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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

Date: 9/22/09

SUBJECT: Fipronil. Human Health Risk Assessment Petition to Support and Maintain the Established Rice Grain Tolerance for Imported Rice

PC Code: 129121
Decision No.: 403380
Petition No.: 8E7480
Risk Assessment Type: Single chemical aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D360652
Registration No.: NA
Regulatory Action: NA (Tolerance for Imports)
Case No.: NA

CAS No.: 120068-37-3
40 CFR: §180.517

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SEP 3 REC'D, 2009

1.0. EXECUTIVE SUMMARY

General Background

BASF Corporation has submitted a tolerance petition, PP#8E7480, to support and maintain the current tolerance for fipronil on rice grain as a tolerance for imported rice. The registration for fipronil use on rice has been cancelled (Federal Register Vol. 69, No. 126, pages 39927-39928; 7/1/04), and BASF has declared no intention of reviving the rice use pattern for fipronil in the U.S. However, BASF does have, or is proposing, fipronil uses for preplant seed treatment uses on rice grown in Australia, Brazil, and Japan and for foliar treatment use on rice grown in Brazil. For these uses and to prevent trade barriers, the petitioner wishes to maintain the established tolerance for rice grain at the same level as an imported commodity.

There are existing permanent tolerances (40 CFR §180.517(a)) for fipronil (+ its 2 metabolites and 1 photodegradate) in/on rice grain (0.04 ppm); rice straw (0.10 ppm); corn, field, grain (0.02 ppm); corn, field, stover (0.30 ppm); corn, field, forage (0.15 ppm); eggs (0.03 ppm); fat of cattle, goat, horse, and sheep (0.40 ppm); hog fat (0.04 ppm); hog liver (0.02 ppm); hog meat (0.01 ppm); hog meat byproducts (except liver) (0.01 ppm); liver of cattle, goat, horse, and sheep (0.10 ppm); meat byproducts of cattle, goat, horse, and sheep (except liver) (0.04 ppm); meat of cattle, goat, horse, and sheep (0.04 ppm); milk, fat (reflecting 0.05 ppm in whole milk) (1.50 ppm); potato (0.03 ppm); potato, wet peel (0.10 ppm); poultry fat (0.05 ppm); poultry meat (0.02 ppm); poultry meat byproducts (0.02 ppm); rice, grain (0.04 ppm); and rice, straw (0.10 ppm). Time-limited tolerances for turnip (1.0 ppm) and rutabaga (1.0 ppm) are in effect until 12/31/10. Finally, tolerances are established for indirect or inadvertent residues of fipronil and metabolites in/on wheat, grain (0.005 ppm); wheat, forage (0.02 ppm); wheat, hay (0.003 ppm); and wheat, straw (0.03 ppm).

There are registered residential uses (pet and termiticide uses and fire ant control) for fipronil. The most recent human health risk assessment for fipronil was conducted in conjunction with an IR-4 request for the use on onion and shallot seed (dry bulb) and a proposed permanent tolerance on tuberous and corm vegetables (crop group 1C) (PP# 5F6948, D331890, B. Hanson, 06/19/2007).

Hazard Assessment

Fipronil is a broad-spectrum insecticide belonging to the pyrazole class of insecticides. The toxicology database provides evidence of neurotoxic activity as evidenced by neurologic signs in several studies and species. Fipronil is also associated with alterations in the thyroid-pituitary hormonal status, resulting in alterations in thyroid hormonal levels and thyroid follicular cell tumors.

The hazard endpoints for dietary exposure were identified based on the Subdivision F Guideline Requirements prior to the new requirement for a series 870.7800 immunotoxicity study. This study is now a data gap for fipronil (see Appendix 1). The Hazard Identification Assessment Review Committee (HIARC) previously requested a 28-day inhalation toxicity study in the rat.

This study was requested to further characterize the inhalation hazard for use in the risk assessment of fipronil. There is otherwise a high confidence in the quality of the existing studies and the reliability of the toxicity endpoints identified for use in risk assessment.

In acute toxicity studies, fipronil exhibits low to moderate toxicity, depending on the route of exposure and species. Fipronil has moderate acute toxicity (toxicity category II) by the oral and inhalation routes in rats. By the dermal route, it is of moderate toxicity in rabbits, and low toxicity in rats (III). Fipronil technical is relatively non-irritating to the skin (IV) and eye (III) of rabbits and is not a dermal sensitizer. Dermal absorption in rats is estimated to be 1% or less based on a dermal absorption study.

Fipronil is neurotoxic in both rats and dogs as evidenced by signs in the acute and subchronic screening batteries in the rat, in developmental neurotoxicity and chronic carcinogenicity studies in the rat, and in two chronic dog studies. Clinical signs of neurotoxicity were not observed in the mouse or rat at 28 or 90 days. The rat and mouse showed evidence of liver and/or thyroid alterations at all time periods (chronic only for the mouse).

