Management Branch, Department of
    Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.
    January 5, 1999.

**Ganapathy, C., C. Nordmark, K. Bennett, A. Bradley, H. Feng, J. Hernandez, and J.
    White, 1997.** Temporal distribution of insecticide residues in four California Rivers.
    Environmental Hazards Assessment Program, Environmental Monitoring and Pest

Management Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. Report EH97-06.

Gart, J.J., D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf, 1986. Statistical Methods in Cancer Research, Vol III - The Design and Analysis of Long-term Animal Experiments. International Agency for Research on Cancer Scientific Publication No. 79. Lyon, France. pp 82-85.

Gaylor, D.W., R.L. Kodell, J.J. Chen, and D. Krewski, 1999. A unified approach to risk assessment for cancer and non-cancer endpoints based on benchmark doses and uncertainty factors. Reg. Toxicol. Pharmacol. 29: 151-157.

Geigy, 1964. Toxicology of GS 13005. Ciba-Geigy Corp. DPR Vol. 298-018, Rec. No. 935972.

Giacobini, E., 2003. Butyrylcholinesterase: Its role in brain function. *In:* Butyrylcholinesterase: It's function and inhibitors (E. Giacobini, ed.). London: Martin Dunitz. pp. 1-19.

Gokalp, O., K. Gulle, O. Sulak, E. Cicek and I. Altuntas, 2003. The effects of methidathion on liver: role of vitamins E and C. Toxicol. Indust. Health 19: 63-67.

Goldenthal, E.I (International Research and Development Corp.), 1986. Methidathion technical - Two-year dietary oncogenicity study in mice. Ciba-Geigy Corp. DPR Vol. 298-079, Rec. No. 45719.

Grisaru, D., M. Sternfeld, A. Eldor, D. Glick, and H. Soreq, 1999. Structural roles of acetylcholinesterase variants in biology and pathology. Eur. J. Biochem., 264: 672-686.

Gurusinghe, P., 2006. Environmental Fate of Methidathion. Methidathion Risk Characterization Document, Vol. III. Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency.

Henderson, J.D., J.T. Yamamoto, D.M. Fry, J.N. Seiber and B.W. Wilson, 1994. Oral and dermal toxicity of organophosphate pesticides in the domestic pigeon (*Columba livia*). Bull. Environ. Contam. Toxicol. 52: 633-640.

Hertner, T., 1988. Methidathion technical (GS-13005) - Tests for other genotoxic effects - Autoradiographic DNA repair test on rat hepatocytes. Ciba-Geigy Corp. DPR Vol. 298-113, Rec. No. 87195.

Hertner, T., 1990. Methidathion technical (GS-13005) - Tests for other genotoxic effects - Autoradiographic DNA repair test on rat hepatocytes. Ciba-Geigy Corp. DPR Vol. 298-113, Rec. No. 87194.

Holbert, M.S. (Stillmeadow, Inc.), 1989. Supracide 2E - Acute inhalation toxicity study in rats. Ciba-Geigy Corp. DPR Vol. 298-114, Rec. No. 91791.

Holbert, M.S. (Stillmeadow, Inc.), 1992. Supracide 25 WP - Acute inhalation toxicity study in rats. Ciba-Geigy Corp. DPR Vol. 298-132, Rec. No. 116917.

Honeycutt, R.C., 1986a. Field soil dissipation study of Supracide® 2E (methidathion) applied to alfalfa in Fresno County, California. Ciba-Geigy Corp. DPR Vol. 298-088, Rec. No. 52716.

Honeycutt, R.C., 1986b. Field soil dissipation study of Supracide® 2E (methidathion) applied to bareground plots in Vero Beach, Florida. Ciba-Geigy Corp. DPR Vol. 298-088, Rec. No. 52717.

Hool, G., 1980a. Sister chromatid exchange study - GS 13005 - Chinese Hamster. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936027.

Hool, G., 1980b. Nucleus anomaly test in somatic interphase nuclei of Chinese hamster. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936021.

Hool, G., 1980c. Nucleus anomaly test in somatic interphase nuclei - GS 12956 - Chinese hamster test for mutagenic effects on bone marrow cells. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936028.

Hummel, H.E., M.A. Youreneff, M.L.A. Giknis, A.T. Arthur, and E.T. Yau, 1987. Methidathion - a teratology (segment II) study in rabbits. Ciba-Geigy Corp. DPR Vol. 298-096, Rec. No. 55140.

IBT (Industrial Bio-Test Laboratories), 1980. Carcinogenicity evaluation with methidathion technical in albino mice. Ciba-Geigy Corp. DPR Vol. 298-016 & -017, Rec. Nos. 936007 & 936012.

Ito, N., R. Hasegawa, K. Imaida, Y. Kurata, A. Hagiwara and T. Shirai, 1995. Effect of ingestion of 20 pesticides in combination at acceptable daily intake levels on rat liver carcinogenesis. Food Chem. Toxicol. 33(2): 159-163.

JMPR, 1999. Interpretation of cholinesterase inhibition. Pesticide Residues in Food – 1998. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Rome, Italy, 21-30 September 1998. FAO Plant Production and Protection Paper 148. Rome: World Health Organization and Food and Agriculture Organization of the United Nations. pp. 17-19.

Johnston, C.D. (Woodard Research Corp.), 1967. GS 13005 - Safety evaluation by two-year feeding studies in rats and dogs. Ciba-Geigy Corp. DPR Vol. 298-010, Rec. No. 935997.

Kahrs, R.A. and M.J. Kanuk, 1969. Determination of residues of GS-13005 in cotton seed and cotton seed fractions by gas chromatography. Ciba-Geigy Corp. DPR Vol. 298-051, Rec. No. 20420.

Kennedy, E.T., 1992. Methidathion - Metabolism of [2-^{14}C]-methidathion in laying hens. Ciba-Geigy Corp. DPR Vol. 298-181, Rec. No. 138612.

Kesterson, a. (PTRL-East, Inc.), 1991. Laboratory volatility of [^{14}C]methidathion. Ciba-Geigy Corp. DPR Vol. 298-176, Rec. No. 138581.

Kieatiwong, S. (PTRL-West, Inc.), 1992. Photodegradation of [^{14}C]methidathion in the vapor phase by natural sunlight. Ciba-Geigy Corp. DPR Vol. 298-174, Rec. No. 138562.

Kishi, M., N. Hirschhorn, M. Djajadosastra, L.N. Satterlee, S. Strowman and R. Ditts, 1995. Relationship of pesticide spraying to signs and symptoms in Indonesian farmers. Scand. J. Work Environ. Health 21: 124-133.

Kuhn, J.O. (Stillmeadow, Inc.), 1989a. Supracide 2E - Acute oral toxicity study in rats. Ciba-Geigy Corp. DPR Vol. 298-114, Rec. No. 91789.

Kuhn, J.O. (Stillmeadow, Inc.), 1989b. Supracide 2E - Acute dermal toxicity study in rabbits. Ciba-Geigy Corp. DPR Vol. 298-114, Rec. No. 91790.

Kuhn, J.O. (Stillmeadow, Inc.), 1989c. Supracide 2E - Primary dermal irritation study in rabbits. Ciba-Geigy Corp. DPR Vol. 298-114, Rec. No. 91793.

Kuhn, J.O. (Stillmeadow, Inc.), 1989d. Supracide 2E - Primary eye irritation study in rabbits. Ciba-Geigy Corp. DPR Vol. 298-114, Rec. No. 91792.

Kuhn, J.O. (Stillmeadow, Inc.), 1989e. Supracide 2E - Dermal sensitization study in guinea pigs. Ciba-Geigy Corp. DPR Vol. 298-114, Rec. No. 91794.

Kuhn, J.O. (Stillmeadow, Inc.), 1992a. Supracide 25 WP - Acute oral toxicity study in rats. Ciba-Geigy Corp. DPR Vol. 298-132, Rec. No. 116912.

Kuhn, J.O. (Stillmeadow, Inc.), 1992b. Supracide 25 WP - Acute dermal toxicity study in rabbits. Ciba-Geigy Corp. DPR Vol. 298-132, Rec. No. 116915.

Kuhn, J.O. (Stillmeadow, Inc.), 1989c. Supracide 25 WP - Primary dermal irritation study in rabbits. Ciba-Geigy Corp. DPR Vol. 298-132, Rec. No. 116921.

Kuhn, J.O. (Stillmeadow, Inc.), 1989d. Supracide 25 WP - Primary eye irritation study in rabbits. Ciba-Geigy Corp. DPR Vol. 298-132, Rec. No. 116919.

Kuhn, J.O. (Stillmeadow, Inc.), 1989e. Supracide 25 WP - Dermal sensitization study in guinea pigs. Ciba-Geigy Corp. DPR Vol. 298-132, Rec. No. 116922.

Kuhn, J.O. (Stillmeadow, Inc.), 1989f. Acute delayed neurotoxicity of methidathion tech FL 890331 in domestic fowl. Ciba-Geigy Corp. DPR Vol. 298-110, Rec. No. 90269.

Lail, L.J., 1991. Technical methidathion - product chemistry. Ciba-Geigy Corp. DPR Vol. 298-156, Rec. No. 138463.

Leffingwell, T., 1989. Evaluation summary of ground water protection data - methidathion. Department of Pesticide Regulation, California Environmental Protection Agency. DPR Vol. 298-106.

Lefkowitz, R. J., B. B. Hoffman and P. Taylor, 1990. Neurohumoral Transmission: The Autonomic and Somatic Motor Nervous Systems. In: Goodman and Gilman's: The Pharmacological Basis of Therapeutics 8th Edition (Gilman, A.G., T. W. Rall, A. S. Nies and P. Taylor, Eds.), pp. 84-130. Pergamon Press, New York. 1811 pp.

Lewis, C.M, T.P. Kellner, A.L. Rubin, T.B. Moore and K.F. Pfeifer, 2006. Cholinesterase data in risk assessment: I. Defining toxicological significance. The Toxicologist. Vol 90 (1): Abstract No. 2290. Proceedings of the 45th Annual Meeting of the Society of Toxicology, March, 2006.

Li, B., J.A. A. Ticu, W. Xie, L.M. Schopfer, P. Hammond, S. Brimijoin, S.H. Hinrichs and O. Lockridge, 2000. Abundant tissue butyrylcholinesterase and its possible function in the acetylcholinesterase knockout mouse. J. Neurochem. 75(3): 1320-1331.

Lippens, R., M. Claeys, C. Waildemauwe, N. Van Larebeke, 1983. Mutagenicity studies on 10 pesticides, on trichloroethane and on diaminobenzidine. Mutat. Res. 113: 277-278.

Lockridge, O. 1990. Genetic variants of human serum cholinesterase influence metabolism of the muscle relaxant succinylcholine. Pharmacol. Ther. 47(1): 35-60.

Lockridge, O. and P. Masson, 2000. Pesticides and susceptible populations: people with butyrylcholinesterase genetic variants may be at risk. Neurotoxicology. 21(1-2): 113-126.

Lodovici, M., S. Aiolli, C. Monserrat, P. Dolara, A. Medica, and P. DiSimplicio, 1994. Effect of a mixture of 15 commonly used pesticides on DNA levels of 8-hydroxy-2-deoxyguanosine and xenobiotic metabolizing enzymes in rat liver. J. Environ. Pathol. Toxicol. Oncol. 13(3): 163-168.

MacCoy, D., K.L. Crepeau, and K.M. Kuivilia, 1995. Dissolved pesticide data for the San Joaquin River at Vernalis and the Sacramento river at Sacramento, California, 1991-1994. U.S. Geological Survey Open-File Report 95-110.

Mainiero, J., E.J. Levy, R.N. Infurna and E.T. Yau, 1987. Methidathion technical - a teratology (Segment II) study in rats. Ciba-Geigy Corp. DPR Vol. 298-095, Rec. No. 55139.

Marcsinsin, J.F., K.V. Wimbert, R.N. Infurna, and E.T. Yau, 1986. Methidathion technical - a dose rangefinding study in pregnant rats. Ciba-Geigy Corp. DPR Vol. 298-094, Rec. No. 55138.

Martinson, J.P. (Springborn Life Sciences, Inc.), 1988. Determination of adsorption and desorption coefficients of methidathion. Ciba-Geigy Corp. DPR Vol. 298-105, Rec. No. 69522.

Matsushita, T. K. Aoyama, K. Yoshimi, Y. Fujita, and A. Ueda, 1985. Allergic contact dermatitis from organophosphate insecticides. Indust. Health 23: 145-153. Also reported in: Matsushita, T. and K. Aoyama, 1981. Cross reactions between some pesticides and the fungicide benomyl in contact allergy. Indust. Health 19: 77-83.

Mattson, A.M., 1975. Methidathion (GS-13005) - Almonds - Results of tests on the amount of residue remaining, including description of the analytical method. Ciba-Geigy Corp. DPR Vol., Rec. No. 20428.

Mattson, A.M. and R.A. Kahrs, 1974. Methidathion (GS-13005) - Sunflower: Results of tests on the amount of residues remaining, including a description of the analytical methods used. Ciba-Geigy Corp. DPR 298-064, Rec. No. 20451.

Min, K.J., C.G. Cha, and W. Popendorf, 2005. Determination of urinary metabolites of phosalone, methidathion, and IBP after oral administration and dermal application to rats. Bull. Environ. Contam. Toxicol. 74: 809-816.

Mionetto, N., R. Rouillon, and J.-L. Marty, 1992. Inhibition of acetylcholinesterase by organophosphorus and carbamates compounds. Studies on free and immobilized enzymes. Z. Wasser-Abwasser-Forsch. 25: 171-174.

Nehéz, M., P. Boros, A. Ferke, J. Mohos, M. Palotás, G. Vetró, M. Zimányi, and I. Dési, 1988. Cytogenetic examination of people working with agrochemicals in the southern region of Hungary. Regul. Toxicol. Pharmacol. 8: 37-44.

Newell, J., 1987. Density of methidathion technical. Ciba-Geigy Corp. DPR Vol. 298-104, Rec. No. 69240.

Nordmark, C. 1997. Preliminary results of acute and chronic toxicity testing of surface water monitored in the Sacramento River watershed, winter 1996-1997. Memorandum to Don Weaver, Environmental Monitoring and Pest Management Branch, Department of Pesticide Regulation, Sacramento, CA. June 6, 1997.

Nordmark, C. 1998. Preliminary results of acute and chronic toxicity testing of surface water monitored in the Sacramento River watershed, winter 1997-1998. Memorandum to Don Weaver, Environmental Monitoring and Pest Management Branch, Department of Pesticide Regulation, Sacramento, CA. July 31, 1998.

OEHHA, 2005. Air Toxics Hot Spot Program Risk Assessment Guidelines. Part II. Technical Support Document Describing Available Cancer Potency Factors. Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. May 2005. (http://www.oehha.ca.gov/air/hot_spots/may2005tsd.html)

Osherhoff, M.R. (Hazleton Laboratories America, Inc.), 1987a. 10-Day dermal dose range finding study in rabbits with methidathion technical. Ciba-Geigy Corp. DPR Vol. 298-092, Rec. No. 55136.

Osherhoff, M.R. (Hazleton Laboratories America, Inc.), 1987b. 21-Day dermal toxicity study in rabbits with methidathion technical. Ciba-Geigy Corp. DPR Vol. 298-093, Rec. No. 55137.

Pantuck, E.J., 1993. Plasma cholinesterase: gene and variations. Anesth. Analg. 77(2): 380-386.

Petersen, B.J., S.H. Youngren and C.L. Walls, 2001. Modeling dietary exposure with special sections on modeling aggregate and cumulative Exposure. *In:* Hanbook of Pesticide Toxicology, vol. 1 (R. Krieger, ed). Academic Press, San Diego, CA. pp. 443-455.

Poletika, N.N. and C.K. Robb, 1998. A monitoring study to characterize chlorpyrifos concentration patterns and ecological risk in an agriculturally dominated tributary of the San Joaquin River. Dow AgroSciencies LLC Study ENV96055. November, 18, 1998.

Powell, S. , 2002. Memorandum: Approximating Confidence Limits for 95th Percentile and Arithmetic Mean Exposures From the Pesticide Handlers Exposure Database (PHED V1.1). Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. May 10, 2002.

Quest, J.A. M.P. Copley, K.L. Hamernik, E. Rinde, B. Fisher, R. Engler, W. L. Burnham, and P.A. Fenner-Crisp, 1990. Evaluation of the carcinogenic potential of pesticides. 2. Methidathion. Reg. Toxicol. Pharmacol. 12: 117-126.

Raabe, O.G. (1988). Inhalation uptake of xenobiotic vapors by people. Contract Number CARB A 5-155-33. Air Resources Board, California Environmental Protection Agency.

Radeleff, R.D. and S.E. Kunz, 1972. Toxicity and hazard of diazinon, ethion, and supracide to turkeys. J. Econ. Entomol. 65(1): 162-165.

Raveh, L., E. Grauer, J. Grunwald, E. Cohen, and Y. Ashani, 1997. The stoichiometry of protection against soman and VX toxicity in monkeys pretreated with human butyrylcholinesterase. Toxicol. Appl. Pharmacol. 145:43-53.

Rordorf, B.F., 1988. Report on vapor pressure - methidathion. Ciba-Geigy Corp. DPR Vol. 298-104, Rec. No. 69242.

Ross, L., 1992. Preliminary results of the San Joaquin River study: summer 1991. Memorandum to Kean Goh, Environmental Hazards Assessment Program, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. May 21, 1992.

Ross, L., 1993. Preliminary results of the San Joaquin River study: summer 1992. Memorandum to Kean Goh, Environmental Hazards Assessment Program, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. September 22, 1993.

Ross, L.J., R. Stein, J. Hsu, J. White, and K. Hefner, 1996. Distribution and mass loading of insecticides in the San Joaquin River, California: winter 1991-92 and 1992-93. Environmental Hazards Assessment Program, Department of Pesticide Regulation, Sacramento, CA. EH 96-02.

Ross, L.J., R. Stein, J. Hsu, J. White, and K. Hefner, 1999. Distribution and mass loading of insecticides in the San Joaquin River, California: spring 1991 and 1992. Environmental Hazards Assessment Program, Environmental Monitoring and Pest Management Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. Report EH 99-01.

Royce, B.R., K.E. Longley and B.H. Gump, 1993. Airborne Concentrations of Methidathion and Methidaoxon in Central Tulare Count from Sampling Conducted in June and July 1991. California Air Resources Board, Contract No. A032-04. Engineering Research Institute, California State University Fresno, CA. (http://www.cdpr.ca.gov/docs/empm/pubs/tac/tacpdfs/methidthn94.pdf)

Salamon, C. (American Biogenics Corp.), 1986. Two-generation reproduction study in albino rats with methidathion technical. Ciba-Geigy Corp. DPR Vol. 298-097, Rec. No. 55142.

Salamon, C. (American Biogenics Corp.), 1987. Methidathion - Two-generation reproduction study in rats. Ciba-Geigy Corp. DPR Vol. 298-098, Rec. No. 55143.

Satou, S., Y. Kimura, K. Yamamoto, and A. Ichihara (Nomura Research Institute), 1979. *In vitro* microbiological assays for mutagenicity testing of DMTP (methidathion). Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936019.

Saxena, A.M. (Hazelton Laboratory America, Inc.), 1989a. Artificial sunlight photodegradation of ^{14}C-methidathion in a buffered aqueous solution. Ciba-Geigy Corp. DPR Vol. 298-171, Rec. No. 138548.

Saxena, A.M. (Hazelton Laboratory America, Inc.), 1989b. Artificial sunlight photodegradation of ^{14}C-methidathion in soil. Ciba-Geigy Corp. DPR Vol. 298-108, Rec. No. 85619.

Saxena, A.M. (Hazelton Laboratories America, Inc.), 1990. Aerobic, aerobic/anaerobic, and sterile soil metabolism of ^{14}C-methidathion. Ciba-Geigy Corp. DPR Vol. 298-111, Rec. No. 90382.

Schlinke, J.C. and J.S. Palmer, 1971. Preliminary toxicologic study of three organophosphate insecticidal compounds in turkeys. 32(3): 495-498.

Silvoy, J.J. (Landis International, Inc.), 1991a. Supracide® 2E field dissipation terrestrial study on citrus in California. Ciba-Geigy Corp. DPR Vol. 298-177, Rec. No. 138583.

Silvoy, J.J. (Landis International, Inc.), 1991b. Supracide® 2E field dissipation terrestrial study on bareground in California. Ciba-Geigy Corp. DPR Vol. 298-178, Rec. No. 138585.

Simmon, V.F. and D. Poole (Stanford Research Institute), 1977. *In vitro* and *in vivo* microbiological assays of six Ciba-Geigy chemicals. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936020.

Simoneaux, B., 1987a. The disposition of radioactivity in rats dosed with carbonyl ^{14}C-methidathion. Ciba-Geigy Corp. DPR Vol. 298-128, Rec. No. 92634.

Simoneaux, B., 1987b. The disposition of radioactivity in rats dosed with methoxy labeled ^{14}C-methidathion. Ciba-Geigy Corp. DPR Vol. 298-128, Rec. No. 92634.

Simoneaux, B., 1987c. The disposition of radioactivity in rats dosed with ^{14}C-methidathion labeled in the ring carbon adjacent to the methoxy group. Ciba-Geigy Corp. DPR Vol. 298-128, Rec. No. 92634.

Simoneaux, B.J., 1991. Nature of methidathion residues in plants - An overview. Ciba-Geigy Corp. DPR Vol. 298-192, Rec. No. 138631.

Simoneaux, B.J., 1993. ^{14}C-Methidathion: Identification of citrus metabolites. Ciba-Geigy Corp. DPR Vol. 298-190, Rec. No. 138627.

Simoneaux, B. and G.J. Marco, 1984. Dermal absorption of thiadiazole-^{14}C-methidathion by mice. Ciba-Geigy Corp. DPR Vol. 298-107, Rec. No. 87683.

Shepler, K. (PTRL-West, Inc.), 1992. Aged leaching of [^{14}C]methidathion in four soil types. Ciba-Geigy Corp. DPR Vol. 298-175, Rec. No. 138578.

Smith, R.P., 1996. Toxic responses of the blood. *In:* Casarett & Doull's Toxicology: The Basic Science of Poisons, 5th ed. (Klaassen, ed.). McGraw-Hill, New York. pp 335-354.

Spencer, W.F., 1987. Volatilization of pesticide residues. *In:* Fate of Pesticides in the Evironment (J.W. Biggar and J.N. Seiber, eds). University of California, Oakland. pp 61-68.

Spencer, W.F., T.D. Shoup, M.M. Cliath, W.J. Farmer and R. Haque, 1979. Vapor pressures and relative volatility of ethyl and methyl parathion. J. Agric. Food Chem. 27:273-278.

Starner, K., 2005. Database Search of DPR Surface Water Monitoring Data. Environmental Monitoring Branch, Department of Pesticide Regulation, Sacramento, CA.

Strasser, F.F., 1980. Point mutation assay with mouse lymphoma cells - Host mediated assay with GS 13005. Ciba-Geigy Corp. DPR Vol. 298-003, Rec. No. 936017.

Sulak, O., I. Altuntas, N. Karahan, B. Yildirim, O. Akturk, H. R. Yilmaz and N. Delibas, 2005. Nephrotoxicity in rats induced by organophosphate insecticide methidathion and ameliorating effects of vitamins E and C. Pest. Biochem. Physiol. 83: 21-28.

Suter, P., 1983. Photolysis of methidathion (Supracide®, Ultracide®) in aqueous medium under laboratory conditions. Ciba-Geigy Corp. DPR Vol. 298-088, Rec. No. 52710

Szolics, I.M., 1987. Disposition of methidathion in the rat (general metabolism). Ciba-Geigy Corp. DPR Vol. 298-128, Rec. No. 92634.

Teitelman, U., M. Alder and I. Levy, 1975. Treatment of massive poisoning by the organophosphate pesticide methidathion. Clin. Toxicol. 8(3): 277-282.

Tong, C., 1982a. The hepatocyte primary culture/DNA repair assay on compound GS-13005-008266 using mouse hepatocytes in culture. Ciba-Geigy Corp. DPR Vol. 298-089, Rec. No. 53774.

Tong, C., 1982b. The hepatocyte primary culture/DNA repair assay on compound GS-13005-008266 using rat hepatocytes in culture. Ciba-Geigy Corp. DPR Vol. 298-089, Rec. No. 53775.

Travaglini, R., 1999. Human Health Risk Assessment - Methidathion. U.S. Environmental Protection Agency, Office of Pesticide Programs, Health Effects Division (7509C). December 8, 1999.

Tsatsakis, A.M., P. Aguridakis, M.N. Michalodimitrakis, A.K. Tsakalov, A.K. Alegakis, E. Koumantakis and G. Troulakis, 1996. Experiences with acute organophosphate poisonings in Crete. Vet. Human Toxicol. 38(2): 101-107.

Ullman, L., no date. Neurotoxicity study in domestic fowls, 42 days. Ciba-Geigy Corp. DPR Vol. 298-012, Rec. No. 935981.

