UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: **November 10, 2010**

SUBJECT: **Fenitrothion.** Risk Assessment to Support Final Registration Review Decision.

PC Code: 105901
Decision No.: 441607
Petition No.: Not Applicable

Risk Assessment Type: Single Chemical Aggregate
T**XR No.:** Not Applicable
MRID No.: None

DP Barcode: D383647
Registration No.: Not Applicable
Regulatory Action: Registration Review Risk Assessment
Case No.: 0445
CAS No.: 122-14-5
40 CFR: 180.540

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TO: Tom Myers, Acting Chief
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Attached is a human health risk assessment to support the registration review of the insecticide fenitrothion. No risks of concern were identified, and no changes to tolerances levels are needed; however, the residue definition in the tolerance expression needs minor modification.

1.0 Executive Summary

HED has prepared a human health risk assessment to support the registration review of the insecticide fenitrothion.

Fenitrothion is an organophosphate (OP) insecticide; its mode of toxic action in mammals is the inhibition of the cholinesterase (ChE) enzyme. Fenitrothion has one import tolerance on wheat gluten from Australia. It is also registered in the U.S. for use in ant and roach bait traps. Based on the existing uses of fenitrothion, residential, occupational, and drinking water exposures are expected to be insignificant and have not been assessed quantitatively. Therefore, the only exposure included in the aggregate assessment is dietary consumption of imported wheat gluten.

The predominant effects seen in various toxicity studies on fenitrothion are those associated with ChE inhibition (plasma, red blood cell, and brain) that occurs following all routes and durations of exposure. Fenitrothion produces the associated clinical signs, such as tremors, ataxia, and labored breathing. Fenitrothion is acutely toxic (Toxicity Category II) via the oral, dermal, and inhalation routes of exposure, causes minor eye and dermal irritation, and is not a dermal sensitizer. Neuropathology was not observed in neurotoxicity studies. Developmental toxicity was observed in the rat and rabbit, but only at doses where significant maternal toxicity was observed. Reproductive toxicity was observed in the rat, as evidenced by decreased fertility in the F_0 generation and decreased number of implantation sites. There is no indication of an increased sensitivity of the offspring of rats or rabbits after pre-natal and/or postnatal exposure to fenitrothion. In all studies, maternal or parental No Observed Adverse Affect Levels (NOAELs) are lower or equivalent to the offspring / fetal NOAELs. No evidence of carcinogenicity was seen in the mouse and rat carcinogenicity studies. There is no concern for mutagenicity.

Because of the limited uses and minimal potential for exposure, OPP has chosen to complete a screening-level risk assessment. OPP has retained the safety factor for the protection of infants and children due to the lack of immunotoxicity and comparative cholinesterase studies; OPP did not request these studies in the final registration review work plan due to minimal human exposure. Points of departure (POD) for acute and chronic dietary risk assessment are based on red blood cell (RBC) cholinesterase inhibition. There are no studies available where cholinesterase was measured after only a single dose; therefore, the acute POD is based on the study with the shortest interval where there were measurements, two weeks. This POD is conservative, as it is likely that a higher dose would be needed to inhibit cholinesterase after only one exposure.

OPP conducted acute and chronic assessments to determine the risk from consuming imported wheat gluten. The assessment included only wheat gluten imported from Australia, since Australia is a major exporter of wheat gluten, and fenitrothion is registered for pre-harvest and post-harvest use on wheat there. The assessment also assumes that all wheat gluten exported from Australia bears tolerance-level residues; the limited wheat gluten monitoring data available has shown that actual residues are likely to be lower. Since wheat gluten consumption data are not available, OPP has compared the amount of wheat gluten available for consumption to the amount of wheat flour available and applied a correction factor in the exposure assessment.

Acute and chronic dietary exposures were below the level of concern for all population groups assessed. The most highly exposed subgroup were children ages 1-2, whose acute exposure is equivalent to 49% of the acute population adjusted dose (aPAD) and whose chronic exposure is at 20% of the cPAD. This assessment can be considered conservative, as it assumes upper-bound tolerance-level residues for all wheat gluten imported from Australia. Studies with other organophosphate pesticides have shown reduction of residues upon cooking; no reduction upon cooking was assumed. Actual human exposures are likely to be lower. Significant refinement to this screening level assessment could be completed with the submission of additional toxicity and exposure data. However, since risks are of no concern even when using these very conservative assumptions, further refinement will not be considered at this time.