There are no data gaps for the assessment of the effects of fipronil on developing animals following *in utero* and/or early postnatal exposure. This conclusion is based on the following acceptable studies: two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits. In addition, an acceptable developmental neurotoxicity study was conducted with fipronil. Although there is no evidence of potential for enhanced pre- or post-natal susceptibility in infants and children in the developmental and reproduction studies, the developmental neurotoxicity study identified a developmental no-observed-adverse-effect-level (NOAEL) which was less than the maternal NOAEL, indicating an apparent susceptibility issue. However, the HIARC concluded that the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence. The Food Quality Protection Act Safety Factor Committee (FQPA SFC) recommended that the 10x factor for enhanced sensitivity to infants and children (as required by FQPA) should be reduced to 1x for fipronil.

The fipronil photodegradate MB 46513, is not an animal metabolite. However, significant quantities are produced in certain crops (*e.g.*, rice). Therefore, it was determined that a hazard assessment for MB 46513 was needed. The HIARC concluded that there were differences as well as similarities between the toxicity profiles for fipronil and MB 46513. Differences included the occurrence of thyroid neoplasia in the rats treated with fipronil, but not MB 46513. Although, in the rat, both fipronil and MB46513 result in clinical signs of neurotoxicity, these signs do not appear with fipronil until later (after 90 days). Chronic exposure to the rat with both compounds results in qualitatively and quantitatively similar neurologic effects. Other measured signs of neurotoxicity (observed in the acute neurotoxicity study), appear to occur at about the same dose for both compounds. Therefore, it appears that, in the rat, the differences between the two compounds are qualitative for thyroid effects; but for neurotoxicity, the differences appear to be more quantitative, with longer exposure to fipronil needed in the rat to result in the same clinical signs as MB 46513. In the dog, the two compounds are similar for neurotoxicity. In the mouse, there is no neurotoxicity with fipronil, but there is with MB 46513. The HIARC

concluded that using the acute and chronic reference doses (RfDs) for fipronil to evaluate the risk due to acute and chronic dietary exposure to MB46513 is health protective because the acute and chronic RfDs for MB 46513 are based on the same study type with the same neurotoxicity endpoints; thus, the RfDs are similar. The HIARC also determined that the potential for increased susceptibility of infants and children from exposure to MB 46513 would be the same as fipronil; therefore, no separate FQPA evaluation is required.

The residues of concern in drinking water and food are fipronil plus metabolites MB46136 and MB45950, and photodegredate MB46513.

Dose Response Assessment

The acute dietary endpoint is based on decreased hindleg splay (a neurological deficit). The short- and intermediate-term incidental oral endpoints are based on decreased body weight, food consumption, and feed efficiency. Chronic dietary and long-term endpoints are based on increased incidence of seizures and death, alterations in clinical chemistry (protein) and changes in thyroid hormone levels.

This chemical has been classified by the HED Cancer Peer Review Committee (CPRC) as a Group C - Possible Human Carcinogen based on increases in thyroid follicular cell tumors in both sexes of the rat.

Occupational Exposure Assessments

Tolerances are established on many raw agricultural commodities. However, because this current action is for the establishment of a tolerance for imported rice only, the occupational risks from domestic uses are not included in this document. For full details on occupational risks from currently registered domestic uses, refer to the 06/19/2007 risk assessment (D331890).

Residue Chemistry

Residue chemistry data pertaining to the proposed use of fipronil on rice were reviewed by HED (D368740, W. Donovan, 08/25/2009). HED recommends a 0.04 ppm tolerance on rice, grain, and revocation of the rice, straw tolerance. Additional rice field trials are needed in Brazil to support the foliar application use pattern. Also, additional use pattern and field trial information is needed to confirm that the available field trial data adequately support the intended use patterns.

Residential Exposure Assessments

Residential application and re-entry exposures from the uses of fipronil on pets and from proposed residential uses of fipronil to control fire ants and other outdoor nuisance pests, were assessed previously (D244048, M. Dow and D. Vogel, 10/24/2000). Residential exposures to fipronil, for children and adults, are below HED's level of concern. Exposure to the photodegradate MB 46513 is not expected as a result of residential uses.

Dietary Risk Estimates

Acute and chronic dietary exposure analyses for fipronil (and metabolites/degredate of concern) were performed using the Dietary Exposure Evaluation Model (DEEM™ version 2.03). The unrefined acute dietary risk assessment (tolerance residues and 100% crop treated) and the refined chronic dietary risk assessment (residues from field trials and % crop treated values) for fipronil show that for all included food commodities and drinking water, the acute and chronic dietary risk estimates are below HED's level of concern. (D368732, P. Savoia, 09/17/2009).

Drinking Water

EFED provided an environmental fate and drinking water assessments for fipronil (+ its 2 metabolites and 1 photodegradate). Fipronil concentrations in surface source drinking water are not expected to exceed **0.002654 ppm** in acute scenarios and **0.000318 ppm** in chronic scenarios. Groundwater EECs (estimated environmental concentrations) for fipronil are lower than those for surface water.