USDA, 2000. Agricultural Chemical Usage, Fruit and Nut Summary - 1999. National Agricultural Statistics Service, U.S. Department of Agriculture, Washington, D.C. July 2000. (http://usda.mannlib.cornell.edu/reports/nassr/other/pcu-bb/agch07002.pdf)

USDA, 2002. Agricultural Chemical Usage, Fruit Summary - 2001. National Agricultural Statistics Service, U.S. Department of Agriculture, Washington, D.C. August 2002. (http://usda.mannlib.cornell.edu/reports/nassr/other/pcu-bb/agcf0802.pdf)

USDA, 2003. Pesticide Data Program - Annual Summary Calendar Year 2001. Science and Technology Programs, Agricultural Marketing Service, U.S. Department of Agriculture, Washington, D.C.

USDA, 2004a.   Agricultural Chemical Usage, Fruit Summary - 2003. National Agricultural Statistics Service, U.S. Department of Agriculture, Washington, D.C. August 2004. (http://usda.mannlib.cornell.edu/reports/nassr/other/pcu-bb/agcf0804.pdf)

USDA, 2004b. Pesticide Data Program - Annual Summary Calendar Year 2002 . Science and Technology Programs, Agricultural Marketing Service, U.S. Department of Agriculture, Washington, D.C.

USDA, 2005. Pesticide Data Program - Annual Summary Calendar Year 2003. Science and Technology Programs, Agricultural Marketing Service, U.S. Department of Agriculture, Washington, D.C.

U.S. EPA, 1982. Pesticide Assessment Guidelines Subdivision O- Residue Chemistry. Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C. Document # EPA-540/9-82-023.

U.S. EPA, 1989. Guidance for the Reregistration of Pesticide Products Containing Methidathion. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C.

U.S. EPA, 1991. For Your Information- Pesticide Tolerances. Pesticide and Toxic Substances (H7506C), August, 1991.

U.S. EPA, 1992. Draft report: A cross-species scaling factor for carcinogen risk assessment based on equivalence of $mg/kg^{3/4}/day$; Notice. Federal Register 57(109): 24152-24173.

U.S. EPA, 1993. An SAB Report: Cholinesterase Inhibition and Risk Assessment. Review of the Risk Assessment Forum's Draft *Guidance on the Use of Data on Cholinesterase Inhibition in Risk Assessment by the SAB/SAP Joint Committee.* U.S. Environmental Protection Agency. EPA-SAB-EHC-93-011.

U.S. EPA, 1994. Pesticide Assessment Guidelines, Subdivision O, Residue Chemistry, Table II Update (June 1994), Raw Agricultural and Processed Commodities and Livestock Feeds Derived from Field Crops. U.S. Environmental Protection Agency.

U.S. EPA, 1995. Memorandum: The HED Metabolism Committee Meeting Held on April 4, 1995: Methidathion (MRID Nos. 43399701 and -02, Barcode D210041). Health Effects Division, Office of Pesticide Programs, U.S. Environmental Protection Agency.

U.S. EPA, 1997a. The Federal Insecticide Fungicide, and Rodenticide Act (FIFRA) and Federal Food, Drug, and Cosmetic Act (FFDCA) as Amended by the Food Quality Protection Act (FQPA) of August 3, 1996. Document no. 730L97001, March 1997. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C.

U.S. EPA, 1997b. 1996 Food Quality Protection Act Implementation Plan. March, 1977. Office of Prevention, Pesticides and Toxic Substances (7506C), U.S. Environmental Protection Agency, Washington, D.C. (http://www.epa.gov/fedrgstr/)

U.S. EPA, 1997c. Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C.

U.S. EPA, 1997d. Raw and Processed Food Schedule for Pesticide Tolerance Reassessment. Federal Register 62(149): 42020-42030.

U.S. EPA, 1998. Memorandum - Methidathion. Chem No. 100301. Acute Dietary Risk Assessment (Monte Carlo analysis) DP Barcode D243700. Health Effects Division, Office of Pesticide Programs, U.S. Environmental Protection Agency. October 16, 1998.

U.S. EPA, 1999. Drinking Water Regulations and Health Advisories. Office of Water, U.S. Environmental Protection Agency. Website: http://www.eoa.gov/oswater/Tools/ dwstds0.html.

U.S. EPA, 2000a. Office of Pesticide Programs Science Policy on the Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorus and Carbamate Pesticides. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. August 18, 2000.

U.S. EPA, 2000b. Fenthion, Methidathion, Naled, Phorate and Profenofos; Proposed Revocation of Tolerances. Federal Register 65(63): 17236-17239.

U.S. EPA, 2001. Preliminary Cumulative Risk assessment of the Organophosphorus Pesticides. Office of Pesticide Programs, U.S. Environmental Protection Agency. December 3, 2001. (http://www.epa.gov/pesticides/cumulative/pra-op)

U.S. EPA, 2002a. Revised OP Cumulative Risk Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency. June 10, 2002. (http://www.epa.gov/pesticides/cumulative/rra-op/)

U.S. EPA, 2002b. Interim Reregistration Eligibility Decision for Methidathion. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. April 9, 2002 (http://www.epa.gov/oppsrrd1/REDs/methidathion_ired.pdf)

U.S. EPA, 2002c. Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity. Office of Pesticide Programs, U.S. Environmental Protection Agency. January 14, 2002. (http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf)

U.S. EPA, 2002d. Consideration of the FQPA Safety Factor and Other Uncertainty Factors in Cumulative Risk Assessment of Chemicals Sharing a Common Mechanism of Toxicity. Draft Document. Office of Pesticide Programs, U.S. Environmental Protection Agency. February 28, 2002. (http://www.epa.gov/pesticides/trac/science/consid_draft.pdf)

U.S. EPA, 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. EPA/630/P-03/001F. March 2005.

U.S. EPA, 2006. OPPTS Harmonized Test Guidelines. Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C. (http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/index.html)

Wallace, P., 1986. Rabbit - Segment II - Dose range-finding teratology study pilot (P-2). Ciba-Geigy Corp. DPR Vol. 298-096, Rec. No. 55141.

Woodard Research, 1965. Demyelination study in the chicken. Ciba-Geigy Corp. DPR Vol. 298-076, Rec. No. 14846.

Woodard Research, 1966a. GS-13005, 25W - Potentiation studies with other organophosphates in the rat. DPR Vol. 298-018, Rec. No. 936037.

Woodard Research, 1966b. GS-13005, 40W - Three-generation reproduction study in the rat. Ciba-Geigy Corp. DPR Vol. 298-018, Rec. No. 33539.

Wyler, H., 1987. Report on water solubility - methidathion. Ciba-Geigy Corp. DPR Vol. 298-102, Rec. No. 59675.

Yau, E.T., D.N. McMartin, I.H. Zaidi, and J.D. Green, 1986. Methidathion - 2-Year oral oncogenicity and toxicity study in albino rats. Ciba-Geigy Corp. DPR Vol. 298-090, Rec. No. 53935.

Yavuz, T., I. Altuntas, N. Delibas, B. Yildirim, O. Candir, A. Corâ, N. Karahan, E. Ibrisim, and A. Kutsal, 2004a. Cardiotoxicity in rats induced by methidathion and ameliorating effect of vitamins E and C. Human Exper. Toxicol. 23: 323-329.

Yavuz, T. N. Delibas, B. Yildirim, I. Altuntas, O. Candir, A. Corâ, N. Karaman, E. Ibrisim, and A. Kutsal, 2004b. Vascular wall damage in rats induced by methidathion and ameliorating effect of vitamins E and C. Arch. Toxicol. 78: 655-659.

Zoppellari, R., L. Targa, P. Tonini and R. Zatelli, 1990. Acute poisoning with methidathion: a case. Human Exper. Toxicol. 9: 415-419.

APPENDICES

Appendix A - Carcinogenicity Computer Model Printout

Appendix B - Dietary and Drinking Water Exposure Analysis Printouts

APPENDIX A

Carcinogenicity Computer Model Printout

```
              DATE: 06-22-00                  TIME: 09:18:12


 MULTI-WEIB  (MAR 1985)
 (C) COPYRIGHT CLEMENT ASSOCIATES, INC. 1983-1987


 K.S. CRUMP & COMPANY, INC.
 1201 GAINES STREET
 RUSTON, LA    71270
 (318) 255-4800
```

       Methidathion, Combined Hepatocellular Adenomas and Carcinomas in Male Mice


```
          THE   20 OBSERVATIONS AT LEVEL  1 WITH A DOSE OF  .000000
```

TIME	# OF ANIMALS	TUMOR INDICATOR	TIME	# OF ANIMALS	TUMOR INDICATOR
57.0	1	1	58.0	1	1
59.0	1	1	62.0	1	1
64.0	1	1	67.0	1	1
73.0	2	1	76.0	1	1
77.0	1	1	78.0	1	1
81.0	1	1	81.0	1	3
83.0	2	1	84.0	1	3
93.0	1	1	95.0	1	1
98.0	3	1	99.0	1	3
100.0	22	1	100.0	6	2

```
          THE   20 OBSERVATIONS AT LEVEL  2 WITH A DOSE OF  .600000E-01
```

TIME	# OF ANIMALS	TUMOR INDICATOR	TIME	# OF ANIMALS	TUMOR INDICATOR
44.0	2	1	48.0	1	1
60.0	1	1	61.0	1	1
64.0	1	1	66.0	1	1
77.0	1	1	79.0	1	2
80.0	1	2	81.0	1	1
89.0	1	2	90.0	1	2
91.0	1	2	91.0	1	1
94.0	1	1	96.0	1	1
98.0	3	1	99.0	1	1
100.0	19	1	100.0	10	2

```
          THE   19 OBSERVATIONS AT LEVEL  3 WITH A DOSE OF  .200000
```

TIME	# OF ANIMALS	TUMOR INDICATOR	TIME	# OF ANIMALS	TUMOR INDICATOR
5.0	1	1	12.0	1	1
25.0	1	1	67.0	2	1
71.0	2	1	76.0	1	1
85.0	1	2	89.0	3	1
90.0	1	1	93.0	2	1

TIME	# OF ANIMALS	TUMOR INDICATOR	TIME	# OF ANIMALS	TUMOR INDICATOR
93.0	1	2	94.0	1	3
96.0	1	1	96.0	1	3
97.0	1	1	98.0	1	1
99.0	3	1	100.0	19	1
100.0	7	2			

THE 21 OBSERVATIONS AT LEVEL 4 WITH A DOSE OF .970000

TIME	# OF ANIMALS	TUMOR INDICATOR	TIME	# OF ANIMALS	TUMOR INDICATOR
44.0	1	1	57.0	1	1
58.0	2	1	59.0	1	1
60.0	2	1	71.0	1	2
75.0	1	1	79.0	1	1
81.0	1	3	81.0	1	2
83.0	1	2	86.0	1	3
86.0	1	1	87.0	1	2
88.0	1	1	90.0	1	1
91.0	1	3	99.0	1	1
99.0	2	3	100.0	16	1
100.0	12	2			

THE 32 OBSERVATIONS AT LEVEL 5 WITH A DOSE OF 1.90000

TIME	# OF ANIMALS	TUMOR INDICATOR	TIME	# OF ANIMALS	TUMOR INDICATOR
22.0	1	1	28.0	1	1
55.0	1	1	56.0	1	1
57.0	1	1	63.0	1	2
68.0	1	2	69.0	1	1
70.0	1	1	72.0	3	2
74.0	1	2	76.0	1	2
78.0	1	3	80.0	1	2
82.0	1	2	85.0	2	2
88.0	1	3	90.0	3	3
91.0	1	2	91.0	1	3
92.0	1	3	93.0	1	3
93.0	1	2	94.0	1	3
95.0	1	3	98.0	2	1
98.0	1	2	98.0	1	3
99.0	2	2	99.0	2	3
100.0	3	1	100.0	9	2

FORM OF PROBABILITY FUNCTION:

$$P(DOSE) = 1 - \exp((-Q0 - Q1 * D - Q2 * D^2 - ... - Q4 * D^4) * (T - T0)^J)$$

THE MAXIMUM LIKELIHOOD ESTIMATION OF:

PROBABILITY FUNCTION COEFFICIENTS

Q(0)= .476305436831E-12
Q(1)= .864812104460E-13
Q(2)= .375761739529E-12
Q(3)= .104589214976E-12
Q(4)= .000000000000

```
                          TIME FUNCTION COEFFICIENTS

                        T0 =  .000000000000
                         J =  5.93342862928


              THE MAXIMUM LIKELIHOOD IS -112.496010523


                  MAXIMUM LIKELIHOOD ESTIMATES OF EXTRA RISK

****************************************************************************



              WEIBULL LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK
              ****************************************************


                                                    CONFIDENCE
                            LOWER BOUND   UPPER BOUND    LIMIT
      RISK        MLE DOSE    ON DOSE       ON RISK    INTERVAL      TIME
      ----        --------    -------       -------    --------      ----
 1.000000E-06  1.571056E-05  1.691143E-06  9.289864E-06   95.0%    100.000


              WEIBULL UPPER CONFIDENCE LIMITS ON RISK FOR FIXED DOSE
              ****************************************************


                                         CONFIDENCE
                            UPPER BOUND      LIMIT
      DOSE        MLE RISK    ON RISK      INTERVAL      TIME
      ----        --------    -------      --------      ----
     1.00000      .341090     .529102       95.0%      100.000


   NORMAL COMPLETION!
```

APPENDIX B

Dietary and Drinking Water Exposure Analysis Printouts

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID Acute analysis for METHIDATHION
Residue file name: H:\MyFiles\DEEM-FCID Files\Methidathion\Methidathionr1acutefood.R98
Analysis Date 10-26-2005          Residue file dated: 10-25-2005/16:02:15/14
Reference dose (NOEL) = 0.3 mg/kg bw/day
----------------------------------------------------------------------------
RDL indices and parameters for Monte Carlo Analysis:
Index Dist Parameter #1           Param #2    Param #3    Comment
  #   Code
----- ---- -----------           ----------- ----------- ----------
  1    6   RDF1 APPLES.rdf
  2    6   RDF2 PLUMS.rdf
  3    6   RDF3 APRICOTS.rdf
  4    6   RDF4 ORANGES.rdf
  5    6   RDF5 PEACHES.rdf
  6    6   RDF6 NECTARINES.rdf
  7    6   RDF7 PEARS.rdf
  8    6   RDF8 CHERRIES.rdf
  9    6   RDF9 PRUNES.RDF

  EPA      Crop Food Name                    Def Res    Adj.Factors RDL  Comment
  Code     Grp                               (ppm)       #1     #2  Pntr
-------- ---- ------------------------------ ---------- ------ ------ --- -------
14000030 14   Almond                         0.050000   1.000  1.000     Tolera
     Full comment: Tolerance
14000031 14   Almond-babyfood                0.050000   1.000  1.000     Tolera
     Full comment: Tolerance
14000040 14   Almond, oil                    0.050000   1.000  1.000     Tolera
     Full comment: Tolerance
14000041 14   Almond, oil-babyfood           0.050000   1.000  1.000     Tolera
     Full comment: Tolerance
11000070 11   Apple, fruit with peel         0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000080 11   Apple, peeled fruit            0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000081 11   Apple, peeled fruit-babyfood   0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000090 11   Apple, dried                   0.007000   8.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000091 11   Apple, dried-babyfood          0.007000   8.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000100 11   Apple, juice                   0.007000   1.300  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000101 11   Apple, juice-babyfood          0.007000   1.300  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000110 11   Apple, sauce                   0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000111 11   Apple, sauce-babyfood          0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
12000120 12   Apricot                        0.050000   1.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
12000121 12   Apricot-babyfood               0.050000   1.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
12000130 12   Apricot, dried                 0.050000   6.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
12000140 12   Apricot, juice                 0.050000   1.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
12000141 12   Apricot, juice-babyfood        0.050000   1.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
95000160 O    Artichoke, globe               0.050000   1.000  1.000     DPR 20
     Full comment: DPR 2002-2004 LOD
01030170 1CD  Artichoke, Jerusalem           0.050000   1.000  1.000     DPR 20
     Full comment: DPR 2002-2004 LOD
14000590 14   Brazil nut                     0.050000   1.000  1.000     Tolera
```

```
          Full comment: Tolerance
14000680 14    Butternut                       0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
14000810 14    Cashew                          0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
12000900 12    Cherry                          0.004000  1.000  1.000    8 PDP Ch
          Full comment: PDP Cherries 2000 & 2001 CA - RDF, 10% PCT
12000901 12    Cherry-babyfood                 0.004000  1.000  1.000    8 PDP Ch
          Full comment: PDP Cherries 2000 & 2001 CA - RDF, 10% PCT
12000910 12    Cherry, juice                   0.004000  1.500  1.000    8 PDP Ch
          Full comment: PDP Cherries 2000 & 2001 CA - RDF, 10% PCT
12000911 12    Cherry, juice-babyfood          0.004000  1.500  1.000    8 PDP Ch
          Full comment: PDP Cherries 2000 & 2001 CA - RDF, 10% PCT
14000920 14    Chestnut                        0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
10001060 10    Citrus citron                   2.000000  1.000  1.000    4 Tolera
          Full comment: Tolerance
10001070 10    Citrus hybrids                  0.007000  1.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10001080 10    Citrus, oil                     0.007000  1.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
95001280 O     Cottonseed, oil                 0.200000  1.000  1.000      Tolera
          Full comment: Tolerance
95001281 O     Cottonseed, oil-babyfood        0.200000  1.000  1.000      Tolera
          Full comment: Tolerance
11001290 11    Crabapple                       0.007000  1.000  1.000    1 PDP Ap
          Full comment: PDP Apple 2002 California LOD
14001550 14    Filbert                         0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
14001560 14    Filbert, oil                    0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
10001800 10    Grapefruit                      0.007000  1.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10001810 10    Grapefruit, juice               0.007000  2.100  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
14001850 14    Hickory nut                     0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
95001950 O     Kiwifruit                       0.050000  1.000  1.000      DPR 20
          Full comment: DPR 2002-2004 LOD
10001970 10    Kumquat                         0.007000  1.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10001990 10    Lemon                           0.007000  1.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002000 10    Lemon, juice                    0.007000  2.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002001 10    Lemon, juice-babyfood           0.007000  2.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002010 10    Lemon, peel                     2.000000  1.000  1.000    4 Tolera
          Full comment: Tolerance
10002060 10    Lime                            0.007000  1.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002070 10    Lime, juice                     0.007000  2.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002071 10    Lime, juice-babyfood            0.007000  2.000  1.000    4 PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
14002130 14    Macadamia nut                   0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
95002150 O     Mango                           0.050000  1.000  1.000      DPR 20
          Full comment: DPR 2002-2004 LOD
95002151 O     Mango-babyfood                  0.050000  1.000  1.000      DPR 20
          Full comment: DPR 2002-2004 LOD
95002160 O     Mango, dried                    0.050000  1.000  1.000      DPR 20
          Full comment: DPR 2002-2004 LOD
95002170 O     Mango, juice                    0.050000  1.000  1.000      DPR 20
```

```
          Full comment: DPR 2002-2004 LOD
95002171 O    Mango, juice-babyfood              0.050000  1.000  1.000      DPR 20
          Full comment: DPR 2002-2004 LOD
12002300 12   Nectarine                          0.004000  1.000  1.000   6  PDP Ne
          Full comment: PDP Nectarine 2000 & 2001 CA - RDF, 10% PCT
95002350 O    Olive                              0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
95002360 O    Olive, oil                         0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
10002400 10   Orange                             0.007000  1.000  1.000   4  PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002410 10   Orange, juice                      0.007000  1.800  1.000   4  PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002411 10   Orange, juice-babyfood             0.007000  1.800  1.000   4  PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002420 10   Orange, peel                       2.000000  1.000  1.000   4  Tolera
          Full comment: Tolerance
12002600 12   Peach                              0.004000  1.000  1.000   5  PDP Pe
          Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002601 12   Peach-babyfood                     0.004000  1.000  1.000   5  PDP Pe
          Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002610 12   Peach, dried                       0.004000  7.000  1.000   5  PDP Pe
          Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002611 12   Peach, dried-babyfood              0.004000  7.000  1.000   5  PDP Pe
          Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002620 12   Peach, juice                       0.004000  1.000  1.000   5  PDP Pe
          Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002621 12   Peach, juice-babyfood              0.004000  1.000  1.000   5  PDP Pe
          Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
11002660 11   Pear                               0.004000  1.000  1.000   7  PDP Pe
          Full comment: PDP Pear 2003 National - RDF, 10% PCT
11002661 11   Pear-babyfood                      0.004000  1.000  1.000   7  PDP Pe
          Full comment: PDP Pear 2003 National - RDF, 10% PCT
11002670 11   Pear, dried                        0.004000  6.250  1.000   7  PDP Pe
          Full comment: PDP Pear 2003 National - RDF, 10% PCT
11002680 11   Pear, juice                        0.004000  1.000  1.000   7  PDP Pe
          Full comment: PDP Pear 2003 National - RDF, 10% PCT
11002681 11   Pear, juice-babyfood               0.004000  1.000  1.000   7  PDP Pe
          Full comment: PDP Pear 2003 National - RDF, 10% PCT
14002690 14   Pecan                              0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
95002780 O    Pine nut                           0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
14002820 14   Pistachio                          0.050000  1.000  1.000      Tolera
          Full comment: Tolerance
12002850 12   Plum                               0.050000  1.000  1.000   2  DPR 20
          Full comment: DPR 2002-2004 - RDF, 15% PCT
12002851 12   Plum-babyfood                      0.050000  1.000  1.000   2  DPR 20
          Full comment: DPR 2002-2004 - RDF, 15% PCT
12002860 12   Plum, prune, fresh                 0.050000  1.000  1.000   9  DPR Pl
          Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002861 12   Plum, prune, fresh-babyfood        0.050000  1.000  1.000   9  DPR Pl
          Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002870 12   Plum, prune, dried                 0.050000  5.000  1.000   9  DPR Pl
          Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002871 12   Plum, prune, dried-babyfood        0.050000  5.000  1.000   9  DPR Pl
          Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002880 12   Plum, prune, juice                 0.050000  1.400  1.000   9  DPR Pl
          Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002881 12   Plum, prune, juice-babyfood        0.050000  1.400  1.000   9  DPR Pl
          Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
10003070 10   Pummelo                            0.007000  1.000  1.000   4  PDP Or
          Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
11003100 11   Quince                             0.007000  1.000  1.000   1  PDP Ap
```

```
     Full comment: PDP Apple 2002 CA - RDF, 15% PCT
20003300 20   Safflower, oil                    0.050000   1.000  1.000        Safflo
     Full comment: Safflower Field Trial High Value
20003301 20   Safflower, oil-babyfood           0.050000   1.000  1.000        Safflo
     Full comment: Safflower Field Trial High Value
15003440 15   Sorghum, grain                    0.200000   1.000  1.000        Tolera
     Full comment: Tolerance
15003450 15   Sorghum, syrup                    0.200000   1.000  1.000        Tolera
     Full comment: Tolerance
95003580 O    Starfruit                         0.100000   1.000  1.000        Tolera
     Full comment: Tolerance
95003610 O    Sugar apple                       0.200000   1.000  1.000        Tolera
     Full comment: Tolerance
20003640 20   Sunflower, seed                   0.220000   1.000  0.500        Sunflo
     Full comment: Sunflower Field Trial High Value, 50% hulls
20003650 20   Sunflower, oil                    0.220000   1.000  0.200        Sunflo
     Full comment: Sunflower Field Trial High Value, 20% Oil
20003651 20   Sunflower, oil-babyfood           0.220000   1.000  0.200        Sunflo
     Full comment: Sunflower Field Trial High Value, 20% Oil
10003690 10   Tangerine                         0.007000   1.000  1.000    4   PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10003700 10   Tangerine, juice                  0.007000   2.300  1.000    4   PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
14003910 14   Walnut                            0.050000   1.000  1.000        Tolera
     Full comment: Tolerance
```

```
California Department of Pesticide Regulation                Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: Methidathionr1acutefood.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
==============================================================================

Summary calculations (per capita):


