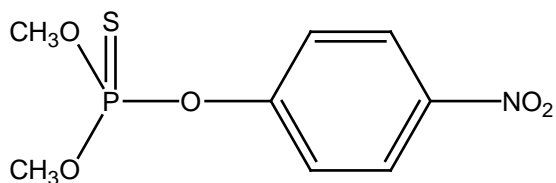


# **METHYL PARATHION**

## **RISK CHARACTERIZATION DOCUMENT**

**OCCUPATIONAL, AMBIENT AIR AND AGGREGATE  
EXPOSURES**

**Addendum to the 2004 Risk Characterization Document for Methyl  
Parathion Dietary and Ambient Air Exposures**



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## 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
BR.....	Breathing Rates
CSFII.....	Continuing Survey of Food Intake by Individuals
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
FOB.....	Functional Observational Battery
FQPA.....	Food Quality Protection Act
IREL.....	Interim Reregistration Eligibility Decision Document
LADD.....	Lifetime Average Daily Dosage
LD <sub>50</sub> .....	Median Lethal Dose
LC <sub>50</sub> .....	Median Lethal Concentration
LOEL.....	Lowest Observed Effect Level
MOE .....	Margin of Exposure
NOEL.....	No Observed Effect Level
OP.....	Organophosphorus ester
PAD .....	Population Adjusted Dose
PDP.....	Pesticide Data Program
RBC.....	Red Blood Cell
RCD.....	Risk Characterization Document
RED.....	Reregistration Eligibility Decision Document
REI .....	Restricted Entry Intervals
RfD .....	Reference Dose
RFC.....	Reference Concentration
RPF .....	Relative Potency Factor
SB950.....	Birth Defect Prevention Act of 1984
TAC.....	Toxic Air Contaminant
TACE .....	Toxic Air Contaminant Evaluation
TEF.....	Toxicity Equivalence Factor
USDA.....	United States Department of Agriculture
USEPA.....	U.S. Environmental Protection Agency
WH&S.....	Worker Health and Safety Branch at DPR

## I. SUMMARY

This risk assessment is an addendum to the 2004 Risk Characterization Document (RCD) for methyl parathion. It addresses the potential human health effects arising from exposure to methyl parathion from the air and occupational activities, as well as aggregate exposures from various combined scenarios that include dietary exposures.

The air exposure for the general population and the occupational exposure for workers from dermal contact were evaluated by the Worker Health and Safety (WH&S) Branch at the Department of Pesticide Regulation (DPR) (Cochran, 2010). The dietary exposure was assessed by the Medical Toxicology Branch at the DPR in the 2004 RCD for methyl parathion (Koshlukova and Reed, 2004). The critical toxicological endpoints used to calculate the risk from exposure to methyl parathion were established from the toxicological database reviewed in the 2004 RCD (Koshlukova and Reed, 2004).

### **I.A. INTRODUCTION**

Methyl parathion is an organophosphate (OP) insecticide and acaricide, which is registered to control insect pests on food, feed and fiber crops. Methyl parathion represents the oldest generation of anticholinesterase insecticides that exhibit marked mammalian toxicity. It is a Category I toxicant, and thus, is classified as a restricted-use pesticide. It can be applied only by certified applicators and there are no residential uses.

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. Methyl parathion was subsequently evaluated by the USEPA in the 2002 cumulative health risk assessment for the OPs and in the 2006 Interim Reregistration Eligibility Decision (IRED). The IRED identified risk reduction measures necessary to support the continued use of methyl parathion.

In California, a health risk assessment was completed in 1999, which evaluated methyl parathion as a Toxic Air Contaminant (TAC). For methyl parathion in the air, Department of Pesticide Regulation (DPR) established an acute inhalation reference concentration (RfC) of 0.42  $\mu\text{g}/\text{m}^3$  as the maximum allowable 24-hour concentration level. Methyl parathion is listed under the California Toxic Air Contaminant Identification and Control Act of 1983 (AB1807) as a Toxic Air Contaminant. In 2003, the DPR measured methyl parathion concentrations in the air following applications in walnut orchards and concluded that the air concentrations exceeded by 10-fold the RfC established in 1999. In 2004, the DPR completed a human risk characterization document (RCD) for dietary and ambient air exposures to methyl parathion. The main conclusion was that the potential acute exposure to methyl parathion from food sources exceeded the level considered protective of human health.

### **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. Dermal absorption of methyl parathion in rats is nearly complete, based on the excretion of over 90% of the total <sup>14</sup>C content or calculated from the amount of p-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<sub>50</sub>) ranged between 6-50 mg/kg (Category I oral toxicant). The dermal rat LD<sub>50</sub> 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 cholinesterase (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.

**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 (DNT)**- 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 increased 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, acute air and acute dermal exposures to methyl parathion.

Subchronic Toxicity: The subchronic oral NOEL of 0.03 mg/kg/day was selected to characterize the risk of seasonal dietary and air exposures 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 an 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.

**Exposure Assessment**- This document evaluated the human exposure to methyl parathion from air and occupational sources. The air exposure was estimated for four population subgroups representing the general population (Infant <6 months, Child 3-5 years old, Adult Female and Adult Male). The occupational exposure was estimated for workers who work with methyl parathion in aerial and ground applications, and for field workers. Aggregate exposures from various combined scenarios that included dietary exposures were also estimated for the general population and the workers.

The exposure from air and occupational sources was presented as an absorbed daily dose (ADD) and seasonal average daily dose (SADD). Chronic exposures from air and at occupational settings were not expected. Therefore, annual or lifetime average daily dosages (AADD or LADD) were not determined (Cochran, 2010).

Air Exposure: The air exposure resulting from the use of methyl parathion was estimated as a total exposure to both methyl parathion and its more toxic metabolite methyl paraoxon. The total exposure was the sum of the ADD for methyl parathion and the ADD for methyl paraoxon. The ADD for methyl paraoxon was multiplied by a toxicity equivalence factor (TEF) of 10 to account for its higher toxicity and then added to the methyl parathion ADD.

Ambient Air: The acute exposure to ambient air was based on the 95<sup>th</sup> percentile concentrations of methyl parathion and methyl paraoxon measured after applications to rice fields. The ADD for an Infant <6 months, a Child 3-5 years old, an Adult Female and an Adult Male was estimated as 0.0517 µg/kg/day, 0.0403 µg/kg/day, 0.0152 µg/kg/day and 0.0185 µg/kg/day, respectively. The SADDs were based on the mean ambient air concentrations of methyl parathion and methyl paraoxon. The total SADD was 0.0158 µg/kg/day (Infant < 6 months), 0.0123 µg/kg/day (Child 3-5 years), 0.0047 µg/kg/day (Adult Female) and 0.0051 µg/kg/day (Adult Male).

Application Site Air: The acute exposure to methyl parathion and methyl paraoxon in the air at the application sites was estimated for residents staying at 10-12 yards from treated walnut orchards. The ADDs were calculated using the highest measured concentrations of methyl parathion and methyl paraoxon (at 10 and 12 yards, respectively). The total ADDs were estimated as 4.311 µg/kg/day (Infant <6 months), 3.357 µg/kg/day (Child 3-5 years), 1.269 µg/kg/day (Adult Female) and 1.541 µg/kg/day (Adult Male).

Occupational Exposure: The occupational exposure for aerial mixer/loaders, ground boom applicators and field workers were estimated from biomonitoring data, collected for 24 h during and after work (Cochran, 2010). The biomonitoring-based ADDs were calculated as the 95<sup>th</sup> percentile of the absorbed dose. The occupational exposure for pilots, ground mixer/loader and airblast applicators was estimated as dermal and inhalation exposure during work hours from the Pesticide Handlers Exposure Database (PHED). For PHED-based exposures, default values of 50% and 100 % were used as human dermal and inhalation absorption, respectively. The ADDs ranged from 26.4 µg/kg/day to 307.0 µg/kg/day for handlers for aerial applications and 15.5 µg/kg/day to 265.0 µg/kg/day for handlers for ground applications. The ADDs for field workers ranged from 0.31 µg/kg/day (Walnut Sweepers) to 39.4 µg/kg/day (Cotton Scouts). The SADD (average absorbed dose for an 8 hour-working day) ranged from 1.3 µg/kg/day to 104 µg/kg/day for aerial application crews and from 0.16 µg/kg/day to 9.40 µg/kg/day for the field workers.

Dietary Exposure from food and drinking water: The dietary exposure was calculated in the 2004 RCD based on residues of methyl parathion in agricultural commodities (Koshlukova and Reed, 2004). The acute dietary exposure was calculated with the probabilistic (Monte Carlo) modeling. In the current document, the acute dietary exposure for Infant <1 year, Children 1-6 years and Males/Females 16+ years was used to estimate the acute aggregate exposure for the general population and workers. At 95<sup>th</sup>, 99<sup>th</sup> and 99.9<sup>th</sup> percentiles, the dietary exposure was 0.448 µg/kg/day, 1.066 µg/kg/day and 2.697 µg/kg/day for Infants < 1 year; 0.425 µg/kg/day, 0.824 µg/kg/day and 1.533 µg/kg/day for Children 1-6 years; and 0.178 µg/kg/day, 0.373 µg/kg/day and 0.769 µg/kg/day for Males/Females 16+ years. The chronic dietary exposure was calculated with the deterministic Point Estimate model for Infants < 1year, Children 1-6 years and the US population (spring season) as 0.002 µg/kg/day, 0.006 µg/kg/day and 0.003 µg/kg/day, respectively. The chronic dietary exposure was used to estimate the seasonal aggregate exposure for the general population and workers.

Exposure from drinking water: The Pesticide Data Program (PDP) multiple year drinking water monitoring showed no detection of methyl parathion or methyl paraoxon in more

than 1,400 samples in California (PDP, 2001-2006). Drinking water exposure estimated at the limit of detection (LOD) for total equivalent methyl parathion (i.e., including methyl paraoxon) resulted in <1% contribution to the dietary exposure.

#### Aggregate Exposure to the General Population.

Aggregate Dietary and Ambient Air Exposure: The potential acute aggregate exposure to methyl parathion was a sum of the acute dietary exposure and the ambient air exposure. The acute aggregate exposure varied from 0.19 µg/kg/day to 2.75 µg/kg/day at the DPR high-end dietary percentiles. Infants < 6 months were identified as the highest exposed population subgroup. The acute dietary exposure accounted for the majority (over 90%) of the aggregate exposure.

The aggregate seasonal exposure was a sum of the chronic dietary exposure (as surrogate for the seasonal dietary exposure) and the seasonal ambient air SADD. The aggregate SADD ranged from 0.0077 µg/kg/day (Adult Female) to 0.0183 (Child 3-5 years). The seasonal air exposure contributed 33%-89% to the aggregate exposure.

Aggregate Dietary and Application Site Air Exposure: The potential acute aggregate exposure to methyl parathion was a sum of the acute dietary exposure and the acute application site air exposure at 10-12 yards from the application site. The acute aggregate exposure varied from 1.45 µg/kg/day (Adult Female) to 4.76 µg/kg/day (Infant <6 months and Child 3-5 years) at the 95<sup>th</sup> dietary percentile; from 1.64 µg/kg/day (Adult Female) to 5.38 µg/kg/day (Infant <6 months) at the 99<sup>th</sup> percentile and from 2.04 µg/kg/day (Adult Female) to 7.01 µg/kg/day (Infant <6 months) at the 99.9<sup>th</sup> percentile. The acute air exposure was 62-91% of the aggregate exposure.

Aggregate Exposure to Workers: For acute exposures, it was assumed that a worker who handles methyl parathion (dermal exposure) could also be residing at 10-12 yards from the application site (inhalation exposure) and consuming food at the upper bound of exposure (oral exposure). The acute aggregate dietary and application site air exposure for Adult Male (1.72 µg/kg/day, 1.91 µg/kg/day and 2.31 µg/kg/day at the 95<sup>th</sup>, 99<sup>th</sup>, and 99.9<sup>th</sup> percentile, respectively) was added to the acute occupational ADDs. The highest acute aggregate exposure was estimated for Pilots (308.72 – 309.31 µg/kg/day at the 95<sup>th</sup>-99.9<sup>th</sup> dietary percentiles). The acute occupational exposure accounted from 84% to over 99% of the aggregate exposure for most of the workers groups (all handlers and the field workers Cotton Scouts and Corn Harvester). However, the non-occupational exposure was a significant contributor (57-88%) to the aggregate exposure for the field workers Walnut Rakers and Walnut Sweepers.

The seasonal aggregate exposure from occupational and non-occupational sources was calculated for workers exposed to methyl parathion for a total period of 21 days per year. The seasonal ambient air exposure to Adult Male (0.0051 µg/kg/day) and the chronic dietary exposure for the US population during the spring season (0.003 µg/kg/day) were added to the SADD for aerial crews and field workers. The seasonal aggregate SADD ranged from 0.16 µg/kg/day (Walnut Rakers) to 104 µg/kg/day (Pilots) and 104 µg/kg/day (Pilots). The occupational exposure accounted for nearly all (>98%) of the aggregate exposure.

## **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 MOEs: The acute MOE values for ambient air exposures to methyl parathion and methyl paraoxon ranged from 484 (Infant < 6 months) to 1,645 (Adult Female); the seasonal MOE values ranged from 1,899 (Infant <6 months) to 6,383 (Adult Female).

Application Site Air MOEs: The MOEs were calculated for acute air exposure to methyl parathion and methyl paraoxon to residents staying at 10-12 yards from the application site. All application site MOEs were less than 100 ranging from 6 (Infant < 6 months) to 20 (Adult Female).

Occupational MOEs. All acute occupational MOEs were less than 100. The MOEs for workers involved in aerial applications varied from < 1 to 2. The MOEs for Field Workers ranged from 1 to 81. The seasonal MOEs ranged from <1 to 23 for workers involved in aerial and ground applications, and from 4 to 97 for field workers. The Walnut Rakers was the only worker group, which had a seasonal occupational MOE greater than 100 (MOE of 188).

Dietary Exposure MOEs: At the 95<sup>th</sup> exposure percentile the acute dietary MOEs were 56, 59 and 140 for Infants <1 year, Children 1-6 years and Males/Females 16+ yrs, respectively. At the 99<sup>th</sup> and 99.9<sup>th</sup> percentiles, the MOEs were less than 100 for all population subgroups (ranging from 9 to 67). Infants were identified to receive the highest acute dietary exposure from methyl parathion. The chronic dietary MOEs were greater than 5,000.

Aggregate Exposure to the General Population.

Aggregate Dietary and Ambient Air Exposure MOEs: All acute aggregate MOEs for dietary and ambient air exposure to methyl parathion were below 100, except for Adult Female and Adult Male at the 95<sup>th</sup> percentile of dietary exposure, which had aggregate MOEs of 129 and 127. The contribution of the acute ambient air exposure to the aggregate exposure was minimal (<4%). Therefore, the aggregate MOEs were not significantly different than the acute dietary MOEs.

Aggregate Dietary and Application Site Air Exposure: The acute aggregate MOE for dietary and air exposure at 10-12 yards from the application site were below 100 for all population subgroups at the DPR high-end percentiles. The acute aggregate MOEs were the lowest for Infant < 6 months (5, 5, and 4) and Child 3-5 years (7, 6 and 5) at the 95<sup>th</sup>, 99<sup>th</sup> and 99.9<sup>th</sup> dietary percentiles, respectively. The acute application site air exposure had a substantial contribution (up to 91%) to the aggregate exposure. Consequently, the combined MOEs were significantly reduced (up to 11-fold) when the application site air exposure was added to the acute dietary exposure.

Aggregate Dietary, Air and Occupational MOEs to Workers: All acute aggregate MOEs were less than 100. The MOEs ranged from <1 to 1 for the aerial and ground crews involved in methyl parathion applications; and from 2 to 12 for field workers who were at the 10-12 yards from the application site and at the 95<sup>th</sup>-99.9<sup>th</sup> percentiles for dietary consumption of methyl parathion. The occupational exposure constituted 84-99% of the acute aggregate exposure for most of the worker groups and, thus, the aggregate MOEs were similar to their respective occupational MOEs. However, the non-occupational (dietary and air) exposure was a substantial component (57% and 88%) of the acute aggregate exposure for the field workers Walnut Rakers and Walnut Sweepers. Hence, the acute aggregate MOEs for these worker groups were significantly lower (up to 8-fold) compared to their occupational MOEs. All aggregate seasonal MOEs were less than 100 (ranging from 1 to 96), except for the worker group Walnut Rakers (MOE of 184). Because the seasonal occupational exposure accounted for nearly all (>98%) of the aggregate exposure the aggregate subchronic MOE were essentially the same as the respective occupational MOEs.

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. 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.

The acute application site air exposure was based on the highest concentrations of methyl parathion and methyl paraoxon measured at 10-12 yards from the application site. All MOEs for this potential “high-end” air exposure were below the benchmark of health protection (100) and thus, would require mitigation measures. Moreover, all MOEs for exposure to methyl parathion and methyl paraoxon at the farthest monitored distance from the field (57 yards) were also below 100. In conclusion, without a legal buffer zone, the 10-12-yard or 57-yard distances remain a probability for exposure. It is noteworthy that the methyl parathion use on walnuts is through a special local need (SLN) registration granted in 1997.

A key issue for the occupational exposure was the use of a default value of 50% as human dermal absorption for methyl parathion (Cochran, 2010). This value may be an underestimation of the real human dermal absorption, since methyl parathion *in vivo* data in animals revealed that the absorption via skin was nearly 100%. If a dermal absorption of 100% is also assumed for humans, the occupational MOEs would be 2-fold lower (ranging from <1 to 94) than those calculated by Cochran (2010).

A second issue for the occupational exposure was the use of biomonitoring data. Cochran (2010) estimated the occupational component from the biomonitoring exposure by subtracting the baseline 24-hr urinary p-nitrophenol (measured on the day prior to occupational exposure) from the 24-hr p-nitrophenol on the day of occupational exposure. The ADDs calculated from the excreted p-nitrophenol during the 0-24 h period may be an underestimation of the real exposure, because of the exclusion of a substantial amount of the p-nitrophenol excreted after the 24 h and at least until the 84 h post-exposure.

