UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ***ETHYL PARATHION*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Nicole C. Paquette, Ph.D. Nicole C. Paquette 3/25/98
Reregistration Branch 2
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary Jess Rowland 3/25/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, K. Clark Swentzel 3/25/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee Mike Metzger 3/26/98
Health Effects Division (7509C)

TO: Alan Nielsen, Branch Senior Scientist
Reregistration Action Branch 2
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PC Code: 057501

On February 26, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **ethyl parathion,** re-assessed the Reference Dose (RfD) established in 1986, and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to ethyl parathion as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

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Committee Members in Attendance

Members present were Karl Baetcke, William Burnam, Robert Fricke, Karen Hamernik, Susan Makris, Mike Metzger, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Member in absentia was Melba Morrow. Data was presented by Nicole Paquette of Reregistration Branch 2 and Robert Zendzian of Science Analysis Branch.

In attendance were also Pauline Wagner, Bonnie Cropp-Kohlligian, Jonathan Becker, William Sproat as observers/team members.

Data Presentation:
and
Report Presentation

Nicole C. Paquette, Ph.D.
Toxicologist

Robert Zendzian, Ph.D.
Senior Pharmacologist

Report Concurrence:

Jess Rowland
Executive Secretary

I. INTRODUCTION

On November 26, 1986, the Health Effects Division RfD Peer Review Committee established an RfD of 0.0003 mg/kg/day based on the one year dog study based on significant plasma and red blood cell cholinesterase inhibition at a LOEL of 0.01 mg/kg. Only an uncertainty factor of 10 was used to account for inter-and intraspecies differences. A modifying factor of 3 was used due to a lack of an established NOEL for the slight but very pronounced effects.

On February 10, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-assessed the existing RfD and the toxicology endpoints selected for acute dietary as well as occupational and residential exposure risk assessments pursuant to the Food Quality Protection Act (FQPA) of 1996. The HIARC also addressed the potential enhanced sensitivity of infants and children as required by FQPA.

This report supersede the previous RfD Committee reports.

II. HAZARD IDENTIFICATION

A. Acute RfD

Study Selected: Acute Oral Neurotoxicity §81-8

MRID No.: 43117901

Executive Summary: Male and female Sprague Dawley rats (10/sex/dose) were orally gavaged once with ethyl parathion (86.2%) at doses of 0 (corn oil), 0.025, 2.5, 10.0 mg/kg for males and 0, 0.025, 0.5, 2.5 mg/kg for females. Neurobehavioral effects (FOB and motor activity) on all animals were evaluated prior to dosing on day 0, at the peak time-of-effect (4 hr after dosing) and on days 7 and 14. Cholinesterase (ChE) determinations were conducted on blood on all animals 2 days prior to dosing; blood and brain ChE were determined 4-hr after dosing (Day 0), and on day 14 (5 rats/sex/dose/time point). Neuropathological examinations were carried out at terminal sacrifice (day 14) on 6 rats/sex/dose.

Two high dose (10.0 mg/kg) male rats died on the day of dosing. Clinical signs and FOB evaluations consistent with acute cholinergic toxicity were noted in all surviving male rats at the highest dose and one high dose female. Hypoactivity, labored breathing, rough coat, chromodacryorrhea, urine stains, muscle fasciculations, tremors, salivation were observed in all high dose males (10 mg/kg) and one high dose female (2.5 mg/kg). Evaluation of the FOB/motor activity data at the 4 hour testing interval revealed a treatment-related increase in abnormal observations in the high dose male and female rats for home cage/hand held, open field, response and performance data. Recovery from cholinergic effects was complete for the majority of high dose male rats (6/8) and all female rats by day 14.

There were statistically significant ($p \leq 0.5$) depressions of plasma and RBC cholinesterase activity at the 4 hour peak time-of-effect in male rats given 10mg/kg (↓18%) and 2.5 mg/kg (↓25% of control) and female rats given 2.5 mg/kg (↓39%). Partial to full recovery was observed at 14 days post dose, however, male rats given 10 mg/kg still had statistical significant ($P \leq 0.5$) reduction (↓40%) in RBC ChE activity.