Aggregate Exposure and Risk Assessment

Aggregate exposure risk assessments were performed for the following: acute aggregate exposure (food + water), short- and intermediate-term aggregate exposure (food + water + residential exposure), and chronic aggregate exposure (food + water). A cancer aggregate risk assessment was *not* performed because HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the chronic exposure assessment.

Acute aggregate risk estimates are below HED's level of concern. The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of fipronil (food and drinking water). For acute dietary risk estimates, HED's level of concern is >100% acute Population Adjusted Dose (aPAD). The acute analysis was performed assuming tolerance-level residues and that 100% of each crop was treated and included an anticipated concentration in water (acute) at 0.002654 ppm. Default processing factors were used for all commodities except for potato, flakes and potato, chips, both of which are dried potato commodities. These are usually given the default processing factor of 6.5. HED determined, via residue data, that the processing factors for these commodities are actually <1. Using a processing factor of 1 allows for a more refined estimate of the acute dietary exposure and risk. Acute dietary risk estimates were 9.6% of the aPAD at the 95th percentile for the general U.S. population and 25% of the aPAD for the highest exposure group, children 1-2 years old. The results of the acute analysis indicate that the **acute dietary risk estimates associated with the registered U.S. uses and proposed foreign uses of fipronil do not exceed HED's level of concern**. Additional refinement by incorporating %CT information may result in even lower exposure estimates.

Short + Intermediate aggregate risk estimates are below HED's level of concern. HED concludes that short- and intermediate-term aggregate risk for children and adults, respectively,

are below HED's level of concern. The Aggregate Risk Index method was used to determine both short- and intermediate-term aggregate risk based on the common endpoint of body weight loss. The children's aggregate risk assessment was conducted using chronic dietary (food + water) combined with dermal and oral exposures from pet uses. The adult aggregate risk assessment was conducted using chronic dietary (food + water) combined with dermal and inhalation exposures from fire ant applications. Child and adult aggregate risk estimates, 1.5 and 2.9, respectively, do not exceed HED's level of concern (i.e. ARIs are greater than or equal to 1).

Chronic aggregate risk estimates are below HED's level of concern. For chronic dietary risk estimates, HED's level of concern is >100% of the chronic population adjusted dose (cPAD). For the chronic analysis (assuming tolerance level residues, DEEM™ default processing factors, and 100% CT information), dietary risk estimates exceeded HED's level of concern (>100% cPAD); therefore, a refined chronic dietary assessment was performed with use of ARs from field trial data, percent crop treated information and processing factors where applicable and water (chronic) at 0.000318 ppm. Chronic dietary risk estimates were 36% of the cPAD for the general U.S. population and 95% of the cPAD for the highest exposed population subgroup, children 1-2 years; therefore, **chronic dietary risk estimates associated with the registered U.S. uses and the proposed foreign uses are below HED's level of concern**.

A cancer aggregate risk assessment was not performed because HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the chronic exposure assessment.

Recommendation for Tolerances and Registration

HED recommends in favor of maintaining the established tolerance for fipronil residues of concern (fipronil + metabolites MB46136 and MB45950 + photodegradate MB46513) in/on rice grain at 0.04 ppm as an import tolerance. The established tolerance for rice straw at 0.10 ppm should be removed or revoked since there are no U.S. registrations for fipronil, and rice straw is not a significant import commodity.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this 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/oepa/guidance/justice/eo12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, non-

dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Human Studies

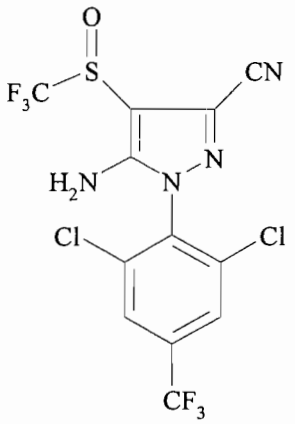
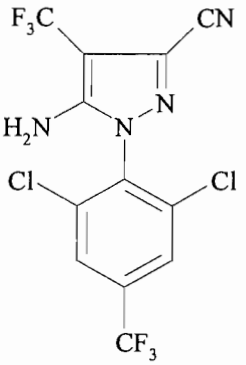
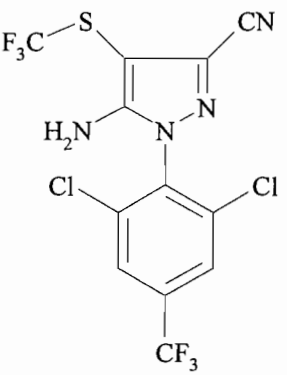
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review. The studies in PHED are considered appropriate (ethically conducted) for use in risk assessments.