## **I.E. CONCLUSIONS**

The health risk assessment of methyl parathion was carried out for the general population and for workers. The assessment from dietary exposure was presented in 2004 (Koshlukova and Reed, 2004). The general population was represented by 4 population subgroups: Infant <6 months, Child 3-5 yrs, Adult Female and Adult Male. The workers included those who work with methyl parathion in aerial and ground applications; or field workers.

Single-route exposure scenarios were evaluated under acute or subchronic conditions for (i) inhalation exposures through the air for the general population and (ii) dermal exposures for workers in occupational settings. Aggregate exposures involving multiple routes were also calculated. The aggregate exposure for the general population included exposure from dietary sources with exposure contributions from ambient air or air at the application site. The aggregate exposures to workers included the occupational exposure with non-occupational contributions from dietary and air sources. A margin of exposure of 100 is considered sufficiently protective of human health when the NOELs are derived from animal studies.

Air Exposure. The acute and seasonal MOE values for ambient air exposures were greater than 480. All acute MOEs for application site air exposures for residents located from 10-12 yards to at least 57 yards from the application site were lower than the benchmark of 100. Consequently, mitigation should be considered for the general population adjacent to methyl parathion application sites and in conjunction with their potential aggregate exposures.

Occupational Exposure: The MOEs for acute exposure from methyl parathion were substantially lower than the benchmark of 100 for all agricultural workers and clearly indicated a health concern. The seasonal MOEs were lower than 100 for nine of the 10 evaluated workers groups. Consequently, mitigation should be considered for all occupational activities involving methyl parathion and in conjunction with the potential aggregate exposures.

Aggregate Exposure for the General Population: The MOEs for acute aggregate exposure from dietary sources with exposure contributions from ambient air were below the benchmark of 100 for Infants and Children at the 95<sup>th</sup> percentiles. The acute aggregate MOEs were below 100 for all population subgroups at the 99<sup>th</sup> and 99.9<sup>th</sup> percentiles.

All MOEs for acute aggregate exposure from dietary sources and air at the application site were below the benchmark of 100.

Aggregate Exposure for Workers: The MOEs for acute and seasonal aggregate exposures from dietary, air and occupational sources were lower than the benchmark of 100 for all agricultural workers.

The two key issues for the occupational exposure were: (1) The use of a default value of 50% as human dermal absorption for methyl parathion. This value may be an underestimation of the real human dermal absorption, since methyl parathion *in vivo* data in animals revealed that the absorption via skin was nearly 100%. If a dermal absorption of 100% is also assumed for humans, the occupational MOEs would be 2-fold lower (ranging from <1 to 94) than those calculated by Cochran (2010), (2) The workers

ADDs estimated from human biomonitoring data were based on the urinary p-nitrophenol from 24-h period measured on the day of occupational exposure. This may be an underestimation of the real exposure, because of the exclusion of a substantial amount of the p-nitrophenol excreted after the 24 h and at least until the 84 h post-exposure.

**Note:** In the 2006 IRED, the USEPA identified risk reduction measures necessary to support the continued use of methyl parathion (USEPA, 2006a). As of May 2007, the use of methyl parathion on 7 commodities (cabbage, dried beans, dried peas, hops, lentils, pecans, and sugar beets) was canceled (USEPA, 2007).

With the exception of cabbage and hops, the rest of the canceled commodities were included in the 2004 DPR dietary exposure assessment of methyl parathion (Koshlukova and Reed, 2004). However, these foods had minimal contribution (less than 1%) to the acute dietary risk. The probabilistic analysis revealed that the commodities Rice and Cottonseed-oil (on which methyl parathion is still registered for use) made the most significant contribution to the acute dietary exposure. The contribution of the different food-forms of Rice and Cottonseed-oil was up to 83% and 29%, respectively, of the total dietary exposure to Infants and Children. Because the impact of the canceled food on the total dietary exposure was insignificant, the dietary risk estimates would be essentially the same if these foods were excluded. Therefore, a new dietary exposure assessment (without the canceled food) was not needed.

On July 27, 2010 the USEPA issued a cancellation order for all product registrations containing methyl parathion, which was voluntarily requested by the registrants (USEPA, 2010). The effective date of these cancelations is December 31, 2012. The use of existing stocks of the end-use products will be prohibited after December, 2013.

## II. INTRODUCTION

### II.A. REGULATORY HISTORY.

The U.S. Environmental Protection Agency (USEPA) completed a Reregistration Eligibility Decision (RED) document for methyl parathion in 1999, which established an oral chronic Population Adjusted Dose (cPAD) of 0.00002 mg/kg/day as the maximum safe daily exposure level (USEPA, 1999). This PAD is one of the lowest of all the widely used pesticides. The main conclusions from the 1999 RED were that the acute dietary exposure of methyl parathion to children exceeded the safety levels by more than 800-fold, and that the occupational exposure to handlers of methyl parathion also posed significant risk concerns. Following the completion of the RED in 1999, the USEPA accepted voluntary cancellation of all methyl parathion uses on fruits and most uses on vegetables to reduce human risk from dietary exposures. Pesticide usage was also cancelled on non-food crops, such as ornamentals, grasses grown for seed, nursery stock and for mosquito control.

In 2002, the USEPA completed a cumulative health risk assessment of human exposure to multiple OPs by multiple pathways (USEPA, 2002). Methyl parathion was one of the evaluated OPs in the food and drinking water exposure pathways. Besides the commonly used uncertainty factors for inter-species and inter-individual sensitivity differences, the USEPA is required under the Food Quality Protection Act (FQPA) of 1996 to consider an additional safety factor of up to 10 to account for pre- and post-natal toxicity (USEPA, 1997b). For methyl parathion, an additional 3X safety factor was chosen to protect infants and children from exposure to methyl parathion. In the cumulative assessment, the FQPA factor of 3 was the highest safety factor used to adjust the toxicity of the OPs.

In 2006 the USEPA issued an Interim Reregistration Eligibility Decision (IRED), which identified risk reduction measures necessary to support the continued use of methyl parathion (USEPA, 2006a). The mitigation measures included canceled methyl parathion uses on 7 commodities, reduced methyl parathion application rates and numbers of applications, and prohibition of the use of human flaggers for methyl parathion applications. The IRED was the first phase in the reregistration process for methyl parathion. The final reregistration eligibility is pending consideration of the cumulative risks of the organophosphate class.

In California, a health risk assessment was completed in 1999, which evaluated methyl parathion as a Toxic Air Contaminant (Reed, 1999). For methyl parathion in the air, Department of Pesticide Regulation (DPR) established an acute inhalation reference concentration (RfC) of 0.42  $\mu\text{g}/\text{m}^3$  (Reed, 1999; Koshlukova and Reed, 2003). This maximum 24-h air concentration, if not exceeded, generally would provide adequate protection from non-oncogenic effects of methyl parathion. Based on the findings in the 1999 document, which was reviewed by the Scientific Review Panel (SRP) on air toxics, methyl parathion was listed under the California Toxic Air Contaminant Identification and Control Act of 1983 (AB1807) as a Toxic Air Contaminant.

Since the 1999 cancellation of many methyl parathion uses by the USEPA, its main use in California (through a SLN registration) has been on walnut trees. In 2003, the DPR measured methyl parathion concentrations in the air following applications in walnut



orchards in Tulare and San Joaquin counties in California (Wofford, 2003). This air monitoring was conducted to determine if new control measures were needed to reduce the public exposure to methyl parathion from its use on walnuts. The 2003 monitoring study concluded that the methyl parathion concentrations in the air exceeded by 10-fold the acute RfC established by the DPR (Reed, 1999).

In 2004, the DPR completed a risk characterization document (RCD) for dietary and ambient air exposures to methyl parathion (Koshlukova and Reed, 2004). The main conclusion was that the potential acute exposure to methyl parathion from food sources exceeded the level considered protective of human health. This was the case for all of the evaluated 19 population subgroups. In the 2004 risk assessment, infants were identified as the most highly exposed population subgroup from methyl parathion in the food. The dietary risk indicated that mitigation measures should be considered to reduce the human risk from acute dietary exposure to methyl parathion. In March 2005, the DPR notified the USEPA of the potential risk to methyl parathion residues in foods.

This risk assessment is an addendum to the 2004 RCD for methyl parathion. It addresses the potential human health effects arising from exposure to methyl parathion from ambient air and occupational activities, as well as aggregate exposures from various combined scenarios that include dietary exposures. The exposure for the general population from the ambient air and the occupational exposure for workers from dermal contact were evaluated by the Worker Health and Safety (WH&S) Branch at the DPR (Cochran, 2010). The dietary exposure was assessed by the Medical Toxicology Branch at the DPR in the 2004 RCD for methyl parathion (Koshlukova and Reed, 2004). The critical toxicological endpoints used to calculate the risk from exposure to methyl parathion were established from the toxicological database reviewed in the 2004 RCD (Koshlukova and Reed, 2004). There are no new toxicological data that would impact the critical endpoints established in the 2004 RCD.

## **II.B. USAGE.**

As of April 2007, methyl parathion is registered for use on alfalfa, almonds, barley, canola, corn, cotton, oats, onions, potatoes, rice, rye, soybeans, sunflowers, sweet potatoes, potatoes, wheat and yams (USEPA, 2006b; USEPA, 2007). The only methyl parathion product registered in California is the microencapsulated formulation Penncap-M®. In California, Penncap-M® is also used on walnuts for a special local need (SLN). This SLN registration was originally granted in 1997, due to the limited number of alternative registered pesticides to control the codling moth, the major walnut insect pest. The SLN has been continued to the present time.

From 1991 to 1999, over 1,100,000 pounds of methyl parathion were used in California. The amount applied in 1999 was 157,594 pounds. However, in 2000 the use in California decreased to 75,169 pounds, due to the cancellation of many food uses by the USEPA in 1999. The amounts applied continued to decrease in 2001 and 2002 (59,620 and 53,644 pounds, respectively), but showed an increased usage in 2003, 2004, 2005, 2006 and 2007 (73,337, 71,525, 78,821, 84,785 and 75,368 pounds, respectively). In 2007, the use on walnuts was 99% of the total methyl parathion use in California. Other uses accounted for less than 1% (DPR, 2007) (<http://www.cdpr.ca.gov/docs/pur/pur07rep/chmrpt07.pdf>).

## **II.C. MECHANISM OF ACTION.**

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.

## **III. TOXICOLOGY PROFILE**

The complete pharmacokinetic and toxicology database for methyl parathion for all routes and durations of exposures was presented in the 2004 RCD and in the 1999 Toxic Air Contaminant Evaluation (Reed, 1999; Koshlukova and Reed, 2004). Since the completion of the 2004 RCD, there were no new toxicological data for methyl parathion that would impact the established critical endpoints. The major pharmacokinetic and toxicology findings from the 2004 RCD, which were pertinent to the risk characterization of the air, occupational and aggregate exposures to methyl parathion in the present document are summarized below under Sections III.A. and III.B.

### **III.A. PHARMACOKINETICS**

Oral absorption of methyl parathion was considered complete (100%) in rat, guinea pigs, dogs and hens (Braeckman *et al.*, 1980; Braeckman *et al.*, 1983; Van Dijk, 1988). 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. Methyl parathion readily crossed the blood-brain barrier and the placenta following oral administrations to pregnant rats.

Dermal absorption of methyl parathion in rats was nearly complete, based on the excretion of over 90% of the total <sup>14</sup>C content (Abu-Qare *et al.*, 2000; Abu-Qare and Abou-Donia, 2000; Sved, 2001).

Pharmacokinetic studies were not available for a direct determination of the absorption from the inhalation route. In the absence of data for inhalation uptake, both the DPR and the USEPA assume a default of 100%. There was, however, experimental evidence that the methyl parathion absorption through the inhalation route may be comparable to the absorption through the oral route (i.e., 100%). In rats, the median lethal dose (LD<sub>50</sub>) following intravenous administration was in the same range as the lethal concentration (LC<sub>50</sub>) following inhalation exposure (Newell and Dilley, 1978). In addition, the same exposure levels from oral and inhalation routes achieved the same level of toxicity (ChE inhibition).

### **III.B. TOXICITY AND HAZARD IDENTIFICATION**

Methyl parathion is classified as a Category I toxicant, based on its acute toxicity. The risk of exposure to methyl parathion was characterized based on non-oncogenic effects, because of lack of clear evidence for oncogenic potential in the rodent bioassays. The experimentally determined highest dose at which no effects were observed (NOEL) was used in delineating the threshold dose for non-oncogenic effects. For methyl parathion, these effects included the inhibition of ChE activity (plasma, RBC, brain) and overt toxicity.

The critical acute oral NOEL of 0.025 mg/kg/day was from an acute oral neurotoxicity study in rats (Minnema, 1994). Acute dermal and inhalation studies were not available to determine the thresholds for acute dermal and inhalation toxicity. Consequently, the critical acute NOEL of 0.025 mg/kg/day for the oral route was used as surrogate for the NOELs for the inhalation and dermal routes.

The subchronic oral NOEL of 0.03 mg/kg/day was from a DNT study (Beyrouy, 2002). Subchronic inhalation studies were not available to determine the threshold for subchronic inhalation toxicity. Therefore, the subchronic NOEL for the oral route was used as surrogate for the NOEL for the inhalation routes.

The subchronic dermal NOEL of 0.03 mg/kg/day was from a 4-Week dermal neurotoxicity study in rats (Beyrouy, 2001). This NOEL was estimated (ENEL) from the lowest tested dose of 0.3 mg/kg/day by applying the default uncertainty factor of 10. The dermal ENEL would be the same as the subchronic NOEL of 0.03 mg/kg/day presented for the oral route.

The major use of methyl parathion in California is from May through August to control the insect pest codling moth on walnut trees. Due to this use pattern, the potential human exposure from air and occupational sources was assumed to be only of acute or subchronic (21 days/year) duration (Cochran, 2010). Because chronic exposures were not estimated in the exposure assessment, chronic NOELs and chronic toxicity endpoints are not discussed in the present document.

Table 1 summarizes the critical acute and subchronic NOELs, and the inhalation reference concentrations (RfCs) as established in the 2004 RCD and 1999 TACE (Reed, 1999; Koshlukova and Reed, 2003; Koshlukova and Reed, 2004).

**Table 1.** Critical NOELs, RfCs and Endpoints for the Risk Characterization of Methyl Parathion.

Route/Duration	NOEL <sup>a</sup> mg/kg/day	RfC <sup>b</sup> µg/m <sup>3</sup>	Critical Endpoint
<b>Acute</b>			
Oral	0.025	-	Inhibition of plasma, RBC and brain ChE <sup>d</sup> activities and neuropathy in an acute oral neurotoxicity study in rats (Minnema, 1994)
Inhalation <sup>c</sup>	0.025	0.42	
Dermal <sup>c</sup>	0.025	-	
<b>Subchronic</b>			
Oral	0.030	-	Inhibition of plasma, RBC and brain ChE activities in an oral DNT study in rats. Treatment was for 36 days: 15 days <i>in utero</i> , 10 days via lactation and 11 days direct dosing of the pups. (Beyrouy, 2002).
Inhalation <sup>e</sup>	0.030	0.51	
Dermal <sup>f</sup>	0.030	-	Inhibition of brain ChE activity and behavioral effects in a 4-week dermal neurotoxicity study in rats (Beyrouy, 2001)

**a/** NOEL, No-Observed Adverse Effect Level as established in the 2004 Risk RCD (Koshlukova and Reed, 2004).

**b/** RfC, Reference Concentration for methyl parathion as estimated by (Reed, 1999; Koshlukova and Reed, 2003).

RfC=NOEL/(MOE×BR). BR, Breathing Rate=0.59 m<sup>3</sup>/kg/day; MOE, Margin of Exposure (risks from non-oncogenic effects). MOE of 100 was considered prudent for protection against the methyl parathion toxicity.

**c/** The acute oral NOEL was used as surrogate for the acute NOEL for the dermal and inhalation routes.

**d/** ChE, Cholinesterase.

**e/** The subchronic oral NOEL was used as surrogate for the subchronic NOEL for the inhalation route.

**f/** This NOEL was estimated (ENEL) from the LOEL of 0.3 mg/kg/day by applying a 10-fold default factor.

## IV. RISK ASSESSMENT

### IV.A. EXPOSURE ASSESSMENT

Human exposure to methyl parathion could result during handling of the chemical by workers (occupational exposure) and from consuming food and water containing the pesticide residues (dietary exposure). The general population in regions where methyl parathion is applied could also be exposed to airborne 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.

#### **IV.A.1. Non-Dietary Exposure**

The occupational exposure for workers and the air exposure for the general population were evaluated in the Exposure Assessment Document (Cochran, 2010). The exposure from non-dietary activities was expressed as an Absorbed Daily Dose (ADD), Seasonal Average Daily Dose (SADD). Annual or Lifetime Average Daily Dosages (AADD or LADD) were not determined.

##### **IV.A.1.1. Air Exposure to the General Population**

The exposure of the general population to methyl parathion was estimated in the ambient air and in the air at the application site. In the ambient environment, methyl parathion is oxidatively converted to the more toxic metabolite, methyl paraoxon. The metabolite methyl paraoxon was found to co-exist with methyl parathion in the ambient air. Therefore, the air exposure resulting from the use of methyl parathion was estimated as a total exposure to both methyl parathion and methyl paraoxon.

The total exposure was estimated using a toxicity equivalence factor (TEF) approach, which was developed for the evaluation of methyl parathion as toxic air contaminant (Reed, 1999). Briefly, the toxicities of the two chemicals were assumed to be additive and the exposure to methyl paraoxon was multiplied by a TEF of 10 to convert to methyl parathion equivalence. This “methyl parathion equivalence” was subsequently added to the exposure of methyl parathion. In the TACE document, the TEF of 10 was established based on toxicity comparison between methyl parathion and methyl paraoxon in acute studies in rats (Reed, 1999). These studies reported the LD<sub>50</sub> values for both, methyl parathion and methyl paraoxon, or their potency in inhibiting plasma and brain cholinesterase activities.

