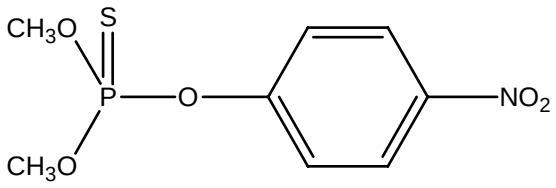
METHYL PARATHION

RISK CHARACTERIZATION DOCUMENT

DIETARY AND AMBIENT AIR EXPOSURES



California Environmental Protection Agency
Department of Pesticide Regulation

October 26, 2004

METHYL PARATHION

RISK CHARACTERIZATION DOCUMENT

DIETARY AND AMBIENT AIR EXPOSURES

Health Assessment Section
Medical Toxicology Branch
Department of Pesticide Regulation
California Environmental Protection Agency

October 26, 2004

CONTRIBUTORS AND ACKNOWLEDGMENTS

Principal Authors:

Svetlana E. Koshlukova, Ph.D.
Associate Toxicologist
Health Assessment Section
Medical Toxicology Branch

Nu-may R. Reed, Ph.D., DABT
Staff Toxicologist
Health Assessment Section
Medical Toxicology Branch

Toxicology Data Review:

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

Joyce F. Gee, Ph.D.
Senior Toxicologist
Data Review Section
Medical Toxicology Branch

Reviewers:

Keith Pfeifer, PhD., DABT
Senior Toxicologist
Health Assessment Section
Medical Toxicology Branch

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

DPR acknowledges the review of this document by the Pesticide Epidemiology Unit, Office of Environmental Health Hazard Assessment.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

AADD…… Annual Average Daily Dosage
AB1807……. California Toxic Air Contaminant Identification and Control Act of 1983
ACh …….. Acetylcholine
AChE…… Acetylcholinesterase
ADD……. Absorbed Daily Dosage
ADI ……... Acceptable Daily Intake
ATSDR……. Agency for Toxic Substances and Disease Registry
BEAD…… Biological and Economical Analysis Division
BMD …… Benchmark Dose
BR…….. Breathing Rates
BuChE …….. Butyrylcholinesterases
CEC…….. Critical Exposure Commodity Analysis
CK……. Creatin Kinase
CMS……. Congenital Myasthenic Syndrome
CSFII……. Continuing Survey of Food Intake by Individuals
CYP……Cytochrome P450
DEEM™…… Dietary Exposure Evaluation Model
DNT……... Developmental Neurotoxicity
DPR …….. Department of Pesticide Regulation
ED…….. Effective Dose
ENEL……. Estimated No Effect Level
FDA……Food and Drug Administration
FFDCA ……..Federal Food, Drug, and Cosmetic Act
FIFRA ……Federal Insecticide, Fungicide, and Rodenticide Act
FOB…….. Functional Observational Battery
FSH…… Follicle-Stimulating Hormone
FQPA……. Food Quality Protection Act
GD……. Gestation Day
IMS…… Intermediate Syndrome
LADD…… Lifetime Average Daily Dosage
LD_{50}…….. Median Lethal Dose
LC_{50}……Median Lethal Concentration
LD…….. Lactation Day
LDH…….. Lactate Dehydrogenase
LH ……. Luteinizing Hormone
LED ……. 95% Confidence Limit of the Effective Dose
LOD……. Limit of Detection
LOEL…… Lowest Observed Effect Level
MOE …… Margin of Exposure
NCBI…….. National Center for Biotechnology Information
ND…… Non-Detected Residues, Non-Detects
NOEL…….No Observed Effect Level
NTE……Neuropathy Target Esterase
OP…….. Organophosphorus ester

OPIDN……. Organophosphate-Induced Delayed Neurotoxicity
OXO…….. Oxotremorine-M Acetate
PAD …….. Population Adjusted Dose
PCT…… Percent of the Crop Treated
PDP…… Pesticide Data Program
PCPA …… Pesticide Contamination and Prevention Act of 1985
PND…….. Postnatal Day
POD……Point of Departure
ppm…… Part per Million
ppb …… Part per Billion
PWG…….. Pathology Working Group
RAC……Raw Agricultural Commodity
QNB……... Quinuclidinyl Benzilate
RBC……... Red Blood Cell
RCD……Risk Characterization Document
RDF……Residue Data File
RED……Reregistration Eligibility Decision Document
REI …… Restricted Entry Intervals
RfD ……Reference Dose
RPF ……Relative Potency Factor
SB950…….Birth Defect Prevention Act of 1984
SCE…… Sister Chromatid Exchange
SNV……Specific Numerical Values
TACE …… Toxic Air Contaminant Evaluation
TEF…… Toxicity Equivalence Factor
USDA…….United States Department of Agriculture
USEPA…….. U.S. Environmental Protection Agency
WHO ……. World Health Organization

I. SUMMARY

I.A. INTRODUCTION

Methyl parathion is a neurotoxic insecticide, which is registered to control insect pests on food, feed and fiber crops. Its toxicity is largely due to the inactivation of the enzyme acetylcholinesterase (AChE) in insects and mammals. Methyl parathion requires metabolic activation to its oxon, methyl paraoxon, to yield an anticholinesterase activity. AChE is responsible for the hydrolysis of acetylcholine (ACh) at cholinergic synapses, which is necessary for the control of the neurotransmission. The prolonged action of the unhydrolyzed ACh results in overstimulation, followed by exhaustion and disruption of the cholinergic pathways in the central and peripheral nervous systems. If the methyl paraoxon-cholinesterase bond is not cleaved by pharmacological intervention, large amounts of AChE are inactivated, causing acute cholinergic effects, long-term morbidity or even death. The cholinergic toxicity is typically treated with atropine, an antagonist of the muscarinic cholinergic receptors and pralidoxime, a reactivator of AChE.

Methyl parathion represents the oldest generation of anticholinesterase insecticides, which exhibit marked mammalian toxicity. It is a Category I toxicant and thus is classified as a restricted-use pesticide. In its 1999 re-registration eligibility document (RED), the U.S. Environmental Protection Agency (USEPA) established an oral chronic Population Adjusted Dose (cPAD) of 0.00002 mg/kg/day for methyl parathion. This maximum safe daily exposure level is one of the lowest of all the widely-used pesticides. In California, a health risk assessment was completed in 1999, which evaluated methyl parathion as a Toxic Air Contaminant. For methyl parathion in the air, Department of Pesticide Regulation (DPR) established a chronic inhalation reference concentration (RfC) of 0.01-0.08 $\mu g/m^3$. Methyl parathion is listed under the California Toxic Air Contaminant Identification and Control Act of 1983 (AB1807) as a chemical known to the State of California to be a Toxic Air Contaminant.

In the environment, methyl parathion is degraded rapidly in soil and water. The major degradation product of methyl parathion is para-nitrophenol. The principle routes of dissipation are microbial degradation, aqueous photolysis, hydrolysis, and incorporation into soil organic matter.

I.B. TOXICOLOGICAL PROFILE

Pharmacokinetics- Methyl parathion is rapidly absorbed by oral, dermal and inhalation routes. Pharmacokinetic studies in rat, guinea pigs, dogs and hens revealed that the oral absorption of methyl parathion was complete (100%). Methyl parathion is metabolized to at least three toxicologically significant metabolites, methyl paraoxon, p-nitrophenol and amino-paraoxon-methyl. Metabolites are excreted primarily in the urine as glucuronide and sulfate conjugates of p-nitrophenol. Methyl parathion readily crosses the blood brain barrier and the placenta. Methyl parathion or its oxon were not detected in milk, meat of goats and hens and hen eggs. Dermal absorption of methyl parathion in rats is nearly complete, based on the excretion of over 90% of the total ^{14}C content or calculated from the amount of para-nitrophenol in the urine. Acute toxicity studies indicated that the methyl parathion absorption is comparable between oral and

inhalation routes. Therefore, adjustment for route-specific absorption was not necessary when oral toxicity data were used to characterize the risk of inhalation exposure.

Acute Toxicity- Methyl parathion is highly toxic via oral and dermal routes. Rats appeared to be the most sensitive species, among the laboratory animals treated with methyl parathion. In rats, the median oral lethal doses (LD_{50}) ranged between 6-50 mg/kg (Category I oral toxicant). The dermal rat LD_{50} was 67 mg/kg (Category I dermal toxicant), indicating that the toxicity of methyl parathion via oral route or via skin is comparable. Methyl parathion was classified as Category II inhalation toxicant, and Category IV eye and skin irritant. An acute (single dose) oral exposure of rats to methyl parathion caused decreases in the ChE activities in the brain, plasma and erythrocytes, cholinergic signs, neurobehavioral effects and neuropathology.

Subchronic Toxicity- Inhibition of the ChE activities in brain, plasma and erythrocytes was the most sensitive toxicological endpoint after subchronic exposures of rats to methyl parathion by oral and dermal routes. Cholinergic signs (including constricted pupils, tremors, gait abnormalities, decreased activity and abnormal breathing), impairment of the cognitive and motor functions and death were observed in the oral and dermal studies (5 to 95-day treatment).

Chronic Toxicity- Chronic dietary exposure to methyl parathion of rats produced decreases in the ChE activities, neurological signs, hematological effects and nerve demyelination. The reduction of the ChE activity in the mice brain was the most sensitive toxicological endpoint. Methyl parathion was not considered to cause cancers in laboratory animals.

Genotoxicity- Methyl parathion was genotoxic in *in vitro* and *in vivo* tests causing gene mutations in bacteria, chromosomal aberrations in mammalian cells, sister chromatid exchange (SCE); and was positive on the sex-linked recessive lethal assay in *Drosophila*. *In vitro*, methyl parathion was shown to bind directly to the cellular DNA.

Oncogenicity- Despite its ability to alter cellular DNA in the genotoxicity tests, the oncogenicity bioassays with methyl parathion in rodents did not show clear evidence of oncogenic potential.

Reproductive Toxicity- The reported effects of methyl parathion on reproduction included: alteration in the levels of the luteinizing hormone in serum and early menopause in humans, decreased pup survival in rats, possible ovarian toxicity in rats and sperm abnormalities in mice.

Developmental Toxicity- Various methyl parathion-induced developmental effects were reported in rats, mice and rabbits, including lower fetal body weight, increased resorption, reduced pup survival, abnormalities and variations of ossification and cleft palate.

Developmental Neurotoxicity- Developmental neurotoxicity studies revealed an increased sensitivity of immature rats to the inhibition of the ChE activity compared to adult rats after a single or repeated exposures to methyl parathion.

Immunotoxicity- In rats methyl parathion caused lymphoid depletion and necrosis of spleen and thymus; increased viable bacteria in the blood and decreased IgG. In mice, this pesticide induced increase mortality after bacterial challenge and increases in the plaque-forming splenocytes.

Hematologic Effects- The commonly reported effects induced by methyl parathion in rats included changes in hematological indices (decreases in the red blood cell number, increases in the RBC distribution width and decreases in the hemoglobin levels).

I.C. RISK ASSESSMENT

Hazard Identification-

Acute Toxicity: The acute oral No-Observed-Effect Level (NOEL) of 0.025 mg/kg/day was based on a reduction in the ChE activities, clinical signs and demyelination of peripheral nerves in rats. This NOEL was utilized in estimating the human risk for acute dietary and and ambient air exposure to methyl parathion.

Subchronic Toxicity: The subchronic oral NOEL of 0.03 mg/kg/day was selected to characterize the risk of subchronic dietary exposure of humans to methyl parathion. This NOEL was based on decreases in the plasma, RBC and brain ChE activities in immature Sprague-Dawley rats. The subchronic dermal NOEL of 0.03 mg/kg/day was chosen to evaluate the human risk due to dermal exposure to methyl parathion. The effects observed at the LOEL of 0.3 mg/kg/day included inhibition of the brain ChE activity and cholinergic toxicity (constricted pupils) in rats. Because the lowest tested dose in the study represented the LOEL, a default factor of 10 was applied to estimate the subchronic dermal NOEL.

Chronic Toxicity: The chronic NOEL of 0.02 mg/kg/day was estimated from the LOEL of 0.2 mg/kg/day using a default factor of 10. This NOEL was based on the inhibition of the brain ChE activity after 2 years of treatment of mice.

Exposure Assessment- This document pertains only to the assessment of the dietary and the ambient air exposure. The occupational exposure to methyl parathion will be addressed subsequently in addendum to this document.

The human exposure to methyl parathion from non-dietary activities was expressed as an absorbed daily dose (ADD), seasonal average daily dose (SADD) and Annual Average Daily Dosage (AADD).

Ambient Air: The exposures to ambient air were based on the concentrations of methyl parathion as well as on the concentrations of its metabolite, methyl paraoxon. The exposure to methyl paraoxon was multiplied by the toxicity equivalence factor (TEF) of 10 to convert to methyl parathion equivalence and subsequently added to the exposure of methyl parathion. The total (methyl parathion and methyl paraoxon) ADD for a 6 year old child, a male adult, and a female adult were estimated as 64.55 ng/kg/day, 24.27 ng/kg/day and 15.93 ng/kg/day. The SADD were 19.64 ng/kg/day (a 6 year old child), 7.45 ng/kg/day (a male adult) and 4.84 ng/kg/day (a female adult). The AADD were 14.78 ng/kg/day (a 6 year old child), 5.56 ng/kg/day (a male adult) and 3.56 ng/kg/day (a female adult).

Dietary Exposure: The dietary exposure was calculated using the probabilistic (Monte Carlo) modeling. The dietary exposure estimates were based on the methyl parathion residues. At the 95^{th} exposure percentile, the estimated acute exposures to methyl parathion ranged from 0.128 μg/kg/day to 0.588 μg/kg/day. The "Non-Hispanic/non-white/non-black" subgroup was identified to receive the highest dietary exposure from methyl parathion. At the 99^{th} and 99.9^{th} percentiles, the population subgroup Infants (nursing and non-nursing) was identified to receive the highest dietary exposure from methyl parathion (1.068 and 2.7 μg/kg/day, respectively). The chronic dietary exposures ranged from 0.001 μg/kg/day for "Nursing infants" to 0.006 μg/kg/day for "Children 1-6 yrs".

Aggregate Non-Occupational (Inhalation and Dietary) Exposure: The acute exposure from methyl parathion in the ambient air was less than 3% compared to the acute dietary exposure. Because of its relatively low contribution, it was not added to the dietary exposure to estimate the total exposure from non-occupational sources.

I.D. RISK CHARACTERIZATION AND RISK APPRAISAL

The critical NOELs for characterizing the risk from exposure to methyl parathion were derived from studies with laboratory animals. Risks were calculated as margin of exposure (MOE), a quotient of the NOEL and the exposure level. A MOE of 100 was considered prudent for protection against the methyl parathion toxicity. The benchmark of 100 includes an uncertainty factor of 10 for interspecies sensitivity and an uncertainty factor of 10 for intraspecies variability.

Ambient air: The acute MOE values for ambient air exposures ranged from 390-1,600; the ambient seasonal MOE values ranged from 1500 to 6300. The chronic MOEs for ambient air exposures varied from 1300 to 5400.

Dietary Exposure: The acute dietary MOEs ranged from 42 to 195 at the 95^{th} exposure percentile. Nine of the evaluated 19 population subgroups had MOEs below 100, including Infants (nursing or non-nursing) and Children 1-12 yrs. At the 99^{th} and 99.9^{th} percentiles, the MOEs were less than 100 for all population subgroups except for the subgroup "Females 13+ nursing". Infants (nursing and non-nursing) were identified to receive the highest acute dietary exposure from methyl parathion, with the corresponding MOE of 23 and 9 at the 99^{th} and 99.9^{th} percentiles, respectively. The estimated chronic exposures to methyl parathion were higher than 3164 for all of the evaluated population subgroups.

Aggregate Non-Occupational (Inhalation and Dietary) Exposure: The inhalation exposure by itself did not indicate a significant risk for humans (MOE>390). However, analysis of the potential aggregate risk from non-occupational exposures revealed that, if included, the ambient air exposure would increase the overall risk. In this respect, the dietary MOE, which would produce an aggregate MOE of at least 100 would have to be 126 (and not the benchmark of 100).

Risk Appraisal: The main uncertainties with the toxicity of methyl parathion were associated with (*i*) the use of animal data to evaluate the toxic effects in humans and (*ii*) the default approach for estimating the NOEL from the LOEL.

The uncertainties in the exposure assessment were introduced with the use of default physiological parameters. In addition, sufficient residue data were not available to determine the true contribution of the metabolite methyl paraoxon to the acute dietary exposure. The uncertainties in the risk characterization were associated with the default assumptions for the 10-fold interspecies sensitivity and the 10-fold variation in the sensitivity within the human population. Furthermore, the risk of exposure of infants and children to methyl parathion could be higher, due to the evidence for an increased pre- and post-natal sensitivity in laboratory animals. Finally, a consideration should be given to the demonstrated cumulative toxicity of methyl parathion and other organophosphate compounds.

I.E. TOLERANCE ASSESSMENT

The tolerance assessment was conducted to estimate the point estimate exposure and risk to a single label-approved commodity with methyl parathion residues at the tolerance. All label-approved commodities were evaluated for the health protectiveness of the tolerance.

The potential exposure to a tolerance level methyl parathion on the majority of the label-approved commodities in California indicated a health concern. The 95th percentile MOEs were less than the benchmark of 100 for each of the 19 population subgroups evaluated, which consumed dry beans, corn, oats, onion, peas, potatoes, rice or wheat containing tolerance levels of methyl parathion. The 95th percetile MOEs were also less than 100 for all, but 4, population subgroups from consumption of barley; and for infants from consumption of soybeans. Among all commodities, consumption of wheat, corn and rice would result in the highest dietary exposures. The corresponding MOE ranges were wheat, 2 – 10; corn, 2 – 12; and rice, 4 – 14 at the 95th percentile.

I.E. CONCLUSIONS

The health risk assessment of methyl parathion was carried out for the general population. Four exposure scenarios were evaluated, including (*i*) exposure from ambient air under acute scenarios and dietary exposures under (*ii*) acute, (*iii*) subchronic conditions and (*iv*) chronic conditions. A margin of exposure of 100 is considered sufficiently protective of human health when the NOELs are derived from animal studies.

The acute dietary MOEs, calculated with the probabilistic (Monte Carlo) model using the most refined assumptions, were below the benchmark of 100 for the majority of the population subgroups at the 95th and the 99th percentiles. The acute dietary MOEs were below 100 for all subgroups at the 99.9th percentile of user-day. Infants were identified as the most highly exposed population subgroup. Altogether, the MOEs for acute dietary exposure indicated a potential health concern and thus mitigation should be considered.

The ambient air exposure, as estimated in the 1999 TACE document, was less than 3% compared to the exposure from dietary sources. Because of its relatively low contribution, the ambient air exposure was not added to the dietary exposure to estimate the non-occupational aggregate exposure.

The 95th percentile MOE for exposure to a tolerance level methyl parathion were less than the benchmark of 100 for the majority of the label-approved commodities in California. Methyl parathion exerts adverse pre- and post- natal effects, which should be taken into consideration when the USEPA reviews the tolerance levels under the Food Quality Protection Act.

II. INTRODUCTION

Methyl parathion, O,O-dimethyl O-(4-nitrophenyl) phosphorothioate is a neurotoxic insecticide and acaricide. It possesses contact and systemic actions and is registered to control insect pests on food, feed and fiber crops. Like the other organophosphorus ester insecticides (OPs), the most prominent toxicity of methyl parathion is associated with binding and inhibition of the enzyme acetylcholinesterase (AChE) in insects and mammals. The subsequent accumulation of the neurotransmitter acetylcholine (ACh) at the neural synapse, in turn, induces overstimulation, followed by exhaustion and disruption of the cholinergic pathways present in the central (CNS) and peripheral (PNS) nervous systems. If the organophosphate-cholinesterase bond is not cleaved by pharmacological intervention, large amounts of AChE are inactivated, causing acute cholinergic effects, long-term morbidity or even death. Methyl parathion requires metabolic activation to methyl paraoxon to yield anticholinesterase activity.

Methyl parathion represents the oldest generation of anticholinesterase insecticides, which are relatively unselective with respect to target and non-target species and exhibit marked mammalian toxicity. Methyl parathion is listed under the California Toxic Air Contaminant Identification and Control Act of 1983 (AB1807) as a chemical known to the State of California to be a Toxic Air Contaminant (California Code of Regulations). Methyl parathion is also listed as a high priority active ingredient under The Birth Defect Prevention Act of 1984 (SB 950).

This Risk Characterization Document (RCD) evaluated the potential health hazard from exposure scenarios to methyl parathion in the ambient air and from dietary sources. The toxicological profile was based on studies on file at the DPR, which were submitted for fulfilling the data requirements for pesticide registration under SB 950. Data available for review consisted of combined chronic toxicity-carcinogenicity studies in rats, chronic toxicity studies in dogs, a carcinogenicity study in mice, a reproductive toxicity study in rats, developmental toxicity studies in rats and rabbits, subchronic oral studies in rodents and non-rodent species, a subchronic dermal study in rabbits, acute and subchronic oral neurotoxicity study in rats, dermal neurotoxicity studies in rats, acute and subchronic developmental neurotoxicity study in rats, acute inhalation studies in rats and a battery of mutagenicity studies. DPR considered the toxicological database for methyl parathion completed (no data gaps). A summary of the toxicology data for methyl parathion is provided in the Attachment V.

Published experimental data were also used to characterize the methyl parathion toxicity. Relevant publications were searched from Medline and Toxnet, the electronic databases at the National Center for Biotechnology Information (NCBI, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi and, http://toxnet.nlm.nih.gov/). The most recent database search was conducted in January 2003 and the document was updated accordingly.

II.A. MECHANISM OF ACTION

II.A.1. Cholinesterase Inhibition and Neurotoxicity.

Cholinesterases are serine hydrolases that preferentially act on choline esters. Their diversity arises at the genetic, post-transcriptional and post-translational levels. The different types of cholinesterases are traditionally distinguished based on their substrate specificity. AChEs hydrolyze ACh faster than other choline esters. Butyrylcholinesterases (BuChE) are more active

on butyrylcholine and propionylcholine than on ACh. AChE and BuChE are also distinguished by their affinity or reactivity to selective inhibitors (Massoulie, 2002).

Invertebrates possess a variable number of cholinesterase genes (e.g. a single gene in *Drosophila* and four different genes in the nematode *Caenorhabditid elegans*; Hall and Spierer, 1986; Arpagaus et al., 1990). Vertebrates have a single AChE gene (Massoulie et al, 1993); in addition, birds and mammals also possess a BuChE gene (Arpagaus et al, 1990). AChE is found at the neuromuscular junction, in the brain and in some non-neuronal cells such as erythrocytes (Massoulie et al., 1998). BuChE represents the majority of the ACh-hydrolyzing activity in the human plasma. However, the ratio between BuChE and AChE in the plasma varies greatly from species to species and between sexes (Edwards and Brimijoin 1983). BuChE is also present at lesser amount at the neuromuscular junction and in the CNS (Mesulam et al, 2002).

The main role of AChE is to terminate the synaptic action of ACh through hydrolysis, and possibly, to serve as cell adhesions factor during the neurite outgrowth (Johnson and Moore, 1999). Although the classical function of AChE is apparently simple, its molecular structures and distribution are very complex. The transcript of the AChE gene is subject to alternative splicing and its protein products can associate with each other to form globular structures or with the collagenous subunit (ColQ) to form asymethric molecules. In addition, the AChE oligomers can be cytoplasmic, membrane-bound or associated with the extracellular matrix. Much of AChE at the neuromuscular junction has the ColQ tail, which is likely to be critical for anchoring the enzyme to the basal lamina, where it hydrolyzes ACh to terminate the synaptic transmission. Globular forms of the enzyme are more uniformly distributed. Another form of AChE consists of glycolphosphatidylinositol (GPI) -anchored dimers. In mammals, this enzyme form is expressed mostly in the hematopoietic cells, where it may participate in the elimination of any ACh from the bloodstream (for review see Massoulie et al, 1993, 1998 and Massoulie 2002).

A complete AChE deficiency in humans has never been reported. Recently, a rare autosomal recessive disease with a partial AChE deficiency was classified in humans as a congenital myasthenic syndrome (CMS), Donger et al, 1998; Ohno et al, 1998). In these individuals, the asymmetric AChE is absent from the endplate, while the activity and kinetic properties of the residual AChE in the muscle as well as the erythrocyte AChE are normal. Patients with CMS have morphological abnormalities of the neuromuscular junction and are severely disabled.

The importance of AChE is further demonstrated by the effects of blocking its activity. The acute neurotoxicity induced by the OPs is largely due to the inactivation of the synaptic AChE. The oxygen analog of methyl parathion, for example, inhibits AChE through binding to the enzyme active site and forming a phosphoryl-cholinesterase complex. Initially, the complex is reversible, but over time, the complex may undergo "aging" (forming dealkylated phosphorylated AChE) and become refractory to AChE reactivation (Chambers and Chambers, 1990). The prolonged action of ACh causes cholinergic hyperactivity, which is referred to as the cholinergic phase of the organophosphorus poisoning or cholinergic crisis. The nicotinic effects from accumulation of acetylcholine at motor end plates cause depolarization of skeletal muscles, resulting in fasciculation, muscle weakness, and hypertension. Muscarinc effects from stimulation of smooth muscles lead to smooth muscle contractions in various organs (lung, GI, eye, bladder, secretory glands) and bradycardia. CNS effects may cause excessive stimulation, convulsions, seizures then depression and coma (Dementi, 1999). On the other hand, some inhibitors of AChE can be therapeutically useful to patients with disease of inadequate neurotransmission due decreased levels of AChRs (such as acquired autoimmune myasthenia

gravis; Engel 1994a) or when insufficient ACh is released (such as familial infantile myasthenia; Engel 1994b).

The function of BuChE in higher vertebrates is less clear. Like AChE, the BuChE monomers assemble into both globular and asymmetric ColQ multimers. There are several known allelic variants of the human BuChE. This enzyme is important pharmacologically, because it hydrolyzes certain ester drugs such as succinylcholine and procaine. However, it is not physiologically essential, since humans lacking BuChE do not show any pathology, unless challenged by neuromuscular blocking agents (Bartels et al, 1992a, 1992b). It appears that BuChE in the plasma of mammals protects against the diffusion of acethylcholine in the bloodstream and serves as a scavenger for toxic compounds including OP pesticides and plant alkaloids (Lockridge and Manson, 2000; Neville et al., 1990; Sun et al., 2001). At the neuromuscular junction, the synapse-associated BuChE may serve as a "backup" to AChE in supporting the cholinergic neurotransmission (Li et al., 2000). In the brain, BuChE is present in much lower concentration than AChE and occurs mainly outside synapses. Because of its location, the function of BuChE in the brain may be to hydrolyze extrasynaptic ACh (Mesulam et al., 2002).

During the embryonic development, AChE and BuChE are localized in many cell types, which are devoid of activity in the adult. Based in part on their complex patterns of expression in embryos and adults, both enzymes have been hypothesized to play non-cholinergic and even non-catalytic roles in the normal development (for review see Layer and Willbold, 1995).

AChE has long been considered as physiologically essential, based on its function in the cholinergic nervous system. This assumption is further supported by the fact that acute inhibition of the synaptic AChE seen after an overexposure to certain OPs, including methyl parathion, is fatal. Interestingly, AChE knockout mice with zero AChE activity were born alive, indicating that adaptation to the absence of AChE occurred during the development (Li et al., 2000). The AChE knockout mice had many common characteristics with the wild-type mice poisoned with OP compounds and exhibited significant physical and behavioral abnormalities (Xie et al., 2000; Mesulam et al, 2002; Duysen et al., 2002). BuChE, which is also capable of hydrolyzing ACh, was implicated in substituting for AChE (Li et al., 2000; Mesulam et al., 2002). The current understanding is that both AChE and BuChE are necessary for maintaining the functional integrity of the cholinergic pathways.

II.A.2. Delayed Neurotoxicity and Intermediate Syndrome

A number of organophosphorus esters have been implicated in causing a syndrome, known as organophosphate-induced delayed neurotoxicity (OPIDN) (Ecobichon, 1994). The delayed neurotoxic effects appear 2-3 weeks following exposure and are characterized by paralysis of lower limbs and degeneration of long axons in the spinal cord and peripheral nerves. OPIDN is unrelated to inhibition of AChE activity, but rather results from phosphorylation and subsequent toxic gain of function of the neuronal enzyme neuropathy target esterase (NTE) (Glynn, 1999, 2000). A third, distinct intermediate syndrome (IMS) of organophosphate neurotoxic effects is also recognized (Senanayake and Karalliedde, 1987). IMS appears after the cholinergic crisis but before the delayed neuropathy and carries a risk of death associated with respiratory muscle paralysis. The biochemical mechanism of IMS is not clear, however the degenerative effects appear to be related to the prolonged inhibition of AChE activity, the elevated levels of ACh at the motor end plate resulting in subsequent impairment of the neuromuscular transmission (De

Bleecker 1995). Currently, in the available database, there is no conclusive evidence to demonstrate that methyl parathion causes IMS or acute delayed neuropathy (Reed, 1999; USEPA, 1998c, 1999a).

A detailed discussion on the mechanism of methyl parathion toxicity has been presented in the Human Health Assessment of the methyl parathion Toxic Air Contaminant Evaluation document (TACE; Reed, 1999). Collectively, the toxicology data reviewed in the TACE document, together with the new findings published after its completion in 1999, support the concept that the acutely toxic effects of methyl parathion manifest through inhibition of the AChE activity (Gupta, 2000; Reed, 1999).

II.A.3. Other Toxic Endpoints

Methyl parathion has been implicated in inducing toxic effects via mechanisms distinct from inhibition of ChE activity, which include: competitive interaction with cholinergic receptors; modulation of ligand binding to muscarinic receptors; interaction with calmodulin and subsequent alteration of Ca^{2+}-dependent cellular processes; inhibition of catecholamine exocytosis, inhibition of voltage-gated Ca^{2+} channels, etc., (reviewed by Reed, 1999).

Recent papers published after the completion of the TACE in 1999, implicated methyl parathion in inducing membrane damage. In the study by Gupta et al., 2000, the loss of cell membrane integrity was tentatively attributed to the depletion of ATP pools in the brain, possibly due to the sustained brain hyperactivity from the AChE inhibition. In the second study, methyl parathion directly caused a perturbation of the structure of artificial lipid membranes, which correlated with its toxicity to mammals (Videira et al., 2001). New findings were published on the methyl parathion targets and activators. Cytochrome P450 2B was identified as the enzyme responsible for the *in vitro* activation of methyl parathion to the neurotoxic metabolite methyl paraoxon in rat brain. (Albores et al., 2001). Another *in vitro* study implicated the cardiac muscarinic receptors m_2 subtype as the non-cholinesterase target for methyl parathion and supported the concept that the organophosphorus esters have the potential to produce several forms of toxicity via distinct targets (Howard and Pope, 2002).

These findings are summarized in section III. L. under "ADDITIONAL INFORMATION FROM THE LITERATURE PUBLISHED AFTER 1999".

II.B. REGULATORY HISTORY

The insecticidal organophosphorus esters, including the methyl homologue of parathion, were originally discovered in the 1930s by German chemists at Bayer AG. Methyl parathion was first registered in USA in 1954 and was one of the most widely employed insecticides throughout the world. Currently, as a Category I toxicant, it is classified as a restricted-use pesticide. In 1997 USEPA initiated a preliminary risk assessment and tolerance reassessment for methyl parathion in regard to its reregistration eligibility (RED), (USEPA, 1997a). In its final regulatory decisions, issued in August 2, 1999, the Agency established an oral chronic Population Adjusted Dose (cPAD) of 0.00002 mg/kg/day (http://www.epa.gov/pesticides/op/methyl_parathion.htm), USEPA, 1999a). cPAD represents a chronic Reference Dose (RfD) to which a 10 fold additional safety is factored to protect infants and children, as mandated by the Food Quality Protection Act of 1996 (USEPA, 1997b). For occupational exposure, the restricted entry intervals (REI) were increased from two to five days. Methyl parathion is classified as a "Group E" carcinogen, indicating no evidence of carcinogenicity in humans (USEPA, 1999a,b).

In August 1999, USEPA accepted voluntary cancellation of all methyl parathion uses on fruits and most uses on vegetables to reduce human risk from dietary exposures. The list of canceled non-food uses includes field-grown ornamentals, flowering plants, nursery stock, roadside areas, wasteland and mosquito control use. There are no labeled methyl parathion indoor uses (USEPA, 1999a).

In California, a health risk assessment was completed in 1999, which evaluated methyl parathion as a Toxic Air Contaminant, as mandated by the Assembly Bill 1807, Toxic Air Contaminant Act (AB-1807). For methyl parathion in the air, Department of Pesticide Regulation (DPR) established a chronic inhalation reference concentration (RfC) of 0.01-0.08 $\mu g/m^3$ (Reed, 1999). (http://www.cdpr.ca.gov/docs/empm/pubs/methylpa/mppartc.pdf).

II.C. TECHNICAL AND PRODUCT FORMULATIONS

Methyl parathion is effective against boll weevils and many biting or sucking insect pests of agricultural crops. It is available as microencapsulated, emulsifiable concentrate and granular formulations. In the US, Cheminova Agro A/S is the main producer of the trade name methyl parathion and Cerexagri Inc. (formerly Elf Atochem, Inc.) is the formulator of the flowable microencapsulated formulation Penncap-M®(20.9% a.i.).

As of January 2003, Penncap-M® is the only product containing methyl parathion that is registered in California for use on food, feed and fiber crops (http://www.cdms.net/manuf/acProducts.asp). This formulation is allowed to be applied to corn, cotton, rice, soybeans, wheat, oats, barley, beans, peas, onions and potatoes. In addition, a Special Local Need (SLN) registration of Penncap-M® was obtained for use on walnuts.

II.D. USAGE

From 1991 to 1999, over 1,100,000 pounds of methyl parathion were used in California. The amounts applied in 1997, 1998 and 1999 were 160,796, 166,328 and 165,517 pounds, respectively. However, in 2000 the use in California decreased to 79,110 pounds, due to the cancellation of many of the food uses by the USEPA in 1999. In 2000, the use on walnuts was 92% of the total methyl parathion use in California. The second major use was on corn (6%). Other uses accounted for less than 1% (DPR 2000a; http://www.cdpr.ca.gov/docs/pur/pur00rep/chmrpt00.pdf).

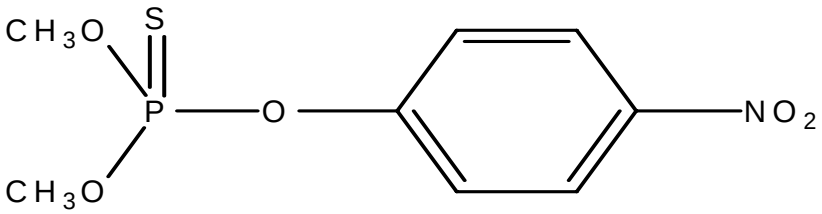
II.E. ILLNESS REPORTS

In California, 18 cases of illnesses from 1986 to 1995 were linked to methyl parathion (DPR, 1997b). These cases were rated as either "definitely", "probably", or "possibly" related to methyl parathion exposures, alone or in combination with other pesticides. Nine of the 12 cases of illness in 1990 were associated with rescue attempts after a midair collision of two crop dusters carrying a pesticide mixture of dimethoate, parathion, and methyl parathion. The majority of the remaining cases were associated with pesticide applications. Unfortunately, clinical signs were not recorded for the two cases identified as “definitely” associated with methyl parathion.

II.F. PHYSICAL AND CHEMICAL PROPERTIES

Chemical name:	O,O-dimethyl O-(4-nitrophenyl) phosphorothioate
CAS Registry number:	298-00-0
Common name(s):	methyl parathion, parathion methyl, metafos
Trade names:	Penncap-M, Amithion, Agrodol, Agro prathion, Metaphos, Metacide, Metron (Farm Chem. Handbook, 2002)
Molecular formula:	$C_8H_{10}NO_5PS$

Chemical Structure



Physical appearance: colorless crystalline solid (pure methyl patathion), light tan (80% purity).

Solubility:	55-60 mg/l water at 25°C. Soluble dichloromethane, 2-propanol
Melting point:	35-36°C
Boiling point:	119°C at 0.13 mbar; 154°C at 1.3 mbar
Vapor pressure:	1.3 mPa at 20°C
Specific gravity:	1.265
Henry's Law constant	10.3×10^{-8} atm $m^3 g.mol^{-1}$

II.G. ENVIRONMENTAL FATE

Summary: In the environment, the principle routes of dissipation for methyl parathion are microbial degradation, aqueous photolysis, hydrolysis, and incorporation into soil organic matter. Methyl parathion degraded rapidly (half-life<5 days) in soil and water. Methyl parathion hydrolyzed slowly in sterile buffered solutions and photodegraded slowly on soil surfaces.

Because of the its mobility in soil, runoff and leaching from the application site could be potential routes of methyl parathion dissipation. However, despite its ability to move into surface and ground waters, the low persistence of methyl parathion is expected to limit the extent off-site movement. Another route of dissipation is the secondary movement through volatilization of methyl parathion from soil and leaf surfaces. Although laboratory studies indicated that

volatilization is not a major route of dissipation, methyl parathion has been detected in air samples in California.

The major degradation product of methyl parathion in the environment is para-nitrophenol. Additional products, which have been found in laboratory studies included methyl paraoxon, monodesmethyl parathion, phosphorothioic acid, O,S-dimethyl O-(4-nitrophenyl)ester, nitrophenyl phosphoric acid, mono (4-nitrophenyl) ester and carbon dioxide. A detailed discussion on the fate of methyl parathion in the environment was presented in the 1999 Toxic Air Contaminant Evaluation Document (Kelly, 1999 - Part A Environmental Fate).

II.G.1. Hydrolysis

The hydrolysis of methyl parathion was investigated in sterile aqueous buffered solutions at 25ºC. Phenyl ring-labeled ^{14}C-methyl parathion (4 mg/l), hydrolyzed with half-lives of 68 days at pH 5; 45 days at pH 7; and 33 days at pH 9. In the acid environment the dominant metabolite was monodesmethylparathion-methyl. In the alkaline solutions para-nitrophenol was identified as the major hydrolysis product of methyl parathion. In the neutral hydrolysis, equal amounts of both products were formed (Wilmes, 1987a).

II.G.2. Photolysis or Photodegradation

The photodegradation of [phenyl-^{14}C]methyl parathion was studied in water, under the conditions of maximum hydrolytic stability (pH 5 at 25ºC). Methyl parathion (5 mg/l) was continuously irradiated with a sunlight-simulating Xenon lamp. The half-life of the photodegradation was 48 hours. Based on this half-life, the environmental half-life was estimated as about 9 days, considering 40 degrees latitude, top layer of the water body, clouds and weather conditions. The major photodegradation products were 4-nitrophenol (10 % of the applied radioactivity) and monodesmethylparathion-methyl (Wilmes, 1987b).

The photodegradation of [phenyl-^{14}C]methyl parathion was investigated on sandy loam soil. [^{14}C]methyl parathion (applied at 0.3 mg/cm^2), was continuously irradiated with a sunlight-simulating Xenon lamp at 27ºC. Methyl parathion degraded with a biphasic half-life with initial half-lives of 3.9 to 4.5 days and a secondary half-lives of 8.6 to 24 days. The major photodegradate was 4-nitrophenol and the final degradation product was carbon dioxide. (Wilmes, 1987c).

II.G.3. Microbial Degradation

The anaerobic metabolism of methyl parathion was investigated on a microbially active, flooded sandy loam soil in the dark, at 25ºC. Under these conditions, the phenyl ring-labeled ^{14}C-methyl parathion degraded with a half-life of 1.1 days. Para-nitrophenol was identified as the major metabolite. Additional metabolites were S-methyl parathion, amino-methyl parathion S-phenylmethyl parathion and methyl paraoxon. The final degradation product was carbon dioxide (Patterson, 1990a).

The aerobic metabolism of methyl parathion was studied on microbially active, sandy loam soil in the dark, at 25ºC. ^{14}C-Methyl parathion, radiolabeled in the ring position, was applied on the soil at a dose rate of 10 μg/g soil. This dose rate was about 22 fold higher that of the actual field use rate. Methyl parathion degraded with a half-life of approximately 4.7 days and completely degraded after 28 days. The most significant metabolite was para-nitrophenol. An additional metabolite was identified as para-nitrophenol-O-methyl-phosphorothioate (Patterson, 1990b).

A subsequent aerobic metabolism study of methyl parathion was conducted on microbially active, flooded sandy loam soil in the dark at 25-30ºC. Phenyl ring radiolabeled methyl parathion degraded with a half-life of approximately 4.1 days. Methyl parathion was primarily associated with the soil fraction; it was not detected in the floodwaters after 2 days of treatment. The only identified metabolite was para-nitrophenol (Patterson, 1991).

II.G.4. Mobility and Field Dissipation

II.G.4.a. Soil

A soil adsorption/desorption study was carried out to characterize the mobility of methyl parathion in soil (Daly, 1989). Aqueous solutions of ^{14}C-methyl parathion were equilibrated for 24 h at 25ºC with four different soil types – slit loam, clay loam, sandy loam and sand. The highest amont of methyl parathion applied to the soils was approximately 200 µg. The soil to water ratio was 1:10 for slit loam and clay loam and 3:10 for sandy loam and sand. The mobility of methyl parathion was classified as low in slit loam and clay loam soils (K_{oc} of 923 and 924, respectively) and medium in sandy loam and sand (K_{oc} of 677 and 357, respectively).

II.G.4.b. Ambient Air

Ambient concentrations of methyl parathion were measured in different rural and urban sites in California, remote from the original application sites. These studies were reviewed in the 1999 Toxic Air Contaminant Evaluation Document (Kelly, 1999; Part A Environmental Fate). The most recent ambient air monitoring study was conducted in Salinas, California. Consecutive six-hour air samples were collected over a four-day period at three residential sites adjacent to agricultural fields. Methyl parathion was detected at 17 ng/m3 (1.6 ppt) in a single sample, which was taken 1200 feet downwind from the nearest agricultural field.

II.G.4.c. Ground and Surface Water

The Pesticide Contamination and Prevention Act (PCPA) of 1985 established a set of data requirements for identifying potential ground water contaminants. Pesticides with parameters exceeding Specific Numerical Values (SNVs) established by DPR, are considered to pose a risk to ground water (Kollman, 1999). The SNVs include: Solubility (SNV>3 ppm), K_{oc} (SNV<1900 cm^3/g), Hydrolysis (SNV>14 days), Aerobic Metabolism (SNV>610 days) and Anaerobic Metabolism (SNV>9days). DPR identified methyl parathion as a potential ground water contaminant based on its high water solubility (70 ppm), relatively low K_{oc} (476 cm^3/g) and long hydrolysis half-life ($t_{1/2}$=45). However, methyl parathion was not detected in water from 1025 wells screened in California between 1986-2000 (DPR, 2001).

DPR sampling of surface water from 1991-2002 resulted in detections of methyl parathion with concentrations ranging from 0.02-0.19 ppb (DPR, 2003).

II.G.5. Field Dissipation

A field dissipation study was performed to evaluate the degradation and mobility of methyl parathion applied to cotton. Methyl parathion (4-pound a.i. per gallon emulsifiable concentrate, 4E) was applied to cotton in Steele, Missouri. Six weekly applications were made at a maximum label rate of 1 pound a.i. per acre. Soil core samples were analyzed for methyl parathion and methyl paraoxon. One day after the final application, the residues were dissipated below the limit

of detection (0.05 ppm). Because of the rapid dissipation of methyl parathion, the dissipation half-life could not be determined (Rice et al., 1990a)

Two field dissipation studies on irrigated crops were carried out to investigate the degradation of methyl parathion. Methyl parathion (4-pound a.i. per gallon emulsifiable concentrate, 4E) was applied to a rice paddy in Madera, California and in Steele, Missouri (Rice et al, 1990b). Six weekly applications were made at a rate of 0.75 pounds a.i. per acre. Soil and water samples were collected from the rice paddy after each application and through day 28 after the final application. To determine the uptake of methyl parathion, irrigation water, soil and plant samples were collected from five irrigated crops planted adjacent to the rice paddy. The adjacent irrigated crops in California included a leaf vegetable (lettuce), a root crop (carrots), a small grain (wheat), and two commonly grown crops in this region (grain sorghum and tomatoes). The adjacent irrigated crops in Missouri included a leaf vegetable (swiss chard), a root crop (sweet potatoes), a small grain (grain sorghum), and two commonly grown crops in this region (corn and soybeans). These crops were irrigated with water from the treated rice paddy 24 h after each application and once a week the final application of methyl parathion. The dissipation of methyl parathion in water was very rapid and a half-life time could not be determined. Residues of methyl parathion, methyl paraoxon or para-nitrophenol were not detected in water, soil or plant samples.

I.G.6. Plant /Metabolism

The plant metabolism of methyl parathion was investigated in cotton, lettuce and potatoes.

Cotton: Phenyl ring-labeled ^{14}C-methyl parathion was applied in cottonseed and leaves either by spraying (376 g/ha) to one whole cotton plant or by leaf application with a syringe. Ten days after the spray application four radioactive products were identified in the seeds. These included methyl parathion, para-nitrophenol, para-nitrophenyl-glucopyranoside and mono-desmethyl-methyl parathion. Fifteen days after the leaf application to two cotton plants five radioactive products were identified in the leaves, including methyl parathion, para-nitrophenol, para-nitrophenyl-glucopyranoside, mono-desmethyl-methyl parathion and mono-desmethyl-methyl-para-oxon-methyl (Linke et al, 1988).

Lettuce: ^{14}C-methyl parathion was applied on lettuce 21 days before harvest. The application rate was the recommended field rate (1.12 kg/ha), and the spray volume was 78.1 ml. Analysis of the plants after 14 days of treatment revealed the presence of the parent compound (2.16 mg/kg, 19% of the recovered radioactivity) and seven additional metabolites. Para-nitrophenol was identified as the major metabolite (2.5 mg/kg). The extracted radioactive compounds after 21 days of treatment included the parent compound (1 mg/kg, 9.9%), para-nitrophenol (2.1 mg/kg, 21%), para-nitrophenyl-glucopyranoside (0.3 mg/kg, 3.4%), para-S-desmethyl-methyl parathion (0.4 mg/lg, 4.2%) and additional unidentified products (Ritter, 1988).

Potatoes: Phenyl ring-labeled ^{14}C-methyl parathion was applied onto 3 month old potato plants at a recommended field rate of 1.5 kg/ha and in at exaggerated rate of 4.7 kg/ha. Para-nitrophenol was the major metabolite in the tubers detected after 5 and 21 days of treatment (25% and 9% of the total recovered radioactivity). The major water-soluble metabolites were para-nitrophenol conjugates and monodesmethyl parathion. Methyl paraoxon was not detected in potatoes (Linke and Brauner, 1988).

Rotational Crop: A rotational crop study was carried out to investigate the uptake and metabolism of ^{14}C-methyl parathion and its soil metabolites by crops. Methyl parathion was applied to the soil at its maximum field rate of 1.5 kg/ha. After 30 days, wheat, red beets and Swiss chard (crop I) were planted and grown until maturity for about 120 days. After harvest, crop II of wheat, red beets and Swiss chard was planted rotationally. Finally, after 270 days, crop III of wheat, red beets and Swiss chard was planted and harvested at maturity. At various intervals, respective plants and plant parts were examined for residual radioactivity and the nature of the metabolites. The radioactivity in the soil decreased from 10.5 mg/kg at day 1 to 2.3 mg/kg at day 29. Except for straw and grains, the residual radioactivity in plants and plant parts ranged from 0.07 mg/kg to 0.4 mg/kg in crop I; in crop II and III these levels were below 0.1 mg/kg. The residual radioactivity in straw was higher, due to the process of dehydration of green wheat. The decrease in radioactivity was the least in grains 0.4 mg/kg (crop I) to 0.3 mg/kg (crop III).

Para-nitrophenol was the major metabolite in all plants and plant parts in crops I, II and III. Additional metabolites comprised conjugates of para-nitrophenol and nitrophenylphosphoric acid. Altogether the results revealed that except for para-nitrophenol, no residual level of methyl parathion and its metabolites were present in rotational plants after 120 and 270 days of treatment. Untreated soil in control areas within the treated fields did not contain significant amounts of radioactivity. However, plants grown in the control areas contained radioactive residues (mainly paranitrophenol and conjugates) as high as those in plants grown on treated field. These results indicated that ^{14}C- radioactivity in plants grown in control areas was from volatile metabolites (Van Dijk, 1990).

III. TOXICOLOGY PROFILE

III.A. PHARMACOKINETICS

Summary: Oral absorption of methyl parathion was considered complete (100%) in rat, guinea pigs, dogs and hens. Methyl parathion was metabolized to at least three toxicologically significant metabolites, methyl paraoxon, p-nitrophenol and amino-paraoxon-methyl. Metabolites were excreted primarily in the urine as glucuronide and sulfate conjugates of p-nitrophenol. Dermal absorption of methyl parathion in rats was nearly complete, based on the excretion of over 90% of the total ^{14}C content. Pharmacokinetic studies were not available for a direct determination of the absorption from the inhalation route.

III.A.1. Oral and Intravenous Studies

III.A.1.a. Absorption

Methyl parathion absorption from the gastrointestinal tract was both rapid and nearly complete. Based on the available data in rats, mice, and dogs presented in this section, a practical level of 100% oral absorption was determined.

Methyl parathion was detected in the plasma and brain of rats 6–8 minutes after a lethal oral dose of 50 mg/kg (Yamamoto et al., 1983). In rats that received a lower single oral dose of 1.5 mg/kg methyl parathion and in guinea pigs that received a single oral dose of 50 mg/kg methyl parathion, the maximum plasma and brain ChE inhibition was reached in 30 minutes (Miyamoto et al., 1963b). Braeckman et al. (1983) reported that the time to the peak blood concentration of methyl parathion in dogs varied between 2 to 9 hours after an oral administration at 20 mg/kg. On the other hand, a much shorter time-to-peak concentration of methyl paraoxon was reported by De Schryver et al. (1987). The peak level was reached within 3–16 minutes in dogs that received an oral administration of 15 mg/kg methyl paraoxon.

Since orally administered methyl parathion is primarily excreted in the urine, the total oral absorption can be estimated based on the recovery of radioactivity in the urine. Using ^{32}P-methyl parathion, Miyamoto et al. (1963a) reported an approximately 70% recovery of radioactivity in the urine within 48 hours after a single gavage dosing of 1.5 mg/kg ^{32}P-methyl parathion to rats or 50 mg/kg ^{32}P-methyl parathion to guinea pigs. A slightly higher recovery was reported in mice by Hollingworth et al. (1967). Approximately 85% of orally administered 3–7 mg/kg ^{32}P-methyl parathion was recovered in the urine.

A pharmacokinetic study in Wistar rats by Van Dijk (1988a) was available on file in DPR. Data from this study also showed a high urinary recovery (>83%) after oral administration. In this study, male and female rats were either given a single oral intubation of 0.5 or 2.5 mg/kg ^{14}C-methyl parathion or 0.5 mg/kg ^{14}C-methyl parathion (uniformly labeled on the phenol ring) after 14 days of pre-loading with non-radiolabeled methyl parathion. The total recovery of radioactivity was 95.6-104.2%. Adjusted for a 100% mass balance, the average (N=5) percentage of administered radioactivity recovered in the urine within 48 hours were 83.6% (females) and 95.2% (males) at 0.5 mg/kg methyl parathion and 79% (females) and 89.9% (males) at 2.5 mg/kg methyl parathion. The urinary recovery after 14-day pre-loading was in the same range for the males (93%) but higher for the females (91.6%). At least 82% of the total urinary excretion was completed by 8 hours of dosing. Approximately 87-95% of the urinary excretion

was in the form of sulphate or glucuronide conjugate of *p*-nitrophenol. Adjusted for 100% recovery, the 48-hour radioactivity recovered in the feces was 3.3-9.6% of the administered activity. At the end of the 48 hours, very little radioactivity was left in the intestinal tract (up to 0.3%), carcass (up to 0.3%), and organ/tissues (up to 0.1%). Less than 0.01% was recovered in the expired air in males that received 2.5 mg/kg methyl parathion.

The oral absorption can also be estimated by comparing the urinary recovery from intravenous (i.v.) and from oral dosing. The estimated oral absorption was 77-79% in dogs that received 3 mg/kg ^{35}S-methyl parathion (Braeckman et al., 1983) and 67% in dogs that received 15 mg/kg ^{35}S-methyl paraoxon (De Schryver et al., 1987). The same range of values was also reflected in the ratio of the oral and i.v. LD_{50} values derived from within a same report (Table 1 in Section 6.2.1). The ratio of the i.v. LD_{50} to oral LD_{50} was 75-81% in rats from the report by Newell and Dilley (1978) and 76% in mice from the report by Miyamoto et al. (1963b).

III.A.1.b. Distribution

Information on the distribution of methyl parathion and its metabolites to tissues and organs of laboratory animals is available in the open literature. Studies in rats and guinea pigs revealed that methyl parathion readily crossed the blood-brain barrier. Transplacental transport of methyl parathion has also been reported in rats and in an *in vitro* human placental perfusion study. No significant amount of methyl parathion or its oxidated analogue was detected in milk and meat of goats or hens and the eggs of hens 8 hours after receiving oral administrations of methyl parathion.

Tissues and organs: Braeckman et al. (1983) studied the pharmacokinetics of methyl parathion in dogs that received 1, 3, 10 or 30 mg/kg methyl parathion intravenously. A correlation analysis of serum concentration per unit dose over 30 hours revealed no dose dependency within the range of methyl parathion tested, including the lethal level of 30 mg/kg. The time-course of serum concentrations of six dogs that received 10 mg/kg methyl parathion can be described by a quadratic or cubic polynomial equation. Except for one dog that did not yield harmonic estimates, the mean terminal half life ($t_{½}$) was 7.2 hours (ranging from 6.6 to 8.8 hours), and the mean volume of distribution was 9.6 *l*/kg (ranging from 4.6 to 12.8 *l*/kg). The authors speculated that the large volume of distribution could be due to high tissue distribution in a peripheral compartment despite the extensive plasma protein binding. Based on the comparison of the area-under-the-curve in plasma concentration-time plots following i.v. injection, Braeckman et al. (1983) reported a relatively lower systemic availability in dogs following oral exposure. The concentration of methyl parathion in the hepatic vein was much lower than in the femoral artery. The authors speculated that high hepatic extraction might have contributed substantially to the low systemic availability after oral exposures (Braeckman et al., 1983).

Methyl parathion has been detected in various tissues of animals after exposure. Within 2.5 minutes after an i.v. administration of ^{32}P-methyl parathion (>98% pure) to rats (at 15 mg/kg) and guinea pigs (at 20 and 40 mg/kg), the radiolabel was detected in many tissues, among which the liver, lung, kidney, brain, and heart had the highest radioactivity (Miyamoto, 1964).

Recently, Abu-Donia's group reported results on the absorption, metabolism and excretion of repeated oral doses of methyl parathion in hens (Abu-Qare et al., 2001a). A 2 mg (2μCi/kg/day) of [^{14}C]methyl parathion in corn oil was given by gavage to adult hens for 10 days. This oral dosing was used to resemble the effect of methyl parathion following chronic exposure. The applied dose corresponded to 1% of the lowest lethal single oral dose in chickens (200 mg/kg)

and 14% of the rat oral LD_{50}; and did not cause cholinergic toxicity. Seven groups of 5 hens were used for each time interval (1 through 48 h after the last dose). After the last dose, the highest concentration of radioactivity was detected in the plasma, kidney, liver and brain. Methyl parathion was the major compound identified in tissues and the metabolite p-nitrophenol was present in the liver and kidney. Methyl paraoxon was below the detection limit in all analyzed tissues. At the end of the 10-day treatment, 99% of the total applied cumulative dose was recovered in the combined fecal-urine excreta. The excreted radioactive material was composed of conjugated metabolites including water-soluble metabolites, bound hot acid hydrolysates and glucuronide and sulfate conjugates of p-nitrophenol. The half-life of the elimination of methyl parathion from plasma was 17.5 h. The observed elimination rate in hens was slower compared to the half-life of methyl parathion elimination of 11h following a single dermal dose of 10 mg/kg in pregnant rats

Blood-brain barrier: Methyl parathion readily crosses the blood-brain barrier. It was detected in the brain of Wistar rats within 6 to 8 minutes after oral dosing at 50 mg/kg and 90 seconds after i.v. injection at 3 mg/kg (Yamamoto et al., 1983). In rats that received 1.5 mg/kg ^{32}P-methyl parathion via gavage, peak concentrations in both brain and blood (whole) were reached at 3 hours after dosing (Miyamoto et al., 1963a). Similarly, in guinea pigs that received 50 mg/kg ^{32}P-methyl parathion via gavage, the peak concentrations in both brain and blood (whole) were achieved at 1 hour of dosing (Miyamoto et al., 1963b).

Transplacental transport: Transplacental transport of methyl parathion has been studied in rats. A reduction of brain ChE was detected histochemically in fetal brain of pregnant Holzmann rats given a single i.p. injection of 4-6 mg/kg methyl parathion (ethanol-propylene glycol vehicle) on day 9 or 15 of gestation (Fish, 1966). Methyl parathion was detected in both, the placenta and fetal liver, brain, and muscle tissues following oral administrations to pregnant rats (Ackermann and Engst, 1970). In an *in vitro* human placental perfusion study with parathion and methyl parathion, Benjaminov et al. (1992) reported the inhibition of placental AChE and the presence of "parathion" in both the placental tissue and the fetal reservoir. Unfortunately, the report did not differentiate between "parathion" and "methyl parathion" in the residue analysis by gas chromatography. It may be assumed that residues of "methyl parathion" instead of "parathion" were detected since the report specified that the former was used as an internal standard for residue extraction.

Milk, meat, and eggs: USEPA has not established tolerances for methyl parathion in milk, meat, and eggs (CFR, 2001). Neither does the Codex Committee for Pesticide Residues establish maximum residue limits (MRLs) for these commodities. Tolerances and MRLs are the highest level of residues permitted to be present in agricultural commodities. Concerns of the widespread use of OPs in the livestock industry in Portugal prompted Lino and Silveira (1992) to monitor the residues of *cis*-mevinphos, methyl parathion, and paraoxon in 25 milk samples taken from commercial circles. No residues of mevinphos or methyl parathion were detected (detection limits of 0.5 ppb for *cis*-mevinphos, 1.0 ppb for methyl parathion). Of the 25 samples, 22 had residues of paraoxon ranging from 1.5 to 8.7 ppb (ave. 3.6 ppb).

Three animal residue studies on methyl parathion are available: two residue studies by Van Dijk were conducted in hens (Van Dijk, 1988b) and in goats (Van Dijk, 1988c), and one study by Baynes and Bowen (1995) was conducted in goats. In the two studies by Van Dijk (1988b, 1988c) using ^{14}C-methyl parathion, radioactivity in tissues and fluids was expressed as the equivalent amount of the parent compound. Samples of chicken eggs and goat milk were

collected at two intervals daily; 8 hours after dosing and prior to the next dosing. Blood samples were taken at various intervals. In the hen study (Van Dijk, 1988b), laying hens were intubated with 0.5 mg/kg ^{14}C-methyl parathion for 1 or 3 days. The highest plasma radioactivity was noted 4 h after a single dosing. The total average radioactivity in edible portions and in the blood of 5 hens was approximately 2% of the total administered radioactivity. The highest radioactivity of 0.03 μg/g in eggs was found after the 3rd dosing. The level was less than 0.1% of the administered radioactivity. In the goat study, one 60 kg lactating goat was intubated with a mean daily dose of 0.58 mg/kg/day ^{14}C-methyl parathion for 3 days and sacrificed one hour after the last dosing (Van Dijk, 1988c). The highest plasma concentration of 0.174 μg/g was noted 1 h after the first dosing. The highest radioactivity of 0.036 μg/g in the milk was found 8 h after the second dosing. The respective radioactivities in the milk prior to the second and third dosings were 0.008 and 0.012 μg/g. Desmethyl paraoxon and amino methyl paraoxon each constituted approximately 34-38% of the total radioactivity in the milk 8 hours after the second dosing. Assuming a daily milk production of approximately 2 liters, the radioactivity in milk was less than 0.2% of the total administered radioactivity.

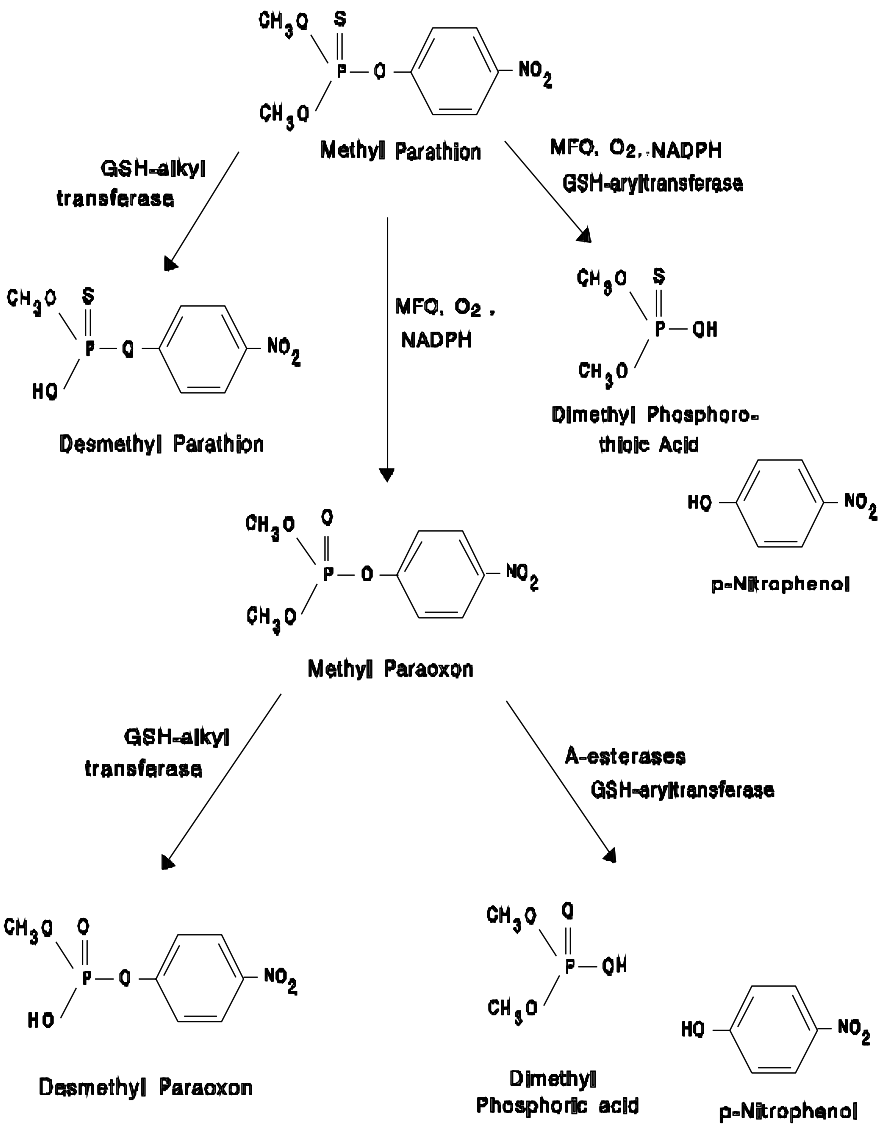
In the study by Baynes and Bowen (1995), four lactating goats received methyl parathion either by gelatin capsules (5 mg/kg/day, 3 days) or through i.v. injection (5 mg/kg, a single dose). Neither methyl parathion nor its metabolites (i.e., methyl paraoxon, methyl phosphate, or methyl thiophosphate) was detected in the milk, plasma or urine. The respective minimum detection limits (MDLs) for these 4 compounds were 0.011, 0.015, 0.074, and 0.204 μg/ml. The average volume of distribution of 5.24 l/kg was determined from the 4 goats that received the i.v. injection.

III.A.1.c. Metabolism

The major pathways of metabolic transformation for methyl parathion are shown in Figure 1. The parent compound is activated to its oxidated analog (i.e., from methyl parathion to methyl paraoxon) through oxidative desulfuration by the mixed function oxidase (MFO), or cytochrome P450, system (Hollingworth et al., 1967; Menzie, 1969; Murphy, 1982; Rao and McKinley, 1969). The oxidative products, not the demethylation product, were shown to inhibit ChE (Rao and McKinley, 1969). Oxidative activation has been demonstrated using cellular preparations from the liver and brain and *in situ* in the lung (Forsyth and Chambers, 1989; Lessire et al., 1996). Alternatively, a recent study using partially purified rat brain preparation, de Lima et al. (1996) demonstrated the activation of methyl parathion through a pathway that did not involve the Cytochrome P450 system. The activated product, capable of inhibiting AChE, appeared to be structurally very similar to methyl parathion. The authors speculated that it could be a methyl parathion isomer.

Detoxification of methyl parathion and methyl paraoxon is accomplished through dearylation or demethylation by glutathione (GSH)-dependent aryl- or alkyl-transferases. It is interesting to note that although demethylation might be an important route of detoxification for methyl parathion and methyl paraoxon, the closely related ethyl parathion and ethyl paraoxon showed very little dealkylation (Benke and Murphy, 1975; Benke et al., 1974; Hollingworth et al., 1967). GSH-dependent demethylation has also been demonstrated in an *in vitro* study with human placenta (Radulovic et al., 1986; 1987). Dearylation of methyl parathion through Cytochrome P450-mediated oxidation, dearylation of methyl paraoxon through hydrolysis by arylesterases (A-esterases or paraoxonase) and/or GSH-dependent aryltransferase all yield p-nitrophenol.

Figure 1. Major Metabolic Pathways of Methyl Parathion



Comparing the GSH-dependent detoxification and microsomal activation, Rao and McKinley (1969) noted a generally higher activity of demethylation than activation in liver enzyme systems from rats, chickens, guinea pigs, and monkeys. In various experimental species, the *in vitro* methyl paraoxon demethylation catalyzed by GSH-transferases had considerably higher rates than the rate for either methyl paraoxon dearylation or methyl parathion demethylation (Benke and Murphy, 1975; Benke et al., 1974; Hollingworth et al., 1973; Radulovic et al., 1987; Rao and McKinley, 1969). However, these *in vitro* studies will most likely not be predictive of the complex balance between hepatic detoxification and activation *in vivo* (Anderson et al., 1992; Huang and Sultatos, 1993). For example, studies with diethyl maleate and buthionine biotransformation pathways might not be of great significance *in vivo* because of the preferential distribution of methyl parathion to the hepatocyte membranes in mice (Sultatos and Woods, 1988; Huang and Sultatos, 1993).

When given orally, methyl parathion is expected to undergo considerable first pass metabolism in the liver (Braeckman et al., 1980; Sultatos, 1987). *In vivo* or *in situ* studies would therefore likely be more useful in providing integrated information on the metabolic pathways. Hepatic biotransformation of methyl parathion has been studied *in situ* in perfused livers of rats (Zhang and Sultatos, 1991) and mice (Sultatos, 1987). Based on the appearance of methyl paraoxon in the effluent perfusate, the net biotransformation of methyl parathion in the liver would appear to be activation.

III.A.1.d. Excretion

Studies in rats and mice showed that the metabolites of methyl parathion after oral exposures are almost exclusively eliminated in the urine (Hollingworth et al., 1967; Menzie, 1969; Morgan et al., 1977). The recovery in feces generally represented less than 10% of the administered dose (Miyamoto et al., 1963a; Hollingworth et al., 1967). Dimethyl phosphoric and phosphorothioic acid, desmethyl phosphate, desmethyl phosphorothioate, methyl phosphoric acid, phosphoric acid, and phosphate were identified in the urine of mice within 24 h after oral administration of 3 or 17 mg/kg ^{32}P-methyl parathion (Hollingworth et al., 1967). The relative proportion of these metabolites in the urine varied with doses.

In a study with four volunteers who were given 1 to 4 mg/kg methyl parathion orally, Morgan et al. (1977) reported that the overall elimination of methyl parathion was nearly complete in 24 h. The amount of p-nitrophenol and dimethyl phosphate in the urine correlated well with the exposure to methyl parathion. The excretion rate of *p*-nitrophenol was rapid and nearly complete by the end of 8 hours of exposure. On the other hand, the rate for dimethyl phosphate was more prolonged and peaked at 4-8 h after exposure (Morgan et al., 1977).

III.A.2. Dermal Studies

Dermal contact is the predominant route of occupational exposures from the pesticidal use of methyl parathion. Dermal absorption was evident in the detection of methyl parathion in the blood, *p*-nitrophenol in the urine, and ChE inhibition among agricultural workers (Nemec et al., 1968; Ware et al., 1974). Dermal absorption of methyl parathion was previously evaluated only *in vitro*, using a human skin diffusion cell apparatus (Sartorelli et al., 1997). The movement of methyl parathion across the skin was compared between the acetone vehicle and the water-diluted commercial formulation. The results showed a greater skin absorption from the water

preparation. The respective penetrations after 24 and 48 hours were 1.35 and 3.58% in acetone and 5.20 and 8.99% in water.

Recently, Abu-Donia's group reported for the first time findings on the *in vivo* dermal absorption of methyl parathion (Abu-Qare et al., 2000; Abu-Qare and Abu-Donia, 2000). A single concentration of 10 mg (10μCi) [^{14}C]methyl parathion/kg in acetone was applied to the unprotected skin of pregnant Sprague-Dawley rats at 14-18 d of gestation. This dose corresponded to 15% of the rat acute dermal LD_{50} (67 mg/kg) of methyl parathion and did not cause cholinergic toxicity. Eight groups of 3 rats were used for each time interval (1 through 96 h). The ^{14}C content at the application site was decreased to 50% and 3% of the administered dose after 1h and 96 h, respectively. Most of the absorbed material (91%) was excreted in the urine; 3% was recovered in feces. The highest concentration of radioactivity was detected within 12 h of dosing in the adipose tissue, kidney and liver; considerable amounts were found in brain, placenta and fetus. Methyl parathion was the major compound identified in the plasma and tissues; the metabolite methyl paraoxon was detected in maternal brain and liver and p-nitrophenol was present only in the liver. Together, these results showed nearly complete dermal absorption of methyl parathion in the rat.

A new pharmacokinetic study was submitted to the DPR, which estimated the dermal absorption of methyl parathion in rats, based on the detected amount of para-nitrophenol in the urine (Sved, 2001). [^{14}C]-Methyl parathion in acetone was applied to a shaven area of the back of Sprague-Dawley rats at dose levels of 0.04 and 0.46 mg/kg (25 and 276 μCi). These doses were over 1200 fold lower than the rat acute dermal LD_{50} (67 mg/kg) for methyl parathion. The treatment site was protected with an occlusive cover and the animals (15 male rats/dose) were exposed for 10 hours. For both dose levels, over 80% of the applied methyl parathion were absorbed through the rat skin. The absorbed material was excreted in the urine during the 10-hour exposure period. Approximately 67-92% of the radioactivity in the urine represented unidentified products of para-nitrophenol or para-nitrophenol conjugates. Based on the total amount of para-nitrophenol-related compounds in the urine, the absorbed dose was calculated as 86% and 97% after dermal application of 0.04 and 0.46 mg/kg methyl parathion, respectively. The average dermal absorption of 92% was very similar to the absorption level determined after dermal treatment of pregnant rats with 10 mg methyl parathion (91%, Abu-Qare et al., 2000; Abu-Qare and Abu-Donia, 2000). The principle finding in the *in vivo* dermal studies in rats was that nearly 100% of methyl parathion was absorbed via the skin.

III.A.3. Inhalation Studies

Without proper respiratory protection, inhalation of methyl parathion can also be a significant route of occupational exposure. Hartwell and Hayes (1965) and Newell and Dilley (1978) reported that formulating plant workers protected by respirators had fewer cases of ChE inhibition and poisonings from exposures to methyl parathion.

Data from direct measurements of inhalation absorption are not available. The absorption can be estimated by a comparison of the i.v. LD_{50} and the inhalation LC_{50} derived from within the same report. Newell and Dilley (1978) reported an i.v. LD_{50} of 9–14.5 mg/kg/day and a 1-h inhalation LC_{50} of 257-287 mg/m^3 in rats (see: Table 1 in Section 6.2.1). Using the DPR current default respiratory rate of 0.96 m^3/kg/day (or 0.04 m^3/kg/hr) for rats, the estimated exposure at the inhalation LC_{50} was 10–12 mg/kg (i.e., the LC_{50} multiplied by 0.04 m^3/kg/hr). This level

was within the same range as the i.v. LD_{50}. The inhalation absorption can also be estimated based on the comparison of the exposure levels that would achieve the same level of ChE inhibition. Newell and Dilley (1978) reported a 41% whole blood ChE inhibition (i.e., the inhibition dose at 41%, or the ID_{41}) one hour after either an oral exposure at 11.7 mg/kg or an inhalation exposure at 264 mg/m^3 (see: Table 3 in Section 6.2.2). Using the DPR current default respiratory rate of 0.96 m^3/kg/day (or 0.04 m^3/kg/hr) for rats, the estimated inhalation exposure was 10.6 mg/kg (i.e., 264 mg/m^3 multiplied by 0.04 m^3/kg/hr). This exposure level was also within the same range of the oral exposure level at 11.7 mg/kg. The above two comparisons (i.e., the i.v. LD_{50} versus LC_{50} and the IC_{41} from i.v. versus inhalation routes) support the conclusion that the absorption of methyl parathion through inhalation can practically be considered as comparable to the absorption through the oral route. Therefore, no adjustment of route-specific absorption was necessary in characterizing the risk from inhalation exposure using threshold levels determined from oral studies.

III.A.4. Biomonitoring

Urinary *p*-nitrophenol has been used extensively as an index of occupational exposure to various OP insecticides. The above study by Morgan et al. (1977) in 4 humans supported the use of urinary *p*-nitrophenol levels as a biomonitoring marker of exposure. The amount of urinary p-nitrophenol within 24 hours of exposure represented 7-29% (average 27%) recovery of the 2 or 4 mg/kg ingested methyl parathion. Based on the findings that recovery of *p*-nitrophenol peaked during the first 4 hours and was nearly complete by 8 hours, the authors emphasized the importance of urine sample collection from the beginning of exposure (Morgan et al., 1977). Chang et al. (1997) studied the correlation between the markers of toxicity and the urinary p-nitrophenol levels in Wistar rats that received 0 (corn oil), 1.4, 2.8, 5.6, or 7.0 mg/kg methyl parathion by gavage. The results showed good correlations between methyl parathion exposures and both the plasma ChE inhibition and the level of urinary p-nitrophenol. The authors recommended using p-nitrophenol at 2.0 mg/g creatinine as the biological exposure index for methyl parathion.

In an effort to identify correlates for estimating the exposure resulting from indoor residential contamination scenarios, Estaban et al. (1996) analyzed the investigation records of the illegal indoor applications of methyl parathion during 1991 to 1994 in more than 200 homes in Lorain county, Ohio. The creatinine-adjusted p-nitrophenol level in the urine was positively correlated with the concentrations of methyl parathion in the air ($r = 0.73$) and the residue on indoor contact surfaces ($r = 0.48$). The median urinary *p*-nitrophenol level for children less than 3 years of age was approximately 5-fold higher than the adults. Further data and analysis are needed for quantitatively modeling the residential exposures based on the air and surface monitoring data. Meanwhile, USEPA issued guidelines in 1997 specifically for responding to methyl parathion contamination due to the illegal indoor applications. Urinary level of p-nitrophenol was established in the guidance as the prime determinant for temporary relocation of residents under the Superfund cleanup programs.

III.B. ACUTE TOXICITY

Summary: Acute toxicity studies are parts of the battery of toxicity studies required for the registration of pesticides in California. These studies were conducted primarily for establishing the median lethal dose (LD_{50}) or concentration (LC_{50}) and determining the toxicity category of the technical grade and the formulations. Depending on the dose range used in the test, it may be possible to establish an acute NOEL (No-Observed-Effect Level) from these limited studies. In risk assessment, NOEL has commonly been used in delineating the threshold dose for non-oncogenic effects. The NOEL is the experimentally determined highest dose at which no effects were observed.

A determination of the critical acute NOEL for risk assessment is not limited to the selected studies presented in this section. Toxicological studies designed for evaluating a specific type of toxicity (e.g., developmental toxicity) may also be useful for identifying acute NOELs based on findings reported shortly after the onset of exposure and/or endpoints that can potentially result from a single (e..g, teratological effects) or short-term of exposure. Since neurotoxicity is the predominant effect of methyl parathion, the toxicity thresholds established from neurotoxicity studies (Section 13.) are particularly pertinent. The selection of the critical acute NOEL for characterizing the risk is presented in Section IV.A.2. **RISK ASSESSMENT - HAZARD IDENTIFICATION.**

In addition, to the required studies, findings published in the open literature also provided pertinent information for risk assessment considerations, specifically regarding the patterns of ChE inhibition and the extent of variation in sensitivity with respect of age.

