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Attachment 1

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MEMORANDUM

SUBJECT: FENTHION: The HED Chapter of the Reregistration Eligibility Decision Document (RED), Case #0290, PC Code 053301

From: William J. Hazel, Ph.D., Chemist /s/
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Thru: Whang Phang, Ph.D., Branch Senior Scientist
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To: Arnold Layne, Chief
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Special Review and Reregistration Division (7508W)

The Human Health Assessment for the Reregistration Eligibility Decision (RED) document for fenthion is attached. This chapter reflects input from the Hazard Assessment from John Doherty in Toxicology Branch 2, the Occupational/Residential Exposure Assessment from Jeff Dawson in Reregistration Branch 1, the Dietary Exposure Assessment, Product Chemistry and Tolerance Reassessment from Christine Olinger in Chemistry Branch 1, and the Dietary Risk Assessment from Brian Steinwand in SAB/DRES.

Summary of Confirmatory Data Requirements / Label Changes / Significant Items

- 1) No acceptable series 85-1 general metabolism study has been submitted by the registrant. This study is required as confirmatory data.
- 2) Based on the lack of acute and subchronic neurotoxicity and the lack of developmental abnormalities, a developmental neurotoxicity study is not needed.
- 3) A subchronic neurotoxicity study (82-4) has been cited in the 1/96 TESC report and Toxicology Chapter as a deficiency. It is felt, based on hazard considerations alone, that there is a need to determine the effects of repeated inhalation exposure because fenthion appears to be

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more toxic via the inhalation than the oral route. HED has not determined whether the registered use patterns preclude repeat exposures; we will decide this in consultation with SRRD (we understand that a waiver was granted in 1989).

4) Since fenthion was demonstrated to be positive in two mutagenicity studies (unscheduled DNA synthesis and mouse micronucleus assay) a dominant lethal assay was requested by the HED RfD Committee to assess for possible effects on germinal cells. Although fenthion was not demonstrated to result in post-implantation lethal effects in mice dosed with single doses of either 10 or 25 mg/kg (MRID No.: 00132352) in a previously run dominant lethal study, this study is considered very old and to have associated uncertainties and a new one following current guidelines for dominant lethal testing is needed as confirmatory data.

5) Ruminant and swine dermal-treatment metabolism studies were reviewed in the 1990 Reregistration Standard Update and a subsequent CBRS report. These studies require upgrading by: (i) additional characterization and identification of residue components; (ii) accounting for large amounts of non-analyzed residues; and (iii) submission of supporting quantitative data.

6) The FDA PESTDATA database dated 1/94 (PAM Vol. I, Appendix II) indicates that fenthion, fenthion oxygen analog, fenthion oxygen analog sulfoxide, and fenthion sulfone are completely recovered using multiresidue method PAM, Vol. I Section 302. No data are available on the recovery of fenthion sulfoxide using FDA multiresidue methods. Because fenthion sulfoxide is a component of the toxic residue in swine, multiresidue testing data are required for this metabolite.

7) Unless the registrant amends the labels to lower the maximum use rate for dermal application to livestock from 0.08 oz ai/100 lb body weight to 0.01 oz ai/100 lb, additional data are required to support tolerances for residues in cattle and swine commodities. The new studies must contain complete sample storage information. Further storage stability data may be required to support the requested residue data and the existing residue data.

8) The registrant must propose modified directions for use including a minimum 21-day PSI. New cattle magnitude of residue studies are required before the cattle tolerances can be reassessed. The study should consist of three treatment groups with three head of cattle in each group. Ear tags should be placed on the animals in the first group of lactating dairy cows and milk should be sampled at weekly intervals until sacrifice after 28 days of treatment. Meat, meat by-products, and fat should be analyzed for the regulated residues of fenthion. Animals in the second treatment group should be treated with the pour-on treatment (at a rate of 0.082 oz. a.i. per 100 lb of animal) and ear tags and sacrificed 21 days after dosing. Although the pour-on treatment is not registered for use on lactating dairy cattle, it would be helpful if dairy cattle were used to obtain additional information on transfer of residues to milk. The use of beef cattle would be acceptable. The third group of animals should be a control group of lactating dairy cattle. No additional swine magnitude of residue studies are required.

9) Short- and intermediate-term dermal and inhalation exposure assessments were made using PHED Version 1.1 surrogate data since no chemical-specific handler data were submitted.

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Fenthion-specific handler studies may be required pending the outcome of recommended discussions with the registrants concerning appropriate risk mitigation options.

Bayer Chemical Company is a member of the ongoing *Outdoor Residential Exposure Taskforce (ORETF)*. As such, studies are to be completed to enable the Agency to evaluate residential exposures due to contact with treated turf (i.e., to generate appropriate activity pattern and transfer coefficient data). Bayer must also develop a strategy to generate chemical-specific transferable residue data to be used in conjunction with the ORETF database in order for the Agency to complete any exposure/risk assessment.

No proprietary data from the Spray Drift Task Force (SDTF) was used in this assessment. Bayer is a member of the SDTF and may refine the AgDRIFT input parameters if data were generated for the Baytex ULV product. Additionally, AgDRIFT was recently presented before the FIFRA Science Advisory Panel. Modifications to the model are possible as a result of the SAP comments. These modifications, however, are anticipated by HED not to significantly alter the results of this assessments. Any significant modifications to the model may require further refinement of this assessment. Even given the potential for modification of the model, the assessment is much more refined than assuming 100 percent of the application rate is deposited on the turf in residential areas where malaria vector control applications occur. This approach is recognized by HED as being unrealistic given what is known concerning the engineering aspects of malaria vector control applications.

Should you have any questions, please let me know.

cc: JDawson (RRB-1), BSteinwand (SAB/DRES), JDoherty (TOX-2), COLinger (RRB-1), MHawkins (Caswell, microfiche).

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FENTHION

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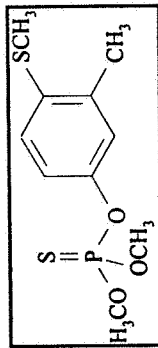
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III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

DESCRIPTION OF CHEMICAL

Fenthion [*O,O*-dimethyl *O*-(4-(methylthio)-*m*-tolyl)phosphorothioate] is an organophosphate insecticide used primarily for livestock dermal treatments and mosquito control (adulticide) in residential areas. Direct dermal treatments to livestock are by spot treatment and pour-on treatment, ear tags are used for dairy cattle (lactating and non-lactating) and beef cattle. Mosquito control (adulticide) applications are to residential areas in Florida by Ultra-low-volume (ULV) spray (aerial and ground application), and by thermal fog (ground application). The maximum single application rate for aerial is 0.1 lb. ai/A, for ground, 0.03 lb ai/A. Mosquito control applications are made on an as-needed basis.



Empirical Formula: $C_{10}H_{15}O_3PS_2$
Molecular Weight: 278.3
CAS Registry No.: 55-38-9
Shaughnessy No.: 053301

IDENTIFICATION OF ACTIVE INGREDIENT

Fenthion is a colorless to yellow-brown oily liquid with a boiling point of $87^{\circ}C$ at 0.01 mm Hg and a specific gravity of 1.25 at $20^{\circ}C$. Fenthion is soluble in dichloromethane, toluene, 2-propanol, and n-hexane, but nearly insoluble in water. The vapor pressure of technical fenthion is 2.1×10^{-6} mm Hg at $20^{\circ}C$.

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MANUFACTURING-USE PRODUCTS

A 10/14/97 search of the Reference Files System (REFS) identified two fenthion manufacturing-use products (MPs) registered to Bayer Corporation under Shaughnessy No. 053301: the 95% technical products (Ts; EPA Reg. Nos. 3125-197 and 11556-36). We note that the 95% emulsifiable concentrate (EC; EPA Reg. No. 3125-148) was identified as a MP in the Fenthion Reregistration Standard Update dated 7/31/90. Bayer has confirmed that the three 95% products are identical and differ only in the label guarantees for EPA Reg. No. 11556-36, which is an animal health product. Only the Bayer 95% Ts and 95% EP/MP are subject to a reregistration eligibility decision.

REGULATORY BACKGROUND

The Fenthion Reregistration Standard dated 4/22/87 required that product chemistry data pertaining to all data requirements be submitted. The Fenthion Reregistration Standard Update dated 7/31/90 reviewed the submitted data and required additional data concerning Guideline Nos. 830.1550, 830.1670, 830.1700, 830.1750, 830.6320, 830.7100, 830.7550, and 830.7950. Additional data were submitted for the 830.15, .16, and .17 series requirements and were reviewed by Registration Division and found acceptable.

The current status of the product chemistry data requirements indicate that the 830.71, .75 and .79 guidelines are outstanding for the Bayer 95% Ts and 95% EC EP/MP. Provided that the registrant submits the data required in the attached data summary table for the 95% MPs, and either certifies that the suppliers of beginning materials and the manufacturing process for the fenthion technical products/MPs have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, HED has no objections to the reregistration of fenthion with respect to product chemistry data requirements.

B. Human Risk Assessment

1. Hazard Assessment

The toxicology data base for fenthion is sufficient to support the Registration Eligibility Decision Document (RED).

a. Acute Toxicity

Table I: Acute Toxicity of Technical Fenthion¹

Guideline/Study #	Results	Toxicity Category	MRID #s
81-1 Acute Oral LD50, rat	405 mg/kg males 566 mg/kg females	II	40186704
81-2 Acute Dermal LD50, rabbit	963 mg/kg	II	40186705
81-3 Acute LC50 inhalation, rat	0.507mg/L males 0.454 mg/L, females	II	40186706
81-4 Primary eye irritation, rabbit	no cornea or iris irritation (some conjunctiva changes noted in 2 days but reversed in 2 days)	III	40186708
81-5 Primary dermal irritation, rabbit	PII = 0	IV	40186709
81-6 Dermal Sensitization, guinea pigs	not a sensitizer	--	40186710
81-7 Acute delayed neurotox, hen	no evidence of delayed neurotoxicity	--	40229201

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81-2
81-3
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81-8 Acute neurotoxicity, rat	Neurotox. NOEL = 1 mg/kg & LOEL = 50 or 75 mg/kg (muscle fascicula- tion, etc.). Plasma, RBC, and brain ChE-I NOEL & LOEL <1 mg/kg.	--	44326401
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1. BAYTEX technical fenthion, 96.9% purity was used in all acute studies except 81-6 which used a German 98.6% pure "E-1752" fenthion and 81-8 for which a 94.6% pure material was used.

In an acute oral toxicity study, groups of fasted adult (5/sex) Sprague-Dawley rats were given an oral dose of fenthion (96.9% purity) in corn oil at dose levels of 100 to 700 mg/kg and observed for 14 days. The oral LD50 in males was 405 (302-681) mg/kg and in females was 566 (461-791) mg/kg. For acute oral toxicity, fenthion is classified as Toxicity Category II based on the LD50 in males. Deaths occurred 1-4 days postdosing. Symptoms were consistent with cholinesterase (ChE)/acetylcholinesterase (AChE) inhibition and were noted in all dose groups and included salivation, diarrhea, tremors and muscle fasciculations which persisted until day 9 or 10 (Guideline 81-1, MRID No.: 40186704).

In an acute dermal toxicity study, New Zealand White rabbits (5/sex/group) were dermally exposed to fenthion (96.9%) undiluted over an area ranging from 17 to 240 cm² at dose levels from 100 to 1200 mg/kg/day and observed for 21 days. The combined dermal LD50 for both sexes was 963 (744-1162) mg/kg. For acute dermal toxicity, fenthion is classified as Toxicity Category II based on both sexes. Deaths occurred 2-5 days postdosing. Clinical signs were noted at dose levels of 800 mg/kg and above and included diarrhea, decreased activity, hyperactivity, hyperpnea, salivation, muscle fasciculations, urine stain, ataxia and tremors. Some symptoms persisted to day 21 (Guideline 81-2, MRID No.: 40186705).

In an acute inhalation toxicity study, groups of ten/sex Sprague-Dawley rats were dosed with atmospheric concentrations of 0.209, 0.293, 0.461, 0.476 or 0.862 mg/L for 4 hours (head only exposure) with MMADs (mass mean aero dynamic diameter) of 1.5 to 1.7 with geometric standard deviations of 1.9 to 2.0. The rats were observed for 14 days. The inhalation LC50 (with 95% confidence interval) in males was 0.507 (0.409 to 0.695) mg/L and in females was 0.454 (0.349 to 0.658) mg/L. Fenthion is placed in Toxicity Category II for acute inhalation based on the acute inhalation LC50 in female rats. The major symptoms were indicative of ChE/AChE inhibition and included tremors, muscle fasciculations, salivation, hypoactivity, ataxia, polypnea, ocular and nasal discharge and dry skin. Tremors and other motor symptoms were present at all dose levels. Some symptoms (i.e. tremors, dry skin, ocular discharge) persisted until day 14 in some rats (Guideline 81-3, MRID No.:40186706 and 40186707).

At In a primary eye irritation study, 0.1 mL of technical fenthion (96.9%) was instilled into the

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conjunctival sac of the left eye of adult New Zealand strain rabbits (3/sex) and left in place. The rabbits were observed for 72 hours post-dosing. No cornea or iris irritation was noted. Discharge, redness and swelling were observed in the conjunctiva in all rabbits. The symptoms reversed after two days. Fenthion is classified as Toxicity Category III for primary eye irritation (Guideline 81-4, MRID No.: 40186708).

In a primary dermal irritation study, adult New Zealand White rabbits (3/sex) were exposed dermally to 0.5 mL of undiluted fenthion (96.9%) on an approximately 6 cm² area. The rabbits were observed for up to 72 hours after dosing. A primary irritation index of 0 resulted. No edema and only very slight erythema resulted which regressed after 24 hours. In this study fenthion is not a dermal irritant and is classified as Toxicity Category IV for primary dermal irritation in both sexes (Guideline 81-5, MRID No.: 40186709).

In a dermal sensitization study, male guinea pigs (10/group) were dosed as controls or with 0.2% fenthion in adjuvant intradermally following the procedure of Magnusson and Kligman followed by a topical induction with 50% fenthion. Challenge was made with a 12.5% topical application. There was no indication of dermal sensitization in the challenge phase. In this study, fenthion was not a dermal sensitizer (Guideline 81-6, MRID No.: 40186710).

A study was conducted to assess the potential of fenthion to cause delayed type neuropathy in hens following both the oral or dermal routes of exposure. Five groups of hens (5-7 months of age) were dosed as controls (6 hens), vehicle controls (6 hens), Tri-ortho Cresyl Phosphate (TOCP) positive controls (5 hens), 40 mg/kg of fenthion orally in Cremophor (15 hens) or 200 mg/kg dermally (15 hens). The oral dose of fenthion was about 1.5 times the unprotected LD50. The hens treated with fenthion were protected from AchE inhibition effects by periodic treatment with atropine. Two doses of fenthion were administered, each 21 days apart for a total of 42 days of observation. Two hens dosed orally and 8 hens dosed dermally died. There were signs indicative of intoxication (staggered gait, ruffed feathers, rapid breathing and sternal recumbency) which regressed by days 5-7. No evidence of delayed type neuropathy was indicated by either persistent motor or posture effects or pathological structural changes in the peripheral nerves (Guideline 81-7, MRID No.: 40229201).

In addition to the guideline study described above there are two additional special studies that assess the capability of fenthion to inhibit the neurotoxic esterase (NTE) enzyme that is regarded as an indicator of the potential of a chemical to cause delayed type neurotoxicity. These studies were conducted by the oral and dermal routes of administration. In the oral study, the hens were dosed with 40 mg/kg and protected with atropine since the acute oral LD50 in hens is 27 mg/kg. In the dermal study, the hens were dosed with 200 or 400 mg/kg (a dose fatal to some of the hens) and also protected with atropine. There was some inhibition of the neurotoxic esterase noted in the hens dosed with fenthion (i.e. < 20% and usually < 10%) but not indicative of a dose or time response. The positive control (100 mg/kg of TOCP) resulted in 90 to 95% inhibition 24 hours after treatment. These studies were classified as SUPPLEMENTARY and are considered useful in making the determination that fenthion should not cause delayed type neurotoxicity. (oral MRID No. 41283401 and dermal MRID No. 41283402)

In an acute neurotoxicity study four groups of 18/sex Wistar strain rats were dosed with fenthion (94.6% purity) in corn oil (5 ml/kg) and assessed daily for clinical signs, FOB and motor activity at about 5 hours post dosing and on days 7 and 14. After sacrifice on day 14, the rats were perfused and assessed for neurohistopathology. The dose levels were 0, 1, 50 or 125 mg/kg for males and 0, 1, 75 or 225 mg/kg for females. At 50 mg/kg for males and 75 mg/kg for females there were several parameters affected to indicate consequences of inhibition of ChE/AChE. The *principle* parameters affected included decreased motor activity, presence of muscle fasciculation (all males and 11/12 females), repetitive chewing (all males and females), gait impairment (all males and females), decreased body temperature (0.9 °C, $p < 0.05$ males), pupil constriction (9/12 males and all females), decreased body weight and gain. At 125 mg/kg in males the same symptoms increased and in addition there were convulsions and several other treatment-related reactions. At 225 mg/kg in females there were 4 deaths as well as increased incidence and severity of the symptoms. The decrease in motor activity reversed slowly with there being some symptoms remaining at day 14. See review for complete list of parameters affected. **For neurotoxicity, the NOEL was 1 mg/kg for both sexes and the LOEL was 50 mg/kg in males and 75 mg/kg in females based mainly on muscle fasciculation and related parameters.** At 1 mg/kg plasma ChE (-23%, not significant), RBC AChE (-22%, $p < 0.05$) and brain AChE (-9%, $p < 0.01$) were inhibited in females. Males showed decreases but they did not reach statistical significance. At 50 mg/kg for males and 75 mg/kg for females and above inhibition was always greater than 76%. **The NOEL and LOEL for inhibition of ChE/ACHE is < 1 mg/kg (females more affected than males).**

b. Subchronic Toxicity

In a special study, three groups of 4 male human volunteers were dosed orally by capsules containing fenthion in corn oil daily for up to 28 days at dose levels of 0, 0.02 or 0.07 mg/kg/day. Blood samples were taken at pretest (4 times) and twice weekly during the scheduled dosing and 24 hours after the last dose primarily for assessment of plasma ChE and RBC AChE. Clinical reactions, clinical chemistry, hematology and urinalysis were also monitored. Plasma ChE was considered to be inhibited relative to group pretest values in the group dosed with 0.07 mg/kg/day (approximately 8%) in less than 24 hours following the initial dose and reached levels up to about 30% inhibition after 3 weeks. The group dosed with 0.02 mg/kg/day reached levels of 5-12% inhibition starting after one week of exposure. The control group was actually increased relative to pretest. The 0.02 mg/kg/day dose group is considered a threshold for inhibition since at least some statistical tests reported by the study author were significant compared to the control group. RBC AChE was not inhibited and there were no changes in clinical observations, chemistry, hematology or urinalysis. The threshold NOEL/LOEL is 0.02 mg/kg/day and a NOEL is not considered definitely established for inhibition of plasma ChE. Although this study is classified as SUPPLEMENTARY, the data are considered very useful for toxicity endpoint selection for risk assessment since this special study was conducted on humans (MRID No. 00147246).

There are two 21-day rabbit dermal toxicity studies for fenthion: a 1979 study (MRID No.: 40808601) and a 1987 study (MRID No.: 40329501). These studies (summarized in the next two

paragraphs) differ in the method of application of fenthion and demonstrate different NOEL and LOEL values for inhibition of plasma ChE and RBC AChE.

In the 1979 21-day dermal toxicity study, New Zealand White rabbits (6/sex/group, 3 groups) were dosed as control, 5 or 25 mg/kg/day of technical fenthion applied as a dilute solution in Cremophor. All of the rabbits in each group were shaved. Half of the rabbits in each group were also abraded. The unabraded female rabbits dosed with 5 mg/kg/day experienced 14% and 19% inhibition of RBC AChE after 10 and 15 applications, respectively. Females also had 22% decrease in plasma AChE and 10% decrease in brain AChE after 15 applications. Higher levels of inhibition for each enzyme source were noted at 25 mg/kg/day. Males dosed with 5 mg/kg/day were shown to have a 31% decrease in RBC AChE after 15 applications and 42% decrease at 25 mg/kg/day. The LOEL is < 5 mg/kg/day based on inhibition of plasma ChE, RBC AChE and brain AChE in females and RBC AChE in males (SUPPLEMENTARY Guideline 82-2, MRID No. 40808601).

In the 1987 study, fenthion (96.9%) was applied dermally to the prepared backs of New Zealand White rabbits at dose levels of control (3 groups), 5, 50, 100, 150, 200 or 400 mg/kg/day. Each group consisted of 5/sex and applications were made 5 times/week for 6 hours for a total of 15 applications. Severe signs of ChE/AChE inhibition including deaths were noted in the 200 and 400 mg/kg/day dose groups. Only occasional incidents (urine staining, languid appearance, polyuria and red fluid discharge urogenital area and soft feces) were noted in the 150 mg/kg/day dose group and no symptoms were reported at lower doses. The LOEL is 150 mg/kg/day based on clinical signs and the NOEL is 100 mg/kg/day. Local dermal irritation (erythema and related scaling) were noted at 50 mg/kg and above. The LOEL for local dermal irritation is 50 mg/kg/day and the NOEL is 5 mg/kg/day. Plasma ChE in males (19% at weeks 1 and 3, $p < 0.05$) and brain AChE in females (week 3, 24%, $p < 0.05$) were inhibited at 100 mg/kg/day. At 150 mg/kg/day progressively higher levels of plasma ChE and RBC and brain AChE were noted. The LOEL for plasma ChE (males) and brain AChE (females) is 100 mg/kg/day and the NOEL is 50 mg/kg/day (Guideline 82-2, MRID No.: 40329501).

In conclusion, the 1979 study conducted with Cremophor as the vehicle is considered to better approximate the exposure to formulations and the LOEL for inhibition of plasma ChE and RBC AChE in females is < 5 mg/kg/day.

In a subchronic neurotoxicity study, fenthion technical (94.3% a.i.) was administered to Wistar rats (12/sex/dose) by feeding at dose levels of 0, 2, 25 or 125 ppm (0, 0.13, 1.63 or 8.50 mg/kg/day for males; 0, 0.17, 2.19 or 12.62 mg/kg/day for females) for 13 weeks. The rats were evaluated by functional observation battery (FOB) and motor activity testing at pretest and during weeks 4, 8, and 13 of treatment. Six rats/sex/group were evaluated for neuropathology and the remaining 6 rats/sex/group were evaluated for cholinesterase activities (plasma, erythrocyte, and brain) during weeks 4 and/or 14 of treatment.

At 25 ppm there was decreased body weight (5-7%, $p < 0.05$) and body weight gain (15-17%) in females, body weight (3-4%) and weight gain (4-10%) in males was also lower but statistical

significance was not attained. At 125 ppm, body weight effects were more pronounced and clinical signs indicated palmo spasms and related reactions, FOB assessment indicated muscle fasciculations (6/12 males and 8-9 females) and related cholinergic responses (gait abnormalities, slight tremors (one female) and stilted gait). Motor activity was also decreased. No pathological lesions in the nerve tissue including the eye and optic nerve or in the epididymis were noted. **For neurotoxicity, the LOEL was 25 ppm (1.63 mg/kg/day for males and 2.19 mg/kg/day for females) based mainly on body weight and muscle fasciculations. The NOEL was 2 ppm (0.13 mg/kg/day for males and 0.17 mg/kg/day for females).**

At 2 ppm, plasma ChE was inhibited 16-17% ($p < 0.05$) in males. Females were also 17-21% lower but statistical significance was not attained probably because of the poor precision of the data (i.e. large standard deviations). At 25 ppm, plasma ChE (~57%♂, 81%♀), RBC AChE (56-65%♂, 78%♀) and brain AChE (47%♂, 58%♀) were definitely inhibited. **The NOEL and LOEL for plasma ChE inhibition is < 2 ppm (0.13 mg/kg/day for males and 0.17 mg/kg/day for females).**

The requirements for subchronic feeding studies with rodents and non-rodents (guidelines 82-1a and 82-1b, respectively) were satisfied by the long-term (chronic) feeding studies in those species.

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(c. Chronic Toxicity and Carcinogenicity)

In a special study, three groups of monkeys (4-5/sex) were dosed by stomach tube with fenthion (98.1% purity) in corn oil for two years at 0, 0.02, 0.07 or 0.20 mg/kg/day. The general condition of the monkeys was monitored and blood was drawn monthly for plasma ChE and RBC AChE and assessed by the radiometric method of Michel. Inhibition of plasma ChE or RBC AChE was only infrequently noted in the controls. Plasma ChE was frequently inhibited at 0.02 mg/kg/day (maximum 67% in the first six months and especially in females) such that this level was deemed to be a threshold level. Progressively more consistent inhibition was noted at 0.07 and 0.20 mg/kg/day. RBC AChE was noted to have a threshold for inhibition at 0.07 mg/kg/day (frequent inhibition at this level up to 39% for the first three months of the study). More consistent inhibition was noted at 0.20 mg/kg/day for RBC AChE. No inhibition of brain AChE was noted and no clinical signs or body weight effects were noted. The threshold NOEL/LOEL for plasma ChE was 0.02 mg/kg/day and LOEL for RBC AChE was 0.07 mg/kg/day. The definite NOEL for plasma ChE inhibition was not established and the NOEL for RBC AChE was 0.02 mg/kg/day. Although this study is classified as SUPPLEMENTARY the data are considered useful when combined with other data for evaluation of risk (MRID No.: 00147245).