Exposures were calculated for 4 population subgroups representing the general population: Infant<6 months, Child 3-5 yrs, Adult Female and Adult Male. The default body weights and breathing rates were 7.6 kg and 4.5m<sup>3</sup>/day (Infant< 6 months), 18 kg and 8.3 m<sup>3</sup>/day (Child 3-5 yrs.), 65.4 kg and 11.4 m<sup>3</sup>/day (Adult Female) and 71.8 kg and 15.2 m<sup>3</sup>/day (Adult Male), (Cochran, 2010).

The total air exposure (Total ADD or Total SADD) was estimated using the following formulas:

$$\text{Exposure}_{\text{MP}} = (\text{C}_{\text{MP}} \times \text{BR}) / \text{BW},$$

$$\text{Exposure}_{\text{MO}} = (\text{C}_{\text{MO}} \times \text{BR}) / \text{BW},$$

$$\text{Total Exposure} = \text{Exposure}_{\text{MP}} + \text{Exposure}_{\text{MO}} \times 10$$

C<sub>MP</sub>, C<sub>MO</sub>, methyl parathion or methyl paraoxon concentrations (shown in Table 3)

BR, Breathing rate and BW, Body Weight for the evaluated population subgroups (shown in Table 3)

**Ambient Air:** The exposure to ambient air concentrations of methyl parathion and methyl paraoxon was estimated at 4 outdoor sites in the rice growing counties of Colusa and Sutter (Cochran, 2010). The data were based on an air monitoring study conducted during the peak season of application to rice fields (Seiber *et al.*, 1987).

The highest ambient air concentration was detected at the Maxwell site in Colusa County (Seiber *et al.*, 1987). At this location, the 95<sup>th</sup> percentile ambient concentrations of methyl

parathion and methyl paraoxon were 29.7 ng/m<sup>3</sup> and 5.76 ng/m<sup>3</sup>, respectively. These values were used to calculate the ADDs methyl parathion and methyl paraoxon for the above four population subgroups (Cochran, 2010). The mean ambient air concentrations of methyl paraoxon and methyl paraoxon (8.44 ng/m<sup>3</sup> and 1.82 ng/m<sup>3</sup>) were used to calculate the SADDs (Cochran, 2010). The total exposure (total ADD or total SADD) was a sum of the exposure to methyl paraoxon multiplied by TEF of 10 and the exposure to methyl parathion (Table 2).

The total ADDs were 0.0517 µg/kg/day, 0.0403 µg/kg/day, 0.0152 µg/kg/day and 0.0185 µg/kg/day for an Infant, a Child (3-5 years old), an Adult Female and an Adult Male, respectively. The total SADDs were 0.0158 µg/kg/day for an Infant, 0.0123 µg/kg/day for a Child and 0.0047 µg/kg/day for an Adult Female and 0.0051 µg/kg/day for an Adult Male (Table 2).

**Table 2.** Exposure to Methyl Parathion and Methyl Paraoxon in the Ambient Air.

Population Subgroups	Absorbed Daily Dosage (ADD) µg/kg/day		
	Methyl Parathion <sup>a</sup>	Methyl Paraoxon <sup>a</sup>	Total Exposure <sup>b</sup>
<b>Infant &lt;6 months</b>	0.0176	0.0034	0.0517
<b>Child 3-5 yrs.</b>	0.0137	0.0027	0.0403
<b>Adult Female</b>	0.0052	0.0010	0.0152
<b>Adult Male</b>	0.0063	0.0012	0.0185
	Seasonal Average Daily Dosage (SADD <sup>c</sup> ) µg/kg/day		
	Methyl Parathion	Methyl Paraoxon	Total Exposure <sup>d</sup>
<b>Infant &lt;6 months</b>	0.0050	0.0011	0.0158
<b>Child 3-5 yrs.</b>	0.0039	0.0008	0.0123
<b>Adult Female</b>	0.0015	0.0003	0.0047
<b>Adult Male</b>	0.0016	0.0004	0.0051

**a/** ADDs for methyl parathion and methyl paraoxon were taken from Cochran (2010). The formula was presented in section IV.A.1.1; the default parameters (BW and BR) and the 95<sup>th</sup> percentile air concentrations at the Maxwell site were shown in Table 3.

**b/** The total ADDs (methyl parathion and methyl paraoxon) were estimated in the current document (see formula in section IV.A.1.1). The exposure of methyl paraoxon was multiplied by the toxicity equivalence factor (TEF) of 10 and added to the exposure of methyl parathion; the total exposure is in methyl parathion equivalence.

**c/** SADDs were based on the mean ambient air concentration of methyl parathion and methyl paraoxon (data were taken from Cochran, 2010, see also Table 3).

**d/** The total SADDs were estimated in the current document. The TEF approach was used to estimate the total exposure as in **b/**.

**Table 3.** Default Parameters and Air Concentrations Used to Calculate the Air Exposure to Methyl Parathion and Methyl Paraoxon.

Exposure Scenario	Default Parameters	
	BW (kg) <sup>a</sup>	BR (m <sup>3</sup> /day) <sup>b</sup>
Infant <1	7.6	4.5
Child 3-5 yrs	18	8.3
Adult Female	65.4	11.4
Adult Male	71.8	15.2
Air Monitoring	Air Concentration	
	MP (ng/m <sup>3</sup> ) <sup>c</sup>	MO (ng/m <sup>3</sup> ) <sup>d</sup>
Ambient Air (Maxwell Site) <sup>e</sup>		
95 <sup>th</sup> percentile	29.70	5.76
Mean	8.44	1.82
Application Site Air (San Joaquin County) <sup>f</sup>		
10 yards	4380	-
12 yards	3720	290
57 yards	1250	130

a/ BW- Body Weight

b/ BR- Breathing Rate

c/ MP, methyl parathion

d/ MO, methyl Paraoxon

e /The air concentrations were from the air monitoring study in Colusa County (Seiber *et al.*, 1987)

f/ The highest measured MP and MO concentrations in the DPR air monitoring study were at the San Joaquin County site at 10 and 12 yards from the application site, respectively (Wofford, 2003). The farthest monitored distance was at 57 yards from the same field. Sample collected at 12 and 57 yards contained pair concentrations of MP and MO.

The highest measured MP and MO values represented the 21-h time weighted average (TWA) concentrations (Wofford, 2003). Twenty-one hour TWA concentrations were derived from combined air concentrations from Sampling Interval 1 (11-hr air sampler run time) and Sampling Interval 2 (10-hr air sampler run time); at 29-ft for methyl parathion and 36-ft for methyl paraoxon, respectively, from the orchard edge.

-, Not detected

**Application Site Air:** The exposure to methyl parathion and methyl paraoxon at the application site was estimated using air concentrations measured near walnut orchards in 2002 at Tulare County and in 2003 at San Joaquin County (Wofford, 2003). The air monitoring studies were conducted by the DPR during the months of June and July, when the overall usage of methyl parathion (pound/season) is highest for walnuts. Only acute exposures were estimated, since seasonal or chronic exposures were not expected at the application sites.

The application site air exposure was calculated using the highest measured concentration of methyl parathion and methyl paraoxon. The highest concentration of methyl parathion (4380 ng/m<sup>3</sup>) was detected at 10 yards from the edge of the field in the San Joaquin County site. This sample did not contain measurable amounts of the metabolite methyl paraoxon. The highest concentration of methyl paraoxon (290 ng/m<sup>3</sup>) was detected at 12 yards from the same orchard. The total exposure was the sum of the ADD for methyl parathion at 10 yards and the ADD for methyl paraoxon at 12 yards. The ADD for methyl paraoxon was converted to a methyl parathion equivalent by applying a TEF of 10 and then added to the methyl parathion ADD (see formulas in Section IV.A.1.1). The default body weights and breathing rates, and the concentrations of methyl parathion and methyl paraoxon are summarized in Table 3. The total ADDs were 4.311 µg/kg/day, 3.357 µg/kg/day, 1.269 µg/kg/day and 1.541 µg/kg/day for an Infant, a Child (3-5 years old), an Adult Female and an Adult Male, respectively (Table 4).

**Table 4.** Acute Exposure to Methyl Parathion and Methyl Paraoxon at the Application Site.

<b>Absorbed Daily Dosage (ADD) µg/kg/day</b>									
<b>Population Subgroups</b>	<b>MP<sup>a</sup></b>	<b>MO<sup>b</sup></b>	<b>Total<sup>c</sup></b>	<b>MP</b>	<b>MO</b>	<b>Total</b>	<b>MP</b>	<b>MO</b>	<b>Total</b>
	<b>10-12yards<sup>d</sup></b>			<b>12 yards<sup>e</sup></b>			<b>57 yards<sup>e</sup></b>		
<b>Infant</b>	2.593	0.172	4.311	2.203	0.172	3.920	0.740	0.077	1.510
<b>Child 3-5 yrs.</b>	2.020	0.134	3.357	1.715	0.134	3.053	0.576	0.060	1.176
<b>Adult Female</b>	0.763	0.051	1.269	0.648	0.051	1.154	0.218	0.023	0.444
<b>Adult Male</b>	0.927	0.061	1.541	0.788	0.061	1.401	0.265	0.028	0.540

a/ MP, methyl parathion, b/ MO, methyl paraoxon

c/ Total exposure to methyl parathion and methyl paraoxon. For “Total Exposure”, the exposure to methyl paraoxon was multiplied by the toxicity equivalence factor (TEF) of 10 and added to the exposure of methyl parathion. The total exposure is in methyl parathion equivalence.

d/ ADDs for methyl parathion and methyl paraoxon were taken from Cochran (2010). MP and MO concentrations at 10 yards from the application site (San Joaquin County) and methyl parathion concentration at 12 yards (San Joaquin County) are shown in Table 3.

e/ Total Exposure to methyl parathion and methyl paraoxon was estimated at 12 and 57 yards from the San Joaquin County site for comparison to the total exposure at 10-12 yards. The air concentrations of methyl parathion and methyl paraoxon were from Wofford (2003), see also Table 3.

The total exposure at 10-12 yards represented the high-end of the potential air exposures. However, this exposure was based on concentrations of methyl parathion and methyl paraoxon measured in different samples. Eight samples collected at the San Joaquin County site contained both methyl parathion and its metabolite methyl paraoxon (Wofford, 2003). The highest measured pair concentrations of methyl parathion and methyl paraoxon was at 12 yards from the field (Table 3). A potential total exposure



based on the pair concentrations at 12 yards was very similar to the “high-end” total exposure (Table 3).

The total exposure was also calculated for the general population at 57 yards. This location was of interest, because it was the farthest monitored distance from the field in the San Joaquin County and a sample collected there contained pair concentrations of methyl parathion and methyl paraoxon (Wofford, 2003). The total exposures at 12 and 57 yards were shown for comparison with the high-end exposure at 10-12 yards (Table 4).

#### **IV.A.1.2. Occupational Exposure to Workers**

The occupational exposure assessment was conducted for workers involved in aerial and ground applications of methyl parathion, and for field workers (Cochran, 2010). The primary route of occupational exposure to methyl parathion was concluded to be through the skin. The WHS branch assumed a human dermal absorption of 50% and inhalation absorption of 100%. The occupational exposure through the inhalation route was less than 7% compared to the exposure from the dermal route.

Cochran (2010) used two different sources of data to estimate the workers’ exposure:

1. The occupational exposure for aerial mixer/loaders, ground boom applicators and field workers were given as estimated from biomonitoring data,

The biomonitoring studies were discussed in the exposure assessment (Cochran, 2010). All biomonitoring studies for aerial mixer/loaders and the field workers corn harvesters were conducted outside CA (i.e., Mississippi, Arizona, Louisiana, Arkansas, Florida, Washington, Wisconsin, Texas). Biomonitoring data from CA were available for the field workers walnut harvesters and cotton scouts. During the work day, the workers used the microencapsulated formulation Penncap-M (20.9% a.i.) and after work they resided in a motel. The metabolite p-nitrophenol was measured as a biomarker for exposure to methyl parathion in the urine of these workers for 24 h during and after work.

The biomonitoring data included exposure from all routes, and thus, represented an aggregate exposure. Cochran (2010) subtracted the baseline 24-h urinary p-nitrophenol (measured on the day prior to occupational exposure) from the 24-h p-nitrophenol on the day of occupational exposure. The resultant “corrected” exposure retained only the occupational exposure component, because the “baseline” exposure from non-occupational sources (e.g., diet and air) was excluded. In an earlier pharmacokinetic human study, 27% of the orally administered methyl parathion (2-4 mg) was recovered as p-nitrophenol in 24 h urine samples (Morgan *et al.*, 1977). Cochran (2010) applied the 27% urinary recovery of p-nitrophenol to the biomonitoring recovery data for workers to estimate their exposure. The total exposure to methyl parathion was calculated as an absorbed daily dose (ADD) using a formula<sup>1</sup> that accounts for the

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<sup>1</sup> ADD=M.V.R/BW (Cochran, 2010)

ADD = Absorbed Daily Dose (µg/kg/day)

M = concentration of p-nitrophenol in urine (µg/L)

V = urinary volume (L)

concentration of p-nitrophenol in the urine and urinary volume. The 95<sup>th</sup> percentile of the absorbed dose was selected as an upper bound of exposure (Cochran, 2010).

2. The occupational exposure for pilots, ground mixer/loader and airblast applicators was estimated as dermal and inhalation exposure during work hours from the Pesticide Handlers Exposure Database (PHED). The 90<sup>th</sup> percentile upper confidence limit of the 95<sup>th</sup> percentile exposure was calculated from the PHED for acute exposures.

The ADDs for workers as calculated by Cochran (2010) are summarized in Table 5. The ADD ranged from 26.4 µg/kg/day to 307.0 µg/kg/day for handlers for aerial applications and 15.5 µg/kg/day to 265.0 µg/kg/day for handlers for ground applications. The ADD estimates for field workers ranged from 0.31 µg/kg/day (Walnut Sweepers) to 39.4 µg/kg/day (Cotton Scouts).

The biomonitoring studies also measured the air concentration of methyl parathion in a field in Arizona. In this study, 5 air samples were collected from a personal breathing zone of 5 mixer/loaders. The average absorbed methyl parathion dose through inhalation during a 6 h work day was estimated as 0.02 µg/kg/day (Cochran, 2010). These authors concluded that the contribution of the air exposure to the total average absorbed dose was insignificant (< 1%). The total average absorbed dose (i.e., all routes of exposure) calculated from the biomonitoring data was 6.38 mg/kg/day. However, it should be noted that personal breathing zone air exposure in Arizona (0.02 µg/kg/day) is 77- fold lower than the air exposure for Adult Male at 10-12 yards from the application site in the San Joaquin County (1.541 µg/kg/day; see Table 4).

In the past, methyl parathion has been most extensively applied on rice and subsequently on tree fruit. Presently, the major use of methyl parathion in California is on walnuts (93% of total use) for control of the codling moth (*Cydia pomonella*), which can cause damage to the developing nut crop. The PennCap-M® Special Local Need (SLN) Label includes dormant and post-harvest applications of methyl parathion on walnut; although it is traditionally applied to walnut orchards by ground or air from May to August (DPR 2000b; (Ando *et al.*, 2002). Based on the seasonal use pattern, the aerial application crews and field workers were assumed to be exposed to methyl parathion for maximum of 21 days per year (Cochran, 2010).

The Seasonal Average Daily Dosage (SADD) was calculated as the average absorbed dose (ADD) for an 8 hour-working day. The SADD for application crews ranged from 1.3 µg/kg/day to 104.0 µg/kg/day for the aerial application crews and from 0.16 µg/kg/day to 9.40 µg/kg/day for the field workers (Table 5). Annual or Lifetime Average Daily Dosages (AADD or LADD) were not determined.

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R = ratio of molecular weights of methyl parathion and p-nitrophenol  
BW = body weight (kg)

**Table 5.** Occupational Exposure Estimates for Methyl Parathion.

<b>Work Task</b>	<b>ADD<sup>a</sup> (µg/kg/day)</b>	<b>SADD<sup>b</sup> (µg/kg/day)</b>
<b>HANDLERS</b>		
<b>Mixer/Loader (aerial)<sup>c</sup></b>	26.40	5.80
<b>Pilot<sup>d</sup></b>	307.00	104.00
<b>Ground Mixer/Loader<sup>d</sup></b>	265.00	66.00
<b>Airblast Applicator<sup>d</sup></b>	96.00	26.00
<b>Ground Boom Applicator<sup>c</sup></b>	15.50	1.30
<b>FIELD WORKERS</b>		
<b>Cotton Scouts<sup>c</sup></b>	39.40	9.40
<b>Corn Harvester<sup>c</sup></b>	11.19	8.33
<b>Walnut Harvest</b>		
<b>Rakers (walnuts)<sup>c</sup></b>	1.30	0.16
<b>Sweepers (walnuts)<sup>c</sup></b>	0.31	0.31

a/ Absorbed Daily Dosages (ADD) were from (Cochran, 2010).

ADDs estimated from biomonitoring studies represented the 95<sup>th</sup> percentile of the absorbed dose and were based on actual body weights of the workers.

ADDs estimated from the Pesticide Handlers Exposure Database (PHED) represented the 90<sup>th</sup> upper confidence limit of the 95<sup>th</sup> percentile exposure and were based on 50% dermal absorption, 100% inhalation absorption for methyl parathion, and an average body weight of workers of 77 kg (Cochran, 2010).

b/ Seasonal Average Daily Dosage (SADD) was calculated as the arithmetic mean absorbed dose normalized from an 8-hour workday. Cochran (2010) assumed a total of 21 days of exposure to methyl parathion during the year.

c/ ADD and SADD were based on biomonitoring data.

d/ ADD and SADD were based on PHED.