The highest dose tested in males (10 mg/kg) and females (2.5 mg/kg) produced statistically significantly ($p<0.5$) decreased brain ChE activity (↓24 % and ↓30%, respectively) in all measured areas of the brain. By day 14, all brain ChE activity returned to normal except the brainstem in male rats given 10 mg/kg (↓33%). There were no treatment related effects noted in the neuropathological examination.

Based on the results of this study, the neurobehavioral NOEL is 2.5 mg/kg for males and 0.5 mg/kg for females; the LOEL is 10 mg/kg for males and 2.5 mg/kg for females as evidenced by the abnormal FOB and clinical signs of cholinergic toxicity.

The NOEL for plasma and RBC cholinesterase inhibition is 0.025 mg/kg for both male and female rats; the LOEL is 2.5 mg/kg for male rats and 0.5 mg/kg for female rats. For brain ChE inhibition the LOEL is 10 mg/kg (HDT) for male rats and 2.5 mg/kg (HDT) for female rats; the NOEL is 2.5 mg/kg, and 0.5 mg/kg, respectively.

Dose and Endpoint for Risk Assessment: NOEL = 0.025 mg/kg based on plasma and RBC cholinesterase inhibition occurring at 2.5 mg/kg for male rats and 0.5 mg/kg for female rats.

Comments about Study/Endpoint: This is a well conducted study and is very appropriate for use in acute dietary risk assessment since the endpoint (plasma and RBC cholinesterase inhibition) was measured after a single oral dose at 4 hours on the day of treatment (i.e., exposure period of concern). In a pilot study, it was determined that female rats were approximately 4 times more sensitive to ethyl parathion toxicity compared to male rats, therefore, different doses were used for each sex. In addition, the dose response gradient for this chemical is steep; 2 male rats at 10.0 mg/kg died on day of dosing and at Day 14 male rats given 10 mg/kg still had statistical significant decreased RBC & brain ChE and some male rats had not fully recovered from cholinergic signs.

Uncertainty Factor (UF): 100 (10x for interspecies extrapolation and 10x for intraspecies variability).

$$\textbf{Acute RfD} = \frac{0.025 \text{ mg/kg}}{100 \text{ (UF)}} = \textbf{0.00025 mg/kg/day}$$

This risk assessment is required.

B. Chronic RfD

The RfD established in 1991 was re-assessed by this Committee pursuant to the FQPA and is discussed below:

Study Selected: One year feeding study in dogs §83-1

MRID No.: Acc# 24664243

Executive Summary: Four groups of beagle dogs (8/sex/dose) were administered ethyl parathion (95.5%) in the diet at doses of 0, 0.01, 0.03, or 0.10 mg/kg/day for 12 months. Clinical signs were determined daily and body weight and food consumption were determined weekly. Hematology and clinical chemistries were performed prior to dosing, monthly thereafter and at termination. Plasma and RBC cholinesterase determinations were made twice before dosing, at months 2, 4 and 12. Brain cholinesterase activity was performed along with gross and microscopic examination of selected tissues at termination. Urinalysis was performed prior to dosing and at months 3 and 12.

All dogs survived the entire study. There were no compound-related clinical signs of toxicity, at any time observed. There were no effects on body weight, body weight gain, food consumption, clinical chemistries, urinalysis, organ weights or histopathology.

There were dose-related statistical significant ($p<0.05$) decreases in plasma and RBC cholinesterase activity in both male and female dogs, compared to control animals. Throughout the study, plasma and RBC cholinesterase activity were sporatically but significantly depressed at all dose levels, at the 2 and 12 month period but not the 4 month interval. By the end of 12 months, however, plasma cholinesterase activity was significantly depressed for both sexes (males: 73-46% of control; females: 85-34% of control). RBC cholinesterase activity was also statistically significantly reduced at all doses (males: 78-58% of control; females: 86-63% of control). Brain cholinesterase was only statistically significantly reduced in female dogs given 0.03 mg/kg (mid-dose) , compared to control.