No cumulative risks of concern were identified for fenitrothion in the most recent organophosphate cumulative risk assessment. No human studies were used in the fenitrothion risk assessment.

2.0 Regulatory Recommendations

Sufficient data are available to support the human health risk assessment of fenitrothion. No changes to current product labels are needed. Although the current tolerance level, 3 ppm, is appropriate, the residue definition in the tolerance expression requires a slight modification to be consistent with the current guidance. HED recommends that the residue definition in 40 CFR 180.540 (a) be modified as follows:

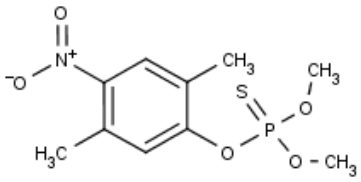
> Tolerances are established for residues of the insecticide fenitrothion, including its metabolites and degradates, in or on the commodity in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only fenitrothion, *O*,*O* -dimethyl *O*-(4-nitro-m-tolyl) phosphorothioate in or on the commodity.

Codex maximum residue levels (MRLs) are established for fenitrothion *per se*. Although the MRLs and U.S. tolerance include the same residue of concern, the U.S. tolerance is for the processed commodity wheat gluten and the Codex MRL is on wheat grain. Therefore, these commodities cannot be directly compared for tolerance harmonization purposes.

3.0 Introduction

The chemical identity and chemical structure for fenitrothion may be found in Table 3.1 below.

Table 3.1 Chemical Identity	
Common Name	Fenitrothion
Chemical Name	O,O-dimethyl O-(4-nitro-m-tolyl) phosphorothioate
PC Code	105901
Chemical Abstracts No.	122-14-5
Chemical Class	Organophosphate

Table 3.1 Chemical Identity	
Chemical Structure	

Technical fenitrothion is a yellowish-brown oil which decomposes at 140-145°C (at 0.1 mmHg) and has a density of 1.32-1.34. Its solubility in water at 20°C and 30°C is 5 mg/kg and 14 mg/kg, respectively. Fenitrothion solubility at 22-25°C in methanol and acetone is >50% w/w and in hexane is <10% w/w.

Fenitrothion is registered in the U.S. only for use in ant and roach bait traps. Considering the design of these traps and the current products registered, residential, occupational, and drinking water exposures are expected to be insignificant. Fenitrothion has one tolerance for imported wheat gluten; OPP has determined that the only significant imports where fenitrothion is used will be from Australia. Therefore, dietary exposure from imported wheat gluten is the only route of exposure quantitatively assessed.

Potential areas of environmental justice concerns, to the extent possible, were considered in the human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/nepa/tools/guidance/Volume1/2-6-EO_12898envjustice.pdf). The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

4.0 Hazard Identification and Dose-Response Assessment

4.1 Toxicological Effects

Fenitrothion is an organophosphate insecticide/acaricide. The predominant effects seen in various toxicity studies on fenitrothion are those associated with ChE inhibition (plasma, erythrocyte, and brain) that occurs following all routes and durations of exposure. Fenitrothion produces the associated clinical signs, such as tremors, ataxia, and dyspnea (labored breathing). Fenitrothion is acutely toxic (Toxicity Category II) via the oral, dermal, and inhalation routes of exposure, causes minor eye and dermal irritation, and is not a dermal sensitizer. No evidence of ocular toxicity was observed in rats following acute and subchronic oral exposure. Fenitrothion did not cause neurological changes indicative of delayed neurotoxicity in the hen. Treatment-related effects on functional observational battery (FOB) parameters and decreased motor activity were observed in the acute neurotoxicity study but not in the subchronic neurotoxicity

study in rats. Neuropathology was not observed in either study. Developmental toxicity was observed in the rat and rabbit, but only at doses where significant maternal toxicity was observed. Reproductive toxicity was observed in the rat, as evidenced by decreased fertility in the F_0 generation and decreased number of implantation sites. There is no indication of an increased sensitivity of the offspring of rats or rabbits after pre-natal and/or postnatal exposure to fenitrothion. In all studies, maternal or parental No Observed Adverse Affect Levels (NOAELs) are lower or equivalent to the offspring NOAELs. No evidence of carcinogenicity was seen in the mouse and rat carcinogenicity studies. There is no concern for mutagenicity.