III.B.1 Acute Toxicity in Animals

III.B.1.a. Median lethal dose and toxicity category

The median lethal doses (LD_{50}) or median lethal concentrations (LC_{50}) are listed in Table 1 for methyl parathion and in Table 2 for methyl paraoxon. Methyl paraoxon is more acutely toxic than its parent compound. The magnitude of difference in toxicity may be estimated by comparing the LD_{50} values for methyl parathion and methyl paraoxon as determined from a given study having the same experimental protocol as well as route of exposure. The comparison revealed that methyl paraoxon is more potent by 6- to 8-fold in rats, 1.5-fold in mice, and 5-fold in guinea pigs. In general, the values of LD_{50} or LC_{50} of methyl parathion and methyl paraoxon are lower for rats than for other species. The overall database in Tables 1 and 2 indicated that among the species tested, females appear to be either equally or less susceptible than males.

Based on the LD_{50} and LC_{50}, technical methyl parathion (80% pure) is a Category I oral toxicant (oral $LD_{50} < 50$ mg/kg), Category II inhalation toxicant (4-hour inhalation LC_{50} at or below 500 mg/m^3 but greater than 50 mg/m^3), Category IV eye irritant (caused conjunctival redness in rabbits that was cleared by 48 hours) and a category IV dermal irritant (caused erythema in rabbits that was cleared by 48 hours). Results of patch tests for contact dermatitis conducted among 200 subjects that were either non-, ex-, or current- agricultural workers, were negative with methyl parathion (Lisi et al., 1986).

III.B.1.b. Cholinesterase Inhibition

The inhibitions of ChE activity associated with acute methyl parathion exposure in various species are summarized in Table 3. Although the inhibition of ChE is extensively documented, in the absence of cholinergic signs of toxicity, the toxicological significance of the inhibition of ChE is not obvious. The effort to characterize any apparent correlation between the plasma and/or RBC ChE inhibitions and clinical signs has been complicated by the variety of protocols for ChE determination used by different investigators. Venkataraman et al. (1994) reported good correlations between RBC ChE and the intensity of clinical signs in adult female Wistar rats that received a single lethal level of methyl parathion at 7.5 mg/kg and without the treatment of either atropine or diazepam.

Table 1. Acute LD_{50} and LC_{50} values for methyl parathion.

SPECIES	LD_{50} or LC_{50}			REFERENCES
	Males	Females	M/F[a]	
Oral (mg/kg)				
Rat	14.0	24.0	-	Gaines, 1969
Rat	24.5	-	-	Miyamoto et al., 1963b
Rat	6.0	-	-	Hirschelmann and Bekemeier, 1975
Rat	12.0	18.0	-	Newell and Dilley, 1978
Rat	11.1	16.0	-	Kronenberg et al., 1978
Rat	4.0	66.3	-	Auletta, 1984a
Rat	2.9	3.2	-	WHO, 1984
Rat	10.8	9.3[b]	-	WHO, 1984
Rat	25.0[c]	62.0[c]	-	Cuthbert and Carr, 1986*
Rat	-		9.2	Galal et al., 1977
Mouse	35.0	-	-	Hirschelmann and Bekemeier, 1975
Mouse	-	-	17.0	Miyamoto et al., 1963b
Mouse	-	-	18.5	Kronenberg et al., 1978
Mouse	-	-	23.0	NIOSH, 1987
Rabbit	10.0	19.4	-	WHO, 1984
Rabbit	-	-	420	NIOSH, 1987
Guinea Pig	417	-	-	Miyamoto et al., 1963b
Guinea Pig	-	-	1270	NIOSH, 1987
Dog	-	-	90	Hirschelmann and Bekemeier, 1975
Inhalation (mg/m³)				
Rat (1-hr)	257	287	-	Newell and Dilley, 1978
Rat (1-hr)	200	-	-	USEPA, 1975
Rat (4-hr)	120	-	-	USEPA, 1975

(Continued)

Table 1. Acute LD_{50} and LC_{50} Values for Methyl Parathion (cont).

SPECIES	LD_{50} or LC_{50}			REFERENCES
	Males	Females	M/F[a]	
Inhalation (mg/m³)				
Rat (4-hr, nose only)	-	-	135[c]	Greenough and McDonald , 1986*
Rat (4-hr)	-	-	34	NIOSH, 1987
Mouse (4-hr)	-	120	-	NIOSH, 1987
Dermal (mg/kg)				
Rat	67	67	-	Gaines, 1969
Rat	110	120	-	Newell and Dilley, 1978
Rat	46	41	-	WHO, 1984
Rat	566[d]	-	-	Ortiz et al., 1995
Rat	-	-	63	NIOSH, 1987
Mouse	-	-	1200[e]	Skinner and Kilgore, 1982
Rabbit	-	-	350-1180	Deichmann, 1950
Rabbit	-	-	300	NIOSH, 1987
Rabbit	-	-	2000	Auletta, 1984b
Intravenous (mg/kg)				
Rat	9.0	14.5		Newell and Dilley, 1978
Rat	4.1	-	-	Miyamoto et al., 1963b
Mouse	-	-	9.8	NIOSH, 1987
Mouse	-	-	13.0	Miyamoto et al., 1963b
Guinea pig	50.0	-	-	Miyamoto et al., 1963b
Intraperitoneal (mg/kg)				
Rat, weanling	3.5	-	-	Brodeur and DuBois, 1963
Rat, adult	5.8	-	-	Brodeur and DuBois, 1963
Rat	-	7.0	-	DuBois and Kinoshita, 1968

(Continued)

Table 1. Acute LD_{50} and LC_{50} Values for Methyl Parathion (cont).

SPECIES	LD_{50} or LC_{50}			REFERENCES
	Males	Females	M/F[a]	
Intraperitoneal (mg/kg)				
Rat 1 day old	0.75	0.75	-	Benke and Murphy, 1975
12 day old	3.50	3.75		Benke and Murphy, 1975
23 day old	4.66	5.66	-	Benke and Murphy, 1975
37 day old	6.90	7.60	-	Benke and Murphy, 1975
60 day old	5.75	8.00	-	Benke and Murphy, 1975
Rat	-	-	3.50	NIOSH, 1987
Mouse	9.30	-	-	DuBois and Kinoshita, 1968
Mouse	11.00	-	-	Benke et al., 1974
Mouse	8.20	-	-	Mirer et al., 1977
Mouse	-	-	8.20	NIOSH, 1987
Sunfish	-	-	>2500	Benke et al., 1974
Subcutaneous (mg/kg)				
Rat	-	-	6.0	NIOSH, 1987
Mouse	-	-	18.0	NIOSH, 1987
Rabbit	-	-	230	Deichman, 1950

* Studies acceptable for fulfilling the acute data requirement for pesticide registration.
a/ Values not sex-specific.
b/ The experimental animals were not fasted.
c/ Technical grade containing 80% methyl parathion. The mass median aerodynamic diameter for the inhalation study by Greenough and McDonald (1986) was 1.95-2.44 μm.
d/ Formulation containing 50% methyl parathion, 47% xylene, and toluene, nitrophenol and nitrobenzene. The LD_{50} is adjusted to the amount of methyl parathion and is based on lethality within 72 hrs. Rat movements were restrained after the dermal application.
e/ Mice were exposed via both feet; a protocol generally results in lower toxicity when compared to treatment on shaved backs, presumably due to the greater cuticle depth (Skinner and Kilgore, 1982).

Table 2. Acute ID_{50} Values for Methyl Paraoxon.

SPECIES	LD_{50} or LC_{50}			REFERENCES
	Males	Females	M/F[a]	
Oral (mg/kg)				
Rat	4.5	-	-	Miyamoto et al., 1963b
Mouse	-	-	10.8	Miyamoto et al., 1963b
Guinea Pig	83	-	-	Miyamoto et al., 1963b
Intravenous (mg/kg)				
Rat	0.5	-	-	Miyamoto et al., 1963b
Guinea Pig	2.2	-	-	Miyamoto et al., 1963b
Intraperitoneal (mg/kg)				
Mouse	7.3	-	-	Benke et al., 1974
Mouse	4.0	-	-	Mirer et al., 1977
Sunfish	17.8	-	-	Benke et al., 1974

a/ Values not sex-specific.

Table 3. Cholinesterase (ChE) Inhibition after Acute Exposures to Methyl Parathion and Methyl Paraoxon.

Species/ Sex	Dose/ Exposure	Post Exposure Time	ChE Activity	% of control	Reference
METHYL PARATHION					
Oral (mg/kg)					
Rat (M)	11.7	1 h	Whole Blood	41	Newell and Dilley, 1978
Rat (F)	2.1	1 h	Palsma	50	Murphy, 1980
	2.8	1 h	Brain	50	
	2.5	1 h	Diaphragm	50	
Rat (M)	5.0	6 h	Plasma	44	Enan et al., 1982
		24 h		43	
	5.0	6 h	Brain	86	
		24 h		53	
		48 h		59	
Hen	100	2 days	Brain	15	
Inhalation (mg/m³)					
Rat (M)	264	1 h	Whole blood	41	Newell and Dilley, 1978
Dermal (mg/kg)					
Rat (M)	110	1 h	Whole Blood	16	Newell and Dilley, 1978
	85	6 h	Whole Blood	36	
Rat (F)	85	6 h	Whole Blood	43	Newell and Dilley, 1978
Rat (F)	10.4	12 h	Plasma	50	Murphy, 1980
	8.9	12 h	Brain	59	
	6.9	12 h	Diaphragm	50	
	9.4	12 h	Liver	50	
Rat (F pregnant)	10.0	2 h	Liver	65	Abu-Qare et al., 2001b
		24 h	Plasma	10	
		48 h	Brain	17	
		2 h	Placenta[a]	55	
		12 h	Placenta[b]	58	

(continued)

Table 3. Cholinesterase (ChE) Inhibition after Acute Exposures to Methyl Parathion and Methyl Paraoxon. (continued)

Species/ Sex	Dose/ Exposure	Post Exposure Time	ChE Activity	(% of control)	Reference
METHYL PARATHION					
Fetuses		4 h	Brain	65	Abu-Qare et al., 2001b
		24 h	Brain	48	Abu-Qare et al., 2001b
		12 h	Plasma	12	
Rat (F)	6.25	48 h	Whole Blood	51	Zhu et al., 2001
	12.50	48 h	Whole Blood	77	
	50	1 h	Whole Blood	88	
Mouse (M)	950[c]	24 h	Plasma	50	Skinner and Kilgore, 1982
	550[c]	24 h	RBC	50	
Intravenous(mg/kg)					
Rat (M)	6.6	1 h	Whole blood	24	Newell and Dilley, 1978
Rat (M)	1.8	1 h	Plasma	50	Miyamoto et al., 1963b
Rat (M)	2.1	1 h	Brain	50	Miyamoto et al., 1963b
Guinea Pig (M)	24.0	1 h	Plasma	50	Miyamoto et al., 1963b
	28.0	1 h	Brain	50	
Dog	10.0	30 min	Plasma	40	Braeckman et al., 1980
	30.0	30 min	Plasma	25	
Subcutaneous (mg/kg)					
Rats (M); 3 months old	7.6	4 h	Plasma	50	Pope and Chakraborti, 1992
	8.8	4 h	Brain	50	
Rats (M/F) 7 days old	0.9	4 h	Plasma	50	
	1.0	4 h	Brain	50	
Intraperitoneal (mg/kg)					
Sunfish	200	24 h	Brain	50	Benke et al., 1974
	600	24 h	Muscle	50	

(continued)

Table 3. Cholinesterase (ChE) Inhibition After Acute Exposures to Methyl Parathion and Methyl Paraoxon (continued).

Species/ Sex	Dose/ Exposure	Post Exposure Time	ChE Activity	(% of control)	Reference
METHYL PARAOXON					
Intravenous (mg/kg)					
Rat (M)	0.4	1 h	Plasma	50	Miyamoto et al., 1963b
	0.3		Brain	50	
Guinea (M)	2.0	1 h	Plasma	50	Miyamoto et al., 1963b
Pig	1.5		Brain	50	
Intraperitoneal (mg/kg)					
Sunfish	6.8	24 h	Brain	50	Benke et al., 1974
	11.5	24 h	Muscle	50	

a/ Placental butyrylcholinesterase activity (BuChE)

b/ Placental acethylcholinesterase activity (AChE)

c/ Mice were exposed via both feet; a protocol which generally results in lower toxicity when compared to treatment on shaved backs, presumably due to the greater cuticle depth (Skinner and Kilgore, 1982).

III.B.3. Age-Related Sensitivity

Benke and Murphy (1975) studied the age-related differences in the oxidative activation and cleavage of methyl parathion in the liver homogenate from male and female Holtzman rats. The ratio of the oxidative detoxification to the activation of methyl parathion appeared to differ by age. The ratio ranged from approximately 0.4 for 1 day old rats to approximately 1.8 for 56-63 day old rats. The increase in detoxification with age was also reported for all other detoxification mechanisms and correlated well with the age-dependent increase in the LD_{50} (see: Table 1).

The extent of the age-related sensitivity to methyl parathion can be estimated by the differences in the LD_{50} and the ED_{50} for ChE inhibition in rats. The LD_{50} via intraperitoneal injection reported by Benke and Murphy (1975) (Table 1) showed as high as approximately 10-fold greater sensitivity in 1 day old neonates than in 37–60 day old Holtzman rats. The plasma and brain ChE inhibition ED_{50} from subcutaneous administration reported by Pope and Chakraborti (1992) (Table 3) showed an approximately 8- to 9-fold greater sensitivity in 7-day old neonates than in 3 months old Sprague-Dawley rats.

A greater than 2-fold difference in age-related sensitivity was also demonstrated in a subcutaneous dosing study by Pope et al. (1991). Greater than 79% of brain ChE inhibition was detected in 7 days old neonates at 7.8 mg/kg while a similar level of brain ChE inhibition was observed in 80-100 days old rats at 18 mg/kg. The authors noted, however, that the recovery of brain ChE level after exposure was faster in neonates than in the adults. Four days after the exposure, neonate brain ChE returned to approximately 80% of the controls while adult brain ChE remained at approximately 40% of the controls.

Recently, a developmental neurotoxicity study was completed for methyl parathion, which allowed a comparison between the ChE inhibition in immature and adult rats (Section III I. *DEVELOPMENTAL NEUROTOXICITY*). Based on the ChE inhibition in the brain, immature rats were over 3-fold more sensitive than the adults after repeated exposure to 0.3 mg/kg/day methyl parathion (Beyrouty 2002c). Based on the ChE inhibition in the erythrocytes, the immature rats were 2-fold more sensitive than the adults. Following acute exposure to 0.3 mg/kg/day methyl parathion, the ChE activities in the brain and the RBC of immature rats was inhibited 18% and 31%, respectively. However, the relative sensitivity could not be determined, because the brain and in the RBC ChE activities in adult rats were not reduced (Beyrouty 2002c).

The specific toxicities of methyl parathion resulting from *in utero* and/or postnatal exposures are collectively presented in Section III.G. *DEVELOPMENTAL TOXICITY and* Section III.I *DEVELOPMENTAL NEUROTOXICITY*.

III.B.4. Thresholds for Acute Toxicity

The database for delineating a threshold for acute (one to several days) toxicity is very limited. One relatively cursory study in humans is available for estimating a threshold for acute toxicity based on ChE inhibitions. Several acute toxicity studies in rats were available. However, most of these studies were conducted for determining the median lethal dose (or concentration) using a high dose range and had limited toxicological observations. In these cases, the lowest test dose

was the lowest-observed-effect level (LOELs) and a NOEL could not be directly established within the studies.

III.B.4.a. Studies in Humans

Rider et al. (1969) conducted a study among prisoners to determine the RBC and plasma ChE inhibitions from the exposures to methyl parathion. Five subjects (body weights not given) received daily oral doses of methyl parathion in capsules, and two subjects receiving corn oil served as controls. Methyl parathion was given in increasing doses for 33 days, beginning at 1 mg/day. The dose was incrementally increased by 0.5 mg/day/subject starting on day 2 of the study and continuing through day 29 (15 mg/day/subject dosage). The dose was subsequently increased by 1 mg/day until a maximum of 19 mg/day/subject on day 33. Before the start and at the end of the study, each subject received a physical examination and had blood counts and clinical chemistry tests including urinalysis and prothrombin time determination. Plasma and RBC ChE levels were measured twice weekly throughout the pre-test (approximately 30-day), test, and post-test periods (unspecified). No signs of toxicity or changes in blood counts or clinical chemistry were detected among the test subjects. Although a 15% decrease in plasma ChE activity was noted at 11 mg/day (day 21), no depression of plasma ChE activity was noted in any of the subsequent higher dose levels (11.5 - 19 mg/day). Based on the lack of ChE inhibition at the final highest dose tested, the 19 mg/day could be considered the NOEL. Assuming a body weight of 70 kg, the dose at the NOEL was 0.27 mg/kg/day. A tolerance to methyl parathion acute toxicity might have developed over the 33 days of incremental dosing. Consequently, the NOEL may not represent a level that will not elicit a cholinergic response when it is given to an individual who has not previously been exposed to methyl parathion.

Rodnitzky et al. (1978) examined the neurobehavioral effects of methyl parathion in humans. Two males, ages 53 and 62 (body weight not reported), were given methyl parathion at 2 mg/day for 5 days and, after a 1 to 8 week rest interval, again at 4 mg/day for 5 days. Assuming a default body weight of 70 kg, the respective estimated doses at 2 and 4 mg/day were 0.029 and 0.057 mg/kg/day. No significant effects were noted for plasma and RBC ChE. The respective levels of plasma and ChE activities were 118 and 103% at 0.029 mg/kg/day and 120 and 95% at 0.057 mg/kg/day (see Table 4). Neither were there effects in several neurobehavioral tests (verbal recall, visual retention, information processing time, language, vigilance, proprioception, anxiety, and depression). Compared to the studies by Rider et al. (1969), this study had more elaborate toxicity evaluations; however, the dose level was much lower. The highest tested dose of 0.057 mg/kg/day could be considered a NOEL for adult humans, albeit with substantial uncertainties due to the small sample size and the unusual age range for test subjects.

III.B.4.b. Oral Studies in Animals

Galal et al., (1977) conducted a study in which 5 rats/sex/dose were administered a single oral dosing of methyl parathion (50% pure, impurities unknown). The toxicity of Sevin and malathion were also included in this study. Not specifying the particular pesticide, the authors reported the following clinical signs: salivation, “shivering”, chromodacryorrhea, exophthalmos, hyperreflexia, respiratory distress (“labored breathing”, “respiratory convulsions”). Methyl parathion at 8.0 - 28.5 mg/kg was reported as the “fatal range” and 5.3 mg/kg as the “maximal tolerated dose”. Based on the very brief report, it could be assumed that the 5.3 mg/kg dose level was the LOEL for this experiment.

In the study conducted by Auletta (1984a), groups of 5 male and female CD rats were exposed to a single oral dose of methyl parathion (purity not stated) at 1, 5, or 20 mg/kg. Clinical signs of toxicity such as nasal and oral discharge, wet rales, and apparent decrease in general activity were observed at 1 mg/kg (incidence not specified). Additional effects reported at 5 and 20 mg/kg were: mortality (5 of the 10 rats at 5 mg/kg and all rats at 20 mg/kg), tremors, ataxia, hypopnea, hypoactivity, and ocular discharge. An apparent deficiency in this study for establishing a NOEL and LOEL for clinical signs is that a control group was not included. However, the effects observed at 1 mg/kg are generally recognized as signs of cholinergic toxicity. Therefore, the dose of 1 mg/kg can be considered as a LOEL from this study.

A study by Cuthbert and Carr (1986) was accepted for filling the acute oral data requirement for pesticide registration. Groups of 5 male and female Sprague-Dawley rats were administered technical methyl parathion (80% pure) at 20, 30, or 40 mg/kg (males), or 40, 70, or 100 mg/kg (females) via gavage in a corn oil vehicle. One day after dosing, one rat died at 20 mg/kg. Hypokinesia, piloerection, soiled coat, and hemodacryorrhoea were observed in the remaining 4 males. The lowest dose of 20 mg/kg (or 16 mg/kg adjusted for 80% purity) can be considered as the LOEL from this study.

In a study by Schulz et al. (1990) that evaluated the behavioral effects in male Wistar rats, groups of 20 male Wistar rats were administered 0, 0.22, or 0.44 mg/kg/day methyl parathion (60% pure, impurities unknown) via gavage. The report did not indicate whether the doses given had been adjusted for the purity of the test material. Although the treatment period lasted 6 weeks, the report mentioned an increased mortality in the treatment groups (15% and 20% respectively at 0.22 and 0.44 mg/kg/day, compared to 5% in the controls) only during the first week of dosing. The results of behavioral tests after subchronic exposures were presented in Section III.H. **NEUROTOXICITY.** The 0.22 mg/kg/day can be considered as an acute LOEL based on the increased mortality within the first week. This is the lowest acute LOEL among the five studies presented in this section. However, uncertainty exists regarding the use of this value in delineating a threshold dose for characterizing the risk of acute exposures to methyl parathion. One area of the uncertainty was the lack of information regarding the potential contribution of the impurities to the overall toxicity. Unfortunately, the studies by Galal et al. (1977) and Auletta (1984a) were also deficient in this regard. Another area of uncertainty was associated with the lack of information regarding the circumstances under which death of animals occurred. Although the methyl parathion-treated groups had higher mortality rates, death also occurred in the control groups (tap-water controls and "handled-only" controls). Moreover, all death appeared to occur only during the first week of dosing. The lack of detail in reporting the acute toxicity may have been because it was not the focal emphasis of the study.

III.B.4.c. Inhalation Toxicity Studies

A study by Greenough and McDonald (1986) was accepted for filling the acute inhalation data requirement for pesticide registration. Groups of 5 male and female Sprague-Dawley rats were exposed to 0.108, 0.168, or 1.134 mg/l technical grade methyl parathion (80% pure) in the air for 4 hours. The respective mass median aerodynamic diameter and the geometric standard deviation (in parenthesis) were 1.95(2.00), 1.96(1.97), and 2.44(1.84) μm. At least 86% of the particles were below 4.7 μm. At 0.108 mg/l, two of the 5 males died within 2 hours of exposure. Clinical signs observed in the surviving male and female rats included: salivation, subdued and hunched appearance, tremors, prostration, depression and labored respiration, hypokinesia, and

opacity in the eye. The 4-hour inhalation exposure at the lowest level of 0.108 mg/*l* technical grade methyl parathion (or 96 mg/m^3 methyl parathion) can be considered as the LOEL from this study. Using the default breathing rate of 0.96 m^3/kg/day (or 0.16 m^3/kg in 4 hours) for rats and a 100% inhalation absorption, the estimated dose at the LOEL was 15.4 mg/kg (96 mg/m^3 x 0.16 m^3/kg).

III.B.4.d. Dermal Toxicity Studies

The effects of a single dermal dose of methyl parathion on the AChE and BuChE activities were examined in pregnant rats (Abu-Qare et al., 2001b). Methyl parathion (10 mg/kg in acetone) was applied to the protected area of the preclipped skin of the back of pregnant Sprague-Dawley rats. This dose corresponded to 15% of the rat dermal LD_{50} and did not produced acute toxicity or change in body or tissue weights. Methyl parathion was used alone or in combination with chlorpyrifos. Rats treated on day 18 of gestation were sacrificed at 1, 2, 4 and 12 h after dosing; rats treated on day 17, 16, 15 and 14 of gestation were sacrificed at 24, 48, 72 and 96 h after dosing, respectively. Five treated and five control rats (treated with the vehicle only) were used for each time point. Within 1 h, methyl parathion produced over 50% reduction in the activity of the maternal brain AChE, whereas significant inhibition of the fetal brain AChE activity (about 40%) was observed after 4 h of treatment (Table 3). Maximum inhibition of the brain enzyme activity was detected at 24 h and 48 h in the fetuses and the maternal animals, respectively; the enzyme activity remained significantly reduced through 96 h of dosing, compared to controls. Application of methyl parathion produced a drastic reduction of the BuChE activity (88-90%) in the maternal and fetal plasma. The plasma BuChE activity remained significantly lower in the maternal animals 96 h after treatment, but recovered in the fetuses to the control levels by 48 h. The faster recovery of fetal BuChE was attributed to the de novo synthesis of ChE by fetal tissues compared to maternal tissues. Methyl parathion had a marked effect on the maternal liver BuChE activity and on the placental AChE and BuChE (35-55% inhibition). In all of the tissues examined, methyl parathion was a more potent ChE inhibitor than chlorpyrifos. The rapid inhibition of the ChE enzyme activities was attributed to the rapid dermal absorption and subsequent distribution of methyl parathion in maternal and fetal tissues.

Toxicological and behavioral studies were carried out to characterize the toxicity of single or repeated dermal doses of methyl parathion in rats (Zhu et al., 2001). The rats were observed for signs of general and cholinergic toxicity (e.g. decline in body weight, tremors, salivation and lacrimation), and the ChE activity was measured in blood samples. Potential alterations in the motor function were assessed by the open field test (for spontaneous locomotor activity) and by the rota-rod treadmill (for neuromuscular coordination). The effects of methyl parathion on the cognitive function were evaluated by the step-down inhibitory avoidance learning test. Methyl parathion was applied to a shaven area of the back of adult female Sprague-Dawley rats (175-200g, 3 animals per group). For a single dermal exposure the rats were treated with 6.25, 12.5 or 50 mg/kg methyl parathion dissolved in ethanol. These doses corresponded to 10%, 20% and 75% of the rat acute dermal LD_{50} (67 mg/kg) of methyl parathion. For repeated dermal exposures, the animals were exposed to low doses of methyl parathion (0.1 and 1 mg/kg/day) for 28 days. The measurements of the ChE activity and the behavioral tests were performed before and 2, 7, 14, 21 and 28 days following the single dermal exposure to methyl parathion; and before and 1, 7, 14, 21 and 28 days after the onset of the repeated treatment.

Single dermal dose. Within 24 h, the highest single dermal dose (50 mg/kg) induced severe acute toxicity and about 17% decline in body weight, which was concomitant with 88% inhibition of plasma ChE activity (Table 3), total loss of spontaneous locomotor activity and neuromuscular coordination. All animals were dead within 72 h. The lower single doses (12.5 and 6.25 mg/kg) did not cause acute toxicity and had no effects on rat cognitive function. However, the dose of 12.5 mg/kg produced about 10% loss of body weight, 77% reduction in the blood ChE activity within 48 h, 50% decrease in spontaneous locomotor activity and 30% loss of neuromuscular coordination. Effects on the motor function were not observed after a single dermal dose of 6.25 mg/kg methyl parathion in rats; however, this dose caused 55% inhibition of the blood ChE activity in 48 h (Table 3). The toxic effects of the single doses of 6.25 and 12.5 mg/kg were reversible within 14 days of treatment. The lowest dose of 6.25 mg/kg, which induced 55% inhibition of the blood ChE activity could be considered as the LOEL from this study.

Repeated dermal doses. Animals dosed for 28 days with 0.1 or 1 mg/kg/day methyl parathion did not show signs of cholinergic toxicity. Repeated dermal administration of 1 mg/kg/day caused a slight decrease in body weight and 50% reduction of blood ChE activity after 7 days of treatment. The body weight of the treated rats recovered to the control levels over the next 21 days; however, the inhibition of the ChE activity was sustained over the course of treatment. Furthermore, 1 mg/kg/day methyl parathion significantly decreased the locomotor activity and the memory retention of the rats after 28 days of repeated treatment. Together, the results in this study revealed two major findings: *1*) a single dermal exposure to methyl parathion to doses lower than those inducing acute toxicity, could cause a reversible blood ChE inhibition and motor function changes in rats, and *2*) daily dermal exposure to low doses of methyl parathion could result in sustained inhibition of the blood ChE activity and impairment of motor function and memory. Based on the inhibition of the blood ChE activity and impairment of the cognitive and motor functions at 1 mg/kg/day, the dose of 0.1 mg/kg/day could be considered as the NOEL.

III.C. SUBCHRONIC TOXICITY

Two human studies and several subchronic (14 days to 3 months) studies in rats, mice, and dogs were available for review and NOEL determination. Data on ChE inhibition, when available, are presented in Table 4. Included in this section is a brief summary of information on inhalation and dermal toxicities published in foreign languages and cited by the World Health Organization (WHO), USEPA, or Agency for Toxic Substances and Disease Registry (ATSDR).

III.C.1. Oral Studies - Humans

Rider and coworkers conducted two studies (Rider et al., 1970, 1971) with male prisoners on the effects of OPs on ChE inhibition. These studies differed from the 1969 study described under the Acute Toxicity section (Section III.B.4.a. **Studies in Humans**) in that fixed doses instead of increasing doses were administered. Five subjects received daily doses of methyl parathion in capsules at 22, 24, or 26 mg/day for 4 weeks (1970 study) or at 28 or 30 mg/day for 30 days (1971 study). The activities of plasma and RBC ChE were monitored twice weekly. These studies were reported only as abstracts (<200 words) for platform presentations in scientific meetings. Assuming a default body weight of 70 kg, the respective estimated doses for 22, 24, and 26 mg/day were 0.31, 0.34, and 0.37 mg/kg/day. No change in ChE was reported at 22 mg/day. At 24 mg/day (0.34 mg/kg/day), the mean plasma and RBC ChE inhibitions for the 5 subjects were 17 and 22%, respectively. However, only two of the 5 subjects showed ChE inhibitions. The subject having a greater effect had 23 and 55% inhibition on plasma and RBC ChE (Table 4). Based on the ChE inhibition, the subchronic NOEL was 22 mg/day (0.31 mg/kg/day). The NOEL of 0.31 mg/kg/day was used by the USEPA in setting a 10-day drinking water Health Advisory of 0.3 mg/*l*. This was calculated based on a daily drinking water consumption of 1 liter for a 10-kg child and applying an uncertainty factor of 10 to account for the inter-individual variations in sensitivity (USEPA, 1988).

In addition to the endpoints of ChE inhibition, Rodnitzky et al. (1978) examined the neurobehavioral effects in two human test subjects after 5 days of methyl parathion ingestion. The treatment was repeated after 1 to 8 weeks rest intervals. This study was previously described in Section 6.3.1. No effects were noted in this study, however, the dose range was much lower than the studies by Rider et al. described above.

Table 4. Cholinesterase (ChE) Activity Following Subchronic Oral Exposure to Methyl Parathion.

Species	Dose mg/kg/day	Time	ChE Activity (% of Control)						Reference
			Males			Females			
			Plasma	RBC	Brain	Plasma	RBC	Brain	
Humans									
n=5	0.31	4 wk	NA[b]	NA[b]	-	-	-	-	Rider et al., 1970
	0.34		77[c]	45[c]					
	0.37		NA[b]	63[c]	-				
n=5	0.40	30 d	-	(81)[d]					Rider et al., 1971
	0.43			(63)[d]					
n=2	0.029	5 d[e]	118	103	-	-	-	-	Rodnitzky et al,
	0.057		120	95	-	-	-	-	1978
Rats									
n=10	0.2	1 mo	118	70*	-	112	97	-	Daly and Rinehart,
	1.9	-	109	57**	-	71**	67*	-	1980a
	5.7		82*	67*		46**	69		
	0.2	3 mo	92	93	110	107	104	99	
	1.9		77	85	95	61**	88	68*	
	5.7		77	80	26**	32**	75	35**	
Mice									
n=10	27.3(M),25.5(F)	4 wk	35**	86**	-	40**	86**	-	Eiben, 1988a
	56.5(M),37.0(F)		39**	86**	-	24**	84**	-	
	27.3(M),25.5(F)	65 d	37**	90**	33**	26**	88**	39**	
	56.5(M),37.0(F)		23	82	33	16**	90**	42**	
n=10	0.93	4 wk	98	89**	-	96	92	-	Eiben, 1988b
	3.82	4 wk	81**	85**	-	75**	84*	-	Eiben, 1988b
n=10	14.96		23**	80**	-	36**	82*	-	
	0.93	66 d	90*	100	92	92**	98	98	
	3.82		78**	92*	92	75**	93*	100	

(continued)

Table 4. Cholinesterase (ChE) Activity Following Subchronic Oral Exposure to Methyl Parathion (cont.)

Species	Dose mg/kg/day	Time	ChE Activity (% of Control)						Reference
			Males			Females			
			Plasma	RBC	Brain	Plasma	RBC	Brain	
Mice									
n=10	14.9		36**	82**	70**	42**	91**	80**	Eiben, 1988b
Dogs	0.3	6 wk	87	79	-	93	94	-	Underwood
n=4	1.0	-	71	67	-	80	82	-	and Tegeris, 1978
	3.0	-	53*	23*	-	42*	34*	-	
	0.3	3 mo	86	80	113	92	87	114	
	1.0		72*	63*	98	84	64*	98	
	3.0		45*	27*	36*	37*	25*	44*	
	0.03	6 wk	82	100	-	96	100	-	Daly, 1989
n=8[f]	0.30		86	98	-	92	98	-	
	3.0		46**	78*		41**	80**	-	
	0.03	13wk	81*	100	92	98	100	92	
	0.30		86	98	100	94	91	100	
	3.0		53**	82	46**	47**	77**	50**	

Levels of statistical significance as compared to the controls: * for $p \leq 0.05$; ** for $p \leq 0.01$. The report by Underwood and Tegeris (1978) provided statistical significance only for $p \leq 0.05$.

a/ The concentration in the diet was either given in the report or converted to mg/kg/day based on food intake data.

(i) Dose levels per body weight in human studies were estimated based on a default body weight of 70 kg for an adult. The corresponding dosing levels were 22, 24 and 26 mg/day for the study by Rider et al. (1970), 28 and 30 mg/day for the study by Rider et al. (1971), and 2 and 4 mg/day for the study by Rodnitzky et al. (1978);

(ii) Dose levels for the study by Daly and Rinehart (1980a) corresponded to 2.5, 25, and 75 ppm in the diet.

b/ NA, not available. In an abstract for a platform presentation, the authors stated as "produced no effects" or "not significantly altered".

c/ Represented the lower of the 2 subjects who showed ChE inhibition.

d/ The ChE data for individuals was not given in an abstract for a platform presentation. Values given in the parenthesis represented the average of 5 subjects, some of which reportedly had no effects.

e/ The 5 day treatment period was repeated after 1 to 8 week rest interval. Data of 2 subjects.

f/ Data on brain ChE was from the pons, with n=4. No ChE effect was noted in the cerebellum.

III.C.2. Oral Studies – Rat

In the study by Galal et al. (1977) described in Section III.B.4. **Thresholds for Acute Toxicity**, three groups of albino rats (5/sex/group) were initially administered methyl parathion at 0.37 mg/kg/day, an equivalence of 4% of the acute oral LD_{50} (9.2 mg/kg) determined from the same study. During the 36 days of dosing, the doses were successively increased by a magnitude of 1.5 geometric progressions (a stepwise dose increase by a factor of 1.5) every fourth day for each group. According to the description on dose increment, the final dose level would be 32 mg/kg/day. Changes in hematological parameters were noted at the end of the study. These included a decrease in RBC counts (approximately 45%), changes in differential leukocytic counts (increases in neutrophils and lymphocytes and decreases in monocytes and eosinophils), and an increase in coagulation time (up to 36%). The studies demonstrated a tolerance to the cholinergic toxicity of methyl parathion with the successive increase in dose. The pattern of dosing precluded the determination of a NOEL or LOEL from this study.

In a 1979 range-finding study by the National Cancer Institute (NCI, 1979), groups of 5 male and female Fischer F344 rats were fed diets containing 0, 10, 20, 30, 40, or 50 ppm methyl parathion (94.6% pure) for 7 weeks followed by a one week observation period. The survival and body weights were reported. All males survived the treatments. The respective survival for the females from the controls to the high dose group were 5/5, 4/5, 5/5, 4/5, 4/5, and 3/5. The microscopic examinations were reported as "essentially normal" at 30 to 50 ppm. Approximately 10% body weight decrease was noted at 40 and 50 ppm. Based on the one death at the lowest tested dose, the LOEL was 10 ppm. Using a default assumption that the food intake is approximately 5% of body weight, the estimated dose at this dietary level was 0.5 mg/kg/day.

A 3-month feeding study conducted by Daly and Rinehart (1980a) is on file at DPR. Groups of 20 Sprague-Dawley rats per sex were fed diets containing 0, 2.5, 25, or 75 ppm methyl parathion (93.65% pure). Based on food consumption data, the respective estimated doses were 0.2, 1.9, and 5.7 mg/kg/day. At 25 ppm, the respective activities of plasma, RBC, and brain ChE were 61-77%, 85 - 88% and 68-95% of the controls (Table 4). Additional treatment-related changes were noted at 75 ppm (5.7 mg/kg/day). These included decreases in: RBC count (12%, females only), hemoglobin (5-12%), hematocrit (9%, females), and blood glucose (15-23%); increases in alkaline phosphatase (36-84%) and blood urea nitrogen (22%, females only); decreases in body weight gain (20-24%) despite higher food consumption (25-29%); as well as staining of the ano-genital area, tremors, and emaciation. At week 4, one male and 14 females either died or were sacrificed moribund. Gastritis, lymphoid depletion and necrosis (lymph nodes, spleen, and thymus), necrosis of the submaxillary salivary glands, and bone marrow hypocellularity were observed mainly in animals that died during the first four weeks of the study. Based on the plasma, RBC, and brain ChE inhibition (as much as 32% reduction in brain ChE) the NOEL was 2.5 ppm in the diet (0.2 mg/kg/day). Although the RBC ChE inhibition in the male rats was 30% and statistically significant at 1 month, the lack of the same low level of inhibition cast some uncertainties to its pertinence. Based on endpoints other than ChE inhibitions (hematological indices, clinical chemistry, body weight gain reduction, ano-genital stain, tremors, emaciation, and death), the NOEL was 25 ppm in the diet (1.9 mg/kg/day).

In a study by Yamamoto et al. (1982), male Wistar rats were orally administered methyl parathion (98.8% pure), at 0.5, 1.5, 3.0, or 5 μmol per rat (body weight of approximately 100 g), for as long as 10 days. Unspecified cholinergic signs of toxicity and slightly lower body weight

(approximately 95% of the controls, estimated from the figure presented in the report) were reported at 0.5 μmol (1.3 mg/kg/day). Methyl parathion treatments at the two higher doses (1.5 and 3.0 μmol) resulted in the death of all the rats by day four of dosing. The plasma and brain ChE were respectively reduced to 70 and 43% of the controls after a single dosing at 5 μmol/rat; and 76 and 57% after 10 days of dosing at 0.5 μmol/rat. No toxicity observations other than death were included in the report. Based on the brain ChE inhibition, the lowest dose of 0.5 μmol (1.3 mg/kg/day) was the LOEL.

III.C.3. Oral Studies - Mice

In a 1979 range-finding study by the NCI (1979), groups of 5 male and female B6C3F1 mice were fed diets containing 0, 20, 40, 60, 125, 250 or 500 ppm methyl parathion (94.6% pure) for 7 weeks followed by a one week observation period. The survival and body weights were reported. Except for one male at 20 ppm, the remaining males and females survived the treatments up to 125 ppm. The microscopic examinations were reported as "essentially normal" at 125 ppm. Approximately 10% body weight decrease was noted at 40 and 60 ppm. Based on the one death at the lowest tested dose, the LOEL was at 20 ppm. The estimated dose at this dietary level was 2 mg/kg/day.

Four studies are on file at DPR. A pilot study for a 90-day study was conducted by Daly and Rinehart (1979). Groups of 5 CD-1 mice per sex were fed diets containing 0, 25, or 50 ppm (93.65% pure) for 29 days. The respective average doses over the study period were 0, 5.5, and 12 mg/kg/day. No effects were noted in daily physical examinations and postmortem gross necropsy. The only effect reported was a significant body weight reduction at 50 ppm. In the subsequent 3-month study (Daly and Rinehart, 1980b), groups of 15 CD-1 mice per sex were fed diets containing 0, 10, 30, or 60 ppm methyl parathion (93.65% pure). The respective doses were 0, 2.4, 7.6, and 15 mg/kg/day. As in the pilot study, no death, treatment-related clinical signs, treatment-related gross or microscopic changes or lesions were observed. Body weights were reduced by 4-20% in the males and 4-11% in the females at 60 ppm, although food consumption was increased (3-20% in the males and 4-23% in the females). The relative brain weight was increased by 3-10%. Some indices which may be more sensitive, such as ChE, hematology, serum chemistry or urinalysis, were not measured.

Eiben (1988a, b) conducted two 65-66 day range-finding studies in mice. Groups of 10 B6C3F1 mice per sex were fed diets containing methyl parathion (96.8% pure) at 0, 50, or 75 ppm (Eiben, 1988a) or 0, 2, 8, 32, 128, or 400 ppm (Eiben, 1988b). The respective doses at 50 and 75 ppm were substantially different for the males and females; 27.3 and 56.5 mg/kg/day for the males and 25.5 and 37.0 mg/kg/day for the females. The doses for the second study by Eiben (1988b) were similar between the males and females; the average male and female doses at 2, 8, and 32 ppm were 0.93, 3.82, and 14.91 mg/kg/day. At 2 ppm (0.93 mg/kg/day), statistically significant ($p<0.01$) inhibition was noted for RBC and plasma ChE (Table 4). Brain ChE inhibition (23-30%) was significant at 32 ppm. Mice at 50 ppm or higher had been reported as having poor general condition, tremors, rough coats, sunken flanks, and loss of weight. Plasma cholesterol level was significantly elevated in the females at 50 and 75 ppm. Based on the brain ChE inhibition, the NOEL was 8 ppm (3.82 mg/kg/day). However, the lowest tested dose of 2 ppm (0.93 mg/kg/day) was the LOEL based on statistically significant ChE inhibitions of the plasma (male and female rats) and the RBC (male rats).

III.C.4. Oral Studies -Dogs

Williams et al. (1959) conducted a study in which dogs were fed diets containing 5, 20, or 50 ppm methyl parathion for 12 weeks. Plasma and RBC ChE inhibitions reached approximately 25-35% at 20 ppm and 45% at 50 ppm.

One 14-day and two 3-month feeding studies are on file at DPR. In the 14-day range-finding study (Underwood and Tegeris, 1977), groups of two dogs per sex received nominal doses of 0, 2.5, 5.0, or 10 mg/kg/day methyl parathion (94.3% pure) in the diet. The authors reported that vomiting, a possible cholinergic sign of toxicity, occurred in dogs (number not specified) at the high dose starting on the third day. Vomiting also occurred in all dogs at the mid-dose and one dog at the low dose, particularly during the second week of dosing. Food consumption and body weight gain were decreased in the mid- and high doses. Based on vomiting and decreases in body weight gain, the lowest test dose of 2.5 mg/kg/day was the LOEL for this study.

In the subsequent study by Underwood and Tegeris (1978), groups of 4 dogs per sex were fed methyl parathion (94.3% pure) in the diet at 0, 0.3, 1, or 3 mg/kg/day for 3 months. No treatment-related effects on mortality, food consumption, body weight gain, hematology, and gross or microscopic observations were noted. Other than occasional (undefined) vomiting in some test animals (at unspecified dose), the only effect noted was ChE inhibition. The activities of plasma and RBC ChE at the mid- and high dose, and brain ChE at the high dose were decreased (Table 4). Plasma and RBC ChE activities in male and female dogs at 1 mg/kg/day were respectively reduced to 72-84% and 63-64% of controls at the end of the treatment period. The NOEL was 0.3 mg/kg/day based on plasma and RBC ChE inhibition. The NOEL was 1 mg/kg/day based on brain ChE inhibition (at 36-44% of the controls at 3 mg/kg/day). The NOEL of 0.3 mg/kg/day was used by the USEPA in setting a long-term drinking water Health Advisory of 0.1 mg/*l* (USEPA, 1998c). This was calculated based on a daily drinking water consumption of 2 liters for a 70-kg adult and applying an uncertainty factor of 100 to account for the interspecies and inter-individual variations in sensitivity.

In a later study by Daly (1989), groups of 8 beagle dogs per sex were fed methyl parathion (94.9% pure) in the diet at 0, 0.03, 0.30, or 3.0 mg/kg/day for 13 weeks. At the end of the dosing period, 4 dogs per sex per group were sacrificed while the remainders were given a 4 to 6 week recovery period before sacrifice. At 3.0 mg/kg/day, the activities of plasma and RBC ChE were depressed at six and 13 weeks and brain ChE at 13 weeks (Table 4). The ChE activities returned to their baseline levels after the recovery period. Intraocular pressure was decreased in the mid-dose females and high dose males after the recovery period but not at the end of the 13-week dosing period. Anti-ChE agents are known to reduce the intraocular pressure and have been used in the management of glaucoma (Taylor, 1985; Gallo and Lawryk, 1991). The toxicological significance of this effect was not clear, especially also considering the lack of a demonstrated dose-response relationship. Electroretinograms and ophthalmoscopic and microscopic examination of the eyes did not show any remarkable changes. Two dogs at 3.0 mg/kg/day showed dehydration, emaciation and a thin appearance. One low-dose male continued to have a thin appearance throughout the recovery period. Based on the brain ChE inhibition (50-53%), the NOEL was 0.3 mg/kg/day. It is important to note that at the lowest dose of 0.03 mg/kg/day the level of plasma ChE inhibition in the males was consistent at both time points of measurement and was statistically significant at week 13. The NOEL for the eye effects would be 0.03 mg/kg/day.

III.C.5. Dermal Studies – Rat

The toxicity of repeated dermal applications was reported in a study by Dikshith et al. (1991). Groups of 10 female albino rats received 2 mg/kg/day methyl parathion (50 EC, impurities unspecified) to the shaved latero-abdominal areas (10% of body surface area) for 7, 15, or 30 days. Four rats died by the end of 30 days. Other effects included reduced relative liver weight after 7 days of treatment (but not at 15 and 30 days of treatment), and degenerative changes reportedly occurred in the liver, kidney, and brain. Brain and RBC ChE activities were inhibited by 35 and 71% respectively after 30 days of treatment. Based on the effects in the liver, kidney, and brain, the 2 mg/kg/day was the LOEL. However, the lack of detail and possible inconsistencies in the reporting prevents further evaluation of this study. It is interesting to note that the dose of 2 mg/kg/day that resulted in 40% mortality was 23- to 283-fold lower than the LD_{50} values reported for acute exposures (Table 1).

In the study by Zhu et al., 2001 (described in Section III.B.4.c. under **Thresholds for Acute Toxicity),** adult female Sprague-Dawley rats were exposed dermally to 0.1 or 1 mg/kg/day methyl parathion for 28 days. Based on the inhibition of the blood ChE activity and impairment of the cognitive and motor functions at 1 mg/kg/day, the dose of 0.1 mg/kg/day could be considered as the NOEL.

In vivo and *in vitro* experiments were carried out to investigate the effects of repeated dermal doses of methyl parathion on the cholinergic neurotransmitter systems in the brain of rats (Ma et al, 2003). Different brain regions were examined for changes in the AChE activity; and methyl parathion binding to the brain muscarinic receptors was assessed in competitive inhibition studies with the nonselective muscarinic antagonist [^{3}H]quinuclidinyl benzolate, [^{3}H]QNB. Methyl parathion was applied to the unprotected clipped skin on the back of the neck of female Sprague-Dawley rats (about 167 g, 5 animals per group). The rats were treated with 0.1 or 1 mg/kg methyl parathion dissolved in ethanol for 95 consecutive days. These doses corresponded to 0.15%, and 1.5% of the rat acute dermal LD_{50} (67 mg/kg) of methyl parathion. Brain tissues were prepared for 20-22 h after the last administration of methyl parathion.

The AChE activity was measured histochemically using acetylthiocholine iodide as a substrate in the presence of an inhibitor of BuChE. The enzyme activity was quantified based on the optical density of the AChE staining intensities. AChE histochemistry confirmed the previous observation that it was distributed heterogeneously throughout the brain. High intensity AChE staining was detected in the caudate-putamen, followed by thalamus, hippocampus and brain stem. At the lower dose (0.1 mg/kg/day) methyl parathion produced statistically significant inhibition of AChE activity (15-23%, $p<0.05$) at the caudate-putamen and thalamic nuclei. Methyl parathion at 1 mg/kg/day inhibited AChE in most of the examined brain regions. The muscarinic receptor density was higher in the hippocampal formation, followed by the cerebral cortex and the caudate-putamen as visualized by [^{3}H]QNB autoradiography. Subchronic dermal exposure of rats to methyl parathion had no effect on [^{3}H]QNB binding in any brain region. In contrast, results from the *in vitro* experiments were consistent with previous reports that methyl parathion directly interacted with the muscarinic receptors in selective brain regions. The principal finding of this study was that methyl parathion at 0.1 mg/kg/day caused statistically significant inhibition of the AChE activity in the rat striatum and thalamus. Among the available subchronic dermal toxicity studies, 0.1 mg/kg/day was the lowest dose of methyl parathion tested for toxic effects. The LOEL for inhibition of the brain AChE is 0.1 mg/kg/day.

Four dermal subchronic toxicity studies were recently submitted to the DPR to characterize the effects of methyl parathion on the behavior, neurochemistry and neuromorphology of rats. These included a 5-Day dermal study performed at the Covance Laboratiory (Weiler, 1999b), and 2-Week (range-finding), 4-Week and 13-Week repeated dermal treatments, which were conducted in the ClinTrials BioResearch laboratory (Beyrouty, 1999a, 1999b, 2001).

In all four studies, methyl parathion was applied to a shaven area of the back of the rats and the animals were exposed for 6 hours/day, 5 days/week, over the indicated period. Sprague-Dawley rats were used in all experiments, which were 11-12 weeks old in the 5-Day study and 47-54 days of age in the other three studies. All four studies were conducted using similar protocols. The treatment site was not covered during the exposure period and subsequently was washed with soap and water. Plastic collars were used in the 5-Day and the 4-Week dermal studies to prevent the ingestion of methyl parathion. The rats were observed for (*i*) signs of general and cholinergic toxicity (changes in body weight, food consumption, dermal irritation, tremors, salivation, lacrimation, mortality, etc.), (*ii*) potential behavioral alterations (evaluated by the Functional Observational Battery, FOB, approach) and (*iii*) changes in the motor activity (assessed by the Figure-8-Enclosures or in a circular open field enclosure). At the end of the treatment period, a set of animals were subjected to neuropathological evaluation. The following tissues were examined for pathology: brain, spinal cord, skeletal muscles, sciatic, sural and tibial nerves, lumber and cervical ventral and dorsal root ganglia, trigeminal ganglia, optic nerve, eye, heart, kidneys, liver, pituitary, salivary and mammary glands, skin, stomach, spleen, thymus and ovaries. In addition, a set of animals was used for ChE activity measurements. ChE activity was measured in the plasma, red blood cells and in three areas of the brain – striatum and hippocampus and cerebral cortex (except in the 5-Day study, which examined the ChE activity in the frontal cortex).

The four subchronic dermal studies, however, were not carried out in a sequential order. For example, the 5-Day dermal treatment (Weiler, 1999) was initiated near the ending of the 13-Week study (Beyrouty, 1999b); the 4-Week study was conducted last. Consequently, the optimal methyl parathion dermal doses were not established and in all cases, the lowest tested dose produced considerable toxic effects. Therefore, the major deficiency in all studies was that the dose range did not include a level of no effect. The utilized doses in these studies varied from 0.3 to 71 mg/kg/day.

The specific experimental details and the observed toxic effects for each of the dermal neurotoxicity studies are presented bellow.

5-Day Dermal Neurotoxicity Study with Methyl Parathion (Weiler, 1999).

Methyl parathion formulation (43.9%, spray mix from emulsifiable concentrate) was applied to the rats at doses, corresponding to 1, 2 or 3 mg/kg/day of the active ingredient. The control groups included vehicle (1:8 spray dilution in water)-treated animals. The clinical observation, FOB and motor activity evaluations were performed on 10 rats/sex/group at pretest and on Days 4 and 6. After 5 days of treatment, 10 rats/sex/group were subjected to neuropahological evaluation. Eight animals/sex/group were used for ChE activity measurements on Days 4 and 6.

General and Cholinergic Toxicity, Motor Activity and Pathology. Overt clinical signs, neuropathological effects or alterations in the motor activity were not observed in the animals following 5 days of dermal treatment with 1-3 mg/kg/day methyl parathion.

Cholinesterase Activity. The lowest tested dose of methyl parathion, 1 mg/kg/day, produced a significant 45 % ($p \leq 0.05$) decrease in the brain cholinesterase activity (striatum region) in female rats on Day 6. The striatum ChE activity was also reduced (40%) in male rats after dermal dosing with 1 mg/kg/day methyl parathion for 5 days; however, this difference was not statistically significant. The highest tested dose (3 mg/kg/day) caused a similar level of inhibition (47-52%) in the activity of the brain ChE activity in female rats on Day 4 (striatum ChE) and Day 6 (cortex ChE).

This report was not a FIFRA guideline study and was considered supplemental by the DPR. The employed methyl parathion doses were very close and did not produce dose-groups with a range of effects. The principal finding of this work that was the substantial inhibition (40-45%) of the brain ChE enzyme observed at 1 mg/kg/day, which indicated that the dermal short-term (5-7 days) NOEL for methyl parathion in rats is below this dose.

2-Week Range-Finding Dermal Toxicity Study with Methyl Parathion in Rats (Beyrouty, 1999a).

A 2-week dermal toxicity study in rats was carried out to select doses for subsequent subchronic neurotoxicity studies with methyl parathion. Methyl parathion was applied to the dorsal surface of the rats at dose levels 7, 15, 33, 75 and 150 mg/kg/day. These doses of the methyl parathion formulation (47.5%) corresponded to 3, 7, 16, 36 and 71 mg/kg/day of the active ingredient. The control groups included vehicle (xylene)-treated animals. Clinical signs were recorded each day, and FOB testing were performed at pretest and during the second week of treatment. The ChE activity was measured at the end of the study.

General Toxicity and Behavioral Effects. All animals in the 71 mg/kg/day dose group and the majority of the rats repeatedly exposed to 36 and 16 mg/kg/day methyl parathion died prior to the completion of the study. The clinical signs for the dying animals included fur staining on the torso and limbs, tremors, gait abnormalities, decreased activity, abnormal respiration/breathing. The one surviving male from the 36 mg/kg/day dose group and the three surviving animals from 16 mg/kg/day group exhibited clinical signs consistent with the inhibition of the cholinesterase activity, such as slight to severe tremors, decreased arousal, urinary staining, deposits around the eye and abnormal gait. Based on the treatment-related death and cholinergic signs observed in the rats at the LOEL of 16 mg/kg/day, the NOEL for clinical signs was 7 mg/kg/day.

Cholinesterase Activity. Repeated dermal administration of methyl parathion at all tested doses caused a significant reduction in the plasma, erythrocyte and brain ChE activities in the rats. The lowest tested dose in this study (3 mg/kg/day) induced considerable toxic effects after 2 weeks of dermal treatment. These effects included 15-43% inhibition of the mean plasma ChE activitiy (males and females, respectively), 81-85% inhibition of the RBC ChE activity and 41-66% inhibition in the activity of the brain ChE (all regions, $p<0.01$). Similar levels of inhibition of the ChE enzymes were reported from the same laboratory after dermal dosing of rats with 3.8 mg/kg/day methyl parathion for 1 or 13 weeks (see Table 7 under the 13-week Dermal Toxicity Study; Beyrouty, 1999b). Based of the inhibition of the plasma, RBC and brain ChE activity, the lowest tested dose of 3 mg/kg/day was the LOEL. This report was not a FIFRA guideline study and was considered supplemental by the DPR.

A 4-Week Dermal Toxicity Study of Methyl Parathion in Rats (Beyrouty, 2001)

In a 4-week dermal neurotoxicity study, methyl parathion (96.5% pure) was applied to the shaved dorsal surface of rats at dose levels of 0.3, 1.0, 2.2 and 5.0 mg/kg/day (Beyrouty, 2001). The control groups included vehicle (0.5% carboxymethylcellulose /0.1% tween 80)-treated animals. The 4-Week exposure period was followed by a recovery period (no treatment) for additional 28 days. Clinical observation and FOB testing were performed on 20 rats/sex/group) at pretest, after dosing on Days 1, 5, 15 and 28 and at the end of the recovery period on Day 56. Ten rats/sex/group were subjected to pathological evaluation on Day 29. The same animals were used for hematology evaluations, including RBC count, hematocrit, hemoglobin, and the erythrocyte indices on Days 5, 28 and 56. In addition, 10 rats/sex/group were used for ChE activity measurements on Days 5, 28 and 56.

General Toxicity, Hematology and Pathology. Two females and one male in the highest dose group (5 mg/kg/day) died prior to the completion of the study. The first animal died after only 4 days of the dermal treatment, the other two rats were found dead on Days 25 and 28. The clinical signs for the dying animals included red fur staining on the muzzle, skin scab on the hindpaw, yellow fur staining at the lumbar region. On Day 56, the females repeatedly exposed to 5.0 mg/kg/day methyl parathion had a significant (6%, $p<0.05$) decrease in hemoglobin and increase (4%, $p<0.01$) in the RBC size distribution width (RDW). Despite these changes, the hemoglobin concentration and the RDW measured the 5 mg/kg/day females on day 56 were within the historical control range. Histopathological (including the nervous system) effects were not detected in the rats after repeated dermal dosing with 0.3-5.0 mg/kg/day methyl parathion.

Behavioral Effects. Various behavioral effects were noticed in the Functional Observational Battery on Days 1, 5 and 28 of the dermal administration of methyl parathion. A higher incidence of constricted (pinpoint) pupils was reported for the females from the 0.3 mg/kg/day group, which became statistically significant ($p<0.05$ or $p<0.01$) in the 1.0, 2.2 and 5.0 mg/kg/day dose groups. Females treated with 5.0 mg/kg/day methyl parathion showed on Day 5 tremors, ataxic gait, gait incapacity, abnormal body position and muzzle staining. Reduced arousal for male rats was observed following 15 days of dermal application of 0.3, 1.0 and 2.2 mg/kg/day methyl parathion. Surprisingly, this effect was not apparent in the 5 mg/kg/day group (Table 5) and none of the female rats exhibited reduced arousal. However, these animals showed a variety of treatment-related effects, including death, behavioral and neurochemical changes (see below).

Cholinesterase Activity. Repeated dermal administration of methyl parathion at 0.3 mg/kg/day (the lowest tested dose in the study) caused 20% decrease ($p \leq 0.01$) in the activity the erythrocyte ChE in females on Days 5. Furthermore, the same dose (0.3 mg/kg/day) applied for 28 days produced 28% inhibition of the RBC ChE activity in females and 18-22% reduction in the brain ChE activity (in all three examined regions in male rats and in the cortex and striatum in the females). The activity of the stratum ChE in the females from the 0.3 mg/kg/day dose group remained inhibited on Day 56 (the end of the recovery period, Table 6). Higher dermal doses of methyl parathion (1.0, 2.2 and 5.0 mg/kg/day) for 5 or 28 day produced a greater inhibition of the ChE activity. In male rats, maximum inhibition was measured in the activity of the brain ChE (all regions, 65-75%, $p<0.01$), after dosing with 5 mg/kg/day methyl parathion for 28 days. In females, the same treatment for 5 days caused a maximum inhibition of plasma, RBC and brain ChE activities (72-79%,) compared to the control levels.

The employed methyl parathion doses in this study produced dose-groups with a range of effects. The highest dose (5 mg/kg/day) resulted in mortality and the intermediate doses (1.1 and 2.0 mg/kg/day) produced a gradation of the toxic effects. However, the dose range did not include a level of no effect, since the lowest tested dose (0.3 mg/kg/day) caused considerable toxicity. This report was not a FIFRA guideline study and was considered supplemental by the DPR. The LOEL for the inhibition of the brain ChE activity and behavioral effects (pinpoint pupils in the female rats) was 0.3 mg/kg/day methyl parathion.

Table 5. Behavioral Effects in Rats Detected in the Functional Observational Battery in a 4-Week Dermal Neurotoxicity Study with Methyl Parathion[a].

		Males					Females				
Dose mg/kg/day		**0**	**0.3**	**1.0**	**2.2**	**5.0**	**0**	**0.3**	**1.0**	**2.2**	**5.0**
No. Animals Tested		**20**	**20**	**20**	**20**	**20[c]**	**20**	**20**	**20**	**20**	**19[b]**
OBSERVATIONS:											
Pinpoint Pupils	Day 1	1	2	0	2	2	0	0	5*	0	6*
	Day 5	3	7	5	4	10	2	4	9*	12**	11**
	Day 28	2	2	0	1	1	0	0	2	5*	0
Tremors Slight	Day 5	0	0	0	0	1	0	0	0	0	5**
Moderate	Day 5	0	0	0	0	0	0	0	0	0	2**
Ataxic Gait	Day 5	0	0	0	0	0	0	0	0	0	2
Gait Incapacity	Day 5	0	0	0	0	0	0	0	0	0	2
Muzzle Staining	Day 5	3	4	5	1	1	1	1	1	4**	5**
Decreased Arousal	Day 15	0	2	4	4	1	0	0	0	0	0

a/ Data from Beyrouty, 2001. The results are expressed as a number of animals, which exhibited a particular effect evaluated by the FOB

b/ One female rat died on Day 4 of the study; another female died on D 25 of the study.

c/ One male rat from this dose-group died on Day 28 of the treatment.

*, **Statistically significant difference from controls at $p \leq 0.05$ and 0.01, respectively (Fisher's Exact test)

Table 6. Cholinesterase Activity in Rats Measured in a 4-Week Dermal Neurotoxicity Study with Methyl Parathion.

Dose (mg/kg/day)		Cholinesterase Activity (% Inhibition)				
		Plasma	RBC	Cerebral Cortex	Striatum	Hippocamp.
Male Rats						
0.3	Day 5	3	13	12	16	0[b]
	Day 28	11	28	21**	18*	19**
	Day 56	14	2	3	9	10
1.0	Day 5	11	31**	28**	15	0
	Day 28	13	27	29**	34**	28**
	Day 56	8	21	13*	10	13**
2.2	Day 5	28*	58**	24*	36**	8
	Day 28	21**	53**	41**	43**	36**
	Day 56	11	11	15**	12	12**
5.0	Day 5	44*	76**	49**	51**	36**
	Day 28	27**	74**	73**	75**	65**
	Day 56	0 [b]	14	22**	22**	24**
Female Rats						
0.3	Day 5	0 [b]	20**	14	25	0
	Day 28	5	28*	17**	22**	10
	Day 56	14	11	3	13**	8
1.0	Day 5	22*	41**	22**	25	15
	Day 28	21	51**	35**	44**	23
	Day 56	13	8	19**	15**	10*
2.2	Day 5	34**	68**	40**	45	33**
	Day 28	31*	68**	54**	60**	42
	Day 56	0	18	19**	20**	19**
5.0	Day 5	72**	89**	77**	80**	72**
	Day 28	47**	76**	77**	79**	74***
	Day 56	8	19	22**	30**	25**

a/ Data from Beyrouty, 2001. Cholinesterase activities were measured in plasma (μmol/l), erythrocytes (μmol/l) and brain (μmol/g). Results are expressed as % inhibition of mean ChE activity, compared to the control levels.

*, **, ***, Statistically significant difference from controls at p≤ 0.05 0.01 and 0.001, respectively, (Dunnett's test); Hippocamp.=Hippocampus.

b/ The mean ChE activity was higher than the levels measured in the control animals

13-Week Dermal Subchronic Toxicity in Rats with Methyl Parathion (Beyrouty, 1999b)

Methyl parathion formulation (47.5%) was applied to a shaven area of the back of the rats at 2.5, 8.0 and 25 mg/kg/day. These doses corresponded to 1.2, 3.8, and 12 mg/kg/day of the active ingredient. The animals were exposed for 13 weeks, followed by a recovery period (no treatment) for an additional 13 weeks. The two control groups included either untreated or vehicle (xylene)-treated animals. Clinical observation, FOB and motor activity testing were performed on 14 rats/sex/group at pretest, after dosing during the 4^{th}, 8^{th}, 13^{th} week, and during the recovery period on weeks 17, 21 and 26. After 13 weeks of treatment, 6 rats/sex/group were subjected to neuropathological evaluation; the remaining animals from the vehicle control and the high dose were kept for a 13 week recovery period. In addition, 24 rats/sex in the vehicle control and the high dose group and 16 rats/sex in the 0 (untreated), 2.5 and 8 mg/kg/day were used for ChE activity measurements at the end of Weeks 1 and 13.

General and Cholinergic Toxicity. Two males and two females in the highest dose group (12 mg/kg/day) died prior to the completion of the study. The clinical signs for the dying animals included: tremors, decreased activity, dehydration, labored breathing, fur staining, reduced core temperature, salivation, incoordination and red flaking skin at the dosing site. Overt clinical signs in the surviving animals were not observed, except for tremors for the animals in the 12 mg/kg/day treatment group.

Behavioral Effects, Motor Activity and Pathology. Males in the high dose group (12 mg/kg/day) exhibited a statistically significant decrease ($p<0.05$) in the number of rearing incidents at weeks 17, 21 and 26 of the recovery period. Neuropathological effects or alterations in the motor activity were not detected in the methyl parathion-treated animals.

Cholinesterase Activity. Repeated dermal administration of the lowest dose employed in this study (1.2 mg/kg/day) produced the following toxic effects (Table 7):

(*1*) After 1 week of exposure, male rats exhibited statistically significant 20-22% reduction ($p<0.01$) in the activities of the plasma and the RBC ChE, and 13% inhibition ($p<0.05$) of the ChE activity in the hippocampus area of the brain, (2) After 5 weeks of treatment, males and females showed a 49% decrease in activity ($p<0.01$) of the RBC ChE, (*4*) After 5 and 13 weeks of treatment, the activity of the RBC ChE in the females was decreased by 51% and 56% ($p<0.01$), respectively, and (4) After 13 weeks of dermal dosing, a substantial inhibition of the brain ChE activity (35-43%, $p<0.05$ or $p<0.01$) was observed in both sexes (Table 7).

Higher doses of methyl parathion (3.8 and 12 mg/kg/day) for 1-13 weeks produced a greater inhibition of the ChE activity. Maximum inhibition was measured in the female brain ChE activity (83%-85%), compared to the control levels following dosing with 12 mg/kg/day methyl parathion for 13 weeks.

Similar to the other subchronic dermal studies submitted to the DPR, the dose range in the 13-week dermal treatment of rats with methyl parathion did not include a level of no effect. This study was considered unacceptable by the DPR to fulfill the data requirement for the subchronic dermal toxicity, because a positive control was not used for the FOB. The LOEL for the inhibition of plasma, RBC and brain ChE activities in male rats was 1.2 mg/kg/day methy parathion.

Table 7. Cholinesterase Activity in Rats following 13-week Subchronic Dietary Exposure to Methyl Parathion[a].

Dose (mg/kg/day)[b]		Cholinesterase Activity (% Inhibition)				
		Plasma	RBC	Cerebral Cortex	Striatum	Hippocamp.
Male Rats						
1.2	Week 1	20**	22**	8	15	13**
	Week 5[c]	3	51**	-	-	-
	Week 13	5	56**	41**	35**	35**
3.8	Week 1	28**	50**	14	25**	18**
	Week 5	17*	66**	-	-	-
	Week 13	14	75**	45**	45**	42**
12.0	Week 1	49**	81**	55**	56**	48**
	Week 5	24**	80**	-	-	-
	Week 13	30*	85**	71**	71**	66**
Female Rats						
1.2	Week 1	0	25	15	15	6
	Week 5	0[d]	51**	-	-	-
	Week 13	5	56**	41**	43*	35**
3.8	Week 1	34**	69**	50**	45**	36**
	Week 5	19	75***	-	-	-
	Week 13	22*	75**	63**	62**	52**
12.0	Week 1	72**	95**	84**	88**	81**
	Week 5	33*	90***	-	-	-
	Week 13	55**	91**	85**	85**	83**

a/ Data from Beyrouty, 1999b. Cholinesterase activities were measured in plasma and erythrocytes (μmol/l), and in brain (μmol/g). Statistically significant difference from controls, * $p<0.05$, ** $p<0.01$, *** $p<0.001$, ((Dunnett's test). Hippocamp.=Hippocampus.

b/ Doses were based on the active ingredient, not on the formulation.

c/ Brain ChE measurements were not performed at Week 5 of the dermal treatment.

d/ The mean ChE activity was higher than the levels measured in the control animals.

Collectively, the results from the six recent subchronic studies with rats on the methyl parathion dermal toxicity indicated that considerable toxicity occurred at doses as low as 1 mg/kg/day. The reported effects included: 20-50% inhibition of the plasma ChE activity, 51-56% inhibition of the RBC enzyme and 41-44% inhibition of the brain AChE enzyme; and behavioral effects, such as pinpoint pupils, decreased locomotor activity and memory retention (after 5 days to 13 weeks of treatment, Weiler, 1999; Beyrouty 1999; Beyrouty, 2001; Zhu et al., 2001). Furthermore, significant toxicity was observed at the lowest tested doses (0.1-0.3 mg/kg/day), which included 15-23% reduction of the brain ChE activity and behavioral effects (pinpoint pupils, Ma et al, 2003; Beyrouty, 2001). Clearly, the experimental evidence indicated that doses lower than 0.1 mg/kg/day should be employed to establish the regulatory toxicological level for short-term and subchronic dermal exposure to methyl parathion.

III.C.6. Subchronic Toxicity Data from Reviews and Summaries

Information on methyl parathion toxicity through inhalation and dermal exposures is largely available only as summarized by World Health Organization (WHO, 1984), USEPA (1984), and Agency for Toxic Substances and Disease Registry (ATSDR, 1992a). Many of the citations were in foreign languages. No deaths or treatment-related histopathological lesions were reported in a study by Thyssen and Mohr (1982; as cited in WHO, 1984) in which, groups of 10 rats per sex were exposed to 0, 0.9, 2.6, or 9.7 mg/m³ methyl parathion, 6 hours/day and 5 days/week, for 3 weeks. Rats at the high dose had significant plasma and brain ChE inhibition (levels not specified), body and organ weight reduction, and cholinergic signs. Slight inhibition of plasma ChE was noted at 2.6 mg/m³. The apparent NOEL was 2.6 mg/m³ (estimated dose of 0.45 mg/kg/day) based on clinical signs of toxicity.

Toxicity associated with dermal exposure to methyl parathion was reported by Mihail and Vogel (1984; as cited by WHO, 1984). Groups of 6 rabbits per sex received un-occluded topical applications of 0, 50, or 250 mg/kg/day methyl parathion (in Cremophor E.I.), 6 hours/day and 5 days/week, for 3 weeks. Epithelial proliferation with hyperkeratosis was noted at the treatment site. Methyl parathion treatments had no effects on hematology, serum chemistry, and organ weights. Activities of RBC and brain ChE were inhibited in both dose groups in a dose-related manner. Cholinergic signs, deaths, and significant inhibition in plasma ChE (level not specified) also occurred at 250 mg/kg/day. A subsequent study was conducted using 10 mg/kg/day in an effort to establish a NOEL. No ChE inhibition or dermal effects were reported at 10 mg/kg/day.

The USEPA (1984) documented several oral exposure studies that were reported in foreign journal publications. Rats that received methyl parathion at 0.15 or 0.75 mg/kg/day for 1, 2 or 4 months had depressed renal tubule succinic dehydrogenase, increased glomerular alkaline acid phosphatase, "morphological changes in myocardial and scar tissues, focal granuloma, vascular sclerosis, bronchitis, stratification of blood vessels, hyperplasia of pulmonary tissue, and lymphatic atrophy" (Zlateva and coworkers, 1977, 1978; as cited in USEPA, 1984). Delayed conditioned reflexes to light and sound were reported in rats that received 30 μg/kg/day (0.03 mg/kg/day) methyl parathion in drinking water for 6-9 months (Cabejszek and Szulinski, 1966; as cited in USEPA, 1984). Decreased white blood cell phagocytic activity, complement titer, serum lysozyme, and nucleic acid content in blood occurred in rabbits that received methyl parathion orally at 5 mg/kg/day (in sunflower oil), 6 days/week for 4 months (Samedov et al., 1979; as cited by USEPA, 1984).

III.D. CHRONIC TOXICITY AND ONCOGENICITY

The toxicity of methyl parathion after chronic (beyond 1 year) exposures has been studied in rats, mice, and dogs. Data on ChE inhibition, when available, are presented in Table 8. Significant brain ChE inhibition was consistently reported in these studies. Among other neurological effects was myelin degeneration reported in a 12 month study in rats.

III.D.1. Chronic Toxicity

III.D.1.a. Oral Studies – Rat

Four studies were included in this section. The studies by Bomhard et al. (1981), Daly and Hogan (1983), and Daly (1991) are on file at DPR. A study by Nagymajtenyi et al. (1995) is available in the open literature. In the study conducted by Bomhard et al. (1981), groups of 50 Wistar rats per sex were fed diets containing 2, 10, or 50 ppm methyl parathion (94.8% pure) for 2 years. The controls consisted of 100 rats per group. Interim sacrifices were performed on additional groups of five animals at 6 and 12 months after the start of the study. There was an approximately 15% increase in food consumption in the females at 50 ppm. However, the body weight of the males and females at 50 ppm was approximately 9% lower than the controls. Based on the food intake data, the corresponding methyl parathion intake was 0.09, 0.46, and 2.6 mg/kg/day for the males and 0.14, 0.71, and 5.0 mg/kg/day for the females. Cumulative mortality data for the first six months showed a statistically significant increase in the females at 50 ppm (16% mortality). Transient alterations in hemoglobin, hematocrit, and reticulocyte counts, as well as decreased plasma protein levels, and increased levels of plasma urea and protein in the urine, were noted at 50 ppm throughout the exposure period. These indices were indicative of liver and kidney injury. The activities of plasma and RBC ChE were significantly reduced at 10 and 50 ppm from as early as week 2 and throughout the treatment period.

Moreover, the RBC ChE inhibition at 2 ppm was statistically significant at many measurement time intervals. Brain ChE inhibition was detected at the end of the study at 10 and 50 ppm (Table 8). The NOEL for brain ChE inhibition was 2 ppm (0.09 mg/kg/day). Based on statistical significance, the lowest dose of 2 ppm was the LOEL for the RBC ChE inhibition. It should be noted that clinical observations were not reported for all animals. In addition, no histopathological examinations of the spinal cord and peripheral nerves were performed. Due to these and other deficiencies (e.g., lacking descriptions of diet preparation and test substance analyses in the diets) this study was judged unacceptable to DPR for filling the SB950 chronic toxicity data requirement based on the FIFRA study guidelines.

A study by Daly and Hogan (1983) was acceptable under FIFRA guidelines for filling the data requirements for chronic and oncogenicity studies in rats. Groups of 60 Sprague-Dawley CD rats per sex were fed diets containing 0, 0.5, 5.0, or 50 ppm methyl parathion (93.7% pure) for 25 months (males) or 28 months (females). Five animals per group were killed at 24 months as an“interim” sacrifice. The body weight of the males and females at 50 ppm was approximately 6-8% lower than the controls. Male rats at 50 ppm had an approximately 4-13% increase in food consumption prior to week 13. Food consumption in the 50 ppm females was initially lower (week 1-2), but became higher (approximately 15-20%) throughout the remainder of the study. Based on the food consumption data, the corresponding intake of methyl parathion at week 52 was 0, 0.02, 0.19, and 2.0 mg/kg/day for the males and 0, 0.03, 0.28, and 3.2 mg/kg/day for the

females. In addition to the effects on body weight and food intake, a number of effects were also noted at 50 ppm. These included: tremors, alopecia, abnormal gait (in females), peripheral (hind limb) neuropathy with demyelination of the sciatic nerves, retinal degeneration and posterior subcapsular cataracts (in females), increases in brain weight (females, 5%) and heart weight (females, 22%), and a decrease in hemoglobin, hematocrit, and erythrocyte counts. In addition, plasma and brain ChE activities were severely inhibited (brain ChE was reduced to 21-24% of the controls; see Table 8). At 5 ppm, abnormal gait was observed in one female rat and hematological alterations (i.e., decreased hemoglobin, hematocrit, and erythrocyte counts) were noted in the males at the end of the experimental period. At least 50% of the animals had chronic interstitial pneumonia. Mortality was high in all groups including the controls, especially on month 17. Approximately 60-68% of the animals survived after 18th months, and only 33-42% survived to the end of 24 months. This deficiency in animal husbandry compromised a comprehensive evaluation of the chronic toxicity of methyl parathion. Based on plasma and brain ChE inhibition and the many clinical signs of effects, the NOEL was 5.0 ppm (0.19 mg/kg/day). It should be noted that at 5.0 ppm, there was a statistically significant decrease in RBC ChE by 9% at week 26 in the males. In addition, the RBC ChE was decreased by 4-11% in male and female rats at the end of the study, although they were not statistically significant. The NOEL was also 0.5 ppm (0.02 mg/kg/day) based on the neurological signs and hematological effects identified at 5 ppm. From the above study, USEPA (1997c) established a NOEL of 0.5 ppm (0.02 mg/kg/day) based on RBC ChE inhibition, neurological signs and nerve degenerations, and hematological effects. This formed the basis for the Reference Dose (RfD) determination (USEPA, 1998c, 1999).