The LOEL was 0.01 mg/kg (LDT) based on decreased plasma and RBC cholinesterase activity in both male and female dogs; a NOEL was not established.

Dose and Endpoint for Establishing RfD: LOEL = 0.01 mg/kg based on decreased plasma and RBC cholinesterase activity in both sexes.

Uncertainty Factor(s): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. An additional uncertainty factor of 3 was applied because of the use of a LOEL (i.e., lack of a NOEL in critical study). Although a NOEL was not established in this study, the Committee determined that an additional factor of 3 was adequate because the study was well conducted and there are sufficient data from subchronic and chronic duration studies in the same species and other species which support cholinesterase inhibition as the critical toxic effect.

Chronic RfD = $\frac{\text{0.01 mg/kg/day (LOEL)}}{\text{300 (UF)}}$ **=0.000033 mg/kg/day**

Comments about Study/Endpoint: The results of a 6-month study in dogs (MRID 41836601) support the results of the 1-year study in dogs and is used as support for the critical study. When a LOEL of 0.01 mg/kg/day is used in conjunction with an additional factor of 3 (lack of NOEL), the resultant dose of 0.0033 mg/kg/day (0.01 ÷ 3 = 0.0033 mg/kg/day) is comparable to the NOEL (0.0024 mg/kg/day) established in the 6-month study for the same endpoint (i.e., plasma and RBC ChE inhibition). Thus, the RfD of 0.000033 mg/kg/day derived from using a LOEL of 0.01 mg/kg/day and an UF of 300 (0.01 ÷ 300 = 0.000033 mg/kg/day) is comparable to the RfD (0.000024 mg/kg/day) that could have been derived from using a NOEL of 0.0024 mg/kg/day and an UF of 100 (0.0024 mg/kg/day ÷ 100 = 0.000024 mg/kg/day). The HIARC selected the 1-year study with the LOEL instead of the 6-month study with a NOEL, because of the longer (1-year) duration which is appropriate for establishing the RfD.

C. Occupational/Residential Exposure

There are no registered residential uses at the present time. Therefore, the following risk assessments are applicable only for occupational exposures.

1. Dermal Absorption

No dermal absorption studies are available. Therefore, the Committee assumed a dermal factor of 100% (default value) for ethyl parathion. This assumption is supported by similar toxicity which results at similar doses in acute oral and dermal studies in several species (rat oral LD_{50}=3 mg/kg, rat dermal LD_{50}= 6.8 mg/kg; rabbit oral LD_{50}=10 mg/kg, rabbit dermal LD_{50}= 15 mg/kg; guinea pig oral LD_{50}=8 mg/kg, guinea pig dermal LD_{50}= 45 mg/kg; mouse oral LD_{50}=5 mg/kg, mouse dermal LD_{50}= 19 mg/kg).

Dermal Absorption Factor: **100% (estimated)**

2. Short-Term Dermal - (1-7 days)

Study Selected: Acute Neurotoxicity Study in Rats §81-8

MRID No.: 43117901

Executive Summary: See summary under Acute RfD (one day)

Dose and Endpoint for Risk Assessment: NOEL = 0.025 mg/kg based on plasma and RBC cholinesterase inhibition occurring at 2.5 mg/kg for male rats and 0.5 mg/kg for female rats.

Comments about Study/Endpoint: The Committee selected the oral NOEL because of the lack of an appropriate dermal toxicity study. Plasma and RBC ChE inhibition occurred in both sexes on the day of dosing which is appropriate for this exposure period of concern (i.e., 1-7 days). Also, male rats given the high dose (10 mg/kg) had RBC and brain ChE inhibition even on Day 14 of

recovery. Since an oral dose was selected, a dermal absorption factor of 100% should be used for this risk assessment.