To support registration review, a search of the open literature was conducted for toxicity studies involving fenitrothion. Androgen-mediated development of the reproductive tract was altered in male offspring exposed *in utero* to maternally toxic dose levels of fenitrothion [Toxicological Sciences **68**, 174-183 (2002)], as evidenced by reduction in anogenital distance on postnatal day 1 and retention of areolae on post-natal day (PND) 13. However, these effects were only transient and there were no indications of abnormal phenotypes or development of androgen-dependent tissues on PND 100. At the dose levels evaluated, fenitrothion was only weakly antiandrogenic *in vivo* compared with other androgen receptor antagonists. However, effects, including fetal deaths, were observed at dose levels above the developmental NOAEL in the registrant's study and those selected as endpoints for risk assessment. Fenitrothion is reported to be a potent competitive androgen receptor antagonist *in* v*itro* (Toxicological Sciences **60**, 56-62 (2001).

4.2 Safety factor for Infants and Children (FQPA Safety Factor)

OPP has evaluated the toxicity and exposure databases to determine if the FQPA safety factor for the protection of infants and children should be retained, reduced, or removed. There is evidence of neurotoxicity but there is no evidence of susceptibility in developmental and reproduction studies. However, the toxicity database for fenitrothion is incomplete. A Data-Call-In (DCI) was issued in September 1999 for a developmental neurotoxicity study (DNT) for OPs. Previously, fenitrothion was given a waiver for the DNT and related comparative ChE study. However, HED has now determined that a comparative cholinesterase study (CCA) study is now required for some OPs previously given waivers. This is based on data from CCA studies from more than 20 OPs, many of which have shown juveniles to be more sensitive than adults. Additionally, an immunotoxicity study is a new requirement under 40 CFR Part 158 as a part of the general data requirements for registration of a pesticide (food and non-food uses). Human exposure is expected to be minimal; the only significant exposure to fenitrothion is in the diet, through imported wheat gluten. Dietary exposure is not underestimated in this assessment, since it is based on the assumption that all imported wheat gluten bears tolerance-level residues, and that there is no reduction of residues upon normal consumer processing. Because of minimal human exposure and conservative assumptions in the exposure assessment, HED believes the resources required to conduct the CCA and immunotoxicity studies are not warranted for this pesticide. However, Section 408 (b)(2)(C) of FFDCA states that the FQPA 10X Safety Factor can be changed only "*on the basis of reliable data*." In the absence of the comparative ChE study and immunotoxicity study, such data would not exist for fenitrothion, thus preventing reduction of the FQPA 10X Safety Factor.

4.3 Dose-Response Assessment

A summary of the studies considered for selecting endpoints for dietary risk assessment may be found in Appendix A of this assessment. When selecting a point of departure (POD) for acute (single-day) dietary exposure OPP considered the available studies: developmental toxicity, reproductive toxicity, and acute neurotoxicity studies. However, none of these studies assessed the most sensitive endpoint generally found for organophosphate pesticides after a single exposure, cholinesterase inhibition. Therefore, OPP also considered repeat-dose studies where cholinesterase inhibition was measured. The study available with the shortest dosing interval where red blood cell (RBC) and brain cholinesterase were measured was the chronic toxicity/carcinogenicity study in rats. RBC Cholinesterase inhibition was observed at 0.5 mg/kg/day after two weeks of dosing; the NOAEL for this effect was 0.25 mg/kg/day. Selection of this NOAEL as the point of departure is considered to be conservative, as it is likely that a higher dose would be required for cholinesterase inhibition to occur after only one exposure. The resulting risk estimates should be considered screening level.

Chronic toxicity studies are available in mice, rats, and dogs. For chronic dietary risk assessment the study with the lowest NOAEL for brain and/or RBC cholinesterase inhibition was the study conducted in the dog. After chronic exposure to fenitrothion, RBC cholinesterase inhibition was observed at 0.25 mg/kg bw/day; the NOAEL (no observed adverse effects level) was selected as the point of departure for risk assessment at 0.125 mg/kg bw/day.

For both chronic and acute assessments the total uncertainty factors are 1000: 10 for intra-species variation, 10 for extrapolation from laboratory animals to human, and 10 for the FQPA database uncertainty factor.