In a rat combined chronic feeding/carcinogenicity study, four groups of 50/sex Fisher 344 strain rats were dosed at 0, 5, 20 or 100 ppm (equivalent to 0, 0.2, 0.8, or 5.2 mg/kg/day for males and 0.3, 1.3, or 7.3 mg/kg/day for females) for two years. Interim sacrifice groups of 20/sex for the control and high dose group were also included. Inhibition of plasma ChE (40%), RBC AChE (up to 19%) and brain AChE (14%) were noted at the lowest dose of 5 ppm (0.2 or 0.3

mg/kg/day for males and females respectively. Thus, the ChE/AChE NOEL is < 0.2 mg/kg/day based on plasma ChE, RBC AChE and brain AChE inhibition. At 20 ppm (0.8 mg/kg/day) there was epididymal pathology (vacuolation), vacuolation of the nasolacrimal duct (in females), pneumonia (in males), lung weight change (males), skin lesions and clinical signs (threshold for males and females). There were ocular effects including effects on eye function and/or pathology in females. At 100 ppm there were body weight decreases, mineralization (stomach and other structures) and vacuolation of the nasolacrimal duct (males). The eye and optic lesions increased in females and became evident in males and included optic nerve pathology (atrophy and neovascularization). The LOEL for systemic toxicity is 0.8 mg/kg/day based epididymal effects in males and 1.3 based on ocular effects in females and other effects. The NOEL for systemic toxicity is 0.2 (males) or 0.3 (females) mg/kg/day (Guideline 83-1a and 83-5, MRID No.: 40327001-interim report, 41743101 and 42699902).

In a chronic feeding study, four groups of 4 beagle dogs/sex were dosed for one year at levels of 0, 2, 10 or 50 ppm (equivalent to 0, 0.056, 0.262 or 1.228 mg/kg/day in males and 0, 0.056, 0.262 or 1.182 mg/kg/day in females). No systemic effects were noted. At 10 ppm, plasma ChE (31-41%) and RBC AChE (15% in males and 3% in females) were inhibited. After one year at 50 ppm: plasma ChE was inhibited 50-70%; RBC AChE was inhibited 54% in males and 53% in females; and, brain AChE was inhibited 30% (not significant) in males and 44% in females (significant). The LOEL is 0.262 mg/kg/day based on plasma ChE and RBC AChE inhibition. The NOEL is 0.056 mg/kg/day (Guideline 83-1b, MRID No.: 40341701-interim report, 41632801 and 42901402).

The NCI assessed the carcinogenicity of fenthion in Fischer 344 rats fed at doses of 0, 10 or 20 ppm (equivalent to 0, 0.5, or 1 mg/kg/day). The control group consisted of 25/sex and the fenthion dosed rats consisted of 50/sex. This study raised the question of possible compound related increases in C-cell adenomas of the thyroid and interstitial-cell tumors of the testes. There was no evidence of increases in these same tumor types in the more recent study at higher dose levels. Thus, fenthion is not considered carcinogenic in the rat in this study (MRID No.: 00147478).

In a recent study, B6C3F1 mice (80/sex/dose) were fed diets containing fenthion at 0, 0.1, 1.0, 5 or 25 ppm (equivalent to 0, 0.014, 0.14, 0.71 or 3.57 mg/kg/day) of technical fenthion for 102 weeks. These dose levels corresponded to 0, 0.03, 0.40, 1.95 and 9.42 mg/kg/day in males and 0, 0.03, 0.47, 2.25, and 10.23 mg/kg/day in females. Groups of 20/sex were sacrificed at 1 year. Liver tumors were higher in the 5 ppm dose group, but not in the 25 ppm dose group and the RfD committee determined that there was no evidence of increased carcinogenicity. There was no evidence of test compound related skin tumors. The low dose of 0.1 ppm was considered a threshold for inhibition of plasma ChE in males and a NOEL and LOEL of 0.1 and 1 ppm for females was established, respectively. RBC AChE was considered to have NOEL and LOELs of 5 and 25 ppm, respectively. Fenthion did not demonstrate carcinogenicity in this study (Guideline 83-2b, MRID No.: 41869201, 42759701 and 42901403).

Fenthion was assessed by the NCI for carcinogenicity in the B6C3F1 strain mice at dose levels of

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0, 10 or 20 ppm (equivalent to 0, 0.5, or 1.0 mg/kg/day) in the diet. There were 50/sex mice dosed with fenthion and only 20/sex in the controls. The study indicated that certain skin tumors (sarcoma, fibrosarcoma and rhabdomyosarcoma) were increased (i.e. up to 4 incidents vs none in the controls) in the animals dosed with fenthion. Since the more recent study did not also show an indication of increased skin tumors in the same strain and at a slightly higher dose level, and for a longer exposure time, fenthion is not considered oncogenic in the mouse in this study (MRID No.: 00147478).

(d. Developmental Toxicity) *bell*

Four groups of 33 Charles River CD strain rats were dosed with fenthion (96.5%) at dose levels of 0, 1, 4.2 or 18 mg/kg/day by gavage in aqueous Emulphor during days 6-16 of pregnancy. A group of 5 dams/dose was sacrificed on day 16 and their blood and brain assessed for ChE/AChE inhibition. The remainder were sacrificed on day 20. Reactions to treatment were noted only in the high dose group dams. Clinical signs included tremors (15/33 dams affected), lacrimation (11/33), exophthalmos (9/33), hypoactivity (5/33), urine stained ventral surface (5/33) and salivation (5/33) and decreases in body weight gain (43% less gain or 19 gms vs 32 gms for controls for days 6-15). The high dose group also had a slightly higher rate of resorptions (in excess of the historical control). The LEL for maternal/ developmental toxicity is 18 mg/kg/day. The NOEL is 4.2 mg/kg/day. Plasma ChE (49.9%, $p < 0.01$, day 16), RBC (20.5% $p < 0.05$, day 20) and brain (19.5%, $p < 0.01$, day 20) AChE were inhibited at 1.0 mg/kg/day and higher for either the 16th or 20th day assessments. Fetal brain AChE was also considered to be inhibited (8.7%, $p < 0.05$) in the high dose group at day 20. The NOEL for plasma ChE and RBC and brain AChE is < 1.0 mg/kg/day, the Lowest Dose Tested (LDT) (Guideline 83-1a, MRID No.: 40329401).

Four groups of American Dutch rabbits were dosed as control, 1, 2.75 or 7.5 mg/kg/day of fenthion in 5% aqueous Emulphor by gavage on days 6 through 18 of gestation. Blood samples were taken on day 19 and 28 for determination of plasma ChE and RBC AChE and they were sacrificed on day 28 of gestation. Treatment-related effects at 2.75 mg/kg/day were limited to "soft stools" at 2.75 mg/kg/day (35% or 6 does) and (71%, 12 does) and a weight gain decrease at 7.5 mg/kg/day. The LEL for maternal toxicity is 2.75 mg/kg/day based on "soft stools". The NOEL for maternal toxicity is 1.0 mg/kg/day. Developmental toxicity was indicated by a slight increase in resorptions (0.4 for the control 1.1 for the high dose group) and possible but equivocal decreases in mean fetal weight in the mid (2.6%) and high (6.8%) dose groups and increases in unossified metacarpals in the high dose group. The LEL for developmental toxicity is 7.5 mg/kg/day based on resorptions. The NOEL for developmental toxicity is 2.75 mg/kg/day. Brain AChE was 20% and 40% inhibited in the 2.75 and 7.5 mg/kg/day dose group on day 28 following 10 days from the last fenthion administration. Plasma ChE (15.6%) and RBC AChE (21.7%, neither statistically significant) were inhibited at day 19 in the mid dose. Higher levels (45.6% and 82.9%) were noted in the 7.5 mg/kg/day dose group. The LEL for plasma ChE, RBC and brain AChE is 2.75 mg/kg/day based mostly on brain AChE inhibition. The NOEL is 1.0 mg/kg/day (Guideline 83-1b, MRID No.: 40462701).

e. Reproductive Toxicity (2-generation) ^{bell}

Five groups of 30/sex Charles River Crl:CD.BR strain rats were dosed in the diet with fenthion as controls, 1, 2, 14 or 100 ppm (approximately equivalent to 0, 0.05, 0.10, 0.70 or 5 mg/kg/day) and mated to produce F1 generation. The F1 litters were bred to produce the F2 generation. Cytoplasmic vacuolation of the epithelial ductal cells of the epididymis and inhibition of plasma ChE and RBC AChE were evident at 14 ppm. At 100 ppm there was: decreased epididymal weight; decreased fertility; increased maternal weight gain during pre-mating; decreased weight gain during gestation; decreased pup weight gain during lactation; and inhibition of brain AChE. The LOEL is 14 ppm (0.7 mg/kg/day) based on both parental and reproductive toxicity. The NOEL is 2 ppm (0.1 mg/kg/day) (Guideline 83-4, MRID No.: 41348601 and 42901401).

f. Mutagenicity (Guideline series 84-2) ^{bell}

Fenthion was assessed for gene mutations in Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 at dose levels of 0, 8, 40, 200, 1000 or 5000 µg/plate. No evidence of mutagenicity was noted in the presence or absence of metabolic activation (MRID No.: 42077301). A second study verified this observation (MRID No.: 41283404).

Fenthion was assessed in an unscheduled DNA synthesis assay in vitro at dose levels of 0, 5, 7.5, 10, 15 or 30 µg/mL in rat primary hepatocytes. Fenthion was considered positive at dose levels of 5 µg/ml and above (MRID No.: 41726301).

Fenthion was assessed in vivo in the micronucleus test in mice (Bor:NMRI strain) at 150 mg/kg and caused a 3 fold increase in polychromatic erythrocytes at 24 hours. Fenthion was considered positive in the micronucleus test in mice (MRID No.: 41451701). An earlier study in this same strain of mice (MRID No.: 00132353) did not indicate that fenthion was mutagenic after two 100 mg/kg doses.

Fenthion was not demonstrated to cause chromosome aberrations in vitro in Chinese Hamster Ovary cells in the presence or absence of metabolic activation at dose levels of 0, 0.02, 0.04, 0.08 or 0.15 µl/mL (MRID No.: 41283403).

Since fenthion was demonstrated to be positive in two of these studies (unscheduled DNA synthesis and mouse micronucleus assay) a dominant lethal assay was requested by the HED RfD Committee to assess for possible effects on germinal cells. Although fenthion was not demonstrated to result in post-implantation lethal effects in mice dosed with single doses of either 10 or 25 mg/kg (MRID No.: 00132352) in a previously run dominant lethal study, this study is considered very old and to have associated uncertainties and a new one following current guidelines for dominant lethal testing is needed.

g. Metabolism ^{bell}

No acceptable series 85-1, general metabolism study has been submitted by the registrant. This

study is required as confirmatory data.

h. Neurotoxicity *bold*

In an acute delayed neurotoxicity study, following a single oral dose of fenthion at 40 mg/kg to hens, there was no evidence of delayed type neuropathy as indicated by either persistent motor or posture effects, no neuropathological changes in the peripheral nerves, and no inhibition of neurotoxic esterase (Guideline 81-7, MRID nos. 40229201, 41283401).

In a subchronic neurotoxicity study, hens (four groups) were dosed by gavage at 0, 0.84, 1.7 or 3.2 mg/kg/day of fenthion in corn oil for 90 days. Blood ChE inhibition and pathological changes in the esophagus, crop, proventriculus and intestine were noted at all doses. At 1.7 mg/kg/day there was feather loss and decreased activity and at 3.2 mg/kg there were ataxia, body weight loss and deaths. The systemic LOEL for ChE/AChE inhibition and systemic effects is < 0.84 mg/kg/day. No evidence of pathological changes in the structure of brain or peripheral nerve indicative of delayed type neuropathy were noted. The NOEL/LOEL for delayed type neurotoxicity in hens is > 3.2 mg/kg/day, the Highest Dose Tested (HDT) (Guideline 82-5, MRID No.: 40933601).

In a follow up special study designed to further assess the effects of fenthion on the esophagus and gastro-intestinal system, two groups of 10 hens were dosed for three months as control or 54 ppm (formula for conversion to mg/kg not available) of fenthion. The treated hens lost 9% of their body weight and blood ChE was inhibited 52% to 64%. Total tissue ChE/AChE in the crop, proventriculus and esophagus was inhibited 70-72% at termination. All ten fenthion treated hens had hypertrophy/hyperplasia of the muscular esophagus and four of the ten hens had hypertrophy/hyperplasia of the glandular esophagus. The LOEL for ChE/AChE inhibition and effects on the esophagus < 54 ppm. No NOEL was established for this unusual finding in hens. This study is classified as SUPPLEMENTARY, this unusual effect is noted and the study provides useful data (Guideline 82-5, MRID No.: 43121401).

In an acute neurotoxicity study four groups of 18/sex Wistar strain rats were dosed with fenthion (94.6% purity) in corn oil (5 ml/kg) and assessed daily for clinical signs, FOB and motor activity at about 5 hours post dosing and on days 7 and 14. After sacrifice on day 14, the rats were perfused and assessed for neurohistopathology. The dose levels were 0, 1, 50 or 125 mg/kg for males and 0, 1, 75 or 225 mg/kg for females.

At 50 mg/kg for males and 75 mg/kg for females there were several parameters affected to indicate consequences of inhibition of ChE/AChE. The *principle* parameters affected included decreased motor activity, presence of muscle fasciculation (all males and 11/12 females), repetitive chewing (all males and females), gait impairment (all males and females), decreased body temperature (0.9 °C, $p < 0.05$ males), pupil constriction (9/12 males and all females), decreased body weight and gain. At 125 mg/kg in males the same symptoms increased and in addition there were convulsions and several other treatment-related reactions. At 225 mg/kg in females there were 4 deaths as well as increased incidence and severity of the symptoms. The

decrease in motor activity reversed slowly with there being some symptoms remaining at day 14. See review for complete list of parameters affected. **For neurotoxicity, the NOEL was 1 mg/kg for both sexes and the LOEL was 50 mg/kg in males and 75 mg/kg in females based mainly on muscle fasciculation and related parameters.**

At 1 mg/kg plasma ChE (-23%, not significant), RBC AChE (- 22 %, $p < 0.05$) and brain AChE (-9%, $p < 0.01$) were inhibited in females. Males showed decreases but they did not reach statistical significance. At 50 mg/kg for males and 75 mg/kg for females and above inhibition was always greater than 76%. **The NOEL and LOEL for inhibition of ChE/AChE is < 1 mg/kg (females more affected than males).**

In a subchronic neurotoxicity study, fenthion technical (94.3% a.i.) was administered to Wistar rats (12/sex/dose) by feeding at dose levels of 0, 2, 25 or 125 ppm (0, 0.13, 1.63 or 8.50 mg/kg/day for males; 0, 0.17, 2.19 or 12.62 mg/kg/day for females) for 13 weeks. The rats were evaluated by functional observation battery (FOB) and motor activity testing at pretest and during weeks 4, 8, and 13 of treatment. Six rats/sex/group were evaluated for neuropathology and the remaining 6 rats/sex/group were evaluated for cholinesterase activities (plasma, erythrocyte, and brain) during weeks 4 and/or 14 of treatment.

At 25 ppm there was decreased body weight (5-7%, $p < 0.05$) and body weight gain (15-17%) in females, body weight (3-4%) and weight gain (4-10%) in males was also lower but statistical significance was not attained. At 125 ppm, body weight effects were more pronounced and clinical signs indicated palmyospasms and related reactions, FOB assessment indicated muscle fasciculations (6/12 males and 8-9 females) and related cholinergic responses (gait abnormalities, slight tremors (one female) and stilted gait). Motor activity was also decreased. No pathological lesions in the nerve tissue including the eye and optic nerve or in the epididymis were noted. **For neurotoxicity, the LOEL was 25 ppm (1.63 mg/kg/day for males and 2.19 mg/kg/day for females) based mainly on body weight and muscle fasciculations. The NOEL was 2 ppm (0.13 mg/kg/day for males and 0.17 mg/kg/day for females).**

At 2 ppm, plasma ChE was inhibited 16-17% ($p < .05$) in males. Females were also 17-21% lower but statistical significance was not attained probably because of the poor precision of the data (i.e. large standard deviations). At 25 ppm, plasma ChE (~57% σ , 81% φ), RBC AChE (56-65% σ , 78% φ) and brain AChE (47% σ , 58% φ) were definitely inhibited. **The NOEL and LOEL for plasma ChE inhibition is < 2 ppm (0.13 mg/kg/day for males and 0.17 mg/kg/day for females).**

It was initially suspected that published studies indicated evidence of neurotoxic effects of fenthion. Upon examination of these published studies, it was concluded in the 3/26/98 HIARC report (J. Rowland) that the published studies generally used higher dose levels and nonconventional routes of administration (i.e., subcutaneous) thus rendering them inconsequential for regulatory risk assessment purposes. The data bases generated by the conventional studies (submitted to the Agency) already establish NOELs and LOELs at lower

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doses based on a sensitive endpoint (i.e., cholinesterase inhibition).

2. Dose-Response Assessment

a. Determination of Safety for Infants and Children

The Agency's Health Effects Division's Hazard Identification Assessment Review Committee (H.A.R.C.) met on September 2, 1997 to reevaluate the reproductive, developmental and neurotoxicity data for fenthion in order to address the sensitivity of infants and children from exposure to fenthion as required by the Food Quality Protection Act (FQPA) of 1996. Evaluation of the toxicology data base indicated the following:

i. Developmental Toxicity

The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to fenthion and comparable NOELs were established for adults and offspring.

In a developmental toxicity study with CD-rats, pregnant animals received oral doses of fenthion at 0, 1, 4.2 or 18 mg/kg/day during gestation days 6 through 16. For maternal and developmental toxicity, the NOEL was 4.2 mg/kg/day and the LOEL was 18 mg/kg/day. The LOEL was based on a decrease in body weight gain and clinical signs (hypoactivity, urine stains) in dams (maternal) and on a possible increase in postimplantation loss and a significant increase in fetal brain ChE activity (developmental) (MRID no. 40329401).

In a developmental toxicity study with New Zealand rabbits, artificially impregnated animals were given oral doses of fenthion at 0, 1, 2.75 or 7.5 mg/kg/day during gestation days 6 through 18. For maternal toxicity the NOEL was 1.0 mg/kg/day and the LOEL was 2.75 mg/kg/day based on soft stools. For developmental toxicity, the NOEL was 2.75 mg/kg/day and the LOEL was 7.5 mg/kg/day based on possible increased resorptions, decreased metacarpal ossification, and decreased incidence of extra ribs in fetuses but not in litters (MRID No. 40462701).

ii. Reproductive Toxicity

In a 2-generation reproduction study, when fenthion was administered in the diet at 0, 0.5, 0.1, 0.7 or 5.0 mg/kg/day to CD rats, no increased sensitivity to pups over the adults was seen. For parental systemic and reproductive toxicity, the NOEL was 0.1 mg/kg/day and the LOEL was 0.7 mg/kg/day based on epididymal vacuolation and inhibition of plasma, erythrocyte and brain ChE activity in F₀ animals; only plasma ChE was inhibited in pups at the LOEL (MRID no. 42348601 and 42901401).

iii. Cholinesterase Inhibition

In rats, the ChEI NOEL in dams was <1.0 mg/kg/day (lowest dose tested) based on plasma (g.day 16), erythrocyte (g.day 20) and brain (g.day 20) ChEI. In fetuses, the ChEI NOEL was 4.2 mg/kg/day based on the brain ChEI observed at 18 mg/kg/day (highest dose tested) on day 20. A similar comparison could not be made in rabbits since ChE activity was measured only in the dams and not in the fetuses.

iv. Need for Developmental Neurotoxicity Study

The HIARC, based on a weight-of-the-evidence approach, determined that a developmental neurotoxicity study is **not required** (see 3/26/98 J. Rowland memorandum). This decision was based on the following factors: 1) no evidence of delayed type neuropathy, inhibition of neurotoxic esterase or neuropathology in the acute delayed neurotoxicity study in hens, 2) no treatment-related histopathological lesions of the nervous system in the acute neurotoxicity study in rats; 3) no treatment-related pathological lesions in the nerve tissues in the subchronic neurotoxicity study in rats; and 4) there was no evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system in the pre- and/or postnatal studies. It is noted that this decision is a reversal of a previous decision in which this study was identified as a Data Gap (HED Doc. No. 011804).

b. Reference Dose (RfD)

The HED RfD Peer Review Committee met on February 23, 1995 and again on October 5, 1995 and established the RfD for fenthion as 0.0007 mg/kg/day based on the threshold NOEL/LOEL of 0.02 mg/kg/day from the monkey chronic ChE/AChE study which was supported by the 28 day ChE/AChE study in humans. An uncertainty factor (UF) of 30 was applied - a 10x factor to account for intra-species variability and an additional 3x factor to account for the lack of a definite NOEL (because the NOEL/LOEL of 0.02 mg/kg/day in the monkey study is treated as a LOEL, the 3x factor is used), the lack of data in females in the human study, and the fact that brain AChE was inhibited at dose levels comparable to those causing minimal plasma ChE inhibition. An extra factor of 10 is normally applied to account for inter-species variability when the endpoint chosen is from an animal study. In this case, only the 10x for intra-species variability was applied since the established NOEL from the monkey chronic ChE/AChE study was supported by a 28-day ChE/AChE oral study in humans. Also note that, in a rat chronic feeding study, systemic NOELs of 0.20 mg/kg/day for epididymal effects in males and 0.30 mg/kg/day for ocular effects in females were observed.

The Agency's Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met on September 2, 1997; at this time, the acute and subchronic neurotoxicity studies had not yet been received. For chronic dietary risk assessment, the Committee determined that the 10x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained for a total UF of 300 [i.e., 10 for intra-species variation x 3 for the lack of a definitive NOEL in the critical study x 10 for FQPA]. Retention of the UF of 10 for infants and children was supported by the absence of acute, chronic, and developmental neurotoxicity studies as well as by evidence in the open literature that fenthion is neurotoxic. Based on the September 2, 1997 Committee meeting, the RfD for infants and children would have been 0.00007

mg/kg/day (for other population subgroups, 0.007 mg/kg/day would have been used as the RfD in chronic dietary risk assessment).

Upon receipt and review of the acute and subchronic neurotoxicity studies, the HIARC met again on March 19, 1998. The Committee recommended that the 10x UF for infants and children be removed based on hazard considerations. They noted, however, that the final decision will be made by HED's FQPA Safety Committee upon consideration of both the hazard and exposure at a later date.

c. Carcinogenic Classification

The carcinogenicity studies reviewed for fenthion reregistration were determined by the RfD Committee to support a classification of Group E - evidence of non-carcinogenicity for humans.

d. Developmental Classification

The developmental toxicity studies submitted for fenthion reregistration were reviewed by the RfD Committee. This Committee did not refer fenthion to the developmental Peer Review Committee because it is not considered to be a developmental toxicant.

e. Other Toxicological Endpoints of Concern

The HED Toxicity Endpoint Selection Committee (TESC) met on December 19, 1995 to consider the toxicity data available for fenthion. Based upon a review of the toxicology database for fenthion, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below.

i. Acute Dietary Exposure (1 day) and Risk Assessment

The endpoint selected for acute dietary risk assessment is based on inhibition of plasma cholinesterase activity at 0.07 mg/kg/day, 24 hours following oral ingestion of fenthion by human volunteers (MRID No. 00147246). Since this 1-day effect in the special human cholinesterase study is well-defined (effects were seen after 24 hours after a single dose in humans), an extra Uncertainty Factor (UF) for lack of a NOEL is not appropriate. Therefore, a MOE of 10 was deemed adequate at that time for acute dietary risk analysis.

To address the FQPA requirement, the HIARC met 9/2/97 and determined that the 10x factor to account for enhanced sensitivity of infants and children (as required by FQPA), should be retained. Therefore, at that time, a Margin of Exposure of 100 would have been required to ensure protection of this population from acute exposure to fenthion based on the lack of neurotoxicity data and evidence of neurotoxicity in published studies.

Upon receipt and review of the acute and subchronic neurotoxicity studies, the HIARC met again 3/19/98 and recommended that, based on hazard considerations, the extra 10x UF for infants and children be removed; the final decision was deferred to HED's FQPA Safety Committee, which will consider hazard and exposure.

ii: Dermal Absorption

No dermal absorption data are available. A dermal absorption value was estimated because the dose selected for short-term dermal risk assessment is from an oral study. An estimate of 20% dermal absorption was made using the comparison between the NOEL from a developmental toxicity study in rabbits (MRID No.: 40462701) and the LOEL from a 21-day dermal toxicity study in rabbits (MRID No.: 40808601) summarized above under the hazard assessment. The 21-day dermal studies were not considered to be appropriate for endpoint selection because a comparison of the effects from the human study with the effects from the rabbit studies indicated that humans are more sensitive. (The comparison of the NOEL from the developmental study to the LOEL from the dermal study is considered valid because the degree of RBC AChE inhibition at the low dose in the dermal study was considered to be relatively low, suggesting that this dose is close to a NOEL.) In the older study (MRID No.: 40808601), fenthion was applied in a Cremophor vehicle; in the more recent study (MRID No.: 40329501), fenthion technical was applied neat. The NOEL from the older study was selected to develop a dermal absorption factor because the committee viewed this study as more representative of a formulated product. Based upon the ChE/AChE NOEL from the developmental toxicity study in rabbits (1.0 mg/kg/day) and the LOEL from the dermal toxicity study in rabbits (5 mg/kg/day, the lowest test dose in the study) the dermal absorption is estimated to be $\approx 20\%$.

iiia. Short Term Occupational/Residential (1-7 days) by dermal route

For short term occupational/residential risk assessment, a LOEL of 0.07 mg/kg/day, based on minimal plasma ChE inhibition from a special study in human volunteers, was selected (MRID No.: 00147246). The effects observed at the 0.07 mg/kg/day dose level were marginal cholinesterase activity with no clinical signs, therefore, this dose was considered to be a NOEL, and no additional Uncertainty Factor (UF) was applied. Since the dose selected is from an oral study, a correction factor for dermal absorption (20%) needs to be incorporated into this dermal risk assessment. A MOE of 10 to account for intraspecies variability is considered protective since the dose is from a human study.

iiib. Short Term Occupational/Residential (1-7 days) by inhalation route

The dose for use in risk assessment reflecting exposure via the inhalation route is 0.209 mg/L (36.34 mg/kg). The dose used is from a single dose, head-only 4-hour exposure study using Sprague-Dawley rats (MRID No.: 40186706). The conversion of the atmospheric exposure level in mg/L to mg/kg was based on an average (male/female) breathing rate of 10.26 L/hr and body weight of 0.236 kg as follows:

$$0.209 \text{ mg fenthion/L} \times 41.04 \text{ L in 4 hours} / 0.236 \text{ kg} = 36.34 \text{ mg/kg}$$

The lowest dose, 0.209 mg/L (36.34 mg/kg), in this study resulted in deaths (2 of 10) in females and ataxia and tremors in both sexes. The major symptoms were indicative of cholinesterase inhibition and included tremors, muscle fasciculations, salivation, hypoactivity, ataxia, polypnea, ocular and nasal discharge and dry skin. Tremors and other motor symptoms were present at all dose levels. Some symptoms persisted to day 14 in some rats.