The potential ocular and neurological effects of methyl parathion were the focus of an investigation by Daly (1991). This is not a FIFRA guideline study. Groups of 70 Sprague-Dawley rats per sex were fed diets containing 0, 0.5, 2.5, 12.5, or 50 ppm methyl parathion (94.6% pure) for 12 months. The respective doses were 0.02, 0.1, 0.48, and 2.0 mg/kg/day, calculated from the data on body weight and food consumption. Alopecia, cage sores/scabs on paws, yellow stains in the ano-genital area, red nasal discharge, altered gait, and decreased body weight gain (the final body weight was 91% of the controls) were noted at 50 ppm. Plasma, RBC, and brain ChE inhibitions (Table 8) and an increase in peripheral neuropathy occurred at 12.5 and 50 ppm. Neurohistopathological findings are summarized in Table 9. Increases in proximal sciatic and tibial/peroneal nerve myelin degeneration were noted at and above 2.5 ppm. Ophthalmologic, electroretinographic, and neuropathologic investigations did not reveal any ocular effects. The NOEL for brain ChE inhibition was 2.5 ppm (0.1 mg/kg/day). The NOEL for neurological effects was 0.5 ppm (0.02 mg/kg/day). Alternatively, USEPA determined that the NOEL was 12.5 ppm (0.1 mg/kg/day) for all endpoints, including ChE inhibition (plasma, RBC, brain) and neuropathology (USEPA, 1999).

Table 8. Cholinesterase (ChE) Activity Following Chronic Dietary Exposure to Methyl Parathion[a].

Sp.	Dose or Conc. in feed	Duration	ChE (% of control) Males Plasma	Males RBC	Males Brain	Females Plasma	Females RBC	Females Brain	Reference
Rats									
n=5	2 ppm	2 wk	91	96*	-	95	93	-	Bomhard
	10 ppm		73**	84**	-	78	76**	-	et al., 1981
	50 ppm		36**	67**	-	21**	67**	-	
	2 ppm	13 wk	85	93*	-	86	80**	-	
	10 ppm		80	73**	-	61*	73**	-	
	50 ppm		36**	66**	-	14**	58**	-	
	2 ppm	26 wk	88	94	-	95	90*	-	
	10 ppm		82	84**	-	69	78**	-	
	50 ppm		61*	82**	-	19**	68**	-	
	2 ppm	52 wk	92	83**	-	89	84**	-	
	10 ppm		73*	75**	-	75	79**	-	
	50 ppm		32**	69**	-	12**	71**	-	
	2 ppm	105 wk	108	94	89	104	94	102	
	10 ppm		111	78**	78*	73	78**	106	
	50 ppm		41**	68**	50**	13**	65**	37**	
n=10	0.5 ppm	26 wk	86	95	-	100	107	-	Daly and
	5 ppm		71	91*	-	90	104	-	Hogan, 1983
	50 ppm		29**	87**	-	14**	100	-	
	0.5 ppm	52 wk	89	100	-	100	101	-	
	5 ppm		100	99	-	84	99	-	
	50 ppm		33**	84*	-	13**	92*	-	
	0.5 ppm	104 wk	109	102	106	100	96	95	
	5 ppm		91	96	99	106	89	98	
	50 ppm		18**	91**	24**	18**	95	21**	

(continued)

Table 8. Cholinesterase (ChE) Activity Following Chronic Dietary Exposure to Methyl Parathion (cont.).

Sp.	Dose or Conc. in feed	Duration	ChE (% of control) Males Plasma	Males RBC	Males Brain	Females Plasma	Females RBC	Females Brain	Reference
Rats									
n=10[b]	0.5 ppm	1 mo	90	93	-	105	103	-	Daly, 1991
	2.5 ppm		101	92	-	81	103	-	
	12.5 ppm		75*	87*	-	67	90*	-	
	50 ppm		48**	80**	-	26**	86**	-	
	0.5 ppm	6 mo	83	101	-	112	103	-	
	2.5 ppm		86	97	-	84	102	-	
	12.5 ppm		65	94	-	72	91	-	
	50 ppm		39**	87**	-	21**	87**	-	
	0.5 ppm	52 wk	91	99	95	105	97	93	
	2.5 ppm		103	96	96	90	93	99	
	12.5 ppm		71	97	96	67*	88**	75**	
	50 ppm		37**	86*	43**	30**	80**	25**	
Mice									
n=10	1 ppm	52 wk	113	92	87	100	103	100	Eiben, 1991
	7 ppm		94	43*	63*	94	51*	99	
	50 ppm		29*	14*	16*	35*	24*	54*	
	1 ppm	104 wk	86	93	81	109	90	97	
	7 ppm		104	48*	77*	104	59*	92	
	50 ppm		25*	11*	33*	39*	20*	38*	
Dogs									
n=8		2 mo							Ahmed and
0.03 mg/kg/day			99	97	-	100	95	-	Sagartz, 1981
0.1 mg/kg/day			108	86*	-	107	86	-	
0.3 mg/kg/day			83*	82*	-	87	65	-	
		4 mo							
0.03 mg/kg/day			99	97	-	81*	93	-	
0.1 mg/kg/day			110	90	-	72*	93	-	
0.3 mg/kg/day			84*	80	-	52*	81	-	

(continued)

Table 8. Cholinesterase (ChE) Activity Following Chronic Dietary Exposure to Methyl Parathion (cont.).

Sp.	Dose or Conc. in feed	Duration	ChE (% of control) Males Plasma	Males RBC	Males Brain	Females Plasma	Females RBC	Females Brain	Reference
Dogs									
		12 mo							Ahmed and
	0.03 mg/kg/day		88	79*	97	97	71*	108	Sagartz, 1981
	0.1 mg/kg/day		86	68*	107	110	71*	92	
	0.3 mg/kg/day		66*	81*	187	99	78*	78	
n=4		1 mo							Hatch, 1998[c]
	0.3 mg/kg/day		100	92	-	81*	89	-	
	1 mg/kg/day		92	61*	-	81**	93	-	
	3 mg/kg/day		54**	33**	-	44**	37	-	
	3.5 mg/kg/day		46**	28**	-	31**	37	-	
	4.0 mg/kg/day		54**	28**	-	31**	37**	-	
		6 mo							
	0.3 mg/kg/day		92	94	-	69**	79	-	
	1 mg/kg/day		85	63**	-	69**	55	-	
	3 mg/kg/day		-	-	-	-	-	-	
	3.5 mg/kg/day		-	-	-	31**	28**	-	
	4.0 mg/kg/day		46**	28**	-	-	-	-	
		12 mo							
	0.3 mg/kg/day		92	79*	67-100	76	84	100-129	
	1 mg/kg/day		85	52**	91-100	65**	60**	75-91	
	3 mg/kg/day		-	-	-	-	-	-	
	3.5 mg/kg/day		-	-	-	35**	36**	25-91	
	4.0 mg/kg/day		46**	24**	20**-40	-	-	-	

Levels of statistical significance as compared to the controls: * for $p \leq 0.05$; ** for $p \leq 0.01$. The reports by Ahmed and Sagartz (1981) and Eiben (1991) provided statistical significance only for $p \leq 0.05$. Dash ("-") indicated no data.

a/ Studies by Daly and Hogan (1983) and Hatch, 1998 were acceptable for filling the data requirement for the specific type of toxicity test.

b/ N=5 for brain ChE measurements

c/ Brain ChE data were from caudate nucleus, hippocampus, and cerebellum.

In October 1998, the DPR received a re-evaluation by Brennecke (1996) of selected peripheral nerve tissues from the 12 Month Oral Toxicity Study with Methyl Parathion [E-120] by Daly (1991). With an increased number of control and high dose rats examined, the total incidence as presented in Table 9 showed no neuropathological effects at any dose levels. However, the background knowledge of the dosing regimen for the specimen was not kept from the pathologist making the re-evaluation (Brennecke, 1996). In February 2002, the DPR received two more pathology re-evaluations of the study by Daly (1991), performed independently by Jortner (2001) and O'Shaughnessy (2001b). The re-evaluated histologic sections included the spinal cord, sciatic and tibial nerves, and teased fiber preparations. Both reports confirmed the presence of demyelinated peripheral nerve fibers (Jortner, 2001) or axonal degeneration (O'Shaughnessy, 2001b); however, unlike the original pathology diagnosis, the evaluating pathologists did not consider the lesions as treatment-related effects. In both re-evaluations, only tissue preparations from the high-dose and control groups were examined.

The USEPA has established a procedure for the submission of revised pathology evaluations (USEPA 1994). According to this procedure, peer-review pathologist must examine the histology sections from the target tissue from all dose groups. The reports from the original study pathologist and the peer-review pathologist, along with all slides with differing diagnosis (as a minimum), must be reviewed by a Pathology Working Group (PWG). The PWG consists of a chair and other experienced pathologists, including the peer-review and the study pathologist. The DPR determined that re-evaluations of the original pathology findings did not conform to these guidelines and, therefore, the results could not be used to replace the initial conclusion regarding the methyl parathion-induced neuropathy.

Table 9. Neurohistopathological Findings in Sprague-Dawley CD Rats after 12 Month of Methyl Parathion Treatment in the Diet.

Myelin bubbles[b]	Concentrations in the diet (ppm[a])									
	Males					Females				
	0	0.5	2.5	12.5	50.0	0	0.5	2.5	12.5	50.0
As reported in Daly, 1991										
Proximal Sciatic	0/5	0/5	1/5	2/5	3/5	0/5	1/5	1/5	3/5	3/5
Tibial/Peroneal	0/5	0/5	1/5	2/5	4/5	0/5	0/5	2/5	0/5	3/5
Re-evaluation by Brennecke, 1996										
Total incidence (%)	12/17 (71%)	3/5 (60%)	3/5 (60%)	4/5 (80%)	8/18 (44%)	9/19 (47%)	2/5 (40%)	4/5 (80%)	1/5 (20%)	6/16 (38%)

a/ The respective doses were 0.02, 0.1, 0.48, and 2.0 mg/kg/day, calculated from the data on body weight and food consumption.

b/ Myelin bubbles represented an early myelin degeneration with focal accumulation of fluid within the myelin sheath. In some cases, myelin bubbles were accompanied by myelin phagocytosis and/or Schwann cell proliferation. These changes were similar to the myelin ovoids in the teased nerve.

Nagymajtenyi et al. (1995) studied the long-term neurological effects of methyl parathion in Wistar rats using a 3-generation exposure protocol typical of a multi-generation reproductive toxicity study. Methyl parathion at 0.22, 0.33, 0.44, and 0.88 mg/kg/day was administered five times a week through gavage. The dosing schedule was changed to 7 days a week during gestation and lactation periods. Statistically significant changes in EEG (electroencephalogram) index (a quotient of the two fast and the two slow frequency bands) were reported in all three cortical areas (somatosensory, visual, auditory) at as low as 0.22 mg/kg/day. A statistically significant decrease in both the mean amplitudes and an increase in the EEG frequencies were also detected at 0.88 mg/kg/day. The authors stated that the EEG parameters appeared to be more sensitive than ChE inhibition in detecting the neurophysiological effects of OPs, including methyl parathion. Moreover, the effects in the second and third generations were reportedly more pronounced. Unfortunately, the report did not provide sufficient detail for a thorough review.

III.D.1.b. Oral Studies – Mice

A chronic study by Eiben (1991) was acceptable under FIFRA guidelines for filling the SB950 data requirements for oncogenicity studies in mice. Groups of 50 B6C3F1/Cr1BR mice per sex were fed diet containing 0, 1, 7, or 50 ppm methyl parathion (95.5% pure) for 104 weeks. Additional groups of 15 mice per sex were included in each dose group for interim sacrifice at 52 weeks. The respective doses were 0, 0.2, 1.6, and 9.2 mg/kg/day for the males and 0, 0.3, 2.1, and 13.7 mg/kg/day for the females. A dose-related brain ChE inhibition was reported in the males at all dose levels (Table 8). At the end of the study, the respective brain ChE activities in male rats from the low to the high dose groups were 81, 77, and 33% of the controls. Substantial brain ChE inhibition was also reported for the females at 50 ppm (38% of the controls). In addition, the activities of RBC ChE were lowered at 7 and 50 ppm in males and females. The respective mortalities for the controls and low to high dose groups were 0, 0, 2, and 6% at week 52 and 16, 0, 20, and 20% at the end of the study. Contrary to the body weight reductions noted in the subchronic studies (Daly and Rinehart, 1979, 1980b), mice at the high dose showed a substantial body weight increase over the controls. By the end of the study, the average body weight of mice at 50 ppm was approximately 10-20% higher than the controls while the food consumption was 13-15% lower. An increase in the absolute weight of liver, kidneys, and brain and a decrease in their relative weights were also noted at 50 ppm, more prominently in the males. There was a dose-related elevation of plasma cholesterol levels that was statistically significant ($p<0.01$) in females at 7 and 50 ppm and males at 50 ppm. In the males, the number of animals noted as having "poor general condition" increased to 8 to 9 animals per dose group at 7 and 50 ppm compared to one animal in the controls. As the dose increased, the lag time for the condition appeared to be shortened (starting on day 2 at 50 ppm compared to day 99 in the controls). Tremors were noted in one male during week 2. Paralysis was noted in one female during week 84. Gross and histopathological examinations did not show any treatment-related effects. Based on the dose-related inhibition of brain ChE, the lowest tested dose of 1 ppm (0.2 mg/kg/day) could be the LOEL, although it is a NOEL based on the statistical analysis since the ChE inhibition was only statistically different ($p<0.05$) from the control at the mid and high doses. However, the statistical power was compromised by the low sample size (5 per dose group). Based on the body and organ weight changes and poor general conditions in the males, the NOEL was 7 ppm (1.6 mg/kg/day).

III.D.1.c. Oral Studies – Dog

Two one-year studies are on file in DPR. In the study by Ahmed and Sagartz (1981), groups of 8 dogs per sex received 0, 0.03, 0.1 or 0.3 mg/kg/day methyl parathion (93.65% pure) through the diet for one year. A reduction in brain ChE activity (down to 78% of the controls) was noted in females at 0.3 mg/kg/day (Table 8). No clinical signs were noted. Males at 0.1 and 0.3 mg/kg/day had an occasional decrease in feed consumption during week 15 and week 30 but this did not result in significant changes in the overall body weight gain. The study was deficient in that the dose selection was not justified and the potential for ophthalmologic effects was not adequately tested. Based on the brain ChE inhibition, the NOEL was 0.1 mg/kg/day. Although the dose level used in this study had apparently not reached the maximum tolerated dose (MTD), the requirement for conducting a study with sufficiently high dose was judged by DPR as no longer necessary because a lower NOEL identified in the rat studies was suitable for risk assessment purposes.

In a recent study, Hatch (1998) investigated the ocular toxicity of methyl parathion. Groups of 4 dogs per sex received 0, 0.3, 1.0, 3.5, and 4.0 mg/kg/day methyl parathion (95.8% pure) through the diet for one year. At 3 months of exposure, the dose of two males was changed from 3.5 mg/kg/day to 4 mg/kg/day while the dose for two females was changed from 4.0 mg/kg/day to 3.5 mg/kg/day. The remaining two dogs from each group were killed. Ocular toxicities were also studied in groups of 4 dogs per sex that received 3.0 mg/kg/day methyl parathion for 3 months and after a 30-day subsequent recovery period (i.e., given untreated diet). No treatment-related ophthalmological changes (intraocular pressure, electroretinogram) were reported at 3, 6, and 12 months of exposure at any dose levels. At 3 mg/kg/day, occasional tremors were noted in two females during week 4 to 10 while all four females had diarrhea. Effects reported at 3.5 and 4.0 mg/kg/day included diarrhea, thinness, statistically significant increase in relative adrenal weight (adrenal to brain ratio), decreased absolute and relative spleen weight, and lymphoid cell depletion in thymus. Plasma, RBC, and brain ChE activities showed dose-related decreases (Table 8). Plasma ChE inhibition occurred in the females at all dose groups, and the effects at 0.3 mg/kg/day were statistically significant ($p \leq 0.01$) at the 1 and 6 months measurements. At this dose, the RBC ChE inhibition in the males was also statistically significant at the end of the study. Substantial brain ChE inhibition was also noted at 3.5 and 4 mg/kg/day. As much as 25% brain inhibition was noted at 1 mg/kg/day, although not reported as statistically significant. Based on the statistical significance in plasma and RBC ChE inhibition, the lowest dose of 0.3 mg/kg/day was the LOEL. The NOEL for a 25% brain ChE inhibition was 0.3 mg/kg/day. The NOEL for the clinical signs of toxicity was 1.0 mg/kg/day.

III.D.2. Oncogenicity

Three studies in rats and 2 studies in mice were available for the evaluation of the human oncogenic potential of methyl parathion. Detailed descriptions for two chronic studies in rats by Bomhard et al. (1981) and Daly and Hogan (1983) and one study in mice by Eiben (1991) were presented in Section III.D.1. **Chronic Toxicity.** Only data pertaining to the oncogenic effects from these studies are given in this section. In addition, the NCI study (NCI, 1979) in rats and mice is presented.

III.D.2.a. Oral Studies – Rats

Limited evidence of oncogenicity was demonstrated in the following three studies. Somewhat elevated incidences of adrenal adenomas in the males and uterus adenocarcinomas in the females were noted in two of the three studies. A marginally statistically significant increase of thyroid adenomas was also noted in one study. The overall oncogenicity evidence in rats is generally "equivocal" or "limited" at best. The current data are insufficient for speculating on the possible implication of these results to human health at the exposure levels commonly experienced by humans.

In the 2-year study with Wistar rats by Bomhard et al. (1981), various types of tumors were found 15 organ/tissue sites. The authors reported that all were within the range of spontaneous rates and were primarily the result of aging. Table 10 presents the incidences of tumor sites that had at least a 10% occurrence in any dose group. There were apparent slight increases in thyroid adenomas in the males and uterus adenocarcinomas in the females. The increase in thyroid adenomas was marginally significant statistically ($p<0.05$) by the Fisher exact pair-wise comparison.

Bomhard and Rinke (1994) published a set of spontaneous tumor incidences in Wistar rats. The historical data were a collection of tumor incidences from the controls (approximately 50 rats per sex per study) of 22 two-year studies conducted in the Institute of Toxicology of BAYER AG in Germany between May 1975 and December 1980. This historical database is a pertinent reference for the methyl parathion study because it was from the same laboratory, by the same author, and included the study period of the methyl parathion study. The concurrent control incidences of adrenal tumors in males and females (Table 10) were on the high end of the historical range and substantially higher than the average spontaneous rates. An exact comparison of the incidence of thyroid tumors cannot be made with the historical data because the report by Bomhard et al. (1981) did not specify whether they were follicular or c-cell tumors. The concurrent control incidence in the males and females were within the historical range of c-cell benign or malignant tumors but exceeded the range for follicular adenomas or carcinomas.

Nevertheless, it is important to note that, the incidences of the thyroid adenomas, although unspecified regarding the cell type, would have exceeded the historical incidence. This is illustrated by the following analysis. The historical incidence was 0-4.4% (ave. 1.1%) for follicular cell adenomas and 0-19.1% (ave. 5.4%) for benign c-cell tumors (Bomhard and Rinke, 1994). Thus, the highest possible historical incidences for both types of benign thyroid tumors would be 23.5%. Accordingly, the 25.5% incidence of thyroid adenomas in males at 50 ppm remained outside of this highest possible historical incidence.

A comparison to the historical control incidence was also made regarding the uterus adenocarcinomas. Although the incidences at the mid and high dose levels were not statistically significantly different from the concurrent controls, they exceeded the historical range while the incidence of controls (8.2%) stayed well within the range. The respective incidences at the mid (10 ppm) and high (50 ppm) dose levels were 18.0% and 19.5% while the historical controls ranged from 0 to 16.3% with an average of 7.8%.

Table 10. Tumor Incidences from a 2-year Feeding Study in Wistar rats Conducted by Bomhard et al., (1981)[a].

Sex/Tumor site/type	0 ppm	2 ppm	10 ppm	50 ppm
(M) Adrenal medulla				
pheochromocytoma	14/49 (28.6%)	3/50 (6.0%)	4/49 (8.2%)	3/47 (6.4%)
(F) Adrenal medulla				
pheochromocytoma	3/49 (6.1%)	0/48 (0%)	0/50 (0%)	0/41 (0%)
(M) Pituitary				
adenoma	10/49 (20.4%)	13/50 (26.0%)	11/49 (22.4%)	4/47 (8.5%)
adenocarcinoma	1/49 (2.0%)	0/50 (0%)	0/49 (0%)	0/47 (0%)
combined	11/49 (22.4%)	13/50 (26.0%)	11/49 (22.4%)	4/47 (8.5%)
(F) Pituitary				
adenoma	6/49 (12.2%)	7/48 (14.6%)	16/50 (32.0%)	3/41 (7.3%)
adenocarcinoma	0/49 (0%)	0/48 (0%)	0/50 (0%)	1/41 (2.4%)
combined	6/49 (12.2%)	7/47 (14.6%)	16/50 (32.0%)	4/41 (9.8%)
(M) Thyroid				
adenoma[b]	4/49 (8.2%)	3/50 (6.0%)	2/49 (4.1%)	12/47 (25.5%)*
adenocarcinoma	1/49 (2.0%)	0/50 (0%)	0/49 (0%)	0/47 (0%)
combined	5/49 (10.4%)	3/50 (6.0%)	2/49 (4.1%)	12/47 (25.5%)*
(F) Thyroid				
adenoma	3/49 (7.3%)	5/48 (10.4%)	9/50 (18.0%)	3/41 (7.3%)
adenocarcinoma	0/49 (0%)	0/48 (0%)	0/50 (0%)	1/41 (2.4%)
combined	3/49 (7.3%)	5/48 (10.4%)	9/50 (18.0%)	4/41 (9.8%)
(F) Uterus				
adenoma	0/49 (0%)	1/48 (2.1%)	0/50 (0%)	0/41 (0%)
adenocarcinoma[c]	4/49 (8.2%)	3/48 (6.3%)	9/50 (18.0%)	8/41 (19.5%)
combined	4/49 (8.2%)	4/48 (8.3%)	9/50 (18.0%)	8/41 (19.5%)
(F) Mammary gland				
adenoma	1/49 (2.0%)	0/50 (0%)	0/50 (0%)	1/41 (2.4%)
adenocarcinoma	0/49 (0%)	0/50 (0%)	1/50 (2.0%)	0/41 (0%)
combined	1/49 (2.0%)	0/50 (0%)	1/50 (2.0%)	1/41 (2.4%)

a/ The incidence was based on animals at risk (animals survived past week 52). Only sites that were highlighted in all 3 rat oncogenicity studies were listed.

b/ The incidence at 50 ppm exceeded the highest possible range of the historical incidence (highest: 23.5%, average: 6.5%) based on 1211 control animals.

c/ The incidences at the 10 and 50 ppm levels exceeded the highest range of historical incidence (0-16.3%, average: 7.8%) based on 1236 control animals.

* Fisher exact test at $p<0.05$.

The lifetime study by Daly and Hogan (1983) in Sprague-Dawley CD rats was accepted for filling the SB950 data requirement of oncogenicity testing in rats. Nevertheless, the evaluation of the oncogenic potential was compromised due to the excessive early mortality (only 33-42% survival at the end of 24 months) and the high incidence (greater than 50%) of chronic interstitial pneumonia in all dose groups. It should also be noted that, in spite of the generally high mortality, the surviving animals were kept beyond the common study period of 2 years. Except for the 5 animals per group killed on day 736 ("interim" sacrifices), the study was not terminated until month 25 for the males and month 28 for the females. The study report highlighted the occurrences of pituitary adenoma, adrenal adenoma and carcinoma, and mammary gland tumors in female rats. However, it stated that they were not treatment related because the incidences were not different between the controls and the treatment groups.

Table 11 summarizes the incidences of endocrine and other tumors highlighted in both this study and the aforementioned study by Bomhard et al. (1981) in Wistar rats. Excluded from the table were pituitary tumors in male and female rats and adrenal tumors in the females because the control incidences were very high: 37.5% for male pituitary adenomas, 71.2% for female pituitary adenomas, and 53.3% for female adrenal tumors. Almost all tumors in the thyroid, mammary gland, and uterus were detected on or beyond day 736, except the thyroid carcinoma detected on day 523 in a female rat at 0.5 ppm and the uterus stromal sarcoma detected on day 401 in a control rat. None of the tumor incidences in the treatment groups were statistically significantly different from the concurrent controls.

Three sets of historical incidences are available for comparison: The data on Sprague-Dawley CD® rats (Crl:CD®BR) compiled by McMartin et al. (1992) from 9 studies between 1984-91, the data compiled by Chandra et al. (1992) from 17 studies between 1986-92, and the data compiled by Lang (1992) from up to 36 studies with VAF® rats between April 1984 to February 1989. The data reported by Chandra et al. (1992) consisted only of the average incidence without the ranges. It appears that substantial variation in the historical data exists between conducting laboratories. The concurrent controls from the study by Daly and Hogan (1983) generally stayed within these wide historical ranges, albeit the incidences at some sites were at the high end of the historical range.

The incidence of adrenal adenomas in the males at 5.0 ppm (21.1%) and 50 ppm (20.3%) exceeded the historical range. The reported historical range was 0-3% (ave. 1.6%) by McMartin et al. (1992) and 1.4-16.4% (ave. 2.88%) by Lang (1992). It should be noted that adrenal cortex adenomas were also found in F_0 male rats in a 2-generation reproduction study by Daly and Hogan (1982) (see: Section III.F., **REPRODUCTIVE TOXICITY**). Among the 10 male rats per treatment groups (0, 0.5, 5.0, 25 ppm methyl parathion in the diet) that were examined histopathologically after only 23 weeks of exposure, 2 rats at the high dose had adenomas in the adrenal cortex while no tumors were found in any other groups. This incidence rate of 20% also exceeded the historical range provided in McMartin et al. (1992) and Lang (1992). In a rebuttal to the evaluation by DPR (formerly under Department of Food and Agriculture) regarding the reproductive toxicity study, the registrant (A/S Cheminova, 1990) noted a historical range of 1.6 to 33% for adrenal cortex adenomas from the conducting laboratory Bio/dynamics. The high end of the range was much higher than the 16.4% recorded in the open literature. The claim of a historical range as high as 33% cannot be validated because the database for the quoted range was not provided in the rebuttal.

One animal per dose group at the low (0.5 ppm) and high (50 ppm) dose groups had uterus endometrial adenocarcinoma while none was reported in the concurrent controls. These tumors appeared to be rare. The reported historical range compiled by McMartin et al. (1992) was 0-1.4% (ave. 0.5%) from a total of 584 animals. The historical data selected from 7 out of 13 sets of data compiled by Lang (1992) to represent the same period of study (1980-85) showed a range of 0-2.8% (ave. 0.7%) out of 421 animals. This included five sets of data with the zero incidence 0/259 (0%) and two sets at 1/90 (1.1%) and 2/72 (2.8%).

Table 11. Tumor Incidences from a Lifetime Feeding Study in Sprague-Dawley CD Rats Conducted by Daly and Hogan (1983)[a]

Sex/Tumor site/type	0 ppm	0.5 ppm	5.0 ppm	50 ppm
(M) Adrenal cortex[b]				
adenoma	9/57 (15.8%)	9/56 (16.1%)	12/57 (21.1%)	12/59 (20.3%)
carcinoma	0/57 (0%)	1/56 (1.8%)	0/57 (0%)	1/59 (1.7%)
combined	9/57 (15.8%)	10/56 (17.9%)	12/57 (21.1%)	13/59 (22.0%)
(M) Thyroid follicular cell				
adenoma	0/56 (0%)	0/55 (0%)	0/57 (0%)	0/54 (0%)
carcinoma	0/56 (0%)	0/55 (0%)	1/57 (1.8%)	2/54 (3.7%)
combined	0/56 (0%)	0/55 (0%)	1/57 (1.8%)	2/54 (3.7%)
(F) Thyroid follicular cell				
adenoma	1/57 (1.8%)	0/60 (0%)	0/58 (0%)	2/53 (3.8%)
carcinoma	0/57 (0%)	3/60 (5%)	1/58 (1.7%)	1/53 (1.9%)
combined	1/57 (1.8%)	3/60 (5%)	1/58 (1.7%)	3/53 (5.7%)
(F) Mammary gland				
adenoma	1/58 (1.7%)	0/54 (0%)	0/56 (0%)	4/52 (7.7%)
carcinoma	5/58 (8.6%)	1/54 (1.9%)	3/56 (5.4%)	3/52 (5.8%)
combined	6/58 (10.3%)	1/54 (1.9%)	3/56 (5.4%)	7/52 (13.5%)
(F) Uterus endometrial				
adenocarcinoma[c]	0/60 (0%)	1/60 (1.7%)	0/60 (0%)	1/54 (1.9%)
stromal sarcoma	1/60 (1.7%)	0/60 (0%)	1/60 (1.7%)	1/54 (1.9%)
Undifferentiated neoplasm	0/60 (0%)	0/60 (0%)	0/60 (0%)	1/54 (1.9%)

a/ The study continued for 25 months in the males and 27.6 months in the females. The incidences were based on animals at risk (animals survived beyond 52 weeks or the first appearance of tumors) and excluded animals whose specific tissues were not examined.

b/ The incidence at 5.0 and 50 ppm exceeded the range of historical incidence (0-3%, ave. 1.6% and 1.4-16.4%, ave. 2.88%) in the two available databases in the literature.

c/ The incidence at 0.5 and 50 ppm exceeded the range of historical incidence (0-1.4%) in the two available databases in the literature.

A third oncogenicity study was conducted by NCI (1979) in Fischer F344 rats. Groups of 50 rats per sex were fed diets containing 20 or 40 ppm methyl parathion (94.6% pure) for 105 weeks. A group of 20 untreated rats per sex served as matched controls. Decreases in the mean body weight at the treatment groups were reported as dose-related. Females at 40 ppm had a much higher mortality rate. The respective survival rates for the control, mid, and high dose groups were 96%, 83% and 46% at the end of the study. None of the tumor incidences in the treatment groups were statistically significantly different (by both Fisher exact test and Cochran-Armitage trend test) from the incidence in the 20 matched controls. The comparison was somewhat limited by the low number of animals in the control groups. Tumor incidences of the specific sites and types highlighted in the previous two studies are presented in Table 12. The tumor types selected for the tabulation also encompassed those that appeared to have higher incidences at the treatment groups from this study, specifically tumors in the adrenal cortex and thyroid follicular cells. For the same reason as noted for the previous study, the incidence of pituitary tumors was not included in the table because of an overall high incidence in all groups (45% and 60% in the males and female controls). The study did not report the incidences of adenoma or carcinoma in the mammary gland or uterus. No evidence of oncogenicity was indicated in this study.

Table 12. Tumor Incidences from a 105-week Feeding Study in F344 rats Conducted by the National Cancer Institute (NCI, 1979)[a]

Sex/Tumor site/type	0 ppm	20 ppm	40 ppm
Adrenal cortex adenoma			
Males	0/20 (0%)	0/50 (0%)	2/50 (4.0%)
Females	1/20 (5.0%)	2/50 (4.0%)	0/47 (0%)
Adrenal pheochromocytoma			
Males	3/20 (15.0%)	6/50 (12.0%)	5/50 (10.0%)
Females	0/20 (0%)	1/50 (2.0%)	0/47 (0%)
Thyroid follicular cell carcinoma			
Males	0/20 (0%)	0/48 (0%)	1/49 (2.0%)
Females[b]	-	- -	
Thyroid C-cell adenoma/carcinoma			
Males	3/20 (15.0%)	3/48 (6.3%)	3/49 (6.1%)
Females	1/20 (5.0%)	1/49 (2.0%)	0/47 (0%)
Mammary gland fibroadenoma			
Males	0/20 (0%)	1/50 (2.0%)	0/50 (0%)
Females	5/20 (25%)	2/50 (4.0%)	0/47 (0%)

a/ The incidences were based on the number of animals examined. No incidence of mammary gland adenoma or carcinoma was reported

b/ Not reported.

III.D.2.b. Oral Studies – Mice

Under the experimental conditions, no statistically significant increase in tumor incidences was found in the two available studies in B6C3F1 mice.

The study by Eiben (1991) in B6C3F1 mice was judged acceptable for filling the SB950 data requirement of testing in mice. The report concluded that no increase in the tumor incidence was evident in this study. The only tumor that showed some increase in the treatment groups was the lung bronchiolo-alveolar tumor. The incidences in the male and females mice are presented in Table 13. The incidences in the treatment groups were not statistically different from the controls. The toxicities at the high dose groups were previously described (see: Section 8.2). Plasma, RBC, and brain ChE measured at 52 and 104 weeks were only 11-54% of the controls (Table 5). Other significant effects included increased death (6%) at week 52, reduced (13-15%) food consumption accompanied by increased body weight (10-20%), decreased relative organ weights, increased incidence of animals with "poor general condition", and the appearance of cholinergic signs (i.e., tremors, paralysis). Based on these effects, it was judged that the dose range was sufficiently high to meet the FIFRA study requirement.

Table 13. Tumor Incidences from a 2-year study in B6C3F1 Mice Conducted by Eiben (1991)[a].

Sex/Tumor site/type	0 ppm	1 ppm	7 ppm	50 ppm
(M) Lung, bronchiolo-alveolar				
adenoma	1/50 (2.0%)	6/50 (12.0%)	4/49 (8.2%)	4/46 (8.7%)
carcinoma	2/50 (4.0%)	3/50 (6.0%)	3/49 (6.1%)	1/46 (2.2%)
combined	3/50 (6.0%)	9/50 (18.0%)	7/49 (14.3%)	5/46 (10.9%)
(F) Lung, bronchiolo-alveolar				
adenoma	2/49 (4.1%)	1/48 (2.1%)	1/49 (2.0%)	2/47 (4.3%)
carcinoma	0/49 (0%)	0/48 (0%)	0/49 (0%)	1/47 (2.1%)
combined	2/49 (4.1%)	1/48 (2.1%)	1/49 (2.0%)	3/47 (6.4%)

a/ The incidence was based on animals at risk (animals survived past week 52).

No evidence of oncogenicity was found in the bioassay conducted by the NCI in B6C3F1 mice (NCI, 1979). Groups of 50 mice per sex were initially fed diets containing 62.5 or 125 ppm methyl parathion (94.6% pure) for 37 weeks. The dose levels for the respective groups of males were then reduced to 20 and 50 ppm for the remaining 65 weeks of the bioassay because of a substantial decrease in body weight gain (down to approximately 70-86% of the controls) by week 37. The time-weighted-average levels in the diet during the entire experimental period were 35 and 77 ppm. The control groups consisted of only 20 untreated mice per sex. The body weight of mice at the high dose level was slightly lower than the controls. No effects on mortality or tumor occurrences were noted at any treatment levels. Similar to the aforementioned study by Eiben (1991), the lung was the only site that showed an apparent increase in the incidence, although they were not statistically different from the controls. The incidence data are summarized in Table 14.

Table 14. Tumor Incidences from a 104-week Feeding Study in B6C3F1 Mice Conducted by the National Cancer Institute (NCI, 1979)[a]

Tumor site/type	0 ppm	62.5 ppm[b]	125 ppm[c]
(M) Lung Alveolar/Bronchiolar			
adenoma	1/19 (5.3%)	5/50 (10.0%)	5/49 (10.2%)
Carcinoma	0/19 (0%)	5/50 (10.0%)	3/49 (6.1%)
combined	1/19 (5.3%)	10/50 (20.0%)	8/49 (16.3%)
(F) Lung Alveolar/Bronchiolar			
adenoma	0/19 (0%)	1/49 (2.0%)	1/48 (2.1%)
Carcinoma	0/19 (0%)	2/49 (4.1%)	1/48 (2.1%)
combined	0/19 (0%)	3/49 (6.1%)	2/48 (4.2%)

a/ The incidences were based on the number of animals examined.
b/ The dose in the males was reduced to 20 ppm after week 37. The time-weighted-average dose was 35 ppm.
c/ The dose in the males was reduced to 50 ppm after week 37. The time-weighted-average dose was 77 ppm.

III.E. GENOTOXICITY

Summary: Methyl parathion was tested for genotoxic potential in many *in vitro* and *in vivo* systems. Reports of studies by Herbold (1980, 1982a,b, 1984) and Curren (1989) are on file at DPR. These studies were judged sufficient for filling the SB950 data requirement of genotoxicity testing. Methyl parathion was tested positive by the Ames tests. In addition, many genotoxicity studies on methyl parathion were also available in the published literature. Collectively, they showed that methyl parathion is genotoxic in laboratory studies. The overall weight of evidence indicates that methyl parathion has the potential to cause changes in genetic materials in humans.

III.E.1. Gene Mutation

The results of *in vitro* and *in vivo* gene mutation assays are summarized in Table 15. Methyl parathion induced base-pair substitution in *S. typhimurium* strains TA100 and TA1535, but not in *E. coli*. Methyl parathion was positive in one of the two sex-linked recessive lethal assays with *Drosophila melanogaster*.

III.E.2. Structural Chromosomal Aberrations

The results of assays on chromosomal damage are summarized in Table 16. Except for the study by Kumar et al. (1993), all are *in vivo* studies. The micronucleus tests in rats and mice were positive except in the mouse study by Herbold (1982b). The dose level in this study may not be sufficiently high, since no toxicity was observed. Two of the three chromosomal aberration tests in Wistar rats showed positive results. The negative study by Nehez et al. (1994) was a longer term study at a lower dose range. The two chromosomal aberration tests in mice were negative. However, chromosomal aberrations were detected among humans after acute suicidal or occupational exposures (van Bao et al., 1974) and in cotton field workers exposed to a number of pesticides including methyl parathion (Rupa et al., 1989). The four dominant lethal tests in mice showed negative results.

III.E.3. Other Genotoxic Effects

Test results on DNA binding, damage, and repair capabilities are summarized in Table 17, with results on sister chromatid exchange presented in Table 18. *In vivo* and *in vitro* binding of methyl parathion to DNA was reported in rats and mice (Bartoli et al., 1991). The *in vitro* binding appeared to require the activation of methyl parathion by P450-dependent mixed function oxidases and microsomal GSH-transferases. DNA damage was also demonstrated in repair-deficient *S. typhimurium* (TA1538/TA1978) (Rashid and Mumma, 1984). A 10-fold elevation of DNA breakage in Col-E1 plasmid was reported (Griffin and Hill, 1978). Marginal induction of mitotic recombination was also reported in *Saccharomyces cerevisiae* D3 (Simmon et al., 1977). No unscheduled DNA synthesis (UDS) was detected in either human WI-38 cells (Simmon et al., 1977) or rat primary hepatocytes (Curren, 1989). The UDS assay detects DNA damage through monitoring the DNA repair capacity. It is relatively insensitive as a mutagenicity screen; i.e., negative results do not refute the potential for mutagenicity while positive results are highly indicative of the mutagenicity potential of a chemical. Methyl parathion was not shown to cause lethality in repair-deficient strains of *E. coli* and *B. subtilis* (Simmon et al., 1977; Rashid and Mumma, 1984).

Table 15. Effects of Methyl Parathion on Gene Mutation[a]

Test System/Strain[b]	Route/Dose	Activation	Results	References	Comments
S. typhimurium TA100, TA1535, TA1537, TA1538	1, 5, 10, 50, 100, 500, 1000 µg/plate (80% pure)	±; m	neg	Simmon et al., 1977	# plates/dose not specified. Positive control for only TA1538 (+S9). No statistical difference between controls and treatment.
S. typhimurium TA98, TA100, TA1535, TA1538	20, 100, 500, 1000, 2000, 2500, 4000, 8000 µg/plate (94.3-94.5% pure)	±; r	pos	Herbold, 1980	4 plates/dose. No control for -S9 series. Positive in TA100 (+S9) and TA1535 (+S9).
S. typhimurium TA98, TA100, TA1535, TA1537	20, 100, 400, 500, 600, 625, 780, 900, 1000-10000 µg/plate (95.6-96.1% pure)	±; r	pos	*Herbold, 1982a	4 plates/dose. Equivocal results in TA98(+S9). Positive in TA100 (+S9).
S. typhimurium TA98, TA100, TA1535, TA1537	10, 33, 100, 333, 445 667, 1000, 1500, 2000 µg/plate (purity ns)	±; r, h	pos	Haworth et al., 1983	Preincubation procedure used. # plates/dose not specified. Positive results in TA100 (+S9).
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	5, 10, 25, 50, 100, 125, 250, 325, 635 1250 µg/plate (99.4% pure)	±; r	pos	Rashid and Mumma, 1984	3-5 plates/dose. Dose-related increase in TA100 (+ S9) (>2-fold at high dose). Cytotoxic at two highest doses in TA1537 (+S9).
S. typhimurium TA100	0.5, 5, 50, 500 µg/plate (purity ns)	±; ns	pos	Breau et al., 1985	3 plates/dose. Positive at 500 µg/ml.

(continued)

Table 15. Effects of Methyl Parathion on Gene Mutation[a] (cont.)

Test System/Strain[b]	Route/Dose	Activation	Results	References	Comments
S. typhimurium TA100NR	50, 100 μg/plate (purity ns)	-	neg	Vijayaraghavan and Nagarajan, 1994	no details provided
E. coli WP2 WP2uvrA WP67 CM611, CM571	250, 500, 1000, 2000 μg/plate (99.4% pure)	±; r	neg	Rashid and Mumma, 1984	3-5 plates/dose. Effect significant at the highest dose (+S9) with WP2,WP2uvrA, and WP67, < 2-x of the control frequency.
E. coli WP2	1, 10, 50, 100 μg/plate (80% pure)	±; m	neg	Simmon et al., 1977	# plates/dose not specified. No treatment-related effects (ave # revertants/plate).
SLRL *D. melanogaster*	0.25 and 5.0 ppm (purity ns)	feed	neg	Waters et al., 1980	Sample size not specified.
SLRL *D. melanogaster* M-5	0.0315, 0.063, 0.125 ppm (purity NS) to 24, 48, & 72 h larvae for 96, 72 & 48 h, respectively.	feed	pos	Tripathy et al., 1987	66-78 males/exposure time/dose. 3 of the 75 24-h larvae at 0.063 ppm had 2 lethal chromosomes each, indicative of mutation in mitotically dividing spermatogonia.

* Studies acceptable for filing the SB950 data requirements.

a/ Abbreviations: ns, purity not stated; ±, with and without microsomal S9 fraction; h, hamster liver microsomal S9 fraction; m, mouse liver microsomal S9 fraction; r, rat liver microsomal S9 fraction; pos: positive results; neg, negative results.

b/ *Salmonella typhimurium*; *Escherichia coli*, *Drosophila melanogaster*; SLRL = Sex-linked recessive lethal test.

Table 16. Effects of Methyl Parathion on Chromosomal Damage - *in vivo* Studies[a].

Test	Species/ cell line	Route/ Dose	Activation	Results	References	Comments
Micro-nuclei	Rat (Wistar)	1, 2, 4 mg/kg (purity ns); single dose	i.p.	pos	Grover & Malhi, 1985	5 males/dose; Bone marrow examined 30 hours after dosing. Effect dose-related.
Micro nuclei	Rat (Wistar)	3, 5 mg/kg (purity ns); single dose	i.p.	pos	Vijayaraghavan & Nagarajan, 1994	4 rats/group, bone marrow examined 1 and 2 days after dosing; ~ 4-fold increase at 5 mg/kg on day 2; statistically significant
Micro-nuclei	Mouse (Bor: NMRI)	5, 10 mg/kg; (95.6-96.1% pure); 2 days	gavage	neg	Herbold, 1982b	5 mice/sex/dose. Bone marrow examined 6 hours after second dosing. No toxicity. Treatment not different from controls ($p<0.05$).
Micro-nuclei	Mouse (Swiss)	9.4, 18.8, 37.5, 75 mg/kg, (purity ns); single dose	gavage	pos	Mathew et al., 1990	4 females/time/dose. Bone marrow examined 24, 48, & 72 hours after dosing. Effect dose-related.
Chrom. Aberration	Rat (Wistar)	0.5, 1.0, 2.0 mg/kg; (purity ns); 5 days	i.p.	pos	Mahli & Grover, 1987	5 males/dose, 30-35 cells/rat. Bone marrow examined 24 Hours after last dose. Effect dose-related.
Chrom, Aberration	Rat (Wistar)	3, 5 mg/kg (purity ns); single dose	i.p.	pos	Vijayaradhavan & Nagarajan, 1994	200 bone marrow cells/rat, 2.5-5-fold increase; statistically significant.

(continued)

Table 16. Effects of Methyl Parathion on Chromosomal Damage - *in vivo* Studies[a] (cont.).

Test	Species/ cell line	Route/ Dose	Activation	Results	References	Comments
Chrom. Aberration	Rats (Wistar)	0.25, 0.33, 0.50 mg/kg; (90% pure); 6 wks	gavage	neg	Nehez et al., 1994	10 male rats per group; chromosomes from bone marrow cells examined 1 day after the last treatment.
Chrom. Aberration	Mouse (Q)	10 mg/kg (99% pure), 1 dose	i.p.	neg	Degraeve et al., 1984a	20 males/dose. Spermatocytes examined 10-15 days after dosing. Treatments not different from controls (Chi-square test)
Chrom. Aberration	Mouse (Q)	0.15 ppm (99% pure), 5 d/wk, 7 wks	drinking water	neg	Degraeve et al., 1984b	8 males/dose. Bone marrow, spermatogonia, and spermatocytes examined after 7 weeks. No treatments-related difference (Chi-square test).
Chrom. Aberration	Human	unknown dose of Wofatox; acute	oral/ exposure	pos/neg other	van Bao et al., 1974	57-100 lymphocytes/person, 4 suicides, 1 worker; age 20-53. Significant effect at 1 month. No effect immediately or 6 months after exposure.
Chrom. Aberration	Human	unknown dose; chronic (1-9 months)	unknown	neg	de Cassia Stocco et al., 1982	200 lymphocytes/person, 15 male workers (age 19-49); blood ChE < 75% of controls (13 men; age 19-38). No statistically significant effects.
Chrom. Aberration	Human	unknown dose; chronic (5-25 yrs) exposure to cotton pesticides	oral/others	pos	Rupa et al., 1989	200 lymphocytes/person, 52 male workers (age 21-47). Increased aberrations over the controls (age 22-42; 25 male workers).

(continued)

Table 16. Effects of methyl parathion on chromosomal damage - *in vivo* studies[a] (cont.).

Test	Species/ cell line	Route/ Dose	Activation	Results	References	Comments
Chrom. Aberration	Human	0.02, 0.04, 0.08, 0.16 µg/ml	*in vitro*	neg	Rupa et al., 1990	tested 3 times; treated for 24, 48, or 72 h. reported no effects (data not shown)
Chrom. Aberration	Human	0.08, 0.16 µg/ml (98% pure)	*in vitro*	pos/neg	Kumar et al., 1993	used peripheral lymphocytes; statistically significant at 0.16 µg/ml in chronic smokers (alcoholics or not); no effects in non-smokers.
Dominant Lethal	Mouse (ICR/ SIM)	20, 40, 80 ppm (80% pure); 7 wks	feed	neg	Simmon et al., 1977	20 males/dose. Mated 1:2 weekly for 8 weeks at the end of 7 week exposure. No statistical difference (Chi-square test; $p>0.01$)
Dominant Lethal	Mouse (Bor: NMRI)	10 mg/kg (95.7% pure); single dose	gavage	neg	*Herbold, 1984	46-50 males/dose. Mated 1:1 every 4 day; 48 days. No statistical difference ($p>0.05$)
Dominant Lethal	Mouse (Q)	0.15 ppm (99% pure), 5 d/wk, 7 wks	drinking water	neg	Degraeve et al., 1984b	20 males/dose. Mated 1:4; 1 week. Examined 14 days after mating. No statistical difference (Chi-square test).
Dominant Lethal	Mouse (Q)	10 mg/kg (99% pure) single dose	i.p. 1 dose	neg	Degraeve & Moutschen, 1984	5 males/dose. Mated 1:4 weekly; 7 weeks. No statistical difference (Chi-square test).

* Study acceptable for filing the SB950 data requirements.

a/ Abbreviations: Chrom, Chromosomal; ns, purity not stated; i.p., intraperitoneal injection.

Table 17. Effects of Methyl Parathion on DNA[a].

Test	Species/ Cell line	Route/ Dose	Activation	Results	References	Comments
DNA Binding	Rat (Wistar) Mouse	1.31, 0.033 μmol/kg[b] (99% pure)	i.p.	pos	Bartoli et al., 1991	*In vivo* (1.31 μmol/kg): 6 male rats, 24 mice; binding to liver, kidney, lung macromolecules (DNA, RNA, proteins). *In vitro* (0.033 μmol/kg): microsomal/cytosolic fractions of organs of 20 treated rats; binding to calf thymus DNA.
UDS	Rat Primary Hepatocytes	0.0003, 0.001, 0.003, 0.01, 0.02, 0.03 μl/ml (purity ns)	–	neg	*Curren, 1989	150 cells/dose. No dose-related increase; no significant increase of net nuclear count ≥ 5.
UDS	Human WI-38	10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3} M (80% pure)	±; m	neg	Simmon et al., 1977	3-6 replicates/dose. No treatment-related effect.
DNA damage	*S. typhimurium*; TA1538/ TA1978	250, 500, 1000 μg/disc (99.4% pure)	–	pos	Rashid & Mumma, 1984	3 plates/dose. Dose-related increase (2-5 fold) in repair-deficient TA1538.
DNA damage	*E. coli* W3110/ P3478	1 mg/disc (80% pure)	–	neg	Simmon et al., 1977	3 replicates. No difference in the diameter of inhibition zone.
DNA damage	*E. coli* K-12; WP2	250, 500, 1000 μg/disc (99.4% pure)	–	neg	Rashid & Mumma, 1984	3 plates/dose. No difference in the diameter of inhibition zone with strains deficient in DNA polymerase A and repair mechanism.

(continued)

Table 17. Effects of Methyl Parathion on DNA[a] (cont.).

Test	Species/ Cell line	Route/ Dose	Activation	Results	References[b]	Comments
DNA damage	*B. subtilis* H17/M45	1 mg/disc (80% pure)	–	neg	Simmon et al.,1977	3 replicates. Same inhibition zone diameter between repair deficient and proficient strains.
DNA break	Col-E1 plasmid	1 μg/ml in hexane (purity ns)	–	pos	Griffin & Hill, 1978	Incubation period ½ day to 4 weeks. DNA break elevated approx. 10-fold.
Mitotic Recomb.	*Sac. cerevisiae;* D3	50 mg/ml (80% pure)	±; m	pos	Simmon et al., 1977	2 trials. Effects marginal; >3-fold increase in. the number of mitotic recombinants.

* Study acceptable for filing the SB950 data requirements.

a/ Abbreviations: UDS, unscheduled DNA synthesis; *S.*, *Salmonella*; *E.*, *Escherichia*; *B.*, *Bacillus*; *Sac., Saccharomyces;* ns - purity not stated; +, with microsomal S9 fraction; -, without microsomal S9 fraction; m, mouse liver microsomal fraction S9.

b/ The reported dose was in mmol/kg. However, according to the study report, the specificity was 76 mCi/mmol. The administered 100 μCi should instead be 1.31 μmol/kg.

Table 18. Effects of Methyl Parathion on *in vitro* Induction of Sister Chromatid Exchanges[a] .

Test[a]	Species/ cell line[b]	Route/ Dose[c]	Activation[d]	Results	References	Comments
SCE	V79	5, 20 μg/ml (96.8% pure)	+; r	pos	Chen et al., 1982	50 cells/dose, one trial. Significant effects at 20 μg/ml.
SCE	V79; Human lymphoma B35M	10, 20, 40 μg/ml (96.8% pure)	–	pos	Chen et al., 1981	50 cells/dose, 2 replicates per cell line. Dose-related cell cycle delay was observed.
SCE	Human lymphoid LAZ007	0.02, 0.2, 2, and 20 μg/ml (purity ns)[4]	±; r	pos	Sobti et al., 1982	25 cells/dose, one trial. Significant SCE increase at 2, 20 μg/ml. S-9 had no additional effect. Dose-related cell cycle delay noted.
SCE	Human lymphocytes	9.5, 19, 38 μg/ml (purity ns)	–	pos	Singh et al., 1984	30 cells/sample/dose, 10 samples. Dose-related delay of cell cycle.
SCE	Human lymphocytes	0.5, 1, 2, 3, 4, 5, 6, 9, 10, 13 ppm (purity ns)	–	pos	Gomez-Arroyo et al., 1987	50 cells/dose, 2 replicates. Dose-dependent increase in SCE up to 4 ppm. Cell death occurred at 13 ppm.
SCE	Human lymphocytes	0.02. 0.04, 0.08, 0.16 μg/ml	–	pos	Rupa et al., 1990	positive at and above 0.04 μg/ml after 48 and 72 hrs of treatment.

a/ Abbreviations: SCE, Sister Chromatid Exchange; V 79: Chinese hamster lung cell line V79; ns. purity not stated; ±, with and without microsomal S9 fraction; r, rat liver microsomal S9 fractio

All six *in vitro* studies on sister chromatid exchange (SCE) (Table 18) showed positive results in the following mammalian cell lines: Chinese hamster lung cell V79, human lymphoma B35M and LAZ007, and human lymphocytes. Technically, SCE is an exchange of identical information between two chromatids. As such, the significance of a positive SCE test in risk assessment is less certain than other genotoxicity studies previously presented. SCE does not generally have good concordance with cancer bioassays. As a screening tool for oncogenicity bioassays, the reported specificity of SCE tests was 45% (Tennant et al., 1987).

III.F. REPRODUCTIVE TOXICITY

There was some indication that OPs in general may affect the menstrual cycle and cause an early menopause in humans. However, no data on human reproductive effects specifically to methyl parathion are available. There was some indication of correlation between serum LH and occupational exposures to three OPs (methyl parathion, ethyl parathion, methamidophos). Three multi generation reproductive toxicity studies in rats were submitted to DPR under the SB950 data requirement. One study was only in a summary form. Decreased pup survival was consistently found in all three studies. The search of the open literature revealed two reports showing ovarian toxicity in rats and one study showing possible sperm abnormalities in mice. Testicular and reproductive effects have also been reported in avian species.

III.F.1. Evidence in Humans

Reproductive effects from exposures to mixtures of OPs have been documented by Nakazawa and Nakazawa (1974) and Mattison (1985) among women in agriculture. These effects included abnormal menstruation (e.g., hypermenorrhea, oligomenorrhea, amenorrhea), and early menopause. On the other hand, Willis et al. (1993) found no effects of pesticide exposures (including methyl parathion) on the pregnancy outcome among 535 women enrolled in a southern California community clinic perinatal program.

No epidemiological data specific to methyl parathion alone are available. Padungtod et al. (1998) studied the profile of reproductive hormone (serum and urinary follicle-stimulating hormone, FSH; luteinizing hormone, LH; testosterone or its metabolite, urinary estrone conjugate E_1C) among 34 male Chinese factory workers, 20-40 years old. The subjects worked for at least 3 months in a factory that manufactured methyl and ethyl parathion, and methamidophos. The analysis showed that only the increase in serum LH was significantly correlated to pesticide exposures. The authors concluded that OP pesticides had a small effect on male reproductive hormones and suggested that the hormone disturbance might be secondary to potential testicular damage by OPs. A larger sample size is needed for detecting the relationship between OP exposure and serum testosterone or urinary E_1C level.

III.F.2. Oral Studies – Rat

Kronenberg et al. (1978) reported a 3-generation study conducted by Lobdell et al. (1966; as cited in Kronenberg et al., 1978). However, an in-depth review of the study was not possible as the study was only available in a summary form. Rats were administered diets containing 0, 10, or 30 ppm methyl parathion. Effects reported at 30 ppm were: tremors in a few F_o rats, reduced survival in weanlings of F_{1a}, F_{1b}, and F_{2a} groups, increased number of stillborn in F_{2b} and F_{3b}, and reduced reproductive performance in F_{2b} at the second mating, with only 41% of the rats having litters. Survival was also reduced (unspecified magnitude) in F_{3a} weanlings at 10 ppm. Therefore, the 10 ppm in the diet would be the LOEL. Alternately, the U.S. EPA (1988) identified 10 ppm in the diet as the No-Observed-Adverse-Effect-Level (NOAEL).

The 2-generation study by Daly and Hogan (1982) was judged acceptable for filling the SB950 data requirement. Groups of 15 male and 30 female Sprague-Dawley rats were fed diets containing 0, 0.5, 5.0, or 25.0 ppm methyl parathion (93.6% pure) for 14 weeks before

mating, and throughout the mating, gestation, and the lactation period. Many of the F_1 and F_2 pups had intestinal worms. The extent that the presence of worms may confound the evaluation of reproductive toxicity of methyl parathion may not be substantial because its occurrence was similar across all the treatment groups. No mortality occurred at any dose group. Marked reduction of the maternal body weight was evident at 25 ppm throughout the lactation period (Table 19). The reduction in pup body weight gain, which was apparently dose-related, was not statistically significantly different from the controls. The survival of the F_2 pups at day 4 was statistically significantly lower (Dunnett's test; $p \leq 0.05$) at 25 ppm. The respective survival rates from the controls to the highest dose group were: 258/263 (98.1%), 280/284 (98.6%), 219/223 (98.2%), and 199/213 (93.4%). Based on the survival of the pups and the maternal weight gain reduction, the reproductive toxicity and maternal toxicity NOEL of 5 ppm was determined. Estimated from the data on body weight and food intake during the weeks before mating, the dose was approximately 0.4 mg/kg/day at 5 ppm and 2.3 mg/kg/day at 25 ppm in the diet. No data were available for calculating the dose during the gestation and lactation periods.

Although this study was conducted for testing the reproductive toxicity of methyl parathion, the histopathological examination revealed adrenal cortex adenomas in two of the 10 F_0 male rats in the 25 ppm dose groups. The significance of these findings was previously discussed in Section III.D.2.a., **Oral Studies – Rats**

Table 19. The Maternal and Pup Body Weight Gain of Sprague-Dawley Rats in a 2-Generation Study by Daly and Hogan (1982).

Conc. (g) in diet (ppm)[a]	Maternal Body Weight gain (g)								Pup Body Weight gain			
	Gestation day 0-20				Lactation day 0-21				Lactation day 0-21			
	F_0	% of control	F_1	% of control	F_0	% of control	F_1	% of control	F_1	% of control	F_2	% of control
0	116	100	129	100	19	100	19	100	37.7	100	34.1	100
0.5	121	104	124	96	18	95	17	89	40.5	107	33.2	97
5.0	121	104	123	95	18	95	14	74	34.6	92	33.3	98
25	123	106	113	88	-3**	(-16)	-7**	(-37)	32.9	89	30.6	90

**: Significantly different from control at $p \leq 0.01$ (Dunnett's test)
a/ The respective doses at 5 and 25 ppm in the diet were approximately 0.4 and 2.3 mg/kg/day.

In a 3-generation reproductive study by Loser and Eiben (1982), groups of 10 male and 20 female Wistar rats were fed diets containing 0, 2, 10, or 50 ppm methyl parathion (95% pure). One rat from each group of female control, female 10 ppm, and male 50 ppm died. According to the report, the death was not attributed to the treatment. In litters with more than 10 pups, the number of pups was culled to 10 pups per litter 5 days after birth. Data on ChE activity and clinical observations were not available. As shown in Table 20, significant reduction in pup survival up to day 5 and at the end of week 4 consistently occurred at 10 and 50 ppm. Maternal body weight and behavior were not affected at the dose range tested. Pup weight reduction and growth retardation occurred at 50 ppm. Based on the reduction of pup survival at 10 ppm, a reproductive toxicity NOEL of 2 ppm was determined. The report lacked a quality assurance statement, diet and test article analysis, food consumption measurements, complete clinical observations, necropsy data, and proper body weight measurements. Without these data, an estimation of dose was not possible. Based on the dietary patterns of Wistar rats as reported in the chronic study by Bomhard et al. (1981), the respective doses at 2 and 10 ppm were estimated as 0.14 and 0.71 mg/kg/day for the females (see: Section III.D.1. **Chronic Toxicity**).

III.F.3. Male and Female Reproductive Toxicity in Rodents

Mathew et al. (1992) used a sperm abnormality assay to evaluate the toxicity of methyl parathion. Increases in the percentage of abnormal sperms were reported in groups of 5 mice, 1 and 5 weeks after receiving a single oral administration of 9.375, 18.75, 37.50, or 75.00 mg/kg Metacid 50 (manufactured in India, purity not specified). The abnormalities included: amorphous, hookless, banana, folded, and double-headed/tailed sperm. The percentage of abnormalities was greater when scored at 5 weeks than 1 week after dosing with the mean of 12.3% at the highest dose. The implication of the effects with respect to the reproductive outcome is not known. Moreover, the dose levels were much higher than the levels used in rat studies and appeared to be at or exceeded the range of the LD_{50} for mice (Table 1). According to the report, however, the dose levels were 1/16 - ½ of the LD_{50} and no signs of acute toxicity were mentioned. The lack of detail in reporting precludes further evaluation of this report for hazard identification. No other studies are available in the literature for evaluating the potential of methyl parathion in causing sperm morphological abnormalities.

The toxic effects of methyl parathion on the ovaries were studied in hemicastrated rats, which had their right ovary removed (Dhondup and Kaliwal 1997, Asmathbanu and Kaliwal 1997). Hemicastration is known to cause compensatory hypertrophy of the surviving ovary. In the report by Dhondup and Kaliwal (1997), groups of at least 6 Wistar rats, 80-100 days old, were administered methyl parathion (metacid, 50% purity) intraperitoneally at 0, 2.5, 3.5, 4.0, and 5.0 mg/kg/day for 15 days. Hemicastration significantly increased both the ovarian weight with approximately 45% compensatory hypertrophy, and the number of healthy and atretic follicles. There was a dose-related increase in the length of estrous cycles from 4.77 days/cycle to 5.0, 9.0, 12.9, and 15 days/cycle from the low to the high dose groups. On the day of sacrifice (day 16 of treatment), all rats treated with methyl parathion were in diestrus while the controls were in proestrus, estrus, or metestrus. In addition to the prolonged estrus cycles, rats at 4.0 and 5.0 mg/kg/day also had reductions in the body weight gain and relative uterus weight, the compensatory hypertrophy, and the number of healthy follicles. Respectively for these two dose groups, body weight gains were 88 and 49% of the

control. The index of ovarian compensatory hypertrophy (OCH) was calculated as the ratio (in percentage) of the relative ovarian weight between the treatment groups to the sham controls. Compared to the OCH of 45% in the hemicastrated controls, the OCH at 4 and 5 mg/kg/day were only 13 and 8%, respectively. The number of healthy follicles in these two high dose groups were 76 and 70% of the controls. The mechanism for these ovarian effects and alteration of estrus cycles was unknown but the authors noted that these effects did not appear to be directly correlated with the body weight reduction.

Table 20. Pup Survival from a 3-Generation Reproductive Toxicity Study in Wistar Rats by Loser and Eiben (1982).

Conc. in diet[a]	Pup survival rates (% of ave. pups/litter at birth) F1a	F1b	F2a	F2b	F3a	F3b
			Survival to Day 5			
0 ppm	97.8	97.7	94.1	99.0	93.7	91.9
2 ppm	99.4	95.7	99.0**	89.9**	99.3*	98.1
10 ppm	93.4	84.9**	96.8	87.4**	94.7	89.5
50 ppm	22.1**	27.1	18.2**	0**	-	-
			Survival to Week 4[b]			
0 ppm	100	98.1	98.9	92.4	84.5	90.8
2 ppm	99.4	96.3	98.4	87.4	97.9**	97.2*
10 ppm	95.5**	95.7	92.9**	83.2*	96.7**	95.3
50 ppm	44.4**	42.9**	50.0**	-	-	-

Levels of statistical significance as compared to the controls: * for $p \leq 0.05$; ** for $p \leq 0.01$.

a/ The respective doses at 2 and 10 ppm in the diet were approximately 0.14 and 0.71 mg/kg/day.

b/ For litters that had more than 10 pups, the number was reduced to 10 per litter on day 5.

Similar results were reported by Asmathbanu and Kaliwal (1997) in groups of 4-6 hemicastrated female Wistar rats, 80-100 days old, received 5 mg/kg/day methyl parathion (metacid, 50% pure) through i.p. injection for 1, 5, 10, and 15 days. Body weight gain and the relative uterus weight showed a decline throughout the 15 days and were respectively 74% and 78% of the controls after 15 days of treatment, although the difference in the body weight gain were not statistically significant. The number of healthy follicles were 84% and

69% of the controls after 10 and 15 days. The number of normal estrous cycles and the duration of estrus and diestrus were prolonged while the duration for metestrus was shortened.

III.F.4. Oral Studies - Avian Species

Solecki et al. (1996) studied the effects of methyl parathion on the reproduction of Japanese Quail. Male and female birds were fed diets containing 0, 3, 12, or 48 ppm methyl parathion (93.1% pure) and mated for 6 weeks. While no clinical symptoms and behavior changes were observed, statistically significant brain AChE inhibition was noted at all treatment groups (approximately 20% inhibition at 3 ppm). Reproductive effects were noted at 48 ppm. These included the reduction in the number of eggs laid (~20% reduction), egg weight (~9% reduction), and eggshell thickness (7-10% reduction).

Maitra and Sarkar (1996) studied the reproductive effects of methyl parathion in male white throated munias from natural population. Birds received a single oral intubation of 5, 10, or 20 μg/100 g/day methyl parathion were sacrificed on day 1, 5, or 10 and evaluated for AChE activities (brain and testes) and histopathologically (testes). Dose-related brain AChE inhibition was statistically significant ($p \leq 0.05$) at 10 and 20 μg/100 g on day 1 (approximately 30% inhibition) and at all dose levels on day 5 and 10 (up to 50% inhibition). Testicular AChE inhibition was statistically significant only at 10 and 20 μg/100 g after 10 days of dosing (approximately 50% inhibition). Dose-related changes included decreases in the percentage of tubules with healthy germ cells (up to approx. 40%) starting day 1, the seminiferous diameter (up to approx. 50% reduction) starting day 5, and the testicular weight (up to approx. 40%) on 10 days of dosing.

III.G. DEVELOPMENTAL TOXICITY

The embryo-, fetal-, and developmental toxicity of methyl parathion have been studied in rats, rabbits, mice, and avian species. Among the effects reported in rats and rabbits were: lower fetal body weight, increased resorption, reduced pup survival, and abnormalities and variations of ossification. There was also some indication of neurobehavioral effects in rat pups that received *in utero* exposures. In addition to a lower fetal body weight, mouse fetuses that received *in utero* exposures at much higher dose levels also had cleft palate and increased death. Injection of methyl parathion into the air space of chicken eggs resulted in cervical lordosis and scoliosis, cervical muscle atrophy, lower body weight, and retarded growth.

III.G.2. Oral, Gavage and Intraperitoneal Studies - Rat

In a study by Fish (1966), groups of 2-3 Holzmann rats received a single intraperitoneal (i.p.) injection of 4 or 6 mg/kg methyl parathion on day 9 or 15 of gestation and were killed on day 21. Fetuses from rats that received 4 mg/kg on gestation day 15 had lower body weight (81% of the controls). A reduction of the maternal RBC ChE activity (values not given) was noted in all treated rats at 4 and 20 hours after dosing. Tanimura et al. (1967) also reported lower fetal body weight (90% of the controls) in rats that received a single i.p. injection of 15 mg/kg of methyl parathion at on day 12 of gestation. The effect was not observed at 5 or 10 mg/kg.

In a study by Crowder et al. (1980) groups of 3 Sprague-Dawley rats received 0 or 1 mg/kg/day methyl parathion (99.9% pure), via gavage, on day 7 through day 15 of gestation. An increase in pup mortality up to day 15 postpartum was reported (30% in the treated group versus 10% in the controls). The results of neurobehavioral tests showed that neonates of dams that received 1 mg/kg/day methyl parathion had slightly shorter grasp-hold time in the reflex test (approximately 30% reduction in hold time for 15 days old pups, as estimated from a figure in the report). The open field test also showed that pups between 25 and 55 days old from the treatment groups covered a greater area of movement. Methyl parathion treated rats tested at 55 days old also showed some compromised ability to transfer knowledge (i.e., switching direction from right to left) in the maze test. Based on the post-partum survival of pups and the behavioral effects, 1 mg/kg/day was the LOEL.

Gupta et al. (1985) also reported neurobehavioral effects in Wistar-Furth rats at the same dose level (1 mg/kg/day) used in the above study by Crowder et al. (1980). Pregnant rats ($\geq$ 12, number not specified) were orally administered methyl parathion at 1.0 or 1.5 mg/kg/day on day 6 through day 20 of gestation. The results showing positive effects are summarized in Table 21.

Muscle fasciculations and tremors occurred in the dams after 3 to 4 days of exposure 1.5 mg/kg/day, beginning 15-30 minutes after dosing and lasted for 2-4 hours. Maternal body weight gain reduction and increased late resorption also occurred at 1.5 mg/kg/day. Dose-related decreases of ChE activities and a concomitant increase in the activity of choline acetyltransferase (an enzyme catalyzing the synthesis of ACh) were also detected in the brain cortex of dams on day 19 of gestation. The inhibition of ChE was detected in the offspring from both treatment groups on postnatal days 1, 7, 14, 21 and 28 at some or all 4 brain regions examined (i.e., frontal cortex, brain stem, striatum, and hippocampus). Data on day 1

and 14 are provided in Table 21. In addition to ChE inhibition, prenatal exposure resulted in behavioral alternations at 1 mg/kg/day. These included reduced accommodated locomotor activity at 2 months of age and decreased latency in cage emergence and changes in operant behavioral (bar pressing patterns) at 3 months of age (Table 21). However, the cage emergence test showed a slightly prolonged, instead of shortened, emergence time at 1.5 mg/kg/day. The maternal NOEL based on the overt clinical signs was 1 mg/kg/day. However, the lowest tested dose of 1 mg/kg/day was the LOEL based on brain ChE inhibitions in the dams and pups. This LOEL was also supported by the indication of neurobehavioral effects.

Two rat teratology studies (Machemer, 1977; Becker et al., 1987) are on file at DPR. In a study by Machemer (1977), groups of 20 Wistar rats received 0, 0.1, 0.3, or 1.0 mg/kg/day methyl parathion (94.4% pure), via gavage, on days 6 through 15 of gestation. The maternal body weight gain during the treatment period was significantly ($p<0.01$) lower (43% reduction) at 1.0 mg/kg/day. A 5% reduction of fetal body weight ($p<0.05$) also occurred at this dose level. The study was deficient in lacking dosing solution analysis, individual data on body weight, food consumption data, necropsy parameters, fetal examinations, fetal body weight, and clinical observations. Based on the reduction of body weight gain, the maternal and fetal NOEL was 0.3 mg/kg/day.

A study by Becker et al., (1987) was judged acceptable in filling the SB950 data requirement for tests conducted in rats. In this study, groups of 25 pregnant Wistar/HAN rats were administered 0, 0.3, 1.0, or 3.0 mg/kg/day methyl parathion (97% pure) via gavage, on days 6 through 15 of gestation. The activities of ChE were monitored in 10 additional rats at 0 and 3.0 mg/kg/day. The results are summarized in Table 22. The maternal plasma, RBC, and brain ChE were significantly inhibited at 3.0 mg/kg/day on gestation day 16 (one day after the last dosing). A definitive NOEL for the brain ChE inhibition cannot be established because ChE activities were not measured in the low and mid dose groups. Cholinergic signs were not reported in the dams at 3.0 mg/kg/day until day 8 of treatment. However, death (5 of 35 dams; 14.3%) occurred beginning day 7. The cholinergic signs included: somnolence, ataxia, dyspnea, salivation, ventral recumbency, repeated chewing and occasional whining. The food consumption was reduced by approximately 8% at the same dose. Substantial body weight gain reduction was noted at 3 mg/kg/day. Excluding the uterus weight, the adjusted body weight gain throughout the gestation period was 7.0 gm in the controls while dams at 3.0 mg/kg/day had a weight loss of 3.9 gm. Fetal effects, including 8% lower fetal body weight (statistically significant at $p<0.05$) and delayed ossification, also occurred at 3.0 mg/kg/day (Table 22). Although not statistically significant, the incidence of resorption appeared to be dose-related. The maternal and fetal NOEL was 1.0 mg/kg/day.

In a study by Kumar and Devi (1996), groups of 10 Wistar rats received 0, 0.5, 1, and 1.5 mg/kg/day methyl parathion (98% pure) by gavage on day 6 through day 20 of gestation. Maternal and fetal effects were noted at 1.5 mg/kg/day. Maternal toxicities included muscle fasciculations, tremors, prostration, mild clonic convulsions, day 0-19 body weight gain reduction (79% of controls), and reduction of the weight of placenta (53% of controls) and amniotic fluid (80% of control). Fetal body weight at 1.5 mg/kg/day was lower (77% of controls). The increase in resorption appeared to be dose-related (0%, 5%, 8%, 49% from controls to high dose groups) and was statistically significant at 1.5 mg/kg/day. Fetal skeletal anomalies include incomplete bipartite or missing sternebrae, extra or rudimental ribs, and

incomplete ossification; however, the incidences were not significantly different than controls.

Table 21. Maternal and Neonatal Toxicity of Methyl Parathion in Wistar-Furth rats (Data from Gupta et al., 1985)[a].

Effects	Controls	1 mg/kg/day	1.5 mg/kg/day
Maternal			
Brain Cortex ChE (gestation day 19)	100±2.9%	79±3.73%*	40±7.5%*
Brain Cortex CAT[b] (gestation day 19)	10.03±0.17	13.07±0.74*	15.25±1.00*
Weight gain (gestation day 15)	16%	-	11%
Muscle fasciculations, tremors (began after 3-4 days of exposure)	negative	negative	positive[c]
Resorption	0%	-	25%
Pup (postnatal day 1)			
Frontal Cortex ChE	(100%)	63.8±4.0*	55.3±6.9*
Brain Stem ChE	(100%)	82.6±1.6*	52.4±3.5*
Pup (postnatal day 14)			
Frontal Cortex ChE	(100%)	98.0±4.1	59.0±4.9*
Brain Stem ChE	(100%)	83.9±4.9*	62.8±6.7*
Striatum ChE	(100%)	86.1±4.1*	58.9±5.1*
Hippocampus ChE	(100%)	99.8±4.5	52.4±3.7*
Postnatal behavioral tests			
2 months: Accommodated locomotor activity (counts)	133±10	118±9*	100±13
3 months: Cage emergence (sec)	598±144	71±31*	720±120
3-6 months: Operant behavior (sec)[d]	6.8	9.5*	-

a/ Methyl parathion treatment on day 6 through day 20 of gestation. Values for ChE activities in the pups were from 5 to 7 litters (2 rats/liter). Values for behavioral tests were from 8 to12 animals.

b/ CAT: choline acetyltransferase; values in nmol acetylcholine synthesized per hour per mg protein.

c/ Incidence data were not available.

d/ Behavior patterns included the latency to bar press and number of days to an asymptotic rate of bar pressing during acquisition. Values estimated from a bar graph.

* Statistical significance at $p<0.05$.

Table 22. Maternal and Fetal Toxicity of Methyl Parathion in Wistar-HAN rats (Data from Becker et al., 1987)[a].

	Dose (mg/kg/day)			
	0	0.3	1.0	3.0
Maternal ChE (gestation day 16)				
plasma	(100)	-	-	59%**
RBC	(100)	-	-	29%**
brain (100)	-	-	78%**	
Maternal Death (day 7-10)	0% (0/35)	0% (0/25)	0% (0/25)	14.3% (5/35)
Maternal Body Weight gain (% of gestation day 6)				
gestation day 8	1.8%	1.7%	1.3%	1.8%
gestation day 10 5.3%	4.8%	4.8%	2.7%**	
gestation day 12 9.6%	8.3%	8.8%	4.9%**	
gestation day 14 13.6%	12.7%	12.3%	4.9%**	
gestation day 15 15.4%	14.8%	14.0%	5.4%**	
gestation day 16 19.7%	18.3%	17.5%	6.2%**	
gestation day 21 43%	41.9%	40.8%	28.9%**	
Fetal Body weight (g)	4.8±0.1	4.9±0.2	4.8±0.2	4.4±0.5**
Resorption				
number of fetus per litter	15/24 (0.6)	18/24 (0.8)	16/24 (0.7)	20/20 (1.0)
number of litter affected	10/24 (42%)	12/24 (50%)	12/24 (50%)	11/20 (55%)
Fetal Ossification				
incomplete: Cranium (occipital)	1/156 (1%)	- -	- -	12/125 (10%)
non-ossified: cervical vertebrate 1-4	2-13%	4-23%	-	6-26%

a/ Pregnant rats were treated during day 6 through day 15 of gestation.
** Statistically significant at $p<0.01$

III.G.3. Oral and Gavage Studies – Rabbit

Two studies (Renhof, 1984; Hoberman, 1991) are on file at DPR. In a study by Renhof (1984), groups of 12-15 inseminated Himalayan rabbits were administered 0, 0.3, 1.0, or 3.0 mg/kg/day methyl parathion orally on days 6 through 18 of gestation. No embryotoxicity, teratogenicity, or maternal toxicity was found in this study.