A summary of the endpoints and doses selected for dietary risk assessment is found below.

Table 4.3.1 Summary of Toxicological Doses and Endpoints for Fenitrothion for Use in Dietary Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL= 0.25 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= UF_{DB} = 10X	Acute RfD = 0.0025 mg/kg/day aPAD = **0.00025** mg/kg/day	Chronic oral toxicity study – rat LOAEL = 0.5 mg/kg/day based on RBC cholinesterase inhibition measured after 2 weeks of dosing (MRID 40420501)
Chronic Dietary (All Populations)	NOAEL= 0.125 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= UF_{DB} = 10X	Chronic RfD = 0.00125 mg/kg/day cPAD = **0.000125** mg/kg/day	Chronic oral toxicity study – dog LOAEL = 0.25 mg/kg/day, based on plasma cholinesterase inhibition and histopathology of lymph nodes (MRID 40058501)

Table 4.3.1 Summary of Toxicological Doses and Endpoints for Fenitrothion for Use in Dietary Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer (oral, dermal, inhalation)	Classification: Group E, evidence of non-carcinogenicity for humans, based on rat and mouse carcinogenicity studies			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. N/A = not applicable.

5.0 Aggregate Exposure and Risk Assessment

Occupational and residential exposures resulting from the proper use of the ant and roach bait traps are expected to be insignificant. HED does not estimate risks for these types of uses because of the expected low potential for exposure. No incidents involving fenitrothion have been reported to the Incident Data System since 2002. In addition, it is highly unlikely that fenitrothion will reach drinking water resources when ant and roach bait traps are properly used. Therefore, the only route of exposure quantitatively assessed is in the diet from imported wheat gluten.

5.1 Residue Profile

A tolerance was established to cover residues of fenitrothion in imported wheat gluten. Australia exported over 136 million pounds of wheat gluten to the US in 2009, and fenitrothion is registered for pre-harvest and post-harvest uses on wheat there as well. Therefore, magnitude of residue studies have been conducted only in Australia. The data support the existing tolerance of 3 ppm. Residues in four trials from four different states in Australia resulted in residues ranging from 0.95 to 2.5 ppm in/on wheat gluten; the average residue was 1.84 ppm. Monitoring data from a commercial wheat gluten processing facility in Australia showed residues ranging from 0.09 to 0.9 ppm, with an average of 0.38 ppm.

5.2 Dietary Exposure and Risk Assessment

The DEEM-FCID™ software which HED uses to evaluate dietary risk does not contain consumption values for wheat gluten, which is used in a manner similar to wheat flour. Therefore, in order to estimate dietary exposure to fenitrothion residues in wheat gluten, HED used wheat flour consumption data and calculated an adjustment factor based on wheat gluten availability relative to wheat flour. The Biological and Economic Analysis Division (BEAD) estimated the amount of wheat gluten available for consumption as 250 million pounds per year. HED obtained a value for wheat flour from the USDA Economic Research Service Wheat

Yearbook for 1997; the total amount of wheat flour available for consumption (subtracting what is available for export) is 40,107 million pounds. This results in a relative ratio of 0.0062, which was then used as an adjustment factor when estimating the dietary exposure to fenitrothion residues.

Usage data is not available for the use of fenitrothion. Therefore, the assessment assumes that all of the wheat gluten imported from Australia has been treated with fenitrothion. BEAD has recommended that HED should assume that 36% of the wheat gluten consumed in this country has been imported from Australia as a risk assessment refinement. In the dietary assessment HED has assumed that all of the wheat gluten exported from Australia bears tolerance level residues.

Fenitrothion acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database DEEM-FCID™, Version 2.03 which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days.

A summary of the dietary exposure and risk assessment is presented in Table 5.2.1. The exposure for all subgroups is less than the level of concern for both acute and chronic exposures. The most highly exposed subgroup is children ages 1-2, with the exposure equivalent to 49% of the acute Population Adjusted Dose (aPAD) and 20% of the cPAD. This assessment is has been slightly refined using percent imported. Actual exposure is likely to be lower, since this assessment assumes that all imported wheat gluten bears residues at the tolerance level; the limited monitoring data available indicate that residues are lower. In addition, this assessment assumes that residues do not degrade during typical commercial and consumer practices. Studies with other organophosphate pesticides have shown reduction of residues during cooking.