The data indicate that the inhalation dose level (36.34 mg/kg/day) resulting in acute toxicity responses (tremors, ataxia and other symptoms) is lower than the dose from the acute oral exposure study (100 mg/kg, MRID #40186704) causing tremors and other symptoms (except ataxia). In the rat developmental toxicity study (MRID #40329401), tremors were noted at 18 mg/kg/day, but after multiple doses, with no deaths. These data suggest that the inhalation route of exposure results in toxicity at lower doses than following an oral dose.

iva. Intermediate and Long Term Occupational/Residential - Dermal

The dose of 0.02 mg/kg/day for the intermediate and long term occupational/residential assessment is the same as that used for deriving the RfD. The dose is the threshold NOEL/LOEL for plasma ChE inhibition from a chronic monkey study (MRID #00147245), supported by a well-defined one day effect in a human oral study. In the chronic monkey study, plasma ChE was frequently inhibited at 0.02 mg/kg/day (maximum 67% in the first six months and especially in females) such that this level was deemed to be a threshold level. Since this is an oral dose, a correction for dermal absorption of 20% should be applied for risk assessment.

For intermediate and long-term exposure, a MOE of 30 is considered protective. An MOE of 10 is appropriate to account for intraspecies variability. An extra 10x to reflect interspecies variability is deemed unnecessary, because although the dose selected is from a monkey study, it is supported by a human study. As the dose is a LOEL and not a NOEL, a UF of 3 is added.

ivb. Intermediate and Long Term Occupational/Residential - Inhalation

As noted above, comparison of the dosages causing clinical signs of acute cholinesterase inhibition in the acute oral and acute inhalation toxicity studies suggests that fenthion may be more toxic via the inhalation than the oral route. There is no subchronic (21-day or 90-day) inhalation toxicity study (82-4) upon which to base a hazard assessment reflecting repeated exposure via the inhalation route. This was noted as a deficiency in the 1/26/96 TESC report and the 1/23/96 Fenthion Toxicology Chapter. Communication with D. Deziel (SRRD) on 4/9/98 indicates that a waiver of this requirement was granted in 1989, apparently based upon arguments that application methods used on livestock are not expected to result in inhalation exposure (pour-on and spot as opposed to spray treatment); no documentation of HED input to this waiver request has been located to date. In consultation with SRRD, HED hazard and exposure considerations will be used to revisit this issue to determine if a waiver of this study is appropriate.

v. MOEs for Occupational/Residential Exposure

For occupational exposure risk assessments, a MOE of 10 is adequate for short-term exposure since the dose selected is from a human study and the population exposed are adults. For intermediate term occupational exposure, a MOE of 30 is adequate. The dose selected for intermediate term exposure is from a monkey study (supported by a human study), reflecting a threshold NOEL/LOEL, treated as a LOEL for the purpose of risk assessment. Note that HED's, FQPA Safety Committee will determine whether the 10x UF, as required by FQPA, should be retained for infants and children. Based on hazard alone, the HIARC recommended on 3/19/98 that the 10x UF be removed.

TABLE II. Summary of Toxicological Endpoints for Fenthion

Exposure Duration/ Route	Endpoint and Toxicological Effect	MOE (Uncertainty Factor)
Acute - Oral	0.07 mg/kg/day (LOEL) based on plasma ChEI in a human oral subchronic toxicity study (MRID #00147246). Plasma ChE was inhibited in the 0.07 mg/kg/day dose group in less than 24 hours following the initial dose.	10
Short-Term (1-7 days) Occupational/Residential: Dermal Inhalation	0.07 mg/kg/day (LOEL) based on plasma ChEI in a human oral subchronic toxicity study (MRID #00147246). Since selected dose is from an oral study, a correction factor for dermal absorption (20%) was incorporated: 20% was derived by a comparison of the rabbit developmental toxicity study and the rabbit dermal toxicity study. 0.209 mg/L (36.34 mg/kg) from LDT in a single dose, head-only, 4 hr. rat exposure study (MRID nos. 40186706, -07). Endpoint based on ChE/AChE inhibition. Absorption of 100% is assumed (default but appears to be appropriate based on acute inhalation study).	10
Intermediate-Term (1wk. to several mos.) Occupational/Residential: Dermal	0.02 mg/kg/day (threshold NOEL/LOEL for plasma ChE inhibition) from a chronic monkey study (MRID # 00147245). Effect is supported by the 28 day ChE/AChE oral study in humans (MRID #00147246).	30
Cancer - Dietary/Dermal/Inhalation	Classified as Group E, evidence of non-carcinogenicity for humans	N/A

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Chronic (non-cancer) Dietary

RfD of 0.00007 mg/kg/day based on threshold NOEL/LOEL of 0.02 mg/kg/day from monkey chronic ChE/AChE study (MRID # 00147245), supported by the 28-day ChE/AChE oral study in humans (MRID #00147246). UF of 30 used (10x for intra-species variability; 3x for lack of definite NOEL, lack of data in females in human study, and brain AChE inhibition at dose levels comparable to those causing minimal plasma ChE inhibition).

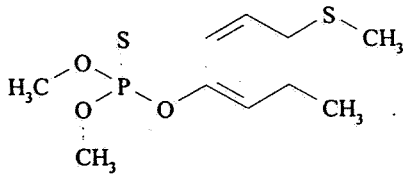
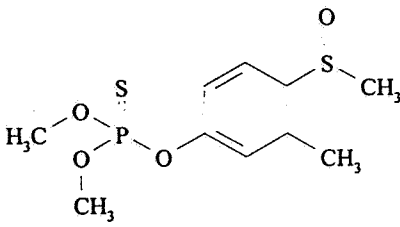
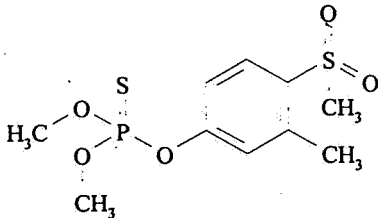
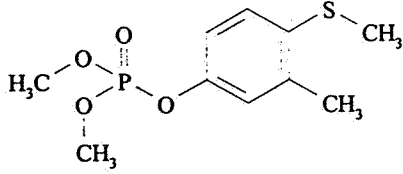
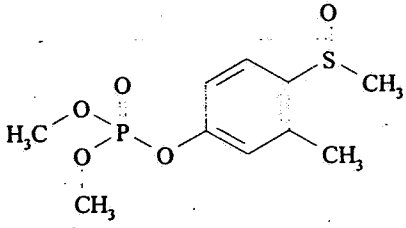
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3. Dietary Exposure and Risk Characterization

a. Dietary Exposure from Food Sources

Figure A. Chemical names and structures of fenthion and its metabolites in plants and animals.

Common/Chemical Name	Structure
<p>Fenthion</p> <p><i>O,O</i>-dimethyl-<i>O</i>-[4-(methylthio)-<i>m</i>-tolyl]phosphorothioate</p>	
<p>Fenthion sulfoxide</p> <p><i>O,O</i>-dimethyl-<i>O</i>-[4-(methylsulfinyl)-<i>m</i>-tolyl]phosphorothioate</p>	
<p>Fenthion sulfone</p> <p><i>O,O</i>-dimethyl-<i>O</i>-[4-(methylsulfonyl)-<i>m</i>-tolyl]phosphorothioate</p>	
<p>Fenthion oxygen analog</p> <p><i>O,O</i>-dimethyl-<i>O</i>-[4-(methylthio)-<i>m</i>-tolyl]phosphate</p>	
<p>Fenthion oxygen analog sulfoxide</p> <p><i>O,O</i>-dimethyl-<i>O</i>-[4-(methylsulfinyl)-<i>m</i>-tolyl]phosphate</p>	

Common/Chemical Name	Structure
Fenthion oxygen analog sulfone <i>O,O</i> -dimethyl- <i>O</i> -[4-(methylsulfonyl)- <i>m</i> -tolyl]phosphate	

GLN 171-3: Directions for Use: A search of the Agency's Reference Files System (REFS) on 5/3/95 indicated that there are five end-use products (EPs) of fenthion presently registered to Bayer, Inc. that may be used on livestock or wide area outdoor sites in the U.S.; these EPs are presented below:

EPA Reg. No.	Label Acceptance Date	Formulation Class	Product Name
3125-148	8/94	95% SC/L	Baytex® Liquid Concentrate Insecticide
11556-34	7/75	3% RTU	Tiguvon® Brand of Fenthion Swine Insecticide Pour-on
11556-37	1/75	20% RTU	Spotton® (Fenthion) Cattle Insecticide 20% Ready-to-Use Solution
11556-48	7/79	7.6% SC/L	Lysoff® Pour-on for Lice and Horn Flies
11556-105	1/95	20% Impr	Cutter Blue® Insecticide Cattle Ear Tag

The 24(c) registrations SLN Nos. FL760013 and FL870008 are based on EPA Reg. No. 3125-148. FL760013, currently active although a 9/81 expiration date is listed, permits application to alfalfa, grass, and rice. FL870008 (active, although a 5/6/92 expiration date is listed) specifies the same wide-area outdoor mosquito control use, with the same restrictions, as the parent label 3125-148. One additional active 24(c), SLN No. OR780027, is not based on a Bayer product. The OR780027 registration allows applications on alfalfa and pasture grass; a 5/83 expiration date is listed for this registration in REFS.

A comprehensive summary of the registered food/feed use patterns of fenthion, based on the Bayer, Inc. product labels, is presented in Table III. When end-use product DCIs are developed (e.g., at issuance of the RED), RD should require that all end-use product labels (e.g., MAI labels, SLNs, and products subject to the generic data exemption) be amended such that they are consistent with the basic producer labels. The registrants must amend their labels to specify a PSI no longer than 21 days.

GLN 171-4 (a): Plant Metabolism: The basic producer, Bayer, Inc., has deleted uses on alfalfa, pasture grass, and rice. Unless the registrant(s) choose to support these uses or the 24(c) registrations permitting application to these crops are supported, plant metabolism data is not required.

GLN 171-4 (b): Animal Metabolism: Ruminant and swine dermal-treatment metabolism studies were reviewed in the 1990 Reregistration Standard Update and a subsequent CBRS report. These studies require upgrading by: (i) additional characterization and identification of residue components; (ii) accounting for large amounts of non-analyzed residues; and (iii) submission of supporting quantitative data.

Both studies were conducted at approximately a 1x rate (0.08 oz. ai/100 lbs). Total radioactive residues (TRR) ranged from 0.03 ppm in milk to 6.1 ppm in the subcutaneous fat of cattle (treatment site), and 0.1 ppm in swine muscle to 3.9 ppm in the treatment site fat. The major residue found in both studies was fenthion; fenthion sulfoxide and fenthion sulfone were also identified.

Although these studies require upgrading, they support the current tolerance definition, which specifies fenthion and its cholinesterase-inhibiting metabolites. It is likely that specific metabolites will be included in the tolerance definition instead of the general statement about the metabolites once the study has been upgraded. In the absence of adequate magnitude-of-the-residue data for a more refined risk assessment, the TRR data from the cattle and swine metabolism studies can be used to conduct a worst-case risk assessment.

GLN 171-4(c) and (d): Residue Analytical Methods - Plants and Animals: Adequate analytical methods are available for fenthion tolerance enforcement. PAM, Vol. II lists as Method I a GC thermionic detection method in which fenthion and its five metabolites of concern are oxidized to a common moiety, fenthion oxygen analog sulfone. Method I encompasses registrant method nos. 20420 for animal tissues, 22933 for milk, and 20417 for plant samples. Method I is based on the registrant's method no. 17152 (GC/EC) which was used to analyze fenthion residues in forage crops, grains, and rice straw. Residues in milk were also analyzed using GC method nos. 16509 and 17887 which are similar to method no. 20420. The requirement for radiovalidation of enforcement method(s) using representative samples from livestock metabolism studies remains outstanding. If additional residues requiring regulation are identified in outstanding metabolism data, additional methods information may be required.

The FDA PESTDATA database dated 1/94 (Pam Vol. I, Appendix II) indicates that fenthion, fenthion oxygen analog, fenthion oxygen analog sulfoxide, and fenthion sulfone are completely recovered using multiresidue method PAM, Vol. I Section 302. No data are available on the recovery of fenthion sulfoxide using FDA multiresidue methods. Because fenthion sulfoxide is a component of the toxic residue in swine, multiresidue testing data are required for this metabolite.

GLN 171-4 (e): Storage Stability Data: Storage stability data reviewed in the Fenthion Residue Chemistry Chapter indicate that fenthion residues are stable in bovine liver, fat, and muscle stored at 24 C for 6 hours. Fenthion oxygen analog sulfone residues are stable in fat and muscle stored for 6 hours at 24 C, but not in liver. Additional data, deemed unacceptable in the Residue Chemistry Chapter, suggest that fenthion residues are stable in fat stored frozen for 11 weeks and in liver for 12 weeks; residues in liver declined ~25% after 26 weeks.

The available magnitude of the residue data indicate that animal tissue and milk samples were stored frozen for intervals of 0-173 days.

Unless the registrant amends the labels to lower the maximum use rate for dermal application to livestock from 0.08 oz ai/100 lb body weight to 0.01 oz ai/100 lb, additional magnitude of the residue data are required to support tolerances for residues in cattle and swine commodities. The new studies must contain complete sample storage information. Further storage stability data are required to support the requested residue data and the existing residue data.

GLN 171-4 (k): Magnitude of the Residue in Plants: The basic producer Bayer, Inc. has deleted uses on alfalfa, pasture grass, and rice. Unless the 24© registrations permitting application to these crops is supported, crop field trials are not required.

An import tolerance for citrus is currently pending.

GLN 171-4 (j): Magnitude of the Residue in Animals: No residue data are available at the existing maximum use rate, 0.080 oz ai/100 lb body weight (21-day PSI). The maximum use rate reflected by available residue data is 0.06 oz ai/100 lb body weight (with multiple PSIs). One study is available with a 21-day PSI, but the rate is much lower, at 0.01 oz ai/100 lb body weight.

The registrant must propose modified directions for use including a minimum 21-day PSI for beef cattle. (Ear tags have a 0-day PSI.) Residue data are required for cattle reflecting the maximum application rate and minimum PSI (21 days). All types of treatments must be represented by adequate residue data.

The Agency will extrapolate TRR data from the existing magnitude of the residue (MOR) data in order to conduct a worst-case risk assessment. Sufficient MOR data are available to reassess the hog tolerances.

No data are required for poultry as the use patterns related to poultry have been canceled.

The existing tolerances and the reassessment of these tolerances are summarized in Table IV.

GLN 171-4 (f/g/h): Magnitude of the Residue in Potable Water, Fish and Shellfish, and Irrigated Crops: Data on these topics are not required as aquatic-use labels now bear sufficient use restrictions to preclude dietary exposure concerns.

GLN 165-1 and 165-2: Magnitude of the Residue in Rotational Crops: The basic producer Bayer, Inc. has deleted uses on alfalfa, pasture grass, and rice. Unless the registrant elects to support these crop uses or the 24(c) registration(s) permitting application to these crops are

supported, rotational crop studies are not required.

Table III. Registered Uses of Fenthion

Site/ Application Methods	Formulation [EPA Reg. No.]	Max. Single Application Rate	Max. # Apps.	Min. Retreatment Interval (Days)	Use Limitations
Direct dermal treatments to livestock					
Dairy Cattle (Non-lactating)					
Spot	20% RTU 11556-37	0.089 fluid oz/100 lbs body weight (~0.020 oz ai/100 lbs. body weight)	2	35 days	Do not slaughter cattle within 45 days of treatment. Do not treat dairy cattle of breeding age, calves less than three months old, sick, convalescent, or stressed animals. Do not treat cattle for 10 days before or after shipping, weaning, dehorning, or exposure to contagious or infectious diseases. Do not treat animals simultaneously or within a few days before or after treatment with or exposure to cholinesterase inhibiting drugs, pesticides or chemicals.
Pour-on	7.6% SC/L 11556-48	1 fluid oz/100 lbs body weight (~0.082 oz ai/100 lbs body weight)	not specified	14 days	Do not slaughter within 21 days following a single treatment. If treated more than once, do not slaughter within 35 days of the last treatment. Do not treat lactating dairy cattle. Do not treat non-lactating dairy cattle within 28 days of freshening. If lactation begins within 28 days after treatment, do not use milk as human food for the balance of the 28-day interval. Do not treat cattle for 10 days before or after shipping, weaning, dehorning, or exposure to contagious or infectious diseases. Do not treat animals simultaneously or within a few days before or after treatment with or exposure to cholinesterase inhibiting drugs, pesticides or chemicals including other fenthion products.
Dairy Cattle (Non-lactating) Continued					
Ear tag	20% Impr 11556-105	0.2 oz ai/animal	not specified	tags are effective for 5 months, replace as necessary	Remove tags at the end of the fly season or before slaughter.
Dairy Cattle (Lactating)					

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Table III. Registered Uses of Fenthion

Site/ Application Methods	Formulation [EPA Reg. No.]	Max. Single Application Rate	Max. # Apps.	Min. Retreatment Interval (Days)	Use Limitations
Ear tag	20% Impr 11556-105	0.2 oz ai/animal	not specified	tags are effective for 5 months, replace as necessary	Remove tags at the end of the fly season or before slaughter.
Beef Cattle					
Spot	20% RTU 11556-37	0.089 fluid oz/100 lbs body weight (~0.020 oz ai/100 lbs body weight)	2	35 days	Do not slaughter cattle within 45 days following treatment. Do not treat calves less than three months old, sick, convalescent, or stressed animals. Do not treat cattle for 10 days before or after shipping, weaning, dehorning, or exposure to contagious or infectious diseases. Do not treat animals simultaneously or within a few days before or after treatment with or exposure to cholinesterase inhibiting drugs, pesticides or chemicals.
Beef Cattle Continued					
Pour-on	7.6% SC/L 11556-48	1 fluid oz/100 lbs body weight (~0.082 oz ai/100 lbs. body weight)	not specified	14 days	Do not slaughter within 21 days following a single treatment. If treated more than once, do not slaughter within 35 days of the last treatment. Do not treat cattle for 10 days before or after shipping, weaning, dehorning, or exposure to contagious or infectious diseases. Do not treat animals simultaneously or within a few days before or after treatment with or exposure to cholinesterase inhibiting drugs, pesticides or chemicals including other fenthion products.
Ear tag	20% Impr 11556-105	0.2 oz ai/animal	not specified	tags are effective for 5 months, replace as necessary	Remove tags at the end of the fly season or before slaughter.
Swine					
Pour-on	3% RTU 11556-34	0.5 fluid oz/100 lbs body weight (~0.016 oz ai/100 lbs body weight)	not specified	not specified	Do not slaughter swine within 14 days of treatment.
Swine Continued					

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Table III. Registered Uses of Fenthion

Site/ Application Methods	Formulation [EPA Reg. No.]	Max. Single Application Rate	Max. # Apps.	Min. Retreatment Interval (Days)	Use Limitations
Spot	20% RTU 11556-37	0.033 fluid oz/30 lbs body weight (~0.024 oz ai/100 lbs body weight)	2	28 days	Do not slaughter swine within 14 days following a single application. If a second treatment is made, do not slaughter within 21 days after the second treatment. Do not treat pigs weighing less than 30 lbs. Do not treat sick, convalescent, or stressed animals. Do not treat animals simultaneously or within a few days before or after treatment with or exposure to cholinesterase inhibiting drugs, pesticides or chemicals.
Mosquito control					
Wide Area Outdoor Application					
Ultra-low- volume (ULV) spray	95% SC/L 3125-148	Aerial: 0.05-0.1 lb ai/A Ground: 0.03 lb ai/A	not specified	repeat as necessary	Do not apply over food crops, forage crops, or rice. Do not use inside homes or buildings where food is processed or stored. Do not apply directly to animals. Do not allow spray treatment to drift into potable water supplies. Do not apply through any type of irrigation system.
Thermal fog		0.03 lb ai/A in 0.2-0.8 qts of oil/A			

* Maximum number of applications is at least three.

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TOLERANCE REASSESSMENT SUMMARY

All tolerances for fenthion residues are currently expressed in terms of fenthion and its cholinesterase-inhibiting metabolites [40 CFR §180.214]. A summary of the fenthion tolerance reassessment and recommended modifications in commodity definitions are presented in Table IV.

Tolerances Listed Under 40 CFR §180.214: The following tolerances should be revoked as there are no registered uses: poultry fat, meat, and meat byproducts, alfalfa, alfalfa hay, grass, grass hay, rice, and rice straw. An import tolerance for citrus is currently pending.

No residue data are available reflecting the currently registered use pattern for dermal treatment of cattle. Sufficient data are available to reassess the hog tolerances. Additional data are required to assess the established tolerances for cattle and milk.

Table IV. Tolerance Reassessment Summary for Fenthion.

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/ <i>Correct Commodity Definition</i>
Tolerances listed under 40 CFR 180.214:			
Alfalfa	5	Revoke	No registered use
Alfalfa hay	18	Revoke	No registered use
Cattle, fat Cattle, meat Cattle (mbyp)	0.1	TBD ^a	Additional residue data are required.
Grass	5	Revoke	No registered use
Grass hay	18	Revoke	No registered use
Hogs, fat Hogs, meat Hogs (mbyp)	0.1	0.1	
Milk	0.01	TBD	Additional residue data are required.
Poultry, fat Poultry (mbyp) Poultry, meat	0.1	Revoke	No registered use
Rice	0.1	Revoke	No registered use
Rice straw	0.5	Revoke	No registered use

^a TBD = To be determined. Reassessment of tolerance(s) cannot be made at this time

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because additional data are required.

CODEX HARMONIZATION

Maximum residue limits (MRLs/CXL) for fenthion have been established by Codex for various commodities. Codex MRLs and the applicable U.S. tolerances are listed in Table V. Codex and U.S. tolerance definitions are virtually comparable as MRLs are expressed in terms of the sum of fenthion, its oxygen analogue, and their sulfoxides and sulfones. The metabolites listed in the MRLs are equivalent to the U.S. tolerance definition, which specifies cholinesterase-inhibiting metabolites of fenthion.

Table V. Codex MRLs and Applicable U.S. Tolerances.

Commodity	MRL (mg/kg)	U.S. Tolerance (ppm)	Recommendation/ Comments
Apple	2	None	
Banana	1	None	
Cabbages, head	1	None	
Cauliflower	1	None	
Cherries	2	None	
Citrus fruits	2	None	
Citrus juice	0.2	None	
Common bean (pods and/or immature seeds)	0.1	None	
Grapes	0.5	None	
Lettuce	2	None	
Meat	2	0.1	Additional data are required to support U.S. tolerances. When U.S. tolerances are reassessed it is likely that the levels will be increased. The potential for tolerance/MRL compatibility will be addressed after the U.S. tolerances are reassessed.
Milks	0.05	0.01	
Olive oil, crude	1	None	
Olives	1	None	
Onion, bulb	0.1	None	
Peach	2	None	
Pear	2	None	
Peas	0.5	None	
Plums (including prunes)	1	None	
Potato	0.05	None	
Rice	0.1	0.1 Rice 0.5 Rice straw	U.S tolerances will be revoked owing to lack of registered use.
Squash, summer	0.2	None	
Strawberry	2	None	
Sweet potato	0.1	None	
Tomato	0.5	None	
Wheat	0.1	None	
Winter squash	0.2	None	

b. Dietary Exposure and Risk from Drinking Water

A drinking water health advisory level for fenthion and/or fenthion metabolites has not been established; however, some groundwater data are available for fenthion. According to the EPA Pesticide in Groundwater Data Base: A Compilation of Monitoring Studies, 1971 - 1991 A National Summary (EPA 734-12-92-001 Sept. '92) between 1986 and 1989, 184 wells were tested for parent in the states of HI (7 wells), IN (161), and CA (16). No residues of fenthion were detected. Because there were no detections does not necessarily mean there is never any exposure. Further, the majority of the states were tested for the parent which is not as persistent as the metabolites. These data are extremely limited and more drinking water data should be generated before any conclusions are drawn. However, the terrestrial agricultural uses are no longer being supported which represent the primary drinking water source of exposure. Therefore, the potential for drinking water exposure is very low. The Agency believes that the only use that is likely to cause any significant contamination of drinking water is the mosquito use which is aerially applied and/or ground applied in thirteen counties in Florida. Fenthion mosquito uses are largely adulticide applications that are limited to residential spraying for mosquito control. The possibility that direct aquatic applications of three granular products exists, as REFS implies, should be investigated. If applicable, EFED may wish to estimate water residues reflecting this use.