                  95th Percentile     99th Percentile     99.9th Percentile
                 Exposure     MOE     Exposure    MOE     Exposure     MOE
                 ----------  --------  ----------  --------  ----------  --------
U.S. Population:
                 0.000037     8219    0.000110    2727     0.000324      927
Western region:
                 0.000042     7216    0.000139    2165     0.000345      868
Hispanics:
                 0.000048     6202    0.000163    1843     0.000456      657
Non-hispanic whites:
                 0.000035     8603    0.000098    3076     0.000281     1067
Non-hispanic blacks:
                 0.000035     8540    0.000108    2765     0.000227     1319
Non-hisp/non-white/non-black:
                 0.000045     6721    0.000157    1910     0.000439      683
All infants:
                 0.000126     2372    0.000207    1449     0.000491      611
Nursing infants (<1 yr old):
                 0.000069     4352    0.000129    2332     0.000244     1227
Non-nursing infants (<1 yr old):
                 0.000146     2055    0.000227    1322     0.000502      597
Females 13+ (preg/not nursing):
                 0.000040     7568    0.000216    1386     0.000294     1021
Females 13+ (nursing):
                 0.000036     8431    0.000284    1057     0.000298     1005
Children 1-2 yrs:
                 0.000094     3187    0.000281    1067     0.000780      384
Children 3-5 yrs:
                 0.000079     3806    0.000216    1390     0.000602      498
```

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION               (1994-98 data)
Residue file: Methidathionr1acutefood.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
=============================================================================

Summary calculations:

                   95th Percentile    99th Percentile    99.9th Percentile
                   Exposure    MOE    Exposure    MOE    Exposure    MOE
                   ---------- -------  ---------- -------  ---------- --------
Children 6-12 yrs:
                   0.000048    6315   0.000132    2266   0.000474     633
Youth 13-19 yrs:
                   0.000029   10505   0.000089    3385   0.000333     899
Adults 20-49 yrs:
                   0.000027   10962   0.000078    3846   0.000214    1403
Adults 50+ yrs:
                   0.000021   14166   0.000071    4241   0.000174    1723
Females 13-49 yrs:
                   0.000028   10711   0.000086    3481   0.000215    1395
Custom demographics 1: Workers, 16+ years:
                   0.000025   11898   0.000077    3906   0.000191    1569
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                      (1994-98 data)
Residue file: Methidathionr1acutefood.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

U.S. Population                       Daily Exposure Analysis  /a
---------------                       (mg/kg body-weight/day)
                                       per Capita    per User
                                      -----------   -----------
            Mean                        0.000010      0.000011
            Standard Deviation          0.000025      0.000025
            Margin of Exposure 2/        28,788        28,423

        Percent of Person-Days that are User-Days =  98.73%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    477,361          90.00      0.000022     13,885
   20.00      0.000001    222,005          95.00      0.000037      8,150
   30.00      0.000002    131,758          97.50      0.000061      4,919
   40.00      0.000003     89,808          99.00      0.000111      2,707
   50.00      0.000005     65,467          99.50      0.000154      1,942
   60.00      0.000006     48,612          99.75      0.000203      1,480
   70.00      0.000009     35,231          99.90      0.000329        913
   80.00      0.000012     24,153


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    538,121          90.00      0.000021     14,035
   20.00      0.000001    236,560          95.00      0.000037      8,219
   30.00      0.000002    137,199          97.50      0.000060      4,960
   40.00      0.000003     92,109          99.00      0.000110      2,727
   50.00      0.000004     66,773          99.50      0.000154      1,949
   60.00      0.000006     49,350          99.75      0.000202      1,487
   70.00      0.000008     35,707          99.90      0.000324        927
   80.00      0.000012     24,459
-------------------------------------------------------------------------------
a/ Analysis based on all two-day participant records in CSFII 1994-98 survey.
2/ Margin of Exposure = NOEL/ Dietary Exposure.
```

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: Methidathionr1acutefood.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
==============================================================================
```

```
Western region                    Daily Exposure Analysis
--------------                    (mg/kg body-weight/day)
                                   per Capita    per User
                                  -----------   -----------
              Mean                 0.000012      0.000012
              Standard Deviation   0.000029      0.000029
              Margin of Exposure     25,371        24,943

         Percent of Person-Days that are User-Days =  98.31%
```

```
  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE         Percentile   Exposure      MOE
 ----------   ----------   ---------    ----------   ----------   ---------
   10.00      0.000001     451,565        90.00      0.000025      11,940
   20.00      0.000001     208,060        95.00      0.000042       7,147
   30.00      0.000002     124,292        97.50      0.000074       4,060
   40.00      0.000003      87,010        99.00      0.000139       2,155
   50.00      0.000005      63,492        99.50      0.000171       1,754
   60.00      0.000007      45,461        99.75      0.000238       1,258
   70.00      0.000009      32,932        99.90      0.000351         854
   80.00      0.000014      21,902
```

```
  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE         Percentile   Exposure      MOE
 ----------   ----------   ---------    ----------   ----------   ---------
   10.00      0.000001     529,683        90.00      0.000025      12,069
   20.00      0.000001     227,216        95.00      0.000042       7,216
   30.00      0.000002     130,682        97.50      0.000072       4,162
   40.00      0.000003      89,696        99.00      0.000139       2,165
   50.00      0.000005      65,263        99.50      0.000170       1,762
   60.00      0.000006      46,480        99.75      0.000238       1,260
   70.00      0.000009      33,356        99.90      0.000345         868
   80.00      0.000014      22,177
```

2

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                 (1994-98 data)
Residue file: Methidathionr1acutefood.R98     Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
==========================================================================

Hispanics                          Daily Exposure Analysis
---------                          (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
              Mean                    0.000013      0.000013
              Standard Deviation      0.000037      0.000037
              Margin of Exposure        23,489        23,056

        Percent of Person-Days that are User-Days =  98.16%


   Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

   Percentile   Exposure      MOE          Percentile   Exposure      MOE
   ----------   ----------   ---------     ----------   ----------   ---------
     10.00       0.000001     593,263        90.00       0.000026      11,683
     20.00       0.000001     255,151        95.00       0.000049       6,100
     30.00       0.000002     145,808        97.50       0.000091       3,303
     40.00       0.000003      95,819        99.00       0.000163       1,839
     50.00       0.000004      68,610        99.50       0.000216       1,388
     60.00       0.000006      49,217        99.75       0.000321         935
     70.00       0.000009      34,199        99.90       0.000456         657
     80.00       0.000013      22,573


   Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

   Percentile   Exposure      MOE          Percentile   Exposure      MOE
   ----------   ----------   ---------     ----------   ----------   ---------
     10.00       0.000000     714,041        90.00       0.000025      11,860
     20.00       0.000001     278,341        95.00       0.000048       6,202
     30.00       0.000002     154,800        97.50       0.000089       3,387
     40.00       0.000003      99,207        99.00       0.000163       1,843
     50.00       0.000004      70,875        99.50       0.000216       1,389
     60.00       0.000006      50,269        99.75       0.000308         975
     70.00       0.000009      34,855        99.90       0.000456         657
     80.00       0.000013      22,983
```

3

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: Methidathionr1acutefood.R98          Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
=============================================================================

Non-hispanic whites                   Daily Exposure Analysis
-------------------                   (mg/kg body-weight/day)
                                       per Capita    per User
                                      ----------    ----------
              Mean                      0.000010      0.000010
              Standard Deviation        0.000022      0.000023
              Margin of Exposure          29,907        29,597

        Percent of Person-Days that are User-Days =  98.97%


   Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------   ----------   ---------      ----------   ----------   ---------
    10.00       0.000001    432,050          90.00       0.000021     14,161
    20.00       0.000001    207,779          95.00       0.000035      8,533
    30.00       0.000002    126,949          97.50       0.000058      5,215
    40.00       0.000003     88,423          99.00       0.000098      3,058
    50.00       0.000005     65,008          99.50       0.000140      2,135
    60.00       0.000006     48,700          99.75       0.000186      1,610
    70.00       0.000008     35,558          99.90       0.000282      1,065
    80.00       0.000012     24,444


   Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------   ----------   ---------      ----------   ----------   ---------
    10.00       0.000001    472,297          90.00       0.000021     14,251
    20.00       0.000001    218,343          95.00       0.000035      8,603
    30.00       0.000002    131,078          97.50       0.000057      5,252
    40.00       0.000003     90,236          99.00       0.000098      3,076
    50.00       0.000005     66,039          99.50       0.000140      2,142
    60.00       0.000006     49,345          99.75       0.000186      1,611
    70.00       0.000008     35,961          99.90       0.000281      1,067
    80.00       0.000012     24,688
```

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION             (1994-98 data)
Residue file: Methidathionr1acutefood.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
========================================================================
```

```
Non-hispanic blacks              Daily Exposure Analysis
-------------------              (mg/kg body-weight/day)
                                  per Capita   per User
                                 -----------  -----------
              Mean                0.000010     0.000010
              Standard Deviation  0.000024     0.000024
              Margin of Exposure    30,518       30,019

      Percent of Person-Days that are User-Days =  98.36%
```

```
 Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE          Percentile   Exposure      MOE
----------  ----------  ---------       ----------  ----------  ---------
   10.00     0.000000    675,350           90.00     0.000020     14,796
   20.00     0.000001    292,872           95.00     0.000036      8,395
   30.00     0.000002    157,746           97.50     0.000059      5,053
   40.00     0.000003     96,807           99.00     0.000109      2,756
   50.00     0.000004     68,788           99.50     0.000150      2,000
   60.00     0.000006     49,984           99.75     0.000180      1,664
   70.00     0.000008     36,216           99.90     0.000227      1,318
   80.00     0.000012     25,402
```

```
 Estimated percentile of per-capita days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE          Percentile   Exposure      MOE
----------  ----------  ---------       ----------  ----------  ---------
   10.00     0.000000    791,548           90.00     0.000020     14,932
   20.00     0.000001    327,087           95.00     0.000035      8,540
   30.00     0.000002    167,978           97.50     0.000058      5,135
   40.00     0.000003    101,088           99.00     0.000108      2,765
   50.00     0.000004     70,291           99.50     0.000149      2,010
   60.00     0.000006     51,037           99.75     0.000180      1,665
   70.00     0.000008     36,954           99.90     0.000227      1,319
   80.00     0.000012     25,801
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                   (1994-98 data)
Residue file: Methidathionr1acutefood.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
==============================================================================

Non-hisp/non-white/non-black        Daily Exposure Analysis
---------------------------          (mg/kg body-weight/day)
                                      per Capita    per User
                                     -----------   -----------
              Mean                     0.000013      0.000013
              Standard Deviation       0.000034      0.000034
              Margin of Exposure        23,303        22,681

        Percent of Person-Days that are User-Days =  97.33%


   Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000000    612,754          90.00      0.000026     11,534
    20.00      0.000001    229,185          95.00      0.000045      6,678
    30.00      0.000002    124,844          97.50      0.000089      3,381
    40.00      0.000004     81,956          99.00      0.000157      1,908
    50.00      0.000005     57,507          99.50      0.000208      1,444
    60.00      0.000007     41,751          99.75      0.000352        852
    70.00      0.000009     31,872          99.90      0.000440        682
    80.00      0.000015     20,627


   Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000000    987,154          90.00      0.000025     12,025
    20.00      0.000001    253,406          95.00      0.000045      6,721
    30.00      0.000002    141,922          97.50      0.000088      3,404
    40.00      0.000003     86,989          99.00      0.000157      1,910
    50.00      0.000005     60,568          99.50      0.000201      1,492
    60.00      0.000007     42,887          99.75      0.000347        864
    70.00      0.000009     32,487          99.90      0.000439        683
    80.00      0.000014     21,091
```

6

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: Methidathionr1acutefood.R98         Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

All infants                        Daily Exposure Analysis
-----------                        (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
              Mean                  0.000039      0.000046
              Standard Deviation    0.000051      0.000052
              Margin of Exposure       7,677         6,573

         Percent of Person-Days that are User-Days =  85.62%


    Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000002    150,568          90.00      0.000103      2,919
    20.00      0.000010     29,901          95.00      0.000138      2,173
    30.00      0.000017     17,208          97.50      0.000178      1,684
    40.00      0.000024     12,371          99.00      0.000218      1,373
    50.00      0.000031      9,704          99.50      0.000284      1,057
    60.00      0.000039      7,638          99.75      0.000357        839
    70.00      0.000052      5,801          99.90      0.000494        607
    80.00      0.000073      4,119


    Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000000  >1,000,000         90.00      0.000098      3,065
    20.00      0.000000  >1,000,000         95.00      0.000126      2,372
    30.00      0.000009     34,472          97.50      0.000166      1,811
    40.00      0.000017     17,258          99.00      0.000207      1,449
    50.00      0.000025     11,898          99.50      0.000269      1,114
    60.00      0.000033      8,997          99.75      0.000347        863
    70.00      0.000045      6,658          99.90      0.000491        611
    80.00      0.000066      4,541
```

```
California Department of Pesticide Regulation                   Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: Methidathionr1acutefood.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

Nursing infants (<1 yr old)        Daily Exposure Analysis
--------------------------         (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
             Mean                    0.000013      0.000024
             Standard Deviation      0.000031      0.000038
             Margin of Exposure        22,235        12,617

       Percent of Person-Days that are User-Days =  56.75%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00     0.000000  >1,000,000          90.00     0.000065      4,645
   20.00     0.000000    604,483           95.00     0.000090      3,327
   30.00     0.000003     99,692           97.50     0.000122      2,465
   40.00     0.000007     40,748           99.00     0.000176      1,702
   50.00     0.000011     27,514           99.50     0.000197      1,526
   60.00     0.000016     19,040           99.75     0.000244      1,231
   70.00     0.000024     12,642           99.90     0.000275      1,091
   80.00     0.000039      7,661


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00     0.000000  >1,000,000          90.00     0.000045      6,640
   20.00     0.000000  >1,000,000          95.00     0.000069      4,352
   30.00     0.000000  >1,000,000          97.50     0.000099      3,016
   40.00     0.000000  >1,000,000          99.00     0.000129      2,332
   50.00     0.000000  >1,000,000          99.50     0.000195      1,539
   60.00     0.000003    106,875           99.75     0.000206      1,455
   70.00     0.000010     30,313           99.90     0.000244      1,227
   80.00     0.000019     15,594
```

8

```
California Department of Pesticide Regulation                 Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                 (1994-98 data)
Residue file: Methidathionr1acutefood.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
==============================================================================

Non-nursing infants (<1 yr old)    Daily Exposure Analysis
-------------------------------    (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
            Mean                     0.000049      0.000051
            Standard Deviation       0.000053      0.000053
            Margin of Exposure          6,149         5,938

        Percent of Person-Days that are User-Days =  96.58%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE          Percentile   Exposure      MOE
----------  ----------  ---------       ----------  ----------  ---------
   10.00     0.000006     49,987           90.00     0.000109      2,754
   20.00     0.000015     19,504           95.00     0.000147      2,037
   30.00     0.000022     13,444           97.50     0.000180      1,665
   40.00     0.000028     10,644           99.00     0.000234      1,281
   50.00     0.000035      8,642           99.50     0.000297      1,011
   60.00     0.000044      6,887           99.75     0.000381        788
   70.00     0.000058      5,167           99.90     0.000504        595
   80.00     0.000078      3,847


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE          Percentile   Exposure      MOE
----------  ----------  ---------       ----------  ----------  ---------
   10.00     0.000003    108,795           90.00     0.000108      2,789
   20.00     0.000013     23,697           95.00     0.000146      2,055
   30.00     0.000021     14,535           97.50     0.000180      1,667
   40.00     0.000027     11,157           99.00     0.000227      1,322
   50.00     0.000033      9,006           99.50     0.000290      1,034
   60.00     0.000042      7,155           99.75     0.000380        790
   70.00     0.000056      5,346           99.90     0.000502        597
   80.00     0.000076      3,945
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                     (1994-98 data)
Residue file: Methidathionr1acutefood.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49    Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
==========================================================================
```

```
Females 13+ (preg/not nursing)      Daily Exposure Analysis
------------------------------      (mg/kg body-weight/day)
                                    per Capita    per User
                                    ----------   ----------
           Mean                      0.000015     0.000015
           Standard Deviation        0.000041     0.000041
           Margin of Exposure          19,816       19,816

        Percent of Person-Days that are User-Days = 100.00%
```

```
 Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE          Percentile   Exposure      MOE
----------  ----------  ---------       ----------  ----------  ---------
  10.00      0.000000    645,612          90.00      0.000022     13,803
  20.00      0.000001    218,754          95.00      0.000040      7,568
  30.00      0.000002    136,609          97.50      0.000215      1,396
  40.00      0.000003     87,814          99.00      0.000216      1,386
  50.00      0.000005     66,124          99.50      0.000293      1,025
  60.00      0.000006     50,881          99.75      0.000293      1,022
  70.00      0.000009     34,498          99.90      0.000294      1,021
  80.00      0.000013     23,814
```

```
 Estimated percentile of per-capita days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE          Percentile   Exposure      MOE
----------  ----------  ---------       ----------  ----------  ---------
  10.00      0.000000    645,612          90.00      0.000022     13,803
  20.00      0.000001    218,754          95.00      0.000040      7,568
  30.00      0.000002    136,609          97.50      0.000215      1,396
  40.00      0.000003     87,814          99.00      0.000216      1,386
  50.00      0.000005     66,124          99.50      0.000293      1,025
  60.00      0.000006     50,881          99.75      0.000293      1,022
  70.00      0.000009     34,498          99.90      0.000294      1,021
  80.00      0.000013     23,814
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                     (1994-98 data)
Residue file: Methidathionr1acutefood.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
=============================================================================

Females 13+ (nursing)              Daily Exposure Analysis
---------------------              (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
            Mean                    0.000014      0.000014
            Standard Deviation      0.000041      0.000041
            Margin of Exposure       21,447        21,447

        Percent of Person-Days that are User-Days = 100.00%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    312,201          90.00      0.000021    14,426
   20.00      0.000002    193,378          95.00      0.000036     8,431
   30.00      0.000002    129,013          97.50      0.000145     2,073
   40.00      0.000003    100,418          99.00      0.000284     1,057
   50.00      0.000004     81,340          99.50      0.000297     1,009
   60.00      0.000005     65,264          99.75      0.000298     1,006
   70.00      0.000006     47,377          99.90      0.000298     1,005
   80.00      0.000009     34,353


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    312,201          90.00      0.000021    14,426
   20.00      0.000002    193,378          95.00      0.000036     8,431
   30.00      0.000002    129,013          97.50      0.000145     2,073
   40.00      0.000003    100,418          99.00      0.000284     1,057
   50.00      0.000004     81,340          99.50      0.000297     1,009
   60.00      0.000005     65,264          99.75      0.000298     1,006
   70.00      0.000006     47,377          99.90      0.000298     1,005
   80.00      0.000009     34,353
```

11

```
California Department of Pesticide Regulation                   Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION              (1994-98 data)
Residue file: Methidathionr1acutefood.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
===============================================================================

Children 1-2 yrs                    Daily Exposure Analysis
----------------                    (mg/kg body-weight/day)
                                     per Capita   per User
                                    -----------  -----------
            Mean                      0.000026     0.000026
            Standard Deviation        0.000059     0.000059
            Margin of Exposure          11,506       11,418

        Percent of Person-Days that are User-Days =  99.23%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000002    179,652          90.00      0.000054      5,585
   20.00      0.000004     82,413          95.00      0.000095      3,173
   30.00      0.000006     51,659          97.50      0.000152      1,974
   40.00      0.000008     36,217          99.00      0.000282      1,064
   50.00      0.000011     26,451          99.50      0.000413        726
   60.00      0.000015     19,566          99.75      0.000562        533
   70.00      0.000021     14,248          99.90      0.000780        384
   80.00      0.000030     10,159


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000002    198,055          90.00      0.000053      5,612
   20.00      0.000004     85,547          95.00      0.000094      3,187
   30.00      0.000006     52,751          97.50      0.000151      1,982
   40.00      0.000008     36,714          99.00      0.000281      1,067
   50.00      0.000011     26,700          99.50      0.000412        727
   60.00      0.000015     19,733          99.75      0.000562        533
   70.00      0.000021     14,346          99.90      0.000780        384
   80.00      0.000029     10,227
```

12

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION             (1994-98 data)
Residue file: Methidathionr1acutefood.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

Children 3-5 yrs                    Daily Exposure Analysis
----------------                    (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------   -----------
           Mean                       0.000024     0.000024
           Standard Deviation         0.000048     0.000048
           Margin of Exposure           12,592       12,540

       Percent of Person-Days that are User-Days =  99.58%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000003    115,277          90.00      0.000048      6,306
    20.00      0.000005     62,963          95.00      0.000079      3,794
    30.00      0.000007     41,945          97.50      0.000125      2,404
    40.00      0.000010     31,106          99.00      0.000216      1,387
    50.00      0.000013     23,729          99.50      0.000297      1,011
    60.00      0.000016     18,412          99.75      0.000414        725
    70.00      0.000021     14,377          99.90      0.000603        497
    80.00      0.000028     10,573


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000003    118,840          90.00      0.000047      6,324
    20.00      0.000005     63,970          95.00      0.000079      3,806
    30.00      0.000007     42,339          97.50      0.000124      2,411
    40.00      0.000010     31,310          99.00      0.000216      1,390
    50.00      0.000013     23,853          99.50      0.000296      1,011
    60.00      0.000016     18,487          99.75      0.000413        727
    70.00      0.000021     14,429          99.90      0.000602        498
    80.00      0.000028     10,601
```

```
California Department of Pesticide Regulation                   Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: Methidathionr1acutefood.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

Children 6-12 yrs                   Daily Exposure Analysis
-----------------                   (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------  -----------
              Mean                    0.000016     0.000016
              Standard Deviation      0.000032     0.000032
              Margin of Exposure       18,844       18,795

         Percent of Person-Days that are User-Days =  99.74%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000002    142,101           90.00      0.000030    10,042
    20.00      0.000004     80,624           95.00      0.000048     6,309
    30.00      0.000005     56,296           97.50      0.000076     3,944
    40.00      0.000007     41,793           99.00      0.000133     2,263
    50.00      0.000009     33,241           99.50      0.000197     1,519
    60.00      0.000011     26,762           99.75      0.000323       928
    70.00      0.000014     20,942           99.90      0.000474       632
    80.00      0.000019     15,496


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000002    144,729           90.00      0.000030    10,060
    20.00      0.000004     81,379           95.00      0.000048     6,315
    30.00      0.000005     56,620           97.50      0.000076     3,947
    40.00      0.000007     41,952           99.00      0.000132     2,266
    50.00      0.000009     33,324           99.50      0.000197     1,519
    60.00      0.000011     26,821           99.75      0.000322       930
    70.00      0.000014     20,983           99.90      0.000474       633
    80.00      0.000019     15,525
```

14

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                 (1994-98 data)
Residue file: Methidathionr1acutefood.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
===============================================================================


Youth 13-19 yrs                    Daily Exposure Analysis
---------------                    (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
            Mean                     0.000010      0.000010
            Standard Deviation       0.000020      0.000020
            Margin of Exposure         30,457        29,984

        Percent of Person-Days that are User-Days =  98.45%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE         Percentile   Exposure      MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00      0.000001    315,827         90.00      0.000019     16,179
   20.00      0.000002    146,144         95.00      0.000029     10,207
   30.00      0.000003     94,705         97.50      0.000047      6,429
   40.00      0.000004     68,526         99.00      0.000091      3,309
   50.00      0.000006     52,013         99.50      0.000128      2,348
   60.00      0.000007     41,192         99.75      0.000189      1,586
   70.00      0.000009     31,867         99.90      0.000334        899
   80.00      0.000013     23,944


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE         Percentile   Exposure      MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00      0.000001    363,427         90.00      0.000018     16,338
   20.00      0.000002    160,380         95.00      0.000029     10,505
   30.00      0.000003     98,875         97.50      0.000046      6,458
   40.00      0.000004     70,503         99.00      0.000089      3,385
   50.00      0.000006     53,021         99.50      0.000127      2,359
   60.00      0.000007     41,869         99.75      0.000189      1,587
   70.00      0.000009     32,261         99.90      0.000333        899
   80.00      0.000012     24,124
```

```
California Department of Pesticide Regulation            Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION            (1994-98 data)
Residue file: Methidathionr1acutefood.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
================================================================================
```

```
Adults 20-49 yrs                   Daily Exposure Analysis
----------------                   (mg/kg body-weight/day)
                                   per Capita    per User
                                   ----------   ----------
              Mean                  0.000008     0.000008
              Standard Deviation    0.000017     0.000017
              Margin of Exposure      36,903       36,454

         Percent of Person-Days that are User-Days =  98.79%
```

```
 Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE         Percentile   Exposure      MOE
 ----------  ----------  ---------      ----------  ----------  ---------
    10.00     0.000001    513,243          90.00     0.000017     18,147
    20.00     0.000001    241,196          95.00     0.000028     10,882
    30.00     0.000002    145,176          97.50     0.000045      6,738
    40.00     0.000003     99,352          99.00     0.000078      3,839
    50.00     0.000004     74,207          99.50     0.000119      2,511
    60.00     0.000005     56,433          99.75     0.000158      1,900
    70.00     0.000007     42,785          99.90     0.000214      1,403
    80.00     0.000010     30,436
```