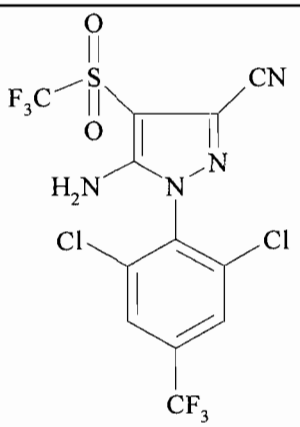
2.0. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1. Identification of Active Ingredient

Chemical Name:	(5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile)
Common Name:	Fipronil
Trade Name:	Regent®
Chemical Type:	Insecticide
PC Code Number:	129121
CAS Registry No.:	120068-37-3
Empirical Formula:	$C_{12}H_4Cl_2F_6N_4$
Molecular Weight:	437.15

2.2. Structural Formula of Fipronil, Metabolites, and Photodegradate

 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile Common Name: Fipronil	 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile Common Name: MB 46513
	

 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile Common Name: MB 46136	5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile Common Name: MB 45950

2.3. Physical and Chemical Properties

Vapor Pressure: 2.8×10^{-9} mm Hg at 20°C
Water Solubility: deionized water: 1.9 mg/L; water, pH 5: 0.0024 g/L; water, pH 9: 0.0022 g/L
Octanol/Water Partition Coefficient: log $P_{ow} = 4.01$

3.0. HAZARD CHARACTERIZATION

The toxicology database for fipronil is adequate according to the Subdivision F Guideline requirements for a food-use chemical. However, a 28-day inhalation toxicity study in the rat has been requested to further characterize the inhalation risk for use in the risk assessment of fipronil. Acceptable developmental studies in the rat and rabbit, a 2-generation rat reproduction study, and a developmental neurotoxicity rat study are available. There is high confidence in the quality of the existing studies and the reliability of the toxicity endpoints identified for use in risk assessment.

There is a new requirement for a series 807.7800 immunotoxicity study (see Appendix 1). The toxicology database for fipronil does not show any definite evidence of treatment-related effects on the immune system. Some decreases in the albumin to globulins were noted in the subchronic and/or chronic studies in rats but were not considered evidence for a direct immunotoxic effect. There were no alterations in leukocytes or effects on thymus or spleen weight reported. No indications of immunotoxicity were indicated in a search of the open literature. The overall weight of evidence suggests that fipronil does not directly target the immune system. Immunotoxicity study is required as a part of the new data requirements in the 40 CFR Part 158 for conventional pesticide registration, however, the Agency does not believe that conducting a functional immunotoxicity study will result in a lower POD than that currently used for overall

risk assessment, and therefore, a database uncertainty factor UF_{DB}) is not needed to account for lack of this study.

3.1. Hazard Profile

The acute toxicity of fipronil technical is shown in Table 1.

Table 1. Acute Toxicity Data on Fipronil Technical.

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity - rat	42918628	LD_{50} = male 92/female 103 mg/kg; male + female 97 mg/kg	II
870.1200 Acute dermal toxicity - rat	42918629	LD_{50} = >2000 mg/kg	III
870.1200 Acute dermal toxicity - rabbit	42918630	LD_{50} = 354 mg/kg	II
870.1300 Acute inhalation toxicity - rat	43544401	LC_{50} = male 0.36/female 0.42 mg/L; male + female 0.39 mg/L	II
870.2400 Acute eye irritation - rabbit	42918632	mild transient ocular irritant	III
870.2500 Acute dermal irritation - rabbit	42918633	slight dermal irritant	IV
870.2600 Skin sensitization - Guinea pig	42918634	non sensitizing	

In acute toxicity studies, fipronil exhibits low to moderate toxicity, depending on the route of exposure and species. Fipronil has moderate acute toxicity (toxicity category II) by the oral and inhalation routes in rats. By the dermal route, it is of moderate toxicity in rabbits, and low toxicity in rats (III). Fipronil technical is relatively non-irritating to the skin (IV) and eye (III) of rabbits and is not a dermal sensitizer. Dermal absorption in rats is estimated to be 1 % or less based on a dermal absorption study.

Fipronil is neurotoxic in both rats and dogs as evidenced by signs in the acute and subchronic screening batteries in the rat; developmental neurotoxicity and chronic carcinogenicity studies in the rat; and in two chronic dog studies. Clinical signs of neurotoxicity were not observed in the mouse or rat at 28 or 90 days. The rat and mouse showed evidence of liver and/or thyroid alterations at all time periods (chronic only for the mouse).

Fipronil has been classified by the HED CPRC (document dated 18-Jul-1997) as a Group C - Possible Human Carcinogen, based on increases in thyroid follicular cell tumors in both sexes of the rat, which were statistically significant by both pair-wise and trend analyses. There is no apparent concern for mutagenicity (no mutagenic activity). The RfD methodology should be used to estimate human risk because the thyroid tumors appear to be related to a disruption in the thyroid-pituitary status. Dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the DEEM™ chronic exposure analysis using the RfD.