#### **IV.A.2. Dietary Exposure**

Exposure from foods: The dietary exposure to methyl parathion residues in food was presented in the 2004 RCD for methyl parathion (Koshlukova and Reed, 2004). The dietary exposure was calculated for the entire U.S. population and 18 selected populations using the Dietary Exposure Evaluation Model (DEEM<sup>TM</sup> v. 7.74, Exponent Inc.) and the food consumption database generated by the United States Department of Agriculture (USDA) during the 1994-1998 Continuing Survey of Food Intake by Individuals (CSFII). The dietary exposure was based on methyl parathion residues measured by monitoring programs such as PDP, DPR and FDA, and in field trials. The acute dietary exposure was assessed with the probabilistic Monte Carlo model and presented at the 95<sup>th</sup>, 99<sup>th</sup>, and 99.9<sup>th</sup> percentiles of exposure, as per the current DPR policy (DPR MT-3, 2006). The chronic dietary exposure was estimated using the arithmetic average of the measured pesticide concentrations in the deterministic Point Estimate model. The acute dietary exposure to methyl parathion was used in the current document to calculate (1) the aggregate exposure from non-occupational (dietary and air)

sources to the general population and (2) the aggregate exposure to workers from dietary, air and occupational sources.

The acute dietary exposure for Infants <1 year, Children 1-6 yrs and Males/Females 16+ yrs, is shown in Table 6. These values could be used as surrogate for the dietary exposure of the general population, which was represented in the air exposure assessment by Infant <6 months, Child 3-5 yrs., Adult Female and Adult Male (Cochran, 2010).

The age groups evaluated for the dietary exposure did not exactly match the general population subgroups.

Infants <1 year vs. Infant <6 months: The default parameters (BR and BW, Table 3) used by Cochran (2010) for Infant<6 months actually represented the midpoint between birth and 1 year old (i.e., 6 months; USEPA, 1997a). Therefore the dietary exposure estimated for the subpopulation Infants <1 year would be applicable for the Infant subgroup defined by Cochran (2010).

Children 1-6 yrs. vs. Child 3-5 yrs.: The food commodities consumed by the children groups 1-6 years and 3-5 years are likely to be similar. In addition, the body weight of Children 1-6 yrs (17 kg, mid point between 1-6 years of age) is close to that of Child 3-5 yrs, (18 kg, midpoint between 3 and-5 years (USEPA, 1997a). A separate DEEM™ dietary analysis indicated that the acute dietary exposure was similar for the children groups 1-6 yrs and 3-5 yrs (data not shown). Therefore the dietary exposure of Children 1-6 yrs. would be applicable for the subgroup Child 3-5 yrs.

Males/Females 16+ years vs. Adult Female and Adult Male: The selected default parameters for Adult Female and Adult Males (see Table 3) matched the age group of 18-74 years (USEPA, 1997a). Therefore the dietary exposure of Males/Females 16+ years population subgroup would be applicable for Adult Female and Adult Male. Males/Females 16+ years would be also used in this document to represent the workers group.

The general population could also be receiving subchronic exposure from methyl parathion residues in foods, due to its specific use pattern (application on walnuts from May to August). The DEEM™ does not have a subchronic module to estimate subchronic dietary exposures. However, the chronic dietary exposure for Infants <1 year and Children 1-6 yrs (Table 6) could be used as surrogate for the dietary exposure of Infant<6 months and Child 3-5 during the 21 day methyl parathion application season. However, it should be noted that the chronic dietary exposure estimate may be an underestimation of the dietary exposure for the population group represented by the high-end acute exposure.

The DEEM™ chronic module provides an estimate of the seasonal dietary exposure for the US population (see Attachment III.2. in (Koshlukova and Reed, 2004). This seasonal exposure is the average of exposure based on average pesticide residue and over the entire spectrum of the US population (age <1 month to 75 years). The seasonal dietary exposure for the US population during the spring season (Table 6) could be used as surrogate for the seasonal dietary exposure for the subpopulations Adult Female and Adult Male.

**Table 6.** Acute Probabilistic Dietary Exposure Estimates for Methyl Parathion.

Population Supgroup	Acute (Monte Carlo) Exposure <sup>a</sup> (µg/kg/day)		
	95 <sup>th</sup> Percentile	99 <sup>th</sup> Percentile	99.9 <sup>th</sup> Percentile
Infants < 1 year <sup>b</sup>	0.448	1.066	2.697
Children (1-6 years) <sup>b</sup>	0.425	0.824	1.533
Males/Females 16+ years <sup>c</sup>	0.178	0.373	0.769
	Chronic Dietary Exposure (µg/kg/day) <sup>d</sup>		
Infants < 1 year chronic <sup>e</sup>	0.002		
Children 1-6 yrs chronic <sup>e</sup>	0.006		
US population spring season <sup>f</sup>	0.003		

**a/** Acute dietary exposure was estimated with the probabilistic (Monte Carlo) modeling using the DEEM™ program based on residues in foods and did not include drinking water (Koshlukova and Reed (2004).

**b/** The acute dietary exposure for Infants <1 year and Children 1-6 yrs was used to estimate the acute aggregate exposure from dietary and air sources to Infant <6 months, Child 3-5 yrs., (see Tables 9 and 10).

**c/** The acute dietary exposure of the subgroup Males/Females 16+ years was used to estimate the acute aggregate exposure from dietary and air sources of Adult Female and Adult Male and the acute aggregate exposure from and dietary, air and occupational sources for workers (see Tables 9-11).

**d/** The chronic dietary exposure was estimated with the deterministic (Point Estimate) model (Koshlukova and Reed, 2004).

**e/** The chronic dietary exposure for Infants <1 year and Children 1-6 yrs was used to estimate the seasonal aggregate exposure from dietary and air sources to Infant <6 months, Child 3-5 yrs., (see Table 9).

**f/** The dietary exposure to the US population during the spring season (0.003 µg/kg/day) was slightly higher than the summer exposure (0.002 µg/kg/day; see Koshlukova and Reed, 2004; Attachment III.2.), and thus, was used to estimate the seasonal aggregate exposure from dietary, air and occupational sources for workers, and the seasonal aggregate dietary and ambient air exposures for Adult Female and Adult Male (Tables 9 and 11).

**Exposure from Drinking Water:** The dietary exposure estimated in the 2004 RCD did not include a drinking water component, because at that time, there were insufficient monitoring data on methyl parathion residues in drinking water (Koshlukova and Reed, 2004). Since then, more data became available through the PDP monitoring program, which is the most representative database, because it is designed to obtain pesticide residue data for risk assessments.

**PDP:** Starting in 2001, PDP began analyzing drinking water systems for methyl parathion and methyl paraoxon residues in various states (PDP, 2001-2006). The selected sites were regions of heavy agriculture, where known amounts of pesticides were applied. The water systems included municipal drinking water, groundwater wells used for potable water, and bottled water. Drinking water from California was sampled in 2001-2003 and 2005-2006. A total of 1418 California water samples were analyzed at the USDA contract laboratories at Sacramento, CA; Albany, NY and Denver, CO. None of the screened samples had quantifiable methyl parathion or methyl paraoxon residues. The residue LOD varied from 4.5 to 195 ppt. The residue LOD of the Sacramento laboratory was one of the lowest (6 ppt for methyl parathion and 9 ppt for methyl paraoxon) among the USDA national contract laboratories (Table 7).

**Table 7.** Anticipated Methyl Parathion and Methyl Paraoxon Residues in the California Drinking Water Used for Acute Dietary Exposure Assessments.

<b>PDP<sup>a</sup> CA drinking water</b>	<b>Year</b>	<b>Number of Samples</b>	<b>Number Detected Samples</b>	<b>LOD ppt<sup>b</sup></b>	<b>Analyzing Laboratory</b>
MP <sup>c</sup>	2001	134	0	6.0	Sacramento, CA
MO <sup>d</sup>		134	0	9.0	
MP	2002	2	0	4.5	Albany, NY
MO		2	0	9.8	
MP	2002	265	0	6.0	Sacramento, CA
MO		265	0	9.0	
MP	2003	272	0	6.0	Sacramento, CA
MO		272	0	9.0	
MP	2005	28	0	195	Denver, CO
MO		28	0	195	
MP	2006	9	0	195	Denver, CO
MO		9	0	195	

a/ PDP, Pesticide Data Program (PDP, 2001-2006)

b/ LOD, Limit of Detection

c/ MP, Methyl Parathion

d/ MO, Methyl Paraoxon

DPR monitors ground and surface water in California for methyl parathion, but with different LODs. There were no quantifiable residues measured in water from 1598 wells screened in California between 1986-2008 (DPR, 1986-2008). The residue LOD varied from 0.002-5 ppb. The DPR surface water screening reported 6341 samples taken between 1991-2006, which had no quantifiable residues. The residue LOD varied from 0.006 ppb to 1 ppb (DPR, 1991-2006).

The DPR water monitoring for concerns of aquatic life during the period of 1991-2006 reported 76 detections of methyl parathion ranging from 0.007 ppb to 1.7 ppb. All of these samples were from irrigation ponds, holding water sites, sloughs or drains (DPR, 1991-2006). In 1990, methyl parathion residues were detected in water samples from Colusa Basin Drain, which drains into the Sacramento River, at levels that were acutely toxic to aquatic organisms (up to 0.66 ppb) (DFG, 1990). The DPR subsequent monitoring studies for protection of the aquatic life resulted in mitigations measures (CDFA, 1991; DPR, 1992a; DPR, 1992b). However, irrigation water or water from holding sites and sloughs is not potable and these levels could not be used for human drinking water risk assessment.

Estimated Drinking Water Exposure: If methyl parathion and methyl paraoxon were assumed to be present at the LOD levels of the PDP California testing laboratory (6 ppt and 9 ppt, respectively, Table 7), the potential 95-99.9<sup>th</sup> percentile acute exposures for the population subgroups in Table 6 would be at or below 0.001 µg/kg/day. These exposures from drinking water would be less than 0.05% of the highest dietary exposure to methyl parathion from foods (Infant subgroup in Table 6). If the TEF of 10 was applied to

account for the higher toxicity of methyl paraoxon, the combined exposure to both methyl parathion and methyl paraoxon in drinking water would be 0.011, which is less than 0.5% of the highest dietary exposure from methyl parathion residues in food (Table 6). These exposures were estimated with the Point Estimate approach as described in the 2004 RCD (Koshlukova and Reed, 2004). Because of its insignificant contribution to the total dietary exposure, drinking water exposure is not included in Table 6. (i.e., the values presented in Table 6 would not change). The chronic exposure based on residues equal to ½ LOD (3 ppt for methyl parathion and 4.5 ppt for methyl paraoxon) was negligible (lower than  $10^{-5}$  µg/kg/day) and thus also not included in the chronic dietary exposure from foods (0.002 µg/kg/day for Infants; Table 6).

#### **IV.A.3. Aggregate Exposure**

Aggregate exposure is defined as exposure to a single chemical by multiple pathways and routes of exposure (USEPA, 2001). A pathway determines how a pesticide may enter the human body, e.g., through food, drinking water, air, occupational uses, etc. The relevant routes of exposure include oral, dermal and inhalation routes. In an aggregate exposure assessment, different routes can be combined when the duration of exposure and the toxic effect of the pesticide correspond.

Methyl parathion residues have been detected in the food and in the air. Consequently, multiple possible scenarios, involving potential exposure via all routes were predicted for the general population and for workers handling the pesticide. In this document, the aggregate exposures to methyl parathion considered:

1. Non-occupational exposures to the general population from dietary sources (oral route) with exposure contributions from ambient air or air at the application site (inhalation route, Table 8).
2. Occupational exposures to workers through the dermal and inhalation routes, with non-occupational contributions from dietary sources and air at the application site (Table 8).

**Table 8.** Components For Aggregate Exposures for the General Population and Workers to Methyl Parathion.

General Population <sup>a</sup>	Aggregate Exposure <sup>c</sup>	Dietary Exposure <sup>d</sup>		Air Exposure
	Acute	Probabilistic exposure		<u>Ambient air:</u> 95 <sup>th</sup> percentile ambient air exposure <u>Application site:</u> Highest measured values at 10-12 yards from the application site
	Seasonal (21 days/year)	Chronic (per capita) exposure as surrogate		<u>Ambient air:</u> Mean of the daily doses
Workers <sup>b</sup>	Aggregate Exposure <sup>d</sup>	Dietary Exposure	Ambient Air Exposure	Occupational Exposure
	Acute	Probabilistic exposure for Male/Female 16+	Highest air exposure for Adult Male at 10-12 yards from application site	95 <sup>th</sup> percentile of absorbed dose based on biomonitoring data 90 <sup>th</sup> upper confidence limit of the 95 <sup>th</sup> percentile dermal and inhalation exposure (based on PHED <sup>d</sup> )
	Seasonal	Chronic (per capita) exposure for US Population	Mean of the daily doses for Adult Male during the non-working hours	Mean absorbed dose from an 8-hour workday for each worker scenario

**a/** General Population (who does not handle methyl parathion) was divided into 4 population subgroups: Infant <6 months old; Child 3-5 years, Adult Female and Adult Male.

**b/** Workers who work with methyl parathion in aerial (Mixer/Loader, Pilot, Airblast Applicator) and ground (Ground Mixer/Loader, Ground Boom Applicator) applications; or field workers (Cotton Scouts, Corn Harvester, Walnut Rakers and Sweepers (Cochran, 2010).

**c/** Aggregate exposure for the general population was a sum of exposures from oral (dietary) and inhalation (air at application site) routes.

**d/** Aggregate exposure for workers was a sum of occupational exposures (dermal and inhalation routes) and non-occupational exposures via oral (dietary) and inhalation (application site air) routes. The occupational exposure for Pilot, Ground mixer/loader and Airblast Applicators was based on Pesticide Handlers Exposure Database (PHED); the occupational exposure for aerial mixer/loader, ground boom applicators and field workers were estimated from biomonitoring data. Exposure scenarios and levels are provided in Tables 9-11.

**e/** Dietary exposure was estimated in the 2004 RCD (Koshlukova and Reed, 2004). Acute dietary exposure was for Infants <1 year, Children 1-6 yrs and Males/Females 16+ yrs. Chronic dietary exposure for Infants <1 year, Children 1-6 yrs and US Population (spring season) was used as surrogate for seasonal exposure.



### IV.A.3.1. Aggregate Exposure to the General Population

#### Aggregate Dietary and Ambient Air Exposure:

The potential acute aggregate exposure to methyl parathion from dietary sources and from ambient air was calculated for the general population (Infant <6 months old, Child 3-5 years, Adult Female and Adult Male; Table 9). The acute dietary exposure was estimated at the 95<sup>th</sup>, 99<sup>th</sup>, and 99.9<sup>th</sup> percentiles (Table 6). The ambient air exposure was based on the 95<sup>th</sup> percentile of the methyl parathion ambient air concentration (Table 2). The dietary exposures for infants and children were added to their respective air exposures. The acute dietary exposure for Males/Females 16+ years old was added to the acute air exposures of Adult Male and Adult Female (Table 9). The acute air exposure was less than 10% of the aggregate (dietary and ambient air) exposure.

During the May-August application season on walnut trees, the general population could be exposed to methyl parathion through air and residues in the food. The aggregate seasonal exposure was estimated using the chronic dietary exposure and the seasonal ambient air exposure of methyl parathion. The chronic dietary exposure was employed as surrogate for the seasonal dietary exposure of the general population (Table 6). The seasonal air exposure was shown in Table 2. The seasonal air exposure was a significant contributor (33%-89%) of the aggregate exposure (Table 9).

**Table 9.** Aggregate Exposure to Methyl Parathion from Dietary and Ambient Air Sources for the General Population.

Population Subgroups	ADD <sup>a</sup> (µg/kg/day)			SADD <sup>b</sup> (µg/kg/day)
	95 <sup>th</sup> percentile	99 <sup>th</sup> percentile	99.9 <sup>th</sup> percentile	
<b>Infant &lt;6 months</b>	0.50	1.12	2.75	0.0178
<b>Child 3-5 yrs.</b>	0.47	0.86	1.57	0.0183
<b>Adult Female</b>	0.19	0.39	0.78	0.0077
<b>Adult Male</b>	0.20	0.39	0.79	0.0081

**a/** Acute aggregate ADD (Absorbed Daily Dosage) was a sum of the total acute ambient air ADD (Table 2) and the acute dietary exposure at the 95<sup>th</sup>, 99<sup>th</sup> or 99.9<sup>th</sup> percentiles (Table 6). Total ADDs were based on exposure to methyl parathion and methyl paraoxon.

**b/** Seasonal aggregate SADD (Seasonal Average Daily Dose) was a sum of the total (to methyl parathion and methyl paraoxon) seasonal ambient air exposure (Table 2) and the chronic dietary exposure (Table 6). The chronic dietary exposure was used as surrogate for the seasonal dietary exposure.

#### Aggregate Dietary and Application Site Air Exposure :

The acute aggregate exposure to methyl parathion from dietary sources and air at the application site was calculated for the general population (Table 10). The acute application site air exposure was shown in Table 4. It was based on the highest measured

concentrations of methyl parathion and methyl paraoxon (at 10-12 yards) at the treated walnut orchards (Cochran, 2010). The acute dietary exposure to methyl parathion at the 95<sup>th</sup>, 99<sup>th</sup>, and 99.9<sup>th</sup> percentiles was presented in Table 6. The dietary exposures for infants and children were added to their respective air exposures. The acute dietary exposure for Males/Females 16+ years old was added to the acute air exposures of Adult Male and Adult Female (Table 10). The acute air exposure accounted for 62%-91% of the aggregate (dietary and application site inhalation) exposure.

**Table 10.** Aggregate Exposure to Methyl Parathion from Dietary Sources and Application Site Air for the General Population.

Population Subgroups	ADD <sup>a</sup> (µg/kg/day)		
	95 <sup>th</sup> dietary exposure	99 <sup>th</sup> dietary exposure	99.9 <sup>th</sup> dietary exposure
<b>Infant &lt;6 months</b>	4.76	5.38	7.01
<b>Child 3-5 yrs.</b>	3.78	4.18	4.89
<b>Adult Female</b>	1.45	1.64	2.04
<b>Adult Male</b>	1.72	1.91	2.31

a/ Acute aggregate ADD (Absorbed Daily Dosage) was a sum of the total application site air ADD (Table 4) and the acute dietary exposure at the 95<sup>th</sup>, 99<sup>th</sup> or 99.9<sup>th</sup> percentiles (Table 6). The total acute application site air ADD was based on highest measured concentrations of methyl parathion and methyl paraoxon at 10 and 12 yards from the field, respectively (Table 3).