A later study by Hoberman (1991) was judged acceptable for filling the SB950 data requirement for tests conducted in rabbits. In this study, groups of 19-20 artificially inseminated New Zealand White rabbits received 0, 0.3, 3.0, and 9.0 mg/kg/day methyl parathion (95.7% pure) by gavage on gestation days 6 through 18. The reduction in maternal RBC ChE activity was statistically significant ($p<0.05$) at all levels of methyl parathion (the respective inhibitions from the low to high dose groups were 18%, 43%, and 75%). The inhibition of plasma ChE was statistically significant ($p<0.01$) only at 9.0 mg/kg/day (at 50% inhibition). No clinical signs of toxicity were observed in the dams during the study. Neither were there any abnormal findings at necropsy. An increased incidence (4 in 141 fetuses) of thickened areas of ossification in the ribs was noted in the fetuses at 9.0 mg/kg/day. The lowest dose of 0.3 mg/kg/day was the maternal LOEL based on a statistically significant RBC ChE inhibition. However, the toxicological significance of 18% RBC ChE inhibition was uncertain without the report of any clinical signs of toxicity. The NOEL for fetal effects was 3.0 mg/kg/day.

III.G.4. Intraperitoneal Studies - Mice

Tanimura et al. (1967) reported developmental effects that were more prominent than what was observed in the aforementioned studies, albeit at a much higher dose range. Cleft palate, increased mortality, and reduced fetal body weight were observed in 13 of the 112 fetuses from mice that received an i.p. injection of methyl parathion at 60 mg/kg on day 10 of gestation. These effects were not found at 20 mg/kg. The dose range applied in this study appeared to exceed the i.p. LD_{50} values compiled in Table 1 (between 8.2 and 11.0 mg/kg). Instead, the report stated that the LD_{50} was near the high dose level. Severe acute toxicities, including ataxia and convulsions, were evident in all treated mice within 30 minutes of dosing. As expected, death occurred to some mice at the high dose.

III.G.5. Additional Studies - Avian Species

A single injection of Wofatox 50 EC (50% methyl parathion emulsifiable concentrate) into the air space of embryonated chicken eggs at 16 and 160 mg/kg and pheasant eggs at 13.5 - 270 mg/kg on day 12 of incubation resulted in cervical lordosis (forward curvature of the spine) and scoliosis (sideway curvature of the spine), and atrophy of the cervical muscles (Varnagy et al., 1984; Varnagy and Deli, 1985). Deli and Kiss (1988) also noted a decrease in cellular content of cytoskeletal proteins (α- and β-tubulin and α-actinin) in the cervical muscles of embryos that received 20 mg/day methyl parathion injections (0.5 ml of 0.4% solution) for 4 or 8 days. The reduction in protein contents may have contributed to the muscular atrophy. Kumar et al. (1992) reported teratogenic signs in developing chickens at much lower dose levels. Chicken embryos were treated with 0, 5, 10, or 50 μg methyl

parathion (in groundnut oil) via a yolk sac route on days 4, 6, and 9 of incubation and sacrificed on day 20. The body weight of the embryos that received 10 and 50 μg methyl parathion was significantly ($p<0.05$) lower (78-83% of the controls). Embryo viability was also reduced at these dose levels. Growth retardation was evident in the shorter body length and leg bones. Teratological effects at these levels included shorter necks, leg muscle hypoplasia, abdominal hernias, and hemorrhagic spots in the brain and upper body.

III.H. NEUROTOXICITY

Methyl parathion caused neurotoxicity in laboratory animals, which was evident from clinical signs, alterations in the behavior and decreases in the ChE activity. Two relatively extensive studies by Minnema (1994a, b) in Sprague-Dawley rats were available to the DPR. Recently, a new acute dietary neurotoxicity study was submitted to the DPR (Weiler, 1999a). Two studies in Wistar rats were published in the open literature (Schulz et al., 1990; Kumar and Desiraju, 1992). The findings by Kumar and Desiraju (1992), which contained data of both acute and subchronic toxicities, are presented under the following Section III.H.1., **Acute Neurotoxicity**.

III.H.1. Acute Neurotoxicity

Kumar and Desiraju (1992) studied the ChE inhibition in 7 regions of the central nervous system in young Wistar rats: cerebellum, motor cortex, hippocampus, hypothalamus, striatum accumbens, ventral brain stem, and spinal cord. Female pups received oral doses of methyl parathion for a number of days: 1-day (1 mg/kg on postnatal day 15), 15-day (0.1 mg/kg from postnatal day 2), or 150-day (0.2 mg/kg/day from postnatal day 2). ChE activities were measured in 3 to 6 rats per dose group. The number of affected CNS regions appeared to increase with the length of the dosing period. The ChE activity was inhibited in the brain stem, motor cortex and cerebellum, beginning at the first measurement interval at 20 minutes after a single exposure (15-25% inhibition). The peak inhibition was approximately 55% at 120 minutes after the exposure. Under the same single dosing regimen, adult (70 days old) rats also showed similar response (approximately 55-60% inhibition) in these 3 regions. Two weeks of dosing resulted in ChE depressions in the brain stem and spinal cord (ChE level not given in the report). The 150-day exposure at 0.2 mg/kg/day starting on postnatal day 2 resulted in at least 24% ChE depression in 5 regions (all but cerebellum and motor cortex). In addition to the changes in the ChE activities, the preliminary study showed that a single exposure of 2.5 mg/kg to rats at postnatal day 15 resulted in death of all pups (number not given). Cholinergic signs ("shivering", salivation, muscular fasciculation) occurred at 1 mg/kg/day, started 15-20 minutes after dosing and lasted for approximately 2 hours. No NOEL can be determined from this study. Based on the brain ChE inhibition and clinical observations, the 1 mg/kg/day was the acute LOEL. Based on the brain ChE inhibition, the 0.2 mg/kg/day was the subchronic LOEL.

An acute neurotoxicity study by Minnema (1994a) is on file at DPR. In this study, groups of 7-8 weeks old male and female Sprague-Dawley Cr1:CD BR rats were given a single gavage administration of methyl parathion (93.1% purity) at 0, 0.025, 7.5, or 10.0 (males) and 15 (females) mg/kg/day. Groups of 10 rats per sex were subject to neurobehavioral tests while groups of 5 rats per sex were assigned for ChE activity determination. Locomotor activity and Functional Observational Battery (FOB) that measured the various aspects of sensory and motor functions were conducted at 1.5 hours, and 1 and 2 weeks after dosing. ChE activities were measured at 1.5 hours (for all dose groups) and 2 weeks (for the controls and the high dose groups) after dosing. The neurobehavioral tests included home-cage and hand-held observations, open-field observations (arousal, circling, gait, posture, stereotypy, tremors, convulsions, and other signs), response observations (light approach, catalepsy, olfactory, pupil, righting reflex, touch, and others), performance measures (grip strength, foot splay, tail flick, and body temperature), and automated auditory startle response. Paraffin- or

plastic-embedded nerve tissues were examined histopathologically. Initially, the examination was conducted for the controls and the high dose groups. When abnormalities were found at the higher dose, tissues from the next lower dose(s) were then examined.

The effects of methyl parathion are summarized in Table 23. Salivation, hypoactivity, muscle fasciculations, ataxia, and tremors were observed at 7.5, 10, and 15 mg/kg/day. In addition, red perinasal crust, chromodacryorrhea, respiratory distress, urine stains, and death were also reported for male and female rats at 10 and 15 mg/kg/day within 2 days of dosing. The reduction of mean body weight gain during day 0 to 7 was statistically significant in the males (49% lower than the controls) at 10 mg/kg/day. Additionally, rats at these dose groups also showed changes in the neurobehavioral parameters within the FOB. These included limp handling/body tone, flattened posture, gait, arousal and hypoalertness, rearing, absence of pupil response, righting reflex, reduced rectal temperature, and fore- and hind-limb grip strength. No effects were reported at the lowest dose. No significant FOB were noted 1 or 2 weeks of the exposure. Focal demyelination showing small foci of myelin vacuolation and fragmentation in the peripheral nervous system, with occasional glial cells associated with the foci were found in lumbar dorsal and ventral root fiber, tibial, and proximal sciatic nerves. The mechanism for demyelination is not understood. These effects were reported in the study as treatment-related at 7.5, 10, and 15 mg/kg/day, secondary to axonal damages common in aging rats. Nevertheless, it should be noted that the rats used in this study were 7-8 weeks old. The report considered that the observations at the controls and low dose were spontaneous. Based on the clear effects of demyelination at and above 7.5 mg/kg, the NOEL was 0.025 mg/kg. However, it should be noted that there was an apparent slight increased incidence of demyelination in the lumbar root fibers at 0.025 mg/kg.

The ChE activities in the plasma, RBC, and various regions of the brain were severely inhibited at 7.5, 10, and 15 mg/kg/day (Table 23). The RBC and brain ChE at the high dose groups showed substantial recovery by day 14 of dosing, albeit remained to be statistically significantly lower than the controls. The ChE activities were not measured for the low and mid dose groups on day 14. The NOEL based on plasma, RBC and brain ChE inhibitions was 0.025 mg/kg/day, although there was a 22% plasma ChE inhibition at this dose level.

In February 2002, the DPR received a re-evaluation by O'Shaughnessy (2001a) of the original pathology readings from the Acute Neurotoxicity Study of Methyl Parathion in Rats (Minnema, 1994a). The re-evaluation was focused on the tissues from the peripheral nervous system from the high-dose and the control groups. While the original findings indicated a dose-related demyelination of peripheral nerves and nerve roots, the re-evaluation argued against the ability of methyl-parathion to induce neuropathy. USEPA has established a procedure for the submission of revised pathology evaluations (USEPA 1994). According to this procedure, the reports from the original study pathologist and the peer-review pathologist, along with all slides with differing diagnosis (as a minimum), must be reviewed by a Pathology Working Group (PWG). The PWG consists of a chair and other pathologists, including the peer-review and the study pathologist. The DPR determined that the re-evaluation of the original pathology findings did not conform to these guidelines, and therefore, could not be used to replace the initial conclusion of the dose-related neurophaty caused by methyl parathion.

Table 23. Effects of Methyl Parathion in Sprague-Dawley Crl:CD BR Rats After a Single Gavage Administration[a].

Effects	Dose (mg/kg)							
	Males				Females			
0	0	0.025	7.5	10	0	0.025	7.5	15
Clinical Observations - Number of rats affected per 10 rats								
Salivation	0	0	8	5	0	0	8	8
Hypoactivity	0	0	9	6	0	0	8	7
Muscle fascicul.	0	0	5	6	0	0	7	8
Ataxia	0	0	8	6	0	0	4	3
Tremors	0	0	10	6	0	0	9	8
Death	0	0	0	3	0	0	0	3
ChE Activities[b] - % Inhibition (5 rats per group)								
Plasma	0	22	65*	75*	0	9	71*	76*
RBC	0	0[c]	56*	56*	0	0	57*	58*
Brain								
CTX	0	3	88*	93*	0	3	82*	90*
CBL	0	0[c]	82*	91*	0	0[c]	79*	88*
HIP	0	0[c]	86*	93*	0	0	79*	91*
STR	0	2	90*	95*	0	0[c]	85*	93*
OLB	0	0[c]	86*	91*	0	0[c]	77*	90*
BRS	0	1	86*	93*	0	2	76*	90*
Demyelination of Nerves - Number of rats affected per 6 rats								
Lumbar; root fibers								
dorsal	0	3	4	5	1	-	0	3
ventral	2	3	4	4	1	-	0	3
Tibial	0	0	1	3	1	-	0	1
Proximal sciatic	1	-	1	3	1	-	0	1
Sural	0	-	0	2	0	-	0	0

a/ Data from Minnema, 1994a.

b/ ChE measured 1.5 hours after a single gavage administration of methyl parathion. Brain regions: CTX: Cortex; CBL: Cerebellum; HIP, hippocampus; STR, striatum; OLB, olfactory bulb; BRS: brainstem.

d/ The mean ChE activity was higher than the levels measured in the control animals Levels of statistical significance as compared to the controls was reported only at $p \leq 0.05$, marked by *.

A new acute dietary toxicity study was conducted to characterize the effects of methyl parathion on the neurobehavior, neurochemistry and neuromorphology in rat (Weiler 1999a, on file at DPR). Methyl parathion (99.6% pure) was administered as a single dietary dose to Sprague-Dawley rats (9-10 weeks old) at target doses of: 1, 1.5, 3.0 and 12 mg/kg. Feeding was restricted to a one-hour period, after which any remaining food was removed. This route of acute administration resulted in considerably lower (than the targeted) methyl parathion dose levels, which varied as much as 11 fold among the animals in a dosing group (Table 25, see also the discussion below).

The rats in the Neurotoxicity group (10 rats/sex/group) were observed for (*i*) signs of general and cholinergic toxicity, (*ii*) potential behavioral alterations (evaluated by the FOB) and (*iii*) changes in the motor activity (assessed by the circular open-field enclosures). In addition, 16 rats/sex/group were used for ChE activity measurements (Cholinesterase animals). The clinical observation, FOB and motor activity evaluations were performed at pretest, at the time-of-peak effect (0.5-1.5 h after dosing) and 15 days after treatment. Eight rats/sex/group from the control and the high dose were subjected to neuropahological evaluation 15 days after the single dose of methyl parathion. The following tissues were examined for pathology: brain, spinal cord, sciatic, sural and tibial nerves, lumber and cervical ventral and dorsal root ganglia and pituitary gland. ChE activity was measured in the plasma, red blood cells and the brain (cerebral cortex, striatum and hippocampus) on Days 1 and 15.

General Toxicity, Behavioral Effects, Motor Activity and Pathology. Methyl parathion induced clinical signs consistent with the ChE inhibition in the treated animals. The reported signs included ataxia, fewer rears and decreased motor activity (female rats) and hypothermia (female and male rats) at the time-of-peak effect on Day 1. These toxic effects were described as treatment-related only for the rats in the high group dose, which were targeted at 12 mg/kg; however, the achieved doses varied from 0 to 11 mg/kg. Tissue examination did not reveal neuropathological alterations following the acute dietary administration with methyl parathion.

Cholinesterase Activity. The mean RBC cholinesterase activity in male rats on Day 1 was decreased 34% compared to the control levels, following acute dietary administration of methyl parathion targeted at 1.5 mg/kg. This was the lowest targeted dose (achieved doses ranging from 0 to 1.3 mg/kg) of methyl parathion to produce a statistically significantly reduction of the mean ChE activity (Table 24).

This study was recently submitted to the DPR and was aimed to provide more accurate NOEL for the acute dietary exposure to methyl parathion. However, despite the elaborated toxicity evaluation (e.g. clinical observations, FOB, ChE activity determination, neuropathology, etc.), the presented findings could not be used to determine acute toxicity endpoints. It should be emphasized that the achieved methyl parathion doses were substantially lower than the targeted and varied greatly among the animals in a given dose group. Differences between the targeted and the achieved doses were observed in all dose groups and the achieved doses overlapped between the groups (Table 25). The reason for the dose variability was that the achieved methyl parathion dose was estimated based on the food consumption by the animals within a given hour. Consequently, a simple correlation between the toxicity and dose could not be established. In addition a clear dose-response pattern could not be seen when data for individual animals in the entire study were pooled together for

analysis (Table 25). For example, the lowest observed effect was at the mean achieved methyl parathion dose of 0.7±0.51 mg/kg (targeted dose of 1.5 mg/kg), which caused 34% (mean value) inhibition of the RBC cholinesterase activity in male rats at Day 1 (Table 24). However, the achieved doses within the animals in this group ranged between 0.0-1.3 mg/kg. Maximum inhibition of the cholinesterase activity (43%) was measured in the RBC of two male rats consuming 0.5 and 1.3 mg/kg methyl parathion (a 3 fold dose difference). Furthermore, 32% inhibition of the cholinesterase activity was measured in the RBC of a male rat in this group, who did not consume any of the provided food containing methyl parathion. Similarly, a male rat in the dose targeted at 12 mg/kg group, who had 0 consumption of methyl parathion had 58% inhibition of the plasma ChE activity, 36% inhibition of the RBC enzyme and up to 65% inhibition of the brain ChE activity, compared to the control animals. These inconsistent results may reflect errors in the estimation of the actual food consumption. Alternatively, some animals might have had very different base levels of the ChE activity. Since baseline ChE activity measurements were not carried out before the treatment (at least for the plasma and RBC ChE), the actual inhibition of the ChE activities caused by methyl parathion in the individual animals could not be estimated. Because of the variability in the measured parameters and the uncertainties with the estimated methyl parathion doses, an acute oral NOEL could not be determined from this study.

Table 24. Statistically Significant Inhibition of the Cholinestarase Activity in Rats after Acute Dietary Exposure to Methyl Parathion[a].

Target Dose (mg/kg)	Achieved Dose-Range (mg/kg)[b]	Achieved Dose Mean ± SD (mg/kg)	Cholinesterase Activity (% Inhibition)				
			Plasma	RBC	Hippoc.	Cortex	Striatum
Male Rats							
1.0	0.0-0.7	0.3±0.22	-	-	-	-	-
1.5	0.0-1.3	0.7±0.52	-	34	-	-	-
3.0	0.8-2.3	1.6±0.64	20	33	-	-	-
12.0	0.0-11.0	6.0±3.21	53	49	53	50	61
Female Rats							
1.0	0.0-0.9	0.0-0.9	-	-	-	-	-
1.5	0.0-1.1	0.0-1.1	-	-	-	-	-
3.0	0.8-2.9	0.8-2.9	-	-	-	-	
12.0	0.0-3.4	0.0-3.4	51	47	53	54	70

a/ Data were from Weiler,1999a. Methyl parathion was administered once in the diet of 8 rats/sex/group (designated as "Cholinesterase Animals") at the indicated target doses.

b/ The achieved methyl parathion dose was estimated based on the food consumption by the animals after 1 hour of feeding. Note that the range of achieved doses was very large in all dose groups, including dose groups having animals that did not consume any of the provided food with methyl parathion.

c/ Cholinesterase activity was measured at the time-of-peak effect on Day 1 and was expressed as a mean % inhibition compared to control levels in untreated animals. Only statistically significant reduction in the mean ChE activity was shown in the Table.

Table 25. Achieved Doses and Cholinesterase Activity in Individual Male Rats from Dose Groups Targeted for 1-12 mg/kg Methyl Parathion[a].

Targeted Dose (mg/kg)	Achieved Dose (mg/kg)	Cholinesterase Activity (% Inhibition)				
		Plasma	RBC	Hippocam.	Cortex	Striatum
1.0	0.0	2	19	0[b]	4	30
1.5	0.0	16	32	0	11	24
12.0	0.0	58	36	32	54	65
1.5	0.1	18	18	5	11	31
1.0	0.2	25	17	11	7	0[b]
1.0	0.2	5	0[b]	11	29	37
1.0	0.2	3	28	5	29	27
1.0	0.3	11	23	32	25	23
1.0	0.4	27	36	5	0[b]	0[b]
1.5	0.4	0[b]	39	20	29	28
1.0	0.5	11	1	21	36	58
1.5	0.5	37	43	0[b]	29	27
1.5	0.5	38	20	0[b]	0[b]	0[b]
1.0	0.7	26	0	16	54	0[b]
3.0	0.8	10	31	5	21	0[b]
3.0	0.9	23	33	0[b]	4	32
3.0	0.9	34	19	26	0	34
1.5	1.2	3	39	5	0[b]	0[b]
1.5	1.3	0[b]	37	5	7	4
1.5	1.3	28	43	26	11	27
3.0	1.5	24	80	42	0[b]	25
3.0	1.8	36	55	26	25	0[b]
3.0	2.1	8	33	42	0	0[b]
3.0	2.3	37	20	0[b]	0[b]	21
3.0	2.3	0[b]	0[b]	0[b]	29	0[b]
12.0	4.6	70	90	48	50	52
12.0	5.1	56	54	68	64	67
12.0	5.2	68	52	58	64	60
12.0	6.8	53	54	68	29	69
12.0	7.1	14	42	50	36	50
12.0	8.5	58	30	68	61	59
12.0	11.0	49	37	53	43	63

a/ Weiler, 1999a. Methyl parathion was administered in a single dose in the diet and the achieved dose was estimated based on the food consumption after 1 hour of feeding. Data for individual male rats from Dose Groups #7, 8 9 and 10 (targeted for 1, 1.5, 3 and 12 mg/kg methyl parathion, respectively), were pooled together for analysis.

b/ The mean ChE activity was higher than the levels measured in the control animals

Note that a correlation between the toxicity and dose could not be established for the animals in any of the dose groups.

III.H. 2. Subchronic Neurotoxicity

In the study by Schulz et al. (1990) described in Section III.B.4., **Thresholds for Acute Toxicity**, the neurobehavioral effects of methyl parathion were evaluated in groups of 20 male Wistar rats after receiving 0, 0.22, or 0.44 mg/kg/day methyl parathion (60% pure, impurities unknown) via gavage, 5 days per week, for six weeks. Behavioral effects were evaluated with the open-field (OF) and elevated plus-maze (EPM) tests. The authors considered a number of indices as demonstrating significant effects of methyl parathion. Based on the data presented, the more noticeable effects included: increased urination, reduced grooming, prolonged latency both for leaving the center field and for rearing (from the OF tests), and decreased defecation (from the EPM tests). These effects were more definitive at 0.44 mg/kg/day. Further interpretation of the behavioral effects cannot be made due to the limited information.

A subchronic neurotoxicity study by Minnema (1994b) is on file at DPR. The study protocol was similar to the acute neurotoxicity by the same author (Minnema, 1994a), except that methyl parathion was administered through dietary inclusion instead of gavage. In this study, groups of 7 weeks old male and female Sprague-Dawley Cr1:CD BR rats received diets containing methyl parathion (93.1% purity) at 0, 0.5, 5, or 50 ppm for 13 weeks. The respective dose at 0.5, 5, and 50 ppm, calculated based on food consumption and body weight data over the period of the study, were 0.029, 0.29, and 2.9 mg/kg/day for the males and 0.037, 0.37, and 4.2 mg/kg/day for the females. Groups of 10 rats per sex were subject to neurobehavioral tests while groups of 5 rats per sex were assigned for ChE activity determinations on week 4, 8 and 13 (neurobehavior tests) or week 14 (ChE measurements). Additional groups of 5 controls and high dose rats were kept beyond the 13 weeks of dosing for a study on recovery (week 16 for neurobehavior tests and week 17 for ChE activity measurements). The once a day cageside observation was performed in the morning. FOB that measured the various aspects of sensory and motor functions were conducted during the dark cycle. It included home-cage and hand-held observations, open-field observations (arousal, circling, gait, posture, stereotypy, tremors, convulsions, and other signs), response observations (light approach, catalepsy, olfactory, pupil, righting reflex, touch, and others), performance measures (grip strength, foot splay, tail flick, and body temperature), and automated auditory startle response. Paraffin- or plastic-embedded nerve tissues from the controls and the high dose groups were examined histopathologically.

The results were summarized in Table 26. Increased incidence of alopecia and skin sore were observed at all dose levels. Other clinical effects reported at 50 ppm included urine stain, hunched posture, tremors, having thin appearance and chromodacryorrhea. A female rat had a small mass in the cervical region. Decreased food consumption and body weight, increased incidence of neurobehavioral effected were additionally reported at 50 ppm. The neurobehavioral effects included latency to first step (3.2 - 6.9 seconds, compared to 1.0 - 1.8 seconds in the controls), absence of pupil response to approaching penlight from each side of head (1 male and 4 females on week 4), other pupillary responses, reduced fore-limb and hind-limb grip strength (up to 30% lower than the controls on week 4), and tremors (2 of 10 females). No remarkable axonal degeneration was reported at 50 ppm (2.9 - 4.2 mg/kg/day). However, it should be noted that demyelination in lumbar root fibers, tibial, peroneal, and proximal sciatic nerves was reported by the same author in rats that received a single exposure at or above 7.5 mg/kg (Minnema, 1994a) and by Daly (1991) in rats after 12

months of exposure to 2.5 ppm methyl parathion in the diet (0.1 mg/kg/day) (see Section III.D.1., under **Chronic Toxicity**).

Table 26. Effects of Methyl Parathion in Sprague-Dawley Crl:CD BR Rats After 13 Weeks of Treatment Through the Diets[a].

Effects	Concentrations in the Diet (ppm)[b]							
	Males				Females			
	0	0.5	5	50	0	0.5	5	50
Clinical Observations - Number of rats affected per 15 rats								
Skin/Pelage								
alopecia	0	3	2	7	1	3	1	6
skin sore	0	0	1	2	0	1	3	1
Urine stain	0	0	0	0	0	0	0	1
Hunched posture	0	0	0	0	0	0	0	1
Tremors	0	0	0	0	0	0	0	2
Body Weight - g								
week 7	488	489	491	447	264	264	256	247
week 13	571	577	580	538	305	298	305	287
Food Intake - g/week								
week 7	190	189	191	183	133	135	129	145
week 13	194	184	190	174	122	114	116	127
ChE Activities[c] - % of Controls (average of 5 rats per group)								
Plasma	100	111	97	39*	100	101	94	15*
RBC	100	102	72*	48*	100	99	77*	45*
Brain								
CTX	100	96	96	39*	100	123	98	18*
CBL	100	103	103	62*	100	103	98	35*
HIP	100	95	94	37*	100	104	93	13*
STR	100	88	95	25*	100	101	86	7*
OLB	100	97	98	39*	100	106	110	17*
BRS	100	114	110	45*	100	101	99	22*

a/ Data from Minnema, 1994b.

b/ The respective average dose at 0.5, 5, and 50 ppm, calculated based on food consumption and body weight data, were 0.029, 0.29, and 2.9 mg/kg/day for the males and 0.037, 0.37, and 4.2 mg/kg/day for the females.

c/ ChE data were those measured 14 weeks after the onset of a 13-week dietary exposures. The Plasma and RBC ChE inhibitions were slightly lower on week 4 and 8. Brain regions: CTX: Cortex; CBL: Cerebellum; HIP, hippocampus; STR, striatum; OLB, olfactory bulb; BRS: brainstem. Statistical significance as compared to the controls was reported only at $p \leq 0.05$, marked by *.

Data on ChE activities were also given in Table 26. Brain ChE activities were severely inhibited at 50 ppm. The RBC ChE activities were lower by 23-28%, which was statistically significant. The NOEL was 5 ppm (0.29-0.37 mg/kg/day) based on the decreased body weight gain and food consumption, and clinical and neurobehavioral effects occurred at 50 ppm. It should be noted that increased alopecia and skin sore occurred at all dose levels (0.5 - 50 ppm, or 0.029 -4.2 mg/kg/day) including at and below the NOEL. The NOEL was 0.5 ppm (0.029-0.037 mg/kg/day) based on the RBC ChE inhibition at 5 ppm.

III.H.3. Delayed Neuropathy

Some OPs can cause degenerative changes in nerves, a process known as organophosphorus-induced delayed polyneuropathy (OPIDP or OPIDN; see Section **II.A.2. Delayed Neurotoxicity and Intermediate Syndrome).** OPIDN is associated with phosphorylation of neuropathy target esterase or neuropathy target enzyme (NTE). Histopathologically, OPIDN is axonopathy of central-peripheral distal sensory-motor nerves (Lotti, 1992). Clinical manifestation in humans is commonly characterized by flaccid paralysis of lower limbs, although upper limbs are also involved in severe cases. These signs are generally not apparent until 2-3 weeks after the exposure. Results of investigations specific for methyl parathion are presented in this section. The available studies showed no evidence that methyl parathion causes acute delayed neuropathy. Neuropathy occurring after chronic exposures was presented in the Chronic Toxicity (Section III. D., **CHRONIC TOXICITY**).

Gaines (1969) studied the neurotoxicity of 9 carbamates and 30 OPs, including methyl parathion. In hens, which were pre-treated with 15 mg/kg atropine and received a subcutaneous injection of 64 mg/kg methyl parathion, leg weakness was observed within 24 hours after dosing. The recovery was complete within 28 days. No effects were observed at 32 mg/kg. In a later study by Ohkawa et al. (1980), 5 to 10 hens (given atropine as needed) were given a single oral dose of 100 mg/kg methyl parathion and kept for 4 weeks for examination. At day 2 after the treatment, neurotoxic esterase levels in the brain were not significantly altered (88% of controls) while the activity of brain ChE was greatly reduced (15% of controls). No signs delayed neuropathy were observed.

On file at DPR is a study in hens conducted by Beavers et al. (1990). This study was judged acceptable for filling the SB950 data requirement for delayed neurotoxicity testing. In this study, 16 adult atropinized hens were given a single initial oral dose (corn oil vehicle) of 250 mg/kg methyl parathion (95.8% pure) and a subsequent dosing at 215 mg/kg (LD_{50}) 21 days afterwards. No clinical signs of delayed neuropathy, ataxia, or histopathological findings were detected.

III.I. DEVELOPMENTAL NEUROTOXICITY

Developmental neurotoxicity (DNT) studies are designed to investigate whether pre- or post-natal exposure to a toxicant affects the neural development. The DNT evaluations of the OP pesticides are focused on the possible adverse neurodevelopment outcomes, including inhibition of the ChE activity. Methyl parathion is one of the first of six OPs, for which DNT studies have been completed (USEPA, 2002b). In these studies, the ChE activity was investigated in adult and immature rats, following either acute or repeated dosing. The recently submitted DNT studies on methyl parathion revealed an increased sensitivity of immature rats to the inhibition of the ChE activity compared to adult rats (Beyrouty 2002a, 2002b and 2002c).

In the range finding DNT study, methyl parathion (96.5%) was administered by gavage to pregnant Sprague-Dawley rats. Ten animals per dose-group were treated from the gestation day (GD) 6 to GD 20 and then continued through the lactation day (LD) 10 at doses of 0.1, 1 and 2 mg/kg/day. The control groups included vehicle (corn oil)-treated animals. After weaning on postnatal day (PND) 10, ten pups per sex per group from these litters were dosed with methyl parathion from PND 11-21 (Beyrouty, 2002a).

Repeated oral treatment of the dams with 2 mg/kg/day methyl parathion resulted in death, lower food consumption (75% of control, $p<0.01$, GD20) and in a decrease in the body weight gain (69% of control, $p<0.01$, GD20). Maternal toxicity at 2 mg/kg/day was also evident by the tremors, salivation, abnormal gait, altered activity and fur staining. These clinical signs correlated with a drastic decrease in ChE activity on GD20 in plasma, RBC and especially in the brain (79%, 88% and 92% respectively, $p<0.01$). The ChE activity at GD20 was also significantly inhibited at 1 mg/kg/day (51% in plasma, 72% in RBC and 63 brain, $p<0.01$). Pup mortality was increased at 2 mg/kg/day; the surviving pups showed a higher incidence of dehydration, cold to touch and empty stomach (indicative of lack of nursing). During the treatment directly to the pups, tremors, salivation, decreased activity, pathological changes in the eyes and a severely reduced ChE activity were observed in the 1 and 2 mg/kg/day groups. At 1 mg/kg/day the decrease in the ChE activity in the pups from both sexes was 80-94% in all examined compartments; at 2 mg/kg/day, the plasma, RBC and brain enzymes were nearly completely inhibited (92%-97%). The LOEL for systemic effects was 1 mg/kg/day for increased pup mortality, cholinergic signs, behavioral effects and eye abnormalities. The NOEL for overt toxicity was 0.1 mg/kg/day. The lowest tested dose in this study (0.1 mg/kg/day) produced a statistically significant 16 % ($p \leq 0.05$) decrease in the plasma ChE activity in male pups on PND21. One implication of this range-finding study was that doses lower than 0.1 mg/kg/day should be utilized to determine the level of no effect for the methyl parathion developmental neurotoxicty. The LOEL was 0.1 mg/kg/day for the inhibition of the plasma ChE activity in male pups.

Methyl parathion was evaluated in a subsequent definitive developmental neurotoxicity study for behavioral, cognitive and neuropathological effects in rats (Beyrouty, 2002b). The protocol was similar to that used in the range-finding experiments. Methyl parathion (96.8%) was administered by gavage to pregnant rats (32/dose) from GD6 through LD10 at doses of 0.03, 0.3, and 0.6 mg/kg/day. Pups from these litters (4 males and 4 females/litter) were exposed via gavage to the same doses of methyl parathion from PND11-21. The dams and the pups were observed for signs of general toxicity and alterations in the behavior and in the

motor activity. The pups (10/sex/group) were assessed for changes in the learning and memory following weaning until 60 days of age. In addition, 10 pups/sex/group were kept until approximately 70 days of age for neuropathological evaluations. One female from the 0.6 mg/kg/day group was euthanized on GD 22, due to distocia. The clinical signs were consistent with cholinergic toxicity, including reduced body temperature, decreased activity, hunched posture, ocular discharge and fur staining. Dams and pups from the high dose group (0.6 mg/kg/day) exhibited increased salivation and tremors. Neuropathologic effects were not observed in the adult rats (70 days of age), which were exposed to 0.03-0.6 mg/kg/day methyl parathion through in utero, lactation, and direct post-natal gavage for 11 days. The dose of 0.6 mg/kg/day was the LOEL for overt toxicity in dams and pups. The NOEL was 0.3 mg/kg/day.

This study was later supplemented with data on the ChE activity, which was measured in the plasma, RBC and brain after acute or repeated dosing with methyl parathion (Beyrouty, 2002c).

ChE Activity after an Acute Treatment with Methyl Parathion. Young rats (49-50 days old, 16/sex/dose) and PND 11 pups (8/sex/dose) from untreated dams were exposed only once to methyl parathion at doses of 0.03, 0.11, 0.3, and 0.6 mg/kg (adults) and 0.03, 0.11, 0.3, and 1 mg/kg (pups). The ChE activity was not affected after an acute oral treatment with methyl parathion of the young adults (both sexes) at any of the doses (Table 27). The acute dose of 0.3 mg/kg was the LOEL, based on the statistically significant inhibition of the ChE activity in the PND11 pups (Table 27). The plasma enzyme was inhibited 25% (both sexes, $p<0.01$), RBC ChE activity was reduced 31% ($p<0.05$) in the in the female pups and the brain enzyme was inhibited 15% in male pups and 18% in the female pups ($p<0.05$ and 0.01). The acute oral NOEL for inhibition of ChE activity in the plasma, RBC and brain in the pups was 0.11 mg/kg.

Repeated Treatment with Methyl Parathion. The ChE activity was measured on GD 20 (20 dams/group and fetuses), PND4 and PND 21 (pups only, 8/sex/group). Repeated oral treatment for 11 days of the pups, which were previously indirectly exposed for 15 days *in utero* and 10 days via lactation, revealed that they are more sensitive to methyl parathion than the dams (Table 28). PND21 pups exposed to 0.3 mg/kg/day the ChE activity was reduced 24-31% ($p<0.01$) in the plasma, 62-65% ($p<0.05$ and 0.01) in the RBC and 26-29% ($p<0.01$) in the brain (Table 28). The dams, which were exposed to the same dose of methyl parathion for 15 days (GD6-20) exhibited decreased ChE activity in the RBC (35%, $p<0.01$) and in the brain (9%, $p<0.01$). The LOEL after repeated treatment with methyl parathion was 0.3 mg/kg/day, based on the inhibition of the ChE activities in the pups and the dams. Similar to the acutely treated PND11 pups (Table 27), the PND11 rats directly exposed for 11 days to methyl parathion were more sensitive to the inhibition of the ChE activity compared to adult rats (Table 28). The subchronic oral NOEL was 0.03 mg/kg/day for inhibition of the ChE activity in the plasma, RBC and brain in the pups.

The last part of the study included the exposure of young adult rats (49-50 days old; 16/sex/group) from untreated mothers for 11 consecutive days to methyl parathion at doses of 0.03, 0.3 and 0.6 mg/kg/day (Table 28). The LOEL was 0.3 mg/kg/day, based on the inhibition of the plasma (25% in the females ($p<0.01$) and RBC (30% males, 35% females).

The subchronic oral NOEL for inhibition of the ChE activity in the plasma and the RBC in young adults was 0.03 mg/kg/day.

Table 27. Cholinesterase Activity in Immature and Adult Rats Following a Single Gavage Administration of Methyl Parathion[a]

Acute Exposure (mg/kg)	Cholinesterase Activity (% Inhibition)[b]			
	Male Pups[c]	Female Pups	Young Males[d]	Young Females
Plasma Cholinesterase Activity				
0.03	0[e]	18	0[e]	0
0.11	4	10	-	-
0.30	25**	25**	7	11
0.60	-	-	18	18
1.00	62**	64**	-	-
Erythrocyte Cholinesterase Activity				
0.03	0	18	10	2
0.11	3	11	-	-
0.30	20	31*	17	1
0.60	-	-	31	26
1.00	74**	73**	-	-
Brain Cholinesterase Activity				
0.03	0	2	0[e]	1
0.11	3	5	-	-
0.30	15*	18*	0[e]	0[e]
0.60	-	-	0[e]	3
1.00	61**	50**	-	-

a/ Data were from Beyrouty, 2002c.
b/ Cholinesterase activities were expressed as % inhibition of the mean ChE activity, compared to the control levels.
c/ PND11 Pups from untreated dams received a single dose of methyl parathion via gavage.
d/ Young rats (49-50 days old, born from untreated dams) were exposed to a single dose methyl parathion via gavage.
e/ The mean ChE activity was higher than the levels measured in the control animals.
*, ** statistically significant different from controls at $p \leq 0.05$ and 0.01, respectively, (Dunnett's test).

Table 28. Cholinesterase Activity in Immature and Adult Rats Following a Subchronic Gavage Administration of Methyl Parathion[a]

Subchronic Exposure (mg/kg/day)	Cholinesterase Activity[b] (% Inhibition)				
	Dams GD20[c]	Male Pups[d]	Female Pups	Young Males[e]	Young Females
	15 doses GD6-20	11 direct doses after exposure *in utero* and via lactation		11 consecutive doses	
Plasma Cholinesterase Activity					
0.03	0[f]	0[f]	0[f]	17	3
0.30	7	31**	24**	25**	14
0.60	29**	61**	56**	28**	34*
RBC Cholinesterase Activity					
0.03	0[f]	11	19	0[f]	9
0.30	35**	62**	65*	30*	35**
0.60	58**	85**	86**	40**	58**
Brain Cholinesterase Activity					
0.03	0[f]	0[f]	2	0[f]	7*
0.30	9**	29**	26**	0[f]	4
0.60	31**	62**	60**	6	13**

a/ Data were from Beyrouty, 2002c.

b/ Cholinesterase activities were expressed as % inhibition of the mean ChE activity, compared to the control levels.

c/ GD, Gestation Day.

d/ Dams were treated with methyl parathion from GD6 to lactation day 10. Pups from these litters were then directly exposed via gavage to methyl parathion from PND 11 to PND 21.

e/ The young rats (49-50 days old, born from untreated dams) were exposed for 11 days methyl parathion.

f/ The mean ChE activity was higher than the levels measured in the control animals

*, ** statistically significant different from controls at $p \leq 0.05$ and 0.01, respectively, (Dunnett's test).

III.J. IMMUNOTOXICITY

Several studies from the open literature showed that methyl parathion has the potential to alter the immune system. However, further research is needed to clearly identify the health implications of some of these immunological changes.

Shtenberg and Dzhunusova (1968) reported a decreased agglutinin titer (1:33 to 1:75, compared to the 1:1200 in the controls) in rats vaccinated with NIISI polyvaccine either 2 weeks before or after, or simultaneous to, the administration of metaphos (the USSR common name for methyl parathion) in the diet at 1.25 mg/kg/day. Samedov et al. (1979; as cited in USEPA, 1984) noted reductions in phagocytic activity of leukocytes, complement titer, serum lysozyme activity, and nucleic acid content of blood in rabbits that received 5 mg/kg/day methyl parathion in sunflower oil, 6 days/week for 4 months.

In a study by Street and Sharma (1975), male rabbits were fed diets containing methyl parathion at 0, 0.6, 2.6, 8.5, or 23 ppm (0, 0.036, 0.16, 0.52, and 1.5 mg/kg/day) for 8 weeks. The treatments did not result in any gross toxicity. At week 4, rabbits were challenged with sheep erythrocytes. The number of gamma-globulin producing plasma cells was significantly decreased ($p<0.05$) in popliteal lymph nodes at all dose levels. Germinal centers in the splenic white pulp were reduced to the same extent at 8.5 and 23 ppm. Total and differential leukocyte counts, hemolysin and hemagglutinin titers, serum gamma-globulin/transferrin ratio, tuberculin reactivity, food consumption, and body and organ weights were not affected. A dose-related increase in the degree of thymus cortex atrophy was observed. The scoring was statistically significant ($p<0.05$) at the 8.5 ppm (1.5 mg/kg/day).

Using cultured human lymphocytes and neutrophils, Park and Lee (1978) reported that methyl parathion at 10 μM showed approximately 25% inhibition in the response of neutrophils to chemotactic stimuli. The responses of lymphocytes to phytochemagglutinin stimulation were 79 and 89% of the control for the whole blood and isolated mononuclear cells. These levels were reported as not statistically significant ($p>0.025$).

In the 3-month rat study by Daly and Rinehart (1980a) (see: Section III.C.2., *Oral Studies in Rats*), lymphoid depletion and necrosis of lymph nodes, spleen, and thymus were noted in rats that were fed diets containing 75 ppm methyl parathion and died within four weeks of dosing. Fan (1980) reported an increase in mortality associated with i.p. challenge of *S. typhimurium* in male Swiss-Webster mice that received 3.0 mg/kg/day methyl parathion in the diet for at least 2 weeks. Increased viable bacteria in the blood, decreased total gamma-globulin and IgG, and reduced response of splenic lymphocytes to mitogen stimulation were concomitantly observed. No effects were reported at the two lower doses (0.08 or 0.7 mg/kg/day).

Rodgers et al. (1986) studied the effects of methyl parathion on the cytotoxic T-lymphocyte (CTL) response in mice (C57B1/6) splenocytes. Following a 1-hour incubation with methyl parathion (with or without the pre-treatment of NADPH-fortified S-9 microsomal enzyme fraction), the splenocytes were sensitized to allogenic tumor target cells. The CTL response was subsequently determined based on the release of ^{51}Cr from radiolabeled target cells. Methyl parathion at 5-10 μg/ml (calculated as 19-38 μM) decreased the ability of splenocytes

to generate a CTL response. With the S-9 pre-incubation, the effect of methyl parathion was 20 fold less than without the S-9.

Institoris et al. (1992) investigated the humoral immune effects of methyl parathion in mice. Male mice were administered methyl parathion (60% pure) prior to the exposure to sheep erythrocytes (SRBC). The purity-adjusted doses of methyl parathion were: 5.3 mg/kg in a single dose given 0-3 days prior to SRBC exposure, and 0.53 or 0.27 mg/kg given for 4 weeks. The authors reported increases in the number of plaque-forming splenocytes (PFC) with no changes in serum antibody titers. The effect, however, did not appear to be dose-related. The brief reporting precluded further evaluation of this study.

The potential for immunotoxicity after long-term exposures was recently reported by Institoris et al. (1995) in a 3-generation study in Wistar rats. The mating and treatment schedule of this study was similar to the protocol of a 3-generation reproductive toxicity study, except for having one instead of two litters per generation. Methyl parathion at 0, 0.218, 0.291, or 0.436 mg/kg was administered via intubation, 5 days per week. The effects that were statistically significant included: decrease in WBC (white blood cells), RBC, hematocrit (most prominent in G_1 - parent generation; at all methyl parathion dose levels), increase in medial RBC cell volume (in G_1), slight increase in relative liver weight (in G_1, G_2, G_3; all three generations) and decrease in relative thymus weight (in G_3), increase in the nucleated cell contents in the femoral bone marrow (in G_2, G_3), and dose-dependent decreases in PFC with SRBC (27% reduction at 0.436 mg/kg in G_1). It is interesting to note that while a decrease of PFC was noted in this study in rats, comparable levels of methyl parathion appeared to cause an increase, instead of decrease, of PFC in mice (Institoris et al., 1992).

A comprehensive study on the immunotoxicity of methyl parathion was recently conducted by Crittenden et al. (1998) in female B6C3F1 mice. The areas of study included dose-response and time-course studies (ChE activities, hematology, thymus/spleen weight and cellularity, antibody-forming cultures, peritoneal macrophage nitrite production, and natural killer cell (NK) activity), cell-mediated and humoral immunity, and host resistance (melanoma cells and *Streptococcus agalactiae)*. Groups of 5-8 mice received 0, 1, 3, or 6 mg/kg/day methyl parathion (>99% pure) via gavage for 7, 14, 21, and 28 days. No effects on body weight or hematology were reported. Brain and plasma ChE inhibitions were noted at or above 3 and 6 mg/kg/day, respectively. Parameters showing immunotoxicity were: splenocytes antibody-forming cells reduction, increased NK activities, and increased nitrite production by peritoneal macrophages. The authors concluded that the overall data did not suggest substantial immunotoxic potential for methyl parathion.

III.K. HEMATOLOGICAL EFFECTS

Hematological effects have been noted in many of the studies presented in this document. The commonly reported effects included decreases in RBC number, increases in the RBC distribution width, decreases in hemoglobin, and hematocrit. In addition to decreases in RBC and differential leukocytic counts, Galal et al. (1977) also noted an increase in coagulation time in rats after 36 days of increasing exposure (see: Section III.C.2., *Oral Studies in Rats*). The LOELs for these effects are summarized below:

1) 5.7 mg/kg/day (75 ppm in the diet) from the 3-month rat study by Daly and Rinehart (1980a) - Section III.C., *Subchronic Toxicity.*

2) 2.6-5.0 mg/kg/day (50 ppm in the diet) from the 2-year rat study by Bomhard et al. (1981) - Section III.D., *Chronic Toxicity.*

3) 5 mg/kg/day from the 4-Week dermal neurotoxicity study in rats (Beyrouty, 2001).

4) 0.19-0.28 mg/kg/day (5.0 ppm in the diet) and 2.0-3.2 mg/kg/day (50 ppm in the diet) from the 25-28 months rat study by Daly and Hogan (1983) - III.D., *Chronic Toxicity.*

5) 0.218, 0.291, and 0.436 mg/kg (5 days per week) from the 3-generation intubation study in rats by Institoris et al. (1995) - Section III.I., *Immunotoxicity.*

The mechanism for these hematological effects is not known. Parent-Massin and Thouvenot (1993) investigated the effects of 12 pesticides on the hematopoietic lineage by several pesticides known to cause changes in hematological indices. The study was conducted with hematopoietic progenitor cultures of colony-forming unit-granulocyte and macrophage (CFU-GM) from humans (obtained from arthroplasty surgeries) and rats. The effects were examined on day 7, 10 and 14 of incubation with test media. Methyl parathion at 0.2, 2, and 20 μg/ml resulted in growth reduction of human CFU-GM colonies (>50 cell aggregates) and clusters (5-50 cells) on day 10 and 14. No effects were noted in cell cultures from rats. It is important to note that based on the 12 pesticides tested, progenitor cell cultures from humans appeared to be generally more sensitive than the cultures from rats.

III.L. ADDITIONAL INFORMATION FROM THE LITERATURE PUBLISHED AFTER 1999.

The new findings published in the literarure after 1999 on the pharmacokinetics (Abu-Qare et al., 2000; Abu-Qare and Abu-Donia, 2000 Abu-Qare et al., 2001a), acute and subchronic toxicities (Zhu et al., 2001, Abu-Qare et al., 2001b) of methyl parathion were included in the appropriate sections: (Section III.A.1.b., *Distribution*; Section III.A.2., **Dermal Studies** and Section III.B.4.d., **Dermal Toxicity Studies**). Although the published experimental data did not define new critical NOELs, they can be considered in weight-of evidence determinations for methyl parathion. More specifically, three of the studies required consideration in that they established: (*i*) the *in vivo* methyl parathion dermal absorption in rats as nearly 100% (Abu Qare, 2000) and (*ii*) daily dermal exposure of rats to low doses of methyl parathion (0.1-1 mg/kg/day), as might occur in occupational and dietary settings, caused inhibition of the AChE in the brain (Ma et al, 2003) and impairment of motor function and memory (Zhu et al., 2001).

The new studies on the mechanism of methyl parathion toxicity, published in the open literature after 1999, are discussed below.

III.L.1. Effects on Cell Membrane Integrity

Toxicological, pharmacological and biochemical studies were carried out to characterize the effects of methyl parathion on the activities and distribution of target enzymes in rat brain, as well as on the brain pool of high energy phosphates (Gupta, et al., 2000). Male rats (Sprague-Dawley) were exposed to a single sublethal dose of methyl parathion (5 mg/kg, by intraperitoneal injection). Within 5-7 min methyl parathion produced severe toxicity of anticholinesterase nature, including seizures and convulsions, which persisted for about two hours. Alteration in the activities of cholinergic and non-cholinergic biomarkers was examined in the cortex, stem, striatum, hypocampus and cerebellum following 1 h of exposure.

Acetylcholinesterase, (AchE). At the acute sublethal concentration tested, methyl parathion produced a marked reduction of AChE activity in all brain regions examined. Maximum enzyme inhibition was observed in the cerebellum (about 95%), whereas the striatal acetylcholine hydrolyzing activity was least affected.

Creatine Kinase (CK). Methyl parathion treatment produced a substantial reduction in CK activity in brain, which coincided with an increase in the activity in serum, comprising brain, muscle and heart-specific isoenzymes. Under normal conditions, the blood-brain barrier prevented leakage of the brain-specific CK isoenzyme (CK-BB) to the serum. The presence of CK-BB in the serum of the acutely intoxicated rats exhibiting seizures, was thus considered indicative of an increased blood-brain barrier permeability.

Lactate dehydrogenase (LDH). LDH is a cytoplasmic enzyme and its leakage from tissues is an indicator of loss of membrane integrity, cytotoxicity or cell death. Rat brain contained five distinct LDH isoenzymes, which activities were differentially reduced 1 h after methyl parathion treatment. The subsequent increase (155-372%) in the activity of the LDH isoenzymes in serum, and the elevated levels of lactate and pyruvate in blood demonstrated cell membrane damage caused by methyl parathion.

High energy phosphates (ATP, ADP, AMP). At the dose used, methyl parathion produced severe inhibition of the brain AChE activity and concomitant brain hyperactivity (status epilepticus). Under the sustained brain hyperactivity, the levels of adenine nucleotides (ATP, ADP and AMP) and phosphocreatine (PCr) were markedly reduced in brain tissue. During brain hyperactivity a greater ATP concentration is required for maintaining cell structure. The authors proposed that the depletion of the energy pool by methyl parathion might lead to loss of membrane integrity and subsequent release of cytoplasmic enzymes, such as LDH and CK.

The data presented, however, did not unequivocally establish that the depletion of ATP was the cause for the increased membrane permeability. Following a nearly lethal dose of methyl parathion, cellular constituents (high energy phosphates, LDH and CK) may be leaking from already injured or dead cells. The observed depletion of ATP could be due to a rapid ATP degradation by the released cellular ATPases when cells die. Clearly, the concept that methyl parathion acute toxicity leads to a depletion of cellular energy and subsequent loss of cell structure needs further experimental verification.

The effects of malathion, methyl parathion and parathion on the physicochemical properties of model dipalmitoylphosphatidylcholine (DPPC) membranes were studied by fluorescent anisotropy and differential scanning calorimetry (Videira, et al., 2001). Both, parathion and methyl parathion (50 μM) increased the fluorescent anisotropy of the probes 1,6-diphenyl-1,3,5-hexatriene (DPH) and [p-(6-phenyl)-1,3,5-hexatrienyl] phenylpropionic acid (DPH-PA). The high degree of anisotropy reflects limited rotational diffusion of the fluorescence probes and is an indication of a higher structural order or low membrane fluidity. The changes in the membrane fluidity correlated with the insecticide toxicity to mammals, represented by their oral LD_{50} values. The most toxic pesticide, parathion (LD_{50}= 2.0 mg/kg) induced the strongest ordering effect of DPPC membranes, followed by methyl parathion (LD_{50}=6.01 mg/kg), whereas the least toxic malathion (LD_{50}= 290 mg/kg) was nearly ineffective. Similarly, the reported perturbation abilities of these pesticides to biological membranes (mitochondrial and sarcoplasmic reticulum) increased with the decrease of their respected LD_{50} values. The methyl parathion concentration used in the fluorescence studies (50 μM) was substantially lower than its potential lethal serum concentration, estimated as 394 μM, based on the LD_{50} of 6.01 mg/kg and assuming total fluid volume of 58 ml/kg. Altogether, it was proposed that the *in vivo* effects of methyl parathion may be in part related to its ability to perturb the phospholipid structure whose integrity is crucial for the normal cell function.

III.L.2. Molecular Targets and Activators

Experiments were carried out to investigate the mechanism of methyl parathion activation and toxicity (Albores et al., 2001). Rat brain extracts were used as an *in vitro* model, since they contained both the activating enzyme (cytochrome P450, CYP) resposible for the methyl parathion oxidative desulfuration and the target for the methyl parathion neurotoxicity (AChE). The extracts were prepared from brain of male Wistar rats (250-350 g). Incubation of the brain extracts with methyl parathion resulted in the inhibition of the AChE activity, which occurred only in the presence of NADPH. AChE activity was non-competitively inhibited by the presence of methyl parathion, indicating that methyl parathion was activated to its reactive metabolite methyl paraoxon. Phenobarbital, a substrate for

cytochrome P450 2B (CYP2B), partially prevented the methyl parathion-dependent inhibition of brain AChE. Brain extracts preincubated with 266 nM phenobarbital exhibited about 21% increase in the AChE activity, compared to the enzyme activity measured in the presence of 20 nM methyl parathion alone. Competitive inhibition experiments revealed that phenobarbital and methyl parathion competed for the same CYP active site and that methyl parathion had a greater affinity for the CYP site. The methyl parathion-dependent inhibition of AChE activity was nearly blocked by the nonspecific CYP inhibitor CO and by antibodies to the isoforms CYP2B1/2B2, but not by CYP1A1 antibodies. These results demonstrated for the first time that the activation of methyl parathion to methyl paraoxon was catalyzed by the rat brain CYP2B. The presence of the CYP2B protein in rat brain extract was further confirmed on Western blot using antibodies specific to CYP2B. Interindividual differences in the expression of the CYP2B isoform and the related CYP enzymes in brain may result in different susceptibility to the methyl parathion toxicity.

The potential of methyl parathion, parathion and chlorpyrifos to bind to the cholinergic muscarinic receptors (mAChR) was evaluated in rat cardiac membranes (Howard and Pope, 2001). While all organophosphorus insecticides act through a common mechanism initiated by inhibition of AChE, recent experimental evidence suggested that some (including methyl parathion) could bind directly to muscarinic receptors and function as agonists. The m_2-subtype G-protein coupled receptors have been identified as the primary type muscarinic receptors in the heart. Hearts were collected from neonatal (7-11 day male and female) and adult (90 day, male only) Sprague-Dawley rats and were used to prepare the cardiac membranes. The muscarinc receptor density (B_{max}) was higher in the neonatal heart membanes, compared to the maximum number measured in adult membranes. The binding of the organophosphorus insecticides (50 pM-10 μM) to the cardiac muscarinic receptors was assessed by their ability to displace the nonselective muscarinic antagonist [^{3}H]quinuclidinyl benzilate, [^{3}H]QNB or the m_2-preferential agonist [^{3}H]oxotremorine-M acetate, [^{3}H]OXO. Methyl paraoxon, paraoxon and chlorpyrifos displaced [^{3}H]OXO binding in adults membranes and neonatal tissues. The oxons potency to displace the [^{3}H]OXO binding was comparable with their *in vitro* potency for inhibition of the brain AChE activity, suggesting that direct interaction with the cardiac muscarinic receptors could occur at toxicologically relevant exposures. With the exception of methyl parathion, the parent compounds had little effect on either [^{3}H]OXO or [^{3}H]QNB binding. Methyl parathion ($\geq$ 0.5 nM) displaced [^{3}H]OXO (37% maximum displacement) from the binding site on the adult membranes, but did not affect the [^{3}H]OXO binding to the neonatal receptors. The potency of methyl parathion in displacing the [^{3}H]OXO from the adult membrane site was similar to that of methyl paraoxon. In addition, the interaction between methyl parathion and the adult m_2 muscarinic receptors appeared to be reversible. Altogether, it was proposed that an interaction of methyl parathion and the muscarinic receptors could potentially modulate the toxic response to AChE or lead to non-cholinergic effects. The m_2 receptors are coupled to inhibition of adenylyl cyclase and cAMP levels and thereby regulate the frequency of muscle contraction. Thus, a direct binding to these receptors could produce long-term changes in cardiac function.

IV. RISK ASSESSMENT

IV.A. HAZARD IDENTIFICATION

IV.A.1. Introduction

Methyl parathion is classified as a Category I toxicant, based on its acute toxicity. Methyl parathion is genotoxic *in vivo* and *in vitro*, as demonstrated by its ability to cause chromosome damage, gene mutation, sister chromatid exchange or to directly bind to DNA (see Section III.E. **GENOTOXICITY**). However, despite the extensive evidence for genotoxicity, the oncogenic potential of methyl parathion as assessed by genetic toxicity studies in rodents has not been confirmed (see Section III. D.2. **Oncogenicity**). Because the weight of evidence was insufficient for a quantitative assessment of oncogenic risk, the characterization of the risk of methyl parathion in this document was based on non-oncogenic effects.

The experimentally determined highest dose at which no effects were observed (NOEL) was used in delineating the threshold dose for non-oncogenic effects. Therefore, the NOELs were presented in the context of the LOEL, the lowest dose in the experiment, at which hazard or toxicity was observed. For methyl parathion, this included both the inhibition of ChE activity (plasma, RBC, brain) and other overt effects. In a toxicity study, the LOEL is the next higher dose above the NOEL.

In some studies, where the lowest tested dose of methyl parathion was the LOEL, a default factor of 10 was applied to estimate the NOEL. Benchmark Dose (BMD) approach was also used to determine the threshold of the methyl parathion toxicity (USEPA, 1995). The BMD method involves fitting a mathematical model to the entire dose-response dataset for a specific endpoint. The BMD is the lower, 95% confidence limit of the effective dose (LED) required to cause a given response (1%, 5% or 10% effect level) in an organism.

IV.A.2. Acute Toxicity

A list of NOELs and LOELs is shown in Table 29. It includes the thresholds established from all pertinent studies described in Section III.B., **ACUTE TOXICITY**, and under any other toxicity categories pertinent to acute exposures, e.g., the threshold for developmental effects that can potentially occur after a single exposure *in utero*. Thresholds based on both ChE inhibitions and overt toxicities (e.g., clinical signs, developmental endpoints) are presented.

a. ChE Inhibition

A series of studies by Rider et al. (1969; 1970 and 1971) provided NOELs determined in humans (Table 22). The focus of these studies was on the effects of plasma and RBC ChE activities. In the earlier study (Rider et al., 1969), test subjects were given increasing doses of methyl parathion from 1 mg/day to 19 mg/day in 33 days. Test subjects in the subsequent studies (Rider et al., 1970, 1971) received fixed doses for 30 days. Greater detail of investigative protocol was reported in the earlier study while the results of the subsequent studies were published only as abstracts. Although the studies differed in the dosing schedule, it is reasonable to assume that the investigative protocols were similar for all the

studies by the same authors. The NOELs from these studies were comparable. The 30-day study (Rider et al., 1970, 1971) had a slightly higher NOEL of 0.31 mg/kg/day. It was based on ChE inhibitions of 23% in the plasma and 55% in the RBC reported at the LOEL of 0.34 mg/kg/day (Table 4).

The NOEL of 0.31 mg/kg/day from the subchronic studies in humans could be used as the NOEL for acute toxicity. However, the NOEL for a shorter term of exposure for the same endpoints of ChE inhibition might be higher. This NOEL (0.31 mg/kg/day) was also used by the U.S. EPA in setting a 10-day drinking water Health Advisory (USEPA, 1988). No clinical signs of toxicity were reported at doses as high as 30 mg/day (0.43 mg/kg/day), the highest dose tested. However, these studies were not designed for detecting more subtle neurological effects.

Studies in laboratory animals provided the thresholds for endpoints not examined in the above human studies. To facilitate the determination of critical NOELs for characterizing the risk of acute exposures, essential information from those studies listed in Table 29 representing the lowest NOELs or LOELs are briefly summarized below.

The lowest NOEL for plasma, RBC, and brain ChE inhibition was 0.025 mg/kg/day in rats (Minnema, 1994a), based on substantial inhibitions of plasma, RBC, and brain ChE at a LOEL of 7.5 mg/kg/day. This single dosing study by Minnema (1994a) was presented in Section III.H., under *NEUROTOXICITY.* With the marked difference between the NOEL and LOEL (i.e., 300-fold), a question could be raised regarding the possibility that the NOEL could be higher had the study design reduced the dose interval within this region. On the other hand, it should be noted that there was a 22% plasma ChE inhibition at this NOEL, although not statistically significant.

A recently submitted acute DNT study with methyl parathion to the DPR provided evidence that the acute NOEL for reduced ChE activity may be 4 fold higher (Beyrouty 2002b, 2002c presented in Section III.I. **DEVELOPMENRAL NEUROTOXICITY**), than the NOEL of 0.025 mg/kg/day (Minnema, 1994a). The experimental protocol consisted of a single treatment of PND11 pups with methyl parathion. The selected doses produced dose-groups with a gradation of the toxic effects and included levels of no effect. At the LOEL of 0.3 mg/kg, a considerable inhibition (18-31%, $p \leq 0.05$ and 0.01) of the ChE activities in the plasma, RBC and brain in the pups was observed. Therefore, the NOEL of 0.11 mg/kg from the acute DNT study appears to represent more accurately the level of no-effect for inhibition of the ChE activity following a single oral dose of methyl parathion (Table 29). However, the lowest tested dose in this study (0.03 mg/kg/day) produced a substantial (18%), albeit not statistically significant, inhibition of the RBC and plasma enzymes. It is interesting to note that the dose of 0.03 mg/kg/day was similar to the NOEL of 0.025 mg/kg/day from the study by Minnema (1994a), at which 22% reduction of the plasma ChE activity was reported.

The lowest LOEL for RBC ChE inhibition was 0.3 mg/kg/day in rabbits from the study by Hoberman (1991), as presented in Section III.G., under **DEVELOPMENTAL TOXICITY**. The lowest LOEL for brain ChE inhibition was 1 mg/kg/day in rats (Kumar and Desiraju, 1992; Gupta et al., 1985 in Table 29). The study by Kumar and Desiraju (1992) was presented in Section III.H., under **NEUROTOXICITY**. Rat pups (15 days old) that received a single oral dosing of 1 mg/kg methyl parathion showed 47% ChE inhibition in the brain

stem region. The study by Gupta et al. (1985) was presented in Section III.G., under **DEVELOPMENTAL TOXICITY.** As high as 36% ChE inhibition was reported in 3 of the 4 brain regions (frontal cortex, brain stem, striatum) of the pups from dams that orally received 1 mg/kg/day methyl parathion during gestation day 6 through day 20.

When the LOEL is the lowest dose tested in a study, a default factor of 10 is often used to estimate the NOEL. Applying the default factor to the aforementioned LOELs, the estimated NOELs would be 0.1 mg/kg/day for brain ChE inhibition in rats and 0.03 mg/kg/day for RBC ChE inhibition in rabbits. However, without taking into account the shape of the dose response curve and the level of response at the LOEL, this default approach introduced substantial uncertainties. A study with a dose range, which includes a level of no effect (NOEL) would afford a greater certainty.

Table 29. Acute No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of Methyl Parathion[a].

Study/ Species	ChE Inhibition			Overt Toxicity			References
	ChE	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Effects at the LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	
Studies in Humans							
1 day[b]	pl, rbc	0.27	-	no effects observed	0.27	-	Rider et al., 1969
5-day	pl, rbc	0.057	-	no effects observed	0.057	-	Rodnitzky et al.,1978
30-day	pl, rbc	0.31	0.34	-	-	-	Rider et al., 1970, 1971
Studies in Rats							
1-day		-	-	salivation, "shivering", lacrimation, exophthalmos, hyperreflexia, respiratory distress	-	5.3	Galal et al., 1977
1-day		-	-	nasal/oral discharge, wet rales, ↓ general activities	-	1.0	Auletta, 1984a
6 weeks		-	-	mortality (1st week only)	-	0.22	Schulz et al., 1990
1-day (pup, 15 days old)	br	-	1.0	"shivering", salivation, muscular fasciculation	-	1.0	Kumar and Desiraju,1992
1-day	pl, rbc, br	0.025	7.5	focal demyelination of peripheral nerves	0.025	7.5	Minnema, 1994a

(continued)

Table 29. Acute No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of Methyl Parathion[a]. (continued)

Study/ Species	ChE Inhibition ChE	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Overt Toxicity Effects at the LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	References
				Developmental Toxicity Studies			
Rat				dam/fetal: body wt ↓ (fetus: 5%; dam: 43%)	0.3	1.0	Machemer, 1977
Rat	-	-		pup: day 15 survival; neurobehavior (reflex, open-field, maze)	-	1.0	Crowder et al., 1980
Rat	br (dam/pup)	-	1.0	dam: muscle fasciculations, tremors (start day 3-4)	1.0	1.5	Gupta et al., 1985
Rat		-	3.0	dam: death (start day 7), wt ↓, cholinergic signs (start day 8), fetal : wt ↓, delayed ossification	1.0	3.0	Becker et al., 1987*
Rabbit	rbc (dam)	-	0.3	fetal: thickened areas of ossification	3.0	9.0	Hoberman, 1991*
				Developmental Neurotoxicity Toxicity Studies			
Rat (pups 11 days old)	pl, rbc,br	0.1	0.3		-	-	Beyrouty, 2002c

a/ The route of exposure is oral for all studies. ChE: at the LOEL; br: brain; pl: plasma; rbc: red blood cell.

b/ Male subjects were exposed to daily increasing doses for a total test period of 33 days.

* Study fulfilled the SB950 data cholinesterase inhibited requirements for the specific type of testing.

b. Overt Toxicity

The lowest LOEL reported for the overt effects was 1.0 mg/kg/day (Auletta, 1984a; Kumar and Desiraju, 1992; Crowder et al., 1980), with the exception of the 0.22 mg/kg/day reported by Schulz et al. (1990). The study by Auletta (1984a) was described in Section III.B.3. Cholinergic signs occurred after a single exposure of 1 mg/kg/day. The study by Kumar and Desiraju (1992) was presented in Section III.H., under **NEUROTOXICITY**). Rat pups (15 days old) that received a single oral dosing of 1 mg/kg methyl parathion showed cholinergic signs of "shivering", salivation, and muscular fasciculation. The study by Crowder et al. (1980) was described in Section III.G.2.). The effects noted in the pups of dams that received methyl parathion orally during gestation day 7 through day 15 included reduced postpartum day 15 survival and neurobehavioral effects. There were substantial uncertainties associated with the increase in mortality reported in the study by Schulz et al. (1990) (see: Section III.B.3. Of the 20 Wistar rats per group, 3 and 4 rats reportedly died at the respective dose levels of 0.22 and 0.44 mg/kg/day, all during the first week of treatment. However, during the same period, death also occurred in one out of the 20 control rats (both the controls that were treated with tap water and the controls that were similarly handled but not intubated). No cause of death was reported and no additional mortality occurred subsequently throughout the remaining 5 weeks of treatment. It is also important to note that although mortality is an expected acute endpoint, none of the studies from the sizable toxicological database reported death occurring at such a low dose level. The lowest acute NOEL for overt effects was 0.025 mg/kg, based on a clear increase in nerve demyelination at the LOEL of 7.5 mg/kg (Minnema, 1994a). Because of the marked difference (300-fold) between the NOEL and LOEL in this study, it was possible that the NOEL for nerve demyelination could be higher. The recently submitted acute DNT study (Beyrouty, 2002c) established a 4-fold higher NOEL for the ChE inhibition, compared to the NOEL of 0.025 mg/kg/day in the study by Minnema (1994a). However, the DNT study was focused only on the effects of methyl parathion on the ChE activity and did not conduct behavioral and neuropathological evaluation. Therefore, a higher NOEL for the methyl parathion-induced neuropathology could not be established. The NOEL of 0.025 mg/kg/day was employed by the DPR to assess the risk from acute inhalation exposure to methyl parathion in the 1999 Toxic Air Contaminant Evaluation document (TACE; Reed, 1999).

The acute NOEL of 0.025 mg/kg/day was also used by USEPA (1998c) in the draft Reregistration Eligibility Decision document (RED) to assess the acute and short-term risk of methyl parathion exposures. Considering the 300-fold difference between the NOEL and LOEL, USEPA subsequently determined that the NOEL of 0.1 mg/kg/day from the 1-year chronic toxicity study in rats by Daly (1991) is most appropriate for use as the NOEL for acute, short-, and intermediate-term toxicity (USEPA, 1999).

When using a NOEL determined in animals to characterize the risk of human exposure to toxicants, the least sensitive human is assumed to be 10 times more sensitive that the most sensitive animal. Therefore, the acute NOEL for humans would be 0.0025 mg/kg/day when extrapolated from the NOEL of 0.025 mg/kg/day in rats based on inhibition of the ChE activity and nerve demyelination. The NOEL of 0.025 mg/kg/day is 23-fold lower than the NOEL of 0.057 mg/kg/day determined in two human adult males from the study by Rodnitzky et al. (1978) described in Section III.C.1. In addition to the difference in species, several key elements might have contributed to the difference in NOELs. Some of these factors included the small sample

size of two test subjects in the human study by Rodnitzky et al. (1978) and the endpoint of brain ChE and histopathological examinations of nerves, which cannot be monitored in humans. Age might be another possible factor. The animal studies included also rat pups on post-natal day 15 (Kumar and Desiraju, 1992), *in utero* exposure scenario (Crowder et al., 1980), and relatively young rats of 7-8 weeks old (Minnema, 1994a).

c. Conclusions

Although the use of a NOEL determined in humans avoids the uncertainties associated with the inter-species extrapolation, these studies were either focusing mainly on the effects of ChE inhibition or did not have sufficient sample size. Therefore, the NOEL 0.025 mg/kg/day for ChE inhibition and neuropathology, which was based on studies in rats, would be used to characterize the risk of acute exposures. The uncertainties associated with the NOELs as presented above are described in Section V.B.1. under **RISK APPRISAL**.

IV.A.3. Subchronic Toxicity

IV.A.3.1. Subchronic Oral Toxicity

Lists of NOELs and LOELs are given in Table 30 for the effects of ChE inhibitions and in Table 31 for overt effects. These lists included pertinent studies described in Section III.C., **SUBCHRONIC TOXICITY** and under any other toxicity categories pertinent to subchronic exposures, e.g., the threshold for reproductive toxicities. In addition, data presented in Table 8 on ChE inhibitions from the chronic toxicity studies were also included for the NOEL determination when the ChE activities were measured during a subchronic time interval (i.e., up to 3-6 months).

a. ChE Inhibition

A human NOEL of 0.31 mg/kg/day was determined based on the inhibition of plasma and RBC ChE at 0.34 mg/kg/day. However, uncertainties existed with only 5 adult subjects in the test groups and the brief reporting (only as abstracts for platform presentations). In addition, the lack of data in brain ChE measurement would dictate that a critical NOEL for risk assessment should also take into account the data from animal studies.

The lowest NOEL of 0.03 mg/kg/day for the inhibition of plasma, RBC and brain ChE activities was established from a recent developmental neurotoxicity study with rats (Beyrouty 2002c). The experimental protocol included a repeated oral treatment for 11 days of the pups, which were previously indirectly exposed for 15 days *in utero* and 10 days via lactation (Section III.I., under **DEVELOPMENTAL NEUROTOXICITY**, Table 28). In the PND21 pups exposed to 0.3 mg/kg/day, the ChE activity was reduced 24-31% in the plasma, 62-65% in the RBC and 26-29% in the brain. It should be emphasized that at the NOEL of 0.03 mg/kg/day, a substantial, but not statistically significant reduction was reported in the ChE activities of the RBC (19%) and plasma (17%).

The same level of inhibition of the plasma ChE activity (19%) was measured at the LOEL of 0.03 in a 13-week feeding study with dogs (Daly 1989; see Section III.C.4. under *SUBCHRONIC TOXICITY* and Table 4). This study was used by the DPR to etsablish the methyl parathion subchronic oral NOEL for the plasma ChE inhibition in the 1999 Toxic Air Contaminant

Evaluation document (Reed, 1999). The NOEL of 0.003 mg/kg/day was estimated from the LOEL, using a default factor of 10.

The lowest NOEL for the inhibition of the erythrocyte AChE was 0.029 mg/kg/day in Sprague-Dawley rats, based on the study by Minnema (1994b). However, a LOEL of 0.09 mg/kg/day was identified in Wistar rats based on the study by Bomhard et al. (1981) as presented in Section III.D.1.a., under **CHRONIC TOXICITY**, and in Table 8. At this LOEL, the activity of the RBC ChE was statistically significantly inhibited by 4-20% after receiving 2 ppm in the diet for 2 - 13 weeks. Since a NOEL cannot be determined from this study, using a default factor of 10, the estimated NOEL for RBC ChE inhibition was 0.01 mg/kg/day. This NOEL was 3-fold lower than the NOEL established in Sprague-Dawley rats but with a greater uncertainty due to the application of a default factor. The NOEL of 0.029 mg/kg/day was used by the DPR to establish the subchronic oral NOEL for the RBC AChE inhibition in the 1999 TACE (Reed, 1999).

The lowest NOEL for the brain ChE inhibition was derived from a study with PND 2 Wistar rats, which were dosed with methyl parathion for 150 days (Kumar and Desiraju, 1992, Section III.C.2, under **SUBCHRONIC TOXICITY**, and in Table 4.). At the LOEL of 0.2 mg/kg/day, the ChE activity was reduced by at least 24% in five regions of the brain. The same authors reported an inhibition of the brain ChE in rats of the same age, which were similarly treated with 0.1 mg/kg/day for only 15 days. However, there was a greater uncertainty in the LOEL of 0.1 mg/kg/day because the actual data for the ChE inhibition were not reported. Since a NOEL cannot be determined from this study, using a default factor of 10 and based on the LOEL of 0.2 mg/kg/day, the estimated NOEL for brain ChE inhibition was 0.02 mg/kg/day.

Table 30. Subchronic No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of Methyl Parathion Based on Inhibition of the Cholinesterase Activity[a].

Species/ Duration	ChE at the LOEL[b] (% inhibition)	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Humans; 30 days	pl (23%), rbc (55%)	0.31	0.34	Rider et al., 1970,1971
Rats; Sprague-Dawley				
1-3 months	pl (39%), rbc (43%), br(32%)	0.2[c]	1.9	Daly & Rinehart, 1980a
1 month	pl (33%), rbc (13%)	0.1	0.48	Daly, 1991
13 weeks	rbc (28%)	0.029	0.29	Minnema, 1994b
11 days	pl (31%), rbc (65%), br (29)	0.03	0.30	Beyrouty, 2002c
Rats; Wistar				
10 days	pl (76%), br (57%)	-	1.3	Yamamoto et al., 1982
15days (2 days old)	br (no data in report)	-	0.1	Kumar & Desiraju, 1992
150 days (2 days old)	br (5 regions, ≥24%)	-	0.2	Kumar & Desiraju, 1992
2-13 weeks	rbc (4-20%)	-	0.09	Bomhard et al., 1981
Mice; B6C3F1				
65-66 days	br (20-30%)	3.82	14.91	Eiben, 1988a,b
	pl (10%); rbc (8%)	-	0.93	
Dogs				
3 months	br (56-64%)	1.0	3	Underwood &
	pl (28%), rbc (37%)	0.3	1.0	Tegeris,1978
13 weeks	br (50-53%)	0.3	3	Daly, 1989
	pl (19%)	-	0.03	
1-6 months	pl (31%)	-	0.3	Hatch, 1998
	rbc (37%)	0.3	1.0	

a/ The route of exposure is oral for all studies.

b/ ChE: cholinesterase activities, given in the highest group percentage of inhibition as compared to the controls. pl: plasma; rbc: red blood cell; br: brain.

c/ At the NOEL, rbc ChE was inhibited by 30% at 1 month, but no significant inhibition was shown at 3 months.

Table 31. Subchronic No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of Methyl Parathion Based on Overt Toxicities[a].

Species/ Study	Effects at the LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	References
Rats; Sprague-Dawley				
Repro study	pup survival (~5%↓); dam body weight gain reduction	0.4	2.3	Daly & Hogan, 1982
13 weeks	alopecia and skin sore	-	0.029	Minnema, 1994b
Rats; Wistar				
Rat; Wistar	↑ urination, latency to leave center and rearing; ↓ grooming, ↓ defecation	-	0.22-0.44	Schulz et al.,1990
Repro study	pup survival (15%- 17%↓)	0.14	0.71	Loser & Eiben,1982
Rats; Fischer F344				
7 weeks	death in 1 of 5 females	-	0.5	NCI, 1979
Mice, B6C3F1				
7 weeks	death of 1 in 5 males at the LOEL; no death in any higher dose groups	-	2	NCI, 1979
Dogs				
14 days	vomiting in one of 2 dogs	-	2.5	Underwood & Tegeris, 1977
13 weeks	reduced intraocular pressure	0.03	0.3	Daly, 1989

a/ The route of exposure is oral for all studies. Studies listed in Table 30 were not repeated unless the NOELs were at or below those listed in Table 30 for brain ChE inhibitions. Repro: reproductive toxicity study.

b. Overt Toxicity

The lowest subchronic NOEL based on overt toxicities was 0.03 mg/kg/day in dogs, based on a reduction of intraocular pressure after 13 weeks of exposure at 0.3 mg/kg/day (Table 31). The study by Daly (1989) was presented in Section III.C.4., under **SUBCHRONIC TOXICITY**. However, in a recent 1-year study in dogs by Hatch (1998) (see: Section III.D.1.c., under **CHRONIC TOXICITY**) no treatment-related ophthalmological changes (intraocular pressure, electroretinogram) were reported in dogs that received 0.3 to 4.0 mg/kg/day for up to one year.