Fipronil appears to be orally absorbed at a similar rate and extent at low or high dosages. Distribution data showed significant amounts of residual radioactivity in carcass, G.I. tract, liver, adrenals, and abdominal fat at 168 hours post-dose. Repeated low oral dosing or a single high oral dose resulted in an overall decrease in the amount of residual radioactivity found, but an increase in the amount in abdominal fat, carcass, and adrenals. Feces appeared to be the major route of excretion for fipronil derived radioactivity, where 45-75% of an administered dose was excreted. Excretion in urine was between 5-25%. Increases in the percentages excreted in urine and feces were observed with repeated low oral dosing or a single high dose, while the percentage found in all tissues combined decreased. There were no significant sex-related differences in excretion. Major metabolites in urine included two ring-opened products of the metabolite MB 45897, two oxidation products (MB 46136 and RPA 200766), and parent chemical (MB 46030). In feces, parent MB 46030 was detected as a significant fraction of the sample radioactivity as well as the oxidation products MB 46136 and MB 45950. Whole blood half-life decreased with increased dosage. The toxicity profile of fipronil (technical) is listed in Table 2.

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
	FIPRONIL	
Fipronil 870.3100 28-Day oral toxicity range finding - rat	44028301 (1996) Acceptable/guideline 0, 25, 50, 100, 200, 400 ppm _ 0, 3.4, 6.9, 13, 24, 45 mg/kg/day _ 0, 3.5, 6.7, 13, 25, 55 mg/kg/day	NOAEL = male <3.4 mg/kg/day LOAEL = 3.4 mg/kg/day based on: (male/female) thyroid follicular hypertrophy, change in protein, and (female) increased liver weight.
Fipronil 870.3100 90-Day oral toxicity - rat	42918643, 43501701 (1991) minimum 0, 1, 5, 30, 300 ppm M 0, 0.70, 0.33, 1.9, 20 mg/kg/day F 0, 0.070, 0.37, 2.3, 24 mg/kg/day	NOAEL = 0.33 mg/kg/day LOAEL = 1.9 mg/kg/day based on: altered serum protein, increased liver, and thyroid weight.

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Fipronil 870.3100 90-Day oral toxicity - mouse	44262804 (1991) Acceptable/nonguideline 0, 1, 3, 10, 25 ppm M 0, 0.13, 0.38, 1.3, 3.2 mg/kg/day F 0, 0.17, 0.57, 1.7, 4.5 mg/kg/day	NOAEL = 1.3 mg/kg/day LOAEL = 3.2 mg/kg/day based on: increased body weight gain (BWG).
Fipronil 870.3150 90-Day oral toxicity - dog	42918642 (1991) guideline capsule 0, 0.5, 2.0, 10 mg/kg/day	NOAEL = male 2.0 mg/kg/day, female 0.5 mg/kg/day LOAEL = male 10 mg/kg/day, female 2.0 mg/kg/day based on: clinical signs of toxicity (male/female), and increased BWG (female).
Fipronil 870.3200 21-Day dermal toxicity - rabbit	42918644 (1993) guideline 0, 0.5, 1.0, 5.0, 10 mg/kg/day	systemic NOAEL = 5.0 mg/kg/day LOAEL = 10 mg/kg/day based on: decreased BWG, decreased food consumption (FC), and hyperactivity. dermal NOAEL = 10 mg/kg/day LOAEL = >10 mg/kg/day.
Fipronil 870.3700a Prenatal developmental - rat	42977903 (1991) minimum 0, 1.0, 4.0, 20 mg/kg/day	**Maternal** NOAEL = 4.0 mg/kg/day LOAEL = 20 mg/kg/day based on: decreased BWG, increased water consumption (WC), decreased FC, and decreased food efficiency (FE). **Developmental** NOAEL = 20 mg/kg/day LOAEL =>20 mg/kg/day.
Fipronil 870.3700b Prenatal developmental - rabbit	42918646 (1990) minimum 0, 0.10, 0.20, 0.50, 1.0 mg/kg/day	**Maternal** NOAEL = <0.10 mg/kg/day LOAEL = 0.10 mg/kg/day based on: decreased BWG, decreased FC, and decreased FE. **Developmental** NOAEL = 1.0 mg/kg/day LOAEL = >1.0 mg/kg/day.
Fipronil 870.3800 Reproduction and fertility effects - rat	42918647 (1992) minimum 0, 3.0, 30, 300 ppm M 0, 0.25, 2.5, 26 mg/kg/day F 0, 0.27, 2.7, 28 mg/kg/day	**Parental/Systemic** NOAEL = 0.25 mg/kg/day LOAEL = 2.5 mg/kg/day based on: (male/female) increased thyroid, and liver weight, (female) decreased pituitary weight, and increased follicular epithelial hypertrophy. **Reproductive** NOAEL = 2.5 mg/kg/day LOAEL = 26 mg/kg/day based on: clinical signs, decreased litter size, decreased BW, decreased mating, decreased fertility index, decreased post-implant survival and offspring postnatal survival, and delayed physical development. **Offspring** NOAEL = 26 mg/kg/day LOAEL = >26 mg/kg/day.
Fipronil 870.4100a Chronic toxicity - rodent	42918648 (1993) Acceptable/guideline 0, 0.5, 1.5, 300 ppm M 0, 0.019, 0.059, 1.3, 13 mg/kg/d	NOAEL = 0.019 mg/kg/day LOAEL = 0.059 mg/kg/day based on: clinical signs, alterations in clinical chemistry, and thyroid parameters.