The Office of Pesticide Programs is in the process of developing procedures and methods for determining the likelihood of a pesticide occurring in drinking water and, if so, the exposure levels and associated risk. Terrestrial agricultural uses are no longer being supported for fenthion and livestock applications (fenthion is either contained within an ear tag or is spot treated to livestock) are not expected to result in significant exposures to drinking water sources. Fenthion is used in mosquito treatment largely as an adulticide, which requires the active ingredient to remain suspended in air for a period of time, rather than quickly settling out. There is potential for this use to result in surface water exposure from spray drift. The AgDRIFT Model, used to estimate residential exposure to fenthion resulting from the mosquitocide use, may be used to predict surface deposition of residues as well as water concentrations in a pond in or adjacent to the treatment area. EFED may wish to consider use of this model to predict concentrations of fenthion in surface water resulting from the mosquitocide use. EFED may wish to estimate water residues reflecting the application of granular products to water for mosquito larvae control (if this use pattern is registered as REFS implies).

Screening Level Estimates for Surface Water

GENEEC estimated EECs were developed for a 1 ha by 2 m deep pond adjacent to a 10 ha treated area. Inputs to GENEEC included an assumed 12 applications at 7 day intervals at a rate of 0.1 lb ai/acre, an assumed aerial spray drift of 5%, an assumed soil half-life of 3 days, a K_{oc} value of 1500, and an assumed aquatic half-life of 6 days.

Over a 3 year period from 1993-1996, fenthion was applied in Lee county FL an average of approximately 4 times/month. Since GENEEC is not designed to simulate applications beyond several months, the GENEEC input is based upon an assumption that fenthion was applied at 0.1 lbs ai/acre/application over a 3 month period with 4 applications/month at 7 day intervals.

The estimated generic EECs to be used for determining drinking water exposure and risk are as follows. The peak concentration for determination of acute exposure and risk is 1.33 $\mu\text{g/L}$ and a 56-day average concentration for determination of chronic exposure and risk is 0.19 $\mu\text{g/L}$. When acute risk values are calculated using the above concentrations, the acute Margins of Exposure (MOEs) are all well above 100 for all population subgroups. When chronic risk values are calculated using the above 56-day average concentration, the chronic risk for all population subgroups is less than 1% of 0.0007, the RfD for fenthion.

c. Dietary Risk Assessment and Characterization

Chronic Dietary from Food Sources

Two chronic dietary analyses were conducted to determine the theoretical maximum residue contribution (TMRC) and the anticipated residue contribution (ARC) for the U.S. population and 22 population subgroups. The Reference Dose (RfD) used for the analysis was 0.0007 mg/kg bwt/day, based on the NOEL from the 2-year monkey study demonstrating cholinesterase inhibition effect and an uncertainty factor of 30 (all discussed in detail previously in this document). The chronic dietary analyses were conducted as follows:

- 1) using all published tolerances listed in Table IV (except alfalfa, rice and poultry which were recommended for revocation and not included in analysis.), based on a use rate of 0.08 oz ai/100 lbs body weight and a 21-45 day pre-slaughter interval) and assuming 100% of the crops/animals were treated.
- 2) using the reassessed tolerance levels being recommended under reregistration (see Table IV). Upper-bound residue estimates on milk and beef were used (see Table VI). It was assumed that 100% of the crops/animals were treated.

The ARs used for the specified dietary analyses were based on a 21-day preslaughter interval following application and are considerably higher than the published tolerance levels. The anticipated residues used in the analyses were 0.5 ppm for meat, 2.0 ppm for fat, 0.5 ppm for meat by-products of cattle, and 0.005 ppm for milk. The anticipated residues used in the analyses for swine were 0.1 for meat, 0.1 ppm for fat and 0.1 ppm for meat by-products. These ARs represent a best estimate using the limited data available, but still result in an over-estimate of the dietary risk. These ARs were extrapolated from existing magnitude of the residue studies since no data were available at the 1x rate and 21-day pre-slaughter interval on livestock and assume the following;

- a 21-day PSI at existing application rates and use patterns and,
- that residues in tissues increase linearly with respect to the application rate.

The values for tissues are likely an overestimate. The AR estimates for milk are considered reasonable since ear tags are the only dairy cattle use and residues are not expected to be detectable as a result of that use.

The values listed in Table VI below are estimates of the residues of fenthion and its cholinesterase-inhibiting metabolites in cattle and swine commodities to be used in both the acute and chronic dietary risk assessments. The data upon which these values are based are very limited, and, therefore, additional magnitude of residue in livestock commodity studies are required. These are upper bound estimates; more accurate estimates cannot be made because the residue data are so limited.

Table VI. Upper-Bound Estimates of Fenthion Residues in Livestock Commodities at a 21-day Pre-Slaughter Interval at Maximum Application Rate

Commodity	Residues (ppm)	Existing Tolerance (ppm)
Cattle, meat	0.5	0.1
Cattle, meat by-products	0.5	0.1
Cattle, fat	2.0	0.1
Milk	0.005	0.01
Swine, meat	0.1	0.1
Swine, fat	0.1	0.1
Swine, meat by-products	0.1	0.1

The results of the chronic analyses/TMRCs and ARCs are presented as percentages of the Reference Dose (RfD) and are summarized below. An Uncertainty Factor (UF) of 30 was used with a RfD of 0.0007.

Table VII: The Results of the Chronic Dietary Analysis: TMRC and ARC.

Population ¹	Chronic Dietary Risk ²	
	TMRC ³	ARC ^{4,5}
U.S. Population	47%	209%
non-nursing infants (< 1 yr)	123%	201%
children ages 1-6 yrs	102%	387%

¹ These three populations/subgroups had the highest percentages of exceedance of the RfD.

² An RfD of >100% exceeds the reference dose and is generally considered a risk concern.

³ TMRC = Theoretical Maximum Residue Contribution

⁴ ARC = Anticipated Residue Contribution

⁵ All population subgroups considered had values > 100% of the RfD.

Acute Dietary Risk from Food Sources

Acute cholinesterase inhibition has been identified as an acute dietary concern for fenthion having a NOEL/LOEL of 0.07 mg/kg/day from a human study (all discussed in detail previously in this document)

The acute analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as reported by respondents in the USDA 1977-1978 Nationwide Food Consumption Survey (NFCS) and estimates the distribution of single day exposures through the diet for the U.S. population and certain subgroups. The analysis assumes uniform distribution of fenthion in the commodity supply. The analysis includes the U.S. population - 48 states and four population subgroups: infants (<1 year), children (1-6 years), females (13+ years) and males (13+ years). All population subgroups were considered for the acute analysis, since the endpoint is cholinesterase inhibition.

The acute dietary margin of exposure (MOE) is a measure of how closely the high end exposure comes to the NOEL (the highest dose at which no effects were observed), and is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). In the case of fenthion, the Agency is not generally concerned about the acute dietary exposure unless the MOE is below 10. The results of the acute dietary exposure are summarized in Table VIII.

Two acute dietary analyses were conducted using:

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- 1) all published tolerances and assuming 100% of the crops/livestock were treated and
- 2) the reassessed tolerance levels being recommended under reregistration. Specifically, the uses on alfalfa, rice and poultry were recommended for revocation and not included in analysis. Upper bound residue estimates on milk and beef were used and any remaining published tolerances (not included in the revocation). The assumption was that 100% of cattle and swine were treated.

Table VIII: The Results of the Acute Dietary Analyses

Population	Acute Dietary MOEs ¹	
	Existing Tolerances	Upper Bound Estimates ²
U.S. Population	35	7
non-nursing infants (< 1 yr)	14 ³	4.7
children ages 1-6 yrs	23	4.7
Males and Females (13+ years)	58 ⁴	7

¹ An MOE of less than 10 indicates a risk concern for this chemical pending consideration by HED's FQPA Safety Committee.

² ALL population subgroups had MOEs of <10. The analysis reflects upper bound estimates of residues in meats based on a 21-day preslaughter interval.

³ Lowest MOE of all of the population subgroups

⁴ Highest MOE of all of the population subgroups

Dietary Risk Characterization

The chronic dietary analysis utilizing the TMRC (Table VII) indicates a risk concern and possibly represents an underestimate of the risk. The acute analysis based on existing tolerances (Table VIII) does not indicate a risk concern for any population subgroup; however, we have low confidence in these MOEs. These two analyses are based on tolerances established using data reflecting less than a 1x rate and a 21-45 day pre-slaughter interval (PSI). PSIs from the residue data were used for determining the existing tolerances; therefore, residues as a result of dermal applications are possibly higher than the tolerance levels. Adequate data were not available reflecting the 1x use rate and a realistic PSI. The chronic dietary analysis and the acute dietary analysis, based on anticipated residues, indicate greater risk concern; however, these risk values are likely a significant overestimation of the risk. The anticipated residues were generated based on the following:

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- 1) the residues in tissues increase linearly with respect to the application rate,
- 2) a 21 day PSI, and
- 3) the assumption of 100% crop/animals treated with fenthion.

In addition, fenthion use on dairy cows is only permitted in the form of an ear tag and residues in milk are not likely to occur. The tolerance for milk is based on a dermal application and an overestimation of the residues. The milk tolerance contributes significantly to the exposure and risk estimates, especially those of the infants (<1 yr) population subgroup. The acute analyses using the TMRC also assume that residues on commodities will not only occur simultaneously, but that these tolerance level residues on multiple commodities will be consumed in a single day. Although, in this sense, the acute exposure and risk are overestimates, they are likely to be counterbalanced by tolerances that are set much too low considering the current use pattern.. In conclusion, there is a chronic dietary risk concern that is likely greater than that indicated using tolerance levels (TMRC), but much lower than the risk indicated using anticipated residues (ARC). The same is true for the acute dietary analyses where there is a risk concern, but it falls between the risk indicated using tolerances and using anticipated residues.

Additionally, monitoring for fenthion residues in meat was conducted by the Food Safety and Inspection Service (FSIS) in the U.S. Department of Agriculture. The number of samples chosen in an annual plan for a given compound-species combination is designed to assure detection of a national problem that affects a specified percentage of the animal population of interest (the number of samples generally is chosen to provide 95% probability of detecting at least one violation when one percent of the animal population sampled is violative). Exceptions are made for minor species and for major species in which problems are suspected; less sampling is done in the former case, more in the latter. Fenthion residue monitoring was conducted in 1985 and 1986 and involved 689 and 1093 samples, respectively. Cattle liver was analyzed for parent and metabolites. No residues were detected in any of these samples.

In order to refine the chronic risk assessment the assumptions need to be refined, for example, using percent crop/animal treated information. In order to refine the acute dietary analysis, data are required reflecting the ear tag use and the dermal application using a 21-day PSI.

4. Occupational and Residential Exposure/Risk Characterization

Exposure data requirements are triggered based on the potential for exposure and the toxicological significance of the active ingredient. All nondietary exposure/risk assessments completed for fenthion are presented in this chapter including for those occupationally exposed and those populations exposed in a residential environment. Use patterns and available products are summarized in a manner appropriate for nondietary risk assessment in *Section 4a: Use Pattern/Available Product Summary For Exposure Assessment*. The exposure/risk assessments that have been completed for each handler and postapplication scenario, for which appropriate data exist, are included in *Section 4b: Occupational and Residential Exposure/Risk Assessment*. The characterization issues associated with, and a summary of the results of each assessment, are included in *Section 4c: Occupational and Residential Risk Characterization*.

a. **Use Pattern/Available Product Summary For Exposure Assessment**

Fenthion products are described in this section. Additionally, available information that describes the manner in which fenthion products are applied is provided in this section (e.g., use categories/sites, application methods, and application rates).

i. End-Use Products

Fenthion [O,O-dimethyl O-(4-(methylthio)-m-tolyl) phosphorothioate], is an organophosphate insecticide that is marketed in a variety of end-use products. Fenthion formulations include liquid concentrates, ready-to-use solutions, treated articles (i.e., cattle ear tags); and granulars. The following table summarizes all active formulations based on a review (1/7/98) of the *Office of Pesticide Programs -- Reference Files System(REFS)*:

Formulation Type	Percent Active Ingredient	EPA Reg. Numbers
Liquid Concentrates	7.6 & 95	3125-148, 11556-48, & FL97000100
Granulars	1.0 & 2.0	5481-83, 5481-84, & 5481-101
Ready-to-Use	3.0, 11, & 20	7579-2, 11556-34, & 11556-37
Treated Articles (Ear Tags)	20	11556-105

All products appear to be marketed solely for occupational use. There are no products intended for sale to homeowners. Products are intended for indoor commercial and industrial uses but there appear to be no products intended for use in greenhouses or in indoor residential environments. The granular and liquid concentrate formulations that are intended for malaria vector control applications can be used to treat residential areas. The 95 percent liquids are intended for neat Ultra-Low-Volume applications.

ii. Mode of Action and Targets Controlled

Fenthion is an organophosphate insecticide used for the control of many types of pests including mosquitoes (Florida only), lice, flies, and ticks. Fenthion is also used for the control of nuisance birds in and around buildings, storage yards, and bridges (e.g., english sparrows, starlings, and pigeons). Given these parameters, fenthion applications can be described as belonging to one of the following categories: malaria vector control (i.e., public health protection); animal flea and tick control; and nuisance bird control.

iii. Registered Use Categories and Sites

An analysis of the current labeling and available use information was completed using the *Office of Pesticide Programs -- Label Use Information System* in addition to *REFS*. This information indicates that fenthion can be used on the following sites:

- **Aquatic Non-Food Outdoor:** ponds; swamps; marshes; salt-water sites; aquaria; and fountains (FL 97000100 -- **Could not find this label, status unclear, not in the jacket**).
- **Residential Outdoor:** outdoor households; rural areas; urban areas; aerial/ULV; wide area; and households and domestic buildings (3125-148 & 5481-83/84/101).
- **Indoor Non-Food:** general treatments; buildings/structures; industrial sites; and commercial transportation facilities (7579-2).
- **Indoor-Food:** nonlactating dairy cattle; beef cattle; and swine (11556-34/37/48/105).
- **Terrestrial Non-Food Crop:** general treatments; agricultural premises; and commercial, institutional, and industrial areas/premises (3125-148 & 5481-83/84/101).

[Note: Fenthion use for mosquito/malaria vector control (residential outdoor and terrestrial non-food crops) is limited to 13 counties in Florida where it is applied from the ground and aerially on an as-needed basis. **Need to ID source of info. included in RED package**]

iv. Application Parameters

Application parameters are generally defined by the physical nature of the use site, by the equipment required to deliver the chemical to the use site, and by the application rate required to achieve an efficacious dose. Fenthion applications intended for mosquito (i.e., malaria vector) control can be made with a variety of aerial and ground equipment. Animal flea and tick control applications can be made using pour-on or ladel-on techniques. Finally, nuisance bird control is completed through the use of a unique product which entails filling a perch with fenthion which is then transferred to the bird species after contacting the perch.

Based on the use data available to HED, either aerial or ground-based ULV (Ultra-Low

Volume) applications account for a vast majority of the malaria vector control applications. Other allowable application scenarios based on current fenthion labels include the use of aerial thermal foggers, wide area ground applications of granulars, and wide area aerial applications of granulars. Aerial ULV application rates specified on the label range from 0.05 to 0.10 lb ai/acre while the specified aerial thermal fogging application rate is 0.03 lb ai/acre (EPA Reg. 3125-148). The ground-based ULV application rate is also 0.03 lb ai/A (EPA Reg. 3125-148). All applications of granular materials for malaria vector control (includes aerial and ground-based) are at an application rate of 0.1 lb ai/A (EPA Regs. 5481-83/84/101). Aerial ULV applications require that between 0.66 and 1.3 oz formulation/A be applied while ground ULV application volumes range from 1.2 oz/minute to 3.6 oz/minute depending on the selected sprayer groundspeed (EPA Reg. 3125-148 specifies a 300 ft wide swath for ground ULV). Aerial thermal fogging applications require that 0.4 oz formulation/A be applied in conjunction with up to 0.8 quarts of fuel oil (EPA Reg. 3125-148). Granular applications require that from 5 to 10 pounds of formulated product be applied aerially or by ground for malaria vector control depending upon the product selected (EPA Regs. 5481-83/84/101).

Data that document the actual quantities of fenthion used for malaria vector (i.e., mosquito) control in various Florida counties (1993-1995) have been identified. These data are presented as they provide insight into typical fenthion use patterns. These data are summarized below:

- In Lee county, applications of fenthion were completed on 146 days over the 3 year period ranging from 1993 through 1995 (i.e., 1993 - 55 days; 1994 - 66 days; and 1995 - 25 days).
- In Lee county, applications of fenthion covered approximately 972,835 acres over the 3 year period ranging from 1993 through 1995 (i.e., 1993 - 401,290 acres; 1994 - 390,985 acres; and 1995 - 180,560 acres). Based on the number of treatment days for Lee County (1993-1995), the average number of acres per treatment day were 7296 A/day in 1993, 5924 A/day in 1994, 7222 A/day, and 6663A/day when all years were considered.
- In 1995, a total of 7,577 gallons of the 95 percent soluble concentrate formulation were applied covering 1,980,414 acres in 7 counties (i.e., Collier, Lee, Volusia, Dade, Hillsborough, Indian River, and Pasco). This volume of soluble concentrate, at 9.67 pounds active ingredient per gallon, contained 73,270 pounds of fenthion.
- In 1995, ground applications accounted for 21.4 percent of the total applied (i.e., 1622 gallons were applied in Dade, Hillsborough, Indian River and Pasco counties) while aerial applications accounted for the remaining 78.6 percent applied (i.e., 5955 gallons were applied in Collier, Lee, and Volusia counties). Ground applications accounted for 48.4 percent of the total acres treated (i.e., 961,124 acres treated in Dade, Hillsborough, Indian River and Pasco) while aerial applications accounted for the remaining 51.4 percent applied (i.e., 1,019,290 acres treated in Collier, Lee, and Volusia). Based on these data, average application rates (at 9.67 lb ai/gal.) for both ground and aerial

application methods, under actual use conditions, were calculated (aerial: 0.056 lb ai/acre and ground: 0.016 lb ai/acre). [Note: The label maximum rates for these methods are 0.1 lb ai/acre for aerial and 0.03 lb ai/acre for ground applications (i.e., actual application * rates were approximately 50 percent of the prescribed maximum for each technique).]

Applications for flea and tick control on food animals (i.e., cattle and swine) can be made by pouring or otherwise directly ladelling solutions onto the backs of the target animals (i.e., ready-to-use or prepared aqueous application solutions). Impregnated ear tags are also used for flea and tick control. Swine were not considered as the basis for this assessment because the applications rates were always higher for cattle. An average cattle weight of 600 pounds per animal served as the basis for this assessment. Application rates for the ready-to-use formulations on livestock range up to 0.089 oz (0.0014 lb ai)/100 lb on cattle (EPA Reg. 11556-37). Using the average cattle weight of 600 pounds per animal, the maximum application rate for the ready-to-use formulation is 0.0084 lb ai/animal (calculated using 2 lb ai/gallon in formulation). The label for the ladel-on specifies a dilution of 0.5 gallons formulation for every 4.5 gallons dilute solution prepared where each such dilution can treat up to 258 animals depending upon size. The maximum application rate for the ladel-on formulation, which equates to the use of 1 oz of dilute solution per 100 cattle pounds, is (0.00067 lb ai)/100 lb (EPA Reg. 11556-48). Again, using an average cattle weight of 600 pounds per animal, the application rate for the ladel-on formulation is 0.004 lb ai/animal (calculated using 0.77 lb ai/gallon in formulation). Each impregnated ear tag weighs 15 grams and contains 20 percent fenthion. Each animal is treated using two ear tags. As such, the application rate is 6 grams ai or 0.013 lb ai per animal.

The Rid-A-Bird formulation (EPA Reg. 7579-2) is a unique product. The product is a ready-to-use liquid that is used to fill artificial perches that transfer fenthion to nuisance bird species upon use as a perch. This product is used to control unwanted species in various indoor settings (e.g., ag buildings, commercial/transportation facilities, and industrial premises). This product is also used outdoors in agricultural and industrial areas/premises. HED estimated an application rate by assuming that each perch refill event would take approximately 1 liter of the RTU product as a label for the Rid-A-Bird formulation (EPA Reg. 7579-2) was not available (REES includes it as an active use, SRBD did not provide and jacket was checked out). Using the volume dose of 1 liter per treated perch and a formulation concentration of 1.12 lb ai/gallon, the application rate per perch was calculated to be 0.30 lb ai/perch.

[Note: Label information that stipulates the concentration of active ingredient per gallon (lb ai/gal) of formulation for the animal use and bird perch formulations was not available. These values were calculated by extrapolating from the available "percent active ingredient" values using the ratio of percent active ingredient to pounds ai per gallons for the liquid ULV malaria formulation.]

b. Occupational and Residential Exposure/Risk Assessment

HED has determined that there is a potential for exposure from handling fenthion

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products during the application process (i.e., mixer/loaders, applicators, flaggers, and mixer/loader/applicators) and from entering residential areas previously treated with fenthion. HED has not identified any significant occupational postapplication scenarios. As such, exposure assessments have been completed for occupational handler and residential post-application scenarios.

i. Calculations/Endpoints Used in the Exposure/Risk Assessment

A series of toxicological endpoints and calculations were used to complete the handler and post-application risk assessments. The specifics for calculating handler and post-application exposures differ because of the way that data for each scenario are presented. As such, the endpoints and equations that have been used to calculate exposures/risks for all scenarios are presented in this section.

Toxicological Endpoints: The endpoints that were used to complete this assessment are summarized below in order to provide a quick reference to the occupational handler and residential postapplication assessments.

- Short-Term Dermal: 0.07 mg/kg/day;
- Intermediate-Term Dermal: 0.02 mg/kg/day;
- Dermal Absorption: 20 percent;
- Inhalation: 0.209 mg/L (36.34 mg/kg/day calculated using a 4 hour study exposure interval and an inhalation rate of 10.26 L/hour and body weight of 0.236 kg for Sprague-Dawley rats (combined male & female); and
- Uncertainty Factors: 10 for short-term and 30 for intermediate-term scenarios.

Handler Exposure/Risk: The daily dermal exposure, daily dose, and hence the risks, to handlers were calculated as described below. The first step was to calculate daily dermal exposure using the following formula:

Daily Dermal Exposure (mg ai/day) =

Unit Exposure (mg ai/lb ai) x Application Rate (lb ai/A) x Daily Acres Treated (A/day)

Where:

Daily Dermal Exposure = Amount deposited on the surface of the skin that is available for dermal absorption, also referred to as potential dose (mg ai/day);

Unit Exposure = Normalized exposure value derived from May 1997 PHED Surrogate Exposure Table, no chemical-specific handler data were available for this assessment (mg ai/pound ai applied);

Application Rate = Normalized application rate based on a logical unit treatment such as acres or on a per animal basis, a maximum value is generally used (lb ai/A or lb ai/animal); and

Daily Acres Treated = Normalized application area based on a logical unit treatment such as acres or numbers of animals (A/day or animals/day).

Daily dermal dose was then calculated by normalizing the daily dermal exposure value by body weight and accounting for dermal absorption (i.e., a biologically available dose resulting from dermal exposure). For adult handlers using fenthion, a body weight of 70 kg was used for all exposure scenarios because the endpoint (cholinesterase inhibition) is not sex-specific. Additionally, a dermal absorption factor of 20 percent was used for all calculations. Daily dermal dose was calculated using the following formula:

$$\text{Daily Dermal Dose} \left(\frac{\text{mg ai}}{\text{kg/day}} \right) = \text{Daily Dermal Exposure} \left(\frac{\text{mg ai}}{\text{day}} \right) \times \left(\frac{\text{DermalAbsorptionFactor}(\%/100)}{\text{Body Weight (kg)}} \right)$$

The next step was to calculate the daily inhalation exposure for handlers. The process used is similar to that used to calculate the daily dermal dose to handlers. Daily inhalation exposure levels were presented as ($\mu\text{g}/\text{lb ai}$) values in the PHED Surrogate Exposure Table of May 1997 (i.e., these values are based on an inhalation rate of 29 liters/minute and an 8 hour exposure interval). Once the unit exposure value is presented in this form and converted to ($\text{mg}/\text{lb ai}$), the calculations essentially mirror those presented above for the dermal route using a value of 100 percent absorption (i.e., a daily inhalation dose is calculated in $\text{mg}/\text{kg}/\text{day}$).

The handler exposure assessment does not include any dietary or drinking water inputs.

Finally, the calculations of daily dermal dose and daily inhalation dose received by handlers were then combined to assess the total risk to handlers for each exposure scenario. Short-term total MOEs were calculated using a NOEL of 0.07 $\text{mg}/\text{kg}/\text{day}$ while the intermediate-term total MOEs were calculated using a NOEL of 0.02 $\text{mg}/\text{kg}/\text{day}$. MOEs based solely on the inhalation route were also calculated based on an inhalation endpoint of 0.209 mg/L (36.34 $\text{mg}/\text{kg}/\text{day}$). The short-term and intermediate-term MOEs were calculated using the following formula (which is similar for the inhalation except the Total Daily Dose is replaced by Daily Inhalation Dose):

$$MOE = \frac{NOEL \left(\frac{\text{mg}}{\text{kg/day}} \right)}{\text{Total Daily Dose} \left(\frac{\text{mg}}{\text{kg/day}} \right)}$$

The short-term endpoint used in this assessment was based on a human study, hence MOE (Margin of Exposure) values of 10 are considered an appropriate risk level. Likewise, the intermediate-term endpoint is based on a monkey study, hence MOE values of 30 are considered an appropriate risk level. MOE values were calculated by application of progressively increasing levels of risk mitigation for each handler exposure scenario until an appropriate risk level was obtained. Both the human and monkey studies used oral dosing. As a result, appropriate absorption factors were applied to calculate total daily dose as indicated above.