The next set of higher NOELs was identified in two reproductive toxicity studies presented in Section III.F.2., under **REPRODUCTIVE TOXICITY**. The NOEL of 0.14 mg/kg/day (2 ppm in the diet) in Wistar rats was based on as much as 13% reduction of pup survival at the LOEL of 0.71 mg/kg/day (10 ppm in the diet) (Loser and Eiben, 1982). The NOEL of 0.4 mg/kg/day (5 ppm in the diet) in Sprague-Dawley rats was based on an approximately 5% reduction in pup survival and a reduction in maternal body weight gain at the LOEL of 2.3 mg/kg/day (25 ppm in the diet) (Daly and Hogan, 1982). Since the effect has consistently been observed in the reproductive toxicity studies, DPR's data review determined that considering these studies collectively, a NOEL for pup survival was 0.4 mg/kg/day. However, it should be noted that applying the approach for a collective NOEL to these two studies using two different strains of rats would assume that there was no sensitivity differences between the Wistar and Sprague-Dawley rats specific to this endpoint.

Two low LOELs for overt toxicities were presented in Table 31. A LOEL of 0.22-0.44 mg/kg/day was based on the neurobehavioral effects reported by Schulz et al. (1990) in Wistar rats after 6 weeks of oral dosing. Another LOEL of 0.029 mg/kg/day (0.5 ppm in the diet) was based on alopecia and skin sores which occurred in rats within 13 weeks of dosing (Minnema, 1994b). Additional support for the LOEL of 0.22-0.44 mg/kg/day were effects noted within the same dose range: 1) reduced pup survival at 0.71 mg/kg/day in the above 3-generation reproductive study in Wistar rats, with the NOEL of 0.14 mg/kg/day (Loser and Eiben, 1982), 2) a statistically significant increase in the degree of thymus atrophy in rabbits 8 weeks after receiving 0.52 mg/kg/day methyl parathion in the diet (Street and Sharma, 1975), and 3) in addition to a decreased relative thymus weight, a 3-generation rat study showing hematological changes (decreased RBC, WBC, hematocrit) at 0.218 mg/kg/day (the lowest dose tested) (Institoris et al., 1995). Applying the default factor of 10 and based on the LOEL of 0.22 mg/kg/day for the neurobehavioral effects (Schulze *et al*., 1990), the estimated NOEL was 0.02 mg/kg/day. This was in the same range as the estimated subchronic NOEL based on brain ChE inhibition.

A NOEL was not estimated from the LOEL of 0.029 mg/kg/day based on the slight increase of alopecia and skin sores. There were some uncertainties associated with the LOEL because the incidence of these effects was similar at the next higher dose of 0.29 mg/kg/day. Nevertheless, these observations would support the above estimated NOEL of 0.02 mg/kg/day.

c. Conclusions

The NOEL of 0.03 mg/kg/day for the inhibition of the plasma, RBC and brain ChE activities in immature Sprague-Dawley rats (Beyrouty, 2002c) was selected to characterize the risk of subchronic dietary exposure to methyl parathion. However, the possibility that the subchronic oral NOEL for methyl parathion is lower than 0.03 mg/kg/day can not be excluded, because of the reported effects at this dose, including: reduction in the ChE activities in the rat RBC and plasma (Beyrouty 2002c) and reduction in the plasma ChE activity in dogs (Daly, 1989).

The NOEL of 0.03 mg/kg/day was similar to the previously used subchronic NOEL by the DPR for inhibition of the RBC AChE (0.029 mg/kg/day, Minnema 1994b), and the estimated NOEL (ENEL) for the brain ChE and behavioral changes (0.02 mg/kg/day, Kumar & Desiraju 1992; Schulz et al., 1990).

IV.A.3.2. Subchronic Dermal Toxicity

Four dermal toxicity studies in Sprague-Dawley rats were considered in selecting the critical NOEL for characterizating the subchronic dermal exposure to methyl parathion (Table 32). In the study by Zhu et al (2001), 3 females per dose-group were dermally exposed to methyl parathion for 28 days (presented in Section III.C.5., **SUBCHRONIC TOXICITY**). The NOEL was 0.1 mg/kg/day, based on the inhibition of the blood ChE activity and impairment of the cognitive and motor functions at 1 mg/kg/day (Table 32). In a 95-day dermal study, female rats were treated with 0.1 and or 1 mg/kg/day methyl parathion (Ma et al, 2003; presented in Section III.C.5.). The LOEL for the inhibition of the brain AChE activity (15-23% in striatum and thalamus) was 0.1 mg/kg/day. The estimated NOEL would be 0.01 mg/kg/day, when applying a default factor of 10 to the LOEL (Table 32).

In the dermal neurotoxicity studies, recently submitted to the DPR, rats were treated with methyl parathion for either 4 weeks (Beyrouty, 2001) or 13 weeks (Beyrouty 1999b, presented in Section III.C.5., Tables 5, 6,and 7). Based on the results from the 13-Week study, the LOEL for the inhibition of plasma (20%), RBC (56%) and brain (35-41%) ChE activities was 1.2 mg/kg/day (Table 32). Using a default factor of 10, the estimated NOEL would be 0.12 mg/kg/day. From the 4-Week study, the LOEL for the inhibition of the brain ChE activity (18-22%) and cholinergic signs was 0.3 mg/kg/day methyl parathion. The estimated NOEL would be 0.03 mg/kg/day, when applying a default factor of 10 to the LOEL (Table 32).

Table 32. Subchronic Dermal No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of Methyl Parathion

Duration	ChE Inhibition	Overt Toxicity	NOEL	LOEL	References
			mg/kg/day		
28 days	Whole blood	Impairment of cognitive and motor functions	0.10	1.0	Zhu et al, 2001
95 days	Brain	-	0.01[a]	0.1	Ma et al, 2003
4 weeks	Brain	Pinpoint pupils in female rats	0.03[a]	0.3	Beyrouty, 2001
13 weeks	Plasma, RBC, Brain	-	0.12[a]	1.2	Beyrouty, 1999b

a/ The NOEL was estimated from the LOEL (ENEL) by applying a default factor of 10.

a. Benchmark Dose Modeling of the ChE Data

In the two dermal toxicity studies by Beyrouty (1999b and 2001), the lowest tested dose of methyl parathion was the LOEL. Consequently, the use of a default factor (10x) was used to estimate the NOEL. As an alternative to the ENEL, the Benchmark Dose (BMD) approach could be considered in determining the threshold of the methyl parathion dermal toxicity. In this approach, the BMD is the lower, 95% confidence limit of the effective dose (LED) required to cause a given response in an organism (USEPA , 1995). Depending on the characteristics and/or the severity of the toxic responses, a 95% lower bound estimate of the 1%, 5% or 10% effect level may be selected as the $LED_{01,}$ LED_{05}, or LED_{10}, respectively. Unlike the ENEL, which is determined based on one data point, the LOEL, the BMD method utilizes response levels at all tested doses and hence minimizes the uncertainty in the determination of the toxicity threshold.

The USEPA Benchmark Dose Software version 1.3.1 (available at http://cfpub.epa.gov/ncea/cfm/bmds.cfm) was used to calculate the methyl parathion dermal threshold of toxicity. The LEDs were derived for the brain ChE data from the 4- and 13-week repeated dermal dosing in rats (Beyrouty 1999b, 2001; Section III.C.5. **SUBCHRONIC TOXICITY**, Tables 5, 6,and 7). These two studies were carried out on the same rat species, in the same laboratory and had similar experimental protocols, but differed in the dose selection and the duration of the dermal treatment. For each study, the LEDs were calculated from 6 datasets, including the ChE activity (μmol/g) measured in the brain cortex, striatum and hippocampus in female and male rats. The LEDs from the 4-week study were derived from the ChE activity on the 28 day of the treatment. The LEDs from the 13-week studies were based on the brain ChE activity measured at the end of the 13 week-treatment. The Hill model generated the best curve fit of the several available algorithms, as indicated by the lowest AIC (Akaike's Information Criterion; see Attachment IV).

For the 4-week dermal neurotoxicity study, the lowest LED_{05} and ED_{05} were 0.05 and 0.07 mg/kg/day respectively (Table 33), and represented 5% inhibition of the striatum ChE activity in female rats. For the 13-week dermal neurotoxicity study, the lowest LED_{05} and ED_{05} were 0.04 mg/kg/day and 0.08 mg/kg/day, respectively, based on 5% inhibition of the cerebral cortex ChE activity in male rats. The respective LOELs, the effects at the LOELs and the ENELs from these two studies are shown in Table 33 for comparison with the LEDs. The LED_{05} from both studies were very similar and close to the conventionally estimated NOEL of 0.03 mg/kg/day from the 4-week treatment.

Table 33. Comparison between the ENEL and BMD for the Methyl Parathion Dermal Toxicity.

Dermal Study	LOEL [a]	ENEL [b]	ED_{05} [c]	LED_{05} [d]	Study Description
	mg/kg/day				
4-Weeks[e]	0.3	0.03	0.07	0.05	**Doses (mg/kg/day):** 0.3, 1.0, 2.2, 5.0 **Effects at LOEL:**18-22% ChEI[e] in brain (all regions) in females; cortex and striatum in male brain
13-Weeks[f]	1.2	0.12	0.08	0.04	**Doses (mg/kg/day):** 1.2, 3.8, 12.0 **Effects at LOEL:** 20% ChEI in plasma; 56% ChEI in RBC; 35-41% ChEI in brain (all regions)

a/ Lowest Observed Effect Level (LOEL) in the study.
b/ Estimated NOEL (ENEL) was derived from the LOEL by applying an uncertainty factor of 10.
c/ ED was the effective dose of methyl parathion, which induced 5% inhibition of the ChE activity in the rat brain.
d/ LED was the lower, 95% confidence limit of the ED; **f**/ ChEI – inhibition of the ChE activity.
e/ Beyrouty 2001; **f**/ Beyrouty 1999b.

b. Conclusions

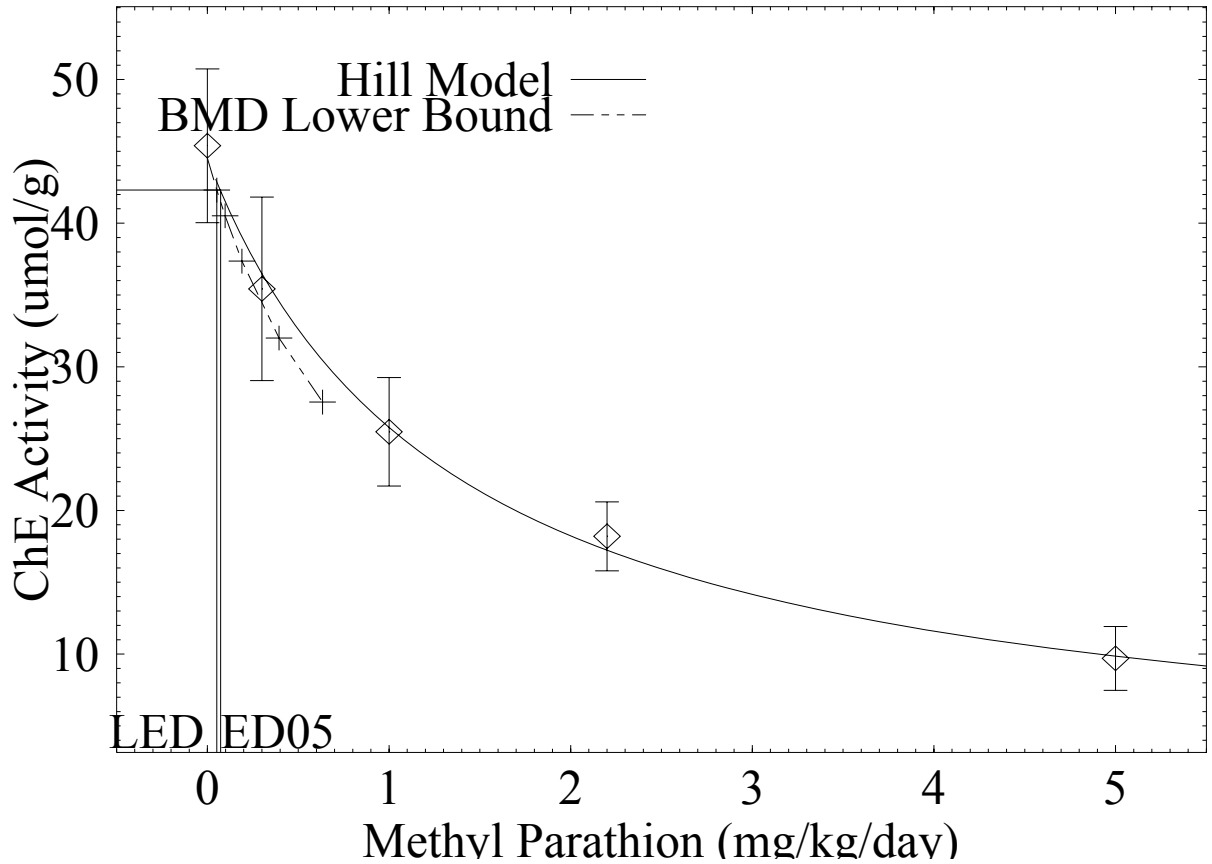
The two lowest subchronic dermal NOELs were 0.01 and 0.03 mg/kg/day, which were estimated from the LOELs established in the 95-Day dermal study (Ma et al, 2003) and 4-Week study (Beyrouty 2001), respectively. The subchronic dermal NOEL of 0.03 mg/kg/day from the 4-Week study (Beyrouty 2001) was selected for characterizing the risk due to dermal exposure to methyl parathion. The 4-Week study (Beyrouty, 2001) was preferred over the 95-Day dermal study (Ma et al, 2003), the 13-Week dermal study (Beyrouty 1999b) and over the study by Zhu et al (2001), because of the following considerations:

1) The 4-week study had higher quality data. It used more dose groups and had a clearer dose-response relationship, which could be described by the continuous BMD model (from USEPA 2002c).

2) The duration of this study (28 days) was similar to the length of the potential seasonal exposure to workers. Methyl parathion can be applied by rice application crews for about 21 days during a two-month application season (see section V.B.1.b. under Exposure Assessment and Tables 35). The study by Zhu et al, 2001 also employed a 4-Week treatment regime, however, it included only two dose-groups and did not measure sensitive parameters such as brain ChE activity and behavioral changes.

3) ENEL of 0.03 mg/kg/day from the 4-Week treatment was supported by the LED_{05} of 0.05 mg/kg/day determined by the BMD method. The LED_{10} (10% effect level) was estimated as 0.1 mg/kg/day, however at this dose level an inhibition of brain AChE activity was reported in the study by Ma et al, 2003.

Figure 2. Estimation of the Threshold of the Methyl Parathion Dermal Toxicity with the BMD model.



Methyl Parathion-Induced Inhibition of the ChE Activity in the Rat Brain. Methyl parathion was applied to the back of the female rats at dose levels of 0.3, 1.0, 2.2 and 5.0 mg/kg/day for 4 weeks (Beyrouty, 2001). The lowest tested dose produced 22% ($p \leq 0.01$) inhibition of the ChE activity in the striatum region of the brain. The BMD approach was used to calculate the effective dose (ED) and the 95% confidence limit of the effective dose (LED), which were required to cause a 5% reduction in the ChE activity. The Hill model generated the best curve fit among the several available algorithms. The ED_{05} and ED_{05} were estimated as 0.07 and 0.05, respectively.

IV.A.4. Chronic Toxicity

A list of NOELs and LOELs is given in Table 34 for pertinent studies described in Section III.D., **CHRONIC TOXICITY**. This list included endpoints of ChE inhibition and other overt toxicities.

a. ChE Inhibition

Three NOELs for plasma ChE inhibition were available: 0.19 mg/kg/day in Sprague-Dawley rats (Daly and Hogan, 1983), 0.1 mg/kg/day in Sprague-Dawley rats (Daly, 1991), and 0.3 mg/kg/day in dogs (Hatch, 1998). A collective NOEL of 0.19 mg/kg/day could be determined from the two rat studies, since they were conducted in the same strain of rats and by the same investigator. Although conducted 8 years apart, the two studies showed a similar level of plasma ChE inhibition (63% and 67%) at 50 ppm, the common high dose level used in both studies.

The NOEL for RBC ChE inhibition was 0.1 mg/kg/day in Sprague-Dawley rats (Daly, 1991). The two LOELs for RBC ChE inhibition were: 0.09 mg/kg/day in Wistar rats (Bomhard et al., 1981), and 0.3 mg/kg/day in dogs (Hatch, 1998). Since a NOEL cannot be determined from the lower LOEL by Bomhard et al. (1981), using the default factor of 10 would result in an estimated NOEL of 0.01 mg/kg/day. It should be noted that in the study by Daly and Hogan (1983) in Sprague-Dawley rats, a 4-11% RBC ChE inhibition was noted at the NOEL of 0.19 mg/kg/day throughout the study, although the inhibition was not statistically significant at all time points. Based on this consideration, the NOEL for RBC ChE would have been 0.02 mg/kg/day, only twice higher than the estimated NOEL of 0.01 mg/kg/day in Wistar rats.

The lowest NOELs for brain ChE inhibition was 0.09 mg/kg/day in Wistar rats (Bomhard et al., 1981). The lowest LOEL was 0.2 mg/kg/day in B6C3F1 mice (Eiben, 1991). As low as 19% brain ChE inhibition was reported at this LOEL, although it did not show statistical significance. Applying the default factor of 10, the estimated NOEL was 0.02 mg/kg/day in mice. However, it should be noted that the overall database did not show a general pattern of higher sensitivity in mice.

b. Overt Toxicity

The lowest NOEL for effects other than ChE inhibition was 0.02 mg/kg/day. This was established both in the 12-month study by Daly (1991) based on peripheral nerve demyelination and in the 25-28 month study by Daly and Hogan (1983) based on abnormal gait, neurotoxicity, and hematological alterations. This is also the same NOEL presented above estimated for brain ChE inhibition. The NOEL of 0.02 mg/kg/day from the study by Daly and Hogan (1983) was also used by USEPA (1998c) in the Reregistration Eligibility Decision Document (RED) to assess the intermediate-term (subchronic) and chronic risk of methyl parathion exposures.

c. Conclusions

The chronic NOELs for ChE inhibitions were: 0.19 mg/kg/day for plasma ChE inhibition in Sprague-Dawley rats; 0.01 mg/kg/day for 17% RBC ChE inhibition in Wistar rats; and 0.02 mg/kg/day for brain ChE inhibition in mice. Since the NOEL for plasma ChE inhibition was generally at or above one order of magnitude than the other NOELs, even for a shorter term of exposure, it would not be used to characterize the risk of chronic exposures. The NOEL for nerve demyelination, neurological signs and hematological effects was 0.02 mg/kg/day.

Table 34. Chronic No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of Methyl Parathion[a].

Species/ Study	Toxicity endpoints at the LOEL	NOEL (mg/kg/day)	LOEL	Reference
Rats; Sprague-Dawley				
25-28 months	br ChE (72%↓), pl ChE (79%↓)	0.19[b]	2.0	Daly & Hogan,1983
	abnormal gait, hematological alterations	0.02	0.19	
12 months	ChE inhibition (pl: 33%; rbc: 19%; br 25%)	0.1	0.48	Daly, 1991
	proximal sciatic, tibial/peroneal nerve myelin degeneration	0.02	0.1	
Rats; Wistar				
2 years	rbc ChE (17% ↓; 1 yr)	-	0.09	Bomhard et al.,1981
	br ChE ((22% ↓; 2 yr)	0.09	0.46	
3-generation	change in EEG index in somatosensory, visual, and auditory areas of cortex. Greater effects in 2nd and 3rd generations	-	0.22	Nagymajtenyi et al., 1995
Mice; B6C3F1				
104 weeks	br ChE (2 yr; 19%↓, statistically insignificant)	-	0.2	Eiben, 1991
	br ChE (1 yr; 37%↓, statistically significant)	0.2	1.6	
	increase in body weight and relative organ weight; poor general condition, tremors, paralysis	1.6	9.2	
Dogs				
1 year	br ChE (22%↓)	0.1	0.3	Ahmed & Sagartz, 1981
1 yr	rbc ChE (21%↓); pl ChE (31%↓)	-	0.3	Hatch, 1998
	br ChE (25%↓)	0.3	1	
	diarrhea, thinness, relative organ weight (↑adrenal, ↓spleen), ↓thymus lymphoid cells, tremors	1	3.5-4	

a/ The route of exposure is oral for all studies. The percentage of ChE inhibition represented the lowest group mean comparison to the controls. Studies by Daly & Hogan, 1983 and Hatch, 1998 were accepted for filling the data requirement for chronic toxicity studies.

b/ At the NOEL, rbc ChE was inhibited by 9% and statistically significant at week 26; the inhibition was 4-11% (not statistically significant) at the end of study.

IV.A.5. Weight of Evidence for Oncogenicity

The available oncogenicity bioassays of methyl parathion did not show clear evidence of oncogenicity in rats and mice. The Scientific Review Panel (SRP), at the June 1999 deliberation under the California Toxic Air Contaminant Act, pointed out the need to emphasize that the rodent bioassays (as presented in Section III.D.2. **ONCOGENICITY**) indicated limited evidence of oncogenicity. This included the marginal increase ($p<0.05$) in thyroid tumors in rats (Bomhard et al., 1981), the uterus and adrenal tumors in rats (Daly and Hogan, 1983), which exceeded historical ranges although not statistically significant, and the apparent increase in lung tumors in mice, although also not statistically significant.

The International Agency for Research on Cancer (IARC) placed methyl parathion in Category 3 which denotes chemicals not classifiable as to their oncogenicity in humans (IARC, 1987). Based on the lack of evidence for oncogenicity in the two chronic/oncogenicity studies in rats (Bomhard et al., 1981; Daly and Hogan, 1983) and the one study in mice (Eiben, 1991), USEPA (1998c, 1999) determined that methyl parathion should be classified in "Group E" (Evidence of Non-carcinogenicity of Humans) regarding human carcinogenicity potential as defined in the USEPA 1986 carcinogen risk assessment guidelines (USEPA, 1986b). Following the USEPA 1996 proposed carcinogen risk assessment guidelines (USEPA, 1996c), methyl parathion would be classified in the "Not Likely" group pertaining to its carcinogenic potential in humans via relevant routes of exposure (USEPA, 1998c, 1999).

It has generally been recognized that genetic toxicity studies are not short-term oncogenicity tests. However, the positive genotoxicity under laboratory conditions raised the need to further explore the significance of genotoxicity observations to humans. In this section, the lack of clear oncogenicity evidence in the bioassays is discussed in the context of genotoxicity and the alkylating potentials of methyl parathion.

IV.A.5.a. Implication of Genotoxicity Potential

Many OPs, including methyl parathion and methyl paraoxon have alkylating potential and abilities to bind to cellular macromolecules (WHO, 1986; Gallo and Lawryk, 1991). A literature review on the biological significance of these properties is briefly presented in this section. Bedford and Robinson (1972) studied the alkylating potential of OPs. Using a calorimetric assay with a moderate nucleophile, 4-(p-nitrobenzyl)pyridine (NBP), the alkylating potential of approximately 20 OPs and/or their breakdown products was quantitatively compared to two powerful alkylating agents, dimethyl sulphate and methyl methanesulphonate (MMS). Compared to a relative second-order alkylation rate constant of 2400 for dimethyl sulphate and 100 for MMS, the two OPs with the highest rates were dichlorvos (DDVP) at 34 and methyl paraoxon at 15. Methyl parathion had a lower rate of 8. In speculating on the biological significance of the demonstrated alkylating potential, the authors pointed out that the electrophilic potential of the phosphoryl site, strengthened by the p-nitrophenolic leaving group, is expected to be greater than the methyl sites. Quantitatively, the reactivity half-life for the phosphoryl site (reflected by the reaction with hydroxide ion) was approximately 2.4-fold shorter than the methyl site (reflected by the reaction with NBP). The authors also pointed out that the overall significance of the spontaneous (i.e., nonenzymatic) electrophilic reaction should be viewed in the context of the concomitant enzymatic reactivities. The biological significance of the electrophilic potential of an OP appeared to be minimal compared to the much greater rates

of its enzymatic reactivities, such as reactions with esterases (e.g., ChE), and the hepatic detoxification pathways (see Figure 1) involving GSH and Cytochrome P450.

Covalent binding of ^{14}C- methyl parathion to cellular macromolecules was reported by Bartoli et al. (1991) in rats and mice (see also Table 17). Using U-^{14}C methyl parathion, the authors studied the binding to DNA, RNA, and proteins in 6 rats and 24 mice (received phenobarbitone 2 days prior to treatment) 22 hours after a single intraperitoneal injection of 1.31 μmol/kg ^{14}C-methyl parathion (based on the study description, the reported dose unit of "mmol/kg" appeared to be a typographic error). The calculated dose was 0.345 mg/kg methyl parathion. The results showed that the binding to RNA and proteins was generally greater than to DNA (the difference was mostly within 10-fold). The respective DNA binding in the liver, kidney, and lung were 0.036, 0.01, and 0.03 pmol/mg in rats and 0.057, 0.11, and 0.08 pmol/mg in mice (the unit was presumed to be pmol methyl parathion bound per mg DNA). *In vitro* studies with microsomal and/or cytosolic fractions from liver, kidney, lung, and brain also showed bindings to calf thymus DNA, with most of them statistically significantly greater than the controls at either $p<0.05$ or <0.001 (Bartoli et al., 1991).

The overall implication of the electrophilic and genotoxic potential of methyl parathion and methyl paraoxon remains unknown. It should be noted that among the many OPs for which data on genotoxic and alkylating potential were available, DDVP showed a substantial similarity to methyl parathion except that, unlike methyl parathion, rodent bioassays for DDVP demonstrated sufficient evidence of oncogenicity for classifying DDVP as a Class C, probable, human carcinogen (USEPA, 1989, 1996a). Thus, a comparison of the database for the two chemicals helps to illustrate the difficulties in determining the oncogenic potential based solely on the auxiliary information (e.g., alkylation and genotoxicity potential) when in the absence of evidence in rodent bioassays. Firstly, the study by Bedford and Robinson (1972) presented above showed that the second-order rate constant of alkylation was approximately 2.3-fold higher for DDVP than for methyl paraoxon. Secondly, a study on DNA-binding of DDVP similar to the study by Bartoli et al. (1991) for methyl parathion was also available for comparison. Segerback (1981) studied the binding of DDVP to DNA in the soft tissues of male mice 5 hours after receiving intraperitoneal injection of 1.9 μmol/kg methyl-^{14}C-DDVP (the calculated dose of 0.420 mg/kg). The alkylation of guanine-N-7 in DNA measured by the radiolabel was 8×10^{-13} mol DDVP/g DNA, or 0.0008 pmol/mg DNA. This level is lower than the level reported by Bartoli et al. (1991) for methyl parathion. The shorter time after the chemical exposure might have contributed to the lower binding. Finally, both methyl parathion and DDVP showed sufficient evidence of genotoxic potential. On the other hand, only DDVP showed sufficient evidence in animal studies to support the carcinogen classification and for generating the cancer potency (the slope of the dose-response relationship at the low dose range) for a quantitative characterization of risk. The lack of clear evidence of oncogenicity under the experimental conditions utilizing sufficiently high dose levels precluded any further characterization of the oncogenicity potential of methyl parathion.

IV.B. EXPOSURE ASSESSMENT

Human non-occupational exposure to methyl parathion could result from consuming food and water containing the pesticide residues (dietary exposure). The general population may be also exposed to airborne methyl parathion in agricultural regions with extensive application of methyl parathion. Exposure from residential uses is not expected to occur, since there are currently no approved uses of methyl parathion for home and/or garden. The occupational exposure to methyl parathion via the dermal and inhalation routes will be addressed subsequently in addendum to this document.

IV. B.1. Non-Dietary Exposure

IV. B.1. a. Ambient Air Exposure

Human exposure to methyl parathion from non-dietary activities was expressed as an absorbed daily dose (ADD), seasonal average daily dose (SADD) and Annual Average Daily Dosage (AADD). The exposures to ambient air concentrations of methyl parathion and methyl paraoxon were estimated from the air monitoring of 4 outdoor sites in Colusa and Sutter counties during high season of application to rice fields (Seiber et al., 1987). The highest ambient air concentrations were detected at the Maxwell site in Colusa county and were used to calculate exposures for three standard population subgroups. The exposure to methyl paraoxon was multiplied by the toxicity equivalence factor (TEF) of 10 to convert to methyl parathion equivalence and subsequently added to the exposure of methyl parathion (Reed 1999, see also section IV.B.2.7. under Exposure Assessment).

The total (methyl parathion and methyl paraoxon) ADDs for a 6 year old child, a male adult, and a female adult were estimated as 64.55 ng/kg/day, 24.27 ng/kg/day and 15.93 ng/kg/day, respectively (Reed, 1999). The SADDs were 19.64 ng/kg/day (a 6 years old child), 7.45 ng/kg/day (a male adult) and 4.84 ng/kg/day (a female adult). The AADDs were 14.78 ng/kg/day (a 6 year old child); 5.56 ng/kg/day (a male adult) and 3.56 ng/kg/day (a female adult). These exposure estimates were based on the following default breathing rates (BR): 0.74 m^3/kg/day for a 6 year old child; 0.28 m^3/kg/day for a male adult and 0.18 m^3/kg/day for a female adult (Reed, 1999).

IV. B.2. Dietary Exposure

IV. B.2.1. Introduction

The Department of Pesticide Regulation conducts dietary exposure assessments to evaluate the risk of human exposure to a pesticide in food and water. Two separate approaches are used to estimate the exposure: (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 section **VI. TOLERANCE ASSESSMENT)**

Dietary exposure is the product of the amount of food that is consumed and the magnitude of the pesticide residue on that food. Consequently, two distinct pieces of information are required to assess the dietary exposure: the amount of the pesticide residue on food and the food consumption for specific population subgroups. For estimating the acute exposure the highest

residue values at or below the tolerance are considered. In contrast, for chronic exposure the mean residue values are appropriate. Finally, acute exposure is calculated per-user, i.e. including in the distribution of exposures only the days of survey that at least one commodity with potential pesticide residues is consumed. Chronic exposure to pesticides is generally calculated using per-capita mean consumption estimates to include the entire population.

The methyl parathion acute and chronic dietary risk assessments, along with the acute tolerance assessment, are discussed below. Acute and chronic exposure analyses were carried out for all combined methyl parathion food uses. USEPA tolerances for residues of methyl parathion are presently established on a number of field and vegetable crops. As of April 2002, there is only one active product containing methyl parathion approved for use in California. Cerexagri, Inc. (formerly Elf Atochem, Inc.) holds the registration for agricultural food use of the PENNCAP-M INSECTICIDE containing 20.9% methyl parathion as an active ingredient. In California, methyl parathion is registered for use on 12 commodities, which include: barley, dry beans, corn, cotton, oats, onions, dry peas, potatoes, rice, soybeans, walnuts and wheat (Table 35; see http://www.cdms.net/manuf/mprod.asp?mp=163&lc=0)

IV. B.2.2.Consumption Data and Dietary Exposure

The Dietary Exposure Evaluation Model (DEEM™, Exponent Inc.) was used to calculate the dietary risk. The food consumption pattern was based on data generated by the United States Department of Agriculture (USDA) during the 1994-1998 Continuing Survey of Food Intake by Individuals (CSFII). The 1994-1998 dataset includes the 1994-1996 food consumption survey along with the 1998 Supplemental Children's Survey (CSFII 1998). Risk estimates, expressed as margin of exposures (MOEs), were provided for the average U.S. population and 18 selected population subgroups, including all infants, nursing or non-nursing infants and children. Subgroups were defined by geographic regions, age, gender or ethnicity.

In addition to calculating the dietary exposure, the DEEM™ Acute Module was used to determine those foods having the greatest contribution to the total exposure of the individuals. The Critical Exposure Commodity (CEC) analysis provides records for individuals at the high end of dietary exposure (in the top 5% or less), as well as the commodities contributing to this level of dietary exposure.

For acute exposure estimates, one-day consumption data comprised all the commodities with current methyl parathion registrations in California. The consumption of each commodity by each individual in a population subgroup was multiplied by a single residue value (point estimate) for a deterministic risk assessment. Alternatively, the entire range of measured residue levels was used in the probabilistic (Monte Carlo) analysis.

For chronic exposure estimates, the average food consumption of each population subgroup was multiplied by the mean residue value. The estimates for both, acute and chronic exposure were expressed as a dosage in μg/kg/day.

IV. B.2.3. Exposure to Methyl Parathion from Food.

Methyl parathion residues that are of toxicological significance in plant commodities include methyl parathion, methyl paraoxon and p-nitrophenol. In animal commodities, an additional metabolite of toxicological concern is amino-paraoxon-methyl.

The NOELs selected for the acute and chronic assessment were based on reduction of the ChE activity and neuropathology as toxicology endpoints. Therefore, only methyl parathion and methyl paraoxon, which exert neurotoxicity mainly via AChE inhibition, were considered in this dietary exposure assessment. Amino-paraoxon-methyl, the most prominent methyl parathion metabolite in animal milk and fat (Van Dijk, 1988c), has been implicated in causing neuropathy (USEPA, 1999). However, this metabolite was not included in the dietary analysis, because of lack of sufficient toxicity and residue data to estimate the human risk. In addition, USEPA tolerances have not been established for residues of methyl parathion or its metabolites in animal commodities. p-Nitrophenol was also not considered in the dietary risk assessment. The toxicity of p-nitrophenol has been associated with hematologic effects rather than inhibition of the cholinesterase activity (ATSDR, 1992). Lack of adequate toxicity (IRIS, 1991) and residue data, however, precluded the evaluation of the p-nitrophenol dietary risk. Currently, p-nitrophenol residues are not included in the tolerances established for the methyl parathion residues. The published tolerances are listed in 40 CFR 180.121 and are expressed for plant commodities as methyl parathion parent compound only (CFR, 2001).

IV. B.2.4. Residue Data Sources

Methyl parathion residue data used in the current risk assessment were based on the following sources, listed in the order of preference:

1. USDA Pesticide Data Program (PDP).
2. DPR Priority Pesticide and Market Basket Surveillance Programs.
3. Food and Drug Administrations (FDA) Regulatory Residue Monitoring Program.
4. Field Trial Residue Studies (submitted by methyl parathion registrants to support tolerances).

1. Pesticide Data Program (PDP)

The Pesticide Data Program (www.ams.usda.gov/science/pdp/download.htm) is designed to obtain pesticide residue data for risk assessments. Samples were collected in ten states, including California, at produce markets and chain store distribution centers close to the consumer level.

PDP analyzes for the pesticide methyl parathion as the parent compound and recently, for the metabolite methyl paraoxon. From 1994 to 1999, PDP has examined several of the commodities with current registrations for methyl parathion use in California. Detectable residues were reported in 1996 and 1997 for wheat. In contrast, quantifiable methyl parathion residues were not reported on the following commodities: processed corn grain (analyzed as high fructose corn syrup, HFCS-55; and Dextrose Equivelent corn syrup, DE-42/43, during the 1998-1999 surveillance period), oats (examined in 1999); potatoes (analyzed in 1994 and 1995), and soybeans (screened during the 1997-1998 surveillance period) (Table 35). The residue limit of detection (LOD) varied from 0.003-0.008 ppm among the national laboratories contracted by USDA to perform the analysis (Table 35).

The commodity dry beans was not included in the PDP survey; however, fresh green beans and processed (canned or frozen) green beans were monitored for methyl parathion during 1993-1995 and 1996-1998 surveillance periods. The residue LOD varied from 0.002-0.013 ppm. Fresh and canned/frozen green beans displayed significantly different residue profiles, in that methyl parathion was frequently detected in processed green beans but was not detected in the fresh commodity. Although these crops are no longer label-approved in California, they could be used

as surrogates to model the dietary exposure from dry beans. Succulent and dried beans are considered related commodities, which are classified in the Crop Group 6 for the purpose of tolerance establishment (40 CRF 180.40). Similarly, PDP did not monitor for methyl parathion in corn grain and dry peas; however, residue values could be extrapolated from the 1994-1996 PDP data for the related foods processed sweet corn and processed sweet peas, respectively. Processed sweet corn samples were analyzed at the USDA contract laboratory at Sacramento, California, and no detectable residues were reported. In contrast, methyl parathion concentrations above the limit of detection were measured on processed sweet peas in 1995 and 1996 (Table 35). The residue LOD varied from 0.002-0.006ppm.

In 1999 and 2000, PDP for the first time monitored raw agricultural (RAC) and processed commodities for both the parent pesticide methyl parathion and its toxicologically relevant metabolite, methyl paraoxon. Among the crops analyzed, oats and potatoes were the only commodities with current registrations for methyl parathion use in California. The limit of detection for methyl parathion and methyl paraoxon on oats was 0.006 and 0.017 ppm, respectively. The LOD on potatoes was 0.003 ppm for both methyl parathion and methyl paraoxon. No quantifiable methyl paraoxon residues were reported for oats and potatoes.

2. DPR Priority Pesticide and Marketplace Surveillance Programs.

Samples from the Priority Pesticide Program are collected from fields, which have been treated with specific pesticides (see http://mitra:8080/3pubs/3pubs-annreports.htm). For the Marketplace Surveillance Program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods. Under the California DPR surveillance programs, methyl parathion is analyzed as the parent compound and as methyl paraoxon. Detected methyl parathion residues in commodities of interest such as dry beans, sweet corn and green onions, were reported in 1995, 1996, and 2000. The residue limit of detection varied from 0.01-005 ppm.

3. FDA Regulatory Residue Monitoring.

FDA analyzes domestic and imported foods for pesticide residue to enforce the tolerances set by EPA (see www.cfsan.fda.gov/~dms/pesrpts.html). Detectable methyl parathion residues in commodities of interest such as rice and wheat were reported in 1995-1997. The residue limit of detection was 0.0033 ppm. Quantifiable methyl parathion residues were not found for the following commodities: potatoes (1995-1997), onions (1994-1997), dry beans (1994-1996), soybeans 1994-1997, and field and sweet corn (1994-1997). The commodities dry beans and wheat were also tested for methyl paraoxon residues. The limit of detection was 0.0033 ppm, and no detectable residues were reported.

Table 35. Anticipated Methyl Parathion Residues Used for Acute and Chronic Dietary Exposure Assessments.

Commodity	Source of Data	Year	Number Samples	Number Detected Samples	Detected Residues (Ppm)	Range LOD (ppm)	% Crop Treated[A]	Adj. Factor[b]	Acute Residue (ppm)		Chronic Average Residue (ppm)
									Point Estimate	Monte Carlo	
Barley	PDP[c] data for wheat	-	See wheat	See wheat	See wheat	0.006	1%	1	0.031	0.031	0.0030
Beans dry (blackeye peas/cowpea, broadbeans, garbanzo/ chick pea, great northern, hyacinth, kidney, lima, navy, pigeon, pinto, others)	PDP data for processed green beans	1996	531	18	0.003-0.38	0.002-0.013	4%	1	0.380	RDF1[d]	0.0024
		1997	707	33							
		1998	360	15							
Corn grain (bran, endosperm, oil, sweet corn)	PDP data for processed sweet corn in CA	1994	69	0	No detectable residues	0.003	7 %	1	0.003	RDF2	0.0015
		1995	139	0							
		1996	40	0							
Corn grain (sugar/hfc, molasses)	PDP data	1998	298	0	No detectable residues	0.008	7%	1.5x	0.008	RDF3	0.0040
		1999	156	0							
Cottonseed (meal and oil)	Field trial data	1985	37	37	0.06-0.66	0.010	17%	1	0.660	0.660	0.3460
Oats	PDP data	1999	332	0	No detectable	0.006	1%	1	0.006	RDF4	0.0030
Onions (dehydrated or dried, dry-bulb cipollini)	DPR data[e]	1991-2000	1221	0	No detectable residues	0.010	9%	9x	0.010	RDF5	0.0050
Onions (green)	DPR data	1995-2000	744	2	0.01-0.03	0.020	9%	1	0.030	RDF6	0.0110

Continued

Commodity	Source of Data	Year	Number Samples	Number Detected Samples	Detected Residues (ppm)	Range LOD (ppm)	% Crop Treated[a]	Adj. Factor[b]	Acute Residue (ppm)		Chronic Average Residue (ppm)
									Point Estimate	Monte Carlo	
Peas Dry (garden)	PDP data for processed sweet peas	1994	433	0	0.004-0.007	0.002-0.006	4 %	1	0.007	RDF7	0.0010
		1995	670	9							
		1996	355	3							
Pecans	Field trial data	1985	4	0	No detectable residues	0.050	2%	1	0.050	0.050	0.0250
Potatoes (white peeled, peel only, whole, white dry)	PDP data in CA	1994	156	0	No detectable residues	0.003	2%	6.5[f]	0.003	RDF7	0.0015
		1995	169	0							
Rice (bran, milled white, rough brown, wild)	FDA[g] data	1994	18	0	0.04-0.11	0.0033	12%	1	0.110	0.110	0.0025
		1995	53	1							
		1996	54	1							
		1997	53	2							
Soybeans (flour defatted, full fat, low fat, mature seeds dry)	PDP data	1997	159	0	No detectable residues	0.004	1%	0.33[h]	0.004	RDF8	0.0020
		1998	589	0							
Walnut oil, Walnuts	Field trial data	1985	6	0	No detectable residues	0.050	12%	1	0.050	0.050	0.0250
Wheat (bran, germ, germ oil, flour)	PDP data	1996	340	1	0.01-0.031	0.006	2%	1	0.031	RDF9	0.0030
		1997	623	1							

a) The Percent Crop Treated was from the 1999 report by the USDA Biological and Economical Analysis Division (BEAD). **b)** DEEM™ default factors to account for changes in the hydration state of foods. **c)** Pesticide Data Program (PDP) implemented by the United States Department of Agriculture (USDA). **d)** Residue Distribution File (RDF) containing all detected residue values to determine the exposure distribution in the Monte Carlo analyses. **e)** Department of Pesticide Regulation (DPR) Priority Pesticide and Market Basket Surveillance Programs. **f)** This hydration factor was used only for potatoes white dry. **g)** Regulatory Residue Monitoring Program of the Food and Drug Administrations (FDA) **h)** This hydration factor was used only for soybeans sprouted seeds.

4. Field Trial Residue Studies.

Elf Atochem and the former registrants Bayer Corporation and Cheminova, Inc. have submitted field studies evaluating the residues on RAC treated with methyl parathion at various label rates, including the maximum. Earlier studies measured methyl parathion as a total chemical, whereas more recent studies analyzed for methyl parathion and for the metabolites, methyl paraoxon and p-nitrophenol. The limit of detection varied from 0.01 to 0.2 ppm, depending on the commodity and the analytical method used. Among the commodities with registrations for use in California, field trial data were available to DPR for field corn, cottonseed, soybeans and other grains, pecans, wheat, potatoes and walnuts.

IV. B.2.5. Acute Exposure

The DPR uses the tiered approach in selecting the appropriate residue values to estimate the acute dietary exposure to a pesticide. The tiered approach begins with the point estimate (deterministic) steps, which are generally less time-consuming and less labor intensive than the refining assessment. The Point Estimate Model employs the tolerance (Tiers 1), the upper bound value or the mean residue value (Tiers 2 and 3). The Monte Carlo probabilistic approach (Tier 4) can be subsequently used to refine the assessment, taking into account the probability of residue occurrences. The analysis provides the probability distribution of exposure.

a. Deterministic (Point Estimate) Dietary Exposure Assessment

The acute dietary exposure to methyl parathion of the US population and various population subgroups was initially assessed using theTier 3 deterministic approach. In this model, a single value (referred to as a point estimate) was selected to represent the concentration of methyl parathion on each of the 13 label-approved commodities in California.

The typical assumptions in the Tier 3 point estimate assessment are: (*i*) all consumed foods contain the highest reported residue below the tolerance (*ii*) pesticide residues below the LOD are equal to that limit, (*iii*) All crops are treated with the pesticide and (*iv*) residue concentrations do not vary from the time of sampling to the time of consumption.

Consequently, the highest measured residues or the highest LOD within a program were selected for the commodities wheat, corn syrup, oats and soybeans from the PDP databases (Table 35).

In cases where PDP data were not available, DPR monitoring studies on methyl parathion were considered for residue selection. The highest measured methyl parathion concentration or the LOD were chosen for the commodities green and dry onions, respectively, from the DPR Marketplace Surveillance Program (Table 35).

Methyl parathion has been reported as the most widely used insecticide on rice in 2000 (USDA 2001). PDP or DPR have not monitored rice for the pesticide residues. Consequently, the highest methyl parathion residue measured on rice was selected from 1997-1999 FDA Regulatory Monitoring database (Table 35).

Federal or state multi-year monitoring data were not available for cottonseeds, pecans and walnuts. The highest pesticide residues measured in field crop trials were chosen to represent the residues for the acute exposure analysis.

For several commodities regulatory monitoring data and registrant field trial studies were either not available or the residue information was not sufficient to be used in the dietary analysis. In these cases, residues reported for similar foods were used as surrogates. The methyl parathion concentration on barley was assumed to be equal to the highest concentration measured by the PDP on wheat (Table 35). Surveillance data were available for dry beans from the FDA Regulatory Monitoring Program, however only summary data were provided. Thus, the residue value for dry beans was extrapolated from the 1996-1998 PDP dataset on processed (frozen or canned) green beans, which consisted of 1598 analyzed samples with 66 detected residues (Table 35). The pesticide residue on dry peas was assumed equal to the highest detected residues on processed sweet peas, reported by the PDP (Table 35). The choice of the most appropriate surrogate commodity was based on the classification of related raw agricultural commodities into crop groups, established in 40 CFR 180.40, and according to the agricultural practices specified in the product label.

In order to estimate the food exposure more realistically, attempts were made to refine the residue values. For acute dietary risk assessment, DPR typically uses the highest limit of detection within a monitoring program or field trials to represent non-detectable pesticide residues. In cases where a sufficient number of samples was analyzed in California, the LOD for methyl parathion of the USDA national contract laboratories was substituted with the substantially lower LOD of the California testing laboratories. Such data were available for methyl parathion on potatoes and processed sweet corn from the PDP database.

Changes in the hydration state of foods can also alter the residue concentration compared to the raw commodities which were monitored. The following default factors, provided in the DEEM™ Acute Module, were utilized to account for concentration or reduction of methyl parathion due to changes in food hydration: 0.33 1.5, 6.5 and 9 for soybeans-sprouted seeds, corn syrup, dry potatoes and dried onions, respectively. No other adjustment factors were employed in the evaluation of the acute dietary exposure.

Based on the paradigms used in this dietary assessment, the 95th percentile of user-day exposures to methyl parathion ranged from 0.338 μg/kg/day to 1.103 μg/kg/day. At the 95th exposure percentile, the population subgroups “Children 1-6 years” and “Hispanics” were identified as the most highly exposed among the evaluated subgroups (Table 36; see also Attachment I).

The acute Critical Exposure Commodity (CEC) analysis identified several commodities including rice, dry beans, wheat flour and cottonseed-oil as making substantial contributions the acute dietary risk. The contribution of these commodities to the high daily exposure of individuals was a result of the methyl parathion residues measured on these crops, and the consumption of the respective food-forms determined during 1994-1998 CSFII. PDP or FDA monitoring data were available for all of these contributors, except for cottonseed-oil, for which the pesticide residues were measured in field trials.

Table 36. Acute (Point Estimate) Dietary Exposure Estimates for Methyl Parathion.

Population Subgroup	ACUTE (POINT ESTIMATE) EXPOSURE	
	95th Exposure Percentile (μg/kg/day)	
	All Commodities[a]	Rice Only[b]
US Population (all seasons)	0.505	0.314
Western Region	0.608	0.408
Hispanics	**0.936**	0.387
Non-Hispanic Whites	0.417	0.207
Non-Hispanic Blacks	0.540	0.334
Non-Hispanic Other	0.828	**0.627**
All infants	0.638	**0.621**
Infants (nursing, <1yr.)	0.496	0.516
Infants (non-nursing,<1yr.)	0.667	**0.636**
Children (1-6 yrs)	**1.103**	0.554
Children (7-12 yrs)	0.650	0.387
Females (13+ yrs, pregnant, not nursing)	0.564	0.414
Females (13+ yrs, nursing)*	0.531	0.181
Females (13-19 yrs, not pregnant or nursing)	0.443	0.284
Females (20+) not pregnant or nursing	0.354	0.224
Females (13-50 yrs)	0.402	0.252
Males (13-19 yrs)	0.567	0.530
Males 20+ yrs	0.461	0.236
Seniors 55+	0.338	0.189

a/ DEEM™ program was used for the analysis with the USDA CSFII from 1994-1998. Acute dietary exposure from all methyl parathion label-approved commodities in California was calculated at the 95th percentile of user-days for all population subgroups.

b/ A Point Estimate-type acute exposure analysis was carried out only for the commodity rice. The methyl parathion residue level on rice was set equal to 0.11 ppm (1994-1997 FDA Regulatory Monitoring database). Acute dietary exposure was calculated at the 95th percentile of user-days for all population subgroups. The highest exposures are indicated in bold.

***** "Females 13^{+} nursing" was represented by less than 100 user days in the 1994-1998 CSFII database.

Dry beans in the food-forms of Beans-dry-pinto-Boiled or Fried and Beans-dry-other-Boiled appeared as the most significant contributor to the dietary exposure for the majority of the evaluated population subgroups. The contribution of dry beans to the total dietary exposure to methyl parathion was the highest for the following population subgroups: Females 13+ nursing (78% of the total dietary exposure), Females 13+ pregnant (59%), Seniors 55+ (56%), Females 13-19 yrs. (51 %), Children 7-12 yrs. (48%) and Males 13-19 yrs. (48%).

Rice in its food-forms Rice-milled (white)-Boiled, Cooked or Canned was the other significant contributor to the dietary exposure, ranging from 15% to 41% of the total exposure of a number of population subgroups including: All Infants (Nursing and Non-nursing, 36-41%), Non-hispanic/non-white/non-black (37%), Children 1-6 yrs. and Females 20+ yrs (22%).

The acute dietary exposure estimates presented in Table 36 characterize a hypothetical scenario where each of the 12 commodities, that could potentially be consumed in a given day, contained the upper-bound methyl parathion residues. Although this consumption scenario is unlikely to occur in the actual practice, a scenario in which only one or two of these commodities possess high methyl parathion residue can not be excluded. To examine whether a significant dietary risk is associated with the consumption of a single commodity with an upper-bound methyl parathion concentration, an acute exposure analysis was carried out only for rice. The methyl parathion concentration on all of the California label-approved commodities, except rice, was assumed to be zero. The residue level on rice was set equal to 0.11 ppm, which was the highest detected concentration by the FDA Regulatory Monitoring.

The exposures to methyl parathion from rice ranged from 0.181 μg/kg/day to 0.636 μg/kg/day at the 95th percentile (Table 36). Infants (non-nursing) and Non-hispanic/non-white/non-black were identified as the most highly exposed population subgroups.

As part of the DPR's tiered approach, the probabilistic analysis was used as the next refining step of the acute dietary exposure assessment of methyl parathion. The probabilistic evaluation, also known as Monte Carlo analysis, uses the entire range of pesticide residues available from a data source to calculate the distribution of exposure for selected population subgroups. Furthermore, the food exposure estimates could be improved by incorporating information on the pesticide use and agricultural or processing practices, such as percent of the crop that is treated, pesticide degradation or food washing and cooking.

b. Acute Probabilistic Exposure Analysis (Monte Carlo)

Dietary exposure assessments were conducted for methyl parathion using the Monte Carlo modeling. Exposures were calculated for two acute dietary intake scenarios. The first scenario described a daily consumption of commodities, assumed to be 100% treated with methyl parathion. The second scenario employed percent-crop-treated adjustments to account for the fact that only a fraction of the total crop acreage was methyl parathion-treated.

Acute Scenario I. Monte Carlo Analysis for Non-PCT-Adjusted Exposures.

For this analysis, the same residue database was used as in the Point Estimate-type dietary exposure assessment. Instead of assuming a single residue value for each crop, the distribution of residues were used for 9 of the 12 commodities with current methyl parathion registrations in California. These

included: dry beans, sweet corn, corn syrup, oats, onions (dried and green), dry peas, potatoes, soybeans and wheat (Attachment II and Table 35). In this dietary exposure assessment, percent of the crop treated (PCT) was not considered for any of the commodities, thus precluding the probability that the residue level could be zero. The samples containing detectable methyl parathion residues were assigned their corresponding value. The rest of the analyzed samples were set equal to the LOD.

The residue distribution data for the remaining four commodities (rice, cottonseed, pecans and walnuts) were either unavailable or insufficient for representing what people eat. A total of 172 rice samples was screened for methyl parathion through the FDA Regulatory Monitoring Program. However, the residue information was incomplete for conducting a distribution because only a range of methyl parathion concentrations was provided. The available residue data on cottonseed were from a field trial study. Similarly, the data for pecans and walnuts were from a registrant field trial, where only 6 and 4 data points, respectively, were reported. Consequently, a single residue value, which was the highest detected methyl parathion concentration, was assigned to cottonseed (0.66 ppm) and rice (0.11 ppm); the LOD was chosen for pecans (0.05 ppm), and walnuts (0.05 ppm). The highest measured pesticide residue on wheat (0.031 pm) was selected to represent the methyl parathion concentration on barley (Table 35).

The acute dietary exposure estimates for each of the examined population subgroups are presented in Table 37. At the 95th exposure percentile, the estimated acute exposures to methyl parathion ranged from 0.146 μg/kg/day to 0.625 μg/kg/day. The **"**Non-hispanic/non-white/non-black" subgroup was identified as having the highest dietary exposure from methyl parathion.

At the 99th percentile, the estimated acute exposures to methyl parathion ranged from 0.288 μg/kg/day to 1.166 μg/kg/day (Table 37). Infants (nursing and non-nursing) were identified to receive the highest dietary exposure from methyl parathion.

Similarly, at the 99.9th exposure percentile, Infants (nursing and non-nursing) were shown to receive the highest dietary exposure from methyl parathion (2.765 μg/kg/day). Females 13+ yrs-nursing received the lowest dietary exposure (0. 390 μg/kg/day).

Acute Scenario II . Monte Carlo Analysis for PCT-Adjusted Exposures

The dietary exposure analysis presented below utilized the same residue database as in the Acute Scenario I. This scenario, however, employed percent-crop-treated adjustments to reflect the actual methyl parathion use pattern. PCT was applied to refine the residue values on the commodities for which distribution of residue levels was used. These included: dry beans, sweet corn, corn syrup, oats, onions (dried and green), dry peas, potatoes, soybeans and wheat.

The theoretical number of samples, which contained methyl parathion residues, was calculated based on the number of samples analyzed and the percent of the crop treated. The PCT information was obtained from the 1999 report by the USDA Biological and Economical Analysis Division (BEAD, see http://www.epa.gov/oppbead1/contacts_bead.htm). In some cases, the number of samples with measured residues was greater than the theoretical number of samples with residue estimated from the PCT data. Consequently, all of the samples containing detectable methyl parathion residues were assigned their corresponding value, whereas the rest of the samples were assigned zero. If the theoretical number of residues, based on the PCT, was greater than the number of measured residues, then those additional samples were set equal to the LOD. The remaining of the analyzed samples were assigned zero (see Attachment II).

Table 37. Probabilistic (Monte Carlo) Dietary Exposure Estimates for Methyl Parathion. Scenario I: Non-PCT-Adjusted Exposures; Scenario II: PCT-Adjusted Exposures.

Population Supgroup	ACUTE (MONTE CARLO) EXPOSURE [a] (µg/kg/day)					
	Non-PCT-Adjusted Exposures[b]			PCT-Adjusted Exposures[c]		
	95th Percentile	99th Percentile	99.9th Percentile	95th Percentile	99th Percentile	99.9th Percentile
US Population (all seasons)	0.264	0.526	0.985	0.223	0.481	0.943
Western Region	0.341	0.644	1.164	0.301	0.615	1.117
Hispanics	0.378	0.715	1.191	0.333	0.633	1.172
Non-Hispanic Whites	0.203	0.371	0.793	0.162	0.327	0.647
Non-Hispanic Blacks	0.293	0.535	0.973	0.250	0.482	0.888
Non-Hispanic Other	**0.625**	0.977	1.748	**0.588**	0.949	1.689
All infants	0.515	**1.161**	**2.765**	0.448	**1.066**	**2.697**
Infants (nursing, <1yr.)	0.424	**1.155**	1.434	0.403	**1.086**	1.404
Infants (non nursing,<1yr.)	0.535	**1.166**	**2.766**	0.455	**1.061**	**2.710**
Children (1-6 yrs)	0.491	0.898	1.612	0.425	0.824	1.533
Children (7-12 yrs)	0.333	0.621	0.921	0.283	0.562	0.872
Females (13+ yrs, pregnant, not nursing)	0.342	0793	0.798	0.292	0.777	0.787
Females (13+ yrs, nursing)*	0.202	0.389	0.390	0.177	0.233	0.241
Females (13-19 yrs, not pregnant or nursing)	0.213	0.370	0.534	0.177	0.349	0.474
Females (20+) not pregnant or nursing	0.179	0.345	0.632	0.154	0.318	0.590
Females (13-50 yrs)	0.201	0.382	0.678	0.177	0.361	0.668
Males (13-19 yrs)	0.301	0.661	0.984	0.269	0.633	0.970
Males 20+ yrs	0.224	0.447	0.771	0.200	0.423	0.720
Seniors 55+	0.146	0.288	0.686	0.128	0.270	0.673

a/ DEEM™ program was used with the following input parameters: (*i*) USDA CSFII from 1994-1998, *(ii*) 500 iterations and Seed of 10 for the Monte Carlo analysis. The acute exposure was calculated at the 95th, 99th, 99.9th percentiles of user-days for all population subgroups. The highest exposures are indicated in bold. **b**/ The residue data for this exposure estimate did not include the percent of the crop treated (PCT). **c**/ The percent crop treated adjustment factors were used for the following commodities: beans, corn (sweet and syrup), oats, onions (dried and green), peas, potatoes, soybeans and wheat. *"Females 13^{+} nursing" was represented by less than 100 user days in the 1994-1998 CSFII database.

For the acute analysis, PCT adjustments were not made for commodities, which were assigned a single residue value (point estimate). This decision was justified with the following considerations. When a single value represents the pesticide concentration on a given commodity, this value is assumed for all points in the consumption distribution. This precludes the possibility that the residue level could be at the LOD or zero.

The acute dietary exposure estimates for each of the population subgroups examined are presented in Table 37. At the 95th exposure percentile, the estimated acute exposures to methyl parathion ranged from 0.128 μg/kg/day to 0.588 μg/kg/day. The **"**Non-hispanic/non-white/non-black" subgroup was identified to receive the highest dietary exposure from methyl parathion.

At the 99th percentile, the population subgroup Infants (nursing and non-nursing) were identified to receive the highest dietary exposure from methyl parathion (1.068 μg/kg/day). The subgroup"Females 13+ pregnant, nursing" received the lowest acute dietary exposure (0.233 μg/kg/day, Table 37).

Similarly, at the 99.9th exposure percentile, the population subgroup Infants (nursing and non-nursing) and Females 13+ pregnant, nursing were shown to receive the highest and the lowest dietary exposure from methyl parathion (2.7 μg/kg/day and 0.241 μg/kg/day, respectively).

The Monte Carlo CEC analysis for both scenarios revealed that the commodities rice and cottonseed-oil made the most significant contribution to the acute dietary risk. The contribution of the food-forms Rice-milled (white)-Boiled, Cooked, or Canned ranged from 38% (Non-hispanic whites) to 79% (Non-nursing infants) and 53% (Non-hispanic whites) to 83% (Infants, nursing or non-nursing) of the total exposure to methyl parathion in the Acute Scenario I and the Acute Scenario II, respectively. The contribution of Cottonseed-oil-Refined ranged from 2% (Females 13+ pregnant, not nursing) to 26-29% (Children 7-12 yrs, Non-hispanics whites and Females 13+ pregnant, nursing) of the total exposure to methyl parathion in both Acute Scenarios.

The two Monte Carlo Dietary Assessments differed in that the percentage of crop treated adjustment factors were used to refine residues measured on most of the commodities in Scenario II. However, assigning LOD (Scenario I) to the previously considered zero residue values (Scenario II) did not result in a significant change in the dietary exposure to methyl parathion to any of the population subgroups at the 95, 99 and 99.9 exposure percentiles.

IV. B.2.6. Chronic Exposure

For chronic risk assessments, the average value of all pesticide residues detected on a commodity was multiplied by the average consumption of each population subgroup. DPR uses certain assumptions when conducting chronic dietary assessment. Typical ones are: (*i*) Residue levels below the limit of detection are at ½ of that limit, (*ii*) commodities that could contain methyl parathion residues contain the average residue levels, (*iii*) the population average daily consumption distribution reflects the longitudinal consumption patterns of individuals.

Therefore, the arithmetic average of the measured pesticide concentrations was used to estimate the combined exposure from all commodities on which methyl parathion can be used in California. In order to account for possible unquantifiable exposures, samples with residues below the limit of detection were assigned ½ of the LOD (in ppm). The anticipated methyl parathion residues, along

with the LOD, are presented in Table 35. The individual residue values are shown in the Residue Distribution Files (Attachment III).

Exposures were calculated for two chronic dietary intake scenarios. The first scenario represented a chronic consumption of commodities, assumed to be 100% treated with methyl parathion. The second scenario employed percent-crop-treated adjustments to account for the fact that only a fraction of the total crop acreage was treated. The PCT was applied to refine the residue values on all of the 12 commodities registered for methyl parathion use in California. The PCT ranged from 1 to 17% (Table 35).

The chronic dietary exposures of the 19 consumer groups (the overall U.S. population and 18 standard population subgroups) were estimated as follows:

Scenario I. Non-PCT Exposures: Based on the paradigms used in this analysis, the estimated chronic exposures to methyl parathion ranged from 0.063 μg/kg/day (Children 1-6 yrs) to 0.012 μg/kg/day (Nursing infants; Table 38).

Scenario II. PCT-Adjusted Exposures**:** Applying adjustment factors to refine the methyl parathion concentrations for percent of the crop treated resulted in a 10 to 12 fold lower chronic dietary exposures, compared to the unmodified (non-PCT) exposures (Scenario I). These exposures ranged from 0.001 μg/kg/day for "Nursing infants" to 0.006 μg/kg/day for "Children 1-6 yrs" (Table 29).

Table 38. Chronic Dietary Exposure Estimates for Methyl Parathion.

Population Subgroup	Chronic Exposure (μg/kg/day)[a]	
	No PCT adjustments[b]	PCT adjustments[c]
US Population (all seasons)	0.027	0.003
Western Region	0.028	0.003
Hispanics	0.030	0.003
Non-Hispanic whites	0.026	0.002
Non-Hispanic Blacks	0.028	0.003
Non-Hispanic Other	0.033	0.004
All infants	0.031	0.002
Infants (nursing, <1yr.)	0.012	0.001
Infants (non-nursing,<1yr.)	0.038	0.003
Children (1-6 yrs)	**0.063**	**0.006**
Children (7-12 yrs)	0.044	0.004
Females (13+ yrs, pregnant, not nursing)	0.021	0.002
Females (13+ yrs, nursing)	0.028	0.003
Females (13-19 yrs, not pregnant or nursing)	0.025	0.002
Females (20+) not pregnant or nursing	0.018	0.002
Females (13-50 yrs)	0.021	0.002
Males (13-19 yrs)	0.031	0.003
Males 20+ yrs	0.021	0.002
Seniors 55+	0.017	0.002

a/ The DEEM™ program was used for the analysis with the USDA CSFII from 1994-1998. The highest exposures are indicated in bold.

b/ The residue data for this exposure estimate did not include the percent of the crop treated (PCT).

c/ The percent crop treated adjustment factors were used for the commodities: beans, barley, corn, cotton, oats, onions (dried and green), peas, potatoes, pecans, rice, soybeans, walnuts and wheat.

IV. B.2.7. Dietary Exposure to Methyl Paraoxon

A detailed discussion on the toxic potential of the methyl parathion metabolite methyl paraoxon has been presented in the TACE document (Reed, 1999). The toxicity comparison between methyl parathion and methyl paraoxon was based on the reported LD_{50} values, as well as on the inhibition of plasma and brain ChE. The available acute studies in rats revealed that methyl paraoxon induced toxic effects at approximately 5 to 8 fold lower concentrations than methyl parathion. Based on these findings a toxicity equivalence factor (TEF) of 10 was established for methyl paraoxon to convert the exposure to this metabolite to a "methyl parathion equivalent". This "methyl parathion equivalent" was subsequently added to the exposure of methyl parathion to estimate the total exposure to both methyl parathion and methyl paraoxon from air (Reed, 1999).

For the current assessment, an additional adjustment to account for the toxicity of methyl paraoxon was not considered in estimating the dietary exposure to methyl parathion. Unlike the risk assessment under the TAC program, in which methyl paraoxon was detected in the air in California (Kelley 1999; Formoli 2000), the existing food residue database lacks sufficient information on the amount of methyl paraoxon on food. Only five crops with current registrations for methyl parathion use were tested for methyl paraoxon residues. PDP has analyzed 332 samples of oats and 106 samples of potatoes, and FDA monitored dry beans (33 samples) dry peas (6 samples) and wheat (10 samples). For both, the acute and chronic dietary assessments, the concentrations of methyl parathion on these five commodities were selected from PDP databases (Table 35). The LOD of the USDA testing laboratory was about 3-fold higher for methyl paraoxon on oats than that for the parent compound methyl parathion (0.017 ppm vs. 0.006 ppm); the LOD was the same for methyl parathion and methyl paraoxon on potatoes (0.003 ppm). The methyl paraoxon LOD for the crops tested by the FDA was significantly lower (0.0033 ppm). No quantifiable methyl paraoxon residues were reported on any of these commodities.

If methyl paraoxon were assumed to be present at or below the LOD levels on commodities tested for this metabolite, the potential exposure to both methyl parathion and methyl paraoxon could be higher, compared to the exposure to methyl parathion alone. However, data were not available to validate this assumption and the total dietary exposure could not be estimated based on no detectable residues of methyl paraoxon. In addition, the tolerances listed in 40 CFR 180.121 are specified only for the methyl parathion parent compound. In conclusion, the lack of sufficient residue data and specification of methyl paraoxon in the current tolerances preclude a dietary assessment at this time.

IV. B.3. Aggregate Exposure

The ambient air exposure was less than 3% compared to the exposure from dietary sources Because of its relatively low contribution, it was not added to the dietary exposure to estimate the total exposure from non-occupational sources. However, the potential risk from the combined exposures to methyl parathion in the ambient air and in food is discussed in section **V.D.4. under RISK APPRAISAL**.

IV.C. RISK CHARACTERIZATION

In the case of methyl parathion, the process of risk characterization involves estimating the margin of exposure (MOE). The MOE for exposure to methyl parathion is calculated as the ratio of the critical NOEL, established for specific exposure duration and an estimate of a human exposure. The critical NOELs were determined from oral and dermal studies; NOELs for the inhalation route were not available. This document pertains only to the assessment of the dietary and the ambient air exposure. Therefore, the critical oral NOEL was utilized in the calculation of the MOE for oral and inhalation routes. The exposures were estimated from oral (dietary) and inhalation (ambient air exposure). The MOE was calculated using the absorbed dose for each route.

The acute, subchronic and chronic NOELs employed for the characterization of the risk from exposure to methyl parathion were derived from studies with laboratory animals. Consequently, a calculated MOE of 100 was considered prudent for protection against the methyl parathion toxicity. The benchmark of 100 includes an uncertainty factor of 10 for interspecies sensitivity and 10 for intraspecies variability.

Methyl Parathion Toxicology Endpoints

Acute Toxicity. The acute NOEL of 0.025 mg/kg/day was selected to calculate the MOE for acute exposures (all routes) to methyl parathion (Minnema, 1994a). This NOEL was derived from an acute gavage neurotoxicity study in rats and was based on the inhibition of ChE activities (plasma, RBC and brain), clinical signs for cholinergic toxicity and peripheral nerve demyelination at the LOEL of 7.5 mg/kg/day.

Subchronic Oral Toxicity. The NOEL of 0.03 mg/kg/day was utilized to calculate the MOE for subchronic (seasonal) dietary exposures. This NOEL was from a developmental neurotoxicity study in rats, which revealed a reduction in the ChE activities in the plasma, RBC and brain at a LOEL of 0.3 mg/kg/day (Beyrouty, 2002c).

Subchronic Dermal Toxicity. The estimated NOEL of 0.03 mg/kg/day was employed to calculate the MOE for subchronic (2-month seasonal) exposures. This ENEL was from a 4-week dermal neurotoxicity study in rats. It was based on the inhibition of the ChE activities in the brain and in the RBC, and cholinergic toxicity at a LOEL of 0.3 mg/kg/day (Beyrouty, 2001).

Chronic Toxicity. The estimated NOEL of 0.02 mg/kg/day was used to calculate the dietary chronic exposure to methyl parathion. This ENEL was based on an inhibition of the brain ChE activity at a dose of 0.2 mg/kg/d (LOEL) in a two-year oral study in mice (Eiben, 1991).

IV. C.1. Non-Dietary Exposure

IV. C.1.a. Ambient Air Exposure

The estimates of exposure to methyl parathion from the ambient air were presented in the 1999 TACE document (Reed, 1999). The single day exposure was calculated based on the 95th percentile of the daily concentrations of methyl parathion and methyl paraoxon in the air. The seasonal exposure at a given location was calculated assuming a daily exposure pattern throughout an entire season of use and at the level reflected by the average daily air concentration. The acute MOEs for ambient air exposures were 390-1,600 based on the rat NOEL of 0.025 mg/kg/day (Minnema, 1994a). The

ambient seasonal MOE values ranged from 1500 to 6300 based on the subchronic NOEL of 0.03 mg/kg/day for inhibition of the brain and RBC ChE activities in rats (Beyrouty, 2002c). The chronic MOEs for ambient air exposures varied from 1300 to 5400 based on the chronic NOEL of 0.02 mg/kg/day (Eiben, 1991).

IV. C.2. Dietary Exposure

IV.C.2.1. Acute Dietary Exposure

a. Deterministic (Point Estimate) Dietary Exposure Assessment.

The acute dietary exposures to methyl parathion, which were estimated using the deterministic (Point Estimate) model, are presented in the Table 36. The corresponding MOEs were less than 100 for all of the population subgroups examined, considering the exposure of 0.025 mg/kg/day as the acute NOEL (Table 39). At the 95th exposure percentile, the population subgroups "Children 1-6 years" and "Hispanics" were identified as the most highly exposed among the evaluated subgroups, with MOE of 24 and 26, respectively (Table 39).

The acute dietary exposures from methyl parathion on rice (Table 36) characterized a hypothetical scenario where a single commodity with an upper-bound methyl parathion concentration was consumed in a given day. The MOEs from exposure to methyl parathion from rice ranged from 39 to 137 μg/kg/day at the 95th percentile (Table 39). Infants (non-nursing) and Non-hispanic/non-white/non-black were identified as the most highly exposed population subgroups with MOEs of 39. The MOEs were greater than 100 only for the following population subgroups: Non-Hispanic Whites, Females 13+ nursing, Females 20+ not pregnant or nursing, Males 20+ and Seniors 55+.

In assessing the acute dietary exposure from pesticide residue, the point estimate analysis considers the highest residue level, below tolerance, found in crops and assumes that 100% of the crop is treated with pesticide. In general, the point estimate approach allows a rapid evaluation of dietary exposure in cases where risks are low. For methyl parathion, however, this model predicted a potential risk of concern, as demonstrated by the MOEs being less than 100 for all of the examined population subgroups. Furthermore, a daily consumption of only one commodity with an upper-bound methyl parathion concentration appears to result in MOEs below the level commonly considered as health protective for the majority of the population subgroups. These results prompted the use of the probabilistic Monte Carlo modeling as the next refining step of the acute dietary exposure assessment of methyl parathion.

Table 39. Acute (Point Estimate) Dietary Risk Estimates for Methyl Parathion.

Population Subgroup	ACUTE MOE[a] (Point Estimate)	
	95th Exposure Percentile	
	All Commodities[b]	Rice Only[c]
US Population (all seasons)	49	79
Western Region	41	61
Hispanics	26	64
Non-Hispanic Whites	59	120
Non-Hispanic Blacks	46	74
Non-Hispanic Other	30	**39**
All infants	39	40
Infants (nursing, <1yr.)	50	48
Infants (non-nursing,<1yr.)	37	**39**
Children (1-6 yrs)	**24**	45
Children (7-12 yrs)	38	64
Females (13+ yrs, pregnant, not nursing)	44	60
Females (13+ yrs, nursing)	47	137
Females (13-19 yrs, not pregnant or nursing)	56	87
Females (20+) not pregnant or nursing	70	111
Females (13-50 yrs)	62	99
Males (13-19 yrs)	44	47
Males 20+ yrs	54	105
Seniors 55+	73	132

a/ DEEM™ program was used for the analysis with the following input parameters: (*i*) USDA CSFII from 1994-1998 and (*ii*) acute NOEL of 0.025 mg/kg/day (based on plasma, RBC and brain ChE inhibition and neuropathology in rats, (Minnema, 1994a). Margin of Exposure (MOE) is defined as NOEL/Acute Dietary Intake.

b/ Acute dietary exposure from all methyl parathion label-approved commodities in California was calculated at the 95th percentile of user-days for all population subgroups. The lowest MOEs are indicated in bold.

c/ A Point Estimate-type acute exposure analysis was carried out only for the commodity rice. The methyl parathion residue level on rice was set equal to 0.11 ppm (1994-1997 FDA Regulatory Monitoring database). Acute dietary exposure was calculated at the 95th percentile of user-days for all population subgroups. The lowest MOEs are indicated in bold.

b. Acute Probabilistic Exposure Analysis (Monte Carlo)

Scenario I. Monte Carlo Analysis for Non-PCT-Adjusted Exposures.

The acute non-PCT-exposure estimates for each of the examined population subgroups are presented in Table 40. Based on the acute NOEL of 0.025 mg/kg/day (Minnema, 1994a), at the 95th exposure percentile, the MOEs ranged from 39 (Non-hispanic/non-white/non-black) to 170 (Seniors 55+, Table 40). The MOEs were less than 100 for the following population subgroups: US population, Western Region, Hispanics, Non-hispanic blacks, Non-hispanic/non-white/non-black, Infants (nursing and non-nursing), Children 1-12 yrs and Females 13+ pregnant/not nursing (Table 40).

At the 99th percentile, the estimated MOEs ranged from 21 to 86 (Table 40). The MOEs were less than 100 for all population subgroups. Infants (nursing and non-nursing) were identified to receive the highest dietary exposure from methyl parathion, with the corresponding MOE of 21.

Similarly, at the 99.9th exposure percentile the MOEs were less than 100 for all population subgroups. Infants (nursing and non-nursing) were shown to receive the highest dietary exposure from methyl parathion (MOE of 9, Table 40).

Acute Scenario II . Monte Carlo Analysis for PCT-Adjusted Exposures.

The estimated acute PCT-adjusted dietary exposures to methyl parathion are presented in the Table 37. At the 95th exposure percentile, the MOEs ranged from 42 **(**Non-hispanic/non-white/non-black) to 195 (Seniors 55+, Table 40). The MOEs, based on the acute NOEL of 0.025 mg/kg/day, were less than 100 for the following population subgroups: Western Region, Hispanics, Non-hispanic blacks Non-hispanic/non-white/non-black, Infants (nursing or non-nursing), Children 1-12 yrs and Females 13+ pregnant/not nursing.

At the 99th percentile, the MOEs were less than 100 for all population subgroups except for the subgroup "Females 13+ nursing". Infants (nursing and non-nursing) were identified to receive the highest dietary exposure from methyl parathion, with the corresponding MOE of 23 (Table 40).

Similarly, at the 99.9th exposure percentile, the infants were shown to receive the highest dietary exposure from methyl parathion (MOE of 9, Table 40). The population subgroup "Females 13+ nursing" was the only one with a MOE greater than 100. It should be noted that the dietary survey sample size for this population subgroup was very limited (only 84 user days) in the entire 1994-1998 CSFII database. Thus the results of the dietary exposure estimation may not be representative, especially at the tail ends of the distribution.

Table 40. Acute Probabilistic (Monte Carlo) Dietary Risk Estimates for Methyl Parathion

Scenario I: Non-PCT-Adjusted Exposures and Scenario II**:** PCT-Adjusted Exposures.