```
 Estimated percentile of per-capita days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE         Percentile   Exposure      MOE
 ----------  ----------  ---------      ----------  ----------  ---------
    10.00     0.000001    571,453          90.00     0.000016     18,232
    20.00     0.000001    254,899          95.00     0.000027     10,962
    30.00     0.000002    151,416          97.50     0.000044      6,817
    40.00     0.000003    101,953          99.00     0.000078      3,846
    50.00     0.000004     75,506          99.50     0.000119      2,524
    60.00     0.000005     57,275          99.75     0.000156      1,918
    70.00     0.000007     43,253          99.90     0.000214      1,403
    80.00     0.000010     30,746
```

16

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                 (1994-98 data)
Residue file: Methidathionr1acutefood.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
===============================================================================


Adults 50+ yrs                     Daily Exposure Analysis
--------------                     (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
             Mean                    0.000006     0.000006
             Standard Deviation      0.000016     0.000016
             Margin of Exposure        46,822       46,294

        Percent of Person-Days that are User-Days =  98.87%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000000    721,921          90.00      0.000013     23,453
    20.00      0.000001    367,768          95.00      0.000021     14,070
    30.00      0.000001    226,220          97.50      0.000038      7,799
    40.00      0.000002    150,752          99.00      0.000071      4,209
    50.00      0.000003    107,448          99.50      0.000109      2,764
    60.00      0.000004     78,434          99.75      0.000146      2,053
    70.00      0.000005     58,091          99.90      0.000175      1,713
    80.00      0.000007     40,296


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000000    792,213          90.00      0.000013     23,683
    20.00      0.000001    388,593          95.00      0.000021     14,166
    30.00      0.000001    233,755          97.50      0.000038      7,861
    40.00      0.000002    154,715          99.00      0.000071      4,241
    50.00      0.000003    109,568          99.50      0.000108      2,771
    60.00      0.000004     79,715          99.75      0.000146      2,055
    70.00      0.000005     58,775          99.90      0.000174      1,723
    80.00      0.000007     40,651
```

17

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                     (1994-98 data)
Residue file: Methidathionr1acutefood.R98          Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49    Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
=============================================================================

Females 13-49 yrs                    Daily Exposure Analysis
-----------------                    (mg/kg body-weight/day)
                                     per Capita    per User
                                     ----------   ----------
            Mean                      0.000008     0.000008
            Standard Deviation        0.000018     0.000018
            Margin of Exposure         36,400       35,902

        Percent of Person-Days that are User-Days =  98.63%


  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000001    525,504           90.00     0.000016     18,457
    20.00     0.000001    256,860           95.00     0.000028     10,619
    30.00     0.000002    154,167           97.50     0.000048      6,265
    40.00     0.000003    104,744           99.00     0.000087      3,467
    50.00     0.000004     78,160           99.50     0.000144      2,079
    60.00     0.000005     58,536           99.75     0.000168      1,784
    70.00     0.000007     43,738           99.90     0.000215      1,394
    80.00     0.000010     31,087


  Estimated percentile of per-capita days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000001    591,723           90.00     0.000016     18,657
    20.00     0.000001    274,213           95.00     0.000028     10,711
    30.00     0.000002    163,066           97.50     0.000047      6,351
    40.00     0.000003    108,045           99.00     0.000086      3,481
    50.00     0.000004     79,658           99.50     0.000144      2,084
    60.00     0.000005     59,517           99.75     0.000168      1,785
    70.00     0.000007     44,348           99.90     0.000215      1,395
    80.00     0.000010     31,295
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: Methidathionr1acutefood.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:38:49   Residue file dated: 10-25-2005/16:02:15/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500        MC list in residue file      MC seed = 1
Run Comment: ""
==============================================================================

Custom demographics 1: Workers, 16+ years
All Seasons
All Regions
Sex: M/F-all/
All Races
Age-Low: 16 yrs    High: 99 yrs
-----------------------------------------

                                Daily Exposure Analysis
                                (mg/kg body-weight/day)
                                 per Capita    per User
                                 -----------  -----------
                Mean                0.000008     0.000008
                Standard Deviation  0.000016     0.000017
                Margin of Exposure    39,458       38,958

        Percent of Person-Days that are User-Days =  98.73%


   Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE            Percentile   Exposure     MOE
 ----------  ----------  ---------        ----------  ----------  ---------
    10.00     0.000001    578,282            90.00     0.000016     19,208
    20.00     0.000001    276,656            95.00     0.000025     11,772
    30.00     0.000002    167,075            97.50     0.000042      7,194
    40.00     0.000003    111,846            99.00     0.000077      3,884
    50.00     0.000004     81,688            99.50     0.000115      2,610
    60.00     0.000005     61,353            99.75     0.000155      1,941
    70.00     0.000007     45,767            99.90     0.000196      1,529
    80.00     0.000009     32,368


   Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE            Percentile   Exposure     MOE
 ----------  ----------  ---------        ----------  ----------  ---------
    10.00     0.000000    645,253            90.00     0.000016     19,346
    20.00     0.000001    295,444            95.00     0.000025     11,898
    30.00     0.000002    173,762            97.50     0.000041      7,237
    40.00     0.000003    114,509            99.00     0.000077      3,906
    50.00     0.000004     83,245            99.50     0.000115      2,617
    60.00     0.000005     62,172            99.75     0.000154      1,944
    70.00     0.000006     46,382            99.90     0.000191      1,569
    80.00     0.000009     32,698
```

```
California Department of Pesticide Regulation                Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION                  1994-98 data
Residue file: H:\MyFiles\DEEM-FCID Files\Methidathion\Methidathionr1chronicfood.R98
                                                    Adjust. #2 used
Analysis Date 10-26-2005        Residue file dated: 10-25-2005/16:11:37/14
Reference dose (NOEL) = 0.15 mg/kg bw/day


-----------------------------------------------------------------------------
Food Crop                                  Residue     Adj.Factors
Comment
EPA Code  Grp  Food Name                    (ppm)
                                                       #1        #2
-------- ---- ------------------------------ ---------- ------    ------   -------
14000030 14   Almond                        0.001250   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
14000031 14   Almond-babyfood               0.001250   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
14000040 14   Almond, oil                   0.001250   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
14000041 14   Almond, oil-babyfood          0.001250   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
11000070 11   Apple, fruit with peel        0.000350   1.000     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000080 11   Apple, peeled fruit           0.000350   1.000     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000081 11   Apple, peeled fruit-babyfood  0.000350   1.000     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000090 11   Apple, dried                  0.000350   8.000     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000091 11   Apple, dried-babyfood         0.000350   8.000     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000100 11   Apple, juice                  0.000350   1.300     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000101 11   Apple, juice-babyfood         0.000350   1.300     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000110 11   Apple, sauce                  0.000350   1.000     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000111 11   Apple, sauce-babyfood         0.000350   1.000     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
12000120 12   Apricot                       0.001300   1.000     1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
12000121 12   Apricot-babyfood              0.001300   1.000     1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
12000130 12   Apricot, dried                0.001300   6.000     1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
12000140 12   Apricot, juice                0.001300   1.000     1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
12000141 12   Apricot, juice-babyfood       0.001300   1.000     1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
95000160 O    Artichoke, globe              0.025000   1.000     1.000    DPR Ar
  Full comment: DPR Artichoke 2002-2004 1/2 LOD, 100% CT
01030170 1CD  Artichoke, Jerusalem          0.025000   1.000     1.000    DPR Ar
  Full comment: DPR Artichoke 2002-2004 1/2 LOD, 100% CT
14000590 14   Brazil nut                    0.025000   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
14000680 14   Butternut                     0.025000   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
14000810 14   Cashew                        0.025000   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
12000900 12   Cherry                        0.000100   1.000     1.000    PDP Ch
  Full comment: PDP Cherries 2000&2001 CA 1/2 LOD, 5% CT
12000901 12   Cherry-babyfood               0.000100   1.000     1.000    PDP Ch
  Full comment: PDP Cherries 2000&2001 CA 1/2 LOD, 5% CT
12000910 12   Cherry, juice                 0.000100   1.500     1.000    PDP Ch
```

```
  Full comment: PDP Cherries 2000&2001 CA 1/2 LOD, 5% CT
12000911 12   Cherry, juice-babyfood           0.000100    1.500    1.000    PDP Ch
  Full comment: PDP Cherries 2000&2001 CA 1/2 LOD, 5% CT
14000920 14   Chestnut                         0.025000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
10001060 10   Citrus citron                    0.050000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
10001070 10   Citrus hybrids                   0.000168    1.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10001080 10   Citrus, oil                      0.000168    1.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
95001280 O    Cottonseed, oil                  0.001000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 1% CT
95001281 O    Cottonseed, oil-babyfood         0.001000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 1% CT
11001290 11   Crabapple                        0.000350    1.000    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
14001550 14   Filbert                          0.025000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
14001560 14   Filbert, oil                     0.025000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
10001800 10   Grapefruit                       0.000168    1.000    1.000    PDP Or
  Full comment: PDP Orange 2000 & 2001 CA Mean Value
10001810 10   Grapefruit, juice                0.000168    2.100    1.000    PDP Or
  Full comment: PDP Orange 2000 & 2001 CA Mean Value
14001850 14   Hickory nut                      0.025000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
95001950 O    Kiwifruit                        0.002500    1.000    1.000    DPR Ki
  Full comment: DPR Kiwifruit 2002-2004 1/2 LOD, 10% CT
10001970 10   Kumquat                          0.000168    1.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10001990 10   Lemon                            0.000168    1.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002000 10   Lemon, juice                     0.000168    2.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002001 10   Lemon, juice-babyfood            0.000168    2.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002010 10   Lemon, peel                      0.050000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
10002060 10   Lime                             0.000168    1.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002070 10   Lime, juice                      0.000168    2.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002071 10   Lime, juice-babyfood             0.000168    2.000    1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
11002100 11   Loquat                           0.000350    1.000    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
14002130 14   Macadamia nut                    0.025000    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
95002150 O    Mango                            0.025000    1.000    1.000    DPR Ma
  Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
95002151 O    Mango-babyfood                   0.025000    1.000    1.000    DPR Ma
  Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
95002160 O    Mango, dried                     0.025000    1.000    1.000    DPR Ma
  Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
95002170 O    Mango, juice                     0.025000    1.000    1.000    DPR Ma
  Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
95002171 O    Mango, juice-babyfood            0.025000    1.000    1.000    DPR Ma
  Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
12002300 12   Nectarine                        0.000100    1.000    1.000    PDP Ne
  Full comment: PDP Nectarine 2000&2001 CA 1/2 LOD, 5% CT
95002350 O    Olive                            0.001250    1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
95002360 O    Olive, oil                       0.001250    1.000    1.000    1/2 To
```

```
  Full comment: 1/2 Tolerance, 5% CT
10002400 10   Orange                         0.000168   1.000     1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002410 10   Orange, juice                  0.000168   1.800     1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002411 10   Orange, juice-babyfood         0.000168   1.800     1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002420 10   Orange, peel                   0.050000   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
12002600 12   Peach                          0.000065   1.000     1.000    PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002601 12   Peach-babyfood                 0.000065   1.000     1.000    PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002610 12   Peach, dried                   0.000065   7.000     1.000    PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002611 12   Peach, dried-babyfood          0.000065   7.000     1.000    PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002620 12   Peach, juice                   0.000065   1.000     1.000    PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002621 12   Peach, juice-babyfood          0.000065   1.000     1.000    PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
11002660 11   Pear                           0.000100   1.000     1.000    PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
11002661 11   Pear-babyfood                  0.000100   1.000     1.000    PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
11002670 11   Pear, dried                    0.000100   6.250     1.000    PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
11002680 11   Pear, juice                    0.000100   1.000     1.000    PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
11002681 11   Pear, juice-babyfood           0.000100   1.000     1.000    PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
14002690 14   Pecan                          0.002500   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 10% CT
95002780 O    Pine nut                       0.025000   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance
14002820 14   Pistachio                      0.002500   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 10% CT
12002850 12   Plum                           0.003750   1.000     1.000    DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 15% CT
12002851 12   Plum-babyfood                  0.003750   1.000     1.000    DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 15% CT
12002860 12   Plum, prune, fresh             0.001250   1.000     1.000    DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002861 12   Plum, prune, fresh-babyfood    0.001250   1.000     1.000    DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002870 12   Plum, prune, dried             0.001250   5.000     1.000    DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002871 12   Plum, prune, dried-babyfood    0.001250   5.000     1.000    DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002880 12   Plum, prune, juice             0.001250   1.400     1.000    DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002881 12   Plum, prune, juice-babyfood    0.001250   1.400     1.000    DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
10003070 10   Pummelo                        0.000168   1.000     1.000    PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
11003100 11   Quince                         0.000350   1.000     1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
20003300 20   Safflower, oil                 0.005000   1.000     1.000    Safflo
  Full comment: Safflower Field Trial 1/2 LOD, 100% CT
20003301 20   Safflower, oil-babyfood        0.005000   1.000     1.000    Safflo
  Full comment: Safflower Field Trial 1/2 LOD, 100% CT
15003440 15   Sorghum, grain                 0.100000   1.000     1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
15003450 15   Sorghum, syrup                 0.100000   1.000     1.000    1/2 To
```

```
   Full comment: 1/2 Tolerance, 100% CT
95003580 O    Starfruit                        0.050000   1.000      1.000    1/2 To
   Full comment: 1/2 Tolerance, 100% CT
95003610 O    Sugar apple                      0.100000   1.000      1.000    1/2 To
   Full comment: 1/2 Tolerance, 100% CT
20003640 20   Sunflower, seed                  0.150000   1.000      0.500    Sunflo
   Full comment: Sunflower Field Trial Mean, 100% CT, 50% hulls
20003650 20   Sunflower, oil                   0.150000   1.000      0.200    Sunflo
   Full comment: Sunflower Field Trial Mean, 100% CT, 20% oil
20003651 20   Sunflower, oil-babyfood          0.150000   1.000      0.200    Sunflo
   Full comment: Sunflower Field Trial Mean, 100% CT, 20% oil
10003690 10   Tangerine                        0.000168   1.000      1.000    PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10003700 10   Tangerine, juice                 0.000168   2.300      1.000    PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
14003910 14   Walnut                           0.001250   1.000      1.000    1/2 To
   Full comment: 1/2 Tolerance, 5% CT
```

```
California Department of Pesticide Regulation                 Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION               (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\Methidathionr1chronicfood.R98
                                            Adjustment factor #2 used.
Analysis Date 10-26-2005/08:48:23    Residue file dated: 10-25-2005/16:11:37/14
NOEL (Chronic) = .15 mg/kg bw/day
===============================================================================
                  Total exposure by population subgroup
-------------------------------------------------------------------------------


                                          Total Exposure
                                   ------------------------------------
            Population              mg/kg       Percent    Margin of
            Subgroup              body wt/day   of NOEL    Exposr 1/
-------------------------------------  ------------  ---------  ---------
U.S. Population (total)                  0.000002       0.00%      69,278

U.S. Population (spring season)          0.000002       0.00%      64,057
U.S. Population (summer season)          0.000003       0.00%      59,163
U.S. Population (autumn season)          0.000002       0.00%      80,339
U.S. Population (winter season)          0.000002       0.00%      78,172

Northeast region                        0.000002       0.00%      61,129
Midwest region                          0.000002       0.00%      88,554
Southern region                         0.000002       0.00%      80,954
Western region                          0.000003       0.00%      51,627

Hispanics                               0.000003       0.00%      44,091
Non-hispanic whites                     0.000002       0.00%      77,085
Non-hispanic blacks                     0.000002       0.00%      75,212
Non-hisp/non-white/non-black            0.000003       0.00%      45,620

All infants (< 1 year)                  0.000015       0.01%      10,038
Nursing infants                         0.000005       0.00%      28,984
Non-nursing infants                     0.000019       0.01%       8,043
Children 1-6  yrs                       0.000006       0.00%      26,076
Children 7-12 yrs                       0.000003       0.00%      55,729

Females 13-19 (not preg or nursing)     0.000002       0.00%      91,507
Females 20+ (not preg or nursing)       0.000001       0.00%     108,077
Females 13-50 yrs                       0.000002       0.00%      82,896
Females 13+ (preg/not nursing)          0.000005       0.00%      28,441
Females 13+ (nursing)                   0.000004       0.00%      35,141

Males 13-19 yrs                         0.000002       0.00%      89,150
Males 20+ yrs                           0.000001       0.00%     110,982
Seniors 55+                             0.000001       0.00%     110,983

Children 1-2 yrs                        0.000007       0.00%      20,203
Children 3-5 yrs                        0.000005       0.00%      29,136
Children 6-12 yrs                       0.000003       0.00%      51,272
Youth 13-19 yrs                         0.000002       0.00%      90,276
Adults 20-49 yrs                        0.000001       0.00%     105,790
Adults 50+ yrs                          0.000001       0.00%     104,219
Females 13-49 yrs                       0.000002       0.00%      98,463


-------------------------------------------------------------------------------
```

```
California Department of Pesticide Regulation                Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION              (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\Methidathionr1chronicfood.R98
                                              Adjustment factor #2 used.
Analysis Date 10-26-2005/08:49:34    Residue file dated: 10-25-2005/16:11:37/14
Q* = 0.34
===============================================================================
                     Total exposure by population subgroup
-------------------------------------------------------------------------------


                                          Total Exposure
                                  ----------------------------------
          Population                   mg/kg           Lifetime risk
          Subgroup                  body wt/day         (Q*= .34)
-------------------------------------  ------------    ------------
U.S. Population (total)                  0.000002        7.36E-07

U.S. Population (spring season)          0.000002        7.96E-07
U.S. Population (summer season)          0.000003        8.62E-07
U.S. Population (autumn season)          0.000002        6.35E-07
U.S. Population (winter season)          0.000002        6.52E-07

Northeast region                         0.000002        8.34E-07
Midwest region                           0.000002        5.76E-07
Southern region                          0.000002        6.30E-07
Western region                           0.000003        9.88E-07

Hispanics                                0.000003        1.16E-06
Non-hispanic whites                      0.000002        6.62E-07
Non-hispanic blacks                      0.000002        6.78E-07
Non-hisp/non-white/non-black             0.000003        1.12E-06

All infants (< 1 year)                   0.000015        5.08E-06
Nursing infants                          0.000005        1.76E-06
Non-nursing infants                      0.000019        6.34E-06
Children 1-6  yrs                        0.000006        1.96E-06
Children 7-12 yrs                        0.000003        9.15E-07

Females 13-19 (not preg or nursing)      0.000002        5.57E-07
Females 20+ (not preg or nursing)        0.000001        4.72E-07
Females 13-50 yrs                        0.000002        6.15E-07
Females 13+ (preg/not nursing)           0.000005        1.79E-06
Females 13+ (nursing)                    0.000004        1.45E-06

Males 13-19 yrs                          0.000002        5.72E-07
Males 20+ yrs                            0.000001        4.60E-07
Seniors 55+                              0.000001        4.60E-07

Children 1-2 yrs                         0.000007        2.52E-06
Children 3-5 yrs                         0.000005        1.75E-06
Children 6-12 yrs                        0.000003        9.95E-07
Youth 13-19 yrs                          0.000002        5.65E-07
Adults 20-49 yrs                         0.000001        4.82E-07
Adults 50+ yrs                           0.000001        4.89E-07
Females 13-49 yrs                        0.000002        5.18E-07


-------------------------------------------------------------------------------
```

```
California Department of Pesticide Regulation                    Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION                  (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\Methidathionr1chronicfood.R98
                                                Adjustment factor #2 used.
Analysis Date 10-26-2005/08:49:21    Residue file dated: 10-25-2005/16:11:37/14
Q* = 0.53
===============================================================================
                     Total exposure by population subgroup
-------------------------------------------------------------------------------


                                              Total Exposure
                                        ---------------------------------
             Population                    mg/kg         Lifetime risk
             Subgroup                    body wt/day      (Q*= .53)
--------------------------------------   ------------    ------------
U.S. Population (total)                     0.000002       1.15E-06

U.S. Population (spring season)             0.000002       1.24E-06
U.S. Population (summer season)             0.000003       1.34E-06
U.S. Population (autumn season)             0.000002       9.90E-07
U.S. Population (winter season)             0.000002       1.02E-06

Northeast region                            0.000002       1.30E-06
Midwest region                              0.000002       8.98E-07
Southern region                             0.000002       9.82E-07
Western region                              0.000003       1.54E-06

Hispanics                                   0.000003       1.80E-06
Non-hispanic whites                         0.000002       1.03E-06
Non-hispanic blacks                         0.000002       1.06E-06
Non-hisp/non-white/non-black                0.000003       1.74E-06

All infants (< 1 year)                      0.000015       7.92E-06
Nursing infants                             0.000005       2.74E-06
Non-nursing infants                         0.000019       9.88E-06
Children 1-6  yrs                           0.000006       3.05E-06
Children 7-12 yrs                           0.000003       1.43E-06

Females 13-19 (not preg or nursing)         0.000002       8.69E-07
Females 20+ (not preg or nursing)           0.000001       7.36E-07
Females 13-50 yrs                           0.000002       9.59E-07
Females 13+ (preg/not nursing)              0.000005       2.80E-06
Females 13+ (nursing)                       0.000004       2.26E-06

Males 13-19 yrs                             0.000002       8.92E-07
Males 20+ yrs                               0.000001       7.16E-07
Seniors 55+                                 0.000001       7.16E-07

Children 1-2 yrs                            0.000007       3.94E-06
Children 3-5 yrs                            0.000005       2.73E-06
Children 6-12 yrs                           0.000003       1.55E-06
Youth 13-19 yrs                             0.000002       8.81E-07
Adults 20-49 yrs                            0.000001       7.51E-07
Adults 50+ yrs                              0.000001       7.63E-07
Females 13-49 yrs                           0.000002       8.07E-07