Table 5.2.1. Summary of Dietary (Food Only) Exposure and Risk for Fenitrothion

Population Subgroup	Acute Dietary (99.9 Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD[1]	Dietary Exposure (mg/kg/day)	% cPAD[1]
General U.S. Population	0.000084	34	0.000010	8.2
All Infants (< 1 year old)	0.000098	39	0.000005	3.7
Children 1 - 2 years old	**0.000123**	**49**	**0.000025**	**20**
Children 3 - 5 years old	0.00011	44	0.000025	20
Children 6 - 12 years old	0.000083	33	0.000018	14
Youth 13 - 19 years old	0.000053	21	0.000011	8.5
Adults 20 - 49 years old	0.000046	19	0.000008	6.6
Adults 50+ years old	0.00004	16	0.000006	5.1
Females 13 - 49 years old	0.000043	17	0.000008	6.3

[1]The values for the highest exposed population for each type of risk assessment are bolded.

6.0 Cumulative Risk Assessment

The Food Quality Protection Act (FQPA) requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. Fenitrothion is a member of the organophosphate common mechanism group. The most recent cumulative risk assessment for the organophosphates was published in August 2006 and is available at http://www.epa.gov/pesticides/cumulative/2006-op/op_cra_main.pdf. No cumulative risks of concern for fenitrothion were identified in that assessment.

7.0 References

Table 7.1. Memoranda Relevant to Registration Review

Author	Barcode	Date	Title
J. Alsadek	none	7/15/10	Updating Values for Imported Wheat Gluten Treated with Fenitrothion
T. Goodlow	358698	2/26/09	Fenitrothion Human Health Assessment Scoping Document in Support of Registration Review.
C. Olinger	256052	5/19/99	Fenitrothion HED RED Chapter; Revised Risk Assessment
D. Edwards	NA	6/31/06	Finalization of Interim Reregistration Eligibility Decisions (IREDs) and Interim Tolerance Reassessment and Risk Management Decisions (TREDs) for the Organophosphate Pesticides, and Completion of the Tolerance Reassessment and Reregistration Eligibility Process for the Organophosphate Pesticides
none	none	8/2006	Organophosphorus Cumulative Risk Assessment – 2006 Update http://www.epa.gov/pesticides/cumulative/2006-op/index.htm
L. Rossi	NA	7/95	Fenitrothion Reregistration Eligibility Decision (RED) document.
C. Olinger	256054	5/19/99	Reregistration of Fenitrothion: Anticipated Residue and Tolerance Reassessment Recommendations
B. Cropp-Kholligian	185375	3/29/93	Fenitrothion: List A Reregistration Case No. 0445: Product and Residue Chemistry Chapters for the Reregistration Eligibility Document (RED).

Appendix A. Summary of Toxicity Studies

Table A.1 Toxicity Studies Considered for Dietary Risk Assessment Endpoint Selection			
Guideline No.	**Study Type**	**MRID No.**	**Summary**
870.3700a	Prenatal developmental in (rat)	40604002	**Maternal** NOAEL = 8 mg/kg/day LOAEL = 25 mg/kg/day based on tremors. **Developmental** NOAEL = 8 mg/kg/day LOAEL = 25 mg/kg/day based on increased incidence of fetuses with one full and one rudimentary 13th ribs In a developmental toxicity study, pregnant Sprague-Dawley rats were given oral doses of Fenitrothion at 0, 3, 8 or 25 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOAEL was 8 mg/kg/day and the LOAEL was 25 mg/kg/day based on tremors and decreases in body weight and body weight gains. For developmental toxicity, the NOAEL was 8 mg/kg/day and the LOAEL was 25 mg/kg/day based on an increased incidence of fetuses and litters with one full and one rudimentary 13th ribs.
870.3700b	Prenatal developmental in (rabbit)	00162548	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day based on mortality, abortions, tremors **Developmental** NOAEL = 30 mg/kg/day (HDT) LOAEL = not established In a developmental toxicity study, pregnant New Zealand rabbits received oral doses of Fenitrothion at 0, 3, 10 or 30 mg/kg/day during gestation days 7 through 19. For maternal toxicity the NOAEL was 10 mg/kg/day and the LOAEL was 30 mg/kg/day based on mortality, abortions, tremors, ataxia, dyspnea and decreased body weight gain. The abortions occurred in the presence of severe maternal toxicity and are considered a sequelae of maternal toxicity (deaths). For developmental toxicity, the NOAEL was 30 mg/kg/day (HDT); a LOAEL was not established.