#### **IV.A.3.2. Aggregate Exposure to Workers**

The occupational exposure assessment assumed that the workers pilots, ground mixer/loader and airblast applicators are exposed to methyl parathion through dermal and inhalation routes during working hours (Cochran, 2010). In addition to the occupational exposure, workers could also be receiving a high-end of the non-occupational aggregate exposure from dietary and air sources, as members of the general population. Therefore, the aggregate exposure for workers involved exposure through the dermal, oral and the inhalation routes.

For acute exposures, it was assumed that a worker who handles methyl parathion could also be residing at 10-12 yards from the application site and consuming food at the upper bound of exposure. The acute dietary exposure to methyl parathion for workers (representative group Males/Females 16+ years old) was estimated at 95<sup>th</sup>, 99<sup>th</sup>, and 99.9<sup>th</sup> percentiles (Table 6). The acute application site air exposure for workers (representative group Adult Male) was estimated based on the methyl parathion and methyl paraoxon concentrations at 10-12 yards from the application site (Table 4). The acute occupational exposure for workers (95<sup>th</sup> percentile of the ADD) was shown in Table 5. The acute aggregate exposure to workers was a sum of their acute dietary exposure, acute application site air exposure and acute occupational exposure (Table 11). The acute occupational exposure accounted for the majority of the aggregate exposure (from 84% to over 99%) for all handlers of methyl parathion and the field workers Cotton Scouts and

Corn Harvester. However, the non-occupational exposure was the major component (57-88%) of the acute aggregate exposure for the field workers Walnut Rakers and Sweepers (Table 11).

**Table 11.** Aggregate Exposure to Methyl Parathion from Dietary, Air and Occupational Sources for Workers

Work Task	ADD <sup>a</sup> (µg/kg/day)			SADD <sup>b</sup> (µg/kg/day)
	95 <sup>th</sup> dietary exposure	99 <sup>th</sup> dietary exposure	99.9 <sup>th</sup> dietary exposure	
<b>HANDLERS</b>				
<b>Mixer/Loader (aerial)</b>	28.12	28.31	28.71	5.80
<b>Pilot</b>	308.72	308.91	309.31	104.00
<b>Ground Mixer/Loader</b>	266.72	266.91	267.31	66.00
<b>Airblast Applicator</b>	97.72	97.91	98.31	26.00
<b>Ground Boom Applicator</b>	17.22	17.41	17.81	1.30
<b>FIELD WORKERS</b>				
<b>Cotton Scouts</b>	41.12	41.31	41.71	9.40
<b>Corn Harvester</b>	13.62	13.81	14.21	8.33
<b>Walnut Harvest</b>				
<b>Rakers (walnuts)</b>	3.02	3.21	3.61	0.16
<b>Sweepers (walnuts)</b>	2.03	2.22	2.62	0.31

a/ Acute aggregate ADD (Absorbed Daily Dosage) was a sum of the acute occupational ADD of workers (Table 5), the total application site air ADD of Adult Male (Table 4) and the acute dietary exposure of Males/Females 16+ years old (Table 6).

b/ Seasonal aggregate SADD (Seasonal Average Daily Dose) was a sum of the seasonal occupational SADD of workers (Table 5), the total ambient air SADD of Adult Male (Table 2) and the chronic dietary exposure of the US Population during the spring season (Table 6).

For seasonal exposure, it was assumed that workers who handle methyl parathion for 21 days/year during the months of May to August could also be exposed to mean concentrations of methyl parathion in the ambient air and mean residues in the food. The seasonal ambient air exposure to Adult Male to methyl parathion and methyl paraoxon was 0.0051 µg/kg/day (Table 2). The seasonal dietary exposure to methyl parathion for the US population during the spring season of 0.003 (Table 6) was used as surrogate for the seasonal dietary exposure for workers. The seasonal occupational exposure to methyl parathion for workers was shown in Table 5. The seasonal aggregate exposure to workers was a sum of their seasonal ambient air exposure, seasonal dietary exposure and seasonal occupational exposure (Table 11). The seasonal occupational exposure accounted for nearly all (>98%) of the aggregate exposure. Consequently, the aggregate SADD were not significantly different than the occupational SADD.

## **IV.B. RISK CHARACTERIZATION**

In the case of methyl parathion, the process of risk characterization involves estimating the margin of exposure (MOE). The MOE for methyl parathion is calculated as the ratio of the critical NOEL, established for specific exposure duration, and an estimate of a human exposure. Critical NOELs were determined from oral and dermal studies, while the exposures were estimated from oral (dietary), inhalation (ambient air or air at the application site) and dermal (occupational) routes. Therefore, the MOE was calculated using the absorbed dose for either single route or aggregated multiple routes of exposure. Based on the available data on pharmacokinetics and toxicity dose-response relationship, the estimated absorption for oral and inhalation routes was 100% (Reed, 1999). A human dermal absorption of 50% was established by Cochran (2010) to determine the occupational exposure. Experimental evidence in laboratory animals, however, indicated that the dermal absorption of methyl parathion was nearly complete (100%, (Abu-Qare *et al.*, 2000; Abu-Qare and Abou-Donia, 2000; Sved, 2001).

The acute and subchronic 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.

The critical NOELs for methyl parathion were presented in Table 1. The acute NOEL of 0.025 mg/kg/day (Minnema, 1994) was used to calculate the MOE for acute exposures via all single routes (oral, inhalation and dermal) or the multiple aggregated routes. The subchronic NOEL of 0.03 mg/kg/day (Beyrouy, 2001; Beyrouy, 2002) was used to calculate the MOE for seasonal exposures via all single or aggregated routes. The estimated human exposures were shown in Tables 2, 4-6, and 9-11. The MOEs for the evaluated exposure scenarios are presented below in Tables 11-16.

### **IV.B.1. Non-Dietary Exposure**

#### **IV.B.1.1. Air Exposure to the General Population**

**Ambient Air MOEs:** The total ambient air exposure (to methyl parathion and methyl paraoxon) was used to calculate the risk for the general population (Table 12). The respective ambient air exposure estimates were presented in Table 2. The single day exposure was calculated based on the 95<sup>th</sup> percentile of the daily concentrations of methyl parathion and methyl paraoxon in the air. The seasonal exposure was calculated assuming a daily exposure pattern throughout an entire season of use (21 days/ year) and at the level reflected by the average daily air concentration (Cochran, 2010).

The acute MOEs for ambient air exposures varied from 484 (Infant<6 months) to 1645 (Adult Female) based on the rat acute NOEL of 0.025 mg/kg/day for (Minnema, 1994). The ambient air MOEs for seasonal exposure ranged from 1899 (Infant<6 months) to 6383 (Adult Female) based on the subchronic rat NOEL of 0.03 mg/kg/day (Beyrouy, 2002).

**Table 12.** Margins of Exposure for Methyl Parathion and Methyl Paraoxon Present in the Air.

Exposure Scenarios	MOE <sup>a</sup>			
	Infant <6 month	Child 3-5 yrs.	Adult Female	Adult Male
Ambient Air <sup>b</sup>				
<b>Acute</b>	484	620	1645	1351
<b>Seasonal</b>	1899	2439	6383	5882
Application Site Air <sup>c</sup>				
<b>Acute</b>				
<b>10-12 yards</b>	6	7	20	16
<b>12 yards</b>	6	8	22	18
<b>57 yards</b>	17	21	56	46

a/ MOE, Margin of Exposure. Acute MOE was defined as acute NOEL/ADD (Absorbed Daily Dosage); the acute oral NOEL of 0.025 mg/kg was based on plasma, RBC and brain ChE inhibition and neuropathology in rats (Minnema, 1994). Seasonal MOE was defined as subchronic NOEL/SADD (Seasonal Average Daily Dose). The subchronic MOE was based on a subchronic oral NOEL of 0.03 mg/kg/day for inhibition of plasma, RBC and brain ChE activities in immature rats (Beyrouy, 2002).

b/ The total ambient air ADDs and SADDs (for methyl parathion and methyl paraoxon) were shown in Table 2.

c/ The total acute application site air ADD (for methyl parathion and methyl paraoxon) were shown in Table 4.

**Application Site Air MOEs:** The acute MOEs were calculated for the general population for exposure of methyl parathion and methyl paraoxon at 10-12 yards from the application site at the San Joaquin County (Table 12). This total exposure represented the high-end of the potential air exposures, because it was based on the highest measured concentrations of methyl parathion (at 10 yards) and methyl paraoxon (at 12 yards). All acute MOEs were less than 100, ranging from 6 (Infant<6 months) to 20 (Adult Female).

MOEs were also calculated for total exposures at 12 yards and 57 yards from the field (Table 4). The sample at 12 yards contained the highest measured pair concentrations of methyl parathion and methyl paraoxon. The sample at 57 yards was of importance, because it was taken at the farthest monitored distance from the application site and also contained pair concentrations of methyl parathion and methyl paraoxon (Table 3). All total MOEs at 12 and 57 yards were lower than 100 (Table 12).

#### **IV.B.1.2. Occupational Exposure to Workers**

The acute and seasonal MOEs for occupational exposure to methyl parathion are presented in Table 13. The respective occupational exposure estimates were presented in Table 5. All acute occupational MOEs were less than 100 based on the acute NOEL of 0.025 mg/kg/day (Minnema, 1994). The MOEs varied from < 1 for Pilots, Ground

Mixer/Loader and Airblast Applicator to 2 for Ground Boom Applicators. The MOEs for Field Workers ranged from 1 (Corn Harvester) to 81 (Walnut Sweepers).

The MOE for seasonal exposures to methyl parathion were based on the subchronic dermal NOEL of 0.03 mg/kg/day (Beyrouty, 2001). The seasonal MOEs ranged from <1 to 23 for Handlers of aerial and ground applications, and from 3 to 188 for field workers. The Walnut Rakers was the only worker group, which had a seasonal occupational MOE greater than 100 (MOE of 188; Table 13).

**Table 13.** Margins of Exposure for Occupational Exposure to Methyl Parathion.

<b>Work Task</b>	<b>Acute MOE<sup>a</sup></b>	<b>Seasonal MOE<sup>b</sup></b>
<b>HANDLERS</b>		
<b>Mixer/Loader (aerial)</b>	1	5
<b>Pilot</b>	<1	<1
<b>Ground Mixer/Loader</b>	<1	<1
<b>Airblast Applicator</b>	<1	1
<b>Ground Boom Applicator</b>	2	23
<b>FIELD WORKERS</b>		
<b>Cotton Scouts</b>	1	3
<b>Corn Harvester</b>	2	4
<b>Walnut Harvest</b>		
<b>Rakers (walnuts)</b>	19	188
<b>Sweepers (walnuts)</b>	81	97

**a/** Margin of Exposure (MOE) was defined as acute NOEL/ADD; the acute oral NOEL of 0.025 mg/kg was based on plasma, RBC and brain ChE inhibition and neuropathology in rats, Minnema, 1994a. The occupational exposure estimates (ADD) for methyl parathion were shown in Table 5.

**b/** MOE was defined as subchronic NOEL/SADD. The subchronic MOE was based on a dermal ENEL of 0.03 mg/kg/day for the inhibition of ChE activities (brain and RBC) and cholinergic toxicity in rats (Beyrouty, 2001). The occupational SADD values were shown in Table 5.

#### **IV.B.2. Dietary Exposure**

The risk from exposure to methyl parathion residues in food and in the drinking water was presented in the 2004 RCD for methyl parathion (Koshlukova and Reed, 2004). The dietary risk of the population subgroups Infants (<1 year), Children 1-6 years) and Males/Females 16+ years, as estimated in the 2004 RCD is presented in Table 14. These population subgroups were used as representative of the general population and the workers in the aggregate exposure assessment.

The acute dietary MOEs were estimated using the acute NOEL of 0.025 mg/kg/day (Minnema, 1994) and the probabilistic exposures in Table 6. At the 95<sup>th</sup> exposure percentile, the MOEs were 56 (Infants <1 year), 59 (Children 1-6 yrs) and 140 (Males/Females 16+ yrs.). At the 99<sup>th</sup> percentile, the MOEs were less than 100 for all three population subgroups (MOEs of 23, 30 and 67, respectively). Similarly, at the 99.9<sup>th</sup> percentile the MOEs were less than 100 for all population subgroups, with Infants receiving the highest dietary exposure from methyl parathion (MOE of 9, Table 14).

The seasonal MOEs are shown in Table 13. They were calculated using the subchronic oral NOEL of 0.03 mg/kg/day (Beyrouy, 2002) and the chronic exposure estimated for Infant<1 year, Children 1-6 yrs. and the US population (during spring season Table 6). All seasonal dietary MOEs were equal or greater than 5,000.

**Table 14.** Margins of Exposure for Dietary Exposure to Methyl Parathion.

Population Supgroup	Acute MOE <sup>a</sup>		
	95 <sup>th</sup> Percentile	99 <sup>th</sup> Percentile	99.9 <sup>th</sup> Percentile
Infants (<1 year)	56	23	9
Children (1-6 years)	59	30	16
Males/Females 16+ years <sup>b</sup>	140	67	33
	Seasonal MOE <sup>c</sup>		
Infants<1 yrs	15000		
Children 1-6 yrs	5000		
US pop. spring season	10000		

a/ Acute Margin of Exposure (MOE) was defined as acute NOEL/acute dietary exposure. The acute oral NOEL of 0.025 mg/kg was based on plasma, RBC and brain ChE inhibition and neuropathology in rats, Minnema, 1994a. The acute probabilistic dietary exposure estimates were shown in Table 6.

b/ Seasonal MOE was defined as subchronic NOEL/chronic dietary exposure. The subchronic oral NOEL of 0.03 mg/kg/day was based on the inhibition of plasma, RBC and brain ChE activities (Beyrouy, 2002). The chronic (per capita) dietary exposure (used as surrogate for seasonal exposure) was shown in Table 6.

### **IV.B.3. Aggregate Exposure**

#### **IV.B.3.1. Aggregate Exposure to the General Population**

Aggregate Dietary and Ambient Air Exposure: The acute aggregate MOEs for dietary and ambient air exposure to methyl parathion were calculated using the acute aggregate exposure estimates (Table 9) and the acute NOEL of 0.025mg/kg/day (Minnema, 1994). At the 95<sup>th</sup> dietary exposure percentile, the MOEs were 50 (Infant<6 months), 54 (Child 1-6 yrs), 129 (Adult Female) and 127 (Adult Male). At the 99<sup>th</sup> and 99.9<sup>th</sup> percentile, the MOEs were less than 100 for all population subgroups (ranging from 9 to 64, Table 15). Since the contribution of the acute ambient air exposure to the aggregate exposure was minimal (<4%), the aggregate MOEs were not significantly different than the acute dietary MOEs.

**Table 15.** Margins of Exposure for Aggregate Exposure to Methyl Parathion from Ambient Air and Dietary Sources for the General Population.

Population Subgroups	Acute MOE			Seasonal MOE <sup>b</sup>
	95 <sup>th</sup> percentile	99 <sup>th</sup> percentile	99.9 <sup>th</sup> percentile	
<b>Infant &lt;6 months</b>	50	22	9	1685
<b>Child 3-5 yrs.</b>	54	29	16	1639
<b>Adult Female</b>	129	64	32	3896
<b>Adult Male</b>	127	64	32	3704

a/ Acute aggregate MOE (Margin of Exposure) was defined as acute NOEL/acute aggregate ADD. The acute NOEL of 0.025 mg/kg was based on plasma, RBC and brain ChE inhibition and neuropathology in rats (Minnema, 1994). The acute aggregate dietary and ambient air exposure estimates were shown in Table 9.

b/ Seasonal aggregate MOE was defined as subchronic NOEL/aggregate SADD. The subchronic NOEL of 0.03 mg/kg/day was based on inhibition of plasma, RBC and brain ChE activities in immature rats (Beyrouy, 2002). The seasonal aggregate dietary and ambient air exposure estimates were shown in Table 9.

The seasonal aggregate MOEs for dietary and ambient air exposure to methyl parathion were greater than 1600 (Table 15). These MOEs were calculated using the seasonal aggregate exposure estimates (Table 9) and the subchronic NOEL of 0.03 mg/kg/day (Minnema, 1994; Beyrouy, 2002).

Aggregate Dietary and Application Site Air Exposure: The acute aggregate MOEs for dietary and application site air exposure to methyl parathion were calculated using the acute aggregate exposure estimates (Table 10) and the acute NOEL of 0.025 mg/kg/day (Minnema, 1994).

The acute aggregate MOEs at 10-12 yards from the application site were below 100 for all population subgroups at the selected high-end dietary exposure percentiles (Table 16). At the 95<sup>th</sup> percentile, the aggregate MOEs ranged from 5 (Infants <6 months) to 17 (Adult Female). Similarly, at the 99<sup>th</sup> and 99.9<sup>th</sup> percentiles, Infants <6 months had the lowest aggregate MOEs (5 and 4, respectively), whereas Adult Female had the highest aggregate MOEs (15 and 12, respectively).

Unlike the acute aggregate MOEs for dietary and ambient air exposure that were very similar to the acute dietary MOEs, the aggregate MOEs for application site air and dietary exposure were significantly lower (up to 11-fold) compared to the acute dietary MOEs. This was because the acute application site air exposure at 10-12 yards had a substantial contribution to the aggregate exposure (up to 91%).



**Table 16.** Margins of Exposure for Aggregate Exposure to Methyl Parathion from Application Site Air and Dietary Sources for the General Population.