Population Subgroup	ACUTE MOE[a,] (Monte Carlo)					
	Non-PCT-Adjusted Exposures[b]			PCT-Adjusted Exposures[c]		
	95th Percentile	99th Percentile	99.9th Percentile	95th Percentile	99th Percentile	99.9th Percentile
US Population (all seasons)	94	47	25	112	51	26
Western Region	73	38	21	83	40	22
Hispanics	66	34	20	75	37	21
Non-Hispanic Whites	122	67	33	153	76	38
Non-Hispanic Blacks	85	46	25	99	51	28
Non-Hispanic Other	**39**	25	14	**42**	26	14
All infants	48	**21**	**9**	55	**23**	**9**
Infants (nursing, <1yr.)	58	**21**	17	61	**23**	17
Infants (non nursing,<1yr.)	46	**21**	**9**	54	**23**	**9**
Children (1-6 yrs)	50	27	15	58	30	16
Children (7-12 yrs)	75	40	40	88	44	28
Females (13+ yrs, pregnant, not nursing)	73	31	31	85	32	31
Females (13+ yrs, nursing)	123	64	64	141	111	103
Females (13-19 yrs, not pregnant or nursing)	117	67	46	141	73	52
Females (20+) not pregnant or nursing	139	72	39	162	78	42
Females (13-50 yrs)	124	65	36	141	69	37
Males (13-19 yrs)	83	37	25	93	39	25
Males 20+ yrs	111	55	32	125	59	34
Seniors 55+	170	86	36	195	92	37

a/ DEEM™ program was used for the analysis with the following input parameters: (*i*) USDA CSFII from 1994-1998, (*ii*) acute NOEL of 0.025 mg/kg (Minnema, 1994a) and *(iii*) 500 iterations and Seed of 10 for the Monte Carlo analysis. MOE is defined as NOEL/Acute Dietary Intake; Acute dietary exposure was calculated at the 95th, 99th, 99.9th percentiles of user-days for all population subgroups. The lowest MOEs are indicated in bold.

b/ The residue data for this exposure estimate did not include the percent of the crop treated (PCT).

c/ The percent crop treated adjustment factors were used for commodities: beans, corn (sweet and syrup), oats, onions (dried and green), peas, potatoes, soybeans and wheat.

IV.C.2.2. Chronic Dietary Exposure

Scenario I. Non-PCT Exposures: The estimated chronic exposures to methyl parathion are presented in the Table 38. The MOEs ranged from 318 (Children 1-6 yrs) to 1735 (Nursing infants;), considering an exposure of 0.02 mg/kg/day (inhibition of the brain ChE activity in rats, Eiben, 1991) as the chronic NOEL (Table 41).

Scenario II. PCT-Adjusted Exposures**:** The estimated chronic exposures to methyl parathion are presented in the Table 38. The MOEs ranged from 3165 for "Nursing infants" to 23215 for "Children 1-6 yrs" (Table 41). Applying adjustment factors to refine the methyl parathion concentrations for percent of the crop treated resulted in a 10-13 fold higher chronic MOEs, compared to the unmodified (non-PCT) MOEs (Scenario I).

Table 41. Chronic Dietary Risk Estimates for Methyl Parathion.

Population Subgroup	CHRONIC MOE [a]	
	No PCT adjustments[b]	PCT adjustments[c]
US Population (all seasons)	742	7673
Western Region	706	7097
Hispanics	669	6638
Non-Hispanic whites	771	8189
Non-Hispanic Blacks	708	7023
Non-Hispanic Other	599	5490
All infants	651	8632
Infants (nursing, <1yr.)	1735	23215
Infants (non-nursing,<1yr.)	526	6970
Children (1-6 yrs)	**318**	**3165**
Children (7-12 yrs)	458	4565
Females (13+ yrs, pregnant, not nursing)	940	10103
Females (13+ yrs, nursing)	715	6714
Females (13-19 yrs, not pregnant or nursing)	799	8150
Females (20+) not pregnant or nursing	1100	11386
Females (13-50 yrs)	968	9948
Males (13-19 yrs)	640	6568
Males 20+ yrs	933	10091
Seniors 55+	1198	12600

a/ The DEEM™ program was used for the analysis with the following input parameters: (*i*) USDA CSFII from 1994-1998, and (*ii*) Chronic NOEL of 0.02 mg/kg/day (inhibition of brain ChE activity in a two-year feeding study in mice, Eiben, 1991). MOE is defined as NOEL/Chronic Dietary Intake. The lowest MOEs are indicated in bold.

b/ The residue data for this exposure estimate did not include the percent of the crop treated (PCT).

c/ The percent crop treated adjustment factors were used for commodities: beans, barley, corn, cotton, oats, onions (dried and green), peas, potatoes, pecans, rice, soybeans, walnuts and wheat.

V. RISK APPRAISAL

V.A. INTRODUCTION

The health risk assessment of methyl parathion was carried out for workers and the general population. Several exposure scenarios were evaluated, including (*i*) acute exposure from ambient air, (*ii*) occupational and dietary exposures under acute and subchronic conditions, (*iii*) chronic dietary exposure and (*iv*) aggregate occupational and dietary exposures under acute and subchronic conditions. Every risk assessment has inherent uncertainties, which reflects limitations in the knowledge to estimate the potential risk to human health. Assumptions and extrapolations are made when the available data are insufficient to identify the hazard, to adequately characterize the dose-response, or to assess the exposure. These, in turn, result in uncertainty in the risk characterization. Specific areas of uncertainty associated with this risk assessment for methyl parathion are delineated in the following discussion.

V.B. HAZARD IDENTIFICATION

The most appropriate toxicity data for the hazard identification of methyl parathion would be from human studies. However, the available human data did not provide sufficient information on the dose-response relationship. Therefore, studies with methyl parathion in laboratory animals were used as a source of information at this time.

Critical NOELs derived from oral and dermal studies were employed to assess the risk from exposure to methyl parathion in the dietary and occupational scenarios. Sufficient information was not available to establish the NOELs for methyl parathion toxicity via the inhalation route.

V.B.1. Acute Toxicity

The critical NOEL used to determine the acute MOE values was derived from an acute neurotoxicity study in rats, which evaluated sensitive parameters such as brain ChE activity, clinical signs, neurobehavioral changes and neuropathology (Minnema, 1994a). The acute NOEL was based on decreased ChE activities (plasma, RBC, brain), cholinergic signs and increased incidence of peripheral nerve demyelination. In this case, the interpretation of the MOE values would involve an uncertainty factor of 100 (a 10-fold factor for interhuman variability and a 10-fold factor for rat-to-human extrapolation). Because of the dose selection, the NOEL in this study (0.025 mg/kg/day) was 300 fold lower than the LOEL. Thus, it is possible that the "true" NOEL could be closer to the LOEL of 7.5 mg/kg/day than to 0.025 mg/kg/day. However, several lines of evidence argued against the possibility for a higher NOEL. First, 22% reduction in the plasma ChE activity was measured following a single dose of 0.025 mg/kg (NOEL) methyl parathion in rats. Although the effect was not statistically significant at this dose, it became statistically significant ($p \leq 0.05$) at the next higher dose (LOEL). Second, an apparent increase in demyelination of dorsal and ventral lumbar root fibers was observed at the NOEL. Finally, the available methyl parathion toxicological database revealed that the majority of the estimated or established NOELs were in the range of 0.02-0.03 mg/kg/day for all endpoints and exposure times.

Recently, a developmental neurotoxicity study was completed for methyl parathion, which included an acute gavage treatment of PND11 pups and young rats (Beyrouty, 2002c). This study indicated an

acute oral NOEL of 0.11 mg/kg for reduced ChE activity pups. However, the critical acute oral NOEL employed in the RCD was 0.025 mg/kg/day, which was 4.4-fold lower than the dose of 0.11 mg/kg determined in the pups (see Sections IV.A.2. under Hazard Identification). The endpoints for the 0.025 mg/kg/day NOEL included not only cholinesterase inhibition, but also peripheral nerve demyelination. Although neuropathologic evaluations were not conducted for pups in the acute DNT study, the subchronic DNT study showed no neuropathologic effects in adult rats, which were exposed to 0.03 mg/kg/day through in utero, lactation, and direct post-natal gavage for 11 days (See section III.I. under Toxicological Profile).

V.B.2. Subchronic Toxicity

V.B.2.a. Subchronic Oral Toxicity

The NOEL for subchronic oral toxicity of 0.03 mg/kg/day was established from a developmental neurotoxicity study with rats (Beyrouty, 2002c). This NOEL was employed to estimate the risk for the subchronic dietary exposure of the US population to methyl parathion. The selection of an animal NOEL required an interspecies extrapolation of the toxicity data, because the limited information on the methyl parathion toxicity in humans precluded the use of a human NOEL for assessing the risk of subchronic exposures. In contrast, the rat DNT study included extensive evaluations of the behavior, motor and cognitive functions, and ChE measurements in plasma, RBC and brain in adult and immature animals. The most sensitive toxicological endpoint in the DNT study was the reduction (24-65%) in the ChE activities in the plasma, RBC and brain in the immature rats at the LOEL of 0.3 mg/kg/day.

There were, however, indications that the NOEL for the methyl parathion subchronic oral toxicity could be lower. A non-statistically significant, but substantial reduction (18%) in the RBC and plasma ChE activities in rats was measured at the NOEL of 0.03 mg/kg/day (Beyrouty 2002c). In addition, similar level of inhibition of the plasma ChE activity was observed in dogs (Daly, 1989). Despite these considerations, the subchronic oral NOEL of 0.03 mg/kg/day was in accordance with the NOELs established for decreases of the ChE activity and overt effects in the majority of the available subchronic toxicity studies, which were in the range of 0.02-0.03 m/kg/day). These included the NOELs for inhibition of the RBC ChE activity in rats (0.029 mg/kg/day; Minnema 1994b), reduction in the brain ChE and neurobehavioral effects (0.03 mg/kg/day Kumar and Desiraju 1992 and Schulz et al, 1990) and reduction of intraocular pressure in dogs (0.03 mg/kg/day; Daly 1989).

V.B.2.b. Subchronic Dermal Toxicity

An estimated NOEL of 0.03 mg/kg/day from a dermal neurotoxicity study in rats was employed to calculate the MOEs for the 2-month seasonal exposures to methyl parathion (Beyrouty, 2001). The most sensitive toxicity endpoints at the LOEL of 0.3 mg/kg/day were brain ChE inhibition and constricted pupils. Uncertainties were introduced when a default factor of 10 was applied to extrapolate the NOEL from the LOEL. In cases where the toxicological effects are mild, a 3-fold uncertainty factor may be appropriate to estimate the no-effect levels. However, the use of a 10-fold uncertainty factor to determine the threshold of the methyl parathion dermal toxicity was justified by the following consideration:

1. The toxic effects at the LOEL were substantial, e.g., statistically significant (18-22%) inhibition of the brain ChE activity, as well as cholinergic signs.

2. Applying the lower uncertainty factor (3-fold) to the LOEL of 0.3 mg/kg/day (Beyrouty, 2001) would result in an ENEL of 0.1 mg/kg/day. However, recent data indicated that the dermal NOEL was lower than 0.1 mg/kg/day. In a 95-day dermal treatment of rats, methyl parathion at 0.1 mg/kg/day produced a statistically significant inhibition of the brain AChE activity (15-23%, Ma et al, 2003).

3. The ENEL of 0.03 mg/kg/day was supported by the BMD modeling, which revealed that the LED was in the same range (0.04-0.05 mg/kg/day) at the 5% effect level (see Table 33).

4. The ENEL for the subchronic dermal toxicity of methyl parathion was the same as the NOEL for the subchronic oral toxicity (0.03 mg/kg/day). The same NOEL for dermal and oral toxicity would be consistent with the pharmacokinetic finding, that the absorption of methyl parathion via oral route or via skin is comparable.

V.B.3. Chronic Toxicity

There was a relatively firm support for the chronic NOEL of 0.02 mg/kg/day for neurotoxicity and hematological effects. It was the same level determined from the two available studies in Sprague-Dawley rats. It was also the same level that could be estimated from the LOELs for other effects. These included the LOEL of 0.2 mg/kg/day for brain ChE inhibition in mice (Eiben, 1991) and the LOEL of 0.22 mg/kg/day for effects in the cortex of Wistar rats reported in the 3-generation study by Nagymajtenyi et al. (1995).

V.C. EXPOSURE ASSESSMENT

Dietary Exposure Assessment

The uncertainty in the exposure assessment is classified in three major categories: (*i*) parameter uncertainty, (*ii*) model uncertainty and (*iii*) scenario uncertainty (USEPA 1992, Peterson et al, 2001).

a. Parameter Uncertainty: Sources of parameter uncertainty in the dietary exposure assessment include completeness of the food residue database, the use of surrogate data and measurement, sampling or reporting errors.

Methyl parathion residue estimates were based primarily on data from the Federal and State Monitoring programs (USDA, DPR and FDA). The USDA PDP was the database of preference, since it was specifically designed for generating data for risk assessments and contained the most extensive residue data. Residue levels measured in field trials were employed only for cottonseed, pecan and walnuts, because multi-year monitoring data were not available for these commodities. Field trial studies are conducted to determine the highest residue level that can result from maximal legal use of the pesticide and do not reflect the actual use pattern. Walnuts and pecans were not revealed as high consumption commodities or contributors to the acute dietary risk, despite the assignment of the field trial-measured residues. However, cottonseed in the form of cottonseed-oil was identified as one of the significant contributors to the dietary risk for the majority of the population subgroups (see CEC analysis for the Point Estimate and the Monte Carlo models).

In cases where monitoring or field trial data were unavailable or insufficient, residues reported for similar foods were used as surrogates. Attempts were made to decrease the degree of uncertainty by selecting surrogate commodities from the crop groups of related commodities established in 40 CFR

180.40. Among the related foods, the most appropriate surrogate commodity was represented by a large number of samples analyzed during a multi-year surveillance with lower LOD. Based on these criteria, the residues measured by the PDP on wheat, processed green beans, processed sweet corn and processed sweet peas were employed to model the exposure for barley, dry beans, sweet corn and dry peas, respectively. The residues on sweet corn and potatoes were refined by substituting the highest LOD within the PDP program with the substantially lower LOD of the California PDP data.

The dietary exposure assessment may exhibit a level of uncertainty in the consumption data contained in the 1994-1998 USDA survey. The uncertainty may result from under-representation of actual dietary consumption, reporting errors, response and variation in the culinary habits over the consumption period. In this respect, the acute exposures estimated for the population subgroup "Females 13+ nursing" often differed substantially from the exposures of the other 13 adult subgroups. The plot file available in the DEEM program revealed that the dietary survey sample size for "Females 13+ nursing" was only 84 user days in the entire 1994-1998 CSFII database. For comparison, the population subgroup Children 1-6 yrs was represented by 14106 user days. Thus, the dietary exposure estimates for population subgroups with small sample size in CSFII may not be representative of actual consumption patterns.

b. Model Uncertainty: Comparison between the 95th percentile Point Estimate exposures verses the 99.9th percentile Monte Carlo exposures.

The DPR presents the 95th percentile as the estimated high-end of exposure when a single upper bound residue and all crop treated assumptions are employed during the acute dietary exposure assessment. The acute dietary exposures to methyl parathion, calculated at the 95th percentile with the Point Estimate model, indicated a potential health concern (Tables 37 and 42). In this case, the acute dietary exposure can be refined through the use of Monte Carlo techniques, which incorporate residue distribution and PCT information. A greater refinement impact is achieved when a point estimate of residue is replaced by distributions, especially for high contributing commodities. This was illustrated here by the probabilistic manipulation of the methyl parathion residues on dry beans. This commodity was identified as one of the main contributors to the high-end Point Estimate-calculated dietary exposure. The contribution of dry beans varied from 6% to 78% of the total exposure (from all foods) for the evaluated 19 population subgroups. In the Monte Carlo model, the upper-bound point estimate residue (0.38 ppm, Table 35) was replaced by residue distributions adjusted for the PCT (4%, USEPA 1999a - BEAD data). In turn, the contribution of dry beans to the total exposure was reduced to less than 1.5% and no longer had an impact on the 95th-99.9th Monte Carlo dietary exposures.

Probabilistically, Monte Carlo exposures at high-end percentiles are often lower than the 95th percentile of the Point Estimate exposures. However, this is not always the case. The outcome is largely dependent on the residue database, especially when residue values could not be treated probabilistically for all food commodities. For example, if distributional data were not available for high contributing commodities (in this case, rice), then the resultant high-end exposure distribution from the Monte Carlo analysis would not be significantly different from the pattern of the point estimate. Thus, the rational for selecting a possibly higher percentile of exposure from Monte Carlo analysis should be considered in this context. USEPA assesses the acute Monte Carlo dietary exposure at the 99.9th percentile, presumably when the residues for measured contributing commodities are distributional (USEPA, 2000).

In the current Monte Carlo analysis, the distribution of residues was employed for 9 commodities labeled for methyl parathion use in California. The residue level on the remaining four foods (rice, cottonseed, pecans and walnuts) were represented by point estimates (Table 35). Despite the use of more refined data, the Monte Carlo-generated exposures at the 99.9th percentile indicated a potential health concern (Table 40). Comparison between the acute dietary exposures to methyl parathion estimated by the two models revealed that the 95th Point Estimate exposures were approximately 2-fold higher than the 95th Monte Carlo exposures, but were comparable to the Monte Carlo estimates at the 99th exposure percentile for all population subgroups. Finally, the 95th Point Estimate exposures were lower than the 99.9th Monte Carlo-estimated exposures for all population subgroups (Tables 37 and 38). The reason for the not achieving lower Monte Carlo exposure at the 95th–99.9th percentile is that the methyl parathion concentrations on high contributing commodities (rice and cottonseed-oil) were represented by a single high-end residue value.

c. Scenario Uncertainty: Several dietary exposure scenarios were evaluated for methyl parathion under acute and chronic conditions. The acute dietary exposure estimates for methyl parathion were calculated using the tiered approach in the selection of the appropriate residue values. The tiered approach began with the use of upper-bound residue values in the Point Estimate Model and progressed to the residue distribution in the Monte Carlo model.

In the initial scenario (see Point Estimate acute dietary exposure) it was assumed that: (*i*) methyl parathion was present on all commodities at the highest LOD or at the highest measured levels, which were all below the tolerance, (*ii*) all crops were treated and (*iii*) the residues for each crop were represented by a single value. The MOEs at the 95th percentile were less than 100 for all of the population subgroups (Table 39). This type of analysis may produce a "worst case" exposure estimate, because it is unlikely that each of the 12 commodities that could be consumed in a given day to contain upper-bound methyl parathion residues. However, this may not always be the case, especially at the percentile of exposure selected for characterizing the risk. Because of the high uncertainty in this scenario, a "reality check" was performed, in which credible upper exposure limits were established. The "reality check" included a scenario in which only one of the "all foods" consumed in a given day contained methyl parathion residues. For the "single food" dietary analysis, the respective food was chosen based on two criteria. First, the commodity made a substantial contribution to the acute dietary exposure; and second, the pesticide residue on this commodity was to be measured on samples collected at centers close to the consumer levels. Two different "single commodity" acute exposure analyses were carried out for methyl parathion on rice only and on dry beans only.

Rice: Rice was identified as making a substantial contribution to the dietary risk, due to the high methyl parathion concentrations detected by the FDA Regulatory Monitoring. At the 95th percentile, the MOEs for exposure to methyl parathion on rice were less than 100 for the majority of the population subgrous examined (Table 39). Comparison between the exposure estimates for consumption of all 12 commodities with upper-bound methyl parathion residues and those for rice only, demonstrated that the MOEs were very similar for a number of population subgroups, including Western Region (MOE of 41 and 61, respectively), Non-Hispanic Other (MOE of 30 and 39), All Infants (MOE of 39 and 40) and Males 13-19 yrs (MOE of 44 and 47). Thus, the one-commodity scenario, which was based on actual residue data (FDA Monitoring) and could occur in the actual practice, predicted a potential level of concern. Furthermore, this analysis demonstrated that the total

point estimate exposure presumed to be from the high residue levels on all commodities could possibly result from a consumption of a single commodity, rice (Table 36).

Dry Beans: Dry Beans were identified as significant contributors to the dietary risk based on the high methyl parathion concentrations detected by the PDP on processed green beans. At the 95th percentile, the MOEs for exposure to methyl parathion on dry beans were less than 100 for all of the population subgroups examined (Table 39). It is interesting to note that the 95th MOEs for dry beans were lower than the 95th MOEs for exposure for all labeled uses (*i.e.*, a higher risk would be associated with the consumption of dry beans only, than with the consumption of all 13 foods, including dry beans). The most plausible interpretation of these results would be that the individuals at the 95th percentile of exposure from dry beans were not within the 95th percentile exposures from all 13 foods with upper-bound methyl parathion residues. Indeed, comparison between the MOEs demonstrated that the 95th MOEs for dry beans were similar to the 99th MOEs for exposures from all labeled food uses.

A key reason behind this apparent disparity is that the individuals framing the expressed percentile of exposure are different for the single verses the multiple commodity analysis. By definition, the population evaluated in the acute dietary assessment consists of any user-day that includes the consumption of at least one commodity with potential pesticide residues. Thus, when the analysis is based on user-day only, the population size increases with each added commodity to the dietary analysis. The above two assessments for rice and dry beans enforced the need to conduct a "reality check" to ensure that the risk of the individuals at the high-end exposure, due to consumption of one commodity, will not be excluded in the overall assessment. Collectively, the two "reality checks" for methyl parathion illustrated that the high-end point estimate exposures resulting from consumption of 12 commodities, all at the highest residue level, could reflect the high end of the exposure to only one commodity.

Because of the low MOEs, additional refinements of the acute scenarios were carried out. The refinement involved the use of residue distribution (probabilistic model) instead of relying on a single point value. In addition, percent of the crop treated was utilized to assign a probability that the residue level could be zero (see Acute Monte Carlo Analysis for PCT-Adjusted Exposures). At the 99.9th exposure percentile, all population subgroups, except "Females 13+ nursing" had MOEs below 100. The MOEs were as low as 9 (All infants, Table 40). The dietary exposure in this scenario may be underestimated, because the PCT adjustment was applied to commodities analyzed by the PDP and DPR monitoring programs. Data collected under these programs are for composite samples and represent the average residue level on commodity units harvested from both pesticide treated and untreated fields. Thus, the reported residue values could have already incorporated the PCT. To assess the effect of the PCT on the residues of blended commodities, a probabilistic analysis was conducted without the PCT adjustments (see Monte Carlo Analysis for Non-PCT-Adjusted Exposures). For methyl parathion, assigning the LOD to the previously considered zero residue values did not significantly increase the exposure estimates for any of the population subgroups (Table 37). The reasons for the lack of impact of the PCT-adjustment on the Monte Carlo exposures are as follows: (*i*) The residue profile consisted of a mixture of point estimates and distribution (Table 35), (*ii*) The commodities contributing to the high-end exposures (rice and cottonseed) were represented by single residue values, whereas foods with distributional residues had much less impact on the dietary exposure, (*iii*) In the Monte Carlo analysis, PCT was applied to refine the residue values only on these commodities for which distribution of residue levels was used and (*iv*) the

methyl parathion LODs on commodities subjected to a residue distribution were much lower (ranging form 0.002 to 0.02 ppm), than the measured point estimate values on rice and cottonseed (0.11ppm and 0.66 ppm respectively). Because the point estimate residue values were largely dominating the high-end Monte Carlo exposures, replacing the zero residue values with the low LOD values on the distributional commodities had very little effect on the 95th-99.9th acute exposures. It should be emphasized, however, that the probabilistic model with the PCT adjustments employed the most refined assumptions. Nevertheless, it predicted exposures of concern (e.g. MOE less than 100) for all, but one population subgroup at 99.9th or at the 99th exposure percentile. Moreover, the MOEs were less than 100 for the majority of the examined subgroups at lower exposure percentiles, such as the 95th percentile (Table 40).

Two chronic dietary exposure scenarios for methyl parathion were evaluated. The first one considered that 100% of the crop was treated and the second scenario employed PCT-adjustment factors. A major assumption in both scenarios was that chronic residue levels below the LOD were at ½ of that limit. The chronic dietary MOEs were greater than 150 for both scenarios. The exposures were significantly reduced by refining the methyl parathion concentrations for the PCT (MOE >1500, Table 41).

d. Toxicity of Methyl Paraoxon: Methyl paraoxon is the toxicologically relevant metabolite of methyl parathion. The available studies with laboratory animals indicated that methyl paraoxon could be from 8 to 23 fold more acutely toxic than methyl parathion. Additional uncertainty with the acute dietary exposure estimates was associated with the lack of residue data for methyl paraoxon. Only four crops with current registrations for methyl parathion use were tested for methyl paraoxon and no quantifiable residues were reported. The total dietary exposure could be estimated based on the *in vivo* conversion of methyl parathion to methyl paraoxon, however, such data were not available for plants.

Using the same point estimate approach employed for methyl parathion, a preliminary acute dietary assessment was carried out to evaluate the potential exposure to methyl paraoxon from food. If methyl paraoxon were assumed to be present at the LOD levels only on commodities tested for this metabolite (dry beans, dry peas, oats, potatoes and wheat), the potential 95-99th percentile acute exposures to both methyl parathion and methyl paraoxon would be 2 fold higher compared to the exposure to methyl parathion alone. Although sufficient residue data were not available to determine the true contribution of methyl paraoxon to the acute dietary exposure, it is important to understand how its potential presence would impact the overall exposure to methyl parathion from food. These considerations provide a rationale for selecting a higher percentile of the estimated acute dietary exposure and should be viewed in the context of the accompanied uncertainties described above.

V.D. RISK CHARACTERIZATION

A margin of exposure of 100 is considered sufficiently protective of human health when data are derived from animal studies. The MOE of 100 assumes that humans are 10 times more sensitive than the laboratory animals and that the sensitivity among human population could vary as much as 10-fold.

V.D.1. Dietary Exposure

The uncertainties associated with the dietary exposure estimates and the critical NOELs, which were used to calculate the dietary MOEs, were discussed in details in the sections V.B.1-3 and V.C.2.

a. Acute MOE

The acute MOE values for exposure to methyl parathion from food ranged from 24 to 73 (Table 39) at the 95th percentile of user-days. These MOEs were estimated using the acute rat NOEL of 0.025 mg/kg/day and dietary exposure assessed by the deterministic (Point Estimate) model.

Employing the most refined assumptions (i.e. PCT and residue distributions) in the probabilistic (Monte Carlo) acute assessment, resulted in acute dietary MOEs from 9 to 52 at the 99.9th percentile of user-days. Infants were identified as the most highly exposed population subgroup. Furthermore, the acute MOEs calculated with the probabilistic model were below the benchmark of 100 for the majority of the population subgroups at the 99th and the 95th percentiles (Table 40). Altogether, the MOEs for acute dietary exposure indicated a potential health concern.

b. Chronic MOEs

The chronic MOEs for exposure to methyl parathion were over 3000, when PCT assumptions were employed to refine the chronic exposure and using the chronic rat NOEL of 0.02 mg/kg/day. The conventional benchmark for the MOE using a NOEL from an animal study is 100, thus indicating that the chronic dietary exposure to methyl parathion would not present a potential risk.

V.D.2. Aggregate Inhalation and Dietary Exposure

The acute exposure from methyl parathion in the ambient air was less than 3% compared to the acute dietary exposure. Because of its relatively low contribution, it was not added to the dietary exposure to estimate the total exposure from non-occupational sources. Nevertheless, the potential impact of the inhalation exposure on the dietary risk needs further considerations.

The aggregate risk for humans from inhalation and dietary exposure can be estimated using the formula below:

$$\frac{1}{MOE\ aggregate} = \frac{1}{MOE\ inhalation} + \frac{1}{MOE\ dietary}$$

In the 1999 TACE document, children were identified to receive the highest acute exposure from ambient air concentrations of methyl parathion (Reed, 1999). The MOE for children was calculated as 390, using a default breathing rate of 0.74 m^3/kg/day (i.e. 16.7 m^3/day for a 22.6 kg child and a NOEL of 0.025 mg/kg/day; Reed 1999). Employing the DPR's current default breathing rate of 0.59 m^3/kg/day for infants and children, this MOE would be 481. Using the above formula with the acute inhalation MOE of 481, the dietary MOE, which would produce an aggregate MOE of at least 100 would have to be at least 126.

In conclusion, while the inhalation exposure by itself did not indicate a potential risk to humans, if included in the aggregate non-occupational exposures, it would increase the total risk. Therefore, the dietary MOE of at least 126 (and not the benchmark of 100) would need to be considered as protective of human health. In the present dietary exposure assessment, infants were identified as receiving the highest exposure to methyl parathion from food. The acute dietary MOEs for infants were 9, 23 and 55 at the 99.9^{th}, 99^{th} and 95^{th} exposure percentiles, respectively (Table 40). These dietary MOE levels were 2-14 fold lower than the benchmark dietary MOE of 126 and indicated a potential health concern.

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

The Food Quality Protection Act of 1996 mandated the USEPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (USEPA, 1997b). The new requirements were based on the recommendations from the 1993 National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NAS, 1993), including: (*1*) a more thorough evaluation of the risks of infants and children, (*2*) the inclusion of all exposures from multiple routes of contact (the "aggregate exposure"), (*3*) the risk of concomitant exposures to multiple chemicals (the "cumulative risk") and (*4*) the potential for endocrine disrupting effects.

V.E.1. Pre- and Post- Natal Sensitivity

The FQPA requires the considerations of an additional safety factor of up to 10 to account for pre- and post-natal toxicity and the completeness of the database. The toxicological database for methyl parathion in rats showed that neonates can be up to 10-fold more sensitive than adults (see: III.B.3.**).** The extent of pre- and post-natal sensitivity can also be further evaluated based on the completed submission of toxicity studies required under the Senate Bill 950 (SB950), particularly the studies on developmental and reproductive toxicities. A possible higher sensitivity was indicated in the developmental toxicity studies. In rats, fetal toxicities icluding ossification, survival, body weight and reduced brain ChE activities occurred at the same doses as the maternal toxicity (maternal weight gain, survival, reduced brain ChE activities; Gupta et al. 1985, Becker et al. 1987). In a rabbit teratology study, methyl parathion doses which caused thickened areas of rib ossification in fetuses had no effects on the dams (Hoberman, 1991). In the two available reproductive toxicity studies, a reduction of pup survival was consistently observed on day 4 (Daly and Hogan, 1982) and up to week 4 (Loser and Eiben, 1982) after birth. In the first study, the reduction of maternal body weight gain and pup survival occurred at the same doses of methyl parathion (Daly and Hogan, 1982), whereas in the second study the decreased pup survival occurred in the absence of maternal toxicity (Loser and Eiben, 1982).

Based on the evidence for an increased pre- and post-natal sensitivity, the USEPA used in their 1999 RED a 10-fold additional safety factor to protect infants and children from exposure to methyl parathion. The 10-fold uncertainty factor was applied to the reference Doses (RfD) to establish the acute and chronic Population Adjusted Doses (PAD) of 0.0001 mg/kg/day and 0.00002 mg/kg/day, respectively (USEPA, 1999a).

Developmental neurotoxicity studies were recently completed for methyl parathion, which investigated whether pre- or post-natal exposure to methyl parathion affected the neural development.

Based on the ChE inhibition in the plasma, RBC and brain, immature rats were 2 to 3-fold more sensitive than the adults after repeated exposure methyl parathion (Beyrouty, 2002c).

V.E.2. Aggregate Exposures

For total non-occupational exposure, the DPR considers contributions to risk from various exposure sources, specifically, food, drinking water, air, and residential sources. The lack of monitoring data on methyl parathion residues in drinking water precluded a drinking water exposure assessment at this time. Residential exposure was not considered, because methyl parathion is not registered for residential uses. Therefore, in the aggregate risk assessment, the risk of exposure from methyl parathion was evaluated from: (*i*) residues in the food (oral route) and (*ii*) ambient air exposure (inhalation route).

The risk of aggregate exposure was addressed in section V.D.4 under **Risk Characterization**). The inhalation exposure by itself did not indicate a potential risk to humans. However, if added to the dietary exposure, it would increase the total risk for aggregate non-occupational exposures. Based on the current ambient air exposure estimates, the MOE for the dietary route alone would need to be at least 126. This threshold (MOE of 126) for the dietary exposure would provide room for the exposure from ambient air, thus ensuring that the total aggregate MOE would be at the benchmark of 100 as health protective.

V.E.3. Cumulative Toxicity

Methyl parathion has been detected on commodities, which also contained other organophosphorous pesticides (OPs). This presents the need to address the risk of concomitant exposure to multiple OPs. However, until recently, a scientific defensible approach to quantitatively estimate such cumulative exposure was not available. Although DPR does not routinely assess the risk from exposure to multiple chemicals, it commonly includes the identical breakdown products of significant toxicological concerns in a single-chemical risk assessment. For example, in the previous ambient air risk assessment of methyl parathion, the exposure to the metabolite methyl paraoxon was accounted for using the "toxicity equivalence factor" (TEF) approach (Reed, 1999). This approach involved the comparison between the toxicity of methyl parathion and methyl paraoxon, based on the data which were available (i.e. reported LD_{50} values and the inhibition of plasma and brain ChE activities). A TEF of 10 was established for methyl paraoxon to convert the exposure to this metabolite to a methyl "parathion equivalent". This "methyl parathion equivalent" was subsequently added to the exposure of methyl parathion to estimate the total exposure to both methyl parathion and methyl paraoxon from air (Reed, 1999, see also section IV. B.2.7. under **EXPOSURE ASSESSEMENT**)

An elaborate methodology was recently developed by USEPA to assess the exposure to multiple chemicals from multiple pathways. The USEPA is required under the FQPA of 1996 to assess the cumulative risk to human health, which could result from exposure to pesticides with a common mechanism of toxicity (USEPA, 1999c, 2001). The organophosphorus pesticides (OPs) were determined to have a common mode of action, which involves the inhibition of the AChE activity and consequent overstimulation of nerves and muscles. 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. The potential cumulative risk of certain members of the carbamate pesticides will also be assessed. (USEPA, 2002a).

The USEPA recently completed a cumulative risk assessment for the OPs. The assessment estimated the potential risk from exposure to multiple OPs by multiple pathways (USEPA, 2001). Thirty one OPs pesticides were included in the risk assessment dated December 3, 2001. 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). Methyl parathion was one of the evaluated OP in the food and drinking water exposure pathways.

Similar to the TEF approach used by the DPR to convert the air exposure to methyl paraoxon to a "methyl parathion equivalent" (Reed, 1999), the USEPA 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, USEPA considered the exposure to OP residues in foods as uniform across the US. 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 methyl parathion on alfalfa was considered in the drinking water exposure modeling. The conclusions from the preliminary OP cumulative risk assessment were that the drinking water is not a major contributor to the total risk. The exposures from OPs in food at percentiles above 95^{th} for all population subgroups were at least one order of magnitude higher.

In June 2002, the USEPA finalized its cumulative risk assessment for the OPs (USEPA, 2002b). The revised assessment included 4 more OPs in the hazard and dose-response evaluations, evaluated additional population subgroups, addressed the pre- and post-natal sensitivity for protection of infants and children and estimated the risk of either single day or subchronic exposures. The FQPA safety factors of 1 or 3 were used to adjust the individual RPFs. For methyl parathion, a 3X FQPA factor was chosen to account for the differential sensitivity between adult and immature animals. The dietary MOE from the 7, 14 and 21-day analyses exceeded the target value of 100 at the 95-99.9^{th} percentiles. The MOEs, however, from the single day dietary exposures were below the benchmark of 100 at the 99.4-99.9^{th} percentiles for children 1to 5 years of age. A few commodity/pesticide combinations were identified as contributors to the high-end cumulative exposures. Under the assumptions and models used in the cumulative dietary risk assessment, methyl parathion was not among the high contributors the OP cumulative risk from food. The USEPA concluded that the "real world" dietary exposure was somewhere between the one-day and seven-day rolling average and that, in general, the MOEs did not represent a health concern. It was acknowledged that the goal of the OP cumulative risk assessment was to provide a range of risks at different percentiles of exposure distribution. However, the decision as to whether mitigation activities are needed should be based on the individual OPs risk assessments.

V.E.4. Endocrine Effects

Information pertinent for the evaluation of endocrine disruption potential of methyl parathion is limited. Data specific to the reproductive and developmental toxicities of methyl parathion were presented in Section III.F. and III.G. Although the reproductive toxicity database (see: Section III.F.) indicated that some OPs may affect the menstrual cycle and cause early menopause in humans, no data on human reproductive effects specific to methyl parathion are available. Decreased pup survival was the consistent reproductive toxicity endpoint in laboratory animals. Ovarian effects in rats, sperm abnormalities in mice, and testicular and reproductive effects in avian species were also reported. The developmental toxicity database in rats, rabbits, mice, and avian species (see: Section III.G.) showed lower fetal body weight, increased resorption, reduced pup survival, and abnormalities and variations of ossification. There were also some indication of neurobehavioral effects in rats and a report of cleft palate and an increased death in mice at a much higher dose. Injection of methyl parathion into the air space of chicken eggs resulted in cervical lordosis and scoliosis, cervical muscle atrophy, lower body weight, and retarded growth.

Studies on the methyl parathion-induced ovarian toxicity in rats (Dhondup and Laliwal, 1997; Asmathbanu and Kaliwal, 1997) and its effect the on male reproductive hormone profile among workers (Padungtod et al., 1998) provided some indication of an endocrine disruption potential. These findings were presented in Section III.F., *REPRODUCTIVE TOXICITY*. Dhondup and Laliwal (1997) and Asmathbanu and Kaliwal (1997) reported lengthened estrous cycles, and reduced compensatory ovarian hypertrorphy, healthy follicles, and relative uterus weight in hemicastrated rats treated with 2.5 to 5.0 mg/kg/day methyl parathion for up to 15 day. Padungtod et al. (1998) reported a significant correlation between serum luteinizing hormone and occupational exposure of 34 male workers in a factory in China manufacturing methyl and ethyl parathion and methidathion.

Using two bioassay systems to determine the direct interaction between estrogen receptor and estrogenic compounds, Petit et al. (1997) tested the estrogenic activity of 49 pesticides, environmental chemicals, and phytoestrogens. The first test used recombinant yeast system which contained a reporter gene with two estrogen-responsive elements, the induction of which is dependent on the rainbow trout estrogen receptor (rtER) and estrogens. The second test for expressing vitellogenin gene in rainbow trout hepatocyte aggregate culture was subsequently used as a complementary assay. Methyl parathion showed weak estrogenic activity in the yeast system but was highly estrogenic in the hepatocyte aggregate cultures. The authors suggested that metabolic transformation of methyl parathion in hepatocytes might account for the high estrogenic activity.

In conclusion, the existing data indicated that methyl parathion may possess endocrine disruption potential. Although reproductive and teratogenic effects of methyl parathion had been reported in laboratory animals, the underlying mechanisms for these effects were not known. Neither were endocrine activities a part of these study protocols. As is generally recognized, testing guidelines and criteria for hazard identification are needed for a clear evaluation of the endocrine disruption potential.

V.F. COMPARISON BETWEEN THE CRITICAL NOELs IN THE PRESENT RCD AND IN THE 1999 TACE.

In an earlier health risk assessment, the DPR assessed methyl parathion as a toxic air contaminant (TACE, Reed 1999). Since the completion of the 1999 TACE, several toxicological studies became available for establishing NOELs to characterize the risk in the current RCD. The levels of these

NOELs were generally within the range of NOELs presented in the 1999 TACE. Two ENELs (estimated NOELs) from the 1999 TACE were not used in the current RCD due to the substantial associated uncertainty. These two ENELs were the subchronic ENEL of 0.003 mg/kg/day and the chronic ENEL of 0.01 mg/kg/day. In both cases, the ENEL was extrapolated as 10-fold below the lowest tested dose, which showed non-statistically significant inhibition of the cholinesterase activity (ChEI, 17-19% in plasma or RBC). The acute and subchronic NOEL in humans from the 1999 TACE was not used in the current RCD because it was based on cursory studies with limited sample size and endpoint observations. The table below compares the critical studies, the toxicological endpoints and the NOELs, which were used in the 1999 methyl parathion Toxic Air Contaminant Evaluation (TACE) document and in the present RCD.

Table 42. Comparison Between the Critical NOELs for Methyl Parathion Used in the 1999 TACE[a] and the Current RCD.

1999 TACE	Current RCD
Acute Oral 1. NOEL=0.025 mg/kg; rat (plasma, RBC, brain ChEI[b] and neuropathy[c]) 2. NOEL=0.31 mg/kg; human (plasma, RBC ChEI)[d]	**Acute Oral** NOEL=0.025 mg/kg; rat (plasma, RBC, brain ChEI and neuropathy[c]
Subchronic Oral NOEL 1. NOEL=0.31 mg/kg; human (plasma, RBC ChEI)[d] 2. ENEL*=0.003 mg/kg/day, dog (plasma ChEI)[e] 3. NOEL=0.029 mg/kg/day, rat (RBC ChEI)[f] 4. ENEL=0.02 mg/kg/day, rat (brain ChEI)[g] **Subchronic Dermal NOEL** none	**Subchronic Oral NOEL** NOEL=0.03 mg/kg/day, rat DNT study study[h] (plasma, RBC, brain ChEI) **Subchronic Dermal NOEL** ENEL =0.03 mg/kg/day, rat (brain ChEI and behavioral effects)[I]
Chronic Oral NOEL 1. ENEL=0.02 mg/kg/day, mice (brain ChEI)[k] 2. ENEL*=0.01 mg/kg/day, rat (RBC ChEI)[j]	**Chronic Oral NOEL** ENEL=0.02 mg/kg/day, mice (brain ChEI) [k]

a/ TACE, Toxic Air Contaminant Evaluation; **b/** ChEI, Cholinesterase Inhibition; **c/** Minnema, 1994a; **d/** Rider, 1970;1971; **e/** Daly, 1989, **f/** Minnema, 1994b; **g/** Kumar and Desiraju, 1992; **h/** Beyrouty 2002c; **i/** Beyrouty 2001; **j/** Bomhard et al., 1981; **k/** Eiben, 1991.

***** Extrapolated from the LOEL with non-statistically significant effects, and thus, carried substantial uncertainties.

VI. TOLERANCE ASSESSMENT

VI.A. BACKGROUND

A tolerance is the legal maximum residue concentration of a pesticide, which may exist in or on a raw agricultural commodity or processed food. USEPA is responsible under the Federal Food, Drug, and Cosmetic Act (FFDCA) for setting tolerances for pesticide residues in raw agricultural commodities (Section 408 of FFDCA) and processed commodities. The tolerances are established at levels necessary for the maximum application rate and frequency, and are not expected to produce deleterious health effects in humans from chronic dietary exposure (USEPA, 1991).

The data requirements for the registration of pesticides and for establishment of tolerances include: (1) residue chemistry which includes measured residue levels from field studies, (2) environmental fate, (3) toxicology, (4) product performance such as efficacy, and (5) product chemistry (Code of Federal Regulations, 2001). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications and the proposed formulations (USEPA, 1982).

In 1996, the Food Quality Protection Act (FQPA) amended the overall regulation of pesticide residues under FIFRA and FFDCA (USEPA, 1997b). One major change was the removal of the Delaney Clause that prohibited residues of cancer-causing pesticides in processed foods. FQPA requires scientific evidence to show that tolerances are safe for children. USEPA must consider applying an additional uncertainty factor of up to 10-fold to take into account potential pre- and post-natal developmental toxicity and the completeness of the data.

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

In California, Assembly Bill 2161 (referred to as the Food Safety Act) requires DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides" (Bronzan and Jones, 1989). In the situation where "any pesticide represents a dietary risk that is deleterious to health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance".

VI.B. ACUTE EXPOSURE

An acute exposure assessment was conducted for each individual methyl parathion label-approved commodity at the tolerance. The DEEM™ software program and the USDA Continuing Survey of Food Intakes of Individuals (CSFII) 1994-1998 were used in this assessment (see section IV.B.2.2., under **EXPOSURE ASSESSMENT**).

The acute tolerance assessment does not routinely address multiple commodities all of which have residues at tolerance levels because the probability of consuming multiple commodities that are all at the tolerance level significantly decreases as the number of commodities included in the assessment increases. Consequently, the residue levels for methyl parathion were set equal to the tolerance to estimate the potential dietary exposure for each commodity with an existing tolerance.

The consumption patterns of a given population subgroup is better represented when the survey sample size is large (i.e. >100 user-days). The total entry of dietary survey data for "Females 13^+ nursing" was 84 in the entire 1994-1998 CSFII database. Therefore, this subgroup was represented by less than 100 user days for all commodities. Other population subgroups, which had less than 100 user days for most of the commodities with methyl parathion tolerances were: Females 13^+ yrs. pregnant, Females 13^+ yrs. nursing and Infants (Nursing and Non-nursing).

DPR currently would exclude from the tolerance assessment population subgroups with less than 25 user days, because of the high uncertainty associated with consumption data. Accordingly, the following population subgroups were not included in the tolerance assessment: Nursing Infants (dry beans,), Females 13+ nursing (dry beans, pecans, walnuts), Females 13+ pregnant (oats, pecans, walnuts), All Infants (pecans, walnuts).

In addition, it should be noted that peas was the commodity with the least number of user days among the evaluated population subgroups. Seven population subgroups had less than 25 user days for peas, and were not considered in the peas tolerance evaluation. These were: Nursing Infants, Females 13^+ nursing, Females 13^+ pregnant, Nursing and Non-nursing Infants, Children 7-12 yrs., Non-Hispanic-non-white-non-black, Females 13-19 yrs., and Males 13-19 yrs.

Nine of the remaining 12 subgroups with peas had more than 25, but less than 100 user days. Although these 9 subgroups were included in the analysis, the exposure and MOE values should be interpreted with caution, because of the relatively small dietary sample size. These included: Western region, Hispanics, Non-hispanic backs, All infants, Children 1-6 yrs., Females 20^+ yrs., Males 20^+ yrs. and Seniors 55^+ yrs.

The range of exposure and MOE values at the 95^{th} exposure percentile for each commodity with methyl parathion tolerance is presented in Table 43.

Walnut, Pecan and Cotton: The commodity with the least amount of dietary exposure at tolerance was walnut (0.025 to 0.0011 mg/kg/day). Pecan and cotton had a tolerance exposure range of 0.033 to 0.018 mg/kg/day and 0.267-0.040 mg/kg/day, respectively. These exposures resulted in MOEs ranging from 981 to 2374 (walnut), 757-1355 (pecans) and 93-632 (cotton), based on the acute NOEL 0.025 mg/kg/day for ChE inhibition and neuropathology in rats (Bomhard et al., 1981). Thus, the MOEs were at or above the benchmark of 100 for all population subgroups exposed to a tolerance level of methyl parathion on walnut, pecan and cotton.

Soybeans and Barley: Soybeans and barley had a tolerance exposure range of 0.736-0.067 mg/kg/day and 4.27-0.07 mg/kg/day, respectively. These exposures resulted in MOE values ranging from 33-370 (soybeans), and 5-336 (barley). The MOEs were greater than 100 for all population subgroups with soybeans, except for infants (nursing and non-nursing). In contrast, the MOEs were greater than 100 for only four population subgroups from consumption of barley containing a tolerance level of methyl parathion. These included: Children 1-6 yrs., Children 7-12 yrs., Pregnant females 13+ yrs., and Females 13-19 yrs. The remaining population subgroups

Table 43. Acute Dietary Risk Estimates for Methyl Parathion Residues at the Tolerance Level.

Commodity	Range of Exposure (µg/kg/day) [a]	Range of Margin of Exposure [b,c]	Tolerance (ppm)
Barley	4.28-0.07	5 – 336[d]	1.00
Beans (dry)	4.47-1.49	5 - 16	1.00
Corn	10.86-2.03	2 - 12	1.00
Cotton	0.27-0.04	93 - 623	0.75
Oats	5.09-0.91	4 - 27	1.00
Onions	1.66-0.70	15 - 35	1.00
Peas (dry)	2.15-0.59	11 - 42	1.00
Pecans	0.03-0.02	757 -1355	0.10
Potatoes	1.13-0.34	22 - 74	0.10
Rice	1.72-5.03	4 - 14	1.00
Soybeans	0.74-0.07	33 – 370[e]	0.10
Walnut	0.03-0.01	981 -2374	0.10
Wheat	8.66-2.48	2 - 10	1.00

a/ Acute dietary exposure assessment was conducted for methyl parathion residues on each of the registered commodities in California at a level equal to the U.S.EPA tolerance. DEEM™ program was used for the analysis with the following input parameters: (*i*) USDA CSFII from 1994-1988 and (*ii*) acute NOEL of 0.025 mg/kg (inhibition of ChE activity and neuropathology in rat, Minnema, 1994a). Acute dietary exposure was calculated at the 97.5th percentile of user-days for all population subgroups.

b/ Margin of Exposure (MOE) is defined as NOEL/Acute Dietary Intake; The number of user-days ranged from 26 to 40070 .

c/ Total of 19 consumer groups were considered to be exposed to tolerance levels of methyl parathion residue. These include: US Population (all seasons), Western Region, Hispanics, Non-Hispanic whites, Non-Hispanic, Blacks, Non-Hispanic Other, All infants, Infants (nursing, <1yr.), Infants (non-nursing,<1yr.), Children 1-6 yrs, Children 7-12 yrs, Females 13+ yrs (pregnant, not nursing), Females 13+ yrs nursing, Females 13-19 yrs (not pregnant or nursing), Females 20+ yrs (not pregnant or nursing), Females 13-50 yrs, Males 13-19 yrs, Males 20+ yrs, Seniors 55+ yrs.

The following population subgroups had less than 25 user-days and were not included in the tolerance assessment: Nursing Infants (dry beans, peas), Females 13+ nursing (dry beans, pecans, walnuts, peas), Females 13+ pregnant (oats, pecans, walnuts, peas), All Infants (pecans, walnuts, peas); Children 7-12 yrs., Non-Hispanic-non-white-non-black, Females 13-19 yrs., and Males 13-19 yrs (peas).

d/ The MOEs were greater than 100 for only four population subgroups with barley at the tolerance value: Children 1-6 yrs., Children 7-12 yrs., Pregnant females 13+ yrs., and Females 13-19 yrs. The remaining population subgroups had MOEs that were 55 or less (see text for details).

e/ The MOEs were greater than 100 for all population subgroups with soybeans, except for all infants (nursing and non-nursing).

with barley at the tolerance value had MOEs that were 55 or less. These MOEs indicated a potential health concern for a number of population subgroups, which consumed soybeans or barley with tolerance levels of methyl parathion.

Dry Beans, Corn, Oats, Onions, Potatoes and Rice: The MOEs were less than 100 for each of the 19 population subgroups evaluated, which consumed dry beans, corn, oats, onion, peas, potatoes, rice or wheat containing tolerance levels of methyl parathion. Among these commodities, consumption of wheat, corn and rice would result in the highest dietary exposures. The corresponding MOE ranges were: wheat, 2 – 10; corn, 2 – 12; and rice, 4 - 14 (Table 43). Therefore, the MOEs for exposure to tolerance level methyl parathion on dry beans, corn, oats, onions, potatoes or rice were below 100 and indicated a potential health concern.

VI.C. CHRONIC EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities was not conducted, because it is highly improbable that an individual would habitually consume single or multiple commodities with pesticide residues at tolerance levels. This conclusion is supported by data from both, federal 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, 1997a).

VII. CONCLUSIONS

The health risk assessment of methyl parathion was carried out for the general population. Four exposure scenarios were evaluated, including (*i*) exposure from ambient air under acute scenarios and dietary exposures under (*ii*) acute, (*iii*) subchronic conditions and (*iv*) chronic conditions. A margin of exposure of 100 is considered sufficiently protective of human health when the NOELs are derived from animal studies.

The acute dietary MOEs, calculated with the probabilistic (Monte Carlo) model using the most refined assumptions, were below the benchmark of 100 for the majority of the population subgroups at the 95th and the 99th percentiles. The acute dietary MOEs were below 100 for all subgroups at the 99.9th percentile of user-day. Infants were identified as the most highly exposed population subgroup. Altogether, the MOEs for acute dietary exposure indicated a potential health concern and thus mitigation should be considered.

The ambient air exposure, as estimated in the 1999 TACE document, was less than 3% compared to the exposure from dietary sources. Because of its relatively low contribution, the ambient air exposure was not added to the dietary exposure to estimate the non-occupational aggregate exposure.

The 95th percentile MOE for exposure to a tolerance level methyl parathion were less than the benchmark of 100 for the majority of the label-approved commodities in California. Methyl parathion exerts adverse pre- and post- natal effects, which should be taken into consideration when the USEPA reviews the tolerance levels under the Food Quality Protection Act.

VIII. REFERENCES

Abu-Qare, A. and Abou-Donia, M. B. 2000. Urinary excretion of metabolites following a single dermal dose of [14C]methyl parathion in pregnant rats. Toxicology 150:119-27.

Abu-Qare, Rahman, A., Kishk, A. and Abou-Donia. 2000. Placenta transfer and pharmacokinetics of a single dermal dose of [^{14}C]methyl parathion in rats. Toxicol. Sciences. 53:5-12

Abu-Qare, A. W., Abdel-Rahman, A. A., Ahmad, H., Kishk, A. M. and Abou-Donia MB. 2001a. Absorption,distribution,metabolism and excretion of daily oral doses of [^{14}C]methyl parathion in hens. Toxicol Lett.125:1-10.

Abu-Qare, A.W., Abdel-Rahman, A., Brownie, C., Kishk, A.M. and Abou-Donia, M.B. 2001b. Inhibition of cholinesterase enzymes following a single dermal dose of chlorpyrifos and methyl parathion, alone and in combination, in pregnant rats. J. Toxicol. Environ. Health A. 63:173-89.

Ackermann, H. and Engst, R. 1970. Presence of organophosphate insecticides in the fetus. Arch. Toxikol. 26:17-22.

Agency for Toxic Substances and Disease Registry (ATSDR). 1992a. Toxicological profile for methyl parathion. Prepared by Clement International Corporation. U.S. Department of Health and Human Services, Public Health Service, ATSDR.

Agency for Toxic Substances and Disease Registry (ATSDR). 1992b. Public Health Statement for Nitrophenols. CAS#; 2-Nitrophenol 88-75-5; 4-Nitrophenol 100-02-7U.S. Department of Health and Human Services, Public Health Service,

Ahmed F. E. and Sagartz, J. W. 1981. (Pharmacopathics Research Labs, Inc.). Methyl parathion: One year dog study. Monsanto. Study No. PRL 77-118. DPR Vol. 121-040, #11166.

Albores, A., Ortega-Mantilla, G., Sierra-Santoyo, A., Cebrian, M.E., Munoz-Sanchez, J.L., Calderon-Salinas, J.V. and Manno, M. 2001. Cytochrome P450 2B (CYP2B)-mediated activation of methyl-parathion in rat brain extracts. Toxicol Lett. 124:1-10.

Anderson, P. N., Eaton, D. L. and Murphy, S. D. 1992. Comparative metabolism of methyl parathion in intact and subscellular fractions of isolated rat hepatocytes. Fund. Appl. Toxicol. 18:221-226.

Ando, C., Johnson, B., Wofford, P., Matsumoto, S., Johnson, B., Ganapathy, C. and Segawa, R. 2002.: Monitoring Methyl Parathion Air Concentrations Adjacent to an Orchard Application. Study Number 211. Division of Pest Management, Environmental Monitoring, Enforcement, and Licensing, Environmental Monitoring Branch, California Environmental Protection Agency, Department of Pesticide Regulation. Sacramento, CA.

Arpagaus, M., Kott, M., Vatsis, K. P., Bartels, C. F., La Du, B. N. and Lockridge, O. 1990. Structure of the gene for human butyrylcholinesterase. Evidence for a single copy. Biochemistry. 29:124-31.

A/S Cheminova. 1990. Response to review of methyl parathion two-generation reproduction study in rats (DPR Number 044-011171) submitted pursuant to SB 950. DPR Vol. 121-081.

Asmathbanu, I. and Kaliwal. B. B. 1997. Temporal effect of methyl parathion on ovarian compensatory hypertrophy, follicular dynamics and estrous cycle in hemicastrated albino rats. Jour. Basic Clin. Physiol. Pharmacol. 8:237-254.

Auletta, C. S. 1984a. Acute oral toxicity study in rats. Test material: Methyl parathion. Monsanto. Study No. 4998-84. DPR Vol. 121-010, #40550.

Auletta, C. S. 1984b. Acute dermal toxicity study in rabbits. Test material: Methyl parathion. Monsanto. Study No. 5006-84. DPR Vol. 121-010, #40551.

Bartels, C.F., James, K. and La Du, B.N. 1992a. DNA mutations associated with the human butyrylcholinesterase J-variant. Am J Hum Genet. 50:1104-14.

Bartels, C. F., Jensen, F.S., Lockridge, O., Van der Spek, A.F., Rubinstein, H.M., Lubrano, T. and La Du, B.N. 1992b. DNA mutation associated with the human butyrylcholinesterase K-variant and its linkage to the atypical variant mutation and other polymorphic sites. Am J Hum Genet. 50:1086-103.

Bartoli, S., Bonora, B. Colacci, A. Neiro, A. and Grilli, S. 1991. DNA damaging activity of methyl parathion. Res. Communi. Chem. Pathol. Pharmacol. 71:209-218.

Baynes, R. E. and J. M. Bowen. 1995. Toxicokinetics of methyl parathion in lactating goats. J. Agric. Food Chem. 43:1598-1604.

Baynes, R. and Riviere, J. 2001. Pesticide Disposition: Dermal Absorption. *In*: Handbook of Pesticide Toxicology. Vol. 1, 515-529.

Beavers, J. B., Foster, J. Cockrell, B. Y. and Jaber, M. J. (Wildlife International LTD.). 1990. Methyl parathion: An acute delayed neurotoxicity study in the laying hen. Study # 323-111. DPR Vol. 121-084, #88519.

Becker, H., Frei, D., Luetkemeier, H., Vogel, W. and Terrier, C. (Research and Consulting Co. Ag). 1987. Embryotoxicity study with E120 technical in the rat. A/S Cheminova. Study No. R4278. DPR Vol. 121-068, #85036.

Bedford, C. T. and Robinson, J. 1972. The alkylating properties of organophosphates. Xenobiotica 2:307-337.

Beyrouty, P. 1999a. A 2-Week Range-Finding Dermal Toxicity Study of the Potential Effects of Methyl Parathion in Rats. ClinTrials BioResearch Ltd. Study No. 97501, DPR vol. 121-137, #185728.

Beyrouty, P. 1999b. A 13-Week Dermal Study of the Potential effects of Methyl Parathion on Behavior, Neurochemistry and Neuromorphology in Rats. ClinTrials BioResearch, Study No. 97499, DPR vol.121-138, # 185729.

Beyrouty, P. 2001. A 4-Week Dermal Toxicity Study of Methyl Parathion in Rats. ClinTrials BioResearch Ltd. Study No. 97533, DPR vol. 121-139, #185730.

Beyrouty, P. 2002a. A Range-Finding Developmental Neurotoxicity Study of Orally Administered (Gavage) Methyl Parathion in The Rat. ClinTrials BioResearch Ltd. Study No. 97530, DPR vol. 121-162, #186607.

Beyrouty, P. 2002b. A Developmental Neurotoxicity Study of Orally Administered Methyl Parathion in The Rat. ClinTrials BioResearch Ltd. Study No. 97574, DPR vol. 121-164, #186610.

Beyrouty, P. 2002c. A Study of the Effects of Orally Administered Methyl Parathion on Cholonesterase Levels in Adult, Juvenile and Neonatal Rats. ClinTrials BioResearch Ltd. DPR vol. 121-163, #186608.

Benjaminov, O., Hoffer, E. and U. Taitelman. 1992. Parathion transfer and acetylcholinesterase activity in an in-vitro perfused term human placenta. Vet. Hum. Toxicol. 34:10-12.

Benke, G. M., Cheever, K. L., Mirer, F. E. and Murphy, S. D. 1974. Comparative toxicity, anticholinesterase action and metabolism of methyl parathion and parathion in sunfish and mice. Toxicol. Appl. Pharmacol. 28:97-109.

Benke, G. M. and Murphy, S. D. 1975. The influence of age on the toxicity and metabolism of methyl parathion and parathion in male and female rats. Toxicol. Appl. Pharmacol. 31:254-269.

Bomhard, E., Loser, E. and Schilde, B. 1981. E 605-methyl (Parathion -methyl) Chronic toxicological study on rats. Bayer AG. Study No. 9889. DPR Vols. 121-051, 052, 063; #37188, 37189, #074202.

Bomhard, E., and M. Rinke. 1994. Frequency of spontaneous tumors in Wistar rats in 2-year studies. Exp. Toxic. Pathol. 46:17-29.

Braeckman, R. A., Godefroot, M. G., Blondeel, G. M., Belpaire, F. M. and Willems, J. L. 1980. Kinetic analysis of the fate of methyl parathion in the dog. Arch. Toxicol. 43:263-271.

Braeckman, R. A., Audenaert, F.,. Willems, J. L., Belpaire, F. M. and Bogaert M. G. 1983. Toxicokinetics of methyl parathion and parathion in the dog after intravenous and oral administration. Arch. Toxicol. 54:71-82.

Breau, A. P., Mitchell, W. M., Swinson, J. and Field, L. 1985. Mutagenic and cell transformation activities of representative phosphorothioate esters in vitro. J. Toxicol. Environ. Health, 16:403-413.

Brennecke, L. H. 1996. Re-evaluation of selected peripheral (sciatic and tibial) nerve tissues from a previously submitted chronic toxicity study of methyl parathion to rats [Huntingdon Life Sciences (formerly Bio/dynamics, Inc.) Proiect #87-3208, Study #3189-346, MRID 418538-01]. Cheminova Agro A/S, study number 3189-346. DPR Vol. 121-131.

Brodeur, J. and DuBois, K. P. 1963. Comparison of acute toxicity of anticholinesterase insecticides to weanling and adult male rats. Proc. Soc. Exp. Biol. Med. 114:509-511.

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.

California Code of Regulations. Title 3. Food and Agriculture. Division 6. Pesticides and Pest Control Operations. Chapter 4. Environmental Protection. Subchapter 2. Air. Section 6860. http://www.cdpr.ca.gov/docs/empm/pubs/tacmenu.htm. Toxic Air Contaminants List.

Chambers, J.E. and Chambers, H.W. 1990. Time course of inhibition of acetylcholinesterase and aliesterases following parathion and paraoxon exposures in rats. Toxicol Appl Pharmacol. 103:420-9.

Chandra, M., Riley, M. G. I. and Johnson, D. E. 1992. Spontaneous neoplasms in aged Sprague-Dawley rats. Arch. Toxicol. 66:496-502.

Chang, M. J. W., Chen, Y. C. and Yang. H. J. 1997. Comparative evaluation on the biological monitoring of exposure to parathion and its methyl analog. Arch. Environ. Contam. Toxicol. 32:422-425.

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

Chen, H., Sirianni, S. R. and Huang, C. 1982. Sister chromatid exchanges in Chinese hamster cells treated with seventeen organophosphorous compounds in the presence of a metabolic activation system. Environ. Mutagen. 4:621-624.

Code of Federal Regulations (CFR). 2001. CFR 40, Part 180.121. July 1, 2001.

Crittenden, P. L., Carr, R. and Pruett, S. B. 1998. Immunotoxicological assessment of methyl parathon in female B6C3F1 mice. J. Toxicol. Environ. Health Part A, 54:1-20.

Crowder, L. A., Lanzaro, G. C. and Whitson, R. S. 1980. Behavioral effects of methyl parathion and toxaphene exposure in rats. J. Environ. Sci. Health B15:365-378.

Curren, R. 1989. Unscheduled DNA synthesis in rat primary hepatocytes. A/S Cheminova Study No. T8702.380. DPR Vol. 121-067, #75728.

Cuthbert, J. A. and Carr, S. M. A. 1986. Methyl parathion 80% technical: Acute toxicity tests. Inveresk Research International Report No. 3473. DPR Vol. 121-072, #86604, #86606, #86607.

Daly, I. W. and Rinehart, W. E. 1979. A four week pilot study in mice with methyl parathion. Monsanto Study No. 79-2365. DPR Vol. 121-043, #11170.

Daly, D. 1989. Soil Adsorption/Desorption with ^{14}C-Methyl Parathion. Analytical Biochemistry Laboratories, Inc., Study No.36963. DPR Vol. 121-062, #58997.

Daly, I. W. 1989. A 13 week subchronic toxicity study of methyl parathion in dogs via the diet followed by a one month recovery period. A/S Cheminova. Project # 87-3204. DPR Vol. 121-070, # 090468.

Daly, I. W. 1991. A twelve month oral toxicity study of methyl parathion (E 120) in the rat via dietary mixture with special focus on ocular and sciatic nerve effects. A/S Cheminova Project No. 87-3208. DPR Vol. 121-091, #89191.

Daly, I. W. and Rinehart, W. E. 1980a. A three month feeding study of methyl parathion in rats. Monsanto Study No. 77-2059. DPR Vol. 121-041, #11167; Vol. 121-99, #127031.

Daly, I.W. and Rinehart, W.E. 1980b. A three month feeding study of methyl parathion in mice. Monsanto Study No. 77-2057. DPR Vol. 121-043, #11169.

Daly, I. W. and Hogan, G. K. 1982. A two generation reproduction study of methyl parathion in rats. Monsanto Study No. 80-2456. DPR Vol. 121-044, #11171.

Daly, I. W. and Hogan, G. K. 1983. A two year feeding study of methyl parathion in rats. Monsanto Study No. 77-2060. DPR Vol. 121-042, #11168, and -045 to -050, #34227-34232.

De Bleecker, J.L. 1995. The intermediate syndrome in organophosphate poisoning: an overview of experimental and clinical observations. J. Toxicol. Clin. Toxicol. 33:683-6.

De Cassia Stocco, R., Becak, W., Gaeta, R. and Rabello-Gay, M.N. 1982. Cytogenetic study of workers exposed to methyl-parathion. Mutat. Res. 103:71-76.

Degraeve, N. and Moutschen, J. 1984. Absence of genetic and cytogenetic effects in mice treated by the organophosphorus insecticide parathion, its methyl analogue, and paraoxon. Toxicol. 32:177-183.

Degraeve, N., Chollet, M. C. and Moutschen, J. 1984a. Cytogenetic effects induced by organophosphorus pesticides in mouse spermatocytes. Toxicol. Lett. 21:315-319.

Degraeve, N., Chollet, M. C. and Moutschen, J. 1984b. Cytogenetic and genetic effects of subchronic treatments with organophosphate insecticides. Arch. Toxicol. 56:66-67.

Deichmann, W. B. 1950. Observations on the immediate oral and cutaneous toxicity of a group of insecticides. The Geary Chemical Co. DPR Vol. 121-003, #927563.

Deli, E. and Kiss, Z. 1988. Effect of parathion and methylparathion on protein content of chicken embryo muscle *in vivo*. Biochem. Pharmacol. 37:3251-3256.

Dementi, B. 1999. Cholinesterase Literature Review and Comment. Pesticides, People and Nature. 1:59-126.

Department of Pesticide Regulation (DPR). 1992. Sampling for Pesticide Residues in California Well Water. Cumulative Report 1986-1992. California Environmental Protection Agency, Department of Pesticide Regulation.

Department of Pesticide Regulation (DPR). 2001. Sampling for Pesticide Residues in California Well Water. Well Inventory Database. California Environmental Protection Agency, Department of Pesticide Regulation.

Department of Pesticide Regulation, ((DPR). 1997a. Residues in Fresh Produce 1994-1997. Pesticide Enforcement Branch, Sacramento, CA. http://mitra:8080/3pubs/3pubs-annreports.htm).

Department of Pesticide Regulation (DPR). 1997b. Cumulative database (1986-1995) on the California Pesticide Illness Surveillance Program. California Environmental Protection Agency, Department of Pesticide Regulation. Sacramento, CA.

Department of Pesticide Regulation, (DPR). 2000a. Summary of Pesticide Use Report Data Indexed by Chemical. Enforcement Branch, Sacramento, CA. http://mitra:8080/3pubs/3pubs-annreports.htm

Department of Pesticide Regulation, (DPR). 2000b. Memorandum Subject: ID#FP-181146, SLN for control of codling moth andnavel orangeworm on walnuts. Dated March 13, 2000. From Kevin Sloari - RegistrationSpecialist. Department of Pesticide Regulation. 1001 I Street. P.O. Box 4015.Sacramento, CA 95812.

De Lima, J. S., Neto, J. C. B., Bastos, V. L. F. C., Cunha, J. C., M. Moraes, F. F., Ferreira, M. F. A., Moreira, J. C. and Faria, M. V. C. 1996. Methyl parathion activation by a partially purified rat brain fraction. Toxicol. Lett. 87:53-60.

De Schryver, E., De Reu, L., Belpaire, F. and Willems, J. 1987. Toxicokinetics of methyl paraoxon in the dog. Arch. Toxicol. 59:319-322.

Dhondup, P. and Kaliwal, B. B. 1997. Inhibition of ovarian compensatory hypertrophy by the administration of methyl parathion in hemicastrated albino rats. Repro. Toxicol. 11:77-84.

Dikshith, T. S. S., Raizada, R. B., Singh, V., Pandey, M. and Srivastava, M. K. 1991. Repeated dermal toxicity of technical HCH and methyl parathion (50EC) to female rats (*Rattus norvigicus*). Indian Jour. Exp. Biol. 29:149-155.

Donger, C., Krejci, E., Serradell, A.P., Eymard, B., Bon, S., Nicole, S., Chateau, D., Gary, F., Fardeau, M., Massoulie, J. and Guicheney, P. 1998. Mutation in the human acetylcholinesterase-associated collagen gene, COLQ, is responsible for congenital myasthenic syndrome with end-plate acetylcholinesterase deficiency (Type Ic). Am J Hum Genet. 63:967-75.

DuBois, K. P. and F. K. Kinoshita. 1968. Influence of induction of hepatic microsomal enzymes by phenobarbitol on toxicity of organic phosphate insecticides. Proc. Soc. Exp. Biol. Med. 129:699-702.

Durkin, P.R., Rubin, L., Withey, J. and Meylan, W. 1995. Methods of assessing dermal absorption with emphasis on uptake from contaminated vegetation. Toxicol. Ind. Health. 11:63-79.

Duysen, E.G., Stribley, J.A., Fry, D.L., Hinrichs, S.H. and Lockridge, O. 2002. Rescue of the acetylcholinesterase knockout mouse by feeding a liquid diet; phenotype of the adult acetylcholinesterase deficient mouse. Brain Res. Dev. Brain Res. 137:43-54.

Ecobichon, D.J. 1994.Organophosphorus ester insecticides. In: Ecobichon D. J. and Joy R. M. Pesticides and Neurological Diseases. 2ed. Boca Raton, FL: CRC, pp.171-249.

Edwards, J.A. and Brimijoin, S. 1983. Effects of hypophysectomy on acetyl-cholinesterase and butyrylcholinesterase in the rat. Biochem Pharmacol. 32:1183-9.

Eiben, R. 1988a. Pilot dose-finding study for a carcinogenicity study in B6C3F1 mice. Administration in the feed over 65 days. Bayer AG Study Number T1025518, Report No. 16853. DPR Vol.121-073, #86613.

Eiben, R. 1988b. Pilot dose-finding study for a carcinogenicity study in B6C3F1 mice. Administration in the feed over 66 days. Bayer AG Study Number T5025378, Report No. 16854. DPR Vol.121-073, #86614.

Eiben, R. 1991. Methyl parathion study for chronic toxicity and carcinogenicity in B6C3F1 mice. Bayer AG Fachbeneich Toxikologie, Study No. T4027023. DPR Vol. 121-094, #C098865.

Enan, E. E., Enan, O. H and El-Sebae, A. E. 1982. Biochemical targets affected by sublethal doses of organophosphorus insecticides. International Pest Control. 24:120-122.

Engel, A.G. 1994a. Acquired autoimmune myasthenia gravis. *In* Myology. A.G. Engel and C. Franzimi-Armstrong, Eds. McGaw Hill, New York. 1769-1798.

Engel, A.G. 1994b. Myasthenic syndrome. *In* Myology. A.G. Engel and C. Franzimi-Armstrong, eds. McGaw Hill, New York. 1798-1835.

Esteban, E., Rubin, C., Hill R., Olson, D. and Pearce, K. 1996. Association between indoor residential contamination with methyl parathion and urinary para-nitrophenol. J. Expos. Anal. Environ. Epidemiol. 6:375-387.

Fan, A. M. 1980. Effects of pesticides on immune competency: Influence of methyl parathion and carbofuran on immumologic responses to salmonella. Dissert., Utah State Univ., Dissertation Information Service, UMI #8104106.

Farm Chemicals Handbook. 2002. Methyl Parathion. Global Guide to Crop Protection, In: R. Meister (ed.). Meister Publishing Company, Willoughby, OH. Vol.88. p. C270.

Feldmann, R. J. and Maibach, H. I. 1974. Percutaneous penetration of some pesticides and herbicides in man. Toxicol. Appl. Pharmacol. 28:126-32.

Fish, S. A. 1966. Organophosphorus cholinesterase inhibitors and fetal development. Amer. J. Obstet. Gyn. 96:1148-1154.

Formoli, T. 2000. Estimation of Exposure of Persons in California to the Pesticide Products that Contain Methyl Parathion. Worker Health and Safety Branch. Department of Pesticide Regulation (DPR). California Environmental Protection Agency, Sacramento, CA.

Forsyth, C. S. and Chambers, J. E. 1989. Activation and degradation of the phosphorothionate insecticides parathion and EPN by rat brain. Biochem. Pharmacol. 38:1597-1603.

Gaines, T. B. 1969. Acute toxicity of pesticides. Toxicol. Appl. Pharmacol. 14:515-534.

Galal, E. E., Samaan, H. A., Nour El Dien, S., Kamel, S., El Saied, M., Sadek, M., Madkour, A., El Saadany, K. and El-Zawahry, A. 1977. Studies on the acute and subchronic toxicities of some commonly used anticholinesterase insecticides in rats. J. Drug Res. Egypt 9:1-17.

Gallo, M. A. and Lawryk, N. K. 1991. Organic phosphorus pesticides. *In:* Handbook of Pesticide Toxicology. W. J. Hayes, Jr. and E. R. Laws, Jr., Eds. Academic Press, Inc. San Diego, USA.

Glynn P. 1999. Neuropathy target esterase. Biochem J. 344:625-631.

Glynn, P. 2000. Neural development and neurodegeneration: two faces of neuropathy target esterase. Prog. Neurobiol. 61:61-74.

Gomez-Arroyo, S., Noriega-Aldana, N., Juarez-Rodriguez D. and Villalobos-Pietrini, R. 1987. Sister chromatid exchanges induced by the organophosphorus insecticides methyl parathion, dimethoate, phoxim and methyl azinphos in cultured human lymphocytes. Contam. Ambient. 3:63-70.

Greenough, R. J. and McDonald, P. 1986. Methyl parathion 80% technical acute inhalation toxicity study in rats. Inveresk Research International Report No. 3478. DPR Vol. 121-072, #86603.

Griffin, D. E. and Hill, W. E. 1978. *In vitro* breakage of plasmid DNA by mutagens and pesticides. Mutat. Res. 52:161-169.

Grover, I. S. and Malhi, P. K. 1985. Genotoxic effects of some organophosphorous pesticides, I. Induction of micronuclei in bone marrow cells in rat. Mutat. Res. 155:131-134.

Gupta, R. C., Rech, R. H., Lovell, K. L., Welsch, F. and Thornburg, J. E. 1985. Brain cholinergic, behavioral, and morphological development in rats exposed *in utero* to methylparathion. Toxicol. Appl. Pharmacol. 77:405-413.

Gupta, R. C., Patterson, G. T., and Dettbarn, W-D. 1991. Comparison of cholinergic and neuromuscular toxicity following acute exposure to sarin and VX in rat. Fund. Appl. Toxicol. 16:449-458.

Gupta, R. C., Goad, J. T., Milatovic, D. and Dettbarn, W.D. 2000. Cholinergic and noncholinergic brain biomarkers of insecticide exposure and effects. Hum. Exp. Toxicol. 19:297-308.

Hall, L. M. and Spierer, P. 1986. The Ace locus of Drosophila melanogaster: structural gene for acetylcholinesterase with an unusual 5' leader. EMBO J. 5:2949-54.

Hartwell, W. V. and Hayes., G. R. 1965. Respiratory exposure to organic phosphorus insecticides. Arch. Environ. Health. 11:564-568.

Hatch, R. C. 1998. One year oral (dietary) toxicity study of methyl parathion in dogs. MPI Research #668-003. DPR Vol. 121-132, #164091.

Haworth, S., Lawlor, T. Mortelmans, K., Speck, W. and Zeiger, E. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutag. (Suppl.) 1:3-142.

Herbold, B. (Bayer Ag). 1980. E 120 Parathion-methyl: Salmonella/ microsome test to evaluate for point mutation. A/S Cheminova. Study No. 9337. DPR Vol. 121-054, #37192.

Herbold, B. (Bayer Ag). 1982a. E 120 FOLIDOL M active ingredient. Salmonella/ microsome test to evaluate for point mutation. A/S Cheminova. Study No. 10993. DPR Vol. 121-054, #37193.