Another study which support this endpoint, includes a 13-week feed study (MRID# 41834501), in which at Week 2 (applicable to this exposure period of concern), female rats had markedly reduced RBC cholinesterase activity at 0.4 mg/kg (LOEL); the NOEL was 0.04 mg/kg. **This risk assessment is required.**

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 180-Day Oral Toxicity Study in Dogs §83-1b

MRID No.: 41836601

Executive Summary: Beagle dogs (5/sex/dose) were orally dosed by capsule with ethyl parathion (98%) at 0 (corn oil in gelatin capsules), 0.0024, 0.079, or 0.7937 mg/kg/day for six months. The following parameters were evaluated: twice daily observations; pretest physical examinations and body weights and then weekly thereafter; food consumption pretest and weekly thereafter; plasma and red blood cell (RBC) cholinesterase activity pretest, and weeks 1, 6, 14, 20 and 26. Brain, retina and ocular muscle cholinesterase activity were determined at termination. Routine opthalmoscopic examinations, slit lamp examinations were performed at pretest, months 3 and 6; electroretinograms, eye refraction, and intraocular pressure determinations were performed at pretest, months 1, 3 and 6. Histopathology of the retina, optic nerve, muscle and ciliary body was conducted at termination.

There was no effect on body weight gain in male dogs at any dose; in the high dose (0.7937 mg/kg) female dogs, there were decreases in body weight gain throughout the study which may have been treatment related. There were no effects on food consumption at any dose in either sex during the study.

Plasma cholinesterase activity was reduced as early as Week 1 and markedly reduced by Week 6 and throughout the rest of the study in both male and female dogs given 0.079 and 0.7937 mg/kg. Compared to pretreatment values, plasma cholinesterase activity in male and female dogs given 0.079 mg/kg was reduced by 20% and 25%, respectively. The highest dose (0.7937 mg/kg) decreased plasma cholinesterase levels in male dogs by 84% (16% of pretreatment value) and in female dogs by 82%, compared to pretreatment values. There was a slight reduction in RBC cholinesterase activity in both male and female dogs given 0.7937 mg/kg; 18% for both sexes compared to pretreatment values. Brain cholinesterase activity was statistically significantly decreased in male rats given 0.7937 mg/kg (HDT).

The LOEL for systemic toxicity was 0.7937 based on decreased body weight gain in female dogs during the whole study; the NOEL was 0.079 mg/kg. The LOEL for plasma ChE inhibition in male and female dogs was 0.079 mg/kg; the NOEL was 0.0024 mg/kg. The LOEL

for RBC and brain ChE inhibition was 0.7937 mg/kg; the NOEL was 0.079 mg/kg.

Dose/Endpoint for Risk Assessment: NOEL = 0.0024 mg/kg based on the markedly reduced plasma ChE in male and female dogs by Week 6 and throughout the study at 0.079 mg/kg.

Comments about Study/Endpoint: The corroborating effects of cholinesterase inhibition associated with ethyl parathion were noted in several other intermediate term (subchronic) studies at similar doses in other species. In a 3 month oral toxicity dog study, (MRID# 71670), groups of 4 male and 4 female beagle dogs were given dietary ethyl parathion (99.4%) at doses of 0, 0.3, 1.0 or 3.0 mg/kg. The only treatment related effect was significant inhibition of plasma cholinesterase at all doses in both sexes at Weeks 6 and 13 and significant inhibition of RBC ChE in females at all doses at Weeks 13. Based on plasma and RBC ChE inhibition, the LOEL was the lowest dose tested, 0.3 mg/kg for both sexes and no NOEL was established.

Although the dog is the most sensitive species, plasma, RBC and brain cholinesterase inhibition was the critical toxic effect in several subchronic oral studies in rats. In a subchronic neurotoxicity study (MRID# 43491501), female rats fed dietary levels of 0.05, 1.25 or 2.5 mg/kg, and male rats fed 0.05, 2.5 or 5.0 mg/kg for 13 weeks, there was a statistically significant decrease in RBC cholinesterase activity in both sexes at 0.05 mg/kg and no NOEL could be established.