Post-Application Exposure/Risk: The calculations used to estimate *Daily Dermal Dose* and *MOE* for the dermal post-application scenarios are similar to those described above for the handler scenarios. The only significant differences are (1) the manner in which the *Daily Dermal Exposure* is calculated using a transfer coefficient, deposition percentage, transferable residue levels, and accounting for the dissipation of fenthion over time (see the post application exposure assessment for further details); (2) inhalation and nondietary ingestion exposures were not calculated for the postapplication scenarios (i.e., *Total Daily Dose* in the MOE calculation only represents dose levels resulting from dermal exposures because it is believed

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to be a bounding estimate); and (3) an average daily dose level has been used to compare to the intermediate-term endpoint (the short-term endpoint comparison is similar to the handlers in that only a point estimate of exposure has been calculated and compared to the endpoint). The only scenarios for which postapplication exposures were calculated are residential turf that is a concern because of malaria vector control applications.

- Application day transferable residue levels (TR) were calculated as follows:

$$TR_{APP. DAY} (\mu g/cm^2) =$$

$$(AR (lb ai/acre) * TRAN (\%/100) * DEP (\%/100) * 4.54E8 (\mu g/lb)) / (43560 (ft^2/acre) * 929 (cm^2/ft^2))$$

Where:

AR	=	Application rate;
TRAN	=	Percentage of deposited material available as transferable residue immediately after application;
DEP	=	Percentage of applied material actually deposited on turf; and
TR _{APP. DAY}	=	Transferable residue on application day.

[Note: Exposures that evaluate residential postapplication risks over a range of application rates were calculated using the average application rate for seven Florida counties in 1995 and the maximum label application rate for each application method.]

- Transferable residue levels (TR) on each day subsequent to application were calculated as follows:

$$TR_{(t)} (\mu g/cm^2) = TR_{APP. DAY} (\mu g/cm^2) * (1-D)^t$$

Where:

TR _{APP. DAY}	=	Transferable Residue on application day;
TR _(t)	=	Transferable Residue at time (t);
D	=	fraction of residue that dissipates daily (%/100); and
t	=	post application interval on which transferable residues are being assessed (day).

- Dermal Dose values on each post-application exposure day were calculated using the following:

$$\text{Dermal Dose}_{(t)} (mg/kg/day) =$$

$$(TR_{(t)} (\mu g/cm^2) \times TC (cm^2/hr) \times DA (\%/100) \times Hr/Day) / (BW (kg) \times 1000 (\mu g/mg))$$

Where:

TR	=	Transferable Residue,
TC	=	Transfer Coefficient,
DA	=	Dermal Absorption,
Hr	=	Hours,
BW	=	Body Weight, and
Dermal Dose _(t)	=	Dose attributable to dermal exposure at time (t) - days after application.

ii. Handler Risk Assessment Assumptions and Factors

A series of assumptions and exposure factors served as the basis for completing the handler risk assessment. The following assumptions and factors were used in order to complete this assessment:

- Average body weight of an adult handler is 70 kg. This body weight is used in all assessments since the endpoints of concern are not sex-specific (i.e., the cholinesterase inhibition could be assumed to occur in males or females).
- Daily areas (as appropriate) to be treated were defined for each handler scenario. HED typically uses a maximum of 1200 acres per day for assessing risks to aerial applicators in agricultural scenarios. Malaria vector control applications, however, are distinctly different from the typical agricultural scenario. For the liquid malaria control formulation, it appears that aerial applications will be ULV (Ultra-Low Volume) or thermal fog (i.e., for the purposes of this handler assessment, they are treated as the same technique -- thermal fog is almost a nonexistent application method even though it remains on the Baytex label). Similarly, ground-based applications are anticipated to be ULV. According to *The Use of Aircraft in Agriculture* (Ackeson and Yates, FAO/UN 1974), the number of acres treated using aerial ULV techniques can reach as high as 5000 acres per hour for fixed-wing aircraft and 1500 acres per hour for helicopters. The average number of acres per day that were treated by air in Florida was defined as 6600 acres per day using 1993 to 1995 data (probably including fixed-wing aircraft and helicopters). Since the exposure scenarios of concern are short- or intermediate-term, a value of 7500 acres per day was selected for the aerial application of liquids exposure scenario. Likewise, for ground-based ULV applications, the techniques and number of acres that can be treated per day are distinctly different from typical agricultural scenarios. Based on the liquid malaria vector control label application parameters, approximately 3000 acres per day can be treated (i.e., 3.6 oz of 95% ULV liquid per minute at 15 mph, 6 hours per day -- note this is approximately only 10 gallons of formulation). *The Use of Aircraft in Agriculture* also indicated that the hopper capacity of a 600 horsepower biplane with a ram air-type granular spreader is 2000 pounds. Since this is a very common aircraft, HED estimated that 200 acres can be treated per load (based on the use of the 1 percent ai formulation and 10 pounds product per acre). HED also estimates that a pilot can apply 4 hopperfulls in a single day and therefore treat 800 acres. For the ground-based granular application scenarios, HED estimates that 5 acres per day can be treated which is the same value commonly used for residential treatment of turf in occupational exposure scenarios. All animal use scenario calculations were based on a daily number of animals treated of 200 (i.e., approximately 1 animal every 2.4 minutes over an 8 hour day). The use of the Rid-A-Bird devices is considered to be very limited and that filling and placement of such devices should be limited to no more than 5 per day.

- All handler calculations were completed at the maximum labeled application rate for each scenario (refer to Section 4a). This is a reasonable approach given that available labels do not allow for large differences between the minimum and maximum application rates (i.e., risk levels are not anticipated to be very sensitive to changes in this parameter). Additionally, the animal assessments were based on cattle since they are larger than swine and the unit application rates (i.e., amount of chemical per 100 pounds animal weight) were higher for cattle. Treated cattle were assumed to weigh 600 pounds. The average cattle weight was determined based on an assessment of cattle weight gain during the finishing process (i.e., a 600 pound animal is early on in the finishing process which would correspond to the use a flea and tick control chemical). The bird perches used for the Rid-A-Bird product were assumed to contain 1 L of the ready-to-use liquid that is used to charge them ~~(i.e., note a label was not available for this scenario)~~.

- Due to a lack of scenario-specific data, HED is often required to calculate unit exposure values using generic protection factors that are applied to represent various risk mitigation options (i.e., the use of PPE or Personal Protective Equipment and engineering controls). PPE protection factors include those representing layers of clothing (50%), chemical-resistant gloves (90%), and respiratory protection (80 to 90% depending upon mitigation selected). Engineering controls are generally assigned a protection factor of 90 percent. Engineering controls may include closed mixing/loading systems and closed cabs/cockpits.

iii. Occupational Handler Exposure/Risk Assessment

HED has determined that exposure to pesticide handlers is likely during the occupational use of fenthion in a variety of environments including agriculture, commercial/industrial premises, and in public health scenarios (e.g., occupational applications in residential environments). There are no apparent homeowner handler or application scenarios. The anticipated use patterns and current labeling indicate 11 major occupational exposure scenarios based on the types of equipment and techniques that can potentially be used to make fenthion applications. These 11 scenarios serve as the basis for the quantitative exposure/risk assessment developed for occupational handlers. These scenarios include:

- (1a) mixing/loading liquids for malaria vector control fixed-wing aerial applications;
- (1b) mixing/loading liquids for malaria vector control ground-based applications;
- (1c) loading granular materials for malaria vector control fixed-wing aerial applications;
- (2) applying liquids using ULV ground equipment for malaria vector control;
- (3) applying liquids using aerial equipment (includes both ULV and thermal fogger) for malaria vector control applications;
- (4) applying granulars using aerial equipment for malaria vector control applications;
- (5) applying the ready-to-use solutions to livestock (cattle and swine);
- (6) applying cattle ear tags;
- (7) flagging during aerial application of liquids;
- (8) flagging during aerial application of granulars;
- (9) filling/refilling bird perches with RTU liquid formulation;
- (10) mixing/loading/applying liquids to livestock via ladeling; and
- (11) loading/applying granulars using for malaria vector control applications.

[Note: Helicopters are a plausible application method for aerial ULV fenthion applications. However, given the poor quality of the PHED data for helicopters, the aerial fixed wing scenario is used as the basis for assessing the aerial ULV application scenario. Flagger exposure scenarios were also included in this chapter even though HED believes that the use of flaggers is unlikely in typical malaria vector applications.]

No chemical-specific handler exposure data were submitted in support of the

reregistration of fenthion, as a result, an exposure assessment for each use scenario was developed using surrogate values calculated by the *Pesticide Handlers Exposure Database (V 1.1)*. PHED data were used to complete an assessment only for those scenarios where the surrogate data were deemed appropriate by HED. PHED was designed by a task force consisting of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a generic database containing voluntarily submitted empirical exposure data for workers involved in the handling or application of pesticides in the field (i.e., currently contains data for over 2000 monitored exposure events). The basic assumption underlying the system is that exposure to pesticide handlers can be calculated generically, based on the available empirical data, for chemicals as exposure is primarily a function of the physical parameters of handling and application process (e.g., packaging type, application method, and clothing scenario). PHED also contains the algorithms necessary for the user to complete surrogate task-based exposure assessments beginning with one of the four main data files contained in the system (i.e., mixer/loader, applicator, flagger, and mixer/loader/applicator).

Users can select data from each major PHED file and construct exposure scenarios that are representative of use patterns associated with specific chemicals. However, to add consistency to the risk assessment process, the EPA in conjunction with the PHED task force has evaluated all data within the system and developed a surrogate exposure table that contains a series of standard unit exposure values for various occupational exposure scenarios (*PHED Surrogate Exposure Guide of May, 1997*). The Surrogate Exposure Guide of May, 1997 serves as the basis for this assessment (i.e., all scenarios are occupational and there are no homeowner handler scenarios). The standard exposure values (i.e., the unit exposure values included in the exposure and risk assessment tables) are based on the "best fit" values calculated by PHED. PHED calculates "best fit" exposure values by assessing the distributions of exposures for each body part included in datasets selected for the assessment (e.g., chest or forearm) and then calculates a composite exposure value representing the entire body. PHED categorizes distributions as normal, lognormal, or in an "other" category. Generally, most data contained in PHED are lognormally distributed or fall into the PHED "other" distribution category. If the distribution is lognormal, the geometric mean for the distribution is used in the calculation of the "best fit" exposure value. If the data are an "other" distribution, the median value of the dataset is used in the calculation of the "best fit" exposure value. As a result, the surrogate unit exposure values that serve as the basis for this assessment generally range from the geometric mean to the median of the selected dataset.

There are three basic risk mitigation approaches considered appropriate for controlling occupational exposures. These include administrative controls, the use of personal protective equipment or PPE, and the use of engineering controls. Occupational handler exposure assessments are completed by HED using a baseline exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve an appropriate margin of exposure or cancer risk. [Note: Administrative controls available generally involve altering application rates for handler exposure scenarios. These are typically not utilized for

completing handler exposure assessments because of the negotiation requirements with registrants.] The baseline clothing/PPE ensemble for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical-resistant gloves (there are exceptions pertaining to the use of gloves and these are noted), and no respirator. The first level of mitigation generally applied is PPE. As reflected in the calculations included herein, PPE involves the use of an additional layer of clothing, chemical-resistant gloves, and a respirator. The next level of mitigation considered in the risk assessment process is the use of appropriate engineering controls which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly used engineering controls include closed tractor cabs, closed mixing/loading/transfer systems, and water-soluble packets.

The exposure/risk assessment that has been completed for the occupational handler scenarios is presented in Tables IX through XIII. HED anticipates that occupational fenthion exposures will only occur in a short-term or intermediate-term pattern. HED anticipates that occupational exposures will not be chronic because HED defines chronic exposures as use of the chemical for approximately 180 days per year and it is anticipated that fenthion as with other typical pesticide compounds will not be used in this manner. Various counties in Florida are likely to have several malaria vector control compounds that are used thereby significantly reducing the likelihood that fenthion exposures during mosquito control applications will be chronic. In fact, the available data indicate that the total number of application days in any county assessed in Florida were less than 100 days per year (the largest number of application days/year in Lee County Florida was 66 days in 1994 during the years 1993 through 1995).

Table IX presents the dermal and inhalation unit exposures for each occupational handler exposure scenario at all levels of mitigation (i.e., baseline, use of personal protective clothing, and engineering controls). [Note: There are no currently registered homeowner uses of fenthion.] Also included in Table IX are the application parameters that are used including maximum application rates and areas treated for each exposure scenario. Table X presents MOEs (Margin of Exposure values) at the baseline exposure scenario (e.g., long pants, long-sleeved shirts, no chemical-resistant gloves -- with exceptions as noted due to the available empirical data). Table XI presents MOEs for the PPE exposure scenario (e.g., extra layer of clothing, respirator, and chemical-resistant gloves). Table XII presents MOEs for the engineering control exposure scenario (e.g., closed cab or closed mixing systems). Tables X through XII also illustrate the procedures used to calculate the MOE values for each level of mitigation. Included in each table are the daily exposures (mg/day) attributable to the dermal and inhalation routes (i.e., dietary and water intakes for occupational handlers are not included in this assessment); absorbed daily dose for those routes; and the total absorbed daily dose levels used in the MOE calculations. Table XIII summarizes the caveats and parameters specific to the data used for each exposure/risk assessment scenario. These caveats include the source of the data and an assessment of the overall quality of the data. The assessment of data quality is based on the number of observations and the available quality control data. The quality control data are assessed based on a grading criteria established by the PHED task force. Additionally, it should be noted that all calculations were completed based on current HED policies pertaining to the completion of

occupational and residential exposure/risk assessments (e.g., rounding, exposure factors, and acceptable data sources).

When inhalation risks were calculated separately from dermal risks, using the endpoint of 0.209 mg/L (36.34 mg/kg/day), acute inhalation MOEs ranged from 2800 to $1.4e^6$ for baseline (no risk mitigation) scenarios. Only the exposure levels which were compared to the toxicology endpoint are included in Tables X and XII. In calculating short-term and intermediate-term MOEs based on cholinesterase inhibition, inhalation exposure has therefore been added to the dose attributable to dermal exposure to calculate total exposure levels. The calculated inhalation exposures are generally orders of magnitude less than the corresponding dermal exposure levels. Therefore, this process does not significantly impact the overall risk picture for fenthion.

Table IX. Numerical Inputs Used For Fenthion Handler Exposure Assessment

No.	Exposure Scenario	Unit Exposures						Application Parameters		
		Baseline ^a		Additional PPE ^b		Engineering Controls ^c		Maximum Application Rate (lb ai/A) ^d	Maximum Area Treated (acre/day) ^e	
		Dermal (mg/lb ai)	Inhalation (μg/lb ai)	Dermal (mg/lb ai)	Inhalation (μg/lb ai)	Dermal (mg/lb)	Inhalation (μg/lb)			
Mixer/Loaders										
1a	Mixing/Loading Liquids for Malaria Vector Control Aerial Applications	2.9	1.2	0.17	0.12	0.0084 (gloves)	0.083	0.1	7500	
1b	Mixing/Loading Liquids for Malaria Vector Control Ground-Based Applications							0.03	3000	
1c	Loading Granulars for Malaria Vector Control Aerial Applications	0.0084	1.7	0.0034	0.17	0.00084	0.17	0.1	800	
Applicators										
2	Applying Liquids Using ULV Ground Equipment For Malaria Vector Control	0.39	4.5	0.23	0.45	0.019 (gloves)	0.45	0.03	3000	
3	Applying Liquids Using Fixed-Wing Aerial Equipment (includes ULV and thermal fogger) for Malaria Vector Control	N/F	N/F	N/F	N/F	0.0050	0.068	0.1	7500	
4	Applying Granulars for Malaria Vector Control Aerial Applications	N/F	N/F	N/F	N/F	0.0024	0.13	0.1	800	
5	RTU Solution on Livestock	2.9	1.2	0.17	0.12	N/F	N/F	0.0084 lb ai/animal	200 animals/day	
6	Cattle Ear Tags	No data	No data	No data	No data	N/F	N/F	0.013 lb ai/animal	200 animals/day	
Flaggers										
7	Flagging for Applications of Liquids Using Aerial Equipment (includes ULY and thermal fogger) During Malaria Vector Control Applications	0.011	0.35	0.011	0.035	0.0011	0.035	0.1	7500	
8	Flagging for Applications of Granulars Using Aerial Equipment During Malaria Vector Control Applications	0.005 (total deposition)	0.15	No data	No data	No data	No data	0.1	800	
Mixer/Loader/Applicator										
9	Filling/Refilling Bird Perches with RTU	2.9	1.2	0.17	0.12	N/F	N/F	0.3 lb ai/perch	5 perches/day	
10	Ladling on Livestock with a Dipper	No data	No data	No data	No data	N/F	N/F	0.004lb ai/animal	200 animals/day	
11	Loading/Applying Granulars for Ground-based Malaria Vector Control Applications	10	62	17	6.2	N/F	N/F	0.1	5	

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Footnotes for Table IX.

"No Data" indicates that no appropriate data are available for incorporation into this cell. "N/F" indicates that this exposure scenario is not considered feasible by HED due to engineering or other practical considerations (e.g., an open cockpit aerial application scenario is not considered feasible as aircraft appropriate for this use are not manufactured with open cockpits).

- a Baseline clothing and PPE scenario: Workers wearing single layer clothing, no gloves, and no respirator. Mixing/loading activities are open. Also open cab for applicators and flaggers. Exceptions are noted on an individual basis.
- b PPE: Workers typically wear double layer of clothing, chemical resistant gloves, and respirator. Exceptions are noted on an individual basis.
- c Engineering controls: Workers wearing single layer clothing and no gloves while using an appropriate engineering control system (e.g., closed mixing, enclosed cabs).
- d See Section 4.a.iv for derivation of application rates. Application rates for all handler scenarios are maximums allowed by label.
- e HED believes these values represent a reasonable estimation of the median to upper percentile of what can be treated in a single day based on the exposure scenario of concern. Users of this table are cautioned to note that these values are based on professional judgement when appropriate data are not available.

Table X. Exposures and Risks For Occupational Fenthion Handlers At The Baseline Clothing Scenario

No.	Exposure Scenario	Daily Exposure (mg/day)*		Absorbed Daily Dose (mg/kg/day) ^b			Short-Term Risk (MOE) ^c	Intermediate-Term Risk (MOE) ^d
		Dermal	Inhalation	Dermal	Inhalation	Total		
Mixer/Loaders								
1a	Mixing/Loading Liquids for Malaria Vector Control Aerial Applications	2175	0.90	6.2	0.013	6.2	<1	<1
1b	Mixing/Loading Liquids for Malaria Vector Control Ground-based Applications	261	0.11	0.75	0.0015	0.75	<1	<1
1c	Loading Granulars for Malaria Vector Control Aerial Applications	0.67	0.14	0.0019	0.0019	0.0039	18	5
Applicators								
2	Applying Liquids Using ULV Ground Equipment For Malaria Vector Control	35.1	0.41	0.10	0.0058	0.11	<1	<1
3	Applying Liquids Using Fixed-Wing Aerial Equipment (Includes ULV and thermal fogger) for Malaria Vector Control	N/F	N/F	N/F	N/F	N/F	N/F	N/F
4	Applying Granulars for Malaria Vector Control Aerial Applications	N/F	N/F	N/F	N/F	N/F	N/F	N/F
5	RTU Solution on Livestock	4.9	0.0020	0.014	2.9e ⁻³	0.014	5	1
6	Cattle Ear Tags	No data	No data	No data	No data	No data	No data	No data
Flaggers								
7	Flagging for Applications of Liquids Using Aerial Equipment (includes ULV and thermal fogger) During Malaria Vector Control Applications	8.3	0.26	0.024	0.0038	0.028	3	<1
8	Flagging for Applications of Granulars Using Aerial Equipment During Malaria Vector Control Applications	0.40	0.012	0.0011	0.00017	0.0013	53	15
Mixer/Loader/Applicator								
9	Filling/Refilling Bird Perches with RTU	4.35	0.0018	0.012	2.6e ⁻³	0.012	6	2
10	Laddling on Livestock with a Dipper	No data	No data	No data	No data	No data	No data	No data
11	Loading/Applying Granulars for Ground-Based Malaria Vector Control Applications	5.0	0.031	0.014	0.00044	0.015	5	1

See below for footnotes (same apply to Tables X through XII). MOE < 10 indicates risk concern for short-term scenarios and MOE < 30 indicate a risk concern for intermediate-term scenarios.

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Table XI. Exposures and Risks For Fenthion Handlers Using Protective Clothing and PPE To Mitigate Exposures

No.	Exposure Scenario	Daily Exposure (mg/day)*		Absorbed Daily Dose (mg/kg/day) ^b			Short-Term Risk (MOE) ^c	Intermediate-Term Risk (MOE) ^d
		Dermal	Inhalation	Dermal	Inhalation	Total		
Mixer/Loaders								
1a	Mixing/Loading Liquids for Malaria Vector Control Aerial Applications	128	0.090	0.36	0.0013	0.37	<1	<1
1b	Mixing/Loading Liquids for Malaria Vector Control Ground-based Applications	15.3	0.011	0.044	0.00015	0.014	2	<1
1c	Loading Granulars for Malaria Vector Control Aerial Applications	0.27	0.014	0.00078	0.00019	0.00097	N/A	21
Applicators								
2	Applying Liquids Using ULV Ground Equipment For Malaria Vector Control	20.7	0.041	0.059	0.00058	0.060	1	<1
3	Applying Liquids Using Fixed-Wing Aerial Equipment (Includes ULV and thermal fogger) for Malaria Vector Control	N/F	N/F	N/F	N/F	N/F	N/F	N/F
4	Applying Granulars for Malaria Vector Control Aerial Applications	N/F	N/F	N/F	N/F	N/F	N/F	N/F
5	RTU Solution on Livestock	0.29	0.00020	0.00082	2.9e ⁻⁴	0.00082	85	24
6	Cattle Ear Tags	No data	No data	No data	No data	No data	No data	No data
Flaggers								
7	Flagging for Applications of Liquids Using Aerial Equipment (includes ULV and thermal fogger) During Malaria Vector Control Applications	8.25	0.26	0.024	0.00038	0.024	3	<1
8	Flagging for Applications of Granulars Using Aerial Equipment During Malaria Vector Control Applications	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Mixer/Loader/Applicator								
9	Filling/Refilling Bird Perches with RTU	0.26	0.00018	0.00073	2.6e ⁻⁴	0.00073	96	27
10	Ladeling on Livestock with a Dipper	No data	No data	No data	No data	No data	No data	No data
11	Loading/Applying Granulars for Ground-Based Malaria Vector Control Applications	8.5	0.0031	0.024	4.4e ⁻⁵	0.024	3	<1

See below for footnotes (same apply to Tables X through XII). MOE < 10 indicates risk concern for short-term scenarios and MOE < 30 indicate a risk concern for intermediate-term scenarios.

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Table XII. Exposures and Risks For Fenthion Handlers Using Engineering Controls To Mitigate Exposures

No.	Exposure Scenario	Daily Exposure (mg/day) ^a		Absorbed Daily Dose (mg/kg/day) ^b			Short-Term Risk (MOE) ^c	Intermediate-Term Risk (MOE) ^d
		Dermal	Inhalation	Dermal	Inhalation	Total		
Mixer/Loaders								
1a	Mixing/Loading Liquids for Malaria Vector Control Aerial Applications	6.3	0.062	0.018	0.00089	0.019	4	1
1b	Mixing/Loading Liquids for Malaria Vector Control Ground-based Applications	0.76	0.0075	0.0022	0.00011	0.0023	31	9
1c	Loading Granulars for Malaria Vector Control Aerial Applications	0.067	0.014	0.00019	0.00019	0.00039	N/A	N/A
Applicators								
2	Applying Liquids Using ULV Ground Equipment For Malaria Vector Control	1.7	0.041	0.0049	0.00058	0.0055	13	4
3	Applying Liquids Using Fixed-Wing Aerial Equipment (Includes ULV and thermal fogger) for Malaria Vector Control	3.75	0.051	0.011	0.00073	0.011	6	2
4	Applying Granulars for Malaria Vector Control Aerial Applications	0.19	0.010	0.00055	0.00015	0.00070	100	29
5	RTU Solution on Livestock	N/F	N/F	N/F	N/F	N/F	N/F	N/F
6	Cattle Ear Tags	N/F	N/F	N/F	N/F	N/F	N/F	N/F
Flaggers								
7	Flagging for Applications of Liquids Using Aerial Equipment (includes ULV and thermal fogger) During Malaria Vector Control Applications	0.83	0.026	0.0024	0.00038	0.0027	26	7
8	Flagging for Applications of Granulars Using Aerial Equipment During Malaria Vector Control Applications	No data	No data	No data	No data	No data	No data	No data
Mixer/Loader/Applicator								
9	Filling/Refilling Bird Perches with RTU	N/F	N/F	N/F	N/F	N/F	N/F	N/F
10	Labeling on Livestock with a Dipper	N/F	N/F	N/F	N/F	N/F	N/F	N/F
11	Loading/Applying Granulars for Ground-Based Malaria Vector Control Applications	N/F	N/F	N/F	N/F	N/F	N/F	N/F

See below for footnotes (same apply to Tables X through XII). MOE < 10 indicates risk concern for short-term scenarios and MOE < 30 indicate a risk concern for intermediate-term scenarios.