-------------------------------------------------------------------------------
```

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID Acute analysis for METHIDATHION
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\methidathionr1acutewater.R98
Analysis Date 10-26-2005          Residue file dated: 10-12-2005/16:17:59/14
Reference dose (NOEL) = 0.3 mg/kg bw/day
-------------------------------------------------------------------
  EPA    Crop                              Def Res   Adj.Factors  Comment
  Code   Grp  Food Name                    (ppm)      #1     #2
-------- ---- ---------------------------- ---------- ------ ------ -------
86010000 O    Water, direct, all sources    0.000021  1.000  1.000PDP 20
         Full comment: PDP 2002-2003, Combined CA LOD
86020000 O    Water, indirect, all sources  0.000021  1.000  1.000PDP 20
         Full comment: PDP 2002-2003, Combined CA LOD
```

```
California Department of Pesticide Regulation               Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                 (1994-98 data)
Residue file: methidathionr1acutewater.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48    Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Summary calculations (per capita):


                95th Percentile      99th Percentile      99.9th Percentile
              Exposure     MOE     Exposure     MOE     Exposure     MOE
              ---------- --------  ---------- --------  ---------- --------
U.S. Population:
              0.000001   273469    0.000002   145594    0.000004    72769
Western region:
              0.000001   234444    0.000002   124196    0.000005    65492
Hispanics:
              0.000001   224430    0.000003   113408    0.000005    65384
Non-hispanic whites:
              0.000001   284343    0.000002   163969    0.000004    78613
Non-hispanic blacks:
              0.000001   263638    0.000002   132579    0.000005    60655
Non-hisp/non-white/non-black:
              0.000001   233949    0.000002   123533    0.000005    65021
All infants:
              0.000004    72532    0.000006    50595    0.000011    28244
Nursing infants (<1 yr old):
              0.000002   134031    0.000005    61065    0.000008    39404
Non-nursing infants (<1 yr old):
              0.000004    68312    0.000006    48940    0.000011    28218
Females 13+ (preg/not nursing):
              0.000001   304384    0.000001   251981    0.000002   193796
Females 13+ (nursing):
              0.000001   245326    0.000002   173506    0.000002   138304
Children 1-2 yrs:
              0.000002   174286    0.000003   104362    0.000004    71758
Children 3-5 yrs:
              0.000002   190787    0.000002   121720    0.000004    74577
```

```
California Department of Pesticide Regulation                 Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: methidathionr1acutewater.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Summary calculations:

                    95th Percentile    99th Percentile    99.9th Percentile
                    Exposure    MOE    Exposure    MOE    Exposure    MOE
                    ---------- -------  ---------- -------  ---------- --------
Children 6-12 yrs:
                    0.000001   274058  0.000002   164824  0.000002   120691
Youth 13-19 yrs:
                    0.000001   337091  0.000001   200355  0.000003   111397
Adults 20-49 yrs:
                    0.000001   295166  0.000002   176256  0.000003    97439
Adults 50+ yrs:
                    0.000001   326851  0.000001   228555  0.000002   140936
Females 13-49 yrs:
                    0.000001   293502  0.000002   182361  0.000003   102832
Custom demographics 1: Workers, 16+ years:
                    0.000001   305915  0.000002   191386  0.000003   102883
```

```
California Department of Pesticide Regulation                     Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                       (1994-98 data)
Residue file: methidathionr1acutewater.R98         Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =  0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

U.S. Population                      Daily Exposure Analysis  /a
---------------                      (mg/kg body-weight/day)
                                      per Capita    per User
                                     ----------    ----------
              Mean                    0.000000      0.000000
              Standard Deviation      0.000000      0.000000
              Standard Error of mean  0.000000      0.000000
              Margin of Exposure 2/    677,442       655,569

       Percent of Person-Days that are User-Days =  96.77%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE          Percentile   Exposure     MOE
 ----------  ----------  ---------      ----------  ----------  ---------
    10.00     0.000000 >1,000,000          90.00     0.000001    347,666
    20.00     0.000000 >1,000,000          95.00     0.000001    270,619
    30.00     0.000000 >1,000,000          97.50     0.000001    205,388
    40.00     0.000000    990,463          99.00     0.000002    143,869
    50.00     0.000000    823,917          99.50     0.000003    116,126
    60.00     0.000000    688,714          99.75     0.000003     96,047
    70.00     0.000001    576,625          99.90     0.000004     72,197
    80.00     0.000001    466,747


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE          Percentile   Exposure     MOE
 ----------  ----------  ---------      ----------  ----------  ---------
    10.00     0.000000 >1,000,000          90.00     0.000001    352,002
    20.00     0.000000 >1,000,000          95.00     0.000001    273,469
    30.00     0.000000 >1,000,000          97.50     0.000001    207,759
    40.00     0.000000 >1,000,000          99.00     0.000002    145,594
    50.00     0.000000    845,921          99.50     0.000003    118,089
    60.00     0.000000    704,240          99.75     0.000003     96,417
    70.00     0.000001    588,578          99.90     0.000004     72,769
    80.00     0.000001    474,018
-------------------------------------------------------------------------------
a/ Analysis based on all two-day participant records in CSFII 1994-98
   with 2 days of valid drinking water records.
2/ Margin of Exposure = NOEL/ Dietary Exposure.
                                1
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                   (1994-98 data)
Residue file: methidathionr1acutewater.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Western region                     Daily Exposure Analysis
--------------                      (mg/kg body-weight/day)
                                     per Capita    per User
                                    ----------    ----------
            Mean                     0.000001      0.000001
            Standard Deviation       0.000000      0.000000
            Standard Error of mean   0.000000      0.000000
            Margin of Exposure        591,316       577,986

        Percent of Person-Days that are User-Days =  97.75%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile  Exposure     MOE          Percentile  Exposure     MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00      0.000000 >1,000,000         90.00      0.000001    308,940
   20.00      0.000000 >1,000,000         95.00      0.000001    231,778
   30.00      0.000000 >1,000,000         97.50      0.000002    176,122
   40.00      0.000000    886,322         99.00      0.000002    122,904
   50.00      0.000000    729,465         99.50      0.000003     96,981
   60.00      0.000000    615,379         99.75      0.000004     76,678
   70.00      0.000001    512,894         99.90      0.000005     65,186
   80.00      0.000001    414,792


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile  Exposure     MOE          Percentile  Exposure     MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00      0.000000 >1,000,000         90.00      0.000001    311,900
   20.00      0.000000 >1,000,000         95.00      0.000001    234,444
   30.00      0.000000 >1,000,000         97.50      0.000002    177,529
   40.00      0.000000    916,623         99.00      0.000002    124,196
   50.00      0.000000    743,135         99.50      0.000003     97,326
   60.00      0.000000    625,112         99.75      0.000004     77,491
   70.00      0.000001    519,825         99.90      0.000005     65,492
   80.00      0.000001    419,711
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                      (1994-98 data)
Residue file: methidathionr1acutewater.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Hispanics                         Daily Exposure Analysis
---------                         (mg/kg body-weight/day)
                                   per Capita    per User
                                  -----------   -----------
             Mean                   0.000001      0.000001
             Standard Deviation     0.000001      0.000001
             Standard Error of mean 0.000000      0.000000
             Margin of Exposure      597,191       587,060

      Percent of Person-Days that are User-Days =  98.30%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE          Percentile   Exposure      MOE
----------   ----------  ---------      ----------   ----------  ---------
   10.00      0.000000 >1,000,000          90.00      0.000001    304,623
   20.00      0.000000 >1,000,000          95.00      0.000001    223,329
   30.00      0.000000 >1,000,000          97.50      0.000002    162,820
   40.00      0.000000    938,331          99.00      0.000003    112,755
   50.00      0.000000    771,135          99.50      0.000003     96,156
   60.00      0.000000    659,413          99.75      0.000004     78,435
   70.00      0.000001    539,115          99.90      0.000005     65,295
   80.00      0.000001    436,717


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE          Percentile   Exposure      MOE
----------   ----------  ---------      ----------   ----------  ---------
   10.00      0.000000 >1,000,000          90.00      0.000001    306,088
   20.00      0.000000 >1,000,000          95.00      0.000001    224,430
   30.00      0.000000 >1,000,000          97.50      0.000002    163,837
   40.00      0.000000    953,717          99.00      0.000003    113,408
   50.00      0.000000    786,909          99.50      0.000003     96,244
   60.00      0.000000    668,726          99.75      0.000004     78,524
   70.00      0.000001    546,044          99.90      0.000005     65,384
   80.00      0.000001    439,438
```

```
California Department of Pesticide Regulation                 Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                 (1994-98 data)
Residue file: methidathionr1acutewater.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Non-hispanic whites                 Daily Exposure Analysis
-------------------                 (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------   -----------
                Mean                  0.000000      0.000000
                Standard Deviation    0.000000      0.000000
                Standard Error of mean 0.000000     0.000000
                Margin of Exposure     694,176       671,076

        Percent of Person-Days that are User-Days =  96.67%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000000  >1,000,000         90.00      0.000001    356,122
   20.00      0.000000  >1,000,000         95.00      0.000001    280,873
   30.00      0.000000  >1,000,000         97.50      0.000001    217,459
   40.00      0.000000    994,921          99.00      0.000002    161,082
   50.00      0.000000    827,657          99.50      0.000002    129,148
   60.00      0.000000    691,373          99.75      0.000003    104,283
   70.00      0.000001    579,989          99.90      0.000004     77,759
   80.00      0.000001    471,062


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000000  >1,000,000         90.00      0.000001    361,669
   20.00      0.000000  >1,000,000         95.00      0.000001    284,343
   30.00      0.000000  >1,000,000         97.50      0.000001    221,429
   40.00      0.000000  >1,000,000         99.00      0.000002    163,969
   50.00      0.000000    852,165          99.50      0.000002    129,967
   60.00      0.000000    709,061          99.75      0.000003    105,747
   70.00      0.000001    590,991          99.90      0.000004     78,613
   80.00      0.000001    478,623
```

4

```
California Department of Pesticide Regulation                Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION               (1994-98 data)
Residue file: methidathionr1acutewater.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
==============================================================================

Non-hispanic blacks                 Daily Exposure Analysis
-------------------                  (mg/kg body-weight/day)
                                     per Capita    per User
                                     ----------   ----------
               Mean                   0.000000     0.000000
               Standard Deviation     0.000000     0.000000
               Standard Error of mean 0.000000     0.000000
               Margin of Exposure      714,020       683,459

       Percent of Person-Days that are User-Days =  95.72%


   Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000000  >1,000,000          90.00     0.000001    356,261
    20.00     0.000000  >1,000,000          95.00     0.000001    257,165
    30.00     0.000000  >1,000,000          97.50     0.000002    184,507
    40.00     0.000000  >1,000,000          99.00     0.000002    131,521
    50.00     0.000000     903,492          99.50     0.000003    110,896
    60.00     0.000000     766,181          99.75     0.000004     84,112
    70.00     0.000000     643,743          99.90     0.000005     60,344
    80.00     0.000001     511,598


   Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000000  >1,000,000          90.00     0.000001    362,316
    20.00     0.000000  >1,000,000          95.00     0.000001    263,638
    30.00     0.000000  >1,000,000          97.50     0.000002    188,323
    40.00     0.000000  >1,000,000          99.00     0.000002    132,579
    50.00     0.000000     952,911          99.50     0.000003    112,910
    60.00     0.000000     787,988          99.75     0.000004     84,619
    70.00     0.000000     660,967          99.90     0.000005     60,655
    80.00     0.000001     524,337
```

5

```
California Department of Pesticide Regulation                      Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: methidathionr1acutewater.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
==============================================================================

Non-hisp/non-white/non-black      Daily Exposure Analysis
----------------------------      (mg/kg body-weight/day)
                                   per Capita    per User
                                  -----------   -----------
              Mean                  0.000001      0.000001
              Standard Deviation    0.000000      0.000000
              Standard Error of mean 0.000000     0.000000
              Margin of Exposure      553,507       541,099

       Percent of Person-Days that are User-Days =  97.76%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile  Exposure      MOE           Percentile  Exposure      MOE
----------  ----------  ---------       ----------  ----------  ---------
   10.00    0.000000  >1,000,000           90.00    0.000001    307,541
   20.00    0.000000  >1,000,000           95.00    0.000001    233,144
   30.00    0.000000    957,718            97.50    0.000002    175,657
   40.00    0.000000    778,230            99.00    0.000002    122,477
   50.00    0.000000    654,304            99.50    0.000003     96,271
   60.00    0.000001    556,650            99.75    0.000003     86,707
   70.00    0.000001    479,768            99.90    0.000005     61,183
   80.00    0.000001    389,562


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile  Exposure      MOE           Percentile  Exposure      MOE
----------  ----------  ---------       ----------  ----------  ---------
   10.00    0.000000  >1,000,000           90.00    0.000001    310,410
   20.00    0.000000  >1,000,000           95.00    0.000001    233,949
   30.00    0.000000    993,756            97.50    0.000002    179,136
   40.00    0.000000    808,568            99.00    0.000002    123,533
   50.00    0.000000    660,880            99.50    0.000003     96,358
   60.00    0.000001    572,191            99.75    0.000003     87,317
   70.00    0.000001    485,199            99.90    0.000005     65,021
   80.00    0.000001    393,351
```

6

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: methidathionr1acutewater.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

All infants                      Daily Exposure Analysis
-----------                      (mg/kg body-weight/day)
                                  per Capita    per User
                                 -----------  -----------
            Mean                  0.000001     0.000002
            Standard Deviation    0.000001     0.000001
            Standard Error of mean 0.000000    0.000000
            Margin of Exposure     205,374      166,461

        Percent of Person-Days that are User-Days =  81.05%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile  Exposure      MOE          Percentile  Exposure      MOE
----------  ----------  ---------      ----------  ----------  ---------
   10.00    0.000000 >1,000,000           90.00    0.000003     86,226
   20.00    0.000001    518,538           95.00    0.000004     68,473
   30.00    0.000001    301,796           97.50    0.000005     58,113
   40.00    0.000001    229,273           99.00    0.000006     48,889
   50.00    0.000002    188,110           99.50    0.000007     42,010
   60.00    0.000002    155,690           99.75    0.000008     36,264
   70.00    0.000002    133,018           99.90    0.000011     28,114
   80.00    0.000003    111,474


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile  Exposure      MOE          Percentile  Exposure      MOE
----------  ----------  ---------      ----------  ----------  ---------
   10.00    0.000000 >1,000,000           90.00    0.000003     91,986
   20.00    0.000000 >1,000,000           95.00    0.000004     72,532
   30.00    0.000000    775,476           97.50    0.000005     60,718
   40.00    0.000001    364,364           99.00    0.000006     50,595
   50.00    0.000001    238,493           99.50    0.000007     42,962
   60.00    0.000002    186,589           99.75    0.000008     39,544
   70.00    0.000002    149,530           99.90    0.000011     28,244
   80.00    0.000002    121,397
```

7

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                      (1994-98 data)
Residue file: methidathionr1acutewater.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48    Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
==============================================================================

Nursing infants (<1 yr old)        Daily Exposure Analysis
---------------------------        (mg/kg body-weight/day)
                                    per Capita    per User
                                    ----------   ----------
              Mean                   0.000001     0.000001
              Standard Deviation     0.000001     0.000001
              Standard Error of mean 0.000000     0.000000
              Margin of Exposure      551,040       297,499

      Percent of Person-Days that are User-Days =  53.99%


  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE          Percentile   Exposure     MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00     0.000000  >1,000,000         90.00     0.000002    138,509
   20.00     0.000000  >1,000,000         95.00     0.000003     99,457
   30.00     0.000000  >1,000,000         97.50     0.000004     68,376
   40.00     0.000000     649,680         99.00     0.000006     50,790
   50.00     0.000001     505,742         99.50     0.000007     41,589
   60.00     0.000001     357,347         99.75     0.000008     39,425
   70.00     0.000001     244,449         99.90     0.000008     39,375
   80.00     0.000002     184,008


  Estimated percentile of per-capita days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE          Percentile   Exposure     MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00     0.000000  >1,000,000         90.00     0.000002    175,188
   20.00     0.000000  >1,000,000         95.00     0.000002    134,031
   30.00     0.000000  >1,000,000         97.50     0.000003     94,490
   40.00     0.000000  >1,000,000         99.00     0.000005     61,065
   50.00     0.000000  >1,000,000         99.50     0.000006     50,707
   60.00     0.000000  >1,000,000         99.75     0.000007     41,556
   70.00     0.000001     561,676         99.90     0.000008     39,404
   80.00     0.000001     319,562
```

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: methidathionr1acutewater.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Non-nursing infants (<1 yr old)     Daily Exposure Analysis
-------------------------------     (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------   -----------
              Mean                    0.000002      0.000002
              Standard Deviation      0.000001      0.000001
              Standard Error of mean  0.000000      0.000000
              Margin of Exposure       166,088       151,568

       Percent of Person-Days that are User-Days =  91.26%


   Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure     MOE           Percentile   Exposure     MOE
----------  ----------  ---------       ----------  ----------  ---------
   10.00     0.000000   707,065            90.00     0.000004    82,107
   20.00     0.000001   337,082            95.00     0.000004    67,084
   30.00     0.000001   241,917            97.50     0.000005    57,503
   40.00     0.000002   199,852            99.00     0.000006    48,613
   50.00     0.000002   170,193            99.50     0.000007    42,500
   60.00     0.000002   143,142            99.75     0.000008    35,990
   70.00     0.000002   124,282            99.90     0.000012    25,506
   80.00     0.000003   105,524


   Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure     MOE           Percentile   Exposure     MOE
----------  ----------  ---------       ----------  ----------  ---------
   10.00     0.000000 >1,000,000          90.00     0.000004    85,396
   20.00     0.000001   589,547            95.00     0.000004    68,312
   30.00     0.000001   289,945            97.50     0.000005    58,291
   40.00     0.000001   223,741            99.00     0.000006    48,940
   50.00     0.000002   184,503            99.50     0.000007    42,703
   60.00     0.000002   151,473            99.75     0.000008    36,043
   70.00     0.000002   129,615            99.90     0.000011    28,218
   80.00     0.000003   108,485
```

```
California Department of Pesticide Regulation                 Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION              (1994-98 data)
Residue file: methidathionr1acutewater.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Females 13+ (preg/not nursing)     Daily Exposure Analysis
------------------------------     (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
              Mean                   0.000000      0.000000
              Standard Deviation     0.000000      0.000000
              Standard Error of mean 0.000000      0.000000
              Margin of Exposure      697,032       674,332

        Percent of Person-Days that are User-Days =  96.74%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE           Percentile   Exposure      MOE
----------  ----------  ---------        ----------  ----------  ---------
   10.00     0.000000  >1,000,000           90.00     0.000001    332,770
   20.00     0.000000  >1,000,000           95.00     0.000001    301,074
   30.00     0.000000  >1,000,000           97.50     0.000001    293,440
   40.00     0.000000  >1,000,000           99.00     0.000001    251,812
   50.00     0.000000    802,948            99.50     0.000001    214,764
   60.00     0.000000    629,495            99.75     0.000002    194,021
   70.00     0.000001    510,135            99.90     0.000002    193,791
   80.00     0.000001    425,574


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE           Percentile   Exposure      MOE
----------  ----------  ---------        ----------  ----------  ---------
   10.00     0.000000  >1,000,000           90.00     0.000001    334,804
   20.00     0.000000  >1,000,000           95.00     0.000001    304,384
   30.00     0.000000  >1,000,000           97.50     0.000001    294,050
   40.00     0.000000  >1,000,000           99.00     0.000001    251,981
   50.00     0.000000    812,225            99.50     0.000001    214,907
   60.00     0.000000    645,758            99.75     0.000002    194,034
   70.00     0.000001    514,491            99.90     0.000002    193,796
   80.00     0.000001    435,362
```

10

```
California Department of Pesticide Regulation                 Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: methidathionr1acutewater.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Females 13+ (nursing)              Daily Exposure Analysis
---------------------              (mg/kg body-weight/day)
                                    per Capita     per User
                                   -----------   -----------
                Mean                 0.000001      0.000001
                Standard Deviation   0.000000      0.000000
                Standard Error of mean  0.000000   0.000000
                Margin of Exposure     490,538       486,794

        Percent of Person-Days that are User-Days =  99.24%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE         Percentile   Exposure      MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00      0.000000  >1,000,000        90.00      0.000001    274,147
   20.00      0.000000  >1,000,000        95.00      0.000001    245,286
   30.00      0.000000    772,985         97.50      0.000001    201,966
   40.00      0.000000    650,062         99.00      0.000002    173,488
   50.00      0.000001    470,169         99.50      0.000002    138,692
   60.00      0.000001    445,621         99.75      0.000002    138,449
   70.00      0.000001    379,856         99.90      0.000002    138,304
   80.00      0.000001    338,288


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE         Percentile   Exposure      MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00      0.000000  >1,000,000        90.00      0.000001    274,320
   20.00      0.000000  >1,000,000        95.00      0.000001    245,326
   30.00      0.000000    778,881         97.50      0.000001    201,989
   40.00      0.000000    651,186         99.00      0.000002    173,506
   50.00      0.000001    470,673         99.50      0.000002    138,696
   60.00      0.000001    446,441         99.75      0.000002    138,451
   70.00      0.000001    380,348         99.90      0.000002    138,304
   80.00      0.000001    338,599
```

```
California Department of Pesticide Regulation                 Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                (1994-98 data)
Residue file: methidathionr1acutewater.R98     Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
==============================================================================

Children 1-2 yrs                    Daily Exposure Analysis
----------------                    (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------   -----------
              Mean                    0.000001      0.000001
              Standard Deviation      0.000001      0.000001
              Standard Error of mean  0.000000      0.000000
              Margin of Exposure       455,515       429,881

       Percent of Person-Days that are User-Days =  94.37%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE          Percentile   Exposure     MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000000 >1,000,000          90.00     0.000001    214,176
    20.00     0.000000 >1,000,000          95.00     0.000002    170,509
    30.00     0.000000    846,910          97.50     0.000002    136,060
    40.00     0.000000    663,182          99.00     0.000003    101,347
    50.00     0.000001    540,108          99.50     0.000003     89,107
    60.00     0.000001    442,835          99.75     0.000004     78,310
    70.00     0.000001    358,620          99.90     0.000004     68,688
    80.00     0.000001    293,357


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE          Percentile   Exposure     MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000000 >1,000,000          90.00     0.000001    218,738
    20.00     0.000000 >1,000,000          95.00     0.000002    174,286
    30.00     0.000000    959,549          97.50     0.000002    138,286
    40.00     0.000000    711,969          99.00     0.000003    104,362
    50.00     0.000001    576,167          99.50     0.000003     89,808
    60.00     0.000001    469,559          99.75     0.000004     79,674
    70.00     0.000001    374,273          99.90     0.000004     71,758
    80.00     0.000001    299,889
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                        (1994-98 data)
Residue file: methidathionr1acutewater.R98          Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48    Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Children 3-5 yrs                    Daily Exposure Analysis
----------------                    (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------   -----------
                Mean                   0.000001      0.000001
                Standard Deviation     0.000001      0.000001
                Standard Error of mean 0.000000      0.000000
                Margin of Exposure      487,539       465,201

        Percent of Person-Days that are User-Days =  95.42%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000000  >1,000,000         90.00      0.000001    237,389
   20.00      0.000000  >1,000,000         95.00      0.000002    188,839
   30.00      0.000000    882,964          97.50      0.000002    151,436
   40.00      0.000000    695,245          99.00      0.000002    120,923
   50.00      0.000001    563,285          99.50      0.000003    108,712
   60.00      0.000001    469,103          99.75      0.000003     90,214
   70.00      0.000001    396,041          99.90      0.000004     70,486
   80.00      0.000001    321,727


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000000  >1,000,000         90.00      0.000001    240,740
   20.00      0.000000  >1,000,000         95.00      0.000002    190,787
   30.00      0.000000    958,812          97.50      0.000002    154,023
   40.00      0.000000    744,372          99.00      0.000002    121,720
   50.00      0.000001    589,463          99.50      0.000003    109,123
   60.00      0.000001    484,342          99.75      0.000003     95,679
   70.00      0.000001    404,364          99.90      0.000004     74,577
   80.00      0.000001    330,036
```

```
California Department of Pesticide Regulation                   Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: methidathionr1acutewater.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Children 6-12 yrs                    Daily Exposure Analysis
-----------------                    (mg/kg body-weight/day)
                                      per Capita    per User
                                      ----------   ----------
              Mean                     0.000000     0.000000
              Standard Deviation       0.000000     0.000000
              Standard Error of mean   0.000000     0.000000
              Margin of Exposure        708,950      676,100

        Percent of Person-Days that are User-Days =  95.37%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE           Percentile   Exposure      MOE
----------   ----------   ---------      ----------   ----------   ---------
   10.00      0.000000  >1,000,000          90.00      0.000001     342,240
   20.00      0.000000  >1,000,000          95.00      0.000001     271,344
   30.00      0.000000  >1,000,000          97.50      0.000001     212,366
   40.00      0.000000  >1,000,000          99.00      0.000002     163,145
   50.00      0.000000     837,015          99.50      0.000002     147,251
   60.00      0.000000     690,483          99.75      0.000002     130,442
   70.00      0.000001     568,402          99.90      0.000002     120,316
   80.00      0.000001     460,014


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile   Exposure      MOE           Percentile   Exposure      MOE
----------   ----------   ---------      ----------   ----------   ---------
   10.00      0.000000  >1,000,000          90.00      0.000001     349,160
   20.00      0.000000  >1,000,000          95.00      0.000001     274,058
   30.00      0.000000  >1,000,000          97.50      0.000001     215,808
   40.00      0.000000  >1,000,000          99.00      0.000002     164,824
   50.00      0.000000     871,824          99.50      0.000002     148,062
   60.00      0.000000     721,891          99.75      0.000002     130,905
   70.00      0.000001     586,481          99.90      0.000002     120,691
   80.00      0.000001     471,723
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                     (1994-98 data)
Residue file: methidathionr1acutewater.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Youth 13-19 yrs                       Daily Exposure Analysis
---------------                       (mg/kg body-weight/day)
                                       per Capita    per User
                                      -----------   -----------
              Mean                      0.000000      0.000000
              Standard Deviation        0.000000      0.000000
              Standard Error of mean    0.000000      0.000000
              Margin of Exposure         937,978       880,262

         Percent of Person-Days that are User-Days =  93.85%


   Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE            Percentile   Exposure      MOE
 ----------  ----------  ---------         ----------  ----------  ---------
    10.00     0.000000  >1,000,000            90.00     0.000001    436,104
    20.00     0.000000  >1,000,000            95.00     0.000001    328,642
    30.00     0.000000  >1,000,000            97.50     0.000001    255,506
    40.00     0.000000  >1,000,000            99.00     0.000002    197,033
    50.00     0.000000  >1,000,000            99.50     0.000002    157,419
    60.00     0.000000     924,782            99.75     0.000002    125,214
    70.00     0.000000     760,153            99.90     0.000003    111,280
    80.00     0.000000     604,158


   Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE            Percentile   Exposure      MOE
 ----------  ----------  ---------         ----------  ----------  ---------
    10.00     0.000000  >1,000,000            90.00     0.000001    444,262
    20.00     0.000000  >1,000,000            95.00     0.000001    337,091
    30.00     0.000000  >1,000,000            97.50     0.000001    261,577
    40.00     0.000000  >1,000,000            99.00     0.000001    200,355
    50.00     0.000000  >1,000,000            99.50     0.000002    158,646
    60.00     0.000000     982,603            99.75     0.000002    125,496
    70.00     0.000000     800,141            99.90     0.000003    111,397
    80.00     0.000000     618,072
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                        (1994-98 data)
Residue file: methidathionr1acutewater.R98         Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48    Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Adults 20-49 yrs                      Daily Exposure Analysis
----------------                      (mg/kg body-weight/day)
                                       per Capita    per User
                                      -----------  -----------
               Mean                     0.000000     0.000000
               Standard Deviation       0.000000     0.000000
               Standard Error of mean   0.000000     0.000000
               Margin of Exposure        725,837      704,533

        Percent of Person-Days that are User-Days =  97.06%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
     10.00     0.000000  >1,000,000          90.00     0.000001    369,420
     20.00     0.000000  >1,000,000          95.00     0.000001    292,203
     30.00     0.000000  >1,000,000          97.50     0.000001    231,504
     40.00     0.000000  >1,000,000          99.00     0.000002    174,904
     50.00     0.000000     860,300          99.50     0.000002    140,612
     60.00     0.000000     721,738          99.75     0.000003    119,656
     70.00     0.000000     606,635          99.90     0.000003     97,156
     80.00     0.000001     490,022