In another 13-week feed study (MRID# 41834501), female rats (the most sensitive sex) were given 0.04, 0.4 or 4.0 mg/kg of ethyl parathion. The NOEL was 0.04 mg/kg based on markedly reduced RBC cholinesterase activity at 0.4 mg/kg at Week 2 of study. Since an oral NOEL was selected, a dermal absorption factor of 100% should be used for this risk assessment.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None

MRID No.: None
Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint: Based on the current use pattern (2-6 applications/season with 5-7 day intervals beween applications), there is minimal potential for Long-Term dermal exposure. In addition, there are only Short-and Intermediate-Term exposures to mixers/loaders/applicators and field workers are not risk since all crops are mechanically harvested.

5. Inhalation Exposure (Short and Intermediate Term)

Based on the high acute toxicity (LC_{50}= 0.084 mg/L) and the use pattern (0.5 - 1.0 lbs a.i/acre) there is considerable concern for potential inhalation exposure or risk. Inhalation of ethyl parathion vapor and/or aerosol leads to rapid absorption with imminent risk of respiratory failure. Therefore, the HIARC selected the oral dose for inhalation risk assessment. Short and intermediate term aggregate risk assessment should follow the route-to-route extrapolation as below:

Step I. The inhalation exposure component (i.e. µg a.i /day) using 100% absorption rate should be converted to an equivalent oral dose (mg/kg/day).

Step II. The dermal exposure component (mg/kg/day) using a 100% dermal absorption rate should be converted to an equivalent oral dose. This dose should then be combined with the oral dose in Step I.

Step III. The combined dose from Step II should then be compared to the oral NOEL's of 0.025 mg/kg/day for short term and 0.0024 mg/kg/day for intermediate term exposures to estimate the combined risk.

This risk assessment is required.

D. Recommendation for Aggregate Exposure Risk Assessments

There are no registered residential uses. Therefore, aggregate exposure risk assessment will be limited to Food + Water only.

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the oral NOEL of 0.025 mg/kg/day to calculate the MOE.

For **short and intermediate** aggregate exposure risk assessment, combine the average values from food + water together with the exposure from dermal (100% absorption) and inhalation (100% absorption) routes and compare it to the oral NOELs to calculate the MOE.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

On June 12, 1991, the Health Effects Division Carcinogenicity Peer Review Committee (CPRC) reevaluated the carcinogenic classification of ethyl parathion. Ethyl Parathion was classified as a Group C (possible human carcinogen) with a RfD approach for human risk characterization. Quantification of risk using the RfD approach requires comparison of the chronic exposure to pesticide residues, to the RfD, a quantitaive measure of the hazard likely to

result from long term exposure to ethyl parathion. The CPRC determined that quantitative risk assessment for ethyl parathion using this methodology will adequately account for all chronic toxicity effects, including carcinogenicity, likely to result from exposure to the pesticide. The HIARC concluded that the weight of evidence had been fully discussed by previous Peer Review meeting (dated August 1, 1986 1986 and July 31, 1989) and that all the information given did not affect the exisiting classification of ethyl parathion based on the increased adrenal cortical tumors in male and female Osborne-Mendel rats and possible trends for thyroid follicular adenomas and pancreatic islet cell carcinomas in male rats in the same study (NCI, 1979).

IV. FQPA CONSIDERATIONS

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for ethyl parathion was evaluated by the Hazard Identification Committee. The database included an acceptable two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits, meeting the FIFRA basic data requirements, as defined for a food-use chemical by 40 CFR Part 158.

1. Neurotoxicity:

Ethyl parathion is a potent inhibitor of acetylcholinesterase in the central and peripheral nervous systems in mammals. Exposure to ethyl parathion causes CNS signs of acetylcholine (AChE) overstimulation including miosis, ciliary spasm, diarrhea, increased salivation, lacrimation, tremors, convulsions and death.

Ethyl parathion is considered to be severely acutely toxic, with rat oral LD_{50}=3 mg/kg, rat dermal LD_{50}= 6.8 mg/kg; rabbit oral LD_{50}=10 mg/kg, rabbit dermal LD_{50}= 15 mg/kg; guinea pig oral LD_{50}=8 mg/kg, guinea pig dermal LD_{50}= 45 mg/kg; mouse oral LD_{50}=5 mg/kg, mouse dermal LD_{50}= 19 mg/kg;

In an acute neurotoxicity study (MRID 43117901), male rats given a single oral doses of 10 mg/kg of ethyl parathion had only partial reversibility of brain ChE inhibition with concomitant incomplete recovery from abnormal FOB measures and cholinergic signs (6/8 males) at 14 days post dose.