Herbold, B. (Bayer Ag). 1982b. Parathion-methyl: Micronucleus test on the mouse to evaluate for mutagenic effect. A/S Cheminova. Study No. 10769. DPR Vol. 121-054, #37194.

Herbold, B. (Bayer Ag). 1984. E 120 FOLIDOL M active ingredient. Dominant lethal test on the male mouse to evaluate for mutagenic effect. A/S Cheminova. Study No. 12731. DPR Vol. 121-054, #37195.

Hirschelmann, R. and Bekemeier. H. 1975. Acute toxicity of demephion and parathion methyl in dogs. Proc. Eur. Soc. Toxicol. 16:273-275.

Hoberman, A. M. 1991. Developmental toxicity (Embryo-fetal toxicity and teratogenic potential) study of methyl parathion technical administered orally via stomach tube to New Zealand white rabbits. Argus Research Laboratories, Inc. Report # 310-007. DPR Vol. 121-095, #111287.

Hollingworth, R. M., R. L. Metcalf, and T. R. Fukuto. 1967. The selectivity of sumithion compared with methyl parathion. Metabolism in the white mouse. J. Agric. Food Chem. 15:242-249.

Hollingworth, R. M., Alstott, R. L. and Litzenberg. R. D. 1973. Glutathione S-aryl transferase in the metabolism of parathion and its analogs. Life Sciences. 13:191-199.

Howard, M.D. and Pope, C.N. 2002. In vitro effects of chlorpyrifos, parathion, methyl parathion and their oxons on cardiac muscarinic receptor binding in neonatal and adult rats. Toxicology. 170:1-10.

Huang, Y. and Sultatos. L. G. 1993. Glutathione-dependent biotransformation of methyl parathion by mouse liver in vitro. Toxicol. Lett. 68:275-284.

International Agency for Research on Cancer (IARC). 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 30. Miscellaneous pesticides. Lyon, France: International Agency for research on Cancer.

Institoris, L., Siroki, O., Toth, S. and Desi, I. 1992. Immunotoxic effects of MPT-IP containing 60% methylparathion in mice. Hum. Experi. Toxicol. 11:11-16.

Institoris, L., Siroki, O. and Desi, I. 1995. Immunotoxicity study of repeated small doses of dimethoate and methylparathion administered to rats over three generations. Hum. Experi. Toxicol. 14:879-883.

Integrated Risk Information System (IRIS). 1991. p-Nitrophenol (CASRN 100-02-7). Environmental Protection Agency; http://www.epa.gov/IRIS/subst/0484.htm.

Johnson, G. and Moore, S.W. 1999. The adhesion function on acetylcholinesterase is located at the peripheral anionic site. Biochem Biophys Res Commun. 258:758-62.

Jortner, B. 2001. Neuropathology Slide R-Read, BioDynamics Study 87-3208. A 12 Month Oral Toxicity Study with Methyl Parathion [E-120] in the rat via Dietary Admixture with Special Focus on Ocular and Sciatic Nerve Effects by Daly 1991. Laboratory for Neurotoxicity Studies, Virginia Tech. DPR vol. 121-143, #185734

Kelly, K. 1999. Evaluation of methyl parathion as a toxic air contaminant. Environmental Fate, Part A. Environmental Monitoring and pest Management Branch. Department of Pesticide Regulation (DPR). California Environmental Protection Agency. Sacramento, CA.

Kollman, S. 1999. Status Report: Pesticide Contamination and Prevention Act. Department of Pesticide Regulation, California Environmental Protection Agency.

Kronenberg, G., Macklin, W. B. and Dolinger, P. M. 1978. Methyl Parathion, Monograph Number 7, Environmental Health Evaluations of California Restricted Insecticides. Peter M. Dolinger Associates, Menlo Park, Ca. DPR Vol. 121-033.

Kumar, K. Sunil, B. and. Devi, K. S. 1992. Teratogenic effects of methyl parathion in developing chick embryos. Vet. Hum. Toxicol. 34:408-410.

Kumar, M. and Desiraju, T. 1992. Effect of chronic consumption of methyl parathion on rat brain regional acetylcholinesterase activity and on levels of biogenic amines. Toxicol. 75:13-20.

Kumar, K. Sunil, B., Ankathil R. and Devi, K. S. 1993. Chromosomal aberrations induced by methyl parathion in human peripheral lymphocytes of alcoholics and smokers. Hum. Experi. Toxicol. 12:285-288.

Kumar, S.B. and Devi, K. S. 1996. Methyl parathion induced teratological study in rats. *J. Environ.Biol*. 17:51-57.

Lang, P. L. 1992. Spontaneous neoplastic lesions and selected non-neoplastic lesions in the Crl:CD®BR rat. Charles River Laboratories. February, 1992.

Layer, P. G. and Willbold, E. 1995. Novel Functions of cholinesterases in development, physiology and disease. Prog. Histochem. Cytochem. 29:1-94.

Lessire, F., Gustin, P., Delaunois, A., Bloden, S., Nemmar, A., Vargas, M. and Ansay. M. 1996. Relationship between parathion and paraoxon toxicokinetics, lung metabolic activity, and cholinesterase inhibition in guinea pig and rabbit lungs. Toxicol. Appl. Pharm. 138:201-210.

Li, B., Stribley, J.A., Ticu, A., Xie, W., Schopfer, L.M., Hammond, P., Brimijoin, S., Hinrichs, S.H. and Lockridge, O. Abundant tissue butyrylcholinesterase and its possible function in the acetylcholinesterase knockout mouse. J. Neurochem. 2000. 75:1320-31.

Linke, P. and Brauner, A. 1988. Parathion –Methyl: Metabolism in Potatoes. Bayer AG, Study No.3049. DPR Vol. 121-76, #86625.

Linke, P., Bornatsch, W., Brauner, A. and Neitzel, N. 1988. Metabolism of [phenul-UL-^{14}C]Parathion-methyl in Cotton Seeds and Leaves. Bayer AG, Study No.3037., DPR Vol. 121-076, #86622.

Lisi, P., S. Caraffini, and Assalve. D. 1986. A test series for pesticide dermatitis. Contact Dermatitis, 15:266-269.

Lino, C.M. and Silveira, M.I. 1992. Organophosphorus pesticide residues in cow's milk: levels of cis-mevinfos, methyl-parathion, and paraoxon. Bull Environ Contam Toxicol. Aug;49(2):211-6.

Lockridge, O. and Masson, P. 2000. Pesticides and susceptible populations: people with butyrylcholinesterase genetic variants may be at risk. Neurotoxicology. 21:113-26.

Loser, E., and Eiben, R. 1982. E 605 parathion-methyl. Multigeneration studies on rats. Bayer Ag. Study No. 10630. DPR Vol. 121-053, #37190.

Lotti, M. 1992. The pathogenesis of organophosphate polyneuropathy. Crit. Rev. Toxicol. 21:465-487.

Ma, T., Kramer, R. E., Baker, R. C., Fan, L. W. and Ho, I. K. 2003. Effects of chronic dermal exposure to nonlethal doses of methyl parathion on brain regional acetylcholinesterase and muscarinic cholinergic receptors in female rats. J. Neurosci. Res. 71:138-45.

Machemer, L. 1977. Parathion-methyl. Evaluation for embryotoxic and teratogenic effects on rats following oral administration. Bayer Ag. Study No. 6825. DPR Vol. 121-055 #37196.

Maitra, S. K. and Sarkar, R. 1996. Influence of methyl parathion on gametogenic and acetylcholinesterase activity in the testis of whitethroated munia (*Lonchura malabarica*). Arch. Environ. Contam. Toxicol. 30:384-389.

Malhi, P. K. and Grover, I. S. 1987. Genotoxic effects of some organophosphorus pesticides. II. In vivo chromosomal aberration bioassay in bone marrow cells in rat. Mutat. Res. 188:45-51.

Massoulie, J., Pezzementi, L., Bon, S., Krejci, E. and Vallette FM. 1993. Molecular and cellular biology of cholinesterases. Prog Neurobiol. 41:31-91.

Massoulie. J., Anselmet, A., Bon, S., Krejci, E., Legay, C., Morel, N. and Simon, S. 1998. Acetylcholinesterase: C-terminal domains, molecular forms and functional localization. J Physiol Paris. 92:183-90.

Massoulie, J. 2002. The origin of the molecular diversity and functional anchoring of cholinesterases. Neurosignals. 11:130-43.

Mathew, G., Rahiman, M. A. and Vijayalaxmi, K. K. 1990. *In vivo* genotoxic effects in mice of Metacid 50, an organophosphorus insecticide. Mutagenesis 5:147-149.

Mathew, G., Vijayalaxmi, K. K. and Rahiman, M. A. 1992. Methyl parathion induced sperm shape abnormalities in mouse. Mutat. Res. 280:169-173.

Mattison, D. R. 1985. Clinical manifestations of ovarian toxicity. *In:* Target Organ Toxicology Series - Reproductive Toxicology. R. L. Dixon, ed. Raven Press, N.Y.

McMartin, D. N., Sahota, P. S., Gunson, D. E., Hsu, H. H. and Spaet, R. H. 1992. Neoplasms and related proliferative lesions in control Sprague-Dawley rats from carcinogenicity studies. Historical data and diagnostic considerations. Toxicol. Pathol. 20:212-225.

Menzie, C. M. 1969. Metabolism of pesticides. *In*: Special Scientific Report-Wildlife No. 127. pp. 264-271. United States Department of the Interior, Bureau of Sport Fisheries and Wildlife. Washington, D.C.

Mesulam, M.M., Guillozet, A., Shaw, P., Levey, A., Duysen, E.G. and Lockridge, O. 2002. Acetylcholinesterase knockouts establish central cholinergic pathways and can usebutyrylcholinesterase to hydrolyze acetylcholine. Neuroscience. 110:627-39.

Minnema, D. J. 1994a. Acute neurotoxicity study of methyl parathion in rats. Hazleton Washington, Inc, #HWA2688-102. DPR Vol.121-129, #164087.

Minnema, D. J. 1994b. Subchronic neurotoxicity study of dietary methyl parathion in rats. Hazleton Washington, Inc, #HWA2688-103. DPR Vol.121-130, #164088.

Mirer, F. E., Levine, B. S. and Murphy, S. D. 1977. Parathion and methyl parathion toxicity and metabolism in piperonyl butoxide and diethyl maleate pretreated mice. Chem.-Biol. Interact. 17:99-112.

Miyamoto, J. 1964. Studies on the mode of action of organophosphorus compounds. Part III. Activation and degradation of sumithion and methylparathion in mammals in vivo. Agric. Biol. Chem. 28:411-421.

Miyamoto, J., Sato, Y., Kadota, T., Fujinami, A. and Endo, M. 1963a. Studies on the mode of action of organophosphorus compounds. Part I. Metabolic fate of P^{32} labeled sumithion and methylparathion in guinea pig and white rat. Agric. Biol. Chem. 27:381-389.

Miyamoto, J., Sato, Y., Kadota, T. and Fujinami. A. 1963b. Studies on the mode of action of organophosphorus compounds. Part II. Inhibition of mammalian cholinesterase in vivo following the administration of sumithion and methylparathion. Agric. Biol. Chem. 27:669-676.

Morgan, D. P., Hetzler, H. L., Slach, E. F. and Lin, L. I. 1977. Urinary excretion of paranitrophenol and alkyl phosphates following ingestion of methyl or ethyl parathion by human subjects. Arch. Environ. Contam. Toxicol. 6:159-173.

Murphy, S. D. 1980. Toxic interactions with dermal exposure to organophosphate insecticides. *In:* Mechanisms of Toxicity and Hazard Evaluation. B. Holmstedt, R. Lauwerys, M. Mercier, and M. Roberfroid, Eds. pp. 615-621. Elsevier/North-Holland Biomedical Press.

Murphy, S. D. 1982. Toxicity and hepatic metabolism of organophosphate insecticides in developing rats. *In*: Environmental Factors in Human Growth and Development. V. R. Hunt, et al., Eds. pp.125-136. Cold Spring Harbor Laboratories, Cold Spring Harbor, New York.

Nakazawa, T. and Nakazawa, T. 1974. Chronic organophosphorus intoxication in women. Nippon Noson Igakkai Zasshi *(*K. Jan. Ass. Rural Med*.)* 22:756-758.

Nagymajtenyi, L., Schulz, H. and Desi. I. 1995. Changes in EEG of freely-moving rats caused by three-generation organophosphate treatment. Arch. Toxicol. Suppl. 17:288-294.

National Academy of Science (NAS). 1993. Pesticides in the diets of infants and children. National Research Council, National Academy Press. Washington, D.C.

National Cancer Institute (NCI). 1979. Bioassay of methyl parathion for possible carcinogenicity. NCI Technical Report Series No. 157. DPR Vol. 121-038.

National Institute for Occupational Safety and Health (NIOSH). 1987. Phosphorothioic acid O,O-dimethyl O-(p-nitrophenyl) ester. *In:* Registry of Toxic Effects of Chemical Substances (RTECS) 1985-86 Edition. D. V. Sweet Ed. pp. 3437-3438. United States Department of Health and Human Services, National Institute for Occupational Safety and Health, Washington, D.C. Publication No. 87-114.

Nehez, M., Toth, C. S. and Desi, I. 1994. The effect of dimethoate, dichlorvos, and parathion-methyl on bone marrow cell chromosomes of rats in subchronic experiments *in vivo*. Ecotoxicol. Environ. Safety, 29:365-371.

Nemec, S. J., Adkisson, P. L. and. Dorough, H. W 1968. Methyl parathion adsorbed on the skin and blood cholinesterase levels of persons checking cotton treated with ultra-low volume sprays. J. Econ. Entomol. 61:1740-1742.

Neville, L.F., Gnatt, A., Loewenstein, Y. and Soreq H. 1990. Aspartate-70 to glycine substitution confers resistance to naturally occurring and synthetic anionic-site ligands on in-ovo produced human butyrylcholinesterase. J Neurosci Res. 27:452-60.

Newell, G. W. and Dilley, J. V. 1978. Teratology and Acute Toxicology of Selected Chemical Pesticides Administered by Inhalation. United States Environmental Protection Agency, Office of Research and Development, Cincinnati, Ohio. Report No. 600/1-78-003, PB277-007.

Ohkawa, H., Oshita, H. and Miyamoto, J. 1980. Comparison of inhibitory activity of various organophosphorous compounds against acetylcholinesterase and neurotoxic esterase of hens with respect to delayed neurotoxicity. Biochem. Pharmacol. 29:2721-2727.

Ohno, K., Brengman, J., Tsujino, A. and Engel, A.G. 1998. Human endplate acetylcholinesterase deficiency caused by mutations in the collagen-like tail subunit (ColQ) of the asymmetric enzyme. Proc. Natl. Acad. Sci. U S A. 95:9654-9.

Ortiz, D., Yanez, L., Gomez, H., Martines-Salazar, J. A. and Diaz-Barriga, F. 1995. Acute toxicological effects in rats treated with a mixture of commercially formulated products containing methyl parathion and permethrin. Ecotoxicol. Environ. Safety 32:154-158.

O'Shaughnessy, D. 2001a. Pathology Re-Evaluation: Acute Neurotoxicity Study of Methyl Parathion in Rats [Hazleton Washington Study 26880102, 1994]. Cheminova A/S, Denmark. DPR vol. 121-145, #185736.

O'Shaughnessy, D. 2001b. Pathology Re-Evaluation: A 12 Month Oral Toxicity Study with Methyl Parathion [E-120] in the rat via Dietary Admixture with Special Focus on Ocular and Sciatic Nerve Effects [by Daly 1991]. Cheminova A/S, Denmark. DPR vol. 121-144, #185735.

O'Shaughnessy, D. 2002. Re-Evaluation of Neuropathology Slides from a Subchronic Neurotoxicity Study of Dietary Methyl Parathion in Rats (by). D. O'O'Shaughnessy Consulting, Inc. NJ, DPR vol. 121-146, #185737.

Padungtod, C., Lasley, B. L. D., Christiani, C., Ryan, L. M. and Xu, X. 1998. Reproductive hormone profile among pesticide factory workers. Jour. Occup. Environ. Medicine 40:1038-1047.

Parent-Massin, D. and Thouvenot, D. 1993. In vitro study of pesticide hematotoxicity in human and rat progenitors. J. Pharmacol. Toxicol. Methods, 30:203-207.

Park, B. H. and Lee ,T. P. 1978. Effects of pesticides on human leukocyte function. In: Inadvertent Modification of the Immune Response, The Effects of Foods, Drugs, and Environmental Contaminants. I.M. Asher, Ed. pp. 273-274. Food and Drug Administration, Office of Health Affairs.

Patterson, C. 1990a. Anaerobic Metabolism of ^{14}C-Methyl Parathion. Analytical Biochemistry Laboratories, Inc., Study No.36962. DPR Vol. 121-089, #89031.

Patterson, C. 1990b. Aerobic Soil Metabolism of ^{14}C-Methyl Parathion. Analytical Biochemistry Laboratories, Inc., Study No.36960. DPR Vol. 121-090, #89082.

Patterson, C. 1991. Aerobic Aquatic Metabolism of ^{14}C-Methyl Parathion. Analytical Biochemistry Laboratories, Inc., Study No. 36961. DPR Vol. 121-093, #96574.

Petersen, B., Yougren and Walls, C. 2001. Modeling Dietary Exposure and Special Section on Modeling Aggregate and Cumulative Exposure. In R. Krieger (Ed). Handbook of Pesticide Toxicology, vol. 1., Academic Press, San Diego, California.

Petit, F., Le Goff, P., Cravedi, J-P., Valotaire, Y. and Pakdel, F. 1997. Two complementary bioassays for screening the estrogenic potnecy of xenobiotics: recombinant yeast for trout estrogen receptor and trout hepatocyte culturres. J. Molecular Endocrin. 19:321-335.

Pope, C. N., Chakraborti, T. K., Chapman, M. L., Farrar, J. D. and Arthun. D. 1991. Comparison of in vivo cholinesterase inhibition in neonatal and adult rats by three organophosphorothioate insecticides. Toxicol. 68:51-61.

Pope, C. N. and Charkraborti, T. K. 1992. Dose-related inhibition of brain and plasma cholinesterase in neonatal and adult rats following sublethal organophosphate exposures. Toxicol. 73:35-43.

Radulovic, L. L., LaFerla, J. J. and Kulkarni, A. P. 1986. Human placental glutathione S-transferase-mediated metabolism of methyl parathion. Biochem. Pharmacol. 35:3473-3480.

Radulovic, L. L., Kulkarni, A. P. and Dauterman. W. C. 1987. Biotransformation of methyl parathion by human feotal liver glutathione S-transferases: An *in vitro* study. Xenobiotica. 17:105-114.

Rao, S. L. N., and W. P. McKinley. 1969. Metabolism of organophosphorus insecticides by liver homogenates from different species. Can. J. Biochem. 47:1155-1159.

Reed, N. R. 1999. Evaluation of methyl parathion as a toxic air contaminant. Human Health Assessment, Part C. Medical Toxicology Branch. Department of Pesticide Regulation (DPR), California Environmental Protection Agency, Sacramento, CA (www.cdpr.ca.gov/docs/empm/pubs/methylpa/mppartc.pdf).

Renhof, M. 1984. Parathion-methyl (Folidol M active ingredient) study for embryotoxic effects on rabbits after oral administration. Bayer Ag. Study No. 12907. DPR Vol. 121-055, #37197.

Rider, J. A., Moeller, H. C., Puletti, E. J. and Swader, J. I. 1969. Toxicity of parathion, systox, octamethyl pyrophosphoramide, and methyl parathion in man. Toxicol. Appl. Pharmacol. 14:603-611.

Rider, J. A., Swader, J. I. and Puletti, E. J. 1970. Methyl parathion and guthion anticholinesterase effects in human subjects. Fed. Proc. 29:349.

Rider, J. A., Swader, J. I. and Puletti, E. J. 1971. Anticholinesterase toxicity studies with methyl parathion, guthion and phosdrin in human subjects. Fed. Proc. 30:443.

Rashid, K. A. and Mumma, R. O. 1984. Genotoxicity of methyl parathion in short term bacterial test systems. J. Environ. Sci. Health. [B] 19:565-577.

Rice, F., Jacobson, B. and Richards, C. 1990a. Terrestrial Field Dissipation and for Methyl parathion. – Crop Application. Analytical Biochemistry Laboratories, Inc., Study No. 36839, DPR Vol. 121-078, #86758.

Rice, F., Jacobson, B. and Richards, C. 1990b. Combined Aquatic Field Dissipation and Accumulation Study on Irrigated Crops for Methyl Parathion. Analytical Biochemistry Laboratories, Inc., Studies No. 36840 and 36841, DPR Vol. 121-079 and 121-080, #86760 and 86761.

Ritter, A. 1988. ^{14}C-Parathion-Methyl: Plant Metabolism Study with Lettuce in the Greenhouse. RCC UMWELTCHEMIE, Switzerland, Study No.092114., DPR Vol. 121-076, #86623.

Rodgers, K. E., Leung, N., Imamura, T. and Devens, B. H. 1986. Rapid *in vitro* screening assay for immunotoxic effects of organophosphorus and carbamate insecticides on the generation of cytotoxic T-lymphocyte responses. Pest. Biochem. Physiol. 26:292-301.

Rodnitzky, R. L., Levin H. S. and Morgan, D. P. 1978. Effects of ingested parathion on neurobehavioral functions. Clin. Toxicol. 13:347-359.

Rupa, D. S., Reddy, P. P. and Reddi, O. S. 1989. Chromosomal aberrations in peripheral lymphocytes of cotton field workers exposed to pesticides. Environ. Res. 49:1-6.

Rupa, D. S., Reddy, P. P. and Reddi, O. S. 1990. Cytogeneticity of quinalphos and methyl parathion in human peripheral lymphocytes. Hum Experi. Toxicol. 9:385-387.

Sartorelli, P., Aprea, C., Bussani, R., Novelli, M. T., Orsi, D. and Sciarra. G. 1997. *In vitro* percutaneous penetration of methyl-parathion from a commercial formulation through the human skin. Occup. Environ. Med. 54:524-525.

Schulz, H., Desi, I. and Nagymajtenyi, L. 1990. Behavioral effects of subchronic intoxication with parathion-methyl in male Wistar rats. Neurotoxicol. Teratol. 12:125-127.

Segerback, D. 1981. Estimation of genetic risks of alkylating agents. V. Methylation of DNA in the mouse by DDVP (2,2-dichlorovinyl dimethyl phosphate). Hereditas, 94:73-76.

Seiber, J. M. and McChesney, M. M. 1987. Measurement and computer model simulation of the volatilization flux of molinate and methyl parathion from a flooded rice field. California Department of Food and Agriculture. Sacramento, CA. Contract #6854.

Senanayake, N. and Karalliedde, L. 1987. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. N. Engl. J. Med. 316:761-3.

Shtenberg, A. I., and Dzhunusova, R. M. 1968. Depression of immunobiological reactivity of animals by some organophosphorus pesticides. Byulleten Eksperimental'noi Biologii i Medistsiny 65:86-88.

Simmon, V. F., Mitchell, A. D. and Jorgenson, T. A. 1977. Evaluation of selected pesticides as chemical mutagens. *In vitro* and *in vivo* studies. United States Environmental Protection Agency, Report No. 600/1-77-028, NTIS PB268 647.

Singh, S., Lehmann-Grube, B. and Goedde, H. W. 1984. Cytogenetic effects of paraoxon and methyl-parathion on cultured human lymphocytes: SCE, clastogenic activity and cell cycle delay. Int. Arch. Occup. Environ. Health. 54:195-200.

Skinner, C. S. and W. W. Kilgore. 1982. Acute dermal toxicities of various organophosphate insecticides in mice. J. Toxicol. Environ. Health. 9:491-497.

Sobti, R. C., Krishan, A. and Pfaffenberger, C. D. 1982. Cytokinetic and cytogenetic effects of some agricultural chemicals on human lymphoid cells *in vitro*: Organophosphates. Mutat. Res. 102:89-102.

Solecki, R., Faqi, A. S., Pfeil, R. and Hilbig, V. 1996. Effects of methyl parathion on reproduction in the Japanese quail. Bull. Environ. Contam. Toxicol. 57:902-908.

Street, J. C., and Sharma, R. P. 1975. Alteration of induced cellular and humoral immune responses by pesticides and chemicals of environmental concern: Quantitative studies of immunosuppression by DDT, Aroclor 1254, carbaryl, carbofuran, and methylparathion. Toxicol. Appl. Pharmacol. 32:587-602.

Sultatos, L. G. 1987. The role of the liver in mediating the acute toxicity of the pesticide methyl parathion in the mouse. Drug Metab. Dispos. 15:613-617.

Sultatos, L. G., and Woods, L. 1988. The role of glutathione in the detoxification of the insecticides methyl parathion and azinphosmethyl in the mouse. Toxicol. Appl. Pharmacol. 96:168-174.

Sun, H., El Yazal, J., Lockridge, O., Schopfer, L.M., Brimijoin, S. and Pang YP. 2001. Predicted Michaelis-Menten complexes of cocaine-butyrylcholinesterase. Engineering effective butyrylcholinesterase mutants for cocaine detoxication. J. Biol. Chem. Mar 23;276(12):9330-6.

Sved, D.W. 2001. A Study to Determine the Urinary Elimination of para-Nitrophenol and its Conjugates Following Dermal Exposure of Rats to Methyl Parathion. WIL Research Laboratories, Inc. No.WIL-157018, DPR Vol.121-136, #188727.

Tanimura, T., Katsuya, T. and Nishimura, H. 1967. Embryotoxicity of acute exposure to methyl parathion in rats and mice. Arch. Environ. Health 15:609-613.

Taylor, P. 1985. Anticholinesterase agents. *In*: Goodman and Gillman's Pharmacological Basis of Therapeutics, Seventh Edition (A.L. Goodman, L.S. Goodman, T.W. Rall, and F. Murad, eds.), pp. 110-129. McMillan Publishing Co., New York.

Tennant, R. W., Margolin, B. H., Shelby, M. D., Zeiger, E., Haseman, J. K., Spalding, J. Caspary, W. Resnick, M. Staseiwicz, St., Anderson, B. and Monor, R. 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science. 236:933-941.

Tripathy, N. K., Dey, L., Majhi, B. and Das, C. C. 1987. Genotoxicity of metacid established through the somatic and germ line mosaic assays and the sex-linked recessive lethal test in Drosophila. Arch. Toxicol. 61:53-57.

Underwood, P. C. and Tegeris, A. S. 1977. Fourteen day feeding study in the dog - Methyl parathion. DPR Vol. 121-039, #17085.

Underwood, P. C. and Tegeris, A. S. 1978. Methyl parathion: Ninety day feeding to dogs. Monsanto Study No. 77-117. DPR Vol. 121-039, #17086.

United States Environmental Protection Agency (USEPA). 1975. Substitute Chemical Program - Initial scientific and minieconomic review of methyl parathion. Midwest Research Inst., Kansas City, MO. EPA 540-1-75-004, EPA 68-01-2448.

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

United States Environmental Protection Agency (USEPA). 1984. Tox Chem No. 372, Methyl Parathion. Toxicology one-liner. United States Environmental Protection Agency, Office of Pesticide Programs, Washington, D.C.

United States Environmental Protection Agency (USEPA). 1986b. Guidelines for carcinogen risk assessment. Federal Register 51(185):33992-34003.

United States Environmental Protection Agency (USEPA). 1988. Health Advisories for 50 Pesticides. United States Environmental Protection Agency, Office of Drinking Water. NTIS PB88-245931. Washington, D.C.

United States Environmental Protection Agency, (USEPA) 1991. For Your Information – Pesticide Tolerances. Pesticide and Toxic Substances (H7506C) August 1991. U.S. Environmental Protection Agency, Washington, D.C

United States Environmental Protection Agency (USEPA). 1994. August 24, 1994. *Notice to the Requests for Re-considerations of Carcinogenicity Peer Review Decisions Based on Changes in Pathology Diagnosis*, from P.A. Fenner-Crisp, Acting Deputy Director, Office of Pesticide Programs.

United States Environmental Protection Agency (USEPA). 1995. The Use of the Benchmark Dose Approach in Health Risk Assessment. Risk Assessment Forum, Office of Research and Development, Washington DC.

United States Environmental Protection Agency (USEPA). 1996c. Proposed guidelines for carcinogen risk assessment. Federal Register 61(79):17960-18011.

United States Environmental Protection Agency (USEPA). 1997a. Methyl parathion (O,0-dimethyl O-p-nitrophenyl phosphorothioate). Hazard Identification Committee Report. (http://www.epa.gov/pesticides/op/methyl_parathion/mphed_att1.pdf)

United States Environmental Protection Agency (USEPA) 1997b. 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.

United States Environmental Protection Agency (USEPA). 1997c. Methyl parathion (O,O-dimethyl)-P-nitrophenyl phosphorothioate: Hazard Identification Committee Report.

United States Environmental Protection Agency (USEPA) 1997d. Raw and Processed Food Schedule for Pesticide Tolerance Reassessment. Federal Register 62(149):42020-42030. U.S. Environmental Protection Agency, Washington, D.C.

United States Environmental Protection Agency (USEPA). 1998a. Integrated Risk Information System (IRIS).

United States Environmental Protection Agency (USEPA). 1998b. Increasing Transparency for the Tolerance Reassessment Process; Availability of Preliminary Risk Assessments for Four Organophosphates. Federal Register 63(243): 70126-70127.

United States Environmental Protection Agency (USEPA). 1998c. Hazard Assessment of the Organophosphates (http://www.epa.gov/pesticides/op/methyl_parathion/mp_09.pdf)

Hazard Identification Assessment Review Committee Report. Office of Pesticide Programs, Health Effects Division.

United States Environmental Protection Agency (USEPA). 1999a. Human Health Risk Assessment - Methyl Parathion. USEPA, Office of Pesticide Programs, Health Effects Division (www.epa.gov/pesticides/op/methyl_parathion.htm).

United States Environmental Protection Agency (USEPA). 1999b. Overview of Methyl Parathion Refined Risk Assessment. USEPA, Office of Pesticide Programs.

United States Environmental Protection Agency (USEPA). 1999c. Guidance for identifying pesticide chemicals and other substances that have common mechanism of toxicity. (http://www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/6055.pdf

United States Environmental Protection Agency (USEPA). 2000. Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern. http://www.epa.gov/oppfead1/trac/science/trac2b054.pdf Office of Pesticide Programs. Washington, DC.

United States Environmental Protection Agency (USEPA). 2001. Organophosphate Pesticides: Preliminary OP Cumulative Risk Assessment. Office of Pesticide Programs http://www.epa.gov/pesticides/cumulative/pra-op/

United States Environmental Protection Agency (USEPA) 2002a. Other Cumulative Risk Assessments. (http://www.epa.gov/pesticides/cumulative/other_cum_assessments.htm).Office of Pesticide Programs.

United States Environmental Protection Agency (USEPA) 2002b. Organophosphate Pesticides: Revised OP Cumulative Risk Assessment. Office of Pesticide Programs. http://www.epa.gov/pesticides/cumulative/rra-op/

United States Environmental Protection Agency (USEPA) 2002c. National Center for Environmental Assessment. About NCEA. Benchmark Dose Software v.1.3.1 http://cfpub.epa.gov/ncea/.

Van Bao T., Szabo, I., Ruzicska, P. and Czeizel, A. 1974. Chromosome aberrations in patients suffering acute organic phosphate insecticide intoxication. Humangenetik 24:33-57.

Van Dijk, A. 1988a.^{14}C-parathion-methyl: Absorption, distribution, excretion and metabolism after single and repeated oral administration to rats. RCC Umweltchemie AG, Switzerland, RCC Project #090876. DPR Vol.121-073.

Van Dijk, A. 1988b. ^{14}C-parathion-methyl: Metabolism, absorption, distribution and excretion after repeated oral administration to laying hens. RCC Umweltchemie AG, Switzerland, RCC Project #091798. DPR Vol.121-074, #86617.

Van Dijk, A. 1988c. 14C-parathion-methyl: Metabolism, absorption, distribution and excretion after repeated oral administration to a lactating goat. RCC Umweltchemie AG, Switzerland, RCC Project #091585. DPR Vol.121-074, #86616..

Van Dijk, A. 1990. ^{14}C-Parathion-Methyl. Confined Rotational Study in the Greenhouse. RCC UMWELTCHEMIE, Switzerland, Study No.202162., DPR Vol. 121-077, #86628.

Varnagy, L., and Deli, E. 1985. Comparative teratological study of insecticide, Wofatox 50 EC (50% methyl parathion) on chicken and pheasant fetuses. Jena Anat. Anz. 158:1-3.

Varnagy, L., M. Korzenszky, and T. Fancsi. 1984. Teratological examination of the insecticide methylparathion (Wofatox 50 EC) on pheasant embryos. 1. Morphological study. Vet. Res. Comm. 8:131-139.

Venkataraman, B. V., Naga Rani, M. A., Andrade, C. and Joseph. T. 1994. Correlation of time course of blood cholinesterase activity and toxic manifestations of acute methylparathion in antidote treated rats. Indian J. Physiol. Pharmacol. 38:214-216.

Videira, R. A., Antunes-Madeira, M. C., Lopes, V. I. and Madeira, V. M. 2001. Changes induced by malathion, methylparathion and parathion on membrane lipid physicochemical properties correlate with their toxicity. Biochim. Biophys. Acta. 1511:360-8.

Vijayaraghavan, M. and Nagarajan, B. 1994. Mutagenic potential of acute exposure to organophosphorus and organochlorine compounds. Mutat. Res. 321:103-111.

Ware, G. W., Morgan, D. P., Estesen, B. J. and W. P. Cahill. 1974. Establishment of reentry intervals for organophosphate-treated cotton fields based on human data. II. Azodrin, ethyl and methyl parathion. Arch. Environ. Contam. Toxicol. 2:117-129.

Waters, M. D., Simmon, V. F., Mitchell, A. D., Jorgenson, T. A. and Valencia, R. 1980. An overview of short-term tests for the mutagenic and carcinogenic potential of pesticides. J. Environ. Sci. Health. [B] 15:867-906.

Weiler, M. 1999a. Acute Dietary Neurotoxicity Study with Methyl Parathion in Rats. Covance Laboratiories Inc. Study No. 6222-116, DPR Vol. 121-141, #185732.

Weiler, M. 1999b. 5-Day Dermal Neurotoxicity Study with Methyl parathion. Covance Laboratiories Inc, Madison, WI. Study No. 622-115, DPR vol.121-134, # 185725.

Wester, R.C. and Maibach, H. I. 1985. In vivo percutaneous absorption and decontamination of pesticides in humans. J. Toxicol. Environ. Health.16:25-37.

Williams, M. W., Fuyat, H. N. and Fitzhugh, O. G. 1959. The subacute toxicity of four organic phosphates to dogs. Toxicol. Appl. Pharmacol. 1:1-7.

Willis, W. O., de Peyster, A., Molgaard, C. A., Walker, C. and MacKendrick, T. 1993. Pregnancy outcome among women exposed to pesticides through work or residence in an agricultural area. J. Occup. Med. 35:943-949.

Wilmes, R. 1987a. Parathion Methyl:Hydrolysis Studies. Baeyr AG. Study No. 2883. DPR Vol. 121-059, #70134.

Wilmes, R. 1987b. Parathion Methyl:Photodegradation on Water. Baeyr AG. Study No. 2884. DPR Vol. 121-059, #70133.

Wilmes, R. 1987c. Parathion Methyl:Photodegradation on Soil. Baeyr AG. Study No. 2885. DPR Vol. 121-059, #70132.

World Health Organization (WHO). 1984. Pesticide Residues in Food. FAO Plant Production and Protection Paper No. 67. Food and Agriculture Organization and The World Health Organization, Switzerland. pp. 685-688.

World Health Organization (WHO). 1986. Organophosphorus Insecticides: A General Introduction. International Programme on Chemical Safety (IPCS) Environmental Health Criteria 63. World Health Organization, Geneva.

Xie, W., Stribley, J.A., Chatonnet, A., Wilder, P.J., Rizzino, A., McComb, R.D., Taylor, P., Hinrichs, S.H. and Lockridge, O. 2000. Postnatal developmental delay and supersensitivity to organophosphate in gene-targeted mice lacking acetylcholinesterase. J. Pharmacol. Exp. Ther. 293:896-902.

Yamamoto, T., Egashira, T. Yoshida, T. and Kuroiwa. Y. 1982. Comparison of the effect of an equimolar and low dose of fenitrothion and methylparathion on their own metabolism in rat liver. J. Toxicol. Sci. 7:35-41.

Yamamoto, T., Egashira, T., Yoshida, T. and Kuroiwa, Y. 1983. Comparative metabolism of fenitrothion and methylparathion in male rats. Acta Pharmacol. et Toxicol. 53:96-102.

Zhang, H. X. and Sultatos, L. G. 1991. Biotransformation of the organophosphorus insecticides parathion and methyl parathion in male and female rat livers perfused *in situ*. Drug Metab. Dispos. 19:473-477.

Zhu, H., Rockhold, R.W., Baker, R.C., Kramer, R.E. and Ho, I.K. 2001. Effects of single or repeated dermal exposure to methyl parathion on behavior and blood cholinesterase activity in rats. J Biomed Sci. 8:467-474.

ATTACHMENT I: DEEM Acute Point Estimate Dietary Exposure Assessment

I.1. POINT ESTIMATE RESIDUE DATA FILE

```
Filename: D:\svetlana\Methyl Parathion\MPacutePE\Acute Point Est-FINAL
v.5\Acute_refine_values_v5.RS7
Chemical: methyl parathion
RfD(Chronic): 1 mg/kg bw/day  NOEL(Chronic): 1 mg/kg bw/day
RfD(Acute): .00025 mg/kg bw/day  NOEL(Acute):  .025 mg/kg bw/day
Date created/last modified: 10-18-2001/16:02:36/14         Program ver. 7.76
Comment: test
```

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
265	15	Barley	0.031000	1.000	1.000	Surrog
		Full comment: Surrogate wheat; PDP				
258	6C	Beans-dry-blackeye peas/cowpea	0.380000	1.000	1.000	Surrog
		Full comment: Surrogate processed green beans				
249	6C	Beans-dry-broadbeans	0.380000	1.000	1.000	PDP; N
		Full comment: PDP; No.1598, 66 det.0.003-0.38				
259	6C	Beans-dry-garbanzo/chick pea	0.380000	1.000	1.000	LOD=0.
		Full comment: LOD=0.002-0.013				
227	6C	Beans-dry-great northern	0.380000	1.000	1.000	--//--
256	O	Beans-dry-hyacinth	0.380000	1.000	1.000	--//--
228	6C	Beans-dry-kidney	0.380000	1.000	1.000	--//--
229	6C	Beans-dry-lima	0.380000	1.000	1.000	--//--
230	6C	Beans-dry-navy (pea)	0.380000	1.000	1.000	--//--
231	6C	Beans-dry-other	0.380000	1.000	1.000	--//--
251	6C	Beans-dry-pigeon beans	0.380000	1.000	1.000	--//--
232	6C	Beans-dry-pinto	0.380000	1.000	1.000	--//--
267	15	Corn grain-bran	0.003000	1.000	1.000	PDP; A
		Full comment: PDP; All n.d.; LOD=0.002-0.013; No.673				
266	15	Corn grain-endosperm	0.003000	1.000	1.000	--//--
289	15	Corn grain-oil	0.003000	1.000	1.000	--//--
268	15	Corn grain/sugar/hfcs	0.008000	1.500	1.000	PDP; A
		Full comment: PDP; All n.d.; LOD =0.008; No.298; syrup				
388	15	Corn grain/sugar-molasses	0.008000	1.500	1.000	PDP; A
		Full comment: PDP; All n.d.; LOD =0.008; No.298; syrup				
237	15	Corn/pop	0.003000	1.000	1.000	PDP; A
		Full comment: PDP; All n.d.; LOD=0.002-0.013; No.673				
238	15	Corn/sweet	0.003000	1.000	1.000	in CA
		Full comment: in CA sweet corn LOD=0.003, No.238				
291	O	Cottonseed-meal	0.660000	1.000	1.000	Fild T
		Full comment: Fild Trial, No.37; LOD=0.01 all> LOD				
290	O	Cottonseed-oil	0.660000	1.000	1.000	Fild T
		Full comment: Fild Trial, No.37; LOD=0.01 all> LOD				
269	15	Oats	0.006000	1.000	1.000	PDP; a
		Full comment: PDP; all n.d.; LOD=0.006, No.332				
206	3	Onions-dehydrated or dried	0.010000	9.000	1.000	DPR,LO
		Full comment: DPR,LOD=0.01,No.1221 MB; all n.d.				
205	3	Onions-dry-bulb (cipollini)	0.010000	1.000	1.000	--//--
262	3	Onions-green	0.030000	1.000	1.000	DPR MB
		Full comment: DPR MB 2 det. No.95, LOD=0.02				
240	6C	Peas (garden)-dry	0.007000	1.000	1.000	12 det
		Full comment: 12 det; sweet peas, 0.004-0.007; LOD=0.002-0.006				
47	14	Pecans	0.050000	1.000	1.000	Fild T
		Full comment: Fild Trial, No.4; LOD=0.05, all n.d.				
210	1C	Potatoes/white-dry	0.003000	6.500	1.000	PDP; A

		Full comment: PDP; All n.d.; LOD=0.002-0.013				
209	1C	Potatoes/white-peeled	0.003000	1.000	1.000	No. 67
		Full comment: No. 673+707				
211	1C	Potatoes/white-peel only	0.003000	1.000	1.000	CA LOD
		Full comment: CA LOD=0.003; No. 420				
208	1C	Potatoes/white-unspecified	0.003000	1.000	1.000	
207	1C	Potatoes/white-whole	0.003000	1.000	1.000	
408	15	Rice-bran	0.110000	1.000	1.000	FDA '9
		Full comment: FDA '94-97; No.182; 4 det. 0.04-0.11				
271	15	Rice-milled (white)	0.110000	1.000	1.000	LOD=0.
		Full comment: LOD=0.0033				
270	15	Rice-rough (brown)	0.110000	1.000	1.000	--//--
409	15	Rice-wild	0.110000	1.000	1.000	--//--
303	6A	Soybean-other	0.004000	1.000	1.000	PDP; a
		Full comment: PDP; all n.d.; No.159;589				
307	6A	Soybeans-flour (defatted)	0.004000	1.000	1.000	LOD=0.
		Full comment: LOD=0.004				
306	6A	Soybeans-flour (low fat)	0.004000	1.000	1.000	--//--
305	6A	Soybeans-flour (full fat)	0.004000	1.000	1.000	--//--
304	6A	Soybeans-mature seeds dry	0.004000	1.000	1.000	--//--
297	6A	Soybeans-oil	0.004000	1.000	1.000	--//--
482	O	Soybeans-protein isolate	0.004000	1.000	1.000	--//--
255	6A	Soybeans-sprouted seeds	0.004000	0.330	1.000	--//--
431	14	Walnut oil	0.050000	1.000	1.000	Fild T
		Full comment: Fild Trial, No 6; LOD=0.05, all n.d.				
48	14	Walnuts	0.050000	1.000	1.000	Fild T
		Full comment: Fild Trial, No 6; LOD=0.05, all n.d.				
278	15	Wheat-bran	0.031000	1.000	1.000	PDP; 2
		Full comment: PDP; 2xDet.=0.01-0.031; No.340+623				
279	15	Wheat-flour	0.031000	1.000	1.000	LOD=0.
		Full comment: LOD=0.006				
277	15	Wheat-germ	0.031000	1.000	1.000	--//--
437	15	Wheat-germ oil	0.031000	1.000	1.000	--//--
276	15	Wheat-rough	0.031000	1.000	1.000	--//--

I.2. ACUTE POINT ESTIMATE EXPOSURES AND RISK ESTIMATES

```
California Department of Pesticide Regulation                        Ver. 7.73
DEEM ACUTE Analysis for METHYL PARATHION                          (1994-98 data)
Residue file: Acute_refine_values_v5.RS7          Adjustment factor #2 NOT used.
Analysis Date: 08-14-2001/13:49:27    Residue file dated: 08-14-2001/13:42:02/14
NOEL (Acute) =   0.025000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "Acute Dietary  Exposure (Point Estimate) - Methyl parathion 08/1
4/01  Rice- FDA  "
================================================================================
```

U.S. Population — Daily Exposure Analysis /a (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000167	0.000168
Standard Deviation	0.000211	0.000211
Standard Error of mean	0.000001	0.000001
Margin of Exposure 2/	149	148
Percent of aRfD	66.97	67.19

Percent of Person-Days that are User-Days = 99.68%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000036	14.48	690	90.00	0.000356	142.55	70
20.00	0.000052	20.83	480	95.00	0.000505	202.09	49
30.00	0.000067	26.97	370	97.50	0.000700	279.84	35
40.00	0.000084	33.54	298	99.00	0.001034	413.49	24
50.00	0.000104	41.54	240	99.50	0.001291	516.51	19
60.00	0.000130	52.05	192	99.75	0.001623	649.33	15
70.00	0.000170	67.86	147	99.90	0.002188	875.30	11
80.00	0.000232	92.97	107				

Western region — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000200	0.000201
Standard Deviation	0.000259	0.000259
Standard Error of mean	0.000003	0.000003
Margin of Exposure	125	124
Percent of aRfD	79.87	80.25

Percent of Person-Days that are User-Days = 99.53%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000038	15.20	657	90.00	0.000437	174.99	57
20.00	0.000056	22.53	443	95.00	0.000608	243.22	41
30.00	0.000073	29.15	343	97.50	0.000885	353.94	28
40.00	0.000094	37.60	265	99.00	0.001284	513.72	19
50.00	0.000120	47.84	209	99.50	0.001600	639.98	15

60.00	0.000156	62.44	160	99.75	0.001989	795.43	12
70.00	0.000205	82.10	121	99.90	0.002462	984.96	10
80.00	0.000280	112.03	89				

Hispanics — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000267	0.000268
Standard Deviation	0.000350	0.000351
Standard Error of mean	0.000005	0.000005
Margin of Exposure	93	93
Percent of aRfD	106.76	107.28

Percent of Person-Days that are User-Days = 99.52%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000038	15.02	665	90.00	0.000632	252.88	39
20.00	0.000059	23.66	422	95.00	0.000936	374.33	26
30.00	0.000085	34.12	293	97.50	0.001216	486.45	20
40.00	0.000113	45.07	221	99.00	0.001615	645.81	15
50.00	0.000147	58.88	169	99.50	0.001980	792.06	12
60.00	0.000199	79.74	125	99.75	0.002499	999.63	10
70.00	0.000277	110.74	90	99.90	0.003550	1419.85	7
80.00	0.000380	152.13	65				

Non-hispanic whites — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000145	0.000145
Standard Deviation	0.000157	0.000157
Standard Error of mean	0.000001	0.000001
Margin of Exposure	172	172
Percent of aRfD	57.83	57.97

Percent of Person-Days that are User-Days = 99.76%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000037	14.85	673	90.00	0.000301	120.54	82
20.00	0.000052	20.79	480	95.00	0.000417	166.83	59
30.00	0.000066	26.28	380	97.50	0.000547	218.74	45
40.00	0.000080	32.11	311	99.00	0.000767	306.92	32
50.00	0.000098	39.01	256	99.50	0.000966	386.48	25
60.00	0.000120	47.86	208	99.75	0.001192	476.80	20
70.00	0.000151	60.44	165	99.90	0.001529	611.66	16
80.00	0.000202	80.75	123				

Non-hispanic blacks — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000170	0.000171
Standard Deviation	0.000237	0.000237
Standard Error of mean	0.000003	0.000003
Margin of Exposure	147	146
Percent of aRfD	67.96	68.31

Percent of Person-Days that are User-Days = 99.49%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000026	10.25	975	90.00	0.000377	150.83	66
20.00	0.000042	16.84	593	95.00	0.000540	215.81	46
30.00	0.000059	23.57	424	97.50	0.000755	302.08	33
40.00	0.000077	30.65	326	99.00	0.001064	425.60	23
50.00	0.000100	39.88	250	99.50	0.001392	556.61	17
60.00	0.000128	51.38	194	99.75	0.001995	797.82	12
70.00	0.000173	69.28	144	99.90	0.002752	1100.62	9
80.00	0.000238	95.30	104				

Non-hisp/non-white/non-black

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000297	0.000299
Standard Deviation	0.000312	0.000312
Standard Error of mean	0.000007	0.000007
Margin of Exposure	84	83
Percent of aRfD	118.83	119.78

Percent of Person-Days that are User-Days = 99.21%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000054	21.79	458	90.00	0.000606	242.29	41
20.00	0.000087	34.88	286	95.00	0.000828	331.20	30
30.00	0.000127	50.78	196	97.50	0.001138	455.39	21
40.00	0.000174	69.73	143	99.00	0.001616	646.49	15
50.00	0.000223	89.04	112	99.50	0.002000	799.99	12
60.00	0.000268	107.17	93	99.75	0.002432	972.75	10
70.00	0.000334	133.71	74	99.90	0.002443	977.32	10
80.00	0.000431	172.43	57				

All infants

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000171	0.000192
Standard Deviation	0.000258	0.000266
Standard Error of mean	0.000005	0.000005
Margin of Exposure	146	130
Percent of aRfD	68.45	76.85

Percent of Person-Days that are User-Days = 89.07%

Estimated percentile of user-days falling below calculated exposure

in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000011	4.52	2,212	90.00	0.000425	170.09	58
20.00	0.000024	9.67	1,033	95.00	0.000638	255.34	39
30.00	0.000060	23.94	417	97.50	0.000864	345.51	28
40.00	0.000090	36.03	277	99.00	0.001348	539.08	18
50.00	0.000119	47.79	209	99.50	0.001582	632.96	15
60.00	0.000152	60.68	164	99.75	0.002316	926.58	10
70.00	0.000197	78.75	126	99.90	0.002754	1101.66	9
80.00	0.000287	114.74	87				

Nursing infants (<1 yr old)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000088	0.000146
Standard Deviation	0.000168	0.000195
Standard Error of mean	0.000006	0.000008
Margin of Exposure	282	171
Percent of aRfD	35.39	58.30

Percent of Person-Days that are User-Days = 60.70%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000005	2.11	4,739	90.00	0.000368	147.01	68
20.00	0.000012	4.75	2,106	95.00	0.000496	198.22	50
30.00	0.000026	10.42	959	97.50	0.000653	261.40	38
40.00	0.000055	22.14	451	99.00	0.001157	462.66	21
50.00	0.000081	32.41	308	99.50	0.001360	544.12	18
60.00	0.000120	48.03	208	99.75	0.001426	570.27	17
70.00	0.000164	65.78	152	99.90	0.001435	574.16	17
80.00	0.000227	90.87	110				

Non-nursing infants (<1 yr old)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000203	0.000203
Standard Deviation	0.000279	0.000279
Standard Error of mean	0.000006	0.000006
Margin of Exposure	123	123
Percent of aRfD	81.01	81.14

Percent of Person-Days that are User-Days = 99.84%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000013	5.17	1,933	90.00	0.000437	174.99	57
20.00	0.000030	12.05	830	95.00	0.000667	266.75	37
30.00	0.000069	27.74	360	97.50	0.000917	366.64	27
40.00	0.000097	38.83	257	99.00	0.001404	561.60	17
50.00	0.000125	50.12	199	99.50	0.001943	777.06	12
60.00	0.000156	62.23	160	99.75	0.002343	937.02	10

70.00	0.000203	81.30	123	99.90	0.002772	1108.63	9
80.00	0.000293	117.29	85				

Children 1-6 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000354	0.000354
Standard Deviation	0.000356	0.000356
Standard Error of mean	0.000003	0.000003
Margin of Exposure	70	70
Percent of aRfD	141.51	141.60

Percent of Person-Days that are User-Days = 99.93%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000115	45.82	218	90.00	0.000681	272.38	36
20.00	0.000150	60.19	166	95.00	0.001030	411.82	24
30.00	0.000182	72.90	137	97.50	0.001361	544.45	18
40.00	0.000215	86.19	116	99.00	0.001835	733.89	13
50.00	0.000252	100.85	99	99.50	0.002302	920.67	10
60.00	0.000296	118.34	84	99.75	0.002818	1127.10	8
70.00	0.000354	141.77	70	99.90	0.003421	1368.41	7
80.00	0.000452	180.83	55				

Children 7-12 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000238	0.000238
Standard Deviation	0.000251	0.000251
Standard Error of mean	0.000005	0.000005
Margin of Exposure	105	105
Percent of aRfD	95.05	95.05

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000075	30.15	331	90.00	0.000457	182.99	54
20.00	0.000101	40.48	247	95.00	0.000650	259.89	38
30.00	0.000125	49.94	200	97.50	0.000874	349.61	28
40.00	0.000146	58.32	171	99.00	0.001151	460.53	21
50.00	0.000170	68.03	146	99.50	0.001519	607.61	16
60.00	0.000200	80.10	124	99.75	0.001850	740.00	13
70.00	0.000244	97.47	102	99.90	0.003195	1277.88	7
80.00	0.000304	121.46	82				

Females 13+ (preg/not nursing) — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000161	0.000165
Standard Deviation	0.000174	0.000174

Standard Error of mean	0.000015	0.000015
Margin of Exposure	155	151
Percent of aRfD	64.33	66.00

Percent of Person-Days that are User-Days = 97.47%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000037	14.98	667	90.00	0.000444	177.77	56
20.00	0.000055	22.04	453	95.00	0.000564	225.46	44
30.00	0.000064	25.54	391	97.50	0.000677	270.95	36
40.00	0.000083	33.01	302	99.00	0.000801	320.31	31
50.00	0.000091	36.52	273	99.50	0.000812	324.61	30
60.00	0.000117	46.65	214	99.75	0.000813	325.07	30
70.00	0.000148	59.39	168	99.90	0.000813	325.35	30
80.00	0.000253	101.39	98				

Females 13+ (nursing)

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000191	0.000191
Standard Deviation	0.000218	0.000218
Standard Error of mean	0.000024	0.000024
Margin of Exposure	130	130
Percent of aRfD	76.57	76.57

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000046	18.57	538	90.00	0.000438	175.20	57
20.00	0.000059	23.65	422	95.00	0.000531	212.23	47
30.00	0.000085	33.85	295	97.50	0.001063	425.38	23
40.00	0.000105	41.92	238	99.00	0.001322	528.67	18
50.00	0.000124	49.79	200	99.50	0.001323	529.35	18
60.00	0.000157	62.61	159	99.75	0.001324	529.69	18
70.00	0.000197	78.84	126	99.90	0.001325	529.90	18
80.00	0.000254	101.44	98				

Females 13-19 (not preg or nursing)

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000150	0.000151
Standard Deviation	0.000185	0.000185
Standard Error of mean	0.000005	0.000005
Margin of Exposure	166	165
Percent of aRfD	60.16	60.28

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000039	15.65	638	90.00	0.000312	124.95	80
20.00	0.000056	22.34	447	95.00	0.000443	177.25	56
30.00	0.000069	27.52	363	97.50	0.000580	232.04	43
40.00	0.000082	33.00	303	99.00	0.000906	362.23	27
50.00	0.000100	40.03	249	99.50	0.001063	425.24	23
60.00	0.000119	47.63	209	99.75	0.001989	795.71	12
70.00	0.000145	58.15	171	99.90	0.002000	800.17	12
80.00	0.000195	77.81	128				

Females 20+ (not preg or nursing)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000117	0.000117
Standard Deviation	0.000136	0.000136
Standard Error of mean	0.000001	0.000001
Margin of Exposure	214	214
Percent of aRfD	46.61	46.73

Percent of Person-Days that are User-Days = 99.75%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000028	11.31	884	90.00	0.000250	100.06	99
20.00	0.000041	16.21	617	95.00	0.000354	141.59	70
30.00	0.000052	20.76	481	97.50	0.000477	190.77	52
40.00	0.000064	25.46	392	99.00	0.000662	264.94	37
50.00	0.000076	30.54	327	99.50	0.000856	342.51	29
60.00	0.000092	36.80	271	99.75	0.001050	419.99	23
70.00	0.000114	45.58	219	99.90	0.001218	487.07	20
80.00	0.000154	61.68	162				

Females 13-50 yrs

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000132	0.000133
Standard Deviation	0.000157	0.000157
Standard Error of mean	0.000002	0.000002
Margin of Exposure	189	188
Percent of aRfD	52.89	53.07

Percent of Person-Days that are User-Days = 99.66%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000032	12.95	772	90.00	0.000281	112.24	89
20.00	0.000046	18.42	542	95.00	0.000402	160.69	62
30.00	0.000059	23.51	425	97.50	0.000532	212.60	47
40.00	0.000072	28.93	345	99.00	0.000773	309.14	32
50.00	0.000087	34.92	286	99.50	0.000999	399.60	25
60.00	0.000106	42.25	236	99.75	0.001185	474.11	21
70.00	0.000130	52.03	192	99.90	0.001971	788.22	12
80.00	0.000177	70.70	141				

Males 13-19 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000186	0.000186
Standard Deviation	0.000236	0.000236
Standard Error of mean	0.000007	0.000007
Margin of Exposure	134	134
Percent of aRfD	74.40	74.40

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000054	21.63	462	90.00	0.000384	153.58	65
20.00	0.000070	27.85	359	95.00	0.000567	226.65	44
30.00	0.000085	34.06	293	97.50	0.000773	309.08	32
40.00	0.000101	40.33	247	99.00	0.001069	427.70	23
50.00	0.000120	48.11	207	99.50	0.001155	461.92	21
60.00	0.000143	57.28	174	99.75	0.001194	477.41	20
70.00	0.000181	72.50	137	99.90	0.003213	1285.31	7
80.00	0.000238	95.09	105				

Males 20+ yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000150	0.000150
Standard Deviation	0.000169	0.000169
Standard Error of mean	0.000002	0.000002
Margin of Exposure	166	166
Percent of aRfD	60.07	60.14

Percent of Person-Days that are User-Days = 99.88%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000037	14.87	672	90.00	0.000320	128.06	78
20.00	0.000051	20.59	485	95.00	0.000461	184.43	54
30.00	0.000066	26.33	379	97.50	0.000607	242.93	41
40.00	0.000080	31.89	313	99.00	0.000846	338.24	29
50.00	0.000097	38.62	258	99.50	0.001039	415.77	24
60.00	0.000118	47.16	212	99.75	0.001265	505.85	19
70.00	0.000150	60.10	166	99.90	0.001568	627.27	15
80.00	0.000207	82.79	120				

Seniors 55+

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User

Mean	0.000109	0.000109
Standard Deviation	0.000130	0.000130
Standard Error of mean	0.000002	0.000002
Margin of Exposure	228	228
Percent of aRfD	43.70	43.76

Percent of Person-Days that are User-Days = 99.87%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000028	11.26	888	90.00	0.000228	91.13	109
20.00	0.000039	15.62	640	95.00	0.000338	135.24	73
30.00	0.000049	19.53	512	97.50	0.000465	186.03	53
40.00	0.000059	23.77	420	99.00	0.000642	256.82	38
50.00	0.000070	28.03	356	99.50	0.000903	361.31	27
60.00	0.000084	33.48	298	99.75	0.001063	425.25	23
70.00	0.000103	41.16	242	99.90	0.001250	500.15	19
80.00	0.000141	56.26	177				

ATTACHMENT II: DEEM Acute Monte Carlo Dietary Exposure Assessment

II.1. MONTE CARLO RESIDUE DATA

```
Filename: D:\svetlana\Methyl Parathion\MPacuteMC\Monte Carlo -Final v9 a+ PCT\Monte Carlo_9.RS7
Chemical: methyl parathion
RfD(Chronic): 1 mg/kg bw/day  NOEL(Chronic): 1 mg/kg bw/day
RfD(Acute): .00025 mg/kg bw/day  NOEL(Acute):  .025 mg/kg bw/day
Date created/last modified: 10-12-2001/13:51:32/14         Program ver. 7.76
Comment: test
--------------------------------------------------------------------------------
RDL indices and parameters for Monte Carlo Analysis:
Index Dist Parameter #1        Param #2  Param #3  Comment
  #   Code
----- ---- ------------        --------  --------  -------
  1    6   GreenBeans1.rdf
  2    6   Cornsweet2.rdf
  3    6   CornSyrup3.rdf
  4    6   Oats4.rdf
  5    6   OnionsDry5.rdf
  6    6   OnionsGreen6.rdf
  7    6   PeasDry7.rdf
  8    6   Potatoes8.rdf
  9    6   Soybeans9.rdf
  10   6   Wheat10.rdf

Food Crop Food Name                        Def Res     Adj.Factors  RDL  Comment
Code  Grp                                   (ppm)       #1     #2   Pntr
---- ---- -------------------------------  ----------  ------ ------ ---  -------
 265 15   Barley                            0.031000   1.000  1.000      Surrog
    Full comment: Surrogate wheat; PDP
 258 6C   Beans-dry-blackeye peas/cowpea    0.380000   1.000  1.000   1  Surrog
    Full comment: Surrogate green beans
 249 6C   Beans-dry-broadbeans              0.380000   1.000  1.000   1  PDP=15
    Full comment: PDP=1597;66 det.,LOD=0.002,PCT=4%
 259 6C   Beans-dry-garbanzo/chick pea      0.380000   1.000  1.000   1  LOD=0.
    Full comment: LOD=0.002-0.013 national
 227 6C   Beans-dry-great northern          0.380000   1.000  1.000   1  --//--
 256 O    Beans-dry-hyacinth                0.380000   1.000  1.000   1  --//--
 228 6C   Beans-dry-kidney                  0.380000   1.000  1.000   1  --//--
 229 6C   Beans-dry-lima                    0.380000   1.000  1.000   1  --//--
 230 6C   Beans-dry-navy (pea)              0.380000   1.000  1.000   1  --//--
 231 6C   Beans-dry-other                   0.380000   1.000  1.000   1  --//--
 251 6C   Beans-dry-pigeon beans            0.380000   1.000  1.000   1  --//--
 232 6C   Beans-dry-pinto                   0.380000   1.000  1.000   1  --//--
 267 15   Corn grain-bran                   0.003000   1.000  1.000   2  PDP-CA
    Full comment: PDP-CA=248, all n.d.; PCT=7%
 266 15   Corn grain-endosperm              0.003000   1.000  1.000   2  --//--
 289 15   Corn grain-oil                    0.003000   1.000  1.000   2  -//--
 268 15   Corn grain/sugar/hfcs             0.008000   1.500  1.000   3  PDP=45
    Full comment: PDP=454; All n.d.; LOD =0.008;PCT=7%
 388 15   Corn grain/sugar-molasses         0.008000   1.500  1.000   3  --//--
 237 15   Corn/pop                          0.003000   1.000  1.000   2  PDP-CA
    Full comment: PDP-CA=248, n.d.; PCT=7%
 238 15   Corn/sweet                        0.003000   1.000  1.000   2  --//-
    Full comment: --//- processed sweet corn data
 291 O    Cottonseed-meal                   0.660000   1.000  1.000      Fild T
    Full comment: Fild Trial, No.13; LOD=0.01;  x 17%CT
 290 O    Cottonseed-oil                    0.660000   1.000  1.000      Fild T
    Full comment: Fild Trial, No.13; LOD=0.01;  x 17%CT
 269 15   Oats                              0.006000   1.000  1.000   4  PDP=33
    Full comment: PDP=332,LOD=0.006, all n.d.,PCT=1%
 206 3    Onions-dehydrated or dried        0.010000   9.000  1.000   5  DPR,LO
    Full comment: DPR,LOD=0.01,No.1221 MB;PCT=9%
 205 3    Onions-dry-bulb (cipollini)       0.010000   1.000  1.000   5  DPR,LO
    Full comment: DPR,LOD=0.01,No.1221 MB, PCT=9%
 262 3    Onions-green                      0.050000   1.000  1.000   6  DPR MB
```

```
   Full comment: DPR MB 2 det. No.744, LOD=0.02=9%
240 6C   Peas (garden)-dry                  0.007000   1.000  1.000   7  12 det
   Full comment: 12 det. surr sweet peas, 0.004-0.007; LOD=0.002-0.006; No.1025
 47 14   Pecans                            0.050000   1.000  1.000      Fild T
   Full comment: Fild Trial, No.4; LOD=0.05, all n.d.
210 1C   Potatoes/white-dry                0.003000   6.500  1.000      PDP; A
   Full comment: PDP; All n.d.; LOD=0.002-0.013
209 1C   Potatoes/white-peeled             0.003000   1.000  1.000   8  No.140
   Full comment: No.1401 national
211 1C   Potatoes/white-peel only          0.003000   1.000  1.000   8  CA LOD
   Full comment: CA LOD=0.003; No. 325; PCT=2%
208 1C   Potatoes/white-unspecified        0.003000   1.000  1.000   8
207 1C   Potatoes/white-whole              0.003000   1.000  1.000   8
408 15   Rice-bran                         0.110000   1.000  1.000      FDA ('
   Full comment: FDA ('94-97); No.182; 4 det 0.04-011
271 15   Rice-milled (white)               0.110000   1.000  1.000      PCT=12
   Full comment: PCT=12% , LOD=0.0033
270 15   Rice-rough (brown)                0.110000   1.000  1.000      --\\--
409 15   Rice-wild                         0.110000   1.000  1.000      --\\--
303 6A   Soybean-other                     0.004000   1.000  1.000   9  PDP; a
   Full comment: PDP; all n.d.; No.748; PCT=1%
307 6A   Soybeans-flour (defatted)         0.004000   1.000  1.000   9  LOD=0.
   Full comment: LOD=0.004
306 6A   Soybeans-flour (low fat)          0.004000   1.000  1.000   9  --//--
305 6A   Soybeans-flour (full fat)         0.004000   1.000  1.000   9  --//--
304 6A   Soybeans-mature seeds dry         0.004000   1.000  1.000   9  --//--
297 6A   Soybeans-oil                      0.004000   1.000  1.000   9  --//--
482 O    Soybeans-protein isolate          0.004000   1.000  1.000   9  --//--
255 6A   Soybeans-sprouted seeds           0.004000   0.330  1.000   9  --//--
431 14   Walnut oil                        0.050000   1.000  1.000      Fild T
   Full comment: Fild Trial, No 6; LOD=0.05, all n.d.
 48 14   Walnuts                           0.050000   1.000  1.000      Fild T
   Full comment: Fild Trial, No 6; LOD=0.05, all n.d.
278 15   Wheat-bran                        0.031000   1.000  1.000  10  PDP; 2
   Full comment: PDP; 2xDet.=0.01-0.031; No.1563
279 15   Wheat-flour                       0.031000   1.000  1.000  10  LOD=0.
   Full comment: LOD=0.006; PCT=2%
277 15   Wheat-germ                        0.031000   1.000  1.000  10  --//--
437 15   Wheat-germ oil                    0.031000   1.000  1.000  10  --//--
276 15   Wheat-rough                       0.031000   1.000  1.000  10  --//--
```

II.2. MONTE CARLO RESIDUE DATA FILES

Acute Scenario I - No PCT Adjustments

RDF1
GREEN BEANS PROCESSED for BEANS-DRY
TOTALNZ=66
TOTALZ=0
TOTALLOD=1531 LODRES=0.002

0.003	0.022
0.032	0.031
0.01	0.01
0.01	0.01
0.01	0.01
0.022	0.01
0.039	0.27
0.01	0.034
0.01	0.005
0.11	0.042
0.38	0.01
0.003	0.024
0.036	0.035
0.008	0.054
0.008	0.078
0.008	0.005
0.019	0.01
0.23	0.01
0.003	0.03
0.067	0.032
0.035	0.022
0.009	0.043

0.01
0.024
0.014
0.003
0.018
0.016
0.01
0.005
0.017
0.079
0.005
0.009
0.005
0.005
0.01
0.005
0.022
0.022
0.022
0.055
0.022
0.092

RDF2
CORN SWEET PROCESSED
TOTALNZ=0
TOTALZ=0
TOTALLOD=248 LODRES=0.003

RDF3
CORN SYRUP
TOTALNZ=0
TOTALZ=0
TOTALLOD=454 LODRES=0.008

RDF4
TOTALNZ=0
TOTALZ=0
TOTALLOD=332 LODRES=0.006

RDF5
ONIONS DRY
TOTALNZ=0
TOTALZ=0
TOTALLOD=1221 LODRES=0.01

RDF6
ONIONS GREEN
TOTALNZ=2
TOTALZ=0
TOTALLOD=742 LODRES=0.02
0.03
0.05

RDF7
PEAS SWEET PROCESSED
(for DRY PEAS)
TOTALNZ=12
TOTALZ=0

0.005	0.004
0.005	0.004
0.005	0.004
0.005	0.004
0.007	0.004
0.007	
0.004	

RDF8
POTATOES
TOTALNZ=0
TOTALZ=0
TOTALLOD=325 LODRES=0.003

RDF9
SOYBEANS
TOTALNZ=0
TOTALZ=0
TOTALLOD=748 LODRES=0.004

RDF10
WHEAT
TOTALNZ=2
TOTALZ=0
TOTALLOD=1561 LODRES=0.006
0.01
0.031

Acute Scenario II - with PCT Adjustments

RDF1
GREEN BEANS PROCESSED for BEANS-DRY
TOTALNZ=66
TOTALZ=1531
TOTALLOD=0 LODRES=0.002
0.003 0.022
0.032 0.031
0.01 0.01
0.01 0.01
0.01 0.01
0.022 0.01
0.039 0.27
0.01 0.034
0.01 0.005
0.11 0.042
0.38 0.01
0.003 0.024
0.036 0.035
0.008 0.054
0.008 0.078
0.008 0.005
0.019 0.01
0.23 0.01
0.003 0.03
0.067 0.032
0.035 0.022
0.009 0.043
0.01 0.005
0.024 0.005
0.014 0.01
0.003 0.005
0.018 0.022
0.016 0.022
0.01 0.022
0.005 0.055
0.017 0.022
0.079 0.092

RDF2
CORN SWEET PROCESSED
TOTALNZ=0
TOTALZ=230
TOTALLOD=18 LODRES=0.003

RDF3
CORN SYRUP
TOTALNZ=0
TOTALZ=422
TOTALLOD=32 LODRES=0.008

RDF4
OATS
TOTALNZ=0
TOTALZ=328
TOTALLOD=4 LODRES=0.006

RDF5
ONIONS DRY
TOTALNZ=0
TOTALZ=1111
TOTALLOD=110 LODRES=0.01

RDF6
ONIONS GREEN
TOTALNZ=2
TOTALZ=677
TOTALLOD=65 LODRES=0.02
0.03
0.05

0.005
0.009

RDF7
PEAS SWEET PROCESSED for DRY PEAS)
TOTALNZ=12
TOTALZ=1399
TOTALLOD=47 LODRES=0.002

0.005	0.004
0.005	0.004
0.005	0.004
0.005	0.004
0.007	0.004
0.007	0.004

RDF8
POTATOES
TOTALNZ=0
TOTALZ=318
TOTALLOD=7 LODRES=0.003

RDF9
SOYBEANS
TOTALNZ=0
TOTALZ=740
TOTALLOD=8 LODRES=0.004

RDF10
WHEAT
TOTALNZ=2
TOTALZ=1531
TOTALLOD=30 LODRES=0.006
0.01
0.031

II.3. MONTE CARLO DIETARY EXPOSURES AND RISK ESTIMATES (NO PCT)

California Department of Pesticide Regulation Ver. 7.73
DEEM ACUTE Analysis for METHYL PARATHION (1994-98 data)
Residue file: Monte Carlo_10.RS7 Adjustment factor #2 NOT used.
Analysis Date: 10-15-2001/16:34:32 Residue file dated: 10-15-2001/16:07:59/14
NOEL (Acute) = 0.025000 mg/kg body-wt/day
Acute Reference Dose (aRfD) = 0.000250 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500 MC list in residue file MC seed = 10
Run Comment: "Acute Monte Carlo 10; No PCT adjustment to any of the 13 commod
ities with Methyl Parathion registrations in CA"

U.S. Population — Daily Exposure Analysis /a (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000085	0.000085
Standard Deviation	0.000105	0.000105
Margin of Exposure 2/	294	294
Percent of aRfD	33.90	34.01

Percent of Person-Days that are User-Days = 99.68%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000018	7.09	1,410	90.00	0.000183	73.37	136
20.00	0.000025	10.20	980	95.00	0.000264	105.56	94
30.00	0.000033	13.22	756	97.50	0.000364	145.43	68
40.00	0.000042	16.60	602	99.00	0.000526	210.23	47
50.00	0.000052	20.86	479	99.50	0.000662	264.65	37
60.00	0.000066	26.48	377	99.75	0.000801	320.43	31
70.00	0.000086	34.44	290	99.90	0.000985	394.09	25
80.00	0.000118	47.23	211				

Western region — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000101	0.000101
Standard Deviation	0.000127	0.000127
Margin of Exposure	248	246
Percent of aRfD	40.30	40.49

Percent of Person-Days that are User-Days = 99.53%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000018	7.32	1,366	90.00	0.000224	89.72	111
20.00	0.000027	10.92	916	95.00	0.000341	136.50	73
30.00	0.000036	14.24	702	97.50	0.000467	186.93	53
40.00	0.000046	18.29	546	99.00	0.000644	257.66	38
50.00	0.000059	23.67	422	99.50	0.000782	312.86	31
60.00	0.000076	30.30	329	99.75	0.000940	376.12	26
70.00	0.000101	40.50	246	99.90	0.001164	465.50	21
80.00	0.000142	56.86	175				

Hispanics

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000115	0.000116
Standard Deviation	0.000143	0.000143
Margin of Exposure	217	216
Percent of aRfD	45.99	46.21

Percent of Person-Days that are User-Days = 99.52%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000018	7.27	1,374	90.00	0.000262	104.66	95
20.00	0.000028	11.31	884	95.00	0.000378	151.10	66
30.00	0.000040	15.97	626	97.50	0.000498	199.33	50
40.00	0.000054	21.73	460	99.00	0.000715	285.80	34
50.00	0.000069	27.73	360	99.50	0.000854	341.59	29
60.00	0.000092	36.86	271	99.75	0.000932	372.78	26
70.00	0.000123	49.04	203	99.90	0.001191	476.44	20
80.00	0.000165	65.86	151				

Non-hispanic whites

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000072	0.000072
Standard Deviation	0.000078	0.000078
Margin of Exposure	347	346
Percent of aRfD	28.79	28.86

Percent of Person-Days that are User-Days = 99.76%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000018	7.22	1,384	90.00	0.000150	60.15	166
20.00	0.000025	10.11	989	95.00	0.000203	81.37	122
30.00	0.000032	12.83	779	97.50	0.000271	108.29	92
40.00	0.000040	15.85	630	99.00	0.000371	148.42	67
50.00	0.000049	19.52	512	99.50	0.000476	190.47	52
60.00	0.000060	24.19	413	99.75	0.000587	234.76	42
70.00	0.000076	30.57	327	99.90	0.000739	295.70	33
80.00	0.000102	40.67	245				

Non-hispanic blacks

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000089	0.000089
Standard Deviation	0.000111	0.000111
Margin of Exposure	281	279
Percent of aRfD	35.57	35.76

Percent of Person-Days that are User-Days = 99.49%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000015	5.92	1,688	90.00	0.000202	80.72	123
20.00	0.000022	8.95	1,117	95.00	0.000293	117.18	85
30.00	0.000030	12.14	823	97.50	0.000388	155.32	64
40.00	0.000039	15.68	637	99.00	0.000535	214.03	46
50.00	0.000054	21.49	465	99.50	0.000688	275.06	36
60.00	0.000070	28.02	356	99.75	0.000794	317.43	31
70.00	0.000093	37.11	269	99.90	0.000973	389.30	25
80.00	0.000129	51.64	193				

Non-hisp/non-white/non-black

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000210	0.000212
Standard Deviation	0.000215	0.000216
Margin of Exposure	118	117
Percent of aRfD	84.13	84.79

Percent of Person-Days that are User-Days = 99.21%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000024	9.80	1,020	90.00	0.000483	193.01	51
20.00	0.000045	17.81	561	95.00	0.000625	250.19	39
30.00	0.000068	27.05	369	97.50	0.000779	311.74	32
40.00	0.000106	42.41	235	99.00	0.000977	390.68	25
50.00	0.000155	62.03	161	99.50	0.001172	468.63	21
60.00	0.000202	80.61	124	99.75	0.001373	549.30	18
70.00	0.000249	99.67	100	99.90	0.001748	699.32	14
80.00	0.000336	134.45	74				

All infants

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000142	0.000160
Standard Deviation	0.000224	0.000231
Margin of Exposure	175	156
Percent of aRfD	56.89	63.87

Percent of Person-Days that are User-Days = 89.07%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000011	4.34	2,304	90.00	0.000373	149.15	67
20.00	0.000022	8.72	1,147	95.00	0.000515	206.01	48
30.00	0.000048	19.35	516	97.50	0.000703	281.19	35
40.00	0.000074	29.46	339	99.00	0.001161	464.28	21
50.00	0.000096	38.34	260	99.50	0.001435	573.82	17

60.00	0.000125	49.92	200	99.75	0.002326	930.28	10
70.00	0.000160	64.04	156	99.90	0.002765	1106.06	9
80.00	0.000229	91.46	109				