Population Subgroups	MOE <sup>a</sup>		
	95 <sup>th</sup> dietary exposure	99 <sup>th</sup> dietary exposure	99.9 <sup>th</sup> dietary exposure
<b>Infant &lt;6 months</b>	5	5	4
<b>Child 3-5 yrs.</b>	7	6	5
<b>Adult Female</b>	17	15	12
<b>Adult Male</b>	15	13	11

a/ Acute aggregate MOE (Margin of Exposure) was defined as acute NOEL/acute aggregate ADD. The acute NOEL of 0.025 mg/kg was based on plasma, RBC and brain ChE inhibition and neuropathology in rats (Minnema, 1994). The acute aggregate dietary and application site exposure estimates were shown in Table 10.

#### **IV.B.3.2. Aggregate Exposure to Workers**

The acute aggregate MOEs for workers from occupational and non-occupational (dietary and application site air) exposures to methyl parathion were calculated using the aggregate exposure estimates (Table 11) and the acute NOEL of 0.025mg/kg/day (Minnema, 1994).

All acute aggregate MOEs were less than 100 (Table 17). The MOEs ranged from  $\leq 1$  for Pilots, Airblast Applicator and Mixer/Loader involved in ground applications to 1 for Aerial Mixer/Loaders and Ground Boom Applicators, which were at 10-12 yards from the field and at the 95<sup>th</sup>-99<sup>th</sup> percentiles for dietary consumption of methyl parathion. For field workers, the lowest acute aggregate MOE was estimated as 1 for Cotton Scouts who resided at 10-12 yards from the field and were at 95<sup>th</sup>-99.9<sup>th</sup> dietary exposure percentiles. Walnut Sweepers and Rakers staying at the 10-12-yard distance had the highest acute aggregate MOEs (8-12 at the 95<sup>th</sup>-99.9<sup>th</sup> dietary percentiles).

The occupational exposure constituted from 84% to over 99% the acute aggregate exposure for most of the workers groups (all handlers and the field workers Cotton Scouts and Corn Harvesters). Consequently, the aggregate MOEs for these workers were very similar to their respective occupational MOEs (Tables 13). However, the acute non-occupational exposure was a substantial component (from 57% to 88%) of the acute aggregate exposure for the field workers Walnut Rakers and Sweepers. Consequently, the acute aggregate MOEs for these worker groups were significantly lower (up to 8-fold) compared to their occupational MOEs (see Tables 13 and 17).

The MOEs for the seasonal aggregate exposure were calculated using the seasonal aggregate exposure estimates (Table 11) and the subchronic NOEL of 0.03 mg/kg/day (Beyrouy, 2001; Beyrouy, 2002). The seasonal aggregate MOEs were less than 100 for all workers, except for the field worker Walnut Rakers (MOE of 184). The seasonal aggregate MOEs for handlers involved in aerial applications ranged from  $<1$  (, Pilot and Airblast Applicator) to 23 (Ground boom Applicators; Table 17). The MOEs for field workers varied from 3 (Cotton Scouts) to 184 (Walnut Rakers). Because the dietary and

ambient air exposures contributed less than 2% to the aggregate exposure, the seasonal aggregate MOE were not significantly different from the seasonal occupational MOEs (Table 17).

**Table 17.** Margins of Exposure for Aggregate Exposure to Methyl Parathion from Ambient Air, Dietary and Occupational Sources for Workers.

Work Task	Acute MOE <sup>a</sup>			Subchronic MOE <sup>b</sup>
	95 <sup>th</sup> dietary exposure	99 <sup>th</sup> dietary exposure	99.9 <sup>th</sup> dietary exposure	
<b>HANDLERS</b>				
<b>Mixer/Loader (aerial)</b>	1	1	1	5
<b>Pilot</b>	<1	<1	<1	<1
<b>Ground Mixer/Loader</b>	<1	<1	<1	1
<b>Airblast Applicator</b>	<1	<1	<1	<1
<b>Ground Boom Applicator</b>	1	1	1	23
<b>FIELD WORKERS</b>				
<b>Cotton Scouts</b>	1	1	1	3
<b>Corn Harvester</b>	2	2	2	4
<b>Walnut Harvest</b>				
<b>Rakers (walnuts)</b>	8	8	8	184
<b>Sweepers (walnuts)</b>	12	11	10	96

a/ Acute aggregate MOE (Margin of Exposure) was defined as acute NOEL/acute aggregate ADD. The acute NOEL of 0.025 mg/kg was based on plasma, RBC and brain ChE inhibition and neuropathology in rats (Minnema, 1994). The acute aggregate dietary, application site air and occupational exposure estimates were shown in Table 11.

b/ Seasonal aggregate MOE was defined as subchronic NOEL/aggregate SADD. The subchronic NOEL was 0.03 mg/kg/day based on inhibition of plasma, RBC and brain ChE activities and behavioral effects in rats (Beyrouty, 2001; Beyrouty, 2002). The seasonal aggregate dietary, ambient air and occupational exposure estimates were shown in Table 11.

## 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 under acute or subchronic conditions, including inhalation exposures through the air for the general population and occupational exposures for workers through dermal contact with methyl parathion. Aggregate exposures involving multiple routes were also calculated for the general population and for workers. The aggregate exposure for the general population included exposure from dietary sources with exposure contributions from ambient air or air at the

application site. The aggregate exposures to workers included the occupational exposure with non-occupational contributions from dietary and air sources.

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 fully 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 uncertainties associated with the hazard identification and the specific database from which NOELs were determined, were discussed in the 2004 RCD for methyl parathion (Koshlukova and Reed, 2004). The following uncertainties were considered noteworthy:

### **Route-to-Route Extrapolation:**

**Acute Toxicity:** Sufficient information was not available to determine acute NOELs for the methyl parathion toxicity through the dermal and inhalation routes. The critical NOEL of 0.025 mg/kg/day established for the oral route in rats was used as a surrogate for the acute dermal and inhalation NOELs. This NOEL was based on decreased ChE activities, cholinergic signs and peripheral nerve demyelination (Minnema, 1994). While potential uncertainties were introduced in the route-to-route extrapolation, several lines of evidence supported the assumption that methyl parathion is equally toxic through the oral, inhalation or dermal routes. First, the extent of absorption was similar among the three routes. This was based on direct measurements of absorption through oral and dermal routes in rats, which was nearly complete (>90% (Abu-Qare *et al.*, 2000; Abu-Qare and Abou-Donia, 2000; Sved, 2001). Data on inhalation absorption were not available. However, the LC<sub>50</sub> following inhalation exposure in rats was very similar to the i.v. LD<sub>50</sub>, thus suggesting that absorption through the inhalation route is comparable to the absorption through the oral route (i.e., 100%, (Newell and Dilley, 1978). Second, similar single doses (10-12 mg/kg/day) given orally (by gavage), dermally or through air exposure over 1 h produced similar effects in rats- 35-55% inhibition of the plasma ChE activity (Newell and Dilley, 1978; Abu-Qare *et al.*, 2001). Altogether, these results would be consistent with a comparable acute toxicity of methyl parathion among the three routes. Without experimental data, the cross-route equivalence of the dose was also assumed for humans.

**Subchronic Toxicity:** The NOEL for the subchronic oral toxicity of methyl parathion in rats was 0.03 mg/kg/day (Beyrouy, 2002). The estimated NOEL for the subchronic dermal toxicity in rats was the same as the NOEL established for the oral route (0.03 mg/kg/day, (Beyrouy, 2001). The subchronic oral and dermal NOELs were for similar durations (36 days of oral doses and 28 days of dermal treatment) and were based on the same toxicity endpoints (inhibition of plasma, RBC and brain ChE activities). The same subchronic NOEL for dermal and oral toxicity further indicated that, in rats, methyl parathion is equally toxic via the oral and the dermal routes. Studies were not available to establish a subchronic inhalation NOELs. Based on the default assumption of equivalent toxicity between the oral and inhalation routes, the level of 0.03 mg/kg/day was also used as a surrogate for subchronic inhalation.

## **V.C. EXPOSURE ASSESSMENT**

### **V.C.1. Non-Dietary Exposure**

#### **V.C.1.1. Air Exposure**

Uncertainties with the air exposure estimates were presented in the Exposure Assessment Document (Cochran, 2010). Specific areas of uncertainties and other considerations are highlighted in this section.

Ambient Air Exposure: The total exposure to ambient air concentrations of methyl parathion and methyl paraoxon was estimated for the general population in California. Air monitoring was conducted in 1986 at 4 outdoor sites in Colusa and Sutter counties during the months of May-June, which is the peak season of application of methyl parathion to rice (Seiber *et al.*, 1987). The highest air concentrations were measured at Maxwell, Colusa County, where the samples were collected at 24 h intervals. The exposures at this site were used to represent the realistic high-end of the potential ambient air exposures.

The ambient air exposure was estimated using the point estimate approach. In this approach, a single value is assigned to each variable parameter (e.g., breathing rates, body weights, air concentrations). The point estimate exposure is associated with uncertainties, because it is based on default exposure values, does not account for the variability of the air concentrations and does not provide information on the potential range of population exposures.

The exposure estimates were based on ambient air concentrations of methyl parathion and methyl paraoxon measured in the rice growing communities. In 1986, the main use of methyl parathion in California was on rice. Presently, the major use of methyl parathion in California is on walnuts (93% of total amount applied). Therefore, the calculated ambient air exposures for the general population may not be reflective of the air exposure to methyl parathion from its use on walnuts.

The ambient air exposure was based on the air concentrations of both the parent compound methyl parathion and its more toxic metabolite methyl paraoxon. Methyl paraoxon was found in 1986 to co-exist with methyl parathion in the air of Colusa County (Seiber *et al.*, 1987). In calculating the total exposure to methyl parathion and methyl paraoxon, a TEF of 10 was assumed for methyl paraoxon (Table 2). The TEF of 10 was established based on toxicity comparison between methyl parathion and methyl paraoxon in acute studies in rats. The TEF could be higher, because limited acute toxicity data in other laboratory animals indicated that methyl paraoxon could be as much as 23-fold more acutely toxic than methyl parathion. Extensive discussion on the TEF approach was presented in the 1999 risk assessment for methyl parathion under the TAC program (Reed, 1999).

Application Site Air Exposure: The air exposure at the application site was based on monitoring studies conducted for walnut applications in 2002 at Tulare County and in 2003 at San Joaquin County (Wofford, 2003). The methyl parathion concentrations measured at the San Joaquin County site were used to estimate the air exposure, because they were much higher (up to 10-fold) than the concentrations at the Tulare County site.

At the San Joaquin site, the highest concentrations of methyl parathion and methyl parathion were measured at 10 and 12 yards, respectively. For a farm-house located at the edge of the field, the 10-12 yard distance could be within its periphery (e.g., back yard). Currently in California, there are no buffer zones (or no-spray zones) between fields and homes to reduce the people's exposure to methyl parathion. Without a buffer zone, the distance of 10-12 yards is a probable position where potential residents could stay. Consequently, the exposure scenario at 10-12 yards was chosen to represent the high-end of the potential air exposures.

A total of 187 air samples were collected at the San Joaquin County site, eight of which contained both methyl parathion and its metabolite methyl paraoxon (Wofford, 2003). Samples were not collected at the orchard edge (0-ft distance) during the application period, because of concerns about contamination of the spray mist directly contacting the sampling equipment. If measured, the concentrations may have been just as high or higher than the highest measured residue levels reported in the study.

The air concentrations of methyl paraoxon ranged from 5% to 30% of the concentrations of methyl parathion. None of these 8 samples were collected at 10 yards from the walnut orchard, where the highest concentration of methyl parathion was measured. Therefore, uncertainty was added in the calculation of the total exposure, because the highest concentrations of methyl parathion and methyl paraoxon were from different samples, albeit, collected at similar distances (10 and 12 yards) from the application site. However, the high-end total exposure at 10-12 yards was very similar to the total exposure based on the pair concentrations of methyl parathion and methyl paraoxon at 12 yards. For example, the high-end total exposure at 10-12 yards for Infants was 4.311  $\mu\text{g}/\text{kg}/\text{day}$ , whereas their total exposure from the pair concentrations at 12 yards was 3.920  $\mu\text{g}/\text{kg}/\text{day}$ , (Table 4).

Finally, it should be noted that the two monitored orchards in the San Joaquin Valley had a total of 37 monitoring stations each collecting 8 samples over a 4-day period (Wofford, 2003). Therefore, the exposure estimated from these limited monitoring data may not capture the highest potential exposure level associated with the use of methyl parathion on walnuts.

### **V.C.1.2. Occupational Exposure**

The uncertainties associated with the occupational exposure assessment were discussed in the Exposure Assessment Document (Cochran, 2010). The following uncertainties were considered noteworthy:

Dermal absorption: Cochran (2010) estimated the acute and seasonal occupational exposures based on the human dermal absorption of 50% (Cochran, 2010). The DPR's WHS branch uses the dermal absorption value of 50% as default in the absence of compound-specific experimental data (DPR, 1996). However, 3 *in vivo* dermal absorption studies were available for methyl parathion. A pharmacokinetic study calculated the dermally absorbed methyl parathion in rats as 86%-97%, based on the amount of p-nitrophenol in the urine (Sved, 2001). In addition, two published papers on the *in vivo* methyl parathion dermal absorption reported that 91% of the administered single dose in rats were recovered in the urine, thus suggesting nearly 100% absorption via skin (Abu-Qare *et al.*, 2000; Abu-Qare and Abou-Donia, 2000). The principle finding

in the *in vivo* dermal studies was that nearly 100% of methyl parathion was absorbed via the skin in rats. Therefore, given the methyl parathion-specific *in vivo* data cited above, the 50% default value may be an underestimation (up to 2 fold) of the real human dermal absorption. USEPA considered 100% dermal absorption for humans as a default value in the 1999 methyl parathion RED document (USEPA, 1999) and for the 2006 IRED (USEPA, 2006a).

Biomonitoring data: Cochran (2010) used human biomonitoring data to estimate the exposure to aerial mixer/loader, ground boom applicators and field workers handling the microencapsulated formulation of methyl parathion. The occupational component from the biomonitoring exposure was calculated by subtracting the baseline 24-hr urinary p-nitrophenol (measured on the day prior to occupational exposure) from the 24-hr p-nitrophenol on the day of occupational exposure. Three areas of uncertainties regarding the use of biomonitoring data are discussed below:

1. Pharmacokinetic differences between dermal and oral routes: Cochran (2010) applied a 27% urinary recovery of p-nitrophenol to the workers' urinary recovery data for estimating their exposure. The 27% p-nitrophenol recovery was determined from a human study with 4 volunteers, which were given 1 to 4 mg methyl parathion orally (Morgan *et al.*, 1977). In the oral study, the excretion rate of p-nitrophenol was nearly complete by the end of 8 hours of exposure and no metabolite was detected beyond 24 hours of exposure. In contrast, the biomonitoring data showed that the urinary p-nitrophenol level was well above the baseline beyond day 3 post-exposure. For example, data in Table 18 for Worker 1 in Mississippi illustrate that the level of p-nitrophenol during the 0-24 h (exposure day) was less than half of the combined level from 0-84 h.

**Table 18.** Selected p-nitrophenol levels (p-NP) from the biomonitoring studies and from the oral studies by Morgan *et al.*, 1977.

Human Data p-PNP µg/l	Pre- screen	-24-0h <sup>a</sup>	0-24 h <sup>b</sup>	24-48 h	48-72h	72-84h	0-84 h
Worker 1 (Biom. MS)	4.86	1.91	13.9	4.37	6.73	8.11	33.11
Worker 6 (Biom. AZ)	3.68	2.26	15.1	5.75	2.43	7.17	30.45
Worker 9 (Biom. AZ)	0.64	1.07	19.6	7.27	1.58	5.39	33.84
Human, oral 4 mg <sup>c</sup>		0	0.34	1%	0	-	-

a/ p-nitrophenol levels used by Cochran,(2009; Table 1-I) as baseline. Biomonitoring data were taken from (Barney, 2001).

b/ Used in Cochran (2009, Table 1-I) to estimate the exposure to methyl parathion. The corrected exposure was total (0-24 h p-NP minus baseline (-24-0 h p-NP).

c/ Data from Morgan *et al.* (1977).

Thus, the 27% elimination data from oral exposure may underestimate the more protracted pharmacokinetics of dermal exposure. This same logic would be valid

for all occupational exposures similarly calculated. A published study in rats also reported markedly different pharmacokinetics of methyl parathion following dermal or oral exposure (Kramer *et al.*, 2002). In conclusion, the acute occupational exposure to methyl parathion estimated from the excreted p-nitrophenol during the 0-24 h period may be an underestimation of the real exposure, because of the exclusion of a substantial amount of the p-nitrophenol excreted after the 24 h and at least until the 84 h post-exposure.

Additional uncertainties with the use of Morgan *et al.* (1977) study are that the study had a very small sample size (only 4 subjects) and that the urinary creatinine data are exceptionally high, on the order of mg/g, compared to reference values (Barr *et al.*, 2002).

2. Pre-exposure baseline p-nitrophenol levels higher than levels after occupational exposure. The biomonitoring data showed some anomalies for having the pre-exposure baseline p-nitrophenol levels higher than the level after the occupational exposure. This was the case for (1) walnut harvesters (Table I-3 in Cochran, 2010) where 7 of 15 workers had up to 3-fold higher p-nitrophenol levels from non-occupational sources and (2) for cotton scouts (Table I-5 in Cochran, 2010) where 2 of 15 workers had higher baseline p-nitrophenol levels. For these cases, the corrected exposure was given as 0 for these workers (Cochran, 2010).
3. Applicability of Arizona data to California exposure scenarios. In the biomonitoring studies, the personal air concentration measured for 5 workers in the Arizona study (Barney, 2001) was 77-fold lower than the air concentration measured at 10-12 yards from the application site in CA, San Joaquin County (Wofford, 2003). Clearly, the air exposure from this biomonitoring study is substantially lower than the air exposure in CA.
4. Lack of clarity in the calculation of ADDs and SADDs based on biomonitoring studies: The derivation of the ADDs and SADDs from the biomonitoring data was not clearly detailed in Cochran (2010), leading to difficulty in reproducing the calculations. This adds to the uncertainty of the occupational exposure estimates based on the biological monitoring data. However, it does not alter the general conclusion of the occupational risk with respect to the benchmark MOE for health protection.