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Footnotes for Tables X through XII.

"No Data" indicates that no appropriate data are available for incorporation into this cell. "N/F" indicates that this exposure scenario is not considered feasible by HED due to engineering or other practical considerations (e.g., an open cockpit aerial application scenario is not considered feasible as aircraft appropriate for this use are not manufactured with open cockpits). N/A indicates that an appropriate risk level has been obtained and there is no need for imposition of a more protective level of risk mitigation. Appropriate risk levels are indicated in individual cells in the tables by **bolding the numerical value.**

- a Daily dermal exposure (mg/day) = Exposure (mg/lb ai) * Appl. Rate (lb ai/A) * Treated (acres).
- b Daily inhalation exposure (mg/day) = Exposure ($\mu\text{g}/\text{lb ai}$) * (1mg/1000ug) unit conversion * Appl Rate (lb ai/A) * Treated (acres).
Absorbed daily dermal dose = daily dermal exposure (mg/day) * dermal absorption (20%) / body weight (70 kg).
Absorbed daily inhalation dose = daily inhalation exposure (mg/day) / body weight (70 kg). [Assumes 100 percent absorption.]
Total absorbed daily dose = absorbed daily dermal dose + absorbed daily inhalation dose.
- c Short-Term MOE = LOEL (0.07 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 10 indicate a risk concern.
- d Intermediate-Term MOE = NOEL (0.02 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 30 indicate a risk concern.

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Table XIII. Exposure Scenario Descriptions For Occupational Fenthion Handlers

No.	Exposure Scenarios	Data Source	Clothing/PPE/Equipment Use Descriptions			Standard Assumptions (8-hr work day)*	Comments ^{a,b,c}
			Baseline	PPE	Engineering Controls		
Mixer/Loaders							
1a/1b	Mixing/Loading Liquids for Malaria Vector Applications Using Both Ground-Based and Aerial Spray Equipment	PHED V1.1 (May 1997 Surrogate Table)	Single layer clothing, no chemical resistant gloves, no respirator, and open mixing	Double layer clothing, chemical resistant gloves, respirator, and open mixing	Single layer clothing, chemical resistant gloves (only empirical data available), no respirator, and closed mixing system	7500 acres per day for aerial applications and 3000 acres for ground techniques	<p>Baseline: Hand, dermal, and inhalation are acceptable grades. Hand = 53 replicates; dermal = 121 replicates; and inhalation = 85 replicates. High confidence in dermal/hand and inhalation data. No protection factors were needed to define any unit exposure value.</p> <p>PPE: The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing and a 90% protection factor to account for the use of a respirator. A protection factor was not required for the hand assessment. Hands = acceptable grades. Hands = 59 replicates. High confidence in hand data.</p> <p>Engineering Control: Hand and inhalation = acceptable grades; and dermal = ABC grade. Dermal = 30 to 36 replicates; hand = 31 replicates; and inhalation = 27 replicates. High confidence in hand and inhalation data. Medium confidence in dermal data. No protection factors were used for this assessment.</p>
1c	Loading Granulars for Malaria Vector Control Aerial Applications	PHED V1.1 (May 1997 Surrogate Table)	Single layer clothing, no chemical resistant gloves, no respirator, and open loading	Double layer clothing, chemical resistant gloves, respirator, and open loading	Single layer clothing, no chemical resistant gloves, no respirator, and closed loading system	800 acres per day	<p>Baseline: Inhalation data are acceptable grade. Hand data are all grade. Dermal data are ABC grade. Hand = 10 replicates; dermal = 33 to 78 replicates; and inhalation = 58 replicates. High confidence in inhalation data. Low confidence in dermal/hand data. No protection factors were needed to define any unit exposure value.</p> <p>PPE: The same inhalation data are used as for the baseline coupled with a 90% protection factor to account for the use of a respirator. A protection factor was not required for the hand or dermal assessments. Hands = acceptable grade and dermal = ABC grade. Hands = 45 replicates and dermal = 12 to 59 replicates. Low confidence in hand/dermal data.</p> <p>Engineering Controls: The same dermal, inhalation, and hand data are used as for the baseline coupled with a 90% protection factor to account for the use of an engineering control (i.e., sitti a vehicle).</p>

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No.	Exposure Scenarios	Data Source	Clothing/PPE/Equipment Use Descriptions			Standard Assumptions (8-hr work day)*	Comments ^{b,c}
			Baseline	PPE	Engineering Controls		
Applicators							
2	Applying Liquids Using ULV Ground Equipment For Malaria Vector Control	PHED V1.1 (May 1997 Surrogate Table)	Single layer clothing, no chemical resistant gloves, no respirator, and open cab application	Double layer clothing, chemical resistant gloves, respirator, and open cab application	Single layer clothing, chemical resistant gloves (only empirical data available), no respirator, and closed cab application	3000 acres per day No empirical data are available for this scenario, instead, airblast application data were used. This assessment must be considered only for use as a range-finder using extremely low confidence data because of the extrapolation that has been completed. See the risk characterization discussion presented in Section 4b. For information purposes only, a summary of the airblast data are presented below. Baseline: Dermal and inhalation = acceptable grades; and hand = ABC grade. Dermal = 31 48 replicates; hands = 31 replicates; and inhalation = 47 replicates. High confidence in dermal and inhalation data. Medium confidence in hand data. No protection factors were required to define any unit exposure value. PPE: The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing and a 90% protection factor to account for the use of a respirator. A protection factor was not required for the hand assessment. Hands = acceptable grades. Hands = 18 replicates. High confidence in hand data. Engineering Control: Dermal and hand = acceptable grades; and inhalation = ABC grade. Dermal = 20 to 30 replicates; hand = 20 replicates; and inhalation = 9 replicates. High confidence in dermal/hand data and low confidence in inhalation data. No protection factors were required to define any unit exposure value.	
3	Applying Liquids Using Fixed-Wing Aerial Equipment (includes ULV and thermal fogger) for Malaria Vector Control	PHED V1.1 (May 1997 Surrogate Table)	Not considered feasible by Agency	Not considered feasible by Agency	Closed cockpit, single layer clothing, no gloves, no respirator	7500 acres Baseline: Not feasible. PPE: Not feasible. Engineering Control: Dermal and inhalation = ABC grade; and hand = acceptable grade. Dermal = 24 to 48 replicates; hand = 34 replicates; and inhalation = 23 replicates. Medium confidence in dermal/hand and inhalation data. No protection factors were required to define a unit exposure value.	
4	Applying Granulars for Malaria Vector Control Aerial Applications	PHED V1.1 (May 1997 Surrogate Table)	Not considered feasible by Agency	Not considered feasible by Agency	Closed cockpit, single layer clothing, no gloves, no respirator	800 acres Baseline: Not feasible. PPE: Not feasible. Engineering Control: Dermal = C grade; hand and inhalation = all grade. Dermal = 9 to 13 replicates; hand = 4 replicates; and inhalation = 13 replicates. Low confidence in all data. A protection factor was used to account for a layer of clothing as the only data available were for total deposition scenario.	

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No.	Exposure Scenarios	Data Source	Clothing/PPE/Equipment Use Descriptions			Standard Assumptions (8-hr work day)*	Comments ^{a,b}
			Baseline	PPE	Engineering Controls		
5	RTU Solution on Livestock	See 1a/1b above	See 1a/1b above	See 1a/1b above	200 animals/day	No empirical data are available for this scenario, instead, open mixing/loading of liquids d. were used. This assessment must be considered only for use as a range-finder using extreme low confidence data because of the extrapolation that has been completed. See the risk characterization discussion presented in Section 4b. For information purposes only, a summary of the mixer/loader data are presented above (see scenario 1a/1b).	
6	Cattle Ear Tags	No data	No data	No data	200 animals/day (2 tags/animal)	No data	
Flaggers							
7	Flagging For Applications of Liquids Using Aerial Equipment (includes ULV and thermal fogger) During Malaria Vector Applications	PHED V1.1 (May 1997 Surrogate Table)	Single layer clothing, no chemical resistant gloves, and no respirator. Standing in or on perimeter of treatment area.	Double layer clothing, chemical resistant gloves, respirator. Standing in or on perimeter of treatment area.	7500 acres	<p>Baseline: Dermal, hand, and inhalation data are acceptable grade. Dermal = 18 to 28 replicate hand = 30 replicates; and inhalation = 28 replicates. High confidence in all data. No protection factors were required to define any unit exposure value.</p> <p>PPE: The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing and a 90% protection factor to account for the use of a respirator. A protection factor was not required for the hand assessment. Hands = acceptable grades. Hands = 6 replicates. Low confidence in hand data.</p> <p>Engineering Controls: The same dermal, inhalation, and hand data are used as for the baseline coupled with a 90% protection factor to account for the use of an engineering control (i.e., sitting in a vehicle).</p>	
8	Flagging for Applications of Granulars Using Aerial Equipment During Malaria Vector Control Applications	PHED V1.1 (May 1997 Surrogate Table)	Total deposition scenario, PHED table warned not to extrapolate to baseline clothing. Standing in or on perimeter of treatment area.	No Data	800 acres	<p>The baseline for this scenario is total deposition data. The surrogate exposure tables specifically warns not to extrapolate from this data.</p> <p>Baseline: Dermal = ABC grade, hand = all grade, and inhalation = E grade. Dermal = 16 replicates; hand = 4 replicates; and inhalation = 4 replicates. Low confidence in all data. No protection factors were required to define any unit exposure value.</p>	
Mixer/Loader/Applicator							
9	Filling/Refilling Bird Perches with RTU	See 1a/1b above	See 1a/1b above	See 1a/1b above	5 perches/day	No empirical data are available for this scenario, instead, open mixing/loading of liquids d. were used. This assessment must be considered only for use as a range-finder using extreme low confidence data because of the extrapolation that has been completed. See the risk characterization discussion presented in Section 4b. For information purposes only, a summary of the mixer/loader data are presented above (see scenario 1a/1b).	

No.	Exposure Scenarios	Data Source	Clothing/PPE/Equipment Use Descriptions			Standard Assumptions (8-hr work day) ^a	Comments ^{b,c}
			Baseline	PPE	Engineering Controls		
10	Ladeling on Pigs, Cattle with dipper	No data	No data	No data	No data	No data	
11	Loading/Applying Granulars for Ground-Based Malaria Vector Control Applications	PHED V1.1 (May 1997 Surrogate Table)	Single layer clothing, no chemical resistant gloves, no respirator, and open mixing.	Double layer clothing, chemical resistant gloves, respirator, and open mixing.	Not feasible	5 acres per day	<p>HED does not anticipate that ground-based applications of fenthion will be a common practice. In fact, HED has based this assessment on the premise that any ground-based malaria vector control scenarios will be spot treatments. No empirical data are available for this scenario, instead, "belly-grinder" loader/appliator data are the basis for this assessment. This assessment must be considered only for use as a rangefinder using extremely low confidence data because of the extrapolation that has been completed. See the risk characterization discussion presented in Section 4b. For information purposes only, a summary of the "belly-grinder" data are presented below.</p> <p>Baseline: Dermal and hand = ABC grade. Inhalation data are acceptable grade. Dermal = 45 replicates; hand = 23 replicates; and inhalation = 40 replicates. High confidence in inhalation data. Medium confidence in dermal/hand data. No protection factors were required to define unit exposure value.</p> <p>PPE: The same dermal and inhalation data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing and a 90% protection factor to account for the use of a respirator. A protection factor was not required for the hand assessment. Hands = ABC grade. Hands = 15 replicates. Medium confidence in hand data.</p>

^a All Standard Assumptions are based on an 8-hour work day as estimated by HED. BEAD data were not available.

^b All handler exposure assessments in this document are based on the "Best Available" data as defined by the PHED SOP for meeting Subdivision U Guidelines (i.e., completing exposure assessments). Best available grades are assigned to data as follows: matrices with A and B grade data (i.e., Acceptable Grade Data) and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality (i.e., All Grade Data) and number of replicates. High quality data with a protection factor take precedence over low quality data with no protection factor. Generic data confidence categories are assigned as follows:

- High = grades A and B and 15 or more replicates per body part
- Medium = grades A, B, and C and 15 or more replicates per body part
- Low = grades A, B, C, D and E or any combination of grades with less than 15 replicates.

^c PHED grading criteria do not reflect overall quality of the reliability of the assessment. Sources of the exposure factors should also be considered in the risk management decision.

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iv. Homeowner Handler Exposure/Risk Assessment

There are currently no products containing fenthion that are marketed for sale to homeowners. As such, no exposure/risk analysis was completed for these use scenarios.

v. Occupational Post-Application Exposure/Risk Assessment

There are currently no products containing fenthion for which HED believes that occupational post-application exposures would be of concern. As such, no exposure/risk analyses were completed for these scenarios. Malaria vector control applications are addressed in section *vi* below as the concern is for residential settings and populations. Animal uses, by definition, are generally also not a postapplication nondietary exposure concern for HED.

vi. Residential Post-Application Deposition Calculations

Background Information: One of the predominant uses of fenthion is for the control of malaria vectors in regions of the country where there are public health concerns over disease transmission. Fenthion, intended for use in public health applications, is marketed as an Ultra Low Volume (ULV) liquid and in various granular formulations. Based on a January 1998 search of REFs, the currently available ULV liquid formulations include EPA Reg. Numbers 3125-148 and FL97000100 (i.e., Baytex, 95% active ingredient). Likewise, the currently available granular formulations include EPA Reg. Numbers 5481-83,-84, and -101 (Duratex, 1 or 2% active ingredient).

According to the use information available to HED it appears that the major application method for fenthion is through ground-based and aerial ULV liquid applications and not through aerial thermal fogging techniques or applications of the granular formulations. As a result, the fenthion postapplication exposure/risk assessment has been completed for the use scenarios described on the Baytex ULV liquid label (EPA Reg. No. 3125-148) and no other label. [Note: The aerial thermal fog application is not considered here because of concerns over environmental releases of the fuel oil component (personal communication between Jeff Dawson and Randy Dominy of EPA Region 4/Atlanta, Georgia).]

The maximum application rates specified on the Baytex label are 0.1 lb ai/acre for aerial ULV applications and 0.03 lb ai/acre for ground-based ULV applications. The Baytex label also stipulated other application parameter requirements that impact deposition patterns which were considered by HED in the development of this exposure/risk assessment. The critical label statements used in the development of this exposure/risk assessment include:

- “Spray droplets should have a median droplet size range from 5 to 20 μm with a Mass Median Diameter (MMD) not to exceed 15 μm . Droplets 45 μm or larger may cause permanent damage to automobile paint finishes.”
- For aerial ULV applications, “No more than 5 percent of the droplets should exceed 80

MMD."

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Agricultural Engineering Considerations: With few notable exceptions such as public health scenarios (e.g., malaria vector control), the general intent during most pesticide applications is to confine the deposition of applied chemicals to specific target areas such as agricultural fields. Economic concerns, health concerns, environmental concerns, and efficacy are the generally recognized rationale for limiting off-target deposition. Pesticide applicators can control deposition patterns through the use of specific types of equipment and by controlling application parameters. Several application parameters can potentially impact deposition patterns of liquid-form pesticides in the environment during application (e.g., nozzle size, application pressure, vehicle configuration and speed, meteorological conditions including environmental stability, and physical-chemical characteristics of the formulation).

As indicated above, ULV malaria vector control applications serve as the basis for this assessment. The general intent of these types of applications is antithetical to most pesticide applications in that spray drift is generally not inhibited but promoted in order to broaden the effective treatment area and ensure that the resulting droplets stay aloft for as long as possible. In fact, the efficacy of mosquito adulticide compounds is based on droplets contacting in-flight mosquitos. As a result, there are significant agricultural engineering differences that were considered by HED in this assessment. These include:

- Release heights for malaria vector control aerial ULV applications are typically 100 to 500 feet (or even higher) as opposed to most typical agricultural aerial applications where the release height is generally as low as the pilot can go (i.e., often 10 feet or less). Release height can significantly impact spray drift (i.e., the higher the release, the longer to time of impact with target area, and the more potential for drift). A release height of 300 feet was used in this assessment (i.e., the upper limit application height allowed in the *AgDRIFT* model).
- Nozzle configurations are such that extremely small droplets are released as opposed to typical aerial applications (i.e., Baytex label specifies MMD of 15 μm while the values for most agricultural applications are 100 μm or more).
- Larger aircraft are generally used to make malaria control applications. For example, Lee County Florida, one of the largest Florida mosquito abatement districts, has a fleet of Douglas DC3s and Huey Helicopters (based on personal communication between Randy Dominy of EPA Region 4 and Jeff Dawson). The DC3 is a much-larger aircraft than the common agricultural application fixed-wing aircraft (e.g., Air Tractor AT401). These differences are significant when predicting deposition and were addressed in the HED calculation of deposition after an aerial ULV application. The DC3 was used as the basis for all *AgDRIFT* calculations completed by HED.
- The Baytex label specifies that only 1.3 fluid ounces of formulation should be applied per acre by air and that the ground-based flow rate should range from 1.2 to 3.6 ounces per minute based on sprayer groundspeed. The aerial scenario significantly differs from

agricultural aerial applications (even most ag label ULV applications) because there is no diluent (i.e., water) and the volume per acre is much less. Most ag ULV applications typically apply approximately 1 gallon per acre of finished spray solution. The use of neat formulation impacts spray drift because of changes in surface tension of the droplets (i.e., this effects evaporation rate and hence deposition).

Predictive Tools and Data: HED has used state-of-the-art tools in order to calculate deposition rates resulting from ground-based and aerial ULV applications as well as to calculate the postapplication dermal exposures that result from entry into areas previously treated with fenthion using these techniques. HED did not calculate airborne concentrations and complete an inhalation based risk assessment because of several issues including the magnitude of the inhalation endpoint for fenthion, the infinite dilution that is anticipated in an outdoor application, and based on the very low application rate. Additionally, HED did not consider postapplication nondietary exposure in this assessment, given the conservative nature of the calculations, for the dermal route based on the use of the Residential SOPs for calculating dermal exposure from deposition (i.e., based on a Jazzercise bounding estimate of dermal exposure).

The first aspect of this exposure/risk assessment required the calculation of realistic deposition rates from the aerial and ground-based ULV applications of fenthion. HED could have taken a very simplistic approach of assigning the application rate as the deposition after an application. However, HED did not utilize this approach given the current state of knowledge pertaining to spray drift and recent industry and agency efforts in this area (i.e., this approach would generally be considered as unrealistic given the intent of malaria vector control applications). There are a number of predictive tools and open literature articles that pertain to this technical area. Given that ground-based and aerial ULV applications are allowable, models and data were identified to support a human health exposure/risk assessment for each scenario. [Note: HED recognizes that there are potential issues with the selection and use of these models in this assessment. As such, the use of each model for completing this exposure/risk assessment is appropriately characterized (see below).]

Aerial ULV: In order to calculate deposition from aerial ULV applications, HED used *AgDRIFT* (V 1.03 -- June 1997) which is the model that was developed as a result of the efforts of the *Spray Drift Task Force (SDTF)*. The SDTF is a coalition of 38 pesticide registrants whose primary objectives were to develop a comprehensive database of off-target drift information in support of pesticide registrations and an appropriate model system. This model was selected based on the consensus of several experts in the spray drift area because it represents the current state-of-the-art. HED discussed the issue of model selection with several experts in the spray drift community prior to selecting *AgDRIFT* (e.g., Sandra L. Bird, U.S. EPA; Steven G. Perry, U.S. EPA; Milton E. Teske, Continuum Dynamics; Pat Skyler, U.S. Forest Service; Arnet Jones, U.S. EPA; and Harold Thistle, U.S. Forest Service). HED considered using the *USDA Forest Service Cramer-Barry-Grim Model* (commonly referred to as *FSCBG*). *FSCBG* was developed through support from the U.S. Forest Service, in cooperation with the U.S. Army, and has been in existence for over 20 years in various iterations. Actual support and development

Exposure Assessments have been used by HED as the basis for calculating dermal exposure levels (i.e., December 11, 1997 version). The SOPs are designed for those that assess exposure to pesticides in a residential setting. The objective of the SOPs is to provide standard default methods for developing residential exposure/risk assessments when chemical- and/or site-specific data are limited or not available. Each SOP provides methods for estimating short-term daily doses for a single route of exposure. These represent estimates of exposure that may be combined with estimates from other routes of exposure and other use sites to estimate aggregate exposures. Techniques for determining aggregate doses are not within the scope of the SOPs. Additionally, the SOPs do not contain the distributional data that would be required in probabilistic risk assessment.

Determination of Deposition Rates: Deposition rates were determined for both aerial and ground-based ULV application methods as a percentage of the nominal application rate (i.e., how much of the target application rate actually deposited on outdoor surfaces such as turf). Both maximum and average application rates (calculated using 1993-1995 Lee County Florida data) served as the basis for this assessment. The rates used for aerial ULV application method were 0.1 lb ai/acre (the label maximum) while the average Lee County Florida rate used was 0.056 lb ai/acre. Likewise, the rates used for ground-based ULV applications was 0.03 lb ai/acre (the label maximum) while the average Lee County Florida rate used was 0.016 lb ai/acre.

As indicated above, *AgDRIFT V 1.03* was used to calculate the deposition rate from aerial ULV applications. The following inputs were used as the basis of the *AgDRIFT* calculations:

- **AgDRIFT Model Tier:** 3.
- **Droplet Size Distribution:** $D_{v0.1} = 7.14 \mu\text{m}$; $D_{v0.5} = 17.06 \mu\text{m}$; $D_{v0.9} = 70 \mu\text{m}$; and $<141 \mu\text{m} = 98$ percent (developed to reflect droplet spectrum requirements of Baytex label). [Note: The droplet distribution was developed based on the Baytex label. No proprietary SDTF data were used in the completion of this assessment.]
- **Spray Material:** User-defined option (oil option). Inputs include: nonvolatile rate 2.5 lb per acre, specific gravity 1.2 (calculated based on approximately 10 pounds per gallon), spray rate 0.25 gallons/acre, active ingredient application rate (0.1 lb ai/acre), and evaporation rate ($1 \mu\text{m}^2/\text{deg C}/\text{sec}$). [Note: Several of these parameters do not exactly coincide with the Baytex label but were used because the Baytex label inputs exceeded the allowable input parameters. These differences are not expected to significantly effect the *AgDRIFT* results because a nonvolatile oil was selected, hence the critical input is the active ingredient application rate. Additionally, no proprietary SDTF physical property data were used in the completion of this assessment.]
- **Aircraft:** User-defined option (fixed-wing option). Inputs include: Douglas DC3, wingspan: 94.6 ft (semispan 47.28 ft), typical application airspeed: 228 mph, weight: 21397 pounds, planform area: 1009.63 ft^2 , propeller RPM: 2550, propeller radius: 5.81

feet, engine vertical distance: -1.22 feet, and engine forward distance: 6.1 feet. [Note: DC3-specific inputs were obtained from the *FSCBG (V4)* aircraft library.]

- **Nozzles:** User-defined option. Inputs include number of nozzles: 60, vertical distance of nozzles from wing: -2.66 feet, horizontal distance from wing: -0.82 feet, and horizontal distance limit: 75 percent.
- **Meteorology:** Inputs were not changed from Tier 3 recommendations of wind speed: 2 mph, wind direction: -90 degrees (perpendicular to flight path), temperature: 86°F, and relative humidity: 50 percent.
- **Control:** Inputs were altered from the Tier 3 recommendations. The parameters that were used included a spray release height of 300 feet, 20 spray lines (aircraft passes) in each application event, a swath width of 500 feet, and a swath displacement based on the aircraft centerline.
- **Advanced Settings:** Inputs were not changed from Tier 3 recommendations of wind speed height (2 meters), maximum compute time (600 seconds), maximum downwind distance (795 meters), vortex decay rate (0.56 m/s), aircraft drag coefficient (0.1), propeller efficiency (0.8), and ambient pressure (1013 mb).