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
     10.00     0.000000  >1,000,000          90.00     0.000001    373,820
     20.00     0.000000  >1,000,000          95.00     0.000001    295,166
     30.00     0.000000  >1,000,000          97.50     0.000001    233,655
     40.00     0.000000  >1,000,000          99.00     0.000002    176,256
     50.00     0.000000     880,629          99.50     0.000002    140,857
     60.00     0.000000     739,505          99.75     0.000002    120,285
     70.00     0.000000     616,920          99.90     0.000003     97,439
     80.00     0.000001     497,428
```

16

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION             (1994-98 data)
Residue file: methidathionr1acutewater.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =  0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Adults 50+ yrs                       Daily Exposure Analysis
--------------                       (mg/kg body-weight/day)
                                      per Capita    per User
                                     -----------  -----------
              Mean                     0.000000     0.000000
              Standard Deviation       0.000000     0.000000
              Standard Error of mean   0.000000     0.000000
              Margin of Exposure        689,433      685,142

         Percent of Person-Days that are User-Days =  99.38%


   Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE           Percentile   Exposure     MOE
 ----------  ----------  ---------        ----------  ----------  ---------
   10.00     0.000000  >1,000,000           90.00     0.000001    394,326
   20.00     0.000000  >1,000,000           95.00     0.000001    325,785
   30.00     0.000000  >1,000,000           97.50     0.000001    282,222
   40.00     0.000000    903,088            99.00     0.000001    228,080
   50.00     0.000000    771,845            99.50     0.000002    194,713
   60.00     0.000000    670,030            99.75     0.000002    165,757
   70.00     0.000001    580,856            99.90     0.000002    140,909
   80.00     0.000001    486,420


   Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure     MOE           Percentile   Exposure     MOE
 ----------  ----------  ---------        ----------  ----------  ---------
   10.00     0.000000  >1,000,000           90.00     0.000001    394,883
   20.00     0.000000  >1,000,000           95.00     0.000001    326,851
   30.00     0.000000  >1,000,000           97.50     0.000001    282,569
   40.00     0.000000    907,579            99.00     0.000001    228,555
   50.00     0.000000    775,433            99.50     0.000002    195,072
   60.00     0.000000    672,397            99.75     0.000002    165,827
   70.00     0.000001    582,317            99.90     0.000002    140,936
   80.00     0.000001    487,454
```

17

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                   (1994-98 data)
Residue file: methidathionr1acutewater.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
===============================================================================

Females 13-49 yrs                      Daily Exposure Analysis
-----------------                      (mg/kg body-weight/day)
                                        per Capita    per User
                                       -----------   -----------
              Mean                      0.000000      0.000000
              Standard Deviation        0.000000      0.000000
              Standard Error of mean    0.000000      0.000000
              Margin of Exposure         728,702       705,946

       Percent of Person-Days that are User-Days =  96.88%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000000  >1,000,000          90.00     0.000001    362,739
    20.00     0.000000  >1,000,000          95.00     0.000001    291,069
    30.00     0.000000  >1,000,000          97.50     0.000001    231,321
    40.00     0.000000  >1,000,000          99.00     0.000002    177,445
    50.00     0.000000    869,166           99.50     0.000002    141,588
    60.00     0.000000    720,379           99.75     0.000002    125,984
    70.00     0.000001    596,076           99.90     0.000003    102,768
    80.00     0.000001    479,775


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000000  >1,000,000          90.00     0.000001    368,554
    20.00     0.000000  >1,000,000          95.00     0.000001    293,502
    30.00     0.000000  >1,000,000          97.50     0.000001    234,326
    40.00     0.000000  >1,000,000          99.00     0.000002    182,361
    50.00     0.000000    892,161           99.50     0.000002    141,846
    60.00     0.000000    740,105           99.75     0.000002    127,748
    70.00     0.000000    609,661           99.90     0.000003    102,832
    80.00     0.000001    484,310
```

```
California Department of Pesticide Regulation                 Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                     (1994-98 data)
Residue file: methidathionr1acutewater.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:41:48   Residue file dated: 10-12-2005/16:17:59/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: ""
==============================================================================

Custom demographics 1: Workers, 16+ years
All Seasons
All Regions
Sex: M/F-all/
All Races
Age-Low: 16 yrs    High: 99 yrs
-----------------------------------------

                              Daily Exposure Analysis
                              (mg/kg body-weight/day)
                               per Capita    per User
                              -----------   -----------
              Mean                0.000000      0.000000
              Standard Deviation  0.000000      0.000000
              Standard Error of mean  0.000000  0.000000
              Margin of Exposure    724,747       706,637

        Percent of Person-Days that are User-Days =  97.50%


   Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------   ----------   ---------     ----------   ----------   ---------
     10.00      0.000000  >1,000,000         90.00      0.000001     381,179
     20.00      0.000000  >1,000,000         95.00      0.000001     303,766
     30.00      0.000000  >1,000,000         97.50      0.000001     249,619
     40.00      0.000000  >1,000,000         99.00      0.000002     190,092
     50.00      0.000000     841,879         99.50      0.000002     149,300
     60.00      0.000000     709,837         99.75      0.000002     129,154
     70.00      0.000000     601,292         99.90      0.000003     102,764
     80.00      0.000001     492,979


   Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------   ----------   ---------     ----------   ----------   ---------
     10.00      0.000000  >1,000,000         90.00      0.000001     384,420
     20.00      0.000000  >1,000,000         95.00      0.000001     305,915
     30.00      0.000000  >1,000,000         97.50      0.000001     251,724
     40.00      0.000000  >1,000,000         99.00      0.000002     191,386
     50.00      0.000000     858,882         99.50      0.000002     151,025
     60.00      0.000000     723,598         99.75      0.000002     129,311
     70.00      0.000000     609,915         99.90      0.000003     102,883
     80.00      0.000001     498,432
```

```
California Department of Pesticide Regulation              Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION               1994-98 data
Residue file: H:\MyFiles\DEEM-FCID Files\Methidathion\methidathionr1chronicwater.R98
                                                  Adjust. #2 used
Analysis Date 10-26-2005          Residue file dated: 10-12-2005/16:19:12/14
Reference dose (NOEL) = 0.15 mg/kg bw/day


------------------------------------------------------------------------------
Food Crop                                  Residue     Adj.Factors    Comment
EPA Code  Grp  Food Name                    (ppm)
                                                       #1      #2
-------- ---- ------------------------------ ---------- ------  ------  -------
86010000 O    Water, direct, all sources     0.000013  1.000   1.000   PDP 20
   Full comment: PDP 2002-2003, 1/2 Combined CA LOD
86020000 O    Water, indirect, all sources   0.000013  1.000   1.000   PDP 20
   Full comment: PDP 2001-2003, 1/2 Combined CA LOD
```

```
California Department of Pesticide Regulation                Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION              (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\methidathionr1chronicwater.R98
                                          Adjustment factor #2 used.
Analysis Date 10-26-2005/08:50:06    Residue file dated: 10-12-2005/16:19:12/14
NOEL (Chronic) = .15 mg/kg bw/day
===============================================================================
                    Total exposure by population subgroup
-------------------------------------------------------------------------------
```

	Total Exposure		

Population	mg/kg	Percent	Margin of
Subgroup	body wt/day	of NOEL	Exposr 1/
U.S. Population (total)	0.000000	0.00%	547,429
U.S. Population (spring season)	0.000000	0.00%	552,285
U.S. Population (summer season)	0.000000	0.00%	509,626
U.S. Population (autumn season)	0.000000	0.00%	566,337
U.S. Population (winter season)	0.000000	0.00%	566,244
Northeast region	0.000000	0.00%	600,096
Midwest region	0.000000	0.00%	541,483
Southern region	0.000000	0.00%	575,923
Western region	0.000000	0.00%	477,793
Hispanics	0.000000	0.00%	482,278
Non-hispanic whites	0.000000	0.00%	561,103
Non-hispanic blacks	0.000000	0.00%	576,710
Non-hisp/non-white/non-black	0.000000	0.00%	446,548
All infants (< 1 year)	0.000001	0.00%	166,974
Nursing infants	0.000000	0.00%	450,205
Non-nursing infants	0.000001	0.00%	134,797
Children 1-6 yrs	0.000000	0.00%	391,831
Children 7-12 yrs	0.000000	0.00%	602,667
Females 13-19 (not preg or nursing)	0.000000	0.00%	777,974
Females 20+ (not preg or nursing)	0.000000	0.00%	548,421
Females 13-50 yrs	0.000000	0.00%	565,863
Females 13+ (preg/not nursing)	0.000000	0.00%	562,988
Females 13+ (nursing)	0.000000	0.00%	395,137
Males 13-19 yrs	0.000000	0.00%	744,021
Males 20+ yrs	0.000000	0.00%	610,940
Seniors 55+	0.000000	0.00%	557,614
Children 1-2 yrs	0.000000	0.00%	368,642
Children 3-5 yrs	0.000000	0.00%	393,781
Children 6-12 yrs	0.000000	0.00%	570,912
Youth 13-19 yrs	0.000000	0.00%	757,324
Adults 20-49 yrs	0.000000	0.00%	586,319
Adults 50+ yrs	0.000000	0.00%	557,285
Females 13-49 yrs	0.000000	0.00%	588,757

```
-------------------------------------------------------------------------------
```

```
California Department of Pesticide Regulation              Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION               (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\methidathionr1chronicwater.R98
                                             Adjustment factor #2 used.
Analysis Date 10-26-2005/08:51:44   Residue file dated: 10-12-2005/16:19:12/14
Q* = 0.34
==============================================================================
                   Total exposure by population subgroup
------------------------------------------------------------------------------


                                            Total Exposure
                                      -----------------------------------
            Population                  mg/kg          Lifetime risk
            Subgroup                  body wt/day        (Q*= .34)
---------------------------------     ------------     -------------
U.S. Population (total)                 0.000000         9.32E-08

U.S. Population (spring season)         0.000000         9.23E-08
U.S. Population (summer season)         0.000000         1.00E-07
U.S. Population (autumn season)         0.000000         9.01E-08
U.S. Population (winter season)         0.000000         9.01E-08

Northeast region                        0.000000         8.50E-08
Midwest region                          0.000000         9.42E-08
Southern region                         0.000000         8.86E-08
Western region                          0.000000         1.07E-07

Hispanics                               0.000000         1.06E-07
Non-hispanic whites                     0.000000         9.09E-08
Non-hispanic blacks                     0.000000         8.84E-08
Non-hisp/non-white/non-black            0.000000         1.14E-07

All infants (< 1 year)                  0.000001         3.05E-07
Nursing infants                         0.000000         1.13E-07
Non-nursing infants                     0.000001         3.78E-07
Children 1-6  yrs                       0.000000         1.30E-07
Children 7-12 yrs                       0.000000         8.46E-08

Females 13-19 (not preg or nursing)     0.000000         6.56E-08
Females 20+ (not preg or nursing)       0.000000         9.30E-08
Females 13-50 yrs                       0.000000         9.01E-08
Females 13+ (preg/not nursing)          0.000000         9.06E-08
Females 13+ (nursing)                   0.000000         1.29E-07

Males 13-19 yrs                         0.000000         6.85E-08
Males 20+ yrs                           0.000000         8.35E-08
Seniors 55+                             0.000000         9.15E-08

Children 1-2 yrs                        0.000000         1.38E-07
Children 3-5 yrs                        0.000000         1.30E-07
Children 6-12 yrs                       0.000000         8.93E-08
Youth 13-19 yrs                         0.000000         6.73E-08
Adults 20-49 yrs                        0.000000         8.70E-08
Adults 50+ yrs                          0.000000         9.15E-08
Females 13-49 yrs                       0.000000         8.66E-08


------------------------------------------------------------------------------
```

```
California Department of Pesticide Regulation                    Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION                   (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\methidathionr1chronicwater.R98
                                              Adjustment factor #2 used.
Analysis Date 10-26-2005/08:51:26    Residue file dated: 10-12-2005/16:19:12/14
Q* = 0.53
===============================================================================
                   Total exposure by population subgroup
-------------------------------------------------------------------------------


                                            Total Exposure
                                   ----------------------------------
         Population                    mg/kg           Lifetime risk
         Subgroup                   body wt/day          (Q*= .53)
--------------------------------   ------------        ------------
U.S. Population (total)               0.000000           1.45E-07

U.S. Population (spring season)       0.000000           1.44E-07
U.S. Population (summer season)       0.000000           1.56E-07
U.S. Population (autumn season)       0.000000           1.40E-07
U.S. Population (winter season)       0.000000           1.40E-07

Northeast region                      0.000000           1.32E-07
Midwest region                        0.000000           1.47E-07
Southern region                       0.000000           1.38E-07
Western region                        0.000000           1.66E-07

Hispanics                             0.000000           1.65E-07
Non-hispanic whites                   0.000000           1.42E-07
Non-hispanic blacks                   0.000000           1.38E-07
Non-hisp/non-white/non-black          0.000000           1.78E-07

All infants (< 1 year)                0.000001           4.76E-07
Nursing infants                       0.000000           1.77E-07
Non-nursing infants                   0.000001           5.90E-07
Children 1-6  yrs                     0.000000           2.03E-07
Children 7-12 yrs                     0.000000           1.32E-07

Females 13-19 (not preg or nursing)   0.000000           1.02E-07
Females 20+ (not preg or nursing)     0.000000           1.45E-07
Females 13-50 yrs                     0.000000           1.40E-07
Females 13+ (preg/not nursing)        0.000000           1.41E-07
Females 13+ (nursing)                 0.000000           2.01E-07

Males 13-19 yrs                       0.000000           1.07E-07
Males 20+ yrs                         0.000000           1.30E-07
Seniors 55+                           0.000000           1.43E-07

Children 1-2 yrs                      0.000000           2.16E-07
Children 3-5 yrs                      0.000000           2.02E-07
Children 6-12 yrs                     0.000000           1.39E-07
Youth 13-19 yrs                       0.000000           1.05E-07
Adults 20-49 yrs                      0.000000           1.36E-07
Adults 50+ yrs                        0.000000           1.43E-07
Females 13-49 yrs                     0.000000           1.35E-07


-------------------------------------------------------------------------------
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID Acute analysis for METHIDATHION
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\Methidathionr1acutecomb.R98
Analysis Date 10-26-2005           Residue file dated: 10-25-2005/16:21:22/14
Reference dose (NOEL) = 0.3 mg/kg bw/day
--------------------------------------------------------------------------
RDL indices and parameters for Monte Carlo Analysis:
Index Dist Parameter #1            Param #2    Param #3    Comment
  #   Code
----- ---- -----------            ----------- ----------- ----------
   1    6   RDF1 APPLES.rdf
   2    6   RDF2 PLUMS.rdf
   3    6   RDF3 APRICOTS.rdf
   4    6   RDF4 ORANGES.rdf
   5    6   RDF5 PEACHES.rdf
   6    6   RDF6 NECTARINES.rdf
   7    6   RDF7 PEARS.rdf
   8    6   RDF8 CHERRIES.rdf
   9    6   RDF9 PRUNES.RDF


  EPA     Crop Food Name                     Def Res    Adj.Factors  RDL  Comment
  Code    Grp                                (ppm)       #1     #2   Pntr
-------- ---- ------------------------------ ---------- ------ ------ --- -------
14000030 14   Almond                         0.050000   1.000  1.000     Tolera
     Full comment: Tolerance
14000031 14   Almond-babyfood                0.050000   1.000  1.000     Tolera
     Full comment: Tolerance
14000040 14   Almond, oil                    0.050000   1.000  1.000     Tolera
     Full comment: Tolerance
14000041 14   Almond, oil-babyfood           0.050000   1.000  1.000     Tolera
     Full comment: Tolerance
11000070 11   Apple, fruit with peel         0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000080 11   Apple, peeled fruit            0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000081 11   Apple, peeled fruit-babyfood   0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000090 11   Apple, dried                   0.007000   8.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000091 11   Apple, dried-babyfood          0.007000   8.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000100 11   Apple, juice                   0.007000   1.300  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000101 11   Apple, juice-babyfood          0.007000   1.300  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000110 11   Apple, sauce                   0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
11000111 11   Apple, sauce-babyfood          0.007000   1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California - RDF, 15% PCT
12000120 12   Apricot                        0.050000   1.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
12000121 12   Apricot-babyfood               0.050000   1.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
12000130 12   Apricot, dried                 0.050000   6.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
12000140 12   Apricot, juice                 0.050000   1.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
12000141 12   Apricot, juice-babyfood        0.050000   1.000  1.000   3 DPR 20
     Full comment: DPR 2002-2004 - RDF, 5% PCT
95000160 O    Artichoke, globe               0.050000   1.000  1.000     DPR 20
     Full comment: DPR 2002-2004 LOD
01030170 1CD  Artichoke, Jerusalem           0.050000   1.000  1.000     DPR 20
     Full comment: DPR 2002-2004 LOD
```

```
14000590 14   Brazil nut                        0.050000  1.000  1.000     Tolera
     Full comment: Tolerance
14000680 14   Butternut                         0.050000  1.000  1.000     Tolera
     Full comment: Tolerance
14000810 14   Cashew                            0.050000  1.000  1.000     Tolera
     Full comment: Tolerance
12000900 12   Cherry                            0.004000  1.000  1.000   8 PDP Ch
     Full comment: PDP Cherries 2000 & 2001 CA - RDF, 10% PCT
12000901 12   Cherry-babyfood                   0.004000  1.000  1.000   8 PDP Ch
     Full comment: PDP Cherries 2000 & 2001 CA - RDF, 10% PCT
12000910 12   Cherry, juice                     0.004000  1.500  1.000   8 PDP Ch
     Full comment: PDP Cherries 2000 & 2001 CA - RDF, 10% PCT
12000911 12   Cherry, juice-babyfood            0.004000  1.500  1.000   8 PDP Ch
     Full comment: PDP Cherries 2000 & 2001 CA - RDF, 10% PCT
14000920 14   Chestnut                          0.050000  1.000  1.000     Tolera
     Full comment: Tolerance
10001060 10   Citrus citron                     2.000000  1.000  1.000   4 Tolera
     Full comment: Tolerance
10001070 10   Citrus hybrids                    0.007000  1.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10001080 10   Citrus, oil                       0.007000  1.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
95001280 O    Cottonseed, oil                   0.200000  1.000  1.000     Tolera
     Full comment: Tolerance
95001281 O    Cottonseed, oil-babyfood          0.200000  1.000  1.000     Tolera
     Full comment: Tolerance
11001290 11   Crabapple                         0.007000  1.000  1.000   1 PDP Ap
     Full comment: PDP Apple 2002 California LOD
14001550 14   Filbert                           0.050000  1.000  1.000     Tolera
     Full comment: Tolerance
14001560 14   Filbert, oil                      0.050000  1.000  1.000     Tolera
     Full comment: Tolerance
10001800 10   Grapefruit                        0.007000  1.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10001810 10   Grapefruit, juice                 0.007000  2.100  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
14001850 14   Hickory nut                       0.050000  1.000  1.000     Tolera
     Full comment: Tolerance
95001950 O    Kiwifruit                         0.050000  1.000  1.000     DPR 20
     Full comment: DPR 2002-2004 LOD
10001970 10   Kumquat                           0.007000  1.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10001990 10   Lemon                             0.007000  1.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002000 10   Lemon, juice                      0.007000  2.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002001 10   Lemon, juice-babyfood             0.007000  2.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002010 10   Lemon, peel                       2.000000  1.000  1.000   4 Tolera
     Full comment: Tolerance
10002060 10   Lime                              0.007000  1.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002070 10   Lime, juice                       0.007000  2.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002071 10   Lime, juice-babyfood              0.007000  2.000  1.000   4 PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
14002130 14   Macadamia nut                     0.050000  1.000  1.000     Tolera
     Full comment: Tolerance
95002150 O    Mango                             0.050000  1.000  1.000     DPR 20
     Full comment: DPR 2002-2004 LOD
95002151 O    Mango-babyfood                    0.050000  1.000  1.000     DPR 20
     Full comment: DPR 2002-2004 LOD
95002160 O    Mango, dried                      0.050000  1.000  1.000     DPR 20
     Full comment: DPR 2002-2004 LOD
```

```
95002170 O    Mango, juice                    0.050000  1.000  1.000      DPR 20
     Full comment: DPR 2002-2004 LOD
95002171 O    Mango, juice-babyfood           0.050000  1.000  1.000      DPR 20
     Full comment: DPR 2002-2004 LOD
12002300 12   Nectarine                       0.004000  1.000  1.000   6  PDP Ne
     Full comment: PDP Nectarine 2000 & 2001 CA - RDF, 10% PCT
95002350 O    Olive                           0.050000  1.000  1.000      Tolera
     Full comment: Tolerance
95002360 O    Olive, oil                      0.050000  1.000  1.000      Tolera
     Full comment: Tolerance
10002400 10   Orange                          0.007000  1.000  1.000   4  PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002410 10   Orange, juice                   0.007000  1.800  1.000   4  PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002411 10   Orange, juice-babyfood          0.007000  1.800  1.000   4  PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10002420 10   Orange, peel                    2.000000  1.000  1.000   4  Tolera
     Full comment: Tolerance
12002600 12   Peach                           0.004000  1.000  1.000   5  PDP Pe
     Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002601 12   Peach-babyfood                  0.004000  1.000  1.000   5  PDP Pe
     Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002610 12   Peach, dried                    0.004000  7.000  1.000   5  PDP Pe
     Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002611 12   Peach, dried-babyfood           0.004000  7.000  1.000   5  PDP Pe
     Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002620 12   Peach, juice                    0.004000  1.000  1.000   5  PDP Pe
     Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
12002621 12   Peach, juice-babyfood           0.004000  1.000  1.000   5  PDP Pe
     Full comment: PDP Peach 2001 & 2002 CA - RDF, 15% PCT
11002660 11   Pear                            0.004000  1.000  1.000   7  PDP Pe
     Full comment: PDP Pear 2003 National - RDF, 10% PCT
11002661 11   Pear-babyfood                   0.004000  1.000  1.000   7  PDP Pe
     Full comment: PDP Pear 2003 National - RDF, 10% PCT
11002670 11   Pear, dried                     0.004000  6.250  1.000   7  PDP Pe
     Full comment: PDP Pear 2003 National - RDF, 10% PCT
11002680 11   Pear, juice                     0.004000  1.000  1.000   7  PDP Pe
     Full comment: PDP Pear 2003 National - RDF, 10% PCT
11002681 11   Pear, juice-babyfood            0.004000  1.000  1.000   7  PDP Pe
     Full comment: PDP Pear 2003 National - RDF, 10% PCT
14002690 14   Pecan                           0.050000  1.000  1.000      Tolera
     Full comment: Tolerance
95002780 O    Pine nut                        0.050000  1.000  1.000      Tolera
     Full comment: Tolerance
14002820 14   Pistachio                       0.050000  1.000  1.000      Tolera
     Full comment: Tolerance
12002850 12   Plum                            0.050000  1.000  1.000   2  DPR 20
     Full comment: DPR 2002-2004 - RDF, 15% PCT
12002851 12   Plum-babyfood                   0.050000  1.000  1.000   2  DPR 20
     Full comment: DPR 2002-2004 - RDF, 15% PCT
12002860 12   Plum, prune, fresh              0.050000  1.000  1.000   9  DPR Pl
     Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002861 12   Plum, prune, fresh-babyfood     0.050000  1.000  1.000   9  DPR Pl
     Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002870 12   Plum, prune, dried              0.050000  5.000  1.000   9  DPR Pl
     Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002871 12   Plum, prune, dried-babyfood     0.050000  5.000  1.000   9  DPR Pl
     Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002880 12   Plum, prune, juice              0.050000  1.400  1.000   9  DPR Pl
     Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
12002881 12   Plum, prune, juice-babyfood     0.050000  1.400  1.000   9  DPR Pl
     Full comment: DPR Plum 2002-2004 - RDF, 5% PCT
10003070 10   Pummelo                         0.007000  1.000  1.000   4  PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
```

```
11003100 11   Quince                        0.007000  1.000  1.000   1  PDP Ap
     Full comment: PDP Apple 2002 CA - RDF, 15% PCT
20003300 20   Safflower, oil                0.050000  1.000  1.000      Safflo
     Full comment: Safflower Field Trial High Value
20003301 20   Safflower, oil-babyfood       0.050000  1.000  1.000      Safflo
     Full comment: Safflower Field Trial High Value
15003440 15   Sorghum, grain                0.200000  1.000  1.000      Tolera
     Full comment: Tolerance
15003450 15   Sorghum, syrup                0.200000  1.000  1.000      Tolera
     Full comment: Tolerance
95003580 O    Starfruit                     0.100000  1.000  1.000      Tolera
     Full comment: Tolerance
95003610 O    Sugar apple                   0.200000  1.000  1.000      Tolera
     Full comment: Tolerance
20003640 20   Sunflower, seed               0.220000  1.000  0.500      Sunflo
     Full comment: Sunflower Field Trial High Value, 50% hulls
20003650 20   Sunflower, oil                0.220000  1.000  0.200      Sunflo
     Full comment: Sunflower Field Trial High Value, 20% Oil
20003651 20   Sunflower, oil-babyfood       0.220000  1.000  0.200      Sunflo
     Full comment: Sunflower Field Trial High Value, 20% Oil
10003690 10   Tangerine                     0.007000  1.000  1.000   4  PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
10003700 10   Tangerine, juice              0.007000  2.300  1.000   4  PDP Or
     Full comment: PDP Orange 2000 & 2001 CA - RDF, 10%
14003910 14   Walnut                        0.050000  1.000  1.000      Tolera
     Full comment: Tolerance
86010000 O    Water, direct, all sources    0.000021  1.000  1.000      PDP 20
     Full comment: PDP 2002-2003, Combined CA LOD
86020000 O    Water, indirect, all sources  0.000021  1.000  1.000      PDP 20
     Full comment: PDP 2002-2003, Combined CA LOD
```

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION              (1994-98 data)
Residue file: Methidathionr1acutecomb.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

Summary calculations (per capita):
```