### **V.C.2. Dietary Exposure**

The general uncertainties associated with the dietary exposure assessment were discussed in the 2004 RCD for methyl parathion (Koshlukova and Reed, 2004). Specific uncertainties associated with the use of the dietary exposure from the 2004 RCD to estimate the aggregate exposure in the current document were presented in Section IV.A.2.

In summary, the age groups evaluated for the dietary exposure in the 2004 RCD did not exactly match the general population subgroups evaluated for air exposure by Cochran (2010). For that reason, the dietary exposure of the population subgroups Infants <1 year, Children 1-6 yrs and Males/Females was used as surrogate for the dietary exposure of the

general population (Infant <6 months, Child 3-5 yrs., Adult Female and Adult Male). In addition, The DEEM™ does not have a subchronic module to estimate subchronic dietary exposures. Consequently, the chronic dietary exposure estimated in the 2004 RCD for Infants <1 year, Children 1-6 yrs and the US population was used as surrogate for the seasonal dietary exposure of the general population subgroups.

### **V.C.3. Aggregate Exposure**

The aggregate non-occupational exposures to the general population included exposure from dietary sources with exposure contributions from ambient air or air at the application site. The aggregate exposures to workers included occupational exposure through the dermal contact, with non-occupational contributions from dietary sources and air at the application site. Specific areas of uncertainties associated with the aggregate exposure are highlighted below.

#### **V.C.3.1. Aggregate Exposure to the General Population**

Aggregate Dietary and Ambient Air Exposure: The potential acute combined exposure to methyl parathion from dietary sources and from ambient air was the highest for Infant <6 months (0.50-2.75) µg/kg/day at the 95<sup>th</sup>-99.9<sup>th</sup> dietary exposure percentiles; Table 9). The dietary exposure accounted for more than 90% of the total exposure.

Aggregate Dietary and Application Site Air Exposure: Infants were also identified to receive the highest combined acute exposure to methyl parathion from dietary sources and air at the application site (Table 10). Their exposure was 4.76-7.01 µg/kg/day at the 95<sup>th</sup>-99.9<sup>th</sup> dietary exposure percentiles. The exposure estimates were based on the methyl parathion and methyl paraoxon air concentrations at 10-12 yards from the field. The air exposure accounted from 62%-91% of the aggregate exposure.

#### **V.C.3.2. Aggregate Exposure to Workers**

The acute aggregate exposure for workers included occupational exposure from dermal contact, the total air exposure at 10-12 yards from the application site for the population subgroup Adult Males and an upper bound of dietary exposure for the population subgroup Males/Females 16+ years old. The occupational exposure accounted for 84-99% of the aggregate exposure for most of the worker's group (Table 11). However, the non-occupational exposure constituted (57-88%) of the aggregate exposure for the worker groups Walnut Rakers and Walnut Sweepers. The acute aggregate exposure could be up to 2-fold higher, if the occupational exposure were based on 100% dermal absorption.

### **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. Non-Dietary Exposure**

### **V.D.1.1. Air Exposure**

Ambient Air Exposure: The acute MOEs for ambient air exposure to methyl parathion and methyl paraoxon in the rice growing communities ranged from 484 (Infant <6 months) to 1645 (Adult Female; Table 12). All seasonal exposures were greater than 1890. These MOEs may not be reflective of the risk to the general population from the current major use of methyl parathion on walnuts.

Application Site Air Exposure: The acute MOEs ranged from 6 (Infant <6 month) to 20 (Adult Female). These MOEs reflected a potential high-end total exposure scenario, in which residents would be exposed to the highest measured concentrations of methyl parathion and methyl paraoxon at 10-12 yards from the treated walnut orchard (Table 12). Without a buffer zone to restrict human presence, the possibility for exposure at 10-12 yards could not be excluded. It should be noted that all MOEs for a total exposure at the farthest monitored distance from the application site (57 yards) were also lower than the benchmark of 100 (ranging from 17 to 56; Table 12). In conclusion, the application site air MOEs were below the health protective level of 100 for residents staying near the application site (10-12 yards) and to at least 57 yards from the treated orchard.

### **V.D.1.2. Occupational Exposure**

The occupational MOEs for acute exposure to methyl parathion varied from <1 to 81 for the different worker exposure scenarios (Table 13). These MOE values were calculated using the animal-based critical acute NOEL of 0.025 mg/kg/day and were clearly below the benchmark level of 100. The MOEs for seasonal exposure to methyl parathion were calculated using a rat NOEL for subchronic dermal exposure of 0.03 mg/kg/day. With their range of <1-97 the seasonal MOEs also did not achieve the human health protective benchmark of 100. Walnut Rakers was the only worker group, which had a seasonal occupational MOE greater than 100 (MOE of 188; Table 13).

The *in vivo* human dermal absorption of methyl parathion is not known. Because of the uncertainty in the dermal absorption of methyl parathion (50%) established by Cochran (2010), providing a reliable estimation of the worker exposure risk would be difficult. In this respect, the occupational MOE values could be 2-fold lower than the MOEs shown in Table 13, if they were based on 100% dermal absorption for methyl parathion reported in the rat *in vivo* studies (Abu-Qare *et al.*, 2000; Abu-Qare and Abou-Donia, 2000; Sved, 2001). In this case, the acute occupational MOEs would range from < 1 to 49 and the seasonal MOEs would range from < 1 to 94.

In conclusion, regardless of the assumed human dermal absorption (50% or 100%), the MOEs for acute and seasonal exposures to methyl parathion were below the health protective level of 100.

## **V.D.2. Dietary Exposure**

The uncertainties associated with the dietary MOEs were discussed in the 2004 RCD (Koshlukova and Reed, 2004). In summary, all acute dietary MOEs were below the benchmark of 100 at the 95-99.9<sup>th</sup> exposure percentiles (Table 14). Males/Females 16+ years was the only population subgroup, which had a dietary MOE greater than 100 (MOE of 140) at the 95<sup>th</sup> percentile.

### **V.D.3. Aggregate Exposure**

#### **V.D.3.1. Aggregate Exposure to the General Population**

Aggregate Dietary and Ambient Air Exposure: With the exception of Adult Females and Adult Males at the 95<sup>th</sup> dietary exposure percentile, all acute aggregate MOEs were lower than 100. The MOEs of Adult Females and Adult Males at the 95<sup>th</sup> dietary exposure percentile were only marginally above the health protective benchmark (129 and 127, respectively, Table 15). The acute exposure from methyl parathion in the ambient air was less than 10% compared to the acute dietary exposure. Consequently, the MOEs for aggregate exposure were not significantly different than the dietary MOEs (Table 14).

Aggregate Dietary and Application Site Air Exposure: All acute aggregate MOEs for residents staying at 10-12 yards from the application site and consuming food at the upper bound of exposure (95<sup>th</sup>, 99<sup>th</sup> or 99<sup>th</sup> percentiles) were less than the benchmark 100.

#### **V.D.3.2. Aggregate Exposure To Workers**

The acute aggregate risk to methyl parathion for workers was calculated for dermal and inhalation exposure at occupational settings, exposure from dietary sources and exposure from air at the application site. All acute aggregate MOEs were less than 100 (Table 17). These MOEs would be further reduced if the occupational exposure were estimated based on 100% dermal absorption rather than the default 50% absorption assumed by Cochran (2010).

All aggregate seasonal MOEs were less than 100, except for the worker group Walnut Rakers (MOE of 184). However, the seasonal MOE for Walnut Rakers would be 2-fold lower (i.e., MOE of 92, which is below the benchmark of 100), if the dermal absorption of methyl parathion were assumed to be 100% rather than the value of 50% used by Cochran (2010).

## V.E. CONCLUSIONS

The health risk assessment of methyl parathion was carried out for the general population and for workers. The assessment from dietary exposure was presented in 2004 (Koshlukova and Reed, 2004). The general population was represented by 4 population subgroups: Infant <6 months, Child 3-5 yrs, Adult Female and Adult Male. The workers included those who work with methyl parathion in aerial and ground applications; or field workers.

Single-route exposure scenarios were evaluated under acute or subchronic conditions for (i) inhalation exposures through the air for the general population and (ii) dermal exposures for workers in occupational settings. Aggregate exposures involving multiple routes were also calculated. The aggregate exposure for the general population included exposure from dietary sources with exposure contributions from ambient air or air at the application site. The aggregate exposures to workers included the occupational exposure with non-occupational contributions from dietary and air sources. A margin of exposure of 100 is considered sufficiently protective of human health when the NOELs are derived from animal studies.

Air Exposure. The acute and seasonal MOE values for ambient air exposures were greater than 480. All acute MOEs for application site air exposures for residents located from 10-12 yards to at least 57 yards from the application site were lower than the benchmark of 100. Consequently, mitigation should be considered for the general population adjacent to methyl parathion application sites and in conjunction with their potential aggregate exposures.

Occupational Exposure: The MOEs for acute exposure from methyl parathion were substantially lower than the benchmark of 100 for all agricultural workers and clearly indicated a health concern. The seasonal MOEs were lower than 100 for nine of the 10 evaluated workers groups. Consequently, mitigation should be considered for all occupational activities involving methyl parathion and in conjunction with the potential aggregate exposures.

Aggregate Exposure for the General Population: The MOEs for acute aggregate exposure from dietary sources with exposure contributions from ambient air were below the benchmark of 100 for Infants and Children at the 95<sup>th</sup> percentiles. The acute aggregate MOEs were below 100 for all population subgroups at the 99<sup>th</sup> and 99.9<sup>th</sup> percentiles.

All MOEs for acute aggregate exposure from dietary sources and air at the application site were below the benchmark of 100.

Aggregate Exposure for Workers: The MOEs for acute and seasonal aggregate exposures from dietary, air and occupational sources were lower than the benchmark of 100 for all agricultural workers.

The two key issues for the occupational exposure were:

(1) The use of a default value of 50% as human dermal absorption for methyl parathion. This value may be an underestimation of the real human dermal absorption, since methyl parathion *in vivo* data in animals revealed that the absorption via skin was nearly 100%. If a dermal absorption of 100% is also assumed for humans, the occupational MOEs would be 2-fold lower (ranging from <1 to 94) than those calculated by Cochran (2010).

(2) The workers ADDs estimated from human biomonitoring data were based on the urinary p-nitrophenol from 24-h period measured on the day of occupational exposure. This may be an underestimation of the real exposure, because of the exclusion of a substantial amount of the p-nitrophenol excreted after the 24 h and at least until the 84 h post-exposure.

**Note:** In the 2006 IRED, the USEPA identified risk reduction measures necessary to support the continued use of methyl parathion (USEPA, 2006a). As of May 2007, the use of methyl parathion on 7 commodities (cabbage, dried beans, dried peas, hops, lentils, pecans, and sugar beets) was canceled (USEPA, 2007).

With the exception of cabbage and hops, the rest of the canceled commodities were included in the 2004 DPR dietary exposure assessment of methyl parathion (Koshlukova and Reed, 2004). However, these foods had minimal contribution (less than 1%) to the acute dietary risk. The probabilistic analysis revealed that the commodities Rice and Cottonseed-oil (on which methyl parathion is still registered for use) made the most significant contribution to the acute dietary exposure. The contribution of the different food-forms of Rice and Cottonseed-oil was up to 83% and 29%, respectively, of the total dietary exposure to Infants and Children. Because the impact of the canceled food on the total dietary exposure was insignificant, the dietary risk estimates would be essentially the same if these foods were excluded. Therefore, a new dietary exposure assessment (without the canceled food) was not needed.

On July 27, 2010 the USEPA issued a cancellation order for all product registrations containing methyl parathion, which was voluntarily requested by the registrants (USEPA, 2010). The effective date of these cancelations is December 31, 2012. The use of existing stocks of the end-use products will be prohibited after December, 2013.

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# Office of Environmental Health Hazard Assessment



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## MEMORANDUM

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**DATE:** January 20, 2010

**SUBJECT:** COMMENTS ON THE DRAFT ADDENDUM TO THE 2004 RISK CHARACTERIZATION DOCUMENT FOR METHYL PARATHION DIETARY AND AMBIENT AIR EXPOSURES

Attached please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) comments for the active ingredient methyl parathion. These comments were prepared in response to the Department of Pesticide Regulation's (DPR) two draft documents: "Methyl Parathion, Risk Characterization Document, Occupational, Ambient Air and Aggregate Exposures," dated June 5, 2009, and "Estimation of Exposure of Persons in California to the Pesticide Products that contain Methyl Parathion," dated May 28, 2009.

OEHHA reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with

California Environmental Protection Agency

*The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption.*

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Gary T. Patterson, Ph.D. and Sue Edmiston, Chief  
January 20, 2010  
Page 2

exposure to pesticides. Pursuant to the FAC Sections 14022 and 14023, OEHHA provides consultation and technical assistance to DPR on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepares health-based findings.

Thank you for providing the draft documents for our review. If you have any questions regarding OEHHA's comments, please contact Dr. David Ting or Dr. Anna Fan at (510) 622-3200.

Attachment

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## ATTACHMENT

### COMMENTS ON THE DRAFT ADDENDUM TO THE 2004 RISK CHARACTERIZATION DOCUMENT FOR METHYL PARATHION DIETARY AND AMBIENT AIR EXPOSURES

#### BACKGROUND INFORMATION

OEHHA previously reviewed DPR's 1999 evaluation of methyl parathion as a Toxic Air Contaminant and 2004 Risk Characterization Document (RCD). At the request of DPR, OEHHA reviewed the 2009 addendum to the 2004 RCD for dietary and ambient air exposures. The addendum consists of an updated air exposure assessment, occupational exposure assessments, and an updated RCD that characterizes the risk from air, occupational, and aggregate exposures. Estimates from the 2004 dietary exposure assessment have been included in the aggregate assessment. In assessing aggregate exposure for the general population, DPR considered air and dietary exposures. In evaluating aggregate exposure for workers, DPR included air, dietary, and occupational exposures.

According to DPR's evaluation, all acute margins of exposure (MOEs) for application site air exposure (based on the highest air concentration measured) were less than the DPR health protective benchmark of 100. Most of the acute (based on the 95<sup>th</sup> percentile exposure estimates) and seasonal (based on the average exposure estimates) MOEs for occupational exposures were less than 100. Almost all acute MOEs for dietary exposures were less than 100 at the  $\geq 95^{\text{th}}$  percentile for various age subgroups. MOEs for acute and seasonal aggregate exposures show similar results.

As part of our review of the addendum, we also revisited the DPR 1999 and 2004 documents for background and context. Our comments below, however, focus primarily on issues identified from the addendum.

#### COMMENTS

##### Exposure pathway model

A conceptual model that provides an overview of the exposure pathways considered by DPR is lacking. DPR indicated that methyl parathion is registered for use on alfalfa, almonds, barley, beans, cabbage, canola, corn, cotton, hops, oats, onions, pecans, potatoes, rice, rye, sugar beets, sunflowers, walnuts, and wheat. Based on these

registered uses, DPR should outline pertinent exposure pathways, and discuss which pathways are deemed complete for purpose of this exposure assessment.

#### Water ingestion pathway

DPR did not discuss exposures from the water ingestion pathway in either the 2009 updated exposure assessment or the 2009 updated RCD. Since a conceptual exposure model was not presented, it is difficult to ascertain the reasons for not including the water ingestion pathway. Trend data presented by DPR show that very little methyl parathion has been applied to rice between 2002 and 2006. If trend data was a basis for not including the water ingestion pathway in the exposure assessment, it seems such a rationale lacks validity so long as methyl parathion is registered for use on rice.

DPR in its 2004 RCD briefly mentioned that the lack of monitoring data precluded a drinking water exposure assessment. However, methyl parathion was detected in the Colusa Water Basin where it was applied in the rice-growing region of Colusa County (Central Valley Regional Water Quality Control Board, 1989 and Department of Fish and Game, 1990 cited in California Department of Food and Agriculture, 1991). In its risk assessment to support the re-registration eligibility decision for methyl parathion, U.S. EPA (2006) discussed surface and ground water levels of methyl parathion in estimating drinking water exposures. U.S. EPA also cited the Colusa studies and noted that spray drift from aerial applications led to as much as 15 percent deposition into water bodies adjacent to rice fields. Methyl parathion was detected up to 6 parts per billion (ppb) in the Colusa Water Basin; however, with imposition of irrigation and application controls, that level was reduced to 0.12 ppb. U.S. EPA deemed the water exposure pathway to be complete and used available data to estimate drinking water exposures. OEHHA recommends that DPR include the water ingestion pathway as a part of its exposure assessment.

#### Paraoxon in drinking water

U.S. EPA noted that methyl parathion could be oxidized to paraoxon during water treatment (U.S. EPA, 2009). This is of concern because methyl paraoxon is more toxic than the parent compound. DPR has established a toxicity equivalence factor of 10 based on a comparison of acute toxicity between methyl parathion and methyl paraoxon in rats. U.S. EPA will consider how this methyl parathion issue should be addressed in its drinking water assessment. OEHHA suggests that DPR also consider and discuss this issue as part of its exposure assessment and risk characterization.

#### Exposure concentration estimation

DPR used average exposure estimates in computing chronic exposures. The average rather than 95 percent upper confidence limit (UCL) of the average was used because DPR feels that assuming long-term exposure with a "high-end" concentration is not

reasonable. U.S. EPA in issuing its guidance indicated that because of the uncertainty associated with any point estimate of exposure concentration, the 95 percent UCL of the average should be used (U.S. EPA, 1989). OEHHA agrees that using the maximum concentration would be unreasonable for chronic exposure; however, using the 95 percent UCL of the average to account for the uncertainty associated with this point estimate is desirable and appropriate. Accordingly, OEHHA recommends that DPR also estimate chronic exposures based on the 95 percent UCL to delineate the uncertainty boundary of the average.

#### Biomonitoring data in estimating aggregate exposure to workers

DPR recognized that use of biomonitoring data may underestimate occupational exposure to methyl parathion. The metabolite, p-nitrophenol in urine, was used as a basis to estimate methyl parathion exposure. This metabolite can be detected in urine up to 84 hours after exposure, but the approach used by DPR only accounted for excretion of p-nitrophenol for the first 24 hours. DPR should elaborate whether an adjustment factor could be used to correct the underestimation.