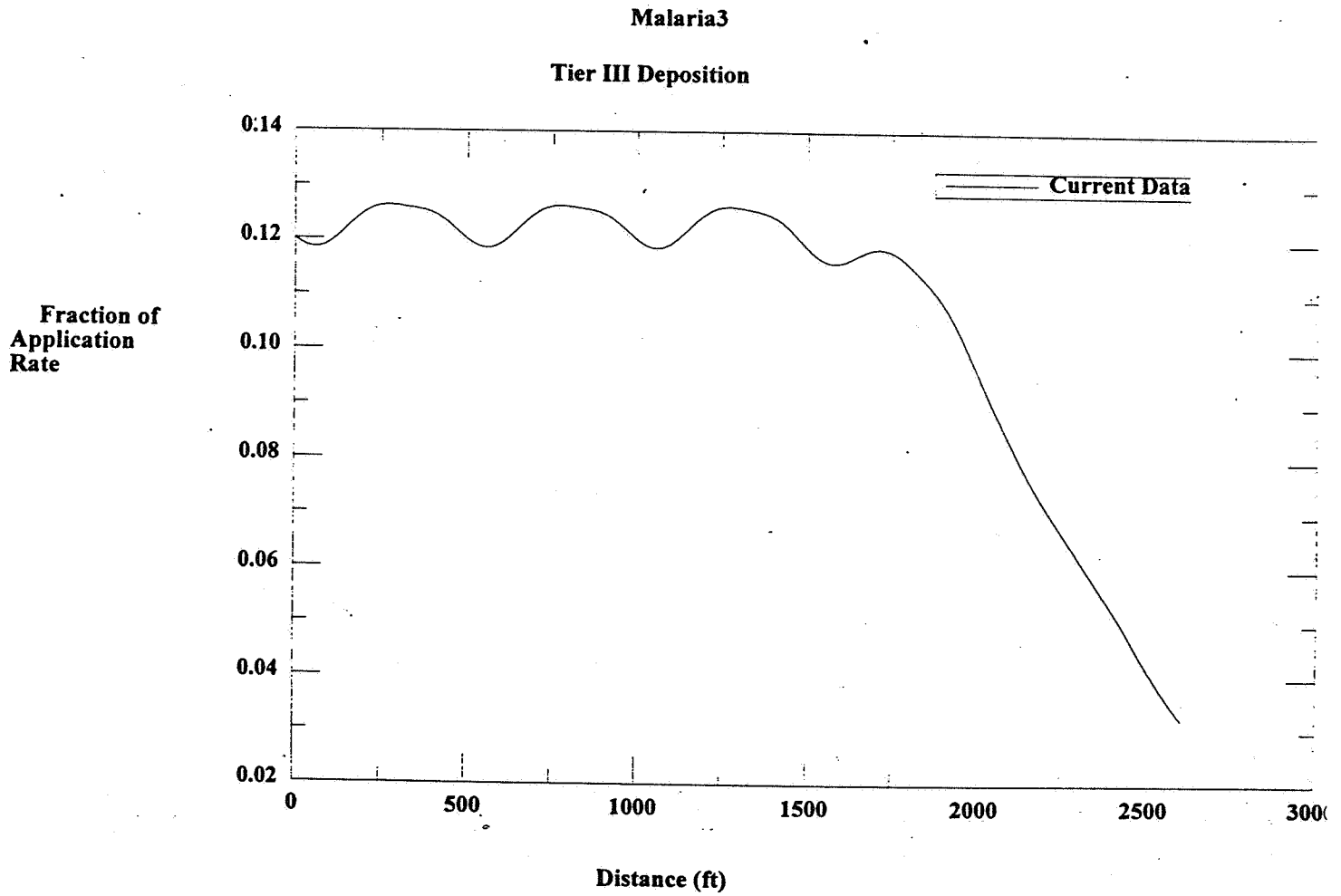
AgDRIFT is capable of producing a variety of useful outputs. The key for HED in this assessment was to determine from the model what percentage of the application volume remained aloft and what percentage of the resulting droplets deposited on the surfaces in the treatment area as well as downwind from the treatment area. AgDRIFT is generally intended to calculate deposition rates in areas that are downwind from the treatment area (i.e., presented from the border of the treatment area to areas of interest downwind). HED has used the values at the border of the treatment area to represent the deposition rate within the treated area. The results that HED used to determine the percentage of application rate that is deposited are presented in Figure 1 (Tier 3 Deposition presented as a Fraction of Application Rate vs. Distance Downwind). It is clear from Figure 1 that from the edge of the treatment area to 2000 feet downwind, approximately 12.5 percent of the theoretical application is deposited. This value is intuitively consistent with what one might suspect would occur considering the agricultural engineering parameters associated with malaria vector applications.

As indicated above, two published journal articles served as the basis for predicting deposition rates, as a percentage of the application rate, after ground-based ULV application for malaria vector control (i.e., Tietze, *et al*, 1994 and Moore, *et al*, 1993). Both of these studies were completed using ULV formulations of malathion (91 and 95 percent). HED anticipates that the "behavior" of these formulations in the referenced studies would not be significantly different from the Baytex 95 percent ULV formulation because the physical-chemical properties of the malathion formulations would be expected to be similar to that of the Baytex formulation (i.e., HED believes the malathion formulations to be acceptable surrogates for Baytex in this analysis).

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Figure 1: AgDRIFT Tier 3 Deposition Calculations (Fraction of Application Rate vs. Distance Downwind)



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In the study conducted by Moore, *et al* both human exposure and deposition was quantified over 5 separate application events. A 91 percent formulation of malathion was applied in April and May of 1989 in the early evening (a time of day for relative atmospheric stability). A Leco HD ULV cold aerosol generator (Lowndes Engineering Company, Valdosta Georgia) was used to make each application. The application parameters included a fluid flow rate of 4.3 fluid ounces per minute, a vehicle groundspeed of 10 mph, and a nominal application rate of 0.05 lb ai/acre (i.e., equates to a deposition rate of $0.51 \mu\text{g}/\text{cm}^2$). Deposition was monitored at three locations downwind from the treatment area (i.e., 15.2m, 30.4m, and 91.2m). For the events considered in the deposition calculations, "average amounts of malathion deposited on ground level at 15.2, 30.4, and 91.2 m were not significantly different." The percentage of the application rate reported to have deposited ranged from 1 to 14 percent. The mean deposition value for all measurements was 4.3 percent (n=35, CV=98).

In the study conducted by Tietze, *et al* only deposition was quantified over 6 separate application events (i.e., one event was not included in deposition calculations "due to negative air stability"). The application parameters were similar to that used by Moore *et al*. A 95 percent formulation of malathion was applied from May to August of 1993. A Leco 1600 ULV cold aerosol generator (Lowndes Engineering Company, Valdosta Georgia) was also used to make each application. The application parameters included a fluid flow rate of 4.3 fluid ounces per minute, a vehicle groundspeed of 10 mph, and a nominal application rate of 0.057 lb ai/acre (i.e., equates to a deposition rate of $0.58 \mu\text{g}/\text{cm}^2$). Deposition was monitored at four locations downwind from the treatment area (i.e., 5 m, 25 m, 100 m and 500 m). For the events considered in the deposition calculations, "malathion mass deposited differed significantly between the 500 m site and the three closer sites (df = 3; F-value = 3.42; P<0.05)." The percentage of the application rate reported to have deposited (not including 500 m samples which were much less) ranged up to 5.8 percent. The mean deposition value for all measurements was 3.8 percent.

Considering the data that are available in the Tietze *et al* and Moore *et al* papers, an off-target deposition rate of 5 percent was used by HED to evaluate ground-based ULV applications. A value slightly higher than the mean values for both studies was selected because of the variability in the data and the limited number of datapoints. It should be noted that this value is also consistent with the draft modeling assessment for ground-ULV approaches completed by S.T. Perry and W.B. Petersen of EPA's Office of Research and Development (i.e., within a factor of 5). Perry and Petersen used "the INPUFF Lagrangian puff model" as the basis for their assessment (Petersen and Lavdas, 1986: *INPUFF 2.0 - A Multiple Source Gaussian Puff Dispersion Algorithm, User's Guide*, EPA/600/8-86/024). Depending on the scenario selected from this document, deposition rates ranged from approximately 2.5 percent deposition 450 m downwind to 15 to 20 percent deposition **immediately adjacent** to the treatment zone.

The following deposition rates presented as a percentage of the application rate served as the basis of the postapplication exposure calculations completed by HED:

- Ground-based ULV = 5 percent of application rate, and
- Aerial ULV = 12.5 percent of application rate.

vii. Residential Post-Application Risk Assessment Assumptions & Factors

The following specific assumptions and factors were used in order to complete the residential postapplication risk assessment:

- Both the short-term and intermediate-term endpoints served as the basis for this assessment as HED believes that exposure patterns meet both criteria. For the short-term assessment, single day exposures calculated to reflect both deposition and residue dissipation rates were compared to the endpoint in order to calculate MOE values (i.e., daily dose levels were compared directly to the endpoint of 0.07 mg/kg/day). For the intermediate-term risk assessment, repetitive area applications for malaria vector control are thought to occur along with routine outdoor activity during mosquito season providing opportunity for exposure. However, it is believed that most repetitive applications will not occur on subsequent days for the extended period that would trigger an intermediate-term MOE calculated using the peak dose level (i.e., on the day of application). By definition, intermediate-term biological effects are not triggered until sustained exposure at the endpoint dose levels occur. Based on this premise, MOEs for the intermediate-term assessment were calculated using a dose level that was derived by taking the average of the dose levels from applications occurring on a monthly basis (i.e., 90 days were not selected as the interval as HED believes applications will occur on a more frequent basis). This approach should also coincide well with actual malaria vector control application management practices. Based on the use data available from Lee County Florida, the maximum number of annual treatment days was 66 which is approximately once per week over an entire county. Considering this information, it is therefore unlikely that the same residential areas will be treated in a manner that does not allow for residue dissipation over time. In other words, sustained maximum application day dose levels are unlikely based on the available data that detail specific management practices and HED has used a monthly average dose level for comparison to the intermediate-term endpoint of 0.02 mg/kg/day for calculation of MOEs. [Note: a 20 percent dermal absorption factor is applied to each endpoint as both are based on an oral dosing regimen.]
- Due to a lack of chemical-specific transferable residue data (TR), a surrogate approach has been used to predict transferable residue levels over time as specified in the residential SOPs. Deposition rates of 12.5 percent of the application rate for aerial ULV and 5 percent of the application rate for ground-based ULV applications are assumed as

described above. Availability of deposited residues after application day are assumed to be 20 percent of the deposition rate and these available residues are assumed to decline at a rate of 10 percent per day. No chemical-specific dissipation data were available. The environmental fate data included in the EFED database were reviewed on 3/16/98 and the aerobic soil half-life was reported as 24 hours for the parent and 72 hours for total residues. The aerobic aquatic half-life was also reported in the range of 7 to 14 days. These values support the use of the surrogate Residential SOP-type dissipation model that has been utilized for fenthion.

- Deposition from aerial and ground-based ULV applications is assumed to be uniform throughout the drift zone even though AgDRIFT indicates minor fluctuations in the region of interest and the empirical data for ground applications indicate some variation. The deposition region of interest has been defined as the region immediately adjacent to the treatment area out to a reasonable model approximated limit (i.e., for aerial -- about 2000 feet, ground -- about 500 feet).
- The average body weight for adults used in all assessments is 70 kg based on current HED policy. This body weight is used in the intermediate-term assessment, since the endpoint of concern is not sex-specific. The average body weight for toddlers used in all assessments is 15 kg based on the residential SOPs.
- A typical occupational work day interval is generally considered 8 hours. However, since the primary concern for post-application bensulide exposure is non-agricultural occupational, and non-occupational exposure to treated turf (e.g., golf courses and residential heavy yard work), the daily exposure interval for the assessment is assumed to be 4 hours/day for adults and 2 hours/day for toddlers (the toddler value is presented in the residential SOPs). These values are believed to be reasonable high end estimates for time spent engaged in specific activities. Additionally, for the intermediate-term assessment the approach is conservative because exposures were modeled at the maximum duration on a daily basis.
- Calculations were completed using the maximum application rates for ground-based and aerial applications (i.e., 0.03 and 0.10 lb ai/A, respectively). Additionally, calculations were completed using the average Lee County, Florida application rates available to HED (i.e., 0.016 and 0.056 lb ai/A, respectively).
- Due to a lack of scenario-specific exposure data, HED has calculated unit exposure values for adults using surrogate dermal transfer coefficients that represent reasonable low (1,000 cm²/hour) and high exposure activities (10,000 cm²/hour) such as mowing, golfing, and yardwork. The transfer coefficient prescribed in the residential SOPs for this scenario for adults is 43,000 cm²/hour. Lower transfer coefficient values were selected for this assessment are considered equally reasonable because of the exposure duration. An extended exposure duration using the 43,000 cm²/hour value is not physically plausible. Based on the residential SOPs, a transfer coefficient of 8,700 cm²/hour was

used to calculate dermal exposures for toddlers. [Note: the calculated exposures do not include Incidental Nondietary Ingestion levels as prescribed in the residential SOPs because of the screening level nature of the dermal assessment.]

viii. Homeowner Post-Application Risk Assessment

After the deposition factors were determined, post application exposure values were calculated using appropriate surrogate exposure values, label stipulated application rates, and application rates based on available use information.

HED determined that there are likely post-application exposures because fenthion is broadly applied to residential and recreational areas such as established lawns and golf courses. HED believes that post-application exposures due to inhalation will be minimal because of the vapor pressure of fenthion and due to infinite dilution. In addition, non-dietary ingestion (as a result of toddler or golfer hand-to-mouth contact) was not considered. As a result, given the lack of chemical-specific dissipation data and the rangefinder nature of this assessment, only dermal exposures were evaluated for this assessment. Based on the anticipated fenthion use patterns and current labelling, four major post-application exposure scenarios were modelled using a surrogate approach for each application method (i.e., aerial and ground ULV for a total of 8 calculations). Two of these scenarios are assessments of exposure to adults while the remaining two scenarios were assessments of exposures to toddlers. These assessments were based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines (7/24/97 Version)* and the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment (12/11/97 Version)*. The four scenarios assessed for each application method include:

- (1) adults involved in a low exposure activity (e.g., golfing) at the average Lee County Florida mosquito abatement district malaria vector control application rate;
- (2) adults involved in a high exposure activity (e.g., heavy yard work) at the label maximum malaria vector control application rate;
- (3) toddlers involved in a high exposure activity (e.g., rolling/playing on lawn) at the average Lee County Florida mosquito abatement district application rate; and
- (4) toddlers involved in a high exposure activity (e.g., rolling/playing on lawn) at the label maximum malaria vector control application rate.

Tables XIV through XVI present the results of the quantitative postapplication risk assessment completed by HED. Table XIV presents the postapplication dose levels resulting from aerial ULV applications of fenthion to residential areas. Likewise, Table XV presents the postapplication dose levels resulting from ground-based ULV applications of fenthion to residential areas (the adult doses calculated by HED, it should be noted, were approximately 2 orders of magnitude less than those measured by *Miller et al* in a very limited experiment -- these

data were not utilized as the basis of the assessment because of limited nature of the data and the exposure scenarios which were evaluated that involved individuals being almost treated directly with the ground-based ULV equipment). Four exposure scenarios were addressed for each application method as indicated above. Each table contains a calculation of dislodgeable foliar residue for the average Lee County, Florida application rate and the maximum label application rate. Transferable residue levels were then used to calculate mg/kg/day dose levels for both adults and toddlers using the appropriate body weights. After calculation of mg/kg/day dose levels, MOEs were calculated by comparison to the short-term endpoint of 0.07 mg/kg/day. As a reminder when interpreting these results, the calculations do not include the nondietary ingestion exposure or inhalation route. Average monthly dose levels were also calculated for comparison to the intermediate-term endpoint of 0.02 mg/kg/day (values calculated in Tables XIV and XV). These values are summarized and a calculation of the intermediate-term MOEs are presented in Table XVI.

c. Occupational and Residential Risk Assessment/Characterization

i. General Risk Characterization Considerations

Several issues must be considered that pertain to the quality of the assessment and when interpreting the results of the occupational handler and residential postapplication risk assessment. These include:

- No chemical-specific exposure or transferable residue data were submitted. As a result, all analyses were completed using surrogate data from sources such as PHED and assumptions related to the behavior of the chemical in the environment (e.g., dissipation of transferable residues on turf).
- Flagger scenarios were included in the assessment even though HED believes that it is unlikely that flaggers will be used to identify flight paths in aerial malaria vector control applications. Additionally, HED has used PHED data for scenarios where extrapolation is required (e.g., open mixing/loading of liquids to assess RTU liquid pour-on to livestock).
- The transfer coefficients used to calculate post-application dermal exposures are generic in nature due to a lack of time-based activity pattern data pertinent to the residential environment and the applicable transfer coefficients. The transfer coefficients used for adults are believed to represent typical low and high exposure activities for the exposed populations. The transfer coefficient used for toddlers is believed to provide a very conservative (i.e., bounding estimate of exposure).
- Several handler assessments were completed using "low quality" PHED data due to the lack of a more acceptable dataset (see Exposure Scenario Table for further details).
- Several generic protection factors were used to calculate handler exposures. The

protection factors used for clothing layers and gloves have not been completely evaluated by HED. The key element being evaluated by HED is the factor for clothing. The value used for respiratory protection is based on the *NIOSH Respirator Decision Logic* and the value for gloves is in the range that OSHA and NIOSH often use.

Table XIV: Postapplication Short-Term Risk Assessment For Aerial ULV Applications

TRANSFERABLE (%):	20	DERMAL ABSORPTION (%):	20
DAILY DISSIPATION (%):	10	ADULT BODY WEIGHT (kg):	70
LOW ADULT TC (cm2/hr):	1000	CHILD BODY WEIGHT (kg):	15
HIGH ADULT TC (cm2/hr):	10000	TOX. ENDPOINT (mg/kg/day):	0.07
CHILD SOP TC (cm2/hr):	8700	ADULT HR/DAY:	4
DEPOSITION (%):	12.5	CHILD HR/DAY:	2
MAXIMUM APPL. RATE (lb ai/A):	0.100	LEE COUNTY AVERAGE APPL. RATE (lb ai/A):	0.056

DAT	DFR (ug/cm2)		ADULT DOSE (mg/kg/day)		ADULT MOE		TODDLER DOSE (mg/kg/day)		TODDLER MOE	
	LEE COUNTY	LABEL MAXIMUM	LOW TC LEE	HIGH TC MAXIMUM	LOW TC LEE	HIGH TC MAXIMUM	SOP TC LEE	SOP TC MAXIMUM	SOP TC LEE	SOP TC MAXIMUM
0	0.0157	0.0280	0.000180	0.003205	390	22	0.00364	0.00651	19	11
1	0.0141	0.0252	0.000162	0.002885	433	24	0.00328	0.00586	21	12
2	0.0127	0.0227	0.000145	0.002596	481	27	0.00295	0.00527	24	13
3	0.0115	0.0204	0.000131	0.002337	535	30	0.00266	0.00474	26	15
4	0.0103	0.0184	0.000118	0.002103	594	33	0.00239	0.00427	29	16
5	0.0093	0.0166	0.000106	0.001893	660	37	0.00215	0.00384	33	18
6	0.0083	0.0149	0.000095	0.001703	734	41	0.00194	0.00346	36	20
7	0.0075	0.0134	0.000086	0.001533	815	46	0.00174	0.00311	40	22
8	0.0068	0.0121	0.000077	0.001380	906	51	0.00157	0.00280	45	25
9	0.0061	0.0109	0.000070	0.001242	1007	56	0.00141	0.00252	50	28
10	0.0055	0.0098	0.000063	0.001118	1118	63	0.00127	0.00227	55	31
11	0.0049	0.0088	0.000056	0.001006	1243	70	0.00114	0.00204	61	34
12	0.0044	0.0079	0.000051	0.000905	1381	77	0.00103	0.00184	68	38
13	0.0040	0.0071	0.000046	0.000815	1534	86	0.00093	0.00165	76	42
14	0.0036	0.0064	0.000041	0.000733	1705	95	0.00083	0.00149	84	47
15	0.0032	0.0058	0.000037	0.000660	1894	106	0.00075	0.00134	93	52
16	0.0029	0.0052	0.000033	0.000594	2104	118	0.00068	0.00121	104	58
17	0.0026	0.0047	0.000030	0.000535	2338	131	0.00061	0.00109	115	65
18	0.0024	0.0042	0.000027	0.000481	2598	145	0.00055	0.00098	128	72
19	0.0021	0.0038	0.000024	0.000433	2887	162	0.00049	0.00088	142	80
20	0.0019	0.0034	0.000022	0.000390	3208	180	0.00044	0.00079	158	88
21	0.0017	0.0031	0.000020	0.000351	3564	200	0.00040	0.00071	176	98
22	0.0015	0.0028	0.000018	0.000316	3960	222	0.00036	0.00064	195	109
23	0.0014	0.0025	0.000016	0.000284	4400	246	0.00032	0.00058	217	121
24	0.0013	0.0022	0.000014	0.000256	4889	274	0.00029	0.00052	241	135
25	0.0011	0.0020	0.000013	0.000230	5432	304	0.00026	0.00047	268	150
26	0.0010	0.0018	0.000012	0.000207	6036	338	0.00024	0.00042	297	166
27	0.0009	0.0016	0.000010	0.000186	6706	376	0.00021	0.00038	330	185
28	0.0008	0.0015	0.000009	0.000168	7451	417	0.00019	0.00034	367	206
29	0.0007	0.0013	0.000008	0.000151	8279	464	0.00017	0.00031	408	228
30	0.0007	0.0012	0.000008	0.000136	9199	515	0.00015	0.00028	453	254
AVERAGE	0.0049	0.0087	0.000056	0.000995	N/A	N/A	0.00113	0.00207	N/A	N/A

MOE of ≥10 represents an acceptable risk level for short-term assessments.

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Table XV: Postapplication Short-Term Risk Assessment For Ground ULV Applications

TRANSFERABLE (%):			20 DERMAL ABSORPTION (%):				20			
DAILY DISSIPATION (%):			10 ADULT BODY WEIGHT (kg):				70			
LOW ADULT TC (cm2/hr):			1000 CHILD BODY WEIGHT (kg):				15			
HIGH ADULT TC (cm2/hr):			10000 TOX. ENDPOINT (mg/kg/day):				0.07			
CHILD SOP TC (cm2/hr):			8700 ADULT HR/DAY:				4			
DEPOSITION (%):			5.0 CHILD HR/DAY:				2			
MAXIMUM APPL. RATE (lb ai/A):			0.030 LEE COUNTY AVERAGE APPL. RATE (lb ai/A):				0.016			
DAT	DFR (ug/cm2)		ADULT DOSE (mg/kg/day)		ADULT MOE		TODDLER DOSE (mg/kg/day)		CHILD MOE	
	LEE COUNTY	LABEL MAXIMUM	LOW TC LEE	HIGH TC MAXIMUM	LOW TC LEE	HIGH TC MAXIMUM	SOP TC LEE	SOP TC MAXIMUM	SOP TC LEE	SOP TC MAXIMUM
0	0.00180	0.00337	0.0000205	0.0003847	3412	182	0.000416	0.000781	168	90
1	0.00162	0.00303	0.0000185	0.0003462	3791	202	0.000375	0.000703	187	100
2	0.00145	0.00273	0.0000166	0.0003116	4213	225	0.000337	0.000632	208	111
3	0.00131	0.00245	0.0000150	0.0002804	4681	250	0.000304	0.000569	231	123
4	0.00118	0.00221	0.0000135	0.0002524	5201	277	0.000273	0.000512	256	137
5	0.00106	0.00199	0.0000121	0.0002271	5779	308	0.000246	0.000461	285	152
6	0.00095	0.00179	0.0000109	0.0002044	6421	342	0.000221	0.000415	316	169
7	0.00086	0.00161	0.0000098	0.0001840	7134	380	0.000199	0.000373	351	187
8	0.00077	0.00145	0.0000088	0.0001656	7927	423	0.000179	0.000336	390	208
9	0.00070	0.00130	0.0000079	0.0001490	8807	470	0.000161	0.000303	434	231
10	0.00063	0.00117	0.0000072	0.0001341	9786	522	0.000145	0.000272	482	257
11	0.00056	0.00106	0.0000064	0.0001207	10873	580	0.000131	0.000245	536	286
12	0.00051	0.00095	0.0000058	0.0001086	12082	644	0.000118	0.000221	595	317
13	0.00046	0.00086	0.0000052	0.0000978	13424	716	0.000106	0.000198	661	353
14	0.00041	0.00077	0.0000047	0.0000880	14916	795	0.000095	0.000179	735	392
15	0.00037	0.00069	0.0000042	0.0000792	16573	884	0.000086	0.000161	816	435
16	0.00033	0.00062	0.0000038	0.0000713	18414	982	0.000077	0.000145	907	484
17	0.00030	0.00056	0.0000034	0.0000641	20460	1091	0.000069	0.000130	1008	538
18	0.00027	0.00051	0.0000031	0.0000577	22734	1212	0.000063	0.000117	1120	597
19	0.00024	0.00045	0.0000028	0.0000520	25260	1347	0.000056	0.000105	1244	664
20	0.00022	0.00041	0.0000025	0.0000468	28066	1497	0.000051	0.000095	1383	737
21	0.00020	0.00037	0.0000022	0.0000421	31185	1663	0.000046	0.000085	1536	819
22	0.00018	0.00033	0.0000020	0.0000379	34650	1848	0.000041	0.000077	1707	910
23	0.00016	0.00030	0.0000018	0.0000341	38500	2053	0.000037	0.000069	1897	1011
24	0.00014	0.00027	0.0000016	0.0000307	42777	2281	0.000033	0.000062	2107	1124
25	0.00013	0.00024	0.0000015	0.0000276	47530	2535	0.000030	0.000056	2341	1249
26	0.00012	0.00022	0.0000013	0.0000249	52812	2817	0.000027	0.000050	2602	1387
27	0.00010	0.00020	0.0000012	0.0000224	58679	3130	0.000024	0.000045	2891	1542
28	0.00009	0.00018	0.0000011	0.0000201	65199	3477	0.000022	0.000041	3212	1713
29	0.00008	0.00016	0.0000010	0.0000181	72444	3864	0.000020	0.000037	3569	1903
30	0.00008	0.00014	0.0000009	0.0000163	80493	4293	0.000018	0.000033	3965	2115
AVERAGE	0.00056	0.00104	0.0000064	0.0001193	N/A	N/A	0.000129	0.000247	N/A	N/A

MOE of ≥10 represents an acceptable risk level for short-term fenthion assessments.

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Table XVI: Postapplication Intermediate-Term Risk Assessment For ULV Applications

Application Method	Population	Application Rate (lb ai/acre)	30 Day Average Dose (mg/kg/day)	MOE
Aerial ULV	Adults	0.056	0.00056	38
		0.100	0.000995	20
	Toddlers	0.056	0.00113	18
		0.100	0.00202	10
Ground ULV	Adults	0.016	0.000064	310
		0.030	0.0001193	170
	Toddlers	0.016	0.000129	160
		0.030	0.000242	83

- MOE \geq 30 represents an acceptable risk level for intermediate-term fenthion assessments.
- NOEL of 0.02 mg/kg/day used to calculate MOE values.
- Application rates represent the maximum allowed by the fenthion label for malaria vector control and the average application rate for Lee County Florida as previously described.
- 30 day average total dose levels are excerpted directly from Tables XIV and XV. These values were calculated by taking the daily dose level for each day after application out to 30 days and then computing the average dose level over that interval.