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
	F 0, 0.025, 0.078, 1.6, 17 mg/kg/d	
Fipronil 870.4100b Chronic toxicity – dog	42918645 (1993) Acceptable dietary 0, 0.075, 0.30, 1.0, 3.0/2.0 mg/kg/day (constant conc.)	NOAEL = M 1.0 mg/kg/day; F 0.30mg/kg/day LOAEL = M 2.0 mg/kg/day; F 1.0 mg/kg/day based on: clinical signs of neurotoxicity.
Fipronil 870.4100b Chronic toxicity – dog	42918645 (1992) guideline capsule 0, 0.2, 2.0, 5.0 mg/kg/day	NOAEL = 0.2 mg/kg/day LOAEL = 2.0 mg/kg/day based on: (male/female) decreased BWG, increased liver weight, liver histopath, and (male) decreased FE and clinical signs of neurotoxicity.
Fipronil 870.4200 Carcinogenicity - rat	42918648 (1993) Acceptable/guideline 0, 0.5, 1.5, 300 ppm M 0, 0.019, 0.059, 1.3, 13 mg/kg/d F 0, 0.025, 0.078, 1.6, 17 mg/kg/d	NOAEL = M 0.019 mg/kg/day, F 0.025 mg/kg/day LOAEL = M 0.059 mg/kg/day based on clinical signs, alterations in clinical chemistry, and thyroid parameters. F 0.078 mg/kg/day based on clinical signs, alterations in clinical chemistry, and thyroid parameters. **Evidence of thyroid carcinogenicity.**
Fipronil 870.4300 Carcinogenicity mouse	42918649, 43501702 (1993) minimum 0, 0.10, 0.50, 10, 30, 60 ppm M 0, 0.011, 0.055, 1.2, 3.4 mg/kg/day F 0, 0.012, 0.063, 1.2, 3.6 mg/kg/day	NOAEL = 0.055 mg/kg/day LOAEL = 1.2 mg/kg/day based on decreased BWG, decreased FE, increased liver weight, and liver histopath. **No evidence of carcinogenicity.**
Gene Mutation Fipronil 870.5100 *Salmonella typhimurium* and *Escherichia coli*	42918652 (1988) Acceptable	In two independent experiments, fipronil (90.6% a.i.) was not mutagenic in 4 strains of S. typhimurium at concentrations up to 500 µg/plate in the presence or absence of S9 activation.
Gene Mutation Fipronil 870.5300 *In vitro* assay in mammalian cells/Chinese hamster V79 cells	42918651 (1993) Acceptable	In two independent experiments, fipronil (97.2% a.i.) was negative for inducing forward gene mutations at the HGPRT locus in cultured Chinese hamster V79 cells at concentrations up to 385.65 µg/ml both with and without S9 activation.
Cytogenetics Fipronil	42918653 (1988)	There was no evidence of a clastogenic effect when human lymphocytes were exposed *in vitro* to fipronil (90.6% a.i.) at

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5375 *in vitro*/human lymphocytes	Acceptable	doses of 75, 150 or 300 µg/ml with and without S9 activation.
Cytogenetics Fipronil 870.5395 *In vivo* mouse micronucleus assay	43680801 (1995) Acceptable	There was no evidence of a clastogenic or aneugenic effect at any MB46030 dose or at any harvest time.
Other Effects Fipronil	none	no study
Fipronil 870.6200a - rat Acute neurotoxicity screening battery	42918635 (1993) minimum 0, 0.5, 5.0, 50 mg/kg	NOAEL = 0.5 mg/kg LOAEL = 5.0 mg/kg based on: decreased hindlimb splay.
Fipronil 870.6200a - rat Acute neurotoxicity screening battery	44431801 (1997) Acceptable(guideline)	NOAEL = 2.5 mg/kg LOAEL = 7.5 mg/kg based on: (male) decreased hindlimb splay; (female) decreased BW, FC, FE, and grooming.
Fipronil 870.6200b - rat Subchronic neurotoxicity screening battery	43291703 (1993) Acceptable 0, 0.5, 5.0, 150 ppm M 0, 0.030, 0.30, 8.9 mg/kg/day F 0, 0.035, 0.35, 11 mg/kg/day	NOAEL = 0.30 mg/kg/day LOAEL = 8.9 mg/kg/day based on: FOB findings.
Fipronil 870.6300 Developmental neurotoxicity - rat	44039002, 44501102, 44501103 (1995) Acceptable/guideline 0, 0.5, 10, 200 ppm 0, 0.05, 0.90, 15 mg/kg/day	**Maternal** NOAEL = 0.9 mg/kg/day LOAEL = 15 mg/kg/day based on: decreased BW, decreased BWG, and decreased FC. **Developmental** NOAEL = 0.05 mg/kg/day LOAEL = 0.9 mg/kg/day based on decreased pup wt, increased preputial separation time. **Neurotox** NOAEL = 0.9 mg/kg/day LOAEL = 15 mg/kg/day based on decreased auditory startle response, decreased swimming direction scores, group mean angle measurements and water "Y" maze times trails, and decreased absolute brain weight.
Fipronil 870.7485 Metabolism and pharmacokinetic –	42918655, 43253701 (1992) minimum 4, 150 mg/kg-single dose 4 mg/kg x 14 days-	The rate and extent of absorption appeared similar among all dose groups (4 and 150 mg/kg (single dose) and 4 mg/kg x 14 days (repeated dose)), but may have been decreased at the high dose. Distribution data showed significant amounts of residual radioactivity in carcass, G.I. tract, liver, adrenals,