In a 13 week study (MRID 43491501), male rats were fed ethyl parathion at 0, 0.05, 2.5, 5.0 mg/kg and female rats fed 0, 0.05, 1.25, 2.5 mg/kg had a dose related decrease in plasma, RBC and brain cholinesterase activity at all doses during the 13 week treatment period. At the end of the 13 weeks, high dose female rats had decreases in forelimb and hindlimb grip strength and high dose male rats had a decrease in hindlimb grip strength.

At the end of a 2-year chronic toxicity study in rats (MRID 40188701), ethyl parathion caused retinal degeneration and sciatic nerve degeneration in male and female rats given the highest dose (1.75 and 2.47 mg/kg, respectively). The optic nerve was structurally deformed as

evidenced by axonal and myelin degeneration. This histopathology was indicative of blindness. Female rats given 2.47 mg/kg generally had more severe signs consisting of overall poor condition, uncoordinated gait and tremors throughout the 2-year study. Similar findings were found in a 2-year chronic study in rats (MRID 252510-252503) given **methyl parathion,** a homologue of ethyl parathion. Female rats fed 3.34 mg/kg of methyl parathion for 2 years had retinal degeneration/atrophy as well as gait abnormalities. Male rats given the highest dose (2.21 mg/kg) had pronounced sciatic nerve degeneration. However, the retinal atrophy and nerve degeneration occur at relatively high doses compared to the cholinergic toxicity (decreased plasma, RBC ChE) which occurs at a considerably lower dose (0.025 mg/kg/day). Therefore, by identifying the dose at which plasma/RBC ChE inhibition is the critical effect in acute and chronic studies, the potential chronic toxicity effects, including eye effects, are adequately accounted for.

Ethyl parathion administered either orally or dermally does not produce delayed neurotoxicity in hens[3].

2. Developmental Toxicity

Groups of 18 pregnant New Zealand white rabbits (MRID 139549) were orally gavaged with ethyl parathion (99.11% a.i.) at doses of 0 (corn oil), 1, 4 or 16 mg/kg from days 7 through 19 of gestation. At the highest dose (16 mg/kg) one female was sacrificed moribund on gestation Day 10 (3 days of dosing) and two more died on Day 19 (12 days of dosing). Body weight and body weight gain were statistically significantly decreased in high dose females for days 14, 19 and 24. No other signs of toxicity were observed in dams.

The number of live fetuses and percent were comparable at 0, 1 and 4 mg/kg but decreased at 16 mg/kg. Although the decrease was not statistically significant, the results indicate a decrease in litter size. There were no treatment related effects on fetal weight, and no external or internal malformations observed.

Based on this study, the maternal toxicity LOEL was 16 mg/kg (HDT) based on increased morbundity and decreased body weights and body weight gain; the NOEL was 4 mg/kg. The developmental toxicity LOEL was 16 mg/kg based on decreased litter size; the NOEL was 4 mg/kg.

Groups of 24 pregnant Sprague Dawley rats (MRID 139547) were orally gavaged with ethyl parathion (99.11% a.i.) at doses of 0 (corn oil), 0.25, 1.00 or 1.50 mg/kg on days 6 through 19 of gestation. Four female of the high dose (1.50 mg/kg) group died by Day 20 of gestation. The cause of deaths was not explained. Mean body weight and body weight gain were statistically significantly decreased at the highest dose on Days 15 and 20 of gestation. No other signs of toxicity were observed in the dams.

There were no treatment related effects on any parameters measured on fetuses. There

were no external or internal malformations observed.

The maternal toxicity LOEL was 1.5 mg/kg (HTD) based on MORTALITY by day 12 of dosing and decreased body weight; the NOEL was 1.00 mg/kg. Developmental toxicity NOEL was 1.5 mg/kg (HDT).