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- Factors used to calculate daily exposures to handlers and for the post-application scenarios (e.g., hours per day for post-application exposure or acres treated per day for each application method) are based on the best professional judgement due to a lack of pertinent data. Exposure descriptors have not been assigned to each scenario that has been assessed because the data to describe distributions for each exposure factor are not available. Available information pertaining to each factor is summarized herein to provide basic characterization information. The PHED surrogate exposure values can be described as values that are generally between the geometric mean and the median of the dataset used for calculation of the value.

Refinement of the ORE exposure and risk assessment calculations presented in this chapter is possible if the issues presented above are addressed by the registrant or if more refined approaches and data become available to HED.

ii. Summary of Total Risks to Occupational Handlers

Total risks for occupational handlers were assessed using the short-term and intermediate-term toxicological endpoints. Results from each assessment are presented below (i.e., Short-term assessment followed by Intermediate-Term assessment). A chronic risk assessment was not completed as HED believes that fenthion use patterns do not lend themselves to chronic exposure scenarios. [Note: Inhalation risks were also calculated separately for all handler exposure scenarios and MOEs ranged from 2800 to $1.4e^6$. As a result, risks due to the inhalation exposure pathway were integrated into a total risk assessment and further discussion of the inhalation pathway is not included.]

HED identified exposure scenarios based on available labels and other use information such as the LUIS report. As indicated above in section 4.b, surrogate data were used to develop the exposure/risk assessment for occupational handlers (i.e., no chemical-specific data were available). In some cases, appropriate surrogate data were not available to serve as the basis for an assessment. The scenarios for which no appropriate data were available are presented below (for both short- and intermediate-term unless noted):

- (6) Application to livestock using impregnated ear tags;
- (8) Flagging for aerial applications at increased exposure mitigation levels (i.e., data were available for a baseline exposure scenario and PHED Surrogate Table specifically precludes extrapolation based on this dataset to increased levels of mitigation -- issue applies only to increasing mitigation for intermediate-term assessment); and
- (10) Ladle-on applications of dilute solutions to livestock for flea/tick control.

Short-Term Occupational Handler Risks

In cases where appropriate surrogate data were available, a risk assessment was

completed. The calculations of short-term total risks indicate that the MOEs are more than 10 at the **baseline clothing** scenario:

- (1c) Loading granulars for malaria vector control aerial applications (based on low confidence unit exposure values, no use of protection factors, the maximum application rate, and an area treated value unique to malaria vector control applications); and
- (8) Flagging for applications of granulars using aerial equipment during malaria vector control applications (based on low confidence unit exposure values; no use of protection factors, the maximum application rate, and an area treated unique to malaria vector control applications).

The calculations of short-term total risks indicate that the MOEs are more than 10 with the use of **additional clothing and PPE** for the following scenarios:

- (5) Application of ready-to-use formulations to livestock (based on high confidence unit exposure values, a protection factor was used to calculate hand exposure levels, the maximum application rate, and **mixer/loader data for liquids was used to calculate the risks for this scenario -- this assessment must be considered only as a rangefinder {MOE = 85 and 10 is protective} using extremely low confidence data because of the extrapolation that has been completed**); and
- (9) Filling/refilling bird perches with ready-to-use formulation (based on high confidence unit exposure values, a protection factor was used to calculate hand exposure levels, the maximum application rate, and **mixer/loader data for liquids was used to calculate the risks for this scenario -- this assessment must be considered only as a rangefinder {MOE = 96 and 10 is protective} using extremely low confidence data because of the extrapolation that has been completed**).

The calculations of short-term total risks indicate that the MOEs are more than 10 with the use of **engineering controls coupled with the baseline clothing/PPE** scenario for the following scenarios:

- (1b) Mixing/loading liquids for malaria vector control ground-based applications (based on high confidence unit exposure values, use of chemical resistant gloves, no use of protection factors, the maximum application rate, and an area treated unique to malaria vector control applications);
- (2) Applying liquids using ULV ground equipment for malaria vector control (based on high confidence unit exposure values, no use of protection factors, the maximum application rate, and **airblast closed cab applicator data was used to calculate the risks for this scenario -- this assessment must be considered only as a rangefinder {MOE = 13 and 10 is protective} using extremely low confidence data because of the**

extrapolation that has been completed);

- (4) Applying granulars for malaria vector control aerial applications (based on low confidence unit exposure values, a protection factor to calculate single-layer clothing dermal exposures from a total deposition scenario, the maximum application rate, and an area treated unique to malaria vector control applications); and
- (7) Flagging for applications of liquids using aerial equipment (includes ULV and thermal fogger) during malaria vector control applications (based on high confidence unit exposure values, a protection factor to calculate exposures with the use of an engineering control, the maximum application rate, and an area treated unique to malaria vector control applications).

Regardless of the level of risk mitigation applied to certain exposure scenarios, MOE values **never exceeded a level of 10**. These scenarios are presented below:

- (1a) Mixing/loading liquids for malaria vector control (assessments at all risk mitigation levels were based on medium to high confidence unit exposure values, the use of protection factors in some instances, the maximum application rate, and an area treated unique to malaria vector control applications);
- (3) Applying liquids using fixed-wing aerial equipment (includes ULV and thermal fogger) during malaria vector control applications (engineering controls are only plausible exposure scenario option as aerial equipment is closed cab, based on medium confidence unit exposure values, no use of protection factors, the maximum application rate, and an area treated unique to malaria vector control applications); and
- (11) Loading/applying granulars for ground-based malaria vector control applications (the use of PPE is the only plausible risk mitigation option, based on medium confidence unit exposure values, protection factors were used to calculate dermal and inhalation exposures, the maximum application rate, and **belly-grinder mixer/loader/applicator data was used to calculate the risks for this scenario -- this assessment must be considered only as a rangefinder {MOE = 3 and 10 is protective} using extremely low confidence data because of the extrapolation that has been completed**).

Intermediate-Term Occupational Handler Risks

In cases where appropriate surrogate data were available, a risk assessment was completed. The calculations of intermediate-term total risks indicate that the MOEs are more than 30 at baseline for the following scenarios:

- none.

The calculations of intermediate-term total risks indicate that the MOEs are more than 30

with the use of **additional clothing and PPE** for the following scenarios:

- none.

The calculations of intermediate-term total risks indicate that the MOEs are more than 30 with the use of **engineering controls coupled with the baseline clothing/PPE scenario** for the following scenarios:

- none.

Regardless of the level of risk mitigation applied to certain exposure scenarios, MOE values **never exceeded a level of 30**. These scenarios are presented below:

- (1a and 1b) Mixing/loading liquids for malaria vector control (assessments at all risk mitigation levels were based on medium to high confidence unit exposure values, the use of protection factors in some instances, the maximum application rate, and an area treated unique to malaria vector control applications);
- (1c) Loading granulars for malaria vector control aerial applications (assessments at all risk mitigation levels were based on low to medium confidence unit exposure values, the use of protection factors in some instances, the maximum application rate, and an area treated unique to malaria vector control applications);
- (2) Applying liquids using ULV ground equipment for malaria vector control (assessments at all risk mitigation levels were based on medium to high confidence unit exposure values, the use of protection factors in some instances, the maximum application rate, an area treated unique to malaria vector control applications, and **airblast closed cab applicator data was used to calculate the risks for this scenario -- this assessment must be considered only as a rangefinder using extremely low confidence data because of the extrapolation that has been completed**);
- (3) Applying liquids using fixed-wing aerial equipment (includes ULV and thermal fogger) during malaria vector control applications (engineering controls are only plausible exposure scenario option as aerial equipment is closed cab, based on medium confidence unit exposure values, no use of protection factors, the maximum application rate, and an area treated unique to malaria vector control applications);
- (4) Applying granulars for malaria vector control aerial applications (engineering controls are only plausible exposure scenario option as aerial equipment is closed cab, based on low confidence unit exposure values, a protection factor to calculate single-layer clothing dermal exposures from a total deposition scenario, the maximum application rate, and an area treated unique to malaria vector control applications);
- (5) Application of ready-to-use formulations to livestock (assessments at all risk

mitigation levels were based on medium to high confidence unit exposure values, the use of protection factors in some instances, the maximum application rate, and **mixer/loader data for liquids was used to calculate the risks for this scenario -- this assessment must be considered only as a rangefinder using extremely low confidence data because of the extrapolation that has been completed**);

- (7) Flagging for applications of liquids using aerial equipment (includes ULV and thermal fogger) during malaria vector control applications (based on low to high confidence unit exposure values, the use of protection factors in some instances, the maximum application rate, and an area treated unique to malaria vector control applications);
- (8) Flagging for aerial applications at increased exposure mitigation levels (data were available for a baseline exposure scenario and PHED Surrogate Table specifically precludes extrapolation based on this dataset to increased levels of mitigation, based on low confidence unit exposure values, no use of protection factors, the maximum application rate, and an area treated unique to malaria vector control applications);
- (9) Filling/refilling bird perches with ready-to-use formulation (based on high confidence unit exposure values, a protection factor was used in some instances, the maximum application rate, and **mixer/loader data for liquids was used to calculate the risks for this scenario -- this assessment must be considered only as a rangefinder using extremely low confidence data because of the extrapolation that has been completed**); and
- (11) Loading/applying granulars for ground-based malaria vector control applications (the use of PPE is the only plausible risk mitigation option, based on medium to high confidence unit exposure values, a protection factor was used in some instances, the maximum application rate, and **belly-grinder mixer/loader/applicator data was used to calculate the risks for this scenario -- this assessment must be considered only as a rangefinder using extremely low confidence data because of the extrapolation that has been completed**).

iv. Total Risks to Residential Handlers

Risks for residential handlers were not assessed as no fenthion products are labelled for homeowner use.

v. Occupational Risks From Postapplication Exposures

Occupational postapplication risks were not assessed as HED believes there are no applicable fenthion product use patterns. Malaria vector control applications have been addressed in the residential postapplication risk assessment summarized below and animal (flea and tick) control applications are not considered an occupational postapplication risk assessment

requirement by HED.

vi. Residential Risks From Postapplication Exposures

Residential risks were assessed for both adults and toddlers based on guidance provided in the *SOPs For Residential Exposure Assessment*. Additionally, the open literature and the SDTF *AgDRIFT* model was used to assess deposition to residential turf after malaria vector applications of ULV liquids. These efforts were necessary to integrate the unique agricultural engineering aspects of malaria vector control applications into the HED risk assessment. Calculations for both adults and toddlers were completed using the maximum application rates for ground-based and aerial application scenarios as well as the typical rates determined by HED based on actual use information from Lee County Florida (1993-1995).

HED also considered a low and high exposure activity for adults. The Residential SOP scenario for toddler dermal exposures was used for that calculation. HED based the postapplication residential exposure assessment on the ULV application scenario because HED believes that malaria vector control applications of fenthion are typically completed using either ground-based or aerial ULV equipment. HED does not believe the use of granular products or the use of the thermal fog technique is a predominant practice by mosquito abatement applicators. No chemical-specific data were available to complete this assessment. Various appropriate data sources were referenced by HED in the completion of this assessment (e.g., half-life data from the EFED One-Liner system was reviewed to assess surrogate residue dissipation model). The postapplication assessment was completed using both the short- and intermediate-term endpoints. The short-term endpoint was compared directly to the daily dose levels calculated over the modeled fenthion dissipation curve. The intermediate-term endpoint was compared to the 30 day average dose over the modeled fenthion dissipation curve.

Only dermal exposure levels for toddlers and adults were calculated because of the conservative assumptions upon which the dermal assessment is based (i.e., nondietary ingestion due to hand/object to mouth and inhalation exposures were not calculated as dermal exposure levels are already not acceptable). The dermal transfer coefficient which is the basis for the toddler calculation is based on a Jazzercise activity which is generally considered to represent a bounding estimate of dermal exposure. Another conservative aspect of the postapplication intermediate-term calculation is that exposed populations are assumed to be in contact with treated turf for an extended duration on a daily basis over the entire 30 day exposure interval (e.g., 4 hours/day for adults and 2 hours/day for toddlers -- both upper percentile estimates based on data available in the *EPA Exposure Factors Handbook*).

For ground-based ULV applications, MOEs for the short-term assessment reached an appropriate level of concern ($MOE \geq 10$) as follows (values should be considered conservative estimates because of the exposure durations, application rates for some scenarios, and transfer coefficients used to calculate dermal exposures):

- **Adults (Typical application rate and low exposure activity):** Application Day;

- **Adults (Maximum application rate and high exposure activity):** Application Day;
- **Toddlers (Typical application rate and high exposure activity):** Application Day; and
- **Toddlers (Maximum application rate and high exposure activity):** Application Day.

For aerial ULV applications, MOEs for the short-term assessment reached an appropriate level of concern ($MOE \geq 10$) as follows (values should be considered conservative estimates because of the exposure durations, application rates for some scenarios, and transfer coefficients used to calculate dermal exposures):

- **Adults (Typical application rate and low exposure activity):** Application Day;
- **Adults (Maximum application rate and high exposure activity):** Application Day;
- **Toddlers (Typical application rate and high exposure activity):** Application Day; and
- **Toddlers (Maximum application rate and high exposure activity):** Application Day.

For the intermediate-term assessment where 30 day average dose levels were compared directly to the intermediate-term endpoint, MOEs were acceptable ($MOE \geq 30$) for all ground-based ULV application scenarios including (values should be considered conservative estimates because of the exposure durations, application rates for some scenarios, methods for calculating monthly average dose, and transfer coefficients used to calculate dermal exposures):

- **Adults (Typical application rate and low exposure activity):** $MOE = 310$;
- **Adults (Maximum application rate and high exposure activity):** $MOE = 170$;
- **Toddlers (Typical application rate and high exposure activity):** $MOE = 160$; and
- **Toddlers (Maximum application rate and high exposure activity):** $MOE = 83$.

For aerial applications, MOEs were acceptable ($MOE \geq 30$) for only one aerial application scenario. The results are summarized below (these values should be considered as conservative estimates because of the exposure durations, application rates for some scenarios, methods for calculating monthly average dose, and transfer coefficients used to calculate dermal exposures):

- **Adults (Typical application rate and low exposure activity):** $MOE = 38$;
- **Adults (Maximum application rate and high exposure activity):** $MOE = 20$;

- **Toddlers (Typical application rate and high exposure activity):** MOE = 18; and
- **Toddlers (Maximum application rate and high exposure activity):** MOE = 10.

vii. Incident reports

The following data bases have been consulted for poisoning incident data on the active ingredient fenthion:

- OPP Incident Data System (IDS), 1992-present
- Poison Control Centers, 1985-1992
- California Department of Food and Agriculture (replaced by the Department of Pesticide Regulation in 1991), 1982-1993
- National Pesticide Telecommunications Network (NPTN), 1984-1991

IDS - There were 18 incidents involving fenthion reported to IDS as of January 29, 1996. The number of incidents and animals/humans involved are as follows:

	<u>Number of Incidents</u>	<u>Number of Animals</u>	<u>Number of Deaths</u>
Cats	1	3	1
Dogs	4	4	1
Calves	1	9	2
Wild Birds	6	Unknown	Unknown
Humans	6	6	2

The signs reported in domestic animals were consistent with organophosphate toxicity. The cases in humans appeared in a literature article describing extrapyramidal manifestations in six patients in Sri Lanka who attempted suicide by ingesting fenthion (for details, see review by V. Dobozy/J. Blondell, HED/OREB, *Fenthion - Review of pesticide Poisoning Incident Data* dated 1/30/96).

Fenthion products for use on domestic animals are regulated by both EPA and FDA. Two concentrations, 3% and 20%, are registered by EPA for use on cattle to control lice. An additional concentration, 3%, is registered for use on cattle and swine by EPA. Products approved by FDA for flea control on dogs contain either 5.6 or 13.8% fenthion. The mechanism of action of fenthion for flea control is through systemic absorption which is the likely basis for its regulation by FDA. Reports of toxicity in dogs and cats may involve either the FDA-approved product, or misuse/inadvertent exposure to the EPA-approved products. The National Animal Poison Control Center reported 101 calls involving dogs and cats during 1986-1987; 50% of the canine calls and 70% of the feline calls were classified as toxicosis or suspected toxicosis. Dogs were involved more than twice as often as cats. It is likely that the majority of these calls involved the FDA-approved product. Some forms of the EPA-regulated RID-A-BIRD (11% fenthion) were occasionally associated with toxicosis in dogs.

Poison Control Center Data - There were a total of 52 cases of occupational exposure to fenthion reported to the Poison Control Centers; 50 (96%) involved exposure to fenthion alone and 2 (4%) involved exposure to multiple chemicals, including fenthion. There were a total of 417 non-occupational exposures; 407 (98%) involved this chemical alone and 10 (2%) were attributed to multiple chemicals.

Incidents with Children - A separate analysis of the number of exposures in children five years of age and under from 1985-1992 was conducted. For fenthion, there were a total of 165 reports; 161 (98%) involved exposure to this chemical alone while 4 (2%) were attributed to multiple chemicals. Further analysis showed that 26.1% with exposure to fenthion alone were seen at a health care facility. The percentage was 26.7 when fenthion was used in combination with other chemicals. Of these cases, the percentage hospitalized was 19.0% and 18.2% with single and

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multiple chemical exposures, respectively.

California Detailed Data - 1982-1993 - Circumstances of Poisoning - There were 6 case reports of adverse reactions received by the California Pesticide Illness Surveillance Program from 1982 to 1993; 3 involved use of fenthion alone while in 3 cases other chemicals were also used. Of the cases involving fenthion alone, one each occurred in the years 1982, 1983 and 1987. The cases in 1982 and 1983 involved wind blowing the pesticide in the face of applicators spraying for mosquitoes. Both experienced systemic effects. The third incident involved a veterinary technician who developed systemic symptoms after spilling the chemical on her smock and wearing it all day.

NPTN - A total of 237 calls on fenthion were handled by NPTN from 1984 to 1991, inclusively. A total of 57 incidents, involving 41 humans and 15 animals, were reported.

Fenthion has relatively low reported usage in agriculture. Therefore, it is not possible to make a meaningful comparison between the number of reported poisonings to the number of applications or pounds reported in use. Fenthion has major use in mosquito control abatement where the population at risk is very different from that found in agricultural settings.

Data from the Poison Control Centers demonstrated that occupational exposure to fenthion was less likely to result in symptoms requiring medical attention than the other organophosphate and carbamate insecticides evaluated. While the non-occupational exposure was less likely to result in referral to a health care facility, those which were referred were more likely to be hospitalized. In addition, those with symptoms were more likely to have life-threatening symptoms. Exposure data requirements are triggered based on the potential for exposure and the toxicological significance of the active ingredient. Exposure analyses have been completed for each handler (i.e., mixer/loader/applicator) scenario for the use/activity patterns associated with fenthion for which there are data.

viii. Data requirements

Short- and intermediate-term dermal and inhalation exposure assessments were made using PHED Version 1.1 surrogate data since no chemical-specific handler data were submitted. Fenthion-specific handler studies may be required pending the outcome of recommended discussions with the registrants concerning appropriate risk mitigation options.

Bayer Chemical Company is a member of the ongoing *Outdoor Residential Exposure Taskforce (ORETF)*. As such, studies are to be completed to enable the Agency to evaluate residential exposures due to contact with treated turf (i.e., to generate appropriate activity pattern and transfer coefficient data). Bayer must also develop a strategy to generate chemical-specific transferable residue data to be used in conjunction with the ORETF database in order for the Agency to complete any exposure/risk assessment.

No proprietary data from the Spray Drift Task Force (SDTF) was used in this assessment. Bayer is a member of the SDTF and may refine the AgDRIFT input parameters if data were generated for the Baytex ULV product. Additionally, AgDRIFT was recently presented before the FIFRA Science Advisory Panel. Modifications to the model are possible as a result of the SAP comments. These modifications, however, are anticipated by HED not to significantly alter the results of this assessments. Any significant modifications to the model may require further refinement of this assessment. Even given the potential for modification of the model, the assessment is much more refined than assuming 100 percent of the application rate is deposited on the turf in residential areas where malaria vector control applications occur. This approach is recognized by HED as being unrealistic given what is known concerning the engineering aspects of malaria vector control applications.

5. Aggregate Risk

Aggregate risk reflects the combined dietary (food and water) and residential exposures and risk. Fenthion has dietary risks from food (livestock uses), and residential exposures and risk resulting from residential mosquito control uses. Aggregate risk calculations for fenthion have not been made.

The acute dietary analysis resulted in unacceptable risks (MOEs < 10) for all population subgroups. The chronic dietary analysis for fenthion resulted in % RfD values of over 200% for all population subgroups using Anticipated Residues. The chronic dietary analysis using TMRC data resulted in unacceptable risks for non-nursing infants and children (1-6 yr). The anticipated residue values represent the best estimate of the dietary risk from fenthion; however, they are overestimates. Since no data were available at the 1x rate and 21-day pre-slaughter interval on livestock, the anticipated residues were extrapolated from existing magnitude of the residue studies, thus resulting in higher risks than those resulting from tolerance-level dietary exposures.

As noted in the drinking water assessment above, chronic risk estimates for fenthion from drinking water sources are extremely low. For all population subgroups, the % RfD from drinking water is <1%. Similarly, acute risks due solely to water consumption are very low (MOE >100 when 10 is protective). The registered uses of fenthion are unlikely to result in significant direct exposures to drinking water sources. Fenthion has no food uses and was assumed not to be applied directly to water (mosquito control uses are largely adulticide uses only). Livestock treatment uses are unlikely to result in significant exposure to drinking water sources. There is potential for inadvertent surface water exposure to fenthion from spray drift resulting from residential spraying for mosquito control; HED recommends that EFED consider the AgDRIFT model for this purpose as it may be used to estimate spray deposition and surface water residues potentially resulting from spray drift. If the use of granular products in aquatic areas for mosquito larvae control is, indeed, registered (as REFS implies), EFED may also wish to estimate water concentrations of fenthion reflecting this use.

The Agency used the AgDRIFT model to assess the risks to bystanders from mosquito control spraying in residential areas. Short-term risks to toddlers and adults reflecting ground and aerial

ULV applications were above the MOE of 10 considered to be protective. Intermediate-term MOEs reflecting aerial ULV applications were less than the protective level of 30 for toddlers at the typical and maximum label rates and for adults at the maximum label rate. Aggregate exposure and risk calculations will not be made at this time.

6. Cumulative Effects

Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also policies and methodologies for conducting cumulative risk assessments. While the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, the Agency does not at this time have the methodology to fully resolve in a meaningful way. The Agency has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable the Agency to apply common mechanism issues to its pesticide risk assessments. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments. Exceptions include pesticides that are toxicologically and structurally dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

In making individual tolerance decisions, the Agency will determine whether:

- 1) it has sufficient information to determine that a pesticide does not appear to share a common mechanism of toxicity with other substances;
- 2) it is unable to conclude that a pesticide does not share a common mechanism of activity with other substances; or
- 3) it is able to conclude that a pesticide does share a common mechanism of activity with other substances.

For pesticides falling into the first category, the Agency will explain its determination and factor the determination into the tolerance decision. For pesticides falling into the second category, the Agency will conclude that it does not have sufficient available information concerning common mechanism of toxicity to scientifically apply that information to the tolerance decision, the tolerance decision will be reached based on the best available and useful information for the individual chemical, and a risk assessment will be performed for the tolerance action assuming that no common mechanism of toxicity exists. However, tolerance decisions falling into the second category will be reexamined by the Agency after it establishes methodologies and

procedures for integrating information concerning common mechanism into its risk assessments. In such circumstances, related registration actions may be conditional upon the provision of such data as may be necessary to evaluate common mechanism of toxicity issues in a risk assessment. For pesticides in the third category, the Agency will perform a cumulative risk assessment before determining whether or not to grant a tolerance.

In the case of the organophosphates, including fenthion, the Agency has not formally concluded how to address the issue of common mechanism of toxicity and whether it is appropriate and how to include this chemical in a cumulative risk assessment. After the Agency develops a methodology for applying common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine these tolerance decisions.

7. Endocrine Disruptor Effects

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end-use products for endocrine disruptor effects.

8. Data Gaps

The following toxicology, residue chemistry, and occupational/residential exposure data are required for the reregistration of fenthion:

Toxicology

85-1 General Metabolism

84-2 Mutagenicity - Dominant Lethal Assay (Mouse)

82-4 Subchronic (21- or 90-day) Inhalation Toxicity (Rat)

Residue Chemistry

860-1300 Nature of the Residue - livestock - additional data to upgrade ruminant and swine dermal treatment metabolism studies:

- (i) additional characterization and identification of residue components;
- (ii) accounting for large amounts of non-analyzed residues; and
- (iii) submission of supporting quantitative data.

98999

860-1340 Residue Analytical Methods - (i) radiovalidation of enforcement methods using representative samples from livestock metabolism studies (ii) multiresidue testing for fenthion sulfoxide recovery using FDA multiresidue methods.

860-1480 Magnitude of the Residue in Animals - residue data at the existing maximum use rate, 0.080 oz. ai/100 lb body weight. The registrant must propose modified use directions including a minimum 21-day PSI. All types of treatment must be represented by adequate residue data.

860-1380 Storage Stability - required to support requested and existing residue data

Occupational and Residential Exposure

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