Table 2. Toxicity Profile of Fipronil Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
rat	repeated dose	and abdominal fat at 168 hours post-dose for all rats in all dose groups. Repeated low oral dosing or a single high oral dose resulted in an overall decrease in the amount of residual radioactivity found, but an increase in the amount in abdominal fat, carcass, and adrenals. Feces appeared to be the major route of excretion for fipronil derived radioactivity (45-75%). Excretion in urine was between 5-25%. Increases in the % excreted in urine and feces were observed with repeated low or a single high doses, while the % found in all tissues combined decreased. There were no significant sex-related differences in excretion. Major metabolites in urine included two ring-opened products of the metabolite MB 45,897, two oxidation products, and the parent chemical. In feces, parent was detected as a significant fraction of the sample radioactivity as well as the oxidation products. Whole blood half- life ranged from 149-200 hours in male and female rats at 4 mg/kg, with 0-168 hours. Area under curves (AUCs) approximately equal between sexes. At 150 mg/kg, whole blood half life was noticeably decreased to 54.4 hours in male rats and 51.2 hours in female rats. Blood AUCs at this dose were approximately proportional to the increase in dose.
Fipronil 870.7600 Dermal penetration - rat	43737308 (1995) Acceptable	<1% at 24 hours.

3.2. FQPA Considerations

The HIARC concluded that there is no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to fipronil. In the prenatal developmental toxicity studies in rats and rabbits and in the two-generation reproduction study in rats, developmental toxicity was not detected in the offspring. However, the developmental neurotoxicity study identified a developmental NOAEL (0.05 mg/kg/day) which is less than the maternal NOAEL of 0.9 mg/kg/day, indicating an apparent susceptibility issue (HIARC Memos, HED Doc. No. 0014399 and 0014400, M. Copley, 12/6/2000) .

The HIARC, however, determined that the evidence regarding appearance of susceptibility was not convincing due to the equivocal nature of the findings (decrease in offspring body weight and delayed time to preputial separation) at 0.9 mg/kg/day. The HIARC, using a conservative approach, established the LOAEL for offspring developmental toxicity at 0.9 mg/kg/day with the understanding that these effects, although statistically significant, were marginal and appeared to define a threshold response level. This conservative approach resulted in the NOAEL for offspring developmental toxicity (0.05 mg/kg/day) being lower than the NOAEL for maternal

toxicity (0.9 mg/kg/day) giving an appearance of increased susceptibility. The HIARC, however, concluded that this increased susceptibility is not valid because the findings in the developmental neurotoxicity study were not supported by the overall weight-of-the-evidence from the fipronil database. Evaluation of the database indicated that: 1) the offspring body weight findings in the developmental neurotoxicity study are not supported by the results of the two-generation reproduction study in rats at similar treatment levels; 2) increased susceptibility to the offspring was not demonstrated in the prenatal developmental toxicity study nor the two-generation reproduction study in rats; and 3) no increased susceptibility was seen in the prenatal developmental toxicity study in rats following *in utero* exposure to the photodegradate, MB 46513.

The FQPA Safety Factor Committee (SFC) met on 04/27/1998 and recommended that the 10x factor for enhanced sensitivity to infants and children (as required by FQPA) should be reduced to 1x for fipronil (Memo, HED Doc. No. 012619, B. Tarplee, 05/12/1998). The rationale behind this decision was:

- The HIARC determined that the data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to fipronil. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats. There was no developmental or offspring toxicity at the highest doses tested which demonstrated maternal toxicity.

- No increased susceptibility was seen in the prenatal developmental toxicity study in rats following *in utero* exposure to the photodegradate, MB 46513.

- The HIARC concluded that the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence.

- Exposure assessments do not indicate a concern for potential risk to infants and children based on: 1) the dietary exposure estimates using field study data and anticipated market share information result in an overestimate of dietary exposure; 2) modeling data is used for ground and surface source drinking water exposure assessments resulting in estimates considered to be reasonable upper-bound concentrations; 3) there is the potential for residential exposure associated with the pet uses, however, the use of chemical and site specific data in the exposure assessment provide a realistic estimate of the potential exposure to infants and children.