3. Reproductive Toxicity:

In a two generational reproduction study (MRID 41418401), four groups of Sprague Dawley rats (28/sex/dose) were given dietary ethyl parathion (96.7%) at doses of 0, 1, 10 or 20 ppm (0, 0.05, 0.5 or 1.0 mg/kg). Parental toxicity (F_0) was characterized as reductions in cholinesterase activities in both sexes at the mid dose and high in plasma, RBCs and brain (females only) at termination. At the high dose cholinesterase activities were further reduced in both sexes in plasma, RBCs, and brain . No other systemic toxicities were noted in parental F_0 generation.

The only treatment related systemic toxicity in the F_1 pups were reduced body weight and body weight gain in the high dose group. Plasma ChE activity was statistically significantly ($p \leq 0.01$) reduced in adult male and female F_1 rats at 0.5 and 1.0 mg/kg. There was a dose related trend in RBC ChE inhibition in both male and female F_1 rats at termination but the decreases were not statistically significant at $p \leq 0.01$. At termination, brain ChE activity was significantly ($p < 0.01$) reduced in F_1 female rats given the highest dose by 55% of control animals. Male F_1 rats at the highest dose had a 15 % reduction in brain ChE which was not significant at $p \leq 0.01$. There were no treatment related effects observed in the F_2 pups at termination. There were no treatment related reproductive toxicity in either sex or either generation throughout the study. It was noted that cholinesterase activity was not measured in offspring in this study.

The LOEL for parental (F_0) systemic toxicity was 0.5 mg/kg based on reductions in plasma, RBC in both male and female rats and brain cholinesterase activity in female rats. The NOEL was 0.05 mg/kg. The LOEL for F_1 adults was 0.5 mg/kg based on reduced plasma ChE activity in male and female rats; the NOEL was 0.05 mg/kg. The LOEL for developmental toxicity was 1.00 mg/kg based on reduced body weight and body weight gain in both F_1 male and female rats; the NOEL was 0.5 mg/kg. The reproductive toxicity NOEL in this study was $\geq$ 1.0 mg/kg (HDT).

4. Additional information from the literature

Although these studies were not submitted to the Agency by the Registrant in support of reregistration, they can be considered in weight-of-evidence determinations for ethyl parathion.

Stamper *et al.*, (1988) demonstrated that postnatal rat pups given subcutaneous ethyl parathion (1.3 mg/kg or 1.9 mg/kg) for 16 days (days 5-20), revealed small deficits in tests of

spatial memory in both the T-maze and the radial arm maze (spatial memory) which was associated with a reduction in muscarinic receptor binding. There were no differences between treatment and control groups in most reflex measures, eye opening or incisor eruption. This study suggested that the reduced muscarinic receptor binding in the brain of postnatal rats following subchronic exposure to ethyl parathion might be related to the differences in the performance in the T-maze test.

In a study by Veronesi and Pope (1990), rat pups dosed subcutaneously with ethyl parathion (0.882 mg/kg), at time points critical to the developing brain (i.e., day 5-20) had significant reductions in muscarinic receptor density and hippocampal acetylcholinesterase (AChE) was depressed by 73%. In treated pups, sacrificed on day 21, histopathology consisted of cellular disruption and necrosis in the specific cholinergic regions of the brain (dentate gyrus, and CA4 regions). The results indicated that subchronic postnatal exposure to ethyl parathion altered the development of cholinergic neurons due to the persistent AChE depression in neonatal rats.

Although these two studies demonstrate evidence of neurotoxic consequence of ethyl parathion-induced cholinesterase inhibition on the developing brain in postnatal rats, they do not provide indication of enhanced susceptibility. The behavioral and biochemical findings in these studies of developing animals are similar to those found in adult rats. McDonald *et al.*, (1988) reported spatial memory deficit (in a T-maze) along with decreased AChE activity and decreased cholinergic (muscarinic) receptor binding in adult rats following 14 days of organophosphate treatment with disulfoton, a structural analog of ethyl parathion.