#### Seasonal dietary exposure

The dietary exposure data of the U.S. population for the spring season was used to assess the seasonal dietary exposure for adult females, adult males, and workers. Considering methyl parathion is mainly used during the summer (from May to August), a justification is needed on the use of dietary exposure data for the spring season.

#### Safety factor for children

As recognized in the 2009 addendum and the 2004 RCD, increased pre- and post-natal sensitivities were observed from animal studies. These include:

- age-related difference in the detoxification of methyl parathion in rats
- age-related difference in lethal doses (LD<sub>50</sub>s) and cholinesterase inhibition in rats following acute methyl parathion exposure
- age-related difference in cholinesterase inhibition following acute and repeated exposure in a developmental neurotoxicity study in rats

In OEHHA's 2003 comments on DPR's draft RCD for the active ingredient methyl parathion dated September 15, 2003, OEHHA recommended an additional uncertainty factor of 10 to protect children and infants based on the increased sensitivities to neurotoxic effects of the chemical observed in young animals (OEHHA, 2003). DPR, however, in its response to OEHHA's comments, indicated that an additional uncertainty factor for children and infants is not necessary based on the following reasons (DPR, 2004):

- the No Observed Effect Level (NOEL) for subchronic exposure was derived from immature rats
- the critical acute NOEL of 0.025 mg/kg-day is lower than the acute NOEL of 0.11 mg/kg-day derived from the pups in a recently available developmental neurotoxicity study (see Table 1)

**Table 1. Summary of studies and endpoints considered by DPR for the risk characterization of methyl parathion**

Route	Species & Age	Duration	Endpoint	Study	NOEL or LOEL (mg/kg-day)
Acute Oral	rat, 7-8 weeks old	single dose	plasma, RBC, and brain ChE; neuropathy	Minnema, 1994	0.025 (NOEL)
	rat, PND11	single dose	plasma, RBC, and brain ChE	Beyrouy, 2002	0.11 (NOEL)
Subchronic Oral	rat, GD6-20, LD1-10, & PND11-21 (direct dosing of the pups)	developmental neurotoxicity study (36 days)	plasma, RBC, and brain ChE	Beyrouy, 2002	0.03 (NOEL)
Subchronic Dermal	rat, 47-54 days of age	4 weeks	brain ChE, behavioral effects	Beyrouy, 2001	0.3 (LOEL)
Chronic Oral	mouse	104 weeks	brain ChE	Eiben, 1991	0.2 (LOEL)

The endpoints used by DPR were cholinesterase inhibition and neuropathy, no endocrine disruption endpoints were considered. As acknowledged in the 2004 RCD, methyl parathion has been indicated to possess endocrine disruption potential. Considering the widespread effects of endocrine disruptors, and increased susceptibility

to endocrine disruption in young versus adult animals, OEHHA recommends an additional safety factor be applied in establishing a methyl parathion health criterion for acute and subchronic exposures for protection of children and infants<sup>1</sup>. Such a health criterion will facilitate the risk characterization of those MOEs applicable to children in the 2009 addendum.

OEHHA also noted that U.S. EPA (2006) applied a ten-fold Food Quality Protection Act (FQPA) safety factor in its assessment to support the re-registration eligibility decision for methyl parathion. The ten-fold factor was later removed by U.S. EPA when it re-analyzed the data in response to public comments (U.S. EPA, 2005 and 2009). U.S. EPA presented a conclusion similar to that reached by DPR that the NOEL used is based on the most sensitive endpoint and will protect all endpoints identified in the developmental neurotoxicity study. U.S. EPA further assessed whether this NOEL would be protective of endocrine effects identified in the open literature. This involved one study that pertains to the inhibition of ovarian compensatory hypertrophy by methyl parathion and another to the hypoinsulinemia and hyperglycemia induced by methyl parathion. U.S. EPA concluded that the chosen NOEL would also adequately protect these endocrine endpoints. OEHHA noted that adult animals were used in these two studies. As such, this "most sensitive" NOEL may be adequate to protect endocrine disruption effect in adults; but the analysis does not demonstrate the adequacy of this NOEL in protecting endocrine disruption effects in children and infants. On that basis, OEHHA also recommends DPR consider an additional safety factor for protection of children and infants.

#### Cumulative risks

U.S. EPA has completed its cumulative risk assessment for organophosphates. It would be helpful if DPR were to include a discussion about methyl parathion in the context of the cumulative toxicity of organophosphate compounds.

#### **Reference**

California Department of Food and Agriculture. 1991. Protocol to Sample Methyl Parathion and Methyl Paraaxon in Paddy Water of Commercial Rice Fields.

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<sup>1</sup> The 2009 addendum focuses on estimating air and occupational exposures. Based on the May through August use pattern of methyl parathion, DPR assumes these exposures are only of acute or subchronic duration. Chronic exposure assessment is not a subject in the 2009 addendum. Because OEHHA's current task is to review the 2009 addendum, we have restricted our recommendation of safety factor for children to establishing a methyl parathion health criterion for acute and subchronic exposures.

DPR. 2009. Final Draft of Exposure Assessment Document on Methyl Parathion-- Estimation of Exposure of Persons in California to the Pesticide Products that Contain Methyl Parathion.

DPR. 2009. Draft Methyl Parathion Risk Characterization Document; Occupational, Ambient Air and Aggregate Exposures; Addendum to the 2004 Risk Characterization Document for Methyl Parathion Dietary and Ambient Air Exposures.

DPR. 2004. Risk Characterization Document for Methyl Parathion Dietary and Ambient Air Exposures.

DPR, 2004. Response to OEHHA Comments to the Methyl Parathion RCD.

DPR. 1999. Evaluation of Methyl Parathion as a Toxic Air Contaminant.  
Feldmann, R. J., and Maibach, H. I. 1974. Percutaneous penetration of some pesticides and herbicides in man. *Toxicol. Appl. Pharmacol* 28: 126-132.

OEHHA, 2003. Comments on DPR's Draft Risk Characterization Document for the Active Ingredient Methyl Parathion.

U.S. EPA. 2009. Methyl Parathion Summary Document, Registration Review: Initial Docket (EPA-HQ-OPP-2009-0332).

U.S. EPA. 2006. Re-registration Eligibility Decision for Methyl Parathion.

U.S. EPA. 2005. The Health Effects Division's Response to Public Comments on EPA's Interim Reregistration Eligibility Decision Document for Methyl Parathion (OPP Docket# OPP-2003-0237). DP Barcode D308015.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund Volume 1: Human Health Evaluation Manual (EPA/540/1-89/002).





Mary-Ann Warmerdam  
Director

MEMORANDUM

TO: Anna M. Fan, Ph.D., Chief, Pesticide and Environmental Toxicology Section, OEHHA

FROM: Gary T. Patterson, Ph.D., Chief, Medical Toxicology Branch, DPR

DATE: March 11, 2010

SUBJECT: Response to OEHHA Comments to the Methyl Parathion RCD

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Thank you for the comments on our draft addendum (dated May 28, 2009) to the 2004 risk characterization document (RCD) for methyl parathion. It addresses the potential human health effects arising from exposure to methyl parathion from the air and occupational activities, as well as aggregate exposures from various combined scenarios that include the dietary exposures as presented in the 2004 RCD.

The following response addressed comments 1-3 and 6-8, concerning the toxicology and the risk characterization parts of the RCD. Comments 4 and 5 concern the occupational exposure assessment and will be addressed separately by the Worker Health and Safety Branch. The addendum, when finalized, will be posted at <http://www.cdpr.ca.gov/docs/risk/rcd.htm>.

OEHHA: Comment No.1- Exposure pathway model

*A conceptual model that provides an overview of the exposure pathways considered by DPR is lacking. DPR indicated that methyl parathion is registered for use on alfalfa, almonds, barley, beans, cabbage, canola, corn, cotton, hops, oats, onions, pecans, potatoes, rice, rye, sugar beets, sunflowers, walnuts, and wheat. Based on these registered uses, DPR should outline pertinent exposure pathways, and discuss which pathways are deemed complete for purpose of this exposure assessment.*

DPR Response. The exposure pathways were discussed in detail in the current RCD. The exposure pathways deemed complete were (i) exposure resulting during handling of methyl parathion by workers (occupational exposure), (ii) exposure from consuming foods containing methyl parathion (dietary exposure) and (iii) exposure to the general population to airborne methyl parathion in areas where methyl parathion is applied. Exposure from residential uses was not expected and, therefore, not evaluated. These discussions can be found in Section IV.A; Section IV.A.3 and Table 7 in the current RCD; and also in section V.E.2. in the 2004 RCD.

OEHHA: Comment No.2 - Water ingestion pathway

*DPR did not discuss exposures from the water ingestion pathway in either the 2009 updated exposure assessment or the 2009 updated RCD. Since a conceptual exposure model was not presented, it is difficult to ascertain the reasons for not including the water ingestion pathway. Trend data presented by DPR show that very little methyl parathion has been applied to rice between 2002 and 2006. If trend data was a basis for not including the water ingestion pathway in the exposure assessment, it seems such a rationale lacks validity so long as methyl parathion is registered for use on rice. DPR in its 2004 RCD briefly mentioned that the lack of monitoring data precluded a drinking water exposure assessment. However, methyl parathion was detected in the Colusa Water Basin where it was applied in the rice-growing region of Colusa County (Central Valley Regional Water Quality Control Board, 1989 and Department of Fish and Game, 1990 cited in California Department of Food and Agriculture, 1991). In its risk assessment to support the re-registration eligibility decision for methyl parathion, U.S. EPA (2006) discussed surface and ground water levels of methyl parathion in estimating drinking water exposures. U.S. EPA also cited the Colusa studies and noted that spray drift from aerial applications led to as much as 15 percent deposition into water bodies adjacent to rice fields. Methyl parathion was detected up to 6 parts per billion (ppb) in the Colusa Water Basin; however, with imposition of irrigation and application controls, that level was reduced to 0.12 ppb. U.S. EPA deemed the water exposure pathway to be complete and used available data to estimate drinking water exposures. OEHHA recommends that DPR include the water ingestion pathway as a part of its exposure assessment.*

DPR Response: In 1990, methyl parathion residues were detected in water samples from Colusa Basin Drain, which drains into the Sacramento River, at levels that were acutely toxic to aquatic organisms (DFG, 1990). The DPR subsequent monitoring studies for protection of the aquatic life resulted in mitigation measures (CDFA, 1991; DPR, 1992). However, irrigation water or water from holding sites is not potable and these levels could not be used for human drinking water risk assessment. Methyl parathion has not been detected in the Sacramento River, in the City of Sacramento drinking intake or tap water (LOD of 0.05 ppb); (DPR, 1992).

As a response to OEHHA comments, a discussion on the drinking water exposure, accompanied by the above explanation, was added to the RCD; section IV.A.2. Also presented is the USDA multiple year drinking water monitoring program showing no detection of methyl parathion or methyl paraoxon in more than 1,400 samples in California (PDP, 2001-2006). Drinking water exposure estimated at the LODs for total equivalent methyl parathion (i.e., including methyl paraoxon) results in <1% contribution to the dietary exposure.

OEHHA: Comment No.3: Paraoxon in drinking water

*U.S. EPA noted that methyl parathion could be oxidized to paraoxon during water treatment (U.S. EPA, 2009). This is of concern because methyl paraoxon is more toxic than the parent compound. DPR has established a toxicity equivalence factor of 10 based on a comparison of acute toxicity between methyl parathion and methyl paraoxon in rats. U.S. EPA will consider how this methyl parathion issue should be addressed in its drinking water assessment. OEHHA*

*suggests that DPR also consider and discuss this issue as part of its exposure assessment and risk characterization.*

DPR Response. Methyl paraoxon was addressed in the discussion of the drinking water exposure in section IV.A.2.

OEHHA: Comment No.6. Seasonal Dietary Exposure:

*The dietary exposure data of the U.S. population for the spring season was used to assess the seasonal dietary exposure for adult females, adult males, and workers. Considering methyl parathion is mainly used during the summer (from May to August), a justification is needed on the use of dietary exposure data for the spring season.*

DPR Response: Dietary exposure is a product of food consumption and residue data (DPR MT-3, 2006). The dietary exposure of methyl parathion consists of 15 of commodities each with varying residue levels from different points of origin. Thus, it is not necessary that the overall dietary exposure should directly coincide with the summer use pattern. Our 2004 dietary analysis showed that the exposure for the spring season was slightly higher (1.5 fold) than the summer exposure Koshlukova and Reed, 2004 RCD; Attachment III.2.). Hence, the dietary exposure during the spring season for the US population was used as surrogate for the seasonal dietary exposure for Adult Female and Adult Male in calculating their aggregate exposures. To avoid future confusion the above sentence was added in Table 6 see section IV.A.2.

OEHHA: Comment No.7. Safety factor for children

*As recognized in the 2009 addendum and the 2004 RCD, increased pre- and post-natal sensitivities were observed from animal studies. These include:*

- *age-related difference in the detoxification of methyl parathion in rats*
- *age-related difference in lethal doses (LD<sub>50</sub>s) and cholinesterase inhibition in rats following acute methyl parathion exposure*
- *age-related difference in cholinesterase inhibition following acute and repeated exposure in a developmental neurotoxicity study in rats*

*In OEHHA's 2003 comments on DPR's draft RCD for the active ingredient methyl parathion dated September 15, 2003, OEHHA recommended an additional uncertainty factor of 10 to protect children and infants based on the increased sensitivities to neurotoxic effects of the chemical observed in young animals (OEHHA, 2003). DPR, however, in its response to OEHHA's comments, indicated that an additional uncertainty factor for children and infants is not necessary based on the following reasons (DPR, 2004):*

- *the No Observed Effect Level (NOEL) for subchronic exposure was derived from immature rats*
- *the critical acute NOEL of 0.025 mg/kg-day is lower than the acute NOEL of 0.11 mg/kg-day derived from the pups in a recently available developmental neurotoxicity study (see Table 1.*

*The endpoints used by DPR were cholinesterase inhibition and neuropathy, no endocrine*

*disruption endpoints were considered. As acknowledged in the 2004 RCD, methyl parathion has been indicated to possess endocrine disruption potential. Considering the widespread effects of endocrine disruptors, and increased susceptibility to endocrine disruption in young versus adult animals, OEHHA recommends an additional safety factor be applied in establishing a methyl parathion health criterion for acute and subchronic exposures for protection of children and infants<sup>1</sup>. Such a health criterion will facilitate the risk characterization of those MOEs applicable to children in the 2009 addendum.*

*OEHHA also noted that U.S. EPA (2006) applied a ten-fold Food Quality Protection Act (FQPA) safety factor in its assessment to support the re-registration eligibility decision for methyl parathion. The ten-fold factor was later removed by U.S. EPA when it reanalyzed the data in response to public comments (U.S. EPA, 2005 and 2009). U.S. EPA presented a conclusion similar to that reached by DPR that the NOEL used is based on the most sensitive endpoint and will protect all endpoints identified in the developmental neurotoxicity study. U.S. EPA further assessed whether this NOEL would be protective of endocrine effects identified in the open literature. This involved one study that pertains to the inhibition of ovarian compensatory hypertrophy by methyl parathion and another to the hypoinsulinemia and hyperglycemia induced by methyl parathion. U.S. EPA concluded that the chosen NOEL would also adequately protect these endocrine endpoints. OEHHA noted that adult animals were used in these two studies. As such, this "most sensitive" NOEL may be adequate to protect endocrine disruption effect in adults; but the analysis does not demonstrate the adequacy of this NOEL in protecting endocrine disruption effects in children and infants. On that basis, OEHHA also recommends DPR consider an additional safety factor for protection of children and infants.*

DPR Response: The DPR has already responded to a similar comments from OEHHA regarding our 2004 RCD (DPR, 2004). To date, there are no new toxicological data or risk assessment policy to warrant re-addressing this issue.

OEHHA Comment No.8. Cumulative Risks:

*U.S. EPA has completed its cumulative risk assessment for organophosphates. It would be helpful if DPR were to include a discussion about methyl parathion in the context of the cumulative toxicity of organophosphate compounds.*

DPR Response: Our 2004 RCD, contains a separate section on the finalized 2002 USEPA cumulative risk assessment for the organophosphorous pesticides (OP; Koshlukova and Reed, 2004, see section V.E.3.). This section also included a discussion on the methyl parathion contribution to the OP cumulative risk. There is no new information regarding the impact of methyl parathion on the cumulative OP exposure.

**REFERENCES:**

- CDFA 1991. Protocol To Sample Methyl Parathion and Methyl Paraoxon in Paddy Water of Commercial Rice Fields. California Department of Food and Agriculture. Environmental Monitoring and Pest Management, Sacramento, CA.
- DFG 1990. Toxicity of Colusa Basin Drain water to young mysids and striped bass. Unpublished report. Department of Fish and Game, Sacramento, CA.
- DPR 1992. Consideration of Approving Department of Pesticide Regulation's 1992 Management Practices for Rice Pesticides. Staff Report. Department of Pesticide Regulation. California Environmental Protection Agency, Sacramento, CA.
- DPR 2004. Memorandum: Response to OEHHA Comments to the Methyl Parathion RCD Dated October 25, 2004. From Gary Patterson, Chief, Medical Toxicology Branch to Anna M. Fan, Chief, Pesticide and Environmental Toxicology Section, OEHHA. Department of Pesticide Regulation. California Environmental Protection Agency, Sacramento, CA.
- DPR MT-3 2006. Guidance for dietary exposure assessment, Version III Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.
- PDP 2001-2006. Pesticide Data Program. Annual Summary. Agricultural Marketing Service. United States Department of Agriculture, Washington, DC.
- CC. Jay Schreider, Ph.D., Senior Toxicologist, Medical Toxicology Branch, DPR  
Svetlana Koshlukova, Ph.D., Staff Toxicologist, Medical Toxicology Branch, DPR