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	MOE	Exposure	MOE	Exposure	MOE
U.S. Population:						
	0.000037	8126	0.000110	2732	0.000320	937
Western region:						
	0.000042	7109	0.000139	2161	0.000338	887
Hispanics:						
	0.000048	6189	0.000163	1838	0.000451	664
Non-hispanic whites:						
	0.000035	8490	0.000098	3064	0.000282	1063
Non-hispanic blacks:						
	0.000035	8558	0.000108	2765	0.000224	1340
Non-hisp/non-white/non-black:						
	0.000045	6673	0.000157	1908	0.000440	682
All infants:						
	0.000127	2353	0.000211	1423	0.000492	610
Nursing infants (<1 yr old):						
	0.000070	4290	0.000128	2348	0.000251	1196
Non-nursing infants (<1 yr old):						
	0.000145	2067	0.000228	1315	0.000503	596
Females 13+ (preg/not nursing):						
	0.000039	7618	0.000216	1391	0.000295	1018
Females 13+ (nursing):						
	0.000037	8117	0.000282	1063	0.000299	1004
Children 1-2 yrs:						
	0.000094	3187	0.000262	1145	0.000777	386
Children 3-5 yrs:						
	0.000079	3813	0.000212	1412	0.000589	509

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: Methidathionr1acutecomb.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
================================================================================

Summary calculations:

                   95th Percentile    99th Percentile     99.9th Percentile
                   Exposure    MOE    Exposure    MOE     Exposure    MOE
                   ---------- -------  ---------- -------  ---------- --------
Children 6-12 yrs:
                   0.000048    6270   0.000133    2252    0.000478     628
Youth 13-19 yrs:
                   0.000030   10104   0.000091    3312    0.000335     894
Adults 20-49 yrs:
                   0.000028   10812   0.000079    3819    0.000214    1405
Adults 50+ yrs:
                   0.000022   13831   0.000071    4252    0.000172    1744
Females 13-49 yrs:
                   0.000028   10576   0.000086    3478    0.000214    1402
Custom demographics 1: Workers, 16+ years:
                   0.000026   11654   0.000077    3889    0.000190    1576
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: Methidathionr1acutecomb.R98          Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================


U.S. Population                       Daily Exposure Analysis  /a
---------------                       (mg/kg body-weight/day)
                                       per Capita    per User
                                      -----------   -----------
            Mean                        0.000011      0.000011
            Standard Deviation          0.000025      0.000025
            Margin of Exposure 2/        27,750        27,694

        Percent of Person-Days that are User-Days =  99.80%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    307,835          90.00      0.000022     13,782
   20.00      0.000002    174,676          95.00      0.000037      8,111
   30.00      0.000003    113,875          97.50      0.000061      4,937
   40.00      0.000004     81,673          99.00      0.000110      2,729
   50.00      0.000005     60,863          99.50      0.000154      1,949
   60.00      0.000006     46,203          99.75      0.000200      1,498
   70.00      0.000009     33,959          99.90      0.000321        935
   80.00      0.000013     23,602


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    311,680          90.00      0.000022     13,805
   20.00      0.000002    176,022          95.00      0.000037      8,126
   30.00      0.000003    114,449          97.50      0.000061      4,942
   40.00      0.000004     81,973          99.00      0.000110      2,732
   50.00      0.000005     61,031          99.50      0.000154      1,951
   60.00      0.000006     46,323          99.75      0.000200      1,499
   70.00      0.000009     34,030          99.90      0.000320        937
   80.00      0.000013     23,643
--------------------------------------------------------------------------------
a/ Analysis based on all two-day participant records in CSFII 1994-98
   with 2 days of valid drinking water records.
2/ Margin of Exposure = NOEL/ Dietary Exposure.
```

1

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: Methidathionr1acutecomb.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
==============================================================================

Western region                    Daily Exposure Analysis
--------------                     (mg/kg body-weight/day)
                                    per Capita    per User
                                   ----------   ----------
           Mean                     0.000012     0.000012
           Standard Deviation       0.000029     0.000029
           Margin of Exposure        24,461       24,393

        Percent of Person-Days that are User-Days =  99.72%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000001    289,619           90.00     0.000025     11,882
    20.00     0.000002    164,789           95.00     0.000042      7,099
    30.00     0.000003    107,441           97.50     0.000072      4,172
    40.00     0.000004     79,052           99.00     0.000139      2,159
    50.00     0.000005     59,027           99.50     0.000171      1,754
    60.00     0.000007     43,013           99.75     0.000237      1,264
    70.00     0.000009     31,629           99.90     0.000339        886
    80.00     0.000014     21,282


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000001    294,676           90.00     0.000025     11,899
    20.00     0.000002    166,582           95.00     0.000042      7,109
    30.00     0.000003    108,149           97.50     0.000072      4,191
    40.00     0.000004     79,418           99.00     0.000139      2,161
    50.00     0.000005     59,271           99.50     0.000171      1,755
    60.00     0.000007     43,156           99.75     0.000237      1,267
    70.00     0.000009     31,705           99.90     0.000338        887
    80.00     0.000014     21,327
```

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION              (1994-98 data)
Residue file: Methidathionr1acutecomb.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================
```

```
Hispanics                        Daily Exposure Analysis
---------                        (mg/kg body-weight/day)
                                  per Capita    per User
                                 -----------  -----------
             Mean                  0.000013     0.000013
             Standard Deviation    0.000035     0.000036
             Margin of Exposure      22,873       22,841

        Percent of Person-Days that are User-Days =  99.86%
```

```
  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    351,039          90.00      0.000026     11,654
   20.00      0.000002    198,977          95.00      0.000049      6,176
   30.00      0.000002    123,081          97.50      0.000087      3,438
   40.00      0.000003     88,189          99.00      0.000163      1,837
   50.00      0.000005     64,328          99.50      0.000214      1,399
   60.00      0.000006     47,087          99.75      0.000298      1,005
   70.00      0.000009     33,183          99.90      0.000451        664
   80.00      0.000013     22,241
```

```
  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    354,243          90.00      0.000026     11,668
   20.00      0.000002    199,974          95.00      0.000048      6,189
   30.00      0.000002    123,533          97.50      0.000087      3,443
   40.00      0.000003     88,406          99.00      0.000163      1,838
   50.00      0.000005     64,437          99.50      0.000214      1,399
   60.00      0.000006     47,172          99.75      0.000298      1,005
   70.00      0.000009     33,229          99.90      0.000451        664
   80.00      0.000013     22,283
```

3

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                (1994-98 data)
Residue file: Methidathionr1acutecomb.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
========================================================================

Non-hispanic whites                  Daily Exposure Analysis
-------------------                  (mg/kg body-weight/day)
                                      per Capita    per User
                                     ----------   ----------
            Mean                       0.000010     0.000010
            Standard Deviation         0.000022     0.000022
            Margin of Exposure          28,748       28,689

       Percent of Person-Days that are User-Days =  99.79%


  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    283,504          90.00      0.000021     13,980
   20.00      0.000002    165,290          95.00      0.000035      8,479
   30.00      0.000003    110,463          97.50      0.000058      5,197
   40.00      0.000004     79,875          99.00      0.000098      3,060
   50.00      0.000005     60,178          99.50      0.000140      2,146
   60.00      0.000007     46,089          99.75      0.000186      1,610
   70.00      0.000009     34,165          99.90      0.000282      1,063
   80.00      0.000013     23,802


  Estimated percentile of per-capita days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    287,081          90.00      0.000021     13,998
   20.00      0.000002    166,473          95.00      0.000035      8,490
   30.00      0.000003    110,988          97.50      0.000058      5,205
   40.00      0.000004     80,182          99.00      0.000098      3,064
   50.00      0.000005     60,337          99.50      0.000140      2,147
   60.00      0.000006     46,211          99.75      0.000186      1,610
   70.00      0.000009     34,238          99.90      0.000282      1,063
   80.00      0.000013     23,848
```

4

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: Methidathionr1acutecomb.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
============================================================================

Non-hispanic blacks                    Daily Exposure Analysis
-------------------                    (mg/kg body-weight/day)
                                        per Capita    per User
                                       -----------   -----------
              Mean                       0.000010      0.000010
              Standard Deviation         0.000023      0.000024
              Margin of Exposure          29,588        29,524

       Percent of Person-Days that are User-Days =  99.78%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    416,710          90.00      0.000020     14,756
   20.00      0.000001    230,212          95.00      0.000035      8,547
   30.00      0.000002    136,552          97.50      0.000058      5,136
   40.00      0.000003     89,560          99.00      0.000109      2,764
   50.00      0.000005     64,980          99.50      0.000148      2,027
   60.00      0.000006     47,926          99.75      0.000180      1,664
   70.00      0.000009     35,194          99.90      0.000224      1,338
   80.00      0.000012     24,892


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000001    422,258          90.00      0.000020     14,770
   20.00      0.000001    232,366          95.00      0.000035      8,558
   30.00      0.000002    137,419          97.50      0.000058      5,143
   40.00      0.000003     89,998          99.00      0.000108      2,765
   50.00      0.000005     65,189          99.50      0.000148      2,030
   60.00      0.000006     48,036          99.75      0.000180      1,664
   70.00      0.000008     35,313          99.90      0.000224      1,340
   80.00      0.000012     24,928
```

```
California Department of Pesticide Regulation                  Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                   (1994-98 data)
Residue file: Methidathionr1acutecomb.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
========================================================================

Non-hisp/non-white/non-black        Daily Exposure Analysis
----------------------------        (mg/kg body-weight/day)
                                     per Capita    per User
                                     ----------   ----------
               Mean                   0.000013     0.000013
               Standard Deviation     0.000034     0.000034
               Margin of Exposure       22,330       22,287

        Percent of Person-Days that are User-Days =  99.81%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000001    343,750           90.00     0.000026     11,467
    20.00     0.000002    176,718           95.00     0.000045      6,672
    30.00     0.000003    110,895           97.50     0.000089      3,387
    40.00     0.000004     74,118           99.00     0.000157      1,908
    50.00     0.000006     54,178           99.50     0.000203      1,477
    60.00     0.000008     39,883           99.75     0.000323        928
    70.00     0.000010     30,329           99.90     0.000440        682
    80.00     0.000015     20,217


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000001    348,794           90.00     0.000026     11,485
    20.00     0.000002    178,031           95.00     0.000045      6,673
    30.00     0.000003    111,761           97.50     0.000089      3,388
    40.00     0.000004     74,353           99.00     0.000157      1,908
    50.00     0.000006     54,333           99.50     0.000203      1,477
    60.00     0.000007     40,000           99.75     0.000323        929
    70.00     0.000010     30,363           99.90     0.000440        682
    80.00     0.000015     20,237
```

```
California Department of Pesticide Regulation                Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                (1994-98 data)
Residue file: Methidathionr1acutecomb.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =  0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================


All infants                        Daily Exposure Analysis
-----------                        (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
              Mean                  0.000040      0.000045
              Standard Deviation    0.000051      0.000052
              Margin of Exposure       7,428         6,671

        Percent of Person-Days that are User-Days =  89.81%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE         Percentile   Exposure      MOE
  ----------  ----------  ---------      ----------  ----------  ---------
    10.00      0.000002    186,378         90.00      0.000103      2,904
    20.00      0.000008     38,249         95.00      0.000136      2,206
    30.00      0.000016     18,567         97.50      0.000174      1,723
    40.00      0.000024     12,391         99.00      0.000217      1,385
    50.00      0.000031      9,703         99.50      0.000282      1,063
    60.00      0.000039      7,626         99.75      0.000350        858
    70.00      0.000052      5,805         99.90      0.000494        607
    80.00      0.000073      4,107


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE         Percentile   Exposure      MOE
  ----------  ----------  ---------      ----------  ----------  ---------
    10.00      0.000000 >1,000,000         90.00      0.000100      3,008
    20.00      0.000002    155,233         95.00      0.000127      2,353
    30.00      0.000010     30,391         97.50      0.000164      1,827
    40.00      0.000019     15,804         99.00      0.000211      1,423
    50.00      0.000027     11,188         99.50      0.000272      1,102
    60.00      0.000035      8,503         99.75      0.000348        863
    70.00      0.000047      6,404         99.90      0.000492        610
    80.00      0.000067      4,452
```

7

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: Methidathionr1acutecomb.R98         Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
==============================================================================

Nursing infants (<1 yr old)        Daily Exposure Analysis
---------------------------        (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
            Mean                    0.000014      0.000022
            Standard Deviation      0.000031      0.000037
            Margin of Exposure        21,319        13,742

        Percent of Person-Days that are User-Days =  64.46%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile  Exposure     MOE          Percentile  Exposure     MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00      0.000000 >1,000,000         90.00      0.000060      4,961
   20.00      0.000000   699,460          95.00      0.000090      3,339
   30.00      0.000001   228,629          97.50      0.000118      2,549
   40.00      0.000004    72,562          99.00      0.000163      1,842
   50.00      0.000010    30,686          99.50      0.000204      1,473
   60.00      0.000013    22,998          99.75      0.000250      1,202
   70.00      0.000022    13,897          99.90      0.000253      1,185
   80.00      0.000037     8,021


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile  Exposure     MOE          Percentile  Exposure     MOE
 ----------  ----------  ---------      ----------  ----------  ---------
   10.00      0.000000 >1,000,000         90.00      0.000047      6,449
   20.00      0.000000 >1,000,000         95.00      0.000070      4,290
   30.00      0.000000 >1,000,000         97.50      0.000101      2,966
   40.00      0.000000 >1,000,000         99.00      0.000128      2,348
   50.00      0.000001   595,289          99.50      0.000202      1,484
   60.00      0.000003    89,833          99.75      0.000207      1,446
   70.00      0.000011    27,469          99.90      0.000251      1,196
   80.00      0.000021    14,599
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                   (1994-98 data)
Residue file: Methidathionr1acutecomb.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

Non-nursing infants (<1 yr old)      Daily Exposure Analysis
-------------------------------      (mg/kg body-weight/day)
                                      per Capita    per User
                                     ----------    ----------
            Mean                      0.000050      0.000051
            Standard Deviation        0.000053      0.000053
            Margin of Exposure          5,963         5,925

        Percent of Person-Days that are User-Days =  99.37%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE           Percentile   Exposure      MOE
 ----------   ----------  ---------       ----------   ----------  ---------
    10.00      0.000005    65,424            90.00      0.000109     2,752
    20.00      0.000014    20,709            95.00      0.000145     2,063
    30.00      0.000023    13,321            97.50      0.000180     1,665
    40.00      0.000029    10,435            99.00      0.000230     1,302
    50.00      0.000036     8,440            99.50      0.000289     1,037
    60.00      0.000044     6,799            99.75      0.000383       782
    70.00      0.000058     5,149            99.90      0.000503       596
    80.00      0.000078     3,827


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE           Percentile   Exposure      MOE
 ----------   ----------  ---------       ----------   ----------  ---------
    10.00      0.000004    70,978            90.00      0.000109     2,759
    20.00      0.000014    21,527            95.00      0.000145     2,067
    30.00      0.000022    13,578            97.50      0.000180     1,666
    40.00      0.000028    10,528            99.00      0.000228     1,315
    50.00      0.000035     8,498            99.50      0.000289     1,038
    60.00      0.000044     6,838            99.75      0.000383       783
    70.00      0.000058     5,178            99.90      0.000503       596
    80.00      0.000078     3,837
```

9

```
California Department of Pesticide Regulation                Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                 (1994-98 data)
Residue file: Methidathionr1acutecomb.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35    Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file      MC seed = 1
Run Comment: ""
==============================================================================

Females 13+ (preg/not nursing)      Daily Exposure Analysis
------------------------------      (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------   -----------
              Mean                    0.000016      0.000016
              Standard Deviation      0.000041      0.000041
              Margin of Exposure        19,297        19,297

        Percent of Person-Days that are User-Days = 100.00%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------   ---------      ----------  ----------   ---------
   10.00      0.000001    365,255          90.00      0.000022     13,547
   20.00      0.000002    173,257          95.00      0.000039      7,618
   30.00      0.000003    116,703          97.50      0.000214      1,402
   40.00      0.000004     75,651          99.00      0.000216      1,391
   50.00      0.000005     61,042          99.50      0.000294      1,020
   60.00      0.000006     49,452          99.75      0.000294      1,019
   70.00      0.000009     33,215          99.90      0.000295      1,018
   80.00      0.000013     22,226


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------   ---------      ----------  ----------   ---------
   10.00      0.000001    365,255          90.00      0.000022     13,547
   20.00      0.000002    173,257          95.00      0.000039      7,618
   30.00      0.000003    116,703          97.50      0.000214      1,402
   40.00      0.000004     75,651          99.00      0.000216      1,391
   50.00      0.000005     61,042          99.50      0.000294      1,020
   60.00      0.000006     49,452          99.75      0.000294      1,019
   70.00      0.000009     33,215          99.90      0.000295      1,018
   80.00      0.000013     22,226
```

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                   (1994-98 data)
Residue file: Methidathionr1acutecomb.R98         Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
==============================================================================

Females 13+ (nursing)              Daily Exposure Analysis
---------------------              (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------   -----------
              Mean                   0.000015      0.000015
              Standard Deviation     0.000042      0.000042
              Margin of Exposure       20,249        20,249

        Percent of Person-Days that are User-Days = 100.00%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000002    194,459          90.00      0.000019     16,120
   20.00      0.000002    143,108          95.00      0.000037      8,117
   30.00      0.000003    108,902          97.50      0.000161      1,868
   40.00      0.000004     83,096          99.00      0.000282      1,063
   50.00      0.000004     67,313          99.50      0.000298      1,007
   60.00      0.000005     54,715          99.75      0.000298      1,005
   70.00      0.000007     45,323          99.90      0.000299      1,004
   80.00      0.000009     33,193


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000002    194,459          90.00      0.000019     16,120
   20.00      0.000002    143,108          95.00      0.000037      8,117
   30.00      0.000003    108,902          97.50      0.000161      1,868
   40.00      0.000004     83,096          99.00      0.000282      1,063
   50.00      0.000004     67,313          99.50      0.000298      1,007
   60.00      0.000005     54,715          99.75      0.000298      1,005
   70.00      0.000007     45,323          99.90      0.000299      1,004
   80.00      0.000009     33,193
```

11

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                    (1994-98 data)
Residue file: Methidathionr1acutecomb.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =  0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

Children 1-2 yrs                   Daily Exposure Analysis
----------------                   (mg/kg body-weight/day)
                                    per Capita   per User
                                   -----------  -----------
           Mean                      0.000026     0.000026
           Standard Deviation        0.000058     0.000058
           Margin of Exposure         11,388       11,371

      Percent of Person-Days that are User-Days =  99.85%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000002    142,440           90.00     0.000054      5,590
    20.00     0.000004     72,042           95.00     0.000094      3,185
    30.00     0.000006     47,699           97.50     0.000151      1,992
    40.00     0.000009     33,904           99.00     0.000262      1,144
    50.00     0.000012     25,339           99.50     0.000398        752
    60.00     0.000016     18,914           99.75     0.000564        531
    70.00     0.000021     14,073           99.90     0.000777        385
    80.00     0.000030     10,061


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000002    144,217           90.00     0.000054      5,597
    20.00     0.000004     72,488           95.00     0.000094      3,187
    30.00     0.000006     47,870           97.50     0.000151      1,993
    40.00     0.000009     34,000           99.00     0.000262      1,145
    50.00     0.000012     25,386           99.50     0.000398        753
    60.00     0.000016     18,946           99.75     0.000564        531
    70.00     0.000021     14,090           99.90     0.000777        386
    80.00     0.000030     10,072
```

12

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                   (1994-98 data)
Residue file: Methidathionr1acutecomb.R98        Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===========================================================================

Children 3-5 yrs                    Daily Exposure Analysis
----------------                    (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------   -----------
              Mean                    0.000024      0.000024
              Standard Deviation      0.000046      0.000046
              Margin of Exposure        12,387        12,387

         Percent of Person-Days that are User-Days = 100.00%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000003    97,409           90.00      0.000048      6,274
   20.00      0.000005    56,578           95.00      0.000079      3,813
   30.00      0.000008    39,090           97.50      0.000124      2,423
   40.00      0.000010    29,438           99.00      0.000212      1,412
   50.00      0.000013    22,816           99.50      0.000296      1,013
   60.00      0.000017    17,891           99.75      0.000410        731
   70.00      0.000021    14,081           99.90      0.000589        509
   80.00      0.000029    10,381


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
   10.00      0.000003    97,409           90.00      0.000048      6,274
   20.00      0.000005    56,578           95.00      0.000079      3,813
   30.00      0.000008    39,090           97.50      0.000124      2,423
   40.00      0.000010    29,438           99.00      0.000212      1,412
   50.00      0.000013    22,816           99.50      0.000296      1,013
   60.00      0.000017    17,891           99.75      0.000410        731
   70.00      0.000021    14,081           99.90      0.000589        509
   80.00      0.000029    10,381
```

13

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                        (1994-98 data)
Residue file: Methidathionr1acutecomb.R98          Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

Children 6-12 yrs                     Daily Exposure Analysis
-----------------                     (mg/kg body-weight/day)
                                       per Capita   per User
                                      -----------  -----------
              Mean                      0.000016     0.000016
              Standard Deviation        0.000032     0.000032
              Margin of Exposure          18,328       18,328

         Percent of Person-Days that are User-Days = 100.00%


  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE           Percentile   Exposure      MOE
 ----------  ----------  ---------        ----------  ----------  ---------
   10.00      0.000003    117,833           90.00      0.000030      9,951
   20.00      0.000004     72,074           95.00      0.000048      6,270
   30.00      0.000006     52,215           97.50      0.000077      3,912
   40.00      0.000008     39,883           99.00      0.000133      2,252
   50.00      0.000009     31,944           99.50      0.000199      1,508
   60.00      0.000012     25,944           99.75      0.000339        883
   70.00      0.000015     20,472           99.90      0.000478        628
   80.00      0.000020     15,259


  Estimated percentile of per-capita days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE           Percentile   Exposure      MOE
 ----------  ----------  ---------        ----------  ----------  ---------
   10.00      0.000003    117,833           90.00      0.000030      9,951
   20.00      0.000004     72,074           95.00      0.000048      6,270
   30.00      0.000006     52,215           97.50      0.000077      3,912
   40.00      0.000008     39,883           99.00      0.000133      2,252
   50.00      0.000009     31,944           99.50      0.000199      1,508
   60.00      0.000012     25,944           99.75      0.000339        883
   70.00      0.000015     20,472           99.90      0.000478        628
   80.00      0.000020     15,259
```

14

```
California Department of Pesticide Regulation                   Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                  (1994-98 data)
Residue file: Methidathionr1acutecomb.R98       Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =  0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
===============================================================================


Youth 13-19 yrs                      Daily Exposure Analysis
---------------                      (mg/kg body-weight/day)
                                     per Capita    per User
                                     ----------   ----------
             Mean                     0.000010     0.000010
             Standard Deviation       0.000020     0.000020
             Margin of Exposure        29,339       29,285

        Percent of Person-Days that are User-Days =  99.82%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000001    258,813          90.00      0.000019     15,877
    20.00      0.000002    133,911          95.00      0.000030     10,054
    30.00      0.000003     88,858          97.50      0.000047      6,386
    40.00      0.000005     64,755          99.00      0.000091      3,303
    50.00      0.000006     50,312          99.50      0.000129      2,322
    60.00      0.000008     39,857          99.75      0.000190      1,576
    70.00      0.000010     31,105          99.90      0.000335        894
    80.00      0.000013     23,481


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000001    262,713          90.00      0.000019     15,910
    20.00      0.000002    135,109          95.00      0.000030     10,104
    30.00      0.000003     89,165          97.50      0.000047      6,389
    40.00      0.000005     64,964          99.00      0.000091      3,312
    50.00      0.000006     50,408          99.50      0.000128      2,335
    60.00      0.000008     39,924          99.75      0.000190      1,576
    70.00      0.000010     31,145          99.90      0.000335        894
    80.00      0.000013     23,511
```