In addition, these neonatal studies were conducted using the subcutaneous route of administration, which is unrelated to the route of human exposure. The subcutaneous route is considered remote from that of the human situation because changes that occur in the liver as a result of oral administration (i.e. bioactivation of parathion to its toxic metabolite, paraoxon) and during absorption are not considered.

In a 1995 review article[5] which surveyed the literature for placental toxicity of organophosphate(OP) and other insecticides, the authors state that the majority of studies in mammalian species (rats, mice, rabbits, hamsters) suggest that organophosphates have high maternal toxicity and are embryolethal but not teratogenic. The high embryolethality precludes the expression of the teratogenic potential and studies of many OPs have failed to demonstrate any teratogenic response although growth retardation and embryotoxicity were increased at maternally toxic doses.

5. Determination of Susceptibility

In the two-generation reproduction study in rats and the prenatal developmental toxicity studies in rats and rabbits, there was no indication of increased sensitivity of the young animals to pre-and/or postnatal exposure to ethyl parathion; effects in the offspring were observed only at

or above treatment levels which resulted in evidence of parental toxicity.

Based on the weight-of-evidence of all available studies, the Committee concluded that there was no increased suceptibility to rat or rabbit fetuses following *in utero* and/or post natal exposure to ethyl parathion.

6. Recommendation for a Developmental Neurotoxicity Study

Based on the following weight-of-evidence considerations, the HIARC determined that a developmental neurotoxicity study in rats is **not** required for ethyl parathion.

i. Evidence that suggest requiring a developmental neurotoxicity study:

- Ethyl parathion is a potent inhibitor of acetylcholinesterase in the central and peripheral nervous systems in mammals. Exposure to ethyl parathion causes CNS signs of acetylcholine (AChE) overstimulation including miosis, ciliary spasm, increased salivation, lacrimation, labored respiration, tremors, convulsions and death.

- Neurobehavioral measures (gait, grip strength) in rats are abnormal after an acute or subchronic exposure to ethyl parathion.

- Neuropathological findings were observed in a 2-year chronic study in rats where retinal atrophy and sciatic nerve degeneration occurred at 1.75 mg/kg in male rats and 2.47 mg/kg in female rats.

ii. Evidence that **do not** support a need for a developmental neurotoxicity study:

- No evidence of abnormalities were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic doses up to 1.5 or 16.0 mg/kg/day, respectively.

- Neither brain weight nor histopathology (nonperfused) of the nervous system were affected in the subchronic and chronic toxicity studies examined.

- Ethyl parathion administered either orally or dermally does not produce delayed neurotoxicity in hens[3].

- The retinal atrophy and nerve degeneration in the 2 year chronic study in rats occur at relatively high doses compared to the cholinergic toxicity (decreased plasma, RBC ChE) which occurs at a considerably lower dose (0.025 mg/kg/day). Therefore, by identifying the lower dose in which plasma/RBC ChE inhibition is the critical effect in acute and chronic studies, the potential chronic toxicity

effects, including eye effects, are adequately accounted for.

- The reviewed literature suggest that organophosphates (OPs) have high maternal toxicity and are embryolethal but not teratogenic. The high embryolethality precludes the expression of the teratogenic potential and studies of many OPs have failed to demonstrate any teratogenic response although growth retardation and embryotoxicity may be increased at maternally toxic doses.

- The reviewed literature studies demonstrated evidence of neurotoxic consequence of ethyl parathion-induced cholinesterase inhibition on the developing brain but the route of administration was inappropriate to humans exposure and the neurochemical and behavioral changes which occurred in neonatal rats also occurred in adult animals. Therefore, the special postnatal developmental toxicity study did not reveal any endpoints of concerns that would trigger a developmental neurotoxicity study.

7. Determination of the FQPA Safety Factor:

The application of a FQPA factor to ensure the protection of infants and children from exposure to ethyl parathion, as required by FQPA, will be determined by the FQPA Safety Factor Assessment Review Committee.

V. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. The Committee determined that based upon the data from the developmental toxicity study in rats, a developmental neurotoxicity study with ethyl parathion is not required; therefore, there are no significant uncertainties in the assessment of functional development following pre- and/or postnatal exposure to ethyl parathion.