3.2.1. Cumulative Risk

EPA does not have, at this time, available data to determine whether fipronil has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that

fipronil has a common mechanism of toxicity with other substances.

3.2.2. Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fipronil may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

3.3. Dose Response Assessment

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Dose and Endpoints for Fipronil for Use in Human Risk Assessment[1].

Exposure Scenario (Fipronil)	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations including infants and children	NOAEL= 2.5 mg/kg UF = 100 **Acute RfD** = 0.025 mg/kg	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.025 mg/kg	Acute neurotoxicity - rat LOAEL = 7.0 mg/kg based on: decreased hindleg splay in males at 7 hours.
Chronic Dietary all populations	NOAEL= 0.019 mg/kg/day UF = 100 **Chronic RfD** = 0.0002 mg/kg/day	FQPA SF = 1 **cPAD** = chr RfD / FQPA SF = 0.0002 mg/kg/d	Chronic/carcinogenicity study - rat LOAEL = 0.059 mg/kg/day based on: increased incidence of seizures and death, alterations in clinical chemistry (protein), increased TSH, and decreased T4.
Short-Term Oral	oral study	**LOC for MOE** = 300	Developmental toxicity Study - rabbit

Table 3. Summary of Toxicological Dose and Endpoints for Fipronil for Use in Human Risk Assessment[1].

Exposure Scenario (Fipronil)	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
(1-7 days)	LOAEL ≤0.1 mg/kg/day UF of 3 for no NOAEL, 100 for interspecies extrapolation and intraspecies variation	(Residential, includes the FQPA SF)	LOAEL = ≤ 0.1 mg/kg/day based on: maternal toxicity of decreased body weight gain, decreased food consumption, and decreased food efficiency.
Intermediate-Term Oral (1 week - several months)	oral study LOAEL ≤0.1 mg/kg/day UF of 3 for no NOAEL, 100 for interspecies extrapolation and intraspecies variation	**LOC for MOE** = 300 (includes the FQPA SF)	Developmental Toxicity Study - rabbit LOAEL = ≤ 0.1 mg/kg/day based on: maternal toxicity of decreased body weight gain, decreased food consumption, and decreased food efficiency.
Short-Term Dermal (1-7 days)	dermal study NOAEL= 5 mg/kg/day	**LOC for MOE** = 100 (includes FQPA SF)	21-Day dermal toxicity study - rabbit LOAEL = 10.0 mg/kg/day based on: decreased body weight gain, and food consumption in both sexes.
Intermediate-Term Dermal (1 week - several months)	dermal study NOAEL= 5 mg/kg/day	**LOC for MOE** = 100 (includes FQPA SF)	21-Day dermal toxicity study - rabbit LOAEL = 10.0 mg/kg/day based on: decreased body weight gain, and food consumption in both sexes.
Long-Term Dermal (several months - lifetime)	oral study NOAEL= 0.019 mg/kg/day (dermal absorption rate = 1%)	**LOC for MOE** = 100 (includes FQPA SF)	Chronic/carcinogenicity study - rat LOAEL = 0.059 mg/kg/day based on: increased incidence of seizures and death, alterations in clinical chemistry (protein), increased TSH, and decreased T4.
Short-Term Inhalation (1-7 days)	oral study NOAEL= 0.05 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (includes FQPA SF)	Developmental neurotoxicity - rat LOAEL = 0.90 mg/kg/day based on: decrease in group mean pup weights during lactation, and significant increase in time of preputial separation in males (dietary).
Intermediate-Term Inhalation (1 week - several months)	oral study NOAEL= 0.05 mg/kg/day (inhalation	**LOC for MOE** = 100 (includes FQPA SF)	Developmental neurotoxicity - rat LOAEL = 0.90 mg/kg/day based on: decrease in group mean pup weights during lactation, and significant increase in time of

Table 3. Summary of Toxicological Dose and Endpoints for Fipronil for Use in Human Risk Assessment[1].

Exposure Scenario (Fipronil)	Dose Used in Risk Assessment, UF	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
	absorption rate = 100%)		preputial separation in males (dietary).
Long-Term Inhalation (several months - lifetime)	oral study NOAEL= 0.019 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (includes FQPA SF)	Chronic/carcinogenicity rat study LOAEL = 0.059 mg/kg/day based on: increased incidence of seizures and death, alterations in clinical chemistry (protein), increased TSH, and decreased T4.
Cancer (oral, dermal, inhalation)	Group C - possible human carcinogen	Use chronic RfD to estimate human risk	Increases in thyroid follicular cell tumors with fipronil (male/female)

[1] UF = uncertainty factor, FQPA SF = FQPA Safety Factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, MOE = margin of exposure.

Acute Dietary Endpoint: The rat acute oral neurotoxicity study was used to derive the endpoint for the acute RfD of 0.025 mg/kg for the general U.S. population (including infants and children). The NOAEL of 2.5 mg/kg was based on decreased hindlimb splay in males at