15

```
California Department of Pesticide Regulation                 Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                (1994-98 data)
Residue file: Methidathionr1acutecomb.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
==============================================================================
```

```
Adults 20-49 yrs                    Daily Exposure Analysis
----------------                    (mg/kg body-weight/day)
                                    per Capita    per User
                                    ----------    ----------
              Mean                    0.000009      0.000009
              Standard Deviation      0.000017      0.000017
              Margin of Exposure        35,099        35,082

        Percent of Person-Days that are User-Days =  99.95%
```

```
 Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------   ----------   ---------     ----------   ----------   ---------
   10.00       0.000001     322,448        90.00       0.000017      17,796
   20.00       0.000002     186,586        95.00       0.000028      10,809
   30.00       0.000002     122,968        97.50       0.000044       6,755
   40.00       0.000003      89,464        99.00       0.000079       3,819
   50.00       0.000004      68,013        99.50       0.000120       2,502
   60.00       0.000006      53,187        99.75       0.000157       1,908
   70.00       0.000007      40,758        99.90       0.000214       1,404
   80.00       0.000010      29,222
```

```
 Estimated percentile of per-capita days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------   ----------   ---------     ----------   ----------   ---------
   10.00       0.000001     323,391        90.00       0.000017      17,799
   20.00       0.000002     186,918        95.00       0.000028      10,812
   30.00       0.000002     123,116        97.50       0.000044       6,757
   40.00       0.000003      89,539        99.00       0.000079       3,819
   50.00       0.000004      68,055        99.50       0.000120       2,503
   60.00       0.000006      53,210        99.75       0.000157       1,909
   70.00       0.000007      40,777        99.90       0.000214       1,405
   80.00       0.000010      29,235
```

16

```
California Department of Pesticide Regulation                    Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                        (1994-98 data)
Residue file: Methidathionr1acutecomb.R98          Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35    Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
=============================================================================

Adults 50+ yrs                       Daily Exposure Analysis
--------------                       (mg/kg body-weight/day)
                                      per Capita    per User
                                     ----------    ----------
            Mean                       0.000007      0.000007
            Standard Deviation         0.000015      0.000015
            Margin of Exposure          43,911        43,899

        Percent of Person-Days that are User-Days =  99.97%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000001    390,144          90.00      0.000013     22,809
    20.00      0.000001    248,593          95.00      0.000022     13,829
    30.00      0.000002    172,505          97.50      0.000038      7,812
    40.00      0.000002    126,193          99.00      0.000071      4,252
    50.00      0.000003     93,893          99.50      0.000108      2,790
    60.00      0.000004     71,177          99.75      0.000147      2,042
    70.00      0.000006     53,597          99.90      0.000172      1,744
    80.00      0.000008     38,133


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure      MOE          Percentile   Exposure      MOE
  ----------  ----------  ---------       ----------  ----------  ---------
    10.00      0.000001    390,644          90.00      0.000013     22,813
    20.00      0.000001    248,793          95.00      0.000022     13,831
    30.00      0.000002    172,614          97.50      0.000038      7,813
    40.00      0.000002    126,253          99.00      0.000071      4,252
    50.00      0.000003     93,928          99.50      0.000108      2,790
    60.00      0.000004     71,197          99.75      0.000147      2,042
    70.00      0.000006     53,608          99.90      0.000172      1,744
    80.00      0.000008     38,142
```

```
California Department of Pesticide Regulation                     Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION                      (1994-98 data)
Residue file: Methidathionr1acutecomb.R98         Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35    Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500       MC list in residue file     MC seed = 1
Run Comment: ""
===============================================================================

Females 13-49 yrs                    Daily Exposure Analysis
-----------------                    (mg/kg body-weight/day)
                                      per Capita    per User
                                     ----------   ----------
            Mean                       0.000009      0.000009
            Standard Deviation         0.000018      0.000018
            Margin of Exposure           34,691        34,674

        Percent of Person-Days that are User-Days =  99.95%


   Estimated percentile of user-days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000001    329,336           90.00     0.000017     18,138
    20.00     0.000002    196,761           95.00     0.000028     10,573
    30.00     0.000002    127,609           97.50     0.000048      6,223
    40.00     0.000003     93,647           99.00     0.000086      3,477
    50.00     0.000004     71,867           99.50     0.000145      2,073
    60.00     0.000005     55,376           99.75     0.000169      1,778
    70.00     0.000007     41,643           99.90     0.000214      1,402
    80.00     0.000010     30,162


   Estimated percentile of per-capita days falling below calculated exposure
      in mg/kg body-wt/day with Margin of Exposure (MOE)

 Percentile   Exposure      MOE          Percentile   Exposure      MOE
 ----------  ----------  ---------       ----------  ----------  ---------
    10.00     0.000001    330,248           90.00     0.000017     18,147
    20.00     0.000002    197,082           95.00     0.000028     10,576
    30.00     0.000002    127,762           97.50     0.000048      6,225
    40.00     0.000003     93,718           99.00     0.000086      3,478
    50.00     0.000004     71,927           99.50     0.000145      2,074
    60.00     0.000005     55,397           99.75     0.000169      1,778
    70.00     0.000007     41,662           99.90     0.000214      1,402
    80.00     0.000010     30,168
```

18

```
California Department of Pesticide Regulation              Ver. 2.02
DEEM-FCID ACUTE Analysis for METHIDATHION               (1994-98 data)
Residue file: Methidathionr1acutecomb.R98      Adjustment factor #2 used.
Analysis Date: 10-26-2005/08:46:35   Residue file dated: 10-25-2005/16:21:22/14
NOEL (Acute) =   0.300000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file    MC seed = 1
Run Comment: ""
=============================================================================

Custom demographics 1: Workers, 16+ years
All Seasons
All Regions
Sex: M/F-all/
All Races
Age-Low: 16 yrs   High: 99 yrs
-----------------------------------------

                                Daily Exposure Analysis
                                (mg/kg body-weight/day)
                                 per Capita    per User
                                 ----------   -----------
              Mean                0.000008     0.000008
              Standard Deviation  0.000016     0.000016
              Margin of Exposure    37,401       37,378

       Percent of Person-Days that are User-Days =  99.94%


  Estimated percentile of user-days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure     MOE         Percentile   Exposure     MOE
  ----------  ----------  ---------      ----------  ----------  ---------
    10.00      0.000001    348,238         90.00      0.000016    18,823
    20.00      0.000001    207,707         95.00      0.000026    11,649
    30.00      0.000002    138,843         97.50      0.000042     7,129
    40.00      0.000003     98,838         99.00      0.000077     3,888
    50.00      0.000004     74,507         99.50      0.000115     2,605
    60.00      0.000005     57,093         99.75      0.000154     1,948
    70.00      0.000007     43,410         99.90      0.000190     1,576
    80.00      0.000010     31,068


  Estimated percentile of per-capita days falling below calculated exposure
     in mg/kg body-wt/day with Margin of Exposure (MOE)

  Percentile   Exposure     MOE         Percentile   Exposure     MOE
  ----------  ----------  ---------      ----------  ----------  ---------
    10.00      0.000001    349,496         90.00      0.000016    18,829
    20.00      0.000001    208,159         95.00      0.000026    11,654
    30.00      0.000002    139,071         97.50      0.000042     7,133
    40.00      0.000003     98,942         99.00      0.000077     3,889
    50.00      0.000004     74,571         99.50      0.000115     2,606
    60.00      0.000005     57,129         99.75      0.000154     1,948
    70.00      0.000007     43,433         99.90      0.000190     1,576
    80.00      0.000010     31,084
```

```
California Department of Pesticide Regulation              Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION               1994-98 data
Residue file: H:\MyFiles\DEEM-FCID Files\Methidathion\Methidathionr1chroniccomb.R98
                                                    Adjust. #2 used
Analysis Date 10-26-2005          Residue file dated: 10-25-2005/16:23:35/14
Reference dose (NOEL) = 0.15 mg/kg bw/day


-----------------------------------------------------------------------------
Food Crop                              Residue     Adj.Factors      Comment
EPA Code  Grp  Food Name               (ppm)
                                                   #1        #2
-------- ---- ------------------------ ---------- ------   ------   -------
14000030 14   Almond                   0.001250   1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
14000031 14   Almond-babyfood          0.001250   1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
14000040 14   Almond, oil              0.001250   1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
14000041 14   Almond, oil-babyfood     0.001250   1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 5% CT
11000070 11   Apple, fruit with peel   0.000350   1.000    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000080 11   Apple, peeled fruit      0.000350   1.000    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000081 11   Apple, peeled fruit-babyfood 0.000350 1.000  1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000090 11   Apple, dried             0.000350   8.000    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000091 11   Apple, dried-babyfood    0.000350   8.000    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000100 11   Apple, juice             0.000350   1.300    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000101 11   Apple, juice-babyfood    0.000350   1.300    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000110 11   Apple, sauce             0.000350   1.000    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
11000111 11   Apple, sauce-babyfood    0.000350   1.000    1.000    PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
12000120 12   Apricot                  0.001300   1.000    1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
12000121 12   Apricot-babyfood         0.001300   1.000    1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
12000130 12   Apricot, dried           0.001300   6.000    1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
12000140 12   Apricot, juice           0.001300   1.000    1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
12000141 12   Apricot, juice-babyfood  0.001300   1.000    1.000    DPR Ap
  Full comment: DPR Apricot 2002-2004 1/2 LOD, 5% CT
95000160 O    Artichoke, globe         0.025000   1.000    1.000    DPR Ar
  Full comment: DPR Artichoke 2002-2004 1/2 LOD, 100% CT
01030170 1CD  Artichoke, Jerusalem     0.025000   1.000    1.000    DPR Ar
  Full comment: DPR Artichoke 2002-2004 1/2 LOD, 100% CT
14000590 14   Brazil nut               0.025000   1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
14000680 14   Butternut                0.025000   1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
14000810 14   Cashew                   0.025000   1.000    1.000    1/2 To
  Full comment: 1/2 Tolerance, 100% CT
12000900 12   Cherry                   0.000100   1.000    1.000    PDP Ch
  Full comment: PDP Cherries 2000&2001 CA 1/2 LOD, 5% CT
12000901 12   Cherry-babyfood          0.000100   1.000    1.000    PDP Ch
  Full comment: PDP Cherries 2000&2001 CA 1/2 LOD, 5% CT
12000910 12   Cherry, juice            0.000100   1.500    1.000    PDP Ch
  Full comment: PDP Cherries 2000&2001 CA 1/2 LOD, 5% CT
```

```
12000911 12   Cherry, juice-babyfood          0.000100   1.500   1.000   PDP Ch
   Full comment: PDP Cherries 2000&2001 CA 1/2 LOD, 5% CT
14000920 14   Chestnut                        0.025000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 100% CT
10001060 10   Citrus citron                   0.050000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 5% CT
10001070 10   Citrus hybrids                  0.000168   1.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10001080 10   Citrus, oil                     0.000168   1.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
95001280 O    Cottonseed, oil                 0.001000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 1% CT
95001281 O    Cottonseed, oil-babyfood        0.001000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 1% CT
11001290 11   Crabapple                       0.000350   1.000   1.000   PDP Ap
   Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
14001550 14   Filbert                         0.025000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 100% CT
14001560 14   Filbert, oil                    0.025000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 100% CT
10001800 10   Grapefruit                      0.000168   1.000   1.000   PDP Or
   Full comment: PDP Orange 2000 & 2001 CA Mean Value
10001810 10   Grapefruit, juice               0.000168   2.100   1.000   PDP Or
   Full comment: PDP Orange 2000 & 2001 CA Mean Value
14001850 14   Hickory nut                     0.025000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 100% CT
95001950 O    Kiwifruit                       0.002500   1.000   1.000   DPR Ki
   Full comment: DPR Kiwifruit 2002-2004 1/2 LOD, 10% CT
10001970 10   Kumquat                         0.000168   1.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10001990 10   Lemon                           0.000168   1.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002000 10   Lemon, juice                    0.000168   2.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002001 10   Lemon, juice-babyfood           0.000168   2.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002010 10   Lemon, peel                     0.050000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 5% CT
10002060 10   Lime                            0.000168   1.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002070 10   Lime, juice                     0.000168   2.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002071 10   Lime, juice-babyfood            0.000168   2.000   1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
11002100 11   Loquat                          0.000350   1.000   1.000   PDP Ap
   Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
14002130 14   Macadamia nut                   0.025000   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 100% CT
95002150 O    Mango                           0.025000   1.000   1.000   DPR Ma
   Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
95002151 O    Mango-babyfood                  0.025000   1.000   1.000   DPR Ma
   Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
95002160 O    Mango, dried                    0.025000   1.000   1.000   DPR Ma
   Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
95002170 O    Mango, juice                    0.025000   1.000   1.000   DPR Ma
   Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
95002171 O    Mango, juice-babyfood           0.025000   1.000   1.000   DPR Ma
   Full comment: DPR Mango 2002-2004 1/2 LOD, 100% CT
12002300 12   Nectarine                       0.000100   1.000   1.000   PDP Ne
   Full comment: PDP Nectarine 2000&2001 CA 1/2 LOD, 5% CT
95002350 O    Olive                           0.001250   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 5% CT
95002360 O    Olive, oil                      0.001250   1.000   1.000   1/2 To
   Full comment: 1/2 Tolerance, 5% CT
```

```
10002400 10   Orange                        0.000168  1.000    1.000   PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002410 10   Orange, juice                 0.000168  1.800    1.000   PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002411 10   Orange, juice-babyfood        0.000168  1.800    1.000   PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10002420 10   Orange, peel                  0.050000  1.000    1.000   1/2 To
  Full comment: 1/2 Tolerance, 5% CT
12002600 12   Peach                         0.000065  1.000    1.000   PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002601 12   Peach-babyfood                0.000065  1.000    1.000   PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002610 12   Peach, dried                  0.000065  7.000    1.000   PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002611 12   Peach, dried-babyfood         0.000065  7.000    1.000   PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002620 12   Peach, juice                  0.000065  1.000    1.000   PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
12002621 12   Peach, juice-babyfood         0.000065  1.000    1.000   PDP Pe
  Full comment: PDP Peach 2001&2002 CA Mean Value, 10% CT
11002660 11   Pear                          0.000100  1.000    1.000   PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
11002661 11   Pear-babyfood                 0.000100  1.000    1.000   PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
11002670 11   Pear, dried                   0.000100  6.250    1.000   PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
11002680 11   Pear, juice                   0.000100  1.000    1.000   PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
11002681 11   Pear, juice-babyfood          0.000100  1.000    1.000   PDP Pe
  Full comment: PDP Pear 2003 NA 1/2 LOD, 5% CT
14002690 14   Pecan                         0.002500  1.000    1.000   1/2 To
  Full comment: 1/2 Tolerance, 10% CT
95002780 O    Pine nut                      0.025000  1.000    1.000   1/2 To
  Full comment: 1/2 Tolerance
14002820 14   Pistachio                     0.002500  1.000    1.000   1/2 To
  Full comment: 1/2 Tolerance, 10% CT
12002850 12   Plum                          0.003750  1.000    1.000   DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 15% CT
12002851 12   Plum-babyfood                 0.003750  1.000    1.000   DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 15% CT
12002860 12   Plum, prune, fresh            0.001250  1.000    1.000   DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002861 12   Plum, prune, fresh-babyfood   0.001250  1.000    1.000   DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002870 12   Plum, prune, dried            0.001250  5.000    1.000   DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002871 12   Plum, prune, dried-babyfood   0.001250  5.000    1.000   DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002880 12   Plum, prune, juice            0.001250  1.400    1.000   DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
12002881 12   Plum, prune, juice-babyfood   0.001250  1.400    1.000   DPR Pl
  Full comment: DPR Plum 2002-2004 1/2 LOD, 5% CT
10003070 10   Pummelo                       0.000168  1.000    1.000   PDP Or
  Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
11003100 11   Quince                        0.000350  1.000    1.000   PDP Ap
  Full comment: PDP Apple 2002 CA 1/2 LOD, 10% CT
20003300 20   Safflower, oil                0.005000  1.000    1.000   Safflo
  Full comment: Safflower Field Trial 1/2 LOD, 100% CT
20003301 20   Safflower, oil-babyfood       0.005000  1.000    1.000   Safflo
  Full comment: Safflower Field Trial 1/2 LOD, 100% CT
15003440 15   Sorghum, grain                0.100000  1.000    1.000   1/2 To
  Full comment: 1/2 Tolerance, 100% CT
15003450 15   Sorghum, syrup                0.100000  1.000    1.000   1/2 To
  Full comment: 1/2 Tolerance, 100% CT
```

```
95003580 O    Starfruit                    0.050000  1.000    1.000   1/2 To
   Full comment: 1/2 Tolerance, 100% CT
95003610 O    Sugar apple                  0.100000  1.000    1.000   1/2 To
   Full comment: 1/2 Tolerance, 100% CT
20003640 20   Sunflower, seed              0.150000  1.000    0.500   Sunflo
   Full comment: Sunflower Field Trial Mean, 100% CT, 50% hulls
20003650 20   Sunflower, oil               0.150000  1.000    0.200   Sunflo
   Full comment: Sunflower Field Trial Mean, 100% CT, 20% oil
20003651 20   Sunflower, oil-babyfood      0.150000  1.000    0.200   Sunflo
   Full comment: Sunflower Field Trial Mean, 100% CT, 20% oil
10003690 10   Tangerine                    0.000168  1.000    1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
10003700 10   Tangerine, juice             0.000168  2.300    1.000   PDP Or
   Full comment: PDP Orange 2000&2001 CA Mean Value, 5% CT
14003910 14   Walnut                       0.001250  1.000    1.000   1/2 To
   Full comment: 1/2 Tolerance, 5% CT
86010000 O    Water, direct, all sources   0.000013  1.000    1.000   PDP 20
   Full comment: PDP 2002-2003 1/2 Combined CA LOD
86020000 O    Water, indirect, all sources 0.000013  1.000    1.000   PDP 20
   Full comment: PDP 2002-2003 1/2 Combined CA LOD
```

```
California Department of Pesticide Regulation                    Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION                   (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\Methidathionr1chroniccomb.R98
                                               Adjustment factor #2 used.
Analysis Date 10-26-2005/08:53:39      Residue file dated: 10-25-2005/16:23:35/14
NOEL (Chronic) = .15 mg/kg bw/day
===============================================================================
                  Total exposure by population subgroup
-------------------------------------------------------------------------------


                                         Total Exposure
                                  ------------------------------------
         Population                 mg/kg        Percent    Margin of
          Subgroup               body wt/day     of NOEL    Exposr 1/
-------------------------------   ------------   ---------  ---------
U.S. Population (total)              0.000002       0.00%      61,496


U.S. Population (spring season)      0.000003       0.00%      57,399
U.S. Population (summer season)      0.000003       0.00%      53,009
U.S. Population (autumn season)      0.000002       0.00%      70,358
U.S. Population (winter season)      0.000002       0.00%      68,689


Northeast region                    0.000003       0.00%      55,478
Midwest region                      0.000002       0.00%      76,107
Southern region                     0.000002       0.00%      70,977
Western region                      0.000003       0.00%      46,593


Hispanics                           0.000004       0.00%      40,397
Non-hispanic whites                 0.000002       0.00%      67,774
Non-hispanic blacks                 0.000002       0.00%      66,535
Non-hisp/non-white/non-black        0.000004       0.00%      41,391


All infants (< 1 year)              0.000016       0.01%       9,469
Nursing infants                     0.000006       0.00%      27,231
Non-nursing infants                 0.000020       0.01%       7,590
Children 1-6  yrs                   0.000006       0.00%      24,449
Children 7-12 yrs                   0.000003       0.00%      51,012


Females 13-19 (not preg or nursing) 0.000002       0.00%      81,877
Females 20+ (not preg or nursing)   0.000002       0.00%      90,284
Females 13-50 yrs                   0.000002       0.00%      72,304
Females 13+ (preg/not nursing)      0.000006       0.00%      27,074
Females 13+ (nursing)               0.000005       0.00%      32,271


Males 13-19 yrs                     0.000002       0.00%      79,611
Males 20+ yrs                       0.000002       0.00%      93,920
Seniors 55+                         0.000002       0.00%      92,561


Children 1-2 yrs                    0.000008       0.01%      19,154
Children 3-5 yrs                    0.000006       0.00%      27,129
Children 6-12 yrs                   0.000003       0.00%      47,047
Youth 13-19 yrs                     0.000002       0.00%      80,661
Adults 20-49 yrs                    0.000002       0.00%      89,620
Adults 50+ yrs                      0.000002       0.00%      87,799
Females 13-49 yrs                   0.000002       0.00%      84,356


-------------------------------------------------------------------------------
```

```
California Department of Pesticide Regulation                  Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION                  (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\Methidathionr1chroniccomb.R98
                                               Adjustment factor #2 used.
Analysis Date 10-26-2005/08:54:26    Residue file dated: 10-25-2005/16:23:35/14
Q* = 0.34
===============================================================================
                    Total exposure by population subgroup
-------------------------------------------------------------------------------


                                              Total Exposure
                                         ----------------------------------
        Population                          mg/kg          Lifetime risk
         Subgroup                         body wt/day       (Q*= .34)
--------------------------------------   ------------      ------------
U.S. Population (total)                     0.000002          8.29E-07

U.S. Population (spring season)             0.000003          8.89E-07
U.S. Population (summer season)             0.000003          9.62E-07
U.S. Population (autumn season)             0.000002          7.25E-07
U.S. Population (winter season)             0.000002          7.42E-07

Northeast region                            0.000003          9.19E-07
Midwest region                              0.000002          6.70E-07
Southern region                             0.000002          7.19E-07
Western region                              0.000003          1.09E-06

Hispanics                                   0.000004          1.26E-06
Non-hispanic whites                         0.000002          7.52E-07
Non-hispanic blacks                         0.000002          7.67E-07
Non-hisp/non-white/non-black                0.000004          1.23E-06

All infants (< 1 year)                      0.000016          5.39E-06
Nursing infants                             0.000006          1.87E-06
Non-nursing infants                         0.000020          6.72E-06
Children 1-6  yrs                           0.000006          2.09E-06
Children 7-12 yrs                           0.000003          1.00E-06

Females 13-19 (not preg or nursing)         0.000002          6.23E-07
Females 20+ (not preg or nursing)           0.000002          5.65E-07
Females 13-50 yrs                           0.000002          7.05E-07
Females 13+ (preg/not nursing)              0.000006          1.88E-06
Females 13+ (nursing)                       0.000005          1.58E-06

Males 13-19 yrs                             0.000002          6.41E-07
Males 20+ yrs                               0.000002          5.43E-07
Seniors 55+                                 0.000002          5.51E-07

Children 1-2 yrs                            0.000008          2.66E-06
Children 3-5 yrs                            0.000006          1.88E-06
Children 6-12 yrs                           0.000003          1.08E-06
Youth 13-19 yrs                             0.000002          6.32E-07
Adults 20-49 yrs                            0.000002          5.69E-07
Adults 50+ yrs                              0.000002          5.81E-07
Females 13-49 yrs                           0.000002          6.05E-07


-------------------------------------------------------------------------------
```

```
California Department of Pesticide Regulation                    Ver. 2.00
DEEM-FCID Chronic analysis for METHIDATHION                     (1994-98 data)
Residue file name: H:\MyFiles\DEEM-FCID
Files\Methidathion\Methidathionr1chroniccomb.R98
                                                Adjustment factor #2 used.
Analysis Date 10-26-2005/08:54:09    Residue file dated: 10-25-2005/16:23:35/14
Q* = 0.53
===============================================================================
                    Total exposure by population subgroup
-------------------------------------------------------------------------------
```

	Total Exposure	
Population Subgroup	mg/kg body wt/day	Lifetime risk (Q*= .53)
U.S. Population (total)	0.000002	1.29E-06
U.S. Population (spring season)	0.000003	1.39E-06
U.S. Population (summer season)	0.000003	1.50E-06
U.S. Population (autumn season)	0.000002	1.13E-06
U.S. Population (winter season)	0.000002	1.16E-06
Northeast region	0.000003	1.43E-06
Midwest region	0.000002	1.04E-06
Southern region	0.000002	1.12E-06
Western region	0.000003	1.71E-06
Hispanics	0.000004	1.97E-06
Non-hispanic whites	0.000002	1.17E-06
Non-hispanic blacks	0.000002	1.19E-06
Non-hisp/non-white/non-black	0.000004	1.92E-06
All infants (< 1 year)	0.000016	8.40E-06
Nursing infants	0.000006	2.92E-06
Non-nursing infants	0.000020	1.05E-05
Children 1-6 yrs	0.000006	3.25E-06
Children 7-12 yrs	0.000003	1.56E-06
Females 13-19 (not preg or nursing)	0.000002	9.71E-07
Females 20+ (not preg or nursing)	0.000002	8.81E-07
Females 13-50 yrs	0.000002	1.10E-06
Females 13+ (preg/not nursing)	0.000006	2.94E-06
Females 13+ (nursing)	0.000005	2.46E-06
Males 13-19 yrs	0.000002	9.99E-07
Males 20+ yrs	0.000002	8.46E-07
Seniors 55+	0.000002	8.59E-07
Children 1-2 yrs	0.000008	4.15E-06
Children 3-5 yrs	0.000006	2.93E-06
Children 6-12 yrs	0.000003	1.69E-06
Youth 13-19 yrs	0.000002	9.86E-07
Adults 20-49 yrs	0.000002	8.87E-07
Adults 50+ yrs	0.000002	9.05E-07
Females 13-49 yrs	0.000002	9.42E-07

```
-------------------------------------------------------------------------------
```