Table A.1 Toxicity Studies Considered for Dietary Risk Assessment Endpoint Selection			
Guideline No.	**Study Type**	**MRID No.**	**Summary**
870.3800	Reproduction and fertility effects (rats)	41589001 and 42668801	**Parental/Systemic** NOAEL = 2.74 mg/kg/day LOAEL = 8.4 mg/kg/day **Reproductive** NOAEL = 2.74 mg/kg/day LOAEL = 8.4 mg/kg/day In a 2-generation reproduction study, Sprague-Dawley rats were fed diets containing Fenitrothion at 0, 10, 40 or 120 ppm (0, 0.68, 2.74 or 8.4 mg/kg/day for males and 0, 0.77, 3.19 or 10.37 mg/kg/day for females) for two successive generations. There was no increased sensitivity of pups over the adults seen. For parental systemic toxicity, the NOAEL was 40 ppm and the LOAEL was 120 ppm based on decreased food consumption, body weight and body weight gain in both generations of both sexes. For reproductive toxicity, the NOAEL was 40 ppm and the LOAEL was 120 ppm based on decreased fertility in the F_0 generation, decreased number of implantation sites, and decreased viability and lactation.
870.4100b	Chronic toxicity (dog)	40058501	NOAEL = 0.125 mg/kg/day LOAEL = 0.25 mg/kg/day based on cholinesterase inhibition A one year feeding study was conducted in beagle dogs. The compound was administered in the diet at 0, 5, 10, and 50 ppm (0, 0.125, 0.25, and 1.25 mg/kg/day). Cholinesterase NOAEL = 5 ppm; Cholinesterase LOAEL = 10 ppm (plasma Cholinesterase inhibited); Systemic NOAEL = 5 ppm; and Systemic LOAEL = 10 ppm (increased incidence of abdominal lymph node hemorrhage).
870.4100a 870.4200	Carcinogenicity (rat)	00071965	NOAEL = not determined for cholinesterase inhibition LOAEL = 0.5 mg/kg/day A two year chronic feeding/oncogenicity study was conducted in the Charles River/CD strain rat. The compound was administered in the diet at doses of 0, 0.5, 1.5 and 5 mg/kg/day (0, 10, 30 and 100 ppm). Brain and plasma cholinesterase inhibition observed at 10 ppm (LDT) (brain and plasma). **No evidence of carcinogenicity**
870.4100a 870.4200	Carcinogenicity (rat)	40420501	NOAEL = 0.25 mg/kg/day LOAEL = 0.5 mg/kg/day A 22 month chronic feeding/oncogenicity study was conducted in the Wistar strain rat. The compound was administered in the diet at doses of 0, 0.125, 0.25, 0.5 mg/kg/day (0, 2.5, 5.0 and 10 ppm). ChE NOAEL = 2.5 ppm ChE LOAEL = 5.0 ppm (plasma). At 10 ppm RBC ChE was reduced. **No evidence of carcinogenicity**