Nursing infants (<1 yr old)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000076	0.000125
Standard Deviation	0.000153	0.000180
Margin of Exposure	328	199
Percent of aRfD	30.45	50.16

Percent of Person-Days that are User-Days = 60.70%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000005	1.96	5,102	90.00	0.000295	118.12	84
20.00	0.000011	4.43	2,255	95.00	0.000424	169.80	58
30.00	0.000021	8.36	1,196	97.50	0.000587	234.80	42
40.00	0.000041	16.59	602	99.00	0.001155	462.14	21
50.00	0.000064	25.59	390	99.50	0.001359	543.52	18
60.00	0.000096	38.24	261	99.75	0.001424	569.64	17
70.00	0.000147	58.95	169	99.90	0.001434	573.52	17
80.00	0.000195	77.90	128				

Non-nursing infants (<1 yr old)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000167	0.000168
Standard Deviation	0.000240	0.000241
Margin of Exposure	149	149
Percent of aRfD	66.93	67.03

Percent of Person-Days that are User-Days = 99.84%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000013	5.10	1,961	90.00	0.000388	155.36	64
20.00	0.000027	10.61	942	95.00	0.000535	213.89	46
30.00	0.000056	22.32	448	97.50	0.000729	291.65	34
40.00	0.000081	32.57	307	99.00	0.001166	466.21	21
50.00	0.000100	40.06	249	99.50	0.001500	600.08	16
60.00	0.000130	52.00	192	99.75	0.002338	935.25	10
70.00	0.000166	66.60	150	99.90	0.002766	1106.54	9
80.00	0.000233	93.10	107				

Children 1-6 yrs

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000180	0.000180
Standard Deviation	0.000173	0.000173
Margin of Exposure	138	138
Percent of aRfD	72.09	72.13

Percent of Person-Days that are User-Days = 99.93%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000056	22.33	447	90.00	0.000361	144.53	69
20.00	0.000074	29.67	337	95.00	0.000491	196.20	50
30.00	0.000092	36.82	271	97.50	0.000647	258.81	38
40.00	0.000110	43.87	227	99.00	0.000898	359.29	27
50.00	0.000128	51.06	195	99.50	0.001121	448.48	22
60.00	0.000152	60.90	164	99.75	0.001314	525.46	19
70.00	0.000185	73.97	135	99.90	0.001612	644.73	15
80.00	0.000246	98.24	101				

Children 7-12 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000122	0.000122
Standard Deviation	0.000112	0.000112
Margin of Exposure	205	205
Percent of aRfD	48.61	48.61

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000039	15.54	643	90.00	0.000242	96.89	103
20.00	0.000051	20.51	487	95.00	0.000333	133.20	75
30.00	0.000062	24.70	404	97.50	0.000442	176.64	56
40.00	0.000075	29.92	334	99.00	0.000621	248.27	40
50.00	0.000087	34.68	288	99.50	0.000730	291.99	34
60.00	0.000103	41.17	242	99.75	0.000839	335.77	29
70.00	0.000126	50.58	197	99.90	0.000921	368.43	27
80.00	0.000163	65.27	153				

Females 13+ (preg/not nursing)

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000082	0.000084
Standard Deviation	0.000117	0.000118
Margin of Exposure	304	296
Percent of aRfD	32.84	33.70

Percent of Person-Days that are User-Days = 97.47%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000018	7.21	1,387	90.00	0.000166	66.47	150
20.00	0.000027	10.97	911	95.00	0.000342	136.70	73
30.00	0.000034	13.50	740	97.50	0.000438	175.13	57
40.00	0.000037	14.77	676	99.00	0.000793	317.11	31
50.00	0.000047	18.77	532	99.50	0.000796	318.26	31
60.00	0.000061	24.35	410	99.75	0.000797	318.83	31
70.00	0.000077	30.64	326	99.90	0.000798	319.18	31

80.00	0.000099	39.40	253

Females 13+ (nursing)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000087	0.000087
Standard Deviation	0.000080	0.000080
Margin of Exposure	287	287
Percent of aRfD	34.75	34.75

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000017	6.84	1,461	90.00	0.000189	75.61	132
20.00	0.000027	10.68	936	95.00	0.000202	80.87	123
30.00	0.000033	13.34	749	97.50	0.000387	154.93	64
40.00	0.000042	16.90	591	99.00	0.000389	155.62	64
50.00	0.000058	23.24	430	99.50	0.000390	155.85	64
60.00	0.000080	32.19	310	99.75	0.000390	155.96	64
70.00	0.000098	39.35	254	99.90	0.000390	156.03	64
80.00	0.000142	56.85	175				

Females 13-19 (not preg or nursing)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000072	0.000072
Standard Deviation	0.000072	0.000072
Margin of Exposure	347	347
Percent of aRfD	28.76	28.82

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000020	7.87	1,270	90.00	0.000151	60.39	165
20.00	0.000028	11.05	905	95.00	0.000213	85.09	117
30.00	0.000034	13.67	731	97.50	0.000289	115.66	86
40.00	0.000040	16.17	618	99.00	0.000370	147.84	67
50.00	0.000050	19.83	504	99.50	0.000478	191.31	52
60.00	0.000059	23.57	424	99.75	0.000495	198.02	50
70.00	0.000074	29.66	337	99.90	0.000534	213.76	46
80.00	0.000096	38.58	259				

Females 20+ (not preg or nursing)

Daily Exposure Analysis (mg/kg body-weight/day)	per Capita	per User
Mean	0.000057	0.000058
Standard Deviation	0.000066	0.000066
Margin of Exposure	435	434

Percent of aRfD	22.95	23.01

Percent of Person-Days that are User-Days = 99.75%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000014	5.67	1,763	90.00	0.000122	48.92	204
20.00	0.000020	7.93	1,260	95.00	0.000179	71.43	139
30.00	0.000025	10.08	991	97.50	0.000240	96.14	104
40.00	0.000031	12.26	815	99.00	0.000345	137.83	72
50.00	0.000037	14.79	676	99.50	0.000414	165.67	60
60.00	0.000046	18.26	547	99.75	0.000498	199.16	50
70.00	0.000057	22.76	439	99.90	0.000632	252.91	39
80.00	0.000076	30.58	327				

Females 13-50 yrs

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000066	0.000066
Standard Deviation	0.000074	0.000074
Margin of Exposure	378	377
Percent of aRfD	26.43	26.52

Percent of Person-Days that are User-Days = 99.66%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000016	6.35	1,574	90.00	0.000140	56.16	178
20.00	0.000022	8.92	1,120	95.00	0.000201	80.49	124
30.00	0.000029	11.45	873	97.50	0.000274	109.62	91
40.00	0.000035	14.06	711	99.00	0.000382	152.60	65
50.00	0.000043	17.17	582	99.50	0.000455	182.16	54
60.00	0.000053	21.25	470	99.75	0.000532	212.81	46
70.00	0.000066	26.56	376	99.90	0.000678	271.38	36
80.00	0.000091	36.28	275				

Males 13-19 yrs

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000096	0.000096
Standard Deviation	0.000114	0.000114
Margin of Exposure	261	261
Percent of aRfD	38.27	38.27

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000026	10.20	980	90.00	0.000183	73.39	136
20.00	0.000034	13.72	728	95.00	0.000301	120.38	83
30.00	0.000042	16.95	589	97.50	0.000411	164.28	60

40.00	0.000052	20.64	484	99.00	0.000661	264.47	37
50.00	0.000063	25.14	397	99.50	0.000782	312.95	31
60.00	0.000073	29.24	341	99.75	0.000945	377.83	26
70.00	0.000090	36.16	276	99.90	0.000984	393.69	25
80.00	0.000122	48.96	204				

Males 20+ yrs

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000075	0.000075
Standard Deviation	0.000085	0.000085
Margin of Exposure	332	332
Percent of aRfD	30.08	30.11

Percent of Person-Days that are User-Days = 99.88%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000018	7.19	1,390	90.00	0.000160	63.98	156
20.00	0.000025	10.11	989	95.00	0.000224	89.72	111
30.00	0.000032	12.78	782	97.50	0.000304	121.70	82
40.00	0.000040	15.87	630	99.00	0.000447	178.83	55
50.00	0.000048	19.33	517	99.50	0.000559	223.72	44
60.00	0.000060	24.00	416	99.75	0.000644	257.48	38
70.00	0.000077	30.65	326	99.90	0.000771	308.31	32
80.00	0.000104	41.58	240				

Seniors 55+

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000050	0.000050
Standard Deviation	0.000058	0.000058
Margin of Exposure	496	495
Percent of aRfD	20.15	20.18

Percent of Person-Days that are User-Days = 99.87%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000014	5.54	1,804	90.00	0.000100	40.05	249
20.00	0.000019	7.64	1,309	95.00	0.000146	58.48	170
30.00	0.000024	9.58	1,044	97.50	0.000196	78.43	127
40.00	0.000029	11.47	872	99.00	0.000288	115.35	86
50.00	0.000034	13.59	735	99.50	0.000389	155.72	64
60.00	0.000041	16.24	615	99.75	0.000496	198.28	50
70.00	0.000050	19.95	501	99.90	0.000686	274.47	36
80.00	0.000066	26.41	378				

II.4. MONTE CARLO DIETARY EXPOSURES AND RISK ESTIMATES (WITH PCT)

```
California Department of Pesticide Regulation                        Ver. 7.73
DEEM ACUTE Analysis for METHYL PARATHION                          (1994-98 data)
Residue file: Monte Carlo_9.RS7                  Adjustment factor #2 NOT used.
Analysis Date: 10-12-2001/14:18:33    Residue file dated: 10-12-2001/13:51:32/14
NOEL (Acute) =   0.025000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 500      MC list in residue file     MC seed = 10
Run Comment: "Monte Carlo_9  for Methyl Parathion: PCT for all RDF; NO PCT for
 point estimate"
================================================================================
```

U.S. Population — Daily Exposure Analysis /a (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000057	0.000057
Standard Deviation	0.000098	0.000098
Margin of Exposure 2/	441	439
Percent of aRfD	22.66	22.73

Percent of Person-Days that are User-Days = 99.68%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000004	1.42	7,044	90.00	0.000143	57.17	174
20.00	0.000007	3.00	3,334	95.00	0.000223	89.25	112
30.00	0.000012	4.67	2,140	97.50	0.000321	128.56	77
40.00	0.000017	6.68	1,496	99.00	0.000481	192.34	51
50.00	0.000023	9.33	1,071	99.50	0.000613	245.27	40
60.00	0.000033	13.31	751	99.75	0.000757	302.81	33
70.00	0.000049	19.69	507	99.90	0.000943	377.07	26
80.00	0.000079	31.69	315				

Western region — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000073	0.000073
Standard Deviation	0.000122	0.000122
Margin of Exposure	344	342
Percent of aRfD	29.02	29.16

Percent of Person-Days that are User-Days = 99.53%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000003	1.39	7,218	90.00	0.000189	75.63	132
20.00	0.000008	3.07	3,254	95.00	0.000301	120.31	83
30.00	0.000013	5.12	1,951	97.50	0.000429	171.65	58
40.00	0.000019	7.51	1,331	99.00	0.000615	245.95	40
50.00	0.000028	11.15	896	99.50	0.000740	296.10	33
60.00	0.000041	16.44	608	99.75	0.000877	351.00	28
70.00	0.000065	26.00	384	99.90	0.001117	446.77	22

80.00	0.000104	41.74	239

Hispanics

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000086	0.000086
Standard Deviation	0.000135	0.000135
Margin of Exposure	291	290
Percent of aRfD	34.31	34.48

Percent of Person-Days that are User-Days = 99.52%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000003	1.35	7,432	90.00	0.000219	87.46	114
20.00	0.000008	3.24	3,084	95.00	0.000333	133.12	75
30.00	0.000014	5.66	1,765	97.50	0.000446	178.55	56
40.00	0.000023	9.03	1,107	99.00	0.000663	265.05	37
50.00	0.000036	14.52	688	99.50	0.000823	329.37	30
60.00	0.000059	23.75	421	99.75	0.000905	361.92	27
70.00	0.000090	36.06	277	99.90	0.001172	468.62	21
80.00	0.000128	51.40	194				

Non-hispanic whites

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000044	0.000044
Standard Deviation	0.000070	0.000070
Margin of Exposure	568	566
Percent of aRfD	17.60	17.65

Percent of Person-Days that are User-Days = 99.76%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000004	1.44	6,929	90.00	0.000107	42.92	233
20.00	0.000007	2.93	3,415	95.00	0.000162	64.96	153
30.00	0.000011	4.51	2,219	97.50	0.000226	90.33	110
40.00	0.000016	6.26	1,597	99.00	0.000327	130.64	76
50.00	0.000021	8.48	1,179	99.50	0.000422	168.75	59
60.00	0.000029	11.76	850	99.75	0.000538	215.26	46
70.00	0.000041	16.51	605	99.90	0.000647	259.00	38
80.00	0.000063	25.05	399				

Non-hispanic blacks

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000061	0.000061
Standard Deviation	0.000101	0.000101
Margin of Exposure	411	409
Percent of aRfD	24.29	24.41

Percent of Person-Days that are User-Days = 99.49%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000003	1.24	8,060	90.00	0.000162	64.98	153
20.00	0.000007	2.75	3,636	95.00	0.000250	100.06	99
30.00	0.000011	4.36	2,291	97.50	0.000336	134.36	74
40.00	0.000016	6.40	1,561	99.00	0.000482	192.86	51
50.00	0.000024	9.42	1,061	99.50	0.000600	239.81	41
60.00	0.000035	13.94	717	99.75	0.000718	287.03	34
70.00	0.000055	21.90	456	99.90	0.000888	355.29	28
80.00	0.000091	36.29	275				

Non-hisp/non-white/non-black

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000183	0.000184
Standard Deviation	0.000213	0.000213
Margin of Exposure	136	135
Percent of aRfD	73.12	73.70

Percent of Person-Days that are User-Days = 99.21%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000006	2.50	4,007	90.00	0.000453	181.38	55
20.00	0.000017	6.67	1,499	95.00	0.000588	235.08	42
30.00	0.000033	13.20	757	97.50	0.000752	300.76	33
40.00	0.000071	28.35	352	99.00	0.000949	379.60	26
50.00	0.000123	49.24	203	99.50	0.001135	453.85	22
60.00	0.000176	70.54	141	99.75	0.001342	536.69	18
70.00	0.000225	90.09	110	99.90	0.001689	675.74	14
80.00	0.000301	120.35	83				

All infants

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000100	0.000112
Standard Deviation	0.000215	0.000225
Margin of Exposure	250	222
Percent of aRfD	39.98	44.88

Percent of Person-Days that are User-Days = 89.07%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000000	0.00	>1,000,000	90.00	0.000314	125.79	79
20.00	0.000000	0.00	>1,000,000	95.00	0.000448	179.20	55
30.00	0.000000	0.00	>1,000,000	97.50	0.000636	254.34	39
40.00	0.000010	3.85	2,598	99.00	0.001066	426.24	23
50.00	0.000031	12.45	803	99.50	0.001390	555.84	17
60.00	0.000060	24.08	415	99.75	0.002238	895.15	11
70.00	0.000105	42.16	237	99.90	0.002697	1078.91	9
80.00	0.000175	70.01	142				

Nursing infants (<1 yr old)

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000061	0.000101
Standard Deviation	0.000147	0.000178
Margin of Exposure	409	248
Percent of aRfD	24.40	40.20

Percent of Person-Days that are User-Days = 60.70%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000000	0.00	>1,000,000	90.00	0.000278	111.39	89
20.00	0.000000	0.00	>1,000,000	95.00	0.000403	161.36	61
30.00	0.000000	0.00	>1,000,000	97.50	0.000544	217.64	45
40.00	0.000007	2.92	3,421	99.00	0.001086	434.50	23
50.00	0.000025	9.82	1,018	99.50	0.001356	542.35	18
60.00	0.000060	24.01	416	99.75	0.001393	557.33	17
70.00	0.000110	44.14	226	99.90	0.001404	561.53	17
80.00	0.000166	66.25	150				

Non-nursing infants (<1 yr old)

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000115	0.000115
Standard Deviation	0.000235	0.000235
Margin of Exposure	217	217
Percent of aRfD	45.89	45.96

Percent of Person-Days that are User-Days = 99.84%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000000	0.00	>1,000,000	90.00	0.000321	128.34	77
20.00	0.000000	0.00	>1,000,000	95.00	0.000455	181.98	54
30.00	0.000000	0.00	>1,000,000	97.50	0.000679	271.46	36
40.00	0.000011	4.33	2,311	99.00	0.001061	424.40	23
50.00	0.000032	12.98	770	99.50	0.001445	577.86	17
60.00	0.000060	24.12	414	99.75	0.002252	900.97	11
70.00	0.000103	41.24	242	99.90	0.002710	1083.82	9
80.00	0.000176	70.53	141				

Children 1-6 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000117	0.000117
Standard Deviation	0.000168	0.000168
Margin of Exposure	214	214
Percent of aRfD	46.62	46.65

Percent of Person-Days that are User-Days = 99.93%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000012	4.77	2,098	90.00	0.000292	116.88	85
20.00	0.000022	8.80	1,137	95.00	0.000425	170.16	58
30.00	0.000032	12.94	772	97.50	0.000586	234.42	42
40.00	0.000044	17.61	567	99.00	0.000824	329.68	30
50.00	0.000058	23.07	433	99.50	0.001036	414.37	24
60.00	0.000077	30.67	326	99.75	0.001217	486.85	20
70.00	0.000107	42.93	232	99.90	0.001533	613.19	16
80.00	0.000171	68.27	146				

Children 7-12 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000076	0.000076
Standard Deviation	0.000108	0.000108
Margin of Exposure	327	327
Percent of aRfD	30.54	30.54

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000008	3.38	2,954	90.00	0.000193	77.02	129
20.00	0.000016	6.21	1,609	95.00	0.000283	113.33	88
30.00	0.000023	9.01	1,109	97.50	0.000390	156.16	64
40.00	0.000029	11.77	849	99.00	0.000562	224.89	44
50.00	0.000038	15.03	665	99.50	0.000665	265.84	37
60.00	0.000049	19.42	514	99.75	0.000763	305.21	32
70.00	0.000070	27.87	358	99.90	0.000872	348.66	28
80.00	0.000106	42.54	235				

Females 13+ (preg/not nursing)

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000059	0.000060
Standard Deviation	0.000117	0.000118
Margin of Exposure	426	415
Percent of aRfD	23.44	24.05

Percent of Person-Days that are User-Days = 97.47%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000004	1.48	6,754	90.00	0.000136	54.59	183
20.00	0.000008	3.27	3,054	95.00	0.000292	116.81	85
30.00	0.000012	4.88	2,047	97.50	0.000420	168.12	59
40.00	0.000015	6.14	1,629	99.00	0.000777	310.91	32
50.00	0.000021	8.36	1,196	99.50	0.000781	312.35	32
60.00	0.000028	11.18	894	99.75	0.000783	313.40	31

70.00	0.000038	15.36	650	99.90	0.000787	314.88	31
80.00	0.000074	29.50	338				

Females 13+ (nursing)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000061	0.000061
Standard Deviation	0.000076	0.000076
Margin of Exposure	407	407
Percent of aRfD	24.53	24.53

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000004	1.41	7,075	90.00	0.000161	64.30	155
20.00	0.000008	3.10	3,222	95.00	0.000177	70.83	141
30.00	0.000012	4.64	2,153	97.50	0.000357	142.71	70
40.00	0.000018	7.36	1,358	99.00	0.000359	143.46	69
50.00	0.000027	10.75	930	99.50	0.000361	144.21	69
60.00	0.000054	21.73	460	99.75	0.000374	149.60	66
70.00	0.000073	29.36	340	99.90	0.000376	150.57	66
80.00	0.000098	39.25	254				

Females 13-19 (not preg or nursing)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000045	0.000045
Standard Deviation	0.000069	0.000069
Margin of Exposure	552	551
Percent of aRfD	18.09	18.13

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000003	1.31	7,610	90.00	0.000118	47.21	211
20.00	0.000008	3.10	3,223	95.00	0.000177	70.74	141
30.00	0.000011	4.60	2,176	97.50	0.000251	100.23	99
40.00	0.000016	6.34	1,576	99.00	0.000341	136.39	73
50.00	0.000021	8.26	1,210	99.50	0.000446	178.48	56
60.00	0.000028	11.21	892	99.75	0.000458	183.01	54
70.00	0.000038	15.38	650	99.90	0.000474	189.52	52
80.00	0.000059	23.46	426				

Females 20+ (not preg or nursing)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000038	0.000039
Standard Deviation	0.000064	0.000064
Margin of Exposure	650	649
Percent of aRfD	15.36	15.40

Percent of Person-Days that are User-Days = 99.75%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000003	1.05	9,552	90.00	0.000100	39.81	251
20.00	0.000005	2.17	4,617	95.00	0.000154	61.53	162
30.00	0.000008	3.37	2,966	97.50	0.000220	87.84	113
40.00	0.000012	4.83	2,070	99.00	0.000318	127.05	78
50.00	0.000016	6.48	1,543	99.50	0.000394	157.49	63
60.00	0.000022	8.75	1,143	99.75	0.000487	194.81	51
70.00	0.000032	12.88	776	99.90	0.000590	236.16	42
80.00	0.000053	21.19	471				

Females 13-50 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000045	0.000045
Standard Deviation	0.000072	0.000072
Margin of Exposure	561	559
Percent of aRfD	17.81	17.87

Percent of Person-Days that are User-Days = 99.66%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000003	1.09	9,138	90.00	0.000116	46.42	215
20.00	0.000006	2.44	4,095	95.00	0.000177	70.81	141
30.00	0.000010	3.92	2,553	97.50	0.000250	100.17	99
40.00	0.000014	5.47	1,826	99.00	0.000361	144.31	69
50.00	0.000019	7.44	1,343	99.50	0.000420	168.16	59
60.00	0.000026	10.50	952	99.75	0.000493	197.30	50
70.00	0.000039	15.54	643	99.90	0.000668	267.19	37
80.00	0.000064	25.68	389				

Males 13-19 yrs

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000063	0.000063
Standard Deviation	0.000112	0.000112
Margin of Exposure	399	399
Percent of aRfD	25.04	25.04

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) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000005	1.99	5,030	90.00	0.000146	58.47	171
20.00	0.000010	3.86	2,592	95.00	0.000269	107.44	93
30.00	0.000015	5.86	1,706	97.50	0.000380	151.84	65
40.00	0.000019	7.75	1,290	99.00	0.000633	253.34	39
50.00	0.000025	10.15	984	99.50	0.000761	304.26	32
60.00	0.000034	13.69	730	99.75	0.000940	376.01	26

70.00	0.000050	19.90	502	99.90	0.000970	388.20	25
80.00	0.000080	31.90	313				

Males 20+ yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000053	0.000053
Standard Deviation	0.000083	0.000083
Margin of Exposure	473	472
Percent of aRfD	21.13	21.15

Percent of Person-Days that are User-Days = 99.88%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000004	1.51	6,608	90.00	0.000137	54.75	182
20.00	0.000008	3.01	3,317	95.00	0.000200	79.92	125
30.00	0.000011	4.59	2,177	97.50	0.000270	108.05	92
40.00	0.000016	6.52	1,534	99.00	0.000423	169.30	59
50.00	0.000023	9.14	1,094	99.50	0.000523	209.34	47
60.00	0.000033	13.05	766	99.75	0.000623	249.13	40
70.00	0.000048	19.29	518	99.90	0.000720	288.10	34
80.00	0.000079	31.61	316				

Seniors 55+ — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000033	0.000033
Standard Deviation	0.000057	0.000057
Margin of Exposure	760	759
Percent of aRfD	13.16	13.17

Percent of Person-Days that are User-Days = 99.87%

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

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000003	1.16	8,642	90.00	0.000081	32.24	310
20.00	0.000005	2.17	4,601	95.00	0.000128	51.27	195
30.00	0.000008	3.28	3,048	97.50	0.000176	70.40	142
40.00	0.000011	4.52	2,211	99.00	0.000270	107.93	92
50.00	0.000015	5.87	1,704	99.50	0.000367	146.71	68
60.00	0.000020	7.81	1,281	99.75	0.000489	195.73	51
70.00	0.000028	11.11	899	99.90	0.000673	269.26	37
80.00	0.000043	17.03	587				

ATTACHMENT III: DEEM Chronic Dietary Exposure Assessment

III.1. CHRONIC DIETARY EXPOSURES AND RISK ESTIMATES (NO PCT)

California Department of Pesticide Regulation Ver. 7.76
DEEM Chronic analysis for METHYL PARATHION (1994-98 data)
Residue file name: D:\svetlana\Methyl Parathion\MP Chronic Residue\Chronic_Ave_No PCT.RS7
Adjustment factor #2 used.
Analysis Date 03-04-2003/14:43:12 Residue file dated: 08-16-2001/11:17:36/14
NOEL (Chronic) = .02 mg/kg bw/day
COMMENT 1: Methyl Parathion Chronic Dietary Assesment, No PCT; Chronic NOEL=0.02 mg/kg/day (mice)

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of NOEL	Total Exposure Margin of Exposr 1/
U.S. Population (total)	0.000027	0.13%	742
U.S. Population (spring season)	0.000027	0.14%	730
U.S. Population (summer season)	0.000026	0.13%	763
U.S. Population (autumn season)	0.000027	0.14%	737
U.S. Population (winter season)	0.000027	0.14%	737
Northeast region	0.000026	0.13%	774
Midwest region	0.000028	0.14%	712
Southern region	0.000026	0.13%	770
Western region	0.000028	0.14%	706
Hispanics	0.000030	0.15%	669
Non-hispanic whites	0.000026	0.13%	771
Non-hispanic blacks	0.000028	0.14%	708
Non-hisp/non-white/non-black	0.000033	0.17%	599
All infants (< 1 year)	0.000031	0.15%	651
Nursing infants	0.000012	0.06%	1,735
Non-nursing infants	0.000038	0.19%	526
Children 1-6 yrs	0.000063	0.31%	318
Children 7-12 yrs	0.000044	0.22%	458
Females 13-19 (not preg or nursing)	0.000025	0.13%	799
Females 20+ (not preg or nursing)	0.000018	0.09%	1,100
Females 13-50 yrs	0.000021	0.10%	968
Females 13+ (preg/not nursing)	0.000021	0.11%	940
Females 13+ (nursing)	0.000028	0.14%	715
Males 13-19 yrs	0.000031	0.16%	640
Males 20+ yrs	0.000021	0.11%	933
Seniors 55+	0.000017	0.08%	1,198

III.2. CHRONIC DIETARY EXPOSURES AND RISK ESTIMATES (WITH PCT)

California Department of Pesticide Regulation Ver. 7.76
DEEM Chronic analysis for METHYL PARATHION (1994-98 data)
Residue file name: D:\svetlana\Methyl Parathion\MP Chronic Residue\Chronic_Ave+PCT.RS7
Adjustment factor #2 used.
Analysis Date 03-04-2003/15:00:56 Residue file dated: 10-12-2001/16:01:40/14
NOEL (Chronic) = .02 mg/kg bw/day
COMMENT 1: Methyl Parathion Chronoc Dietary Assesment + PCT
, Chronic NOEL=0.02 (mice)

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of NOEL	Total Exposure Margin of Exposr 1/
U.S. Population (total)	0.000003	0.01%	7,673
U.S. Population (spring season)	0.000003	0.01%	7,544
U.S. Population (summer season)	0.000002	0.01%	8,010
U.S. Population (autumn season)	0.000003	0.01%	7,591
U.S. Population (winter season)	0.000003	0.01%	7,557
Northeast region	0.000002	0.01%	8,115
Midwest region	0.000003	0.01%	7,527
Southern region	0.000003	0.01%	7,940
Western region	0.000003	0.01%	7,097
Hispanics	0.000003	0.02%	6,638
Non-hispanic whites	0.000002	0.01%	8,189
Non-hispanic blacks	0.000003	0.01%	7,023
Non-hisp/non-white/non-black	0.000004	0.02%	5,490
All infants (< 1 year)	0.000002	0.01%	8,632
Nursing infants	0.000001	0.00%	23,215
Non-nursing infants	0.000003	0.01%	6,970
Children 1-6 yrs	0.000006	0.03%	3,165
Children 7-12 yrs	0.000004	0.02%	4,565
Females 13-19 (not preg or nursing)	0.000002	0.01%	8,150
Females 20+ (not preg or nursing)	0.000002	0.01%	11,386
Females 13-50 yrs	0.000002	0.01%	9,948
Females 13+ (preg/not nursing)	0.000002	0.01%	10,103
Females 13+ (nursing)	0.000003	0.01%	6,714
Males 13-19 yrs	0.000003	0.02%	6,568
Males 20+ yrs	0.000002	0.01%	10,091
Seniors 55+	0.000002	0.01%	12,600

ATTACHMENT IV: Benchmark Dose Modeling. Hill Model

Methyl Parathion Dermal Treatment of Female Rats
ChE Activity Inhibition in the Brain (Striatum)

```
        Hill Model. $Revision: 2.1 $ $Date: 2000/10/11 21:21:23 $
         Input Data File: D:\BMDS\DATA\SUBCHRONIC DERMAL METHYL PARATHION\FEMALE 4 W
STRIATUM\FEMALE_4W_STRIATUM.(d)
         Gnuplot Plotting File:  D:\BMDS\DATA\SUBCHRONIC DERMAL METHYL PARATHION\FEMALE 4 W
STRIATUM\FEMALE_4W_STRIATUM.plt
                                                    Thu Feb 20 11:18:03 2003
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = MEAN
   Independent variable = COLUMN1
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = alpha * mean(i) ^ rho

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =     0.304454
                            rho =      1.41587
                      intercept =        45.39
                              v =       -35.69
                              n =      1.20578
                              k =     0.854724


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                   alpha          rho    intercept            v            k

     alpha             1        -0.98         0.12        -0.15       -0.048

       rho         -0.98            1        -0.13         0.16        0.048

 intercept          0.12        -0.13            1        -0.41        -0.65

         v         -0.15         0.16        -0.41            1        -0.37

         k        -0.048        0.048        -0.65        -0.37            1


                          Parameter Estimates
```

Variable	Estimate	Std. Err.
alpha	0.254436	0.299895
rho	1.46071	0.366423
intercept	44.5306	2.24511
v	-43.9614	2.79201
n	1	NA
k	1.35487	0.35472

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	10	45.4	7.48	44.5	8.07	0.106
0.3	10	35.4	8.93	36.6	6.99	-0.162
1	10	25.5	5.28	25.9	5.43	-0.0704
2.2	10	18.2	3.35	17.3	4.05	0.216
5	10	9.7	3.11	9.94	2.7	-0.0896

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = alpha*(Mu(i))^rho

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-112.571483	6	237.142966
A2	-104.448668	10	228.897336
A3	-105.914900	7	225.829801
fitted	-106.154876	5	222.309753
R	-156.791496	2	317.582993

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	104.686	8	<.0001
Test 2	16.2456	4	0.002707
Test 3	2.93246	3	0.4022
Test 4	0.479952	1	0.4884

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .05.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .05.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .05.  The model chosen seems
to adequately describe the data


 Benchmark Dose Computation
Specified effect =          0.05

Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =     0.0722814

            BMDL =     0.0514493
```

ATTACHMENT V: Summary of Toxicology Data for Methyl Parathion

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
METHYL PARATHION

Chemical Code # 000394, Tolerance # 00121
SB 950 # 043

November 3, 1986
Revised 10/18/89; 1/19/90; 5/23/90; 7/2/90; 12/l/92; 10/31/95; 5/6/96, 11/19/97, 11/25/98, 1/20/04

I. DATA GAP STATUS

Combined, rat:	No data gap, possible adverse effect.
Chronic, dog:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, possible adverse effect.
Teratology, rat:	No data gap, possible adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, possible adverse effect.
Chromosomal aberration:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	No data gap, no adverse effect.

Toxicology one-liners are attached.
All studies identified through document 0174 208922 have been examined.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T04/01/20 Revised by: G. Chernoff, 7/2/90; Kishiyama & Silva, 12/l/92; Silva, 10/31/95 & 5/6/96; Aldous (minor editing during revision to current software: no new data and no fundamental changes in content), 9/24/97. Revised 11/19/97 by J. Gee; M. Silva, 11/25/98 & 1/20/04

These pages contain summaries only. Individual worksheets may identify additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

(Chronic/Oncogenicity)

Subchronic, Rat:

099 127031 "A Three Month Feeding Study of Methyl Parathion in Rats," (I. W. Daly & W.E. Rinehart; Project #: 77-2059 (BD-78-9); Bio/dynamics, Inc., East Millstone, NJ; 2/28/80). Methyl parathion (93.65% pure) was fed in diet to Sprague-Dawley CD rats (20/sex/dose) at 0, 2.5, 25 and 75 ppm for 3 months. Systemic NOEL = 2.5 ppm (At 75 ppm, 14 females and 1 male died or were sacrificed moribund during the first 4 weeks on study. All females and 5/20 males showed tremors, emaciation and staining of the anogenital area at 75 ppm. Body weights were decreased and food consumption was increased in both sexes at 75 ppm. Erythrocytes, hemoglobin and hematocrit were decreased and SGOT was increased in females at 75 ppm. Alkaline phosphatase was increased at $\geq$ 25 ppm. BUN was increased while glucose, total protein, albumin and globulin levels were decreased in females at 75 ppm. Males showed decreased globulin, total protein and glucose levels at 75 ppm. Specific gravity in urine was elevated in both sexes at 75 ppm and associated with positive urinary protein determinations of 100 mg/dl or greater in most animals. Male and female organ weights were reduced as follows: testes/ovaries (5%, 22%), heart (8%, 12%), kidneys (10%, 13%) and liver (15%, 26%) at 75 ppm. In addition, relative (organ/brain & organ/body weight) were increased due to decreased terminal body weights. Lesions in the non-glandular mucosa (discolored areas/foci, raised white areas and abrasions, black/brown tar-like gastric contents) occurred in both sexes at 75 ppm. In addition, acute ulcerative gastritis, lymphoid depletion and necrosis (lymph nodes, spleen & thymus), necrosis of the submaxillary salivary glands and hypocellularity of the bone marrow occurred in both sexes at 75 ppm.) Cholinesterase NOEL = 2.5 ppm (RBC and plasma Cholinesterase levels in both sexes were decreased at > 25 ppm. Brain Cholinesterase was decreased in females at > 25 ppm and males at 75 ppm. **Possible adverse effect.** The data are supplemental. M. Silva, 10/17/95.

Combined, rat:

** **042 011168, 045-050 034227-034232, 098 126319,** "Two Year Chronic Feeding Study of Methyl Parathion in Rats", (Biodynamics, 12/22/83). Methyl parathion (93.65% pure) was fed in diet to Sprague-Dawley (CD) rats (60/sex/group) at 0, 0.5, 5.0 and 50 ppm for 25 months (males) or 28 months (females). Systemic NOEL = 5.0 ppm (Decreased body weight gain was observed in both sexes at 50 ppm. Increased food consumption was observed at > 5.0 mg/kg. Clinical signs, including alopecia, anogenital staining and tremors at 50 ppm and altered gait at $\geq$ 5.0 ppm were observed in females. There was an increased incidence in posterior subcapsular cataracts and retinal degeneration at 50 ppm in both sexes. In addition, females showed decreased Hb and both sexes showed decreased HCT and RBC's at 50 ppm. Histopathologically, both sexes showed peripheral (hindlimb) neuropathy by demyelination of the proximal and distal sciatic nerves at 50 ppm.) Cholinesterase NOEL = 5.0 ppm (Significant decreases in plasma and brain cholinesterase were observed at 50 ppm.) **Possible adverse effects:** Significant brain cholinesterase inhibition and peripheral neuropathies occurred at 50 ppm. Retinal degeneration and posterior subcapsular cataracts occurred in females at 50 ppm. NOTE: Record #011168 has been examined several times, with associated changes in acceptability status. The study was initially submitted and found adequate to fill the data gap for a chronic toxicity (Schreider, 3/18/85). Upon submission of additional information (034227-034232), this study was then reviewed as a combined (chronic/oncogenicity) study and considered to be unacceptable but upgradeable (Christopher, 10/7/85). Subsequently, the reports were re-reviewed and the status was still unacceptable, based on animal husbandry problems (see 11/24/92 review sheet by M. Silva for details). After submission of the

information requested in the 1992 review, and in consideration of the data in several long-term rat studies, this study has been upgraded to **acceptable** with deficiencies as previously noted (see worksheet by M. Silva, 10/3/95).

EPA ONE-LINER: Oncogenic NOEL>50 ppm (HDT). Neurologic NOEL not defined. Degenerative changes of sciatic nerve in males at high dose level. Thickening of myelin sheaths in high dose females. NOEL (except for neurologic changes) = 0.5 ppm (abnormal gait, slight to moderate decreases in mean hemoglobin, hematocrit and erythrocyte levels in males at 24 months). Effects at 50 ppm include greater incidence of alopecia (particularly in females), bilateral retinal degeneration (females only). CORE grade: minimum (oncogenicity) and supplementary (2 year feeding).

121 - 0172 208916 "Reevaluation of Neuropathology Slides from A Two-Year Chronic Feeding Study of Methyl Parathion in Rats," (O'Shaughnessy, D.; BioDynamics Study #: 77-2060; D. O'Shaughnessy Consulting, Inc., Sparta, NJ; 2/8/02). This volume stated that "The morphometric results of the original report were incorrectly derived and interpreted and should be discounted." It was also stated that "A thorough qualitative examination of nervous system slides of high dose and control animals from both special neurotoxity and routine pathology subgroups provides good evidence that methyl parathion did not cause any dose-related neuropathological effects at any dose tested." Reevaluations were performed by a private pathology consultant (O'Shaughnessy Consulting, Inc.) that is not held to the guidelines of an EPA selected Pathology Working Group. The data are therefore supplemental. No worksheet. M.Silva, 1/16/04.

091 089191, "A Twelve Month Oral Toxicity Study of Methyl Parathion (E 120) in the Rat Via Dietary Admixture with Special Focus on Ocular and Sciatic Nerve Effects". (I. W. Daly, Bio/dynamics, Inc., Project No. 873208, 1/7/91). Methyl Parathion (purity = 94.6%) was administered in the feed at concentrations of 0 (acetone), 0.5, 2.5, 12.5, or 50.0 ppm to Sprague-Dawley rats (70/sex/group) for at least 12 months. A group scheduled to serve 3 months in recovery was canceled. Systemic NOEL = 2.5 ppm [Decreased body weight gain was observed in both sexes at 50 ppm. Increased food consumption was observed, primarily in females, at $\geq$ 12.5 mg/kg. Clinical signs, including aggressiveness, tremors, scabs, sores, and altered gait (primarily females) were observed at 50 ppm.] Cholinesterase NOEL = 2.5 ppm [Plasma Cholinesterase was inhibited significantly in both sexes at 50 ppm. RBC Cholinesterase was inhibited slightly (no greater than 19.5%) at 50 ppm. Brain Cholinesterase was inhibited significantly at 50 ppm in males and at $\geq$ 12.5 ppm in females.] Neurotoxicity NOEL = 0.5 ppm (there was an increase in peripheral neuropathy at $\geq$ 12.5 ppm in both sexes). In addition, there was an increase in proximal sciatic and tibial/paroneal nerve myelin bubbles at > 2.5 ppm in both sexes. Ophthalmological exams performed at month 12 (retina and optic nerve) failed to show treatment related effects. **NOTE: retinal degeneration and posterior subcapsular cataracts were reported at 50 ppm in an earlier chronic study** (DPR Record #11168), occurring at both 24 and 28 months. Not Acceptable (Not a FIFRA Guideline study). Considered to be supplemental only. Kishiyama & Silva, 11/13/92.

121 - 063 076585 (This is the protocol for Record No. 089191, above).
121 - 0170 208911 "Pathology Re-Evaluation; A 12-Month Oral Toxicity Study of Methyl Patathion (E120) in the Rat Via Dietary Admixture with Special Focus on Ocular and Sciatic Nerve Effects," (O'Shaughnessy, D.; Cheminova A/S, Lemvig, Denmark; 3/21/01). In this report of the reread of neuronal pathology from the 12-month study reviewed by DPR (DPR volume/record #: 121 - 091/089191), Dr. O'Shaughnessy recommended a complete reread by an independent expert in toxicologic neuropathology. A report amendment was considered warrented. Information is supplemental. No worksheet. M. Silva, 1/14/04.

121 - 0171 208914 "Methyl Parathion: A Review of the One Year Rat (Daly 1992B) and the 2 Year Rat (Daly 1983) Feeding Studies," (Foster, J.R.; Cheminova Agro, DK; Report #: CTL/P/5696; Final report dated: 1997). This volume contains an analysis of previous studies and data from the 12 month and 2 year rat feeding studies with methyl parathion. Conclusions were as follows:

I. Methyl parathion inhibits AchE
II. At high doses and at high cholinesterase inhibition clinical symptoms of cholinergic block occur.
III. Clinical symptoms are reversible when exposure to methyl parathion is discontinued.
IV. Methyl parathion does not cause OPIDN
V. Exposure to high doses of methyl parathion induces neuropathological changes consistent with demyelination in the peripheral nervous system. These changes are a consequence of the prolonged high level inhibition of AChE and have a threshold dose response and a clear NOEL.

These data are supplemental. No worksheet. M. Silva, 1/16/04.

121 - 0173 208918 "A Two-Year Chronic Feeding Study of Methyl Parathion in Rats," (Jortner, B.S.; BioDynamics Study #: 77-2060; Blacksburg, VA; 10/9/02). This volume contains a slide re-read of sections of spinal cord, cauda equina, and peripheral nerve from the BioDynamics Study #: 77-2060 performed by a veterinary neuropathologist. The 2 components of the study were Special Neuropathology and Regular Study components, comparing high dose and control rats. No treatment related alterations were observed in the Special Neuropathology portion of the study. The Regular Study slides could not be evaluated due to the histological quality of the sections. These data are supplemental. The slides were reviewed by an independent laboratory and were not reevaluated according to an EPA Pathology Working Group regulations. No worksheet. M. Silva, 1/16/04

121 - 0174 208922 "Review of Existing Studies with Neuropathological Evaluation of Rats Treated with Methyl Parathion and Conclusions Regarding the Potential for Methyl Parathion to Cause Peripheral Neuropathy," (O'Shaughnessy, D.; D. O'Shaughnessy Consulting Inc., Sparta, NJ; 6/17/02). This volume contains the argument that earlier studies examining neuropathology were limited by the specialized and detailed neuropathology directed by (then) new guidelines. "Both technical preparation of tissues with perfusion fixation, osmium post-fixation and epoxy plastic embedding and sectioning, as well as recognition by pathologists of the enhanced morphology of lesions or of artifacts introduced by and made more visible by the technical changes and their shortcomings, made reporting of these studies less certain." Due to the specialized nature of the slide preparation and evaluation, this report (including open literature studies) was put forth to assist readers in understanding the technical and interpretational issues involved. These data are useful, but supplemental. No worksheet. M. Silva, 1/16/04

131 164089 "Re-evaluation of Selected Peripheral (Sciatic and Tibial) Nerve Tissues from a Previously Submitted Chronic Toxicity Study of Methyl Parathion to Rats [Huntingdon Life Sciences (formerly Bio/dynamics, Inc.) Project #87-3208; Study #3189-346, MRID 418538-01]," (Brennecke, L.H., Pathology Associated International; Cheminova Agro A/S, Lemvig, Denmark; Jellinek, Schwartz & Connolly, Inc., December 30, 1996). The author concluded there were no treatment-related effects. The re-read of the slides did not conform with EPA guidelines for a Pathology Working Group (PWG). These data were considered supplemental. No worksheet. M. Silva, 11/25/98.

CHRONIC TOXICITY, RAT

051, 052, 063 037188, 037189, 074202, "E 605 - Methyl (Parathion-methyl) Chronic Toxicological Study on Rats (Feeding Experiments Over Two Years)"; (Bayer, 3/31/81). Methyl parathion (94.8%) fed in the diet at 0, *2,* 10 and 50 ppm for 2 years; 50/sex/group; plasma and RBC cholinesterase inhibition indicated adequate dosing; blood chemistry measurements indicated liver and kidney effects at the high dose level, no evidence of oncogenicity effects; NOEL = 2 ppm (cholinesterase effects); initially reviewed as unacceptable (no diet analysis to verify levels of test article, needed frequency and description of diet preparation, spinal cord and peripheral nerves not examined by histopathology, needed summary tables

with actual number of tissues examined, no clinical observations on individual animals); but upgradeable (Remsen, 12/6/85). Record # 074202 contains diet analyses and stability (temperature and conditions not stated), individual clinical observations for a limited number of animals and individual gross autopsy findings. Still UNACCEPTABLE. Now not upgradeable. Gee, 10/16/89.
EPA One liner: Core Grade Supplementary as a chronic study; Core Minimum as an oncogenicity study.

CHRONIC TOXICITY, DOG

** 132 164091 "One Year Oral (Dietary) Toxicity Study of Methyl Parathion in Dogs," (Hatch, R.C., MPI Research, Mattawan, MI; Lab ID #: 668-003; 9/4/98). Methyl Parathion (95.8% pure) was fed in diet to beagle dogs (4/sex/dose) at 0, 0.3, 1.0, 3.0, 3.5 and 4 mg/kg/day at the beginning of the study. After 3 months on study, the 3.0 mg/kg/day group was placed on recovery (given untreated diet) for 30 days and then euthanized and discarded after measuring intraocular pressure. In addition, at this time 2 of the 4.0 mg/kg/day females were moved to the 3.5 mg/kg/day group and 2 of the 3.5 mg/kg/day males were moved to the 4.0 mg/kg/day group. The remaining 4.0 mg/kg/day females (2 dogs) and 3.5 mg/kg/day males (2 dogs) which were not transferred to other groups were euthanized and discarded. Systemic NOEL = 1.0 mg/kg--Females; 1.0 mg/kg--Males (Clinical signs: males at 4.0 mg/kg showed an increase in diarrhea and thinness and a female at 3.5 mg/kg developed clinical signs of epilepsy (this effect may have been idiopathic). Some biochemical parameters (calcium, albumin, total protein) were intermittently decreased in males (6-12 months) at 4.0 mg/kg/day. Females had decreased calcium, total protein, albumin and globulin were observed at 4.0 mg/kg/day (6 months--not measured at 12 months). Relative (adrenal/brain% x 10^3) adrenal weights were increased in a dose-related manner (significant at 4.0 mg/kg/day) after 12 months. Females at 3.5 mg/kg showed significantly decreased, dose-related absolute and relative spleen weights after 12 months. Males (2/4) at 4.0 mg/kg showed mild lymphoid cell depletion in the thymus gland after 12 months. Females showed pituitary gland cysts (mild) at 12 months, primarily at 3.5 mg/kg/day.) ChE NOAEL = 0.3 mg/kg (Males showed significantly inhibited Plasma ChE at 0.3 mg/kg. Plasma and RBC ChE were significantly decreased in both sexes at $\geq$ 1.0 mg/kg throughout the study.) Brain ChE NOEL = 1.0 mg/kg (Males showed significantly decreased caudate nucleus ChE at 4.0 mg/kg.) There were no treatment-related ophthalmological effects, including intraocular pressure and electroretinograms. Acceptable. M. Silva, 11/12/98.
040 011166, "Methyl Parathion: One Year Dog Study", (Pharmacopathics, 8/21/81). Methyl parathion (93.65%) in the diet at 0, 0.03, 0.1 and 0.3 mg/kg/day for one year; 8/sex/group; no effects noted; NOEL = 0.3 mg/kg/day (HDT); UNACCEPTABLE (MTD not achieved, incomplete histology); NOT UPGRADEABLE. Schreider, 3/20/85. In addition, this study is not acceptable since no ophthalmology was performed.
EPA One liner: Core Grade Supplementary.

098 No record number: Response to DPR review of the chronic dog study on methyl parathion. No worksheet, no data. M. Silva, 10/3/95.

070, 085; 090468, "A 13-Week Subchronic Toxicity Study of Methyl Parathion in Dogs Via the Diet Followed by a One-Month Recovery Period", (I.W. Daly, Bio/dynamics, Inc., Project No. 87-3209, 11/20/89). Methyl Parathion, 94.9%, lot #233690479, was administered in the diet to groups of 8 beagle dogs per sex at treatment levels of 0 (diet only), 0.03, 0.30, or 3.0 mg/kg/day for 13 weeks. At the end of the treatment period, 4 dogs per sex per group were terminated, and the remainder were placed on the control diet for a 4 to 6 week recovery period. Ophthalmoscopic, tonometric, and electroretinographic examinations were conducted, and cholinesterase levels measured, prior to, during, and after the treatment period. Plasma, RBC, and brain cholinesterase levels were consistently decreased at 3.0 mg/kg/day during the treatment period. Intra-ocular pressure was sporadically decreased (mid-dose females and high dose males) only in the recovery period. Systemic NOEL = 0.03 mg/kg/day (decreased intra-ocular

pressure); Systemic NOAEL > 3.0 mg/kg/day; Cholinesterase NOEL = 0.3 mg/kg/day. This is ACCEPTABLE AS A SUPPLEMENTAL STUDY, and no adverse effect is indicated (G. Chernoff, 5/22/90).

065 073970, 073974, Supplemental to 090468; draft study design and protocol; no worksheet (Gee, 10/16/89).

SUMMARY: The subchronic study (DPR No. 090468) was submitted for consideration in filling the deficiencies noted in the chronic study (DPR No. 011166), specifically, the concern regarding the lack of an MTD. In the subchronic study, significant plasma, RBC, and brain cholinesterase depression effects were observed at 3.0 mg/kg/day. This dose is 10 times greater than the high dose used in the chronic study (0.3 mg/kg/day). DPR now finds there are sufficient data to fill the chronic dog data gap. M. Silva, 5/2/96.

088 095250 "Data Evaluation Record, Methyl Parathion, Subchronic Oral Toxicity Study in Dogs," (Weir, R.J., EPA evaluation of the subchronic dog study, 9/18/90). This information was submitted to show that EPA had waived further requirements for a chronic dog study. M. Silva, 11/24/92.

No record number, pages only: A letter dated 9/11/90, from Cheminova was a request that DPR not make further decisions about methyl parathion in chronic dog studies until the US-EPA review had been received and evaluated. M. Silva, 11/24/92.

114 145815-145818 "Material in Support of Request for Reconsideration of Acceptability of Dog Chronic Toxicity Data," was submitted by Cheminova, Ltd., as a rebuttal document (March 27, 1996). No worksheet. M. Silva, 4/17/96.
118 150561 Twelve page 3-month interim report on a 1-year dog study with methyl parathion in beagle dogs initiated at MPI Research on April 30, 1996. The report, dated October 18, 1996, contains preliminary data on plasma and RBC cholinesterase inhibition and summary and individual data on intraocular pressure. Doses were 0, 0.3, 1.0, 3.0, 3.5 and 4.0 mg/kg. The mid-dose group of 3.0 was taken off treatment after 3 months and fed control diet for a 4 week recovery period. Cholinesterase was significantly inhibited at $\geq$ 1.0 mg/kg. No effect on intraocular pressure was noted up to the 3-month measurement. No worksheet. J. Gee, 11/19/97.

119 153151 Four page summary of results on the 1-year dog study with data for plasma and RBC cholinesterase results for 1, 3 and 6 months. See # 150561 for additional details. No worksheet. J. Gee, 11/19/97.

ONCOGENICITY, RAT

038 049211, "Bioassay of Methyl Parathion for Possible Carcinogenicity (Rats)", (Litton for NCI, 1979). Methyl parathion (94.6%) fed in the diet at 0, 20 and 40 ppm for 102 weeks; 20/sex in control group, 50/sex/treated group; decreased survival in females at high dose level; insufficient information to gauge potential adverse effects; insufficient data to set a NOEL; unacceptable (only two dose levels, no analysis of diet for test article, inadequate number of control animals, no analysis of time to tumor, no measurement of food consumption, no pathology summary, no hematology or blood chemistry), NOT UPGRADEABLE. Schreider, 3/21/85.
EPA 1-liner: Core Grade Supplementary. Not carcinogenic.

ONCOGENICITY, MOUSE

**094 098865, "Methyl Parathion: Study for Chronic Toxicity and Carcinogenicity in B6C3Fl Mice," (R. Eiben, Bayer AG Fachbereich Toxikologie, Study No.: T4027023, May 17, 1991). Methyl parathion (E120 technical grade, purity = 95.5%) was administered in the feed at concentrations of 0 (peanut oil), 1, 7, or 50 ppm to 15 or 50 B6C3Fl mice/sex/group for 52 or 104 weeks, respectively. Cholinesterase NOEL = 1 ppm/day based on inhibition of RBC Cholinesterase at $\geq$ 7 ppm and inhibition of plasma and brain Cholinesterase at 50 ppm. Systemic NOEL = 7 ppm based on increased body weights with decreased food consumption and increased liver and kidney weights in both sexes at 50 ppm. A treatment-related oncogenic effect was not observed in this study. Acceptable with no adverse effect. J. Kishiyama & M. Silva, 11/24/92.

038 927589 "Bioassay of Methyl Parathion for Possible Carcinogenicity (Mouse)", (Litton for NCI, 1979). Methyl parathion (94.6%) fed in the diet at 0, 62.5 and 125 ppm (changed to 20 and 50 ppm at week 37) for 102 weeks; 20/sex in control group, 50/sex/treated group, B6C3Fl mice; no adverse effects reported; NOEL cannot be established; UNACCEPTABLE (only two dose levels, no analysis of diet for test article, inadequate number of control animals, no analysis of time to tumor, no pathology summary, no hematology or blood chemistry, no food consumption data), NOT UPGRADEABLE. Schreider, 3/21/85.
EPA 1-liner: Core Grade Supplementary. Not carcinogenic.

086 088521, "Oncogenicity Feeding Study in Mice With E-120", (Bayer Study No. T4027023). Protocol for new study (see Record No. 098865, above). No worksheet (G. Chernoff, 7/2/90).
086 088522, "Pilot Dose-Finding Study for a Carcinogenicity Study in B6C3Fl Mice, Administration in the Feed Over 66 Days", (Eiben, R., Bayer AG, Study No. T5025378, 7/87). Results of a range finding study. No worksheet (G. Chernoff, 7/2/90).

086 088523, "Pilot Dose-Finding Study for a Carcinogenicity Study in B6C3Fl Mice, Administration in the Feed Over 65 Days", (Eiben, R., Bayer AG, Study No. T1025518, 7/87). Results of a range finding study. No worksheet (G. Chernoff, 7/2/90).

REPRODUCTION, RAT

****044 011171**, "Two-Generation Reproductive Study of Methyl Parathion in Rats", (Bio/dynamics, Report No. BD-80-139, 7/18/82). Methyl parathion, 93.6% pure, was given in the diet to Sprague-Dawley CD rats (15 males & 30 females/group) at 0 (acetone = vehicle), 0.5, 5.0 and 25 ppm for two generations (one litter/generation). Maternal NOEL = 5 ppm (marginal decrease in weight gain at the end of lactation); Maternal NOAEL > 25 ppm; Reproductive NOEL and NOAEL = 5 ppm (decreased pup survivability). Formerly reviewed as unacceptable (Schreider, 3/18/85) for no justification of dose levels, no characterization of test article, no litter standardization, and incomplete histopathology. The study was upgraded to ACCEPTABLE (M. Silva, 1/19/90) based on an EPA Memorandum resulting in a re-review of the study. Another reevaluation of the study, prompted by the rebuttal in Record No. 086795, resulted in the decreased pup survivability being identified as a POSSIBLE ADVERSE HEALTH EFFECT (G. Chernoff, 5/21/90).
EPA One liner: Core Grade Minimum.

081 086795, Supplemental to 011171; rebuttal arguments (G. Chernoff, 5/21/90).

053 037190, 037191, "E 605-Methyl (Methyl Parathion) Multigeneration Studies on Rats (Reproduction)", (Bayer, 2/8/82). Methyl parathion (95%) was given in the diet at 0, *2,* 10 and 50 ppm

for a three generation study; 10 males/group, 20 females/group. There were no pups surviving at the end of F2 generation in the high dose group; NOEL = 2 ppm; UNACCEPTABLE (needs QA statement and final report revisions, no analysis of diet for test article, food consumption not measured, no clinical observations. presented, incomplete necropsy data, gestation and lactation weights included in weekly female weights), NOT UPGRADEABLE. Parker, 12/5/85.

033 927643, "Methyl Parathion - Monograph Number Seven - Environmental Health Evaluation of California Restricted Insecticides (Toxicological Evaluations)", (P.M. Dolinger Assoc., 1979?, page 51). Summary of 3-generation study using methyl parathion (10 and 30 ppm in the diet) conducted by Woodard Research Corp. Reductions in survival noted for Fla, F1b, and F2a generations at 30 ppm and in the F-3a generation at 10 ppm; stillbirth rates were increased in F1b and F3b generations at 30 ppm; UNACCEPTABLE (no data), NOT UPGRADEABLE.
EPA One liner: Core Grade Supplementary.

SUMMARY: A consistent finding in the three rat reproduction studies on file was a decrease in pup survivability. In two of the studies (#Is 927643 and 037190) where the doses included 0, *2,* 10, 30 and 50 ppm, decreased survivability was observed at 10 ppm. In the third study (#011171) where the doses were 0, 0.5, 5.0, and 25 ppm, survivability was decreased at 25 ppm. Taken together, these data indicate decreased pup survivability is a consistent possible adverse effect with a NOEL = 5 ppm (Chernoff, 5/23/90).

TERATOLOGY, RAT

****068 085036,** "Embryotoxicity (Including Teratogenicity) Study with E120 TECHNICAL (Common Name: PARATHION-METHYL) in the Rat" (Research and Consulting Company AG, RCC 083553, 12/31/87). Technical methyl parathion, batch 230 606 003, 97% pure in 0.5% aqueous Cremophor EL was administered by oral intubation to groups of 25 mated Wistar/HAN female rats at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6 through 15 of gestation. An additional 10 females each were added to the 0 and 3.0 mg/kg/day groups for cholinesterase activity measurement. **Possible adverse effects:** Decreased maternal cholinesterase activity, maternal signs of organophosphate toxicity, decreased maternal weight gain, decreased maternal food consumption, fetal developmental delay determined by decreased fetal weight and delayed ossification, and a tendency toward increased resorptions, all at 3.0 mg/kg/day. Maternal NOEL = 1.0 mg/kg/day (signs of organophosphate toxicity, cholinesterase inhibition, decreased food consumption and weight gain). Developmental NOEL = 1.0 mg/kg/day (developmental delay and marginal increase in resorptions). ACCEPTABLE study. G. Chernoff, 10/12/89.

055 037196, "Parathion-Methyl Evaluation For Embryotoxic and Teratogenic Effects on Rats Following Oral Administration", (Bayer, 6/3/77). Methyl parathion (94.4%) by oral gavage at 0, 0.1, 0.3 and 1.0 on days 6-15 of gestation; 20 pregnant females/group; fetal body weight decreased in high dose group; NOEL cannot be determined; UNACCEPTABLE (need analysis of dosing solution; need individual data for body weight, food consumption, necropsy parameters, fetal exams, fetal weights and clinical observations.), POSSIBLY UPGRADEABLE. Parker, 12/4/85.
EPA One liner: Core Grade Supplementary.

031 927582, EPA summary of study identified as record #037196.

033 038392, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Teratogenicity, Mammalian Rat Studies", (Dolinger Assoc. Report, pages 48-49). Summary of journal article by Fish (1966) in which rats were injected i.p. with methyl parathion on day 9 or 15 of gestation; insufficient data for evaluation. Study by Tanimura et al. (1967) suggests that one i.p. injection of methyl parathion at 15 mg/kg on day 12 of gestation reduced fetal weight.
EPA One liner: Core Grade Supplementary.

TERATOLOGY, RABBIT

095 111287, "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Methyl Parathion Technical Administered Orally via Stomach Tube to New Zealand White Rabbits", (Alan M. Hoberman, Argus Research Laboratories, Inc., Horsham, PA., Report # 310-007, 11/16/91). Methyl parathion technical (95.7% pure) was administered by gavage to artificially inseminated New Zealand White [Hra:(NZW)SPF] female rabbits (19 or 20/group) on gestation days 6 through 18 at 0 (corn oil), 0.3, 3.0, and 9.0 mg/kg/day. Maternal cholinesterase NOEL < 0.3 mg/kg/day (Significant RBC Cholinesterase inhibition occurred at $\geq$ 3.0 mg/kg/day. A significant decrease in plasma Cholinesterase occurred at 9.0 mg/kg/day. Maternal Systemic NOEL: There were no significant maternal effects at any dose. Developmental NOEL = 3.0 mg/kg/day (There was an increased incidence in thickened areas of ossification in the ribs at 9.0 mg/kg/day). **Acceptable, with no adverse effects**. (H. Green & M. Silva, 11/6/92)

055 037197, "Parathion-methyl (Folidol M Active Ingredient) Study for Embryotoxic Effects on Rabbits After Oral Administration", (Renhof, M., Bayer AG Institute of Toxicology, Report No. 12907, 9/4/84). Methyl parathion, 95.7% pure in 0.5% aqueous Cremophor EL emulsion vehicle was administered by oral gavage to groups of 12-15 pregnant Himalayan CHBB:HM rabbits at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6-18 of gestation. No adverse effects were noted. Maternal and Developmental NOEL > 3 mg/kg/day. Initially reviewed as unacceptable but possibly upgradeable with submission of justification of dosing levels, all the individual animal data, a description of the dosing solution preparation, and an analysis of the dosing solution (Parker, 12/4/85). After review of the supplemental information provided in record nos. 085035 and 088518, the study remains UNACCEPTABLE and is now considered not upgradeable due to the lack of a MTD (G. Chernoff, 6/29/90).
EPA One liner: Core Grade Minimum

068 085035, "Supplement to Methyl Parathion (El2O) Study for Embryonic Effects on Rabbits After Oral Administration", (Bayer, 12/22/87). Supplemental to record no. 037197, consisting of a retrospective range finding study in rabbits at doses of 0, 0.3, 1.0, and 3.0 mg/kg/day. The only notable finding was a minimal reduction in RBC cholinesterase activity on days 14 and 19 in the high dose group (G. Chernoff, 7/2/90).

083 088518, "Additional Information to Methyl Parathion Study for Embryotoxic Effects on Rabbits After Oral Administration", (Renhof, M., Bayer AG, Report No. 12907, 12/22/87). Supplemental to record no. 037197, consisting of a dose justification based on a rat teratology study, individual animal data, test compound analysis, and an abbreviated study protocol (G. Chernoff, 7/2/90).

NOTE: Justification for the dose selection used in the rabbit teratology study (DPR Record No. 037197) has been provided in two separate documents. In the first (DPR Record No. 085035), the results of a retrospective range-finding study were presented. The only finding indicative of an MTD was a marginal decrease in RBC cholinesterase levels at 3.0 mg/kg/day, the highest dose tested. Plasma and brain cholinesterase levels were unaffected by the treatment, as were appearance, behavior, weight gain,

autopsy findings, and maternal deaths. The second justification (DPR Record No. 088518), was based on the results of an unacceptable rat teratology study (DPR Record No. 037196), in which a maternal MTD was not clearly established. These data for the rat study are considered inadequate, and inappropriate for dose justification in the rabbit study. Since the demonstration of a clear MTD was not achieved in either the original rabbit teratology study, or in the retrospective range finding study, this information is not sufficient to fill the data gap. DPR Record No. 111287 (Argus Research Laboratories, 11/16/91), however, is an acceptable rabbit teratology study and therefore, the data gap is filled. (M. Silva, 12/l/92).

TERATOLOGY, MOUSE

033 038392, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Teratogenicity, Mammalian Mouse Studies", (Dolinger Assoc. Report, page 49). Summary of journal article by Tanimura et al. (1967) in which mice were injected once i.p. with 20 or 60 mg/kg on day 10 of gestation; in high dose group 13 of 112 fetuses had cleft palate, fetal deaths elevated at the high dose level.
EPA One liner: Core Grade Supplementary.

GENE MUTATION

054 037192, "E120 Parathion-Methyl Salmonella/Microsome Test to Evaluate for Point Mutations (Salmonella Typhimurium)", (Bayer, 8/l/80). Methyl parathion (94.5%) tested at 0, 20, 100, 500, 2500, or 12,500 ug/plate +/- S9 with Salmonella strains TA 1535, TA 1537, TA 98 and TA 100; positive response with TA 1535 with S9 and TA 100 with and without S9; confirmed in repeat experiment; UNACCEPTABLE (no individual plate counts, no controls for -S9 series, unclear description of bacteriostatic activity, incomplete description of methodology), POSSIBLY UPGRADEABLE. Remsen, 12/6/85.

****054 037193,** "E120 Parathion-Methyl Folidol M Active Ingredient Salmonella/Microsome Test to Evaluate for Point Mutations (Salmonella Typhimurium)", (Bayer, 8/l/80). Methyl parathion (96.1%) tested at 0, 20, 100, 500, 2500 or 12500 ug/plate +/- S9 on Salmonella strains TA 1535, TA 1537, TA 98 and TA 100; positive response in TA 100 and probably TA 98; confirmed with repeat experiments; ACCEPTABLE. See also 37192. Remsen, 12/6/85.

033 038391, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Mutagenicity Microbial Studies", (Dolinger Report, pages 47-48). Summary of several journal articles on the potential genotoxic activity of methyl parathion; insufficient information to evaluate; weakly mutagenic to E. coli at 0.1 M, positive results for mutagenicity in four microbial systems were reported, references were also made to studies with bacterial systems in which methyl parathion did not increase mutation frequency (Schreider, 2/21/85).

CHROMOSOME EFFECTS

054 037194 “E120 Parathion-Methyl Folidol M - Active Ingredient Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect", (Bayer, 3/29/82). Methyl parathion (95.6%) tested in mouse micronucleus assay at 0, 10 or 20 mg/kg by oral gavage given twice at 24-hour interval; 5/sex/group; animals sacrificed after 6 hrs; 1000 PCE's evaluated; no increase noted, but positive control effective; UNACCEPTABLE (only a 6 hr sampling time, only 2 dose levels with no evidence of toxicity - dose

selection based on a pilot study where 2 x 10 mg/kg caused "somnolence"), NOT UPGRADEABLE. Remsen, 12/6/85.

**054, 064 037195, 074209-212, "E 120 Parathion Methyl - Dominant Lethal Test on the Male Mouse to Evaluate for Mutagenic Effect", (Bayer AG, 6/7/84). Methyl parathion (95.7%) tested at 0 or 10 mg/kg by oral gavage in mouse dominant-lethal assay; 46 males/group; mated 1:1 for 12 X 4 days; no adverse effect reported; initially reviewed as unacceptable (no positive controls included and no historical controls). Remsen, 12/6/85. Submission of document 121-064 containing three positive control studies with Endoxan in the same strain of mice and a compilation of historical control data in females over a period of years upgrades the study to ACCEPTABLE. Gee, 10/16/89.
031 927582, "Initial Scientific and Microeconomic Review of Parathion: Subpart II. B. Pharmacology and Toxicology", (EPA 540/1-75-001). Summary of a journal article. Single dose of methyl parathion tested on guinea pigs for testicular chromosome aberration. Although potential adverse effect on chromosome abnormalities was indicated, data are inadequate for evaluation. Remsen, 12/6/85.

033 038391, "Methyl Parathion - Monograph Number Seven: Environmental Health Evaluation of California Restricted Insecticides, Toxicological Evaluation Mutagenicity Microbial - Studies", (Dolinger Report, page 48). Summary of a journal article by Huang (1973) in which the effect of i.p.-injected methyl parathion on mouse chromosomes was examined; no aberrations were noted in bone marrow chromosomes in a group treated with 20 mg/kg. Remsen, 12/6/85.

DNA DAMAGE

**067 075728, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes - Methyl Parathion", (Microbiologica1 Associates, 6/22/89). Methyl parathion, lot 95IA-84, no purity stated; tested with primary rat hepatocytes from Fischer 344 male rat(s) at 0 (ethanol and medium), 0.0003, 0.001, 0.003, 0.01, 0.02 and 0.03)µl/ml of medium; tritiated thymidine incorporation over 18 - 20 hour incubation by autoradiography; scored 50 nuclei per each of three slides; 0.03 µl/ml was too toxic to score; no evidence of induction of unscheduled DNA synthesis; ACCEPTABLE. Gee, 10/16/89.

NEUROTOXICITY

**084 088519, "Methyl Parathion: An Acute Delayed Neurotoxicity Study in the Laying Hen (Gallus gallus domesticus)", (Beavers, J.B., J. Foster, B.Y. Cockrell and M.J. Jaber, Wildlife International Ltd., Project No. 232-111, May 1, 1990). Methyl parathion technical without xylene, 95.8%, Batch #95-lA-57, was administered to 16 adult hens at an initial dose of 250 mg/kg/day (16% above the LD50) with atropine, followed by a second dose of 215 mg/kg/day on day 21. Six hens died within a few days of the initial dosing, and two died within a few days of the second dosing. There were no deaths reported in the negative (corn oil vehicle) control, or the positive TOCP (600 mg/kg) control. Based on the absence of persistent clinical signs, ataxia, or remarkable histopathological findings, there is no evidence to suggest that methyl parathion causes acute delayed neurotoxicity within the experimental conditions of this study. The study is ACCEPTABLE, and no adverse health effect is noted (G. Chernoff, 6/29/90).

103 129644 This document is an adverse health disclosure for an acute neurotoxicity study with methyl parathion in rats. No worksheet. M. Silva, 10/10/95.

**** 129 164087** "Acute Neurotoxicity Study of Methyl Parathion in Rats," (Minnema, D.J., Hazleton Washington, Inc., Vienna, Virginia; Lab. Project ID #: HWA 2688-102; 5/31/94). Methyl Parathion technical (93.1% pure) was administered in a single gavage dose to Sprague-Dawley Crl:CD® BR rats at

0, 0.025, 7.5, 10.0 (males only) and 15.0 (females only) mg/kg. A Functional Operational Battery (FOB) and Locomotor Activity (LMA) were conducted at pre-test and 1.5 hours (time of peak effect), 1 and 2 weeks post-dosing (10/sex/dose). Assessments of plasma, RBC and regional brain cholinesterase were performed at pre-test, 1.5 hours post-dose (all dose groups) and at 2 weeks (control and high dose only). Neurotoxicity NOEL = 0.025 mg/kg (There were increased clinical observations and neurobehavioral effects observed in both sexes at $\geq$ 7.5 mg/kg. Males at $\geq$ 7.5 mg/kg and females at 15.0 mg/kg showed increased incidence and severity of demyelination. Cholinesterase NOEL = 0.025 mg/kg (There was significantly decreased plasma, RBC and brain ChE observed at $\geq$ 7.5 mg/kg in both sexes. At day 14, effects continued at the high dose (low and mid-doses were not assessed.)) Possible adverse effect (increased demyelination, neurobehavioral effects and significantly decreased ChE). Acceptable. M. Silva, 11/19/98.

121 - 0168 208907 "Pathology Re-Evaluation; Acute Neurotoxicity Study of Methyl Parathion in Rats," (O'Shaughnessy, D.; Hazleton Washington Study 2688-102, 1994; Cheminova A/S, Lemvig, Denmark; 3/21/01). This amendment to the study (DPR volume/record #: 121-129/164087) contains several corrections which do not alter the results or conclusions from the original report. Supplemental data. No worksheet. M. Silva, 1/14/04.

121 - 0169 208909 "Hazleton Study #2688-102 Acute Neurotoxicity Study of Methyl Parathion in Rats. Neuropathology Slide Reread." (Jortner, B.S.; Veterinary Neuropathologist, Blacksburg, VA; 6/19/02). This amendment to the study (DPR volume/record #: 121-129/164087) contains a reread of the pathology slides by Jortner, B., Pathologist. This reread was not performed according to USEPA Pathology Working Group recommendations, the information is considered to be supplemental. No worksheet. M. Silva, 1/14/04.

**** 130 164088** "Subchronic Neurotoxicity Study of Dietary Methyl Parathion in Rats," (Minnema, D.J.; Hazleton Washington, Inc. (HWA), Vienna, VA; Lab Project ID #: HWA 2688-103; 12/19/94). Methyl parathion technical (93.1% pure) was fed in diet to Sprague-Dawley Crl:CD®BR rats (10/sex) at 0, 0.5, 5 and 50 ppm for 13 weeks. Additional animals from the control and high dose animals (5/sex/dose) were designated as recovery (behavioral and cholinesterase) animals (weeks 14 - 17). These animals were also used for a limited FOB testing at weeks 13 & 16 or ChE at week 17. Systemic NOEL = 5.0 ppm (There were increased clinical observations, decreased food consumption and body weights in both sexes at 50 ppm. There were increased effects in the FOB (latency to first step, pupil response, fore-limb and hind-limb grip strength, tremors and other signs) in both sexes at 50 ppm. Alopecia was observed in both sexes at 50 ppm (1/6).) ChE NOEL = 0.5 ppm (Plasma ChE was significantly decreased in males at 50 ppm and in females at $\geq$ 5.0 ppm. RBC ChE was significantly decreased in both sexes at $\geq$ 5.0 ppm. Regional brain ChE was significantly decreased in males at $\geq$ 5.0 ppm and in females at 50 ppm.) No histopathological findings, including degenerative lesions, were reported. Possible adverse effect: Significant decrease in RBC and brain ChE, which, in some cases, did not return completely to control values after the recovery period. Acceptable. M. Silva, 11/25/98.

** 121 - 164 186610 "A Developmental Neurotoxicity Study of Orally Administered Methyl Parathion in the Rat," (Beyrouty, P.; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Laboratory Project ID#: 97574; 3/1/02). Methyl parathion (96.8% pure) was administered by gavage to mated Crl:CD®(SD)IGS BR (Sprague-Dawley; *Rattus norvegicus*) rats (32/dose) at 0 (corn oil), 0.03, 0.3 and 0.6 mg/kg from gestation day 6 to lactation day 10 and their offspring were treated by oral gavage at the same dose levels from day 11 to 21 *post partum*. Pups were allowed to grow to adulthood, then were tested for behavioral/activity/neurotoxicity effects at 60 days, then terminated at 70 days of age. Maternal NOEL = 0.3 mg/kg (F0 generation had increased salivation at 0.6 mg/kg.) Pup NOEL = 0.3 mg/kg (F1 pups at 0.6 mg/kg showed tremors and salivation post dosing.) Untreated F1 adult NOEL > 0.6 mg/kg (Effects observed in F1 pups/weanlings were not observed in adults when tested at 60 days of age or at

termination (70 days).) Cholinesterase activity was not measured. There were no treatment-related differences in brain measurements, observational battery or motor activity. No adverse effect. Acceptable. M. Silva, 5/24/02

121 - 0166 208898 "Positive Control Data from ClinTrials BioResearch Laboratory relevant to the Methyl Parathion Developmental Neurotoxicity Study," (Beyrouty, P., Robinson, K., ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Laboratory Project ID #s: 35109, 95353, 95352.1; 9/24/02). This volume was submitted in support of the definitive developmental neurotoxicity study in rat (DPR volume/record #: 121 - 164/186610), reviewed by DPR. These are supplementary data. No worksheet. M. Silva, 1/14/04.

121 - 125 164083 "Comments from Cheminova Agro A/S on California Department of Pesticide Regulation's Evaluation of Methyl Parathion as a Toxic Air Contaminant," (Reiss, R., Severn, D.J. and Neal, B.; Cheminova Agro A/S, Lemvig, Denmark; Jellinek, Schwartz & Connolly, Inc., October 20, 1998). This is supplemental information relevant to risk assessment for methyl parathion. No worksheet. M. Silva, 11/25/98.

121 - 0165 208894 "Cheminova's Response to a Draft Risk Assessment for Methyl Parathion Prepared by the California Department of Pesticide Regulation," (Cheminova A/S, Lemvig, Denmark; 12/19/03). This volume contains a response to various issues put forth in the DPR draft risk assessment for methyl parathion. This information is supplemental. No worksheet. Silva, 1/14/04

121 - 0167 208904 "Methyl Parathion - Review of Dermal Penetration Study in Rats (MRID #: 45471801)," (Shah, P.V., 5/29/02). This volume contains an EPA review of dermal penetration for methyl parathion. Nominal doses of [^{14}C-U ring]-methyl parathion were 1 and 12 ug/cm^2 (equivalent to 0.04 and 0.46 mg/kg body weight) with a dose exposure of 10 hours with a post-dose period of 4 days. Results of the applied dose ranged from 81.4% to 96.6% recovery. At both low and high doses, the dermal penetration of radioactivity was rapid. Absorption (Sum of cage wash, urine, feces, carcass) averaged 84.4 (± 7.6%) for the low dose and 79.4 (± 3.9%) for the high dose. Little remained in skin (including exposed skin and skin under the protective device)10 hours post-dosing (1.4 - 2.6%) and < 1% remained in the carcass. Excretion was primarily in the urine (78% low dose; 81.8% high dose). Greater than 96% of the absorbed dose was recovered in the urine of every animal. Feces contained a mean of 0.70% (low dose) and 1.4% (high dose) of the applied dose. These data are supplemental. M. Silva, 1/20/04.