Table A.1 Toxicity Studies Considered for Dietary Risk Assessment Endpoint Selection			
Guideline No.	**Study Type**	**MRID No.**	**Summary**
870.4300	Carcinogenicity (mouse)	41925201 425077-01 415077-04	NOAEL = 0.45 mg/kg/day LOAEL = 1.45 mg/kg/day based on [ ]. A two year chronic feeding/oncogenicity study was conducted in B6C3F1 mice. The compound was administered in the diet at 0, 3, 10, 100, and 1000 ppm (0, 0.45, 1.51, 13.1, and 144 mg/kg/day for the females, and at 0.37, 1.45, 12.6, and 134 mg/kg/day for the male). The study was conducted at adequate dosage based on a 26-29% suppression in body weight gain in 1000 ppm (both sexes) and a depression of cholinesterase observed in 100 and 1,000 ppm (both sexes). Systemic NOAEL = 3 ppm (0.45 mg/kg/day); Systemic LOAEL = 10 ppm (1.45 mg/kg/day) based on decreased body weight gains; decreased RBC, brain, and plasma cholinesterase activity. **No evidence of carcinogenicity**
870.6200a	Acute neurotoxicity screening battery	42666901	NOAEL = 12.5 mg/kg/day LOAEL = 50 mg/kg/day based on FOB effects No treatment-related pathological lesions were seen in the central or peripheral nervous systems following single oral doses at 0, 12.5, 50 or 200 mg/kg to male and 0, 50, 200 or 800 mg/kg to female Sprague-Dawley rats. For neurotoxicity, the NOAEL was 12.5 mg/kg and the LOAEL was 50 mg/kg based on treatment-related effects on FOB parameters (tremors, gait incapacity, ataxia, low arousal, decrease in grip strength, righting reflex, and decreased body temperature) and decreased motor activity. No cholinesterase activity was measured.
870.6200b	Subchronic neurotoxicity screening battery	42099201 42884701	NOAEL = 0.46 mg/kg/day LOAEL = 1.56 mg/kg/day, based on plasma, RBC, and brain cholinesterase inhibition In a subchronic neurotoxicity study, Sprague-Dawley rats received dietary administration of Fenitrothion at 0, 6, 20, 60, 200 ppm (0, 0.4, 1.32, 3.99, or 13.8 mg/kg/day in males and 0, 0.46, 1.56, 4.85 or 17.6 mg/kg/day in females, respectively) for 90-days. Treatment had no effect on FOB, motor activity or neuropathology. For plasma, red blood cell and brain cholinesterase inhibition, the NOAEL and LOAEL were 20 and 60 ppm (1.32 and 3.99 mg/kg/day) in males and 6 and 20 ppm (0.46 and 1.56 mg/kg/day) in females

Appendix B. BEAD Memo on Gluten Imports

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 15 2010

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

SUBJECT: Updating Values for Imported Wheat Gluten Treated with Fenitrothion (PC Code: 105901)

FROM: Jihad Alsadek, Ph.D., Economist Jihad A Alsadek
Science Information and Analysis Branch
Biological and Economic Analysis Division (7503P)

TO: Tom Myers, Team Leader
Risk Management and Implementation Branch II
Pesticide Re-evaluation Division (7508P)

Pesticide Re-Evaluation Division (PRD) requested that BEAD update previous estimates of import data for wheat gluten from Australia (4/28/99 and 11/24/08). Specifically, this memo provides updates for the amount of wheat gluten available for domestic consumption and the amount of wheat gluten treated with fenitrothion.

To provide this information, BEAD used data from United States International Trade Commission (USITC). The data have been converted from kilograms to pounds.

The data shown in the table below indicate that import shares for wheat gluten is on the rise. To be on the conservative side, BEAD suggests using the 2009 percentage (36%) in any risk refinement. Since we import almost 80 percent of wheat gluten from Australia, the European Union and China, it is safe to assume the 36 percent import share from Australia, in 2009, as the percent of wheat gluten treated with fenitrothion.

Annual Australian Import Data for Wheat Gluten

Year	Quantity Imported from Australia (1,000 lbs)	Total Quantity Imported from All Countries (1,000 lbs)	Australian Share of Wheat Gluten Imports (Col. 2/Col. 3*100)
2005	69,452	339,651	20%
2006	72,816	385,792	19%
2007	81,268	374,999	22%
2008	113,168	402,857	28%
2009	136,561	376,297	36%

The data accompanying this memorandum were reviewed by Arthur Grube, Senior Economist.

For questions, comments and other usage or label use information requests, please contact Jihad Alsadek at 703-308-8140. Other requests for information may be addressed to **OPP Usage and Label Use Team**, our group e-mail address in Lotus Notes.

References:
http://dataweb.usitc.gov/

Appendix C. Input File for Dietary Exposure Assessment

Filename: C:\Documents and Settings\colinger\My Documents\Fenitrot\DietaryAssessment\FenitrothionToleranceValuePCT_36.R98
Chemical: Fenitrothion PC105901
RfD(Chronic): .000125 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day
RfD(Acute): .00025 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day
Date created/last modified: 11-04-2010/14:04:11/8 Program ver. 2.03
Comment: Wheat Gluten Only; assume 0.62% of wheat flour is gluten

EPA Code	Crop Grp	Commodity Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
15004020	15	Wheat, flour	3.000000	0.006	0.360	
15004021	15	Wheat, flour-babyfood	3.000000	0.006	0.360	

Appendix D. Results File for Acute and Chronic Dietary Exposure Assessments

```
U.S. Environmental Protection Agency                                    Ver. 2.02
DEEM-FCID ACUTE Analysis for FENITROTHION PC105901                  (1994-98 data)
Residue file: FenitrothionToleranceValuePCT_36.R98
    Adjustment factor #2 used.
Analysis Date: 11-04-2010/14:05:14    Residue file dated: 11-04-2010/14:04:11/8
Daily totals for food and foodform consumption used.
Run Comment: "Wheat Gluten Only;  assume 0.62% of wheat flour is gluten"
================================================================================

Summary calculations (per capita):
```

	95th Percentile Exposure	95th Percentile % aRfD	99th Percentile Exposure	99th Percentile % aRfD	99.9th Percentile Exposure	99.9th Percentile % aRfD
U.S. Population:						
	0.000030	11.84	0.000050	19.90	0.000084	33.54
All infants:						
	0.000025	10.12	0.000050	20.12	0.000098	39.10
Children 1-2 yrs:						
	0.000061	24.27	0.000087	34.70	0.000123	49.11
Children 3-5 yrs:						
	0.000058	23.15	0.000082	32.82	0.000110	44.02
Children 6-12 yrs:						
	0.000041	16.44	0.000059	23.79	0.000083	33.31
Youth 13-19 yrs:						
	0.000025	10.02	0.000037	14.99	0.000053	21.14
Adults 20-49 yrs:						
	0.000020	8.19	0.000030	11.97	0.000046	18.59
Adults 50+ yrs:						
	0.000015	6.12	0.000023	9.28	0.000040	16.08
Females 13-49 yrs:						
	0.000020	7.86	0.000028	11.28	0.000043	17.10

U.S. Environmental Protection Agency Ver. 2.00
DEEM-FCID Chronic analysis for FENITROTHION PC105901 (1994-98 data)
Residue file name: C:\Documents and Settings\colinger\My Documents\Fenitrot\DietaryAssessment\FenitrothionToleranceValuePCT_36.R98
Adjustment factor #2 used.
Analysis Date 11-04-2010/14:06:07 Residue file dated: 11-04-2010/14:04:11/8
Reference dose (RfD, Chronic) = .000125 mg/kg bw/day
COMMENT 1: Wheat Gluten Only; assume 0.62% of wheat flour is gluten

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.000010	8.2%
U.S. Population (spring season)	0.000010	8.3%
U.S. Population (summer season)	0.000010	8.0%
U.S. Population (autumn season)	0.000010	8.3%
U.S. Population (winter season)	0.000010	8.3%
Northeast region	0.000011	8.9%
Midwest region	0.000011	8.8%
Southern region	0.000010	7.7%
Western region	0.000010	7.8%
Hispanics	0.000010	7.6%
Non-hispanic whites	0.000010	8.4%
Non-hispanic blacks	0.000010	8.0%
Non-hisp/non-white/non-black	0.000010	7.7%
All infants (< 1 year)	0.000005	3.7%
Nursing infants	0.000002	1.9%
Non-nursing infants	0.000005	4.4%
Children 1-6 yrs	0.000025	19.8%
Children 7-12 yrs	0.000017	13.6%
Females 13-19 (not preg or nursing)	0.000009	7.6%
Females 20+ (not preg or nursing)	0.000007	5.6%
Females 13-50 yrs	0.000008	6.6%
Females 13+ (preg/not nursing)	0.000008	6.4%
Females 13+ (nursing)	0.000010	7.7%
Males 13-19 yrs	0.000012	9.5%
Males 20+ yrs	0.000008	6.6%
Seniors 55+	0.000006	5.1%
Children 1-2 yrs	0.000025	19.8%
Children 3-5 yrs	0.000025	20.3%
Children 6-12 yrs	0.000018	14.3%
Youth 13-19 yrs	0.000011	8.5%
Adults 20-49 yrs	0.000008	6.6%
Adults 50+ yrs	0.000006	5.1%
Females 13-49 yrs	0.000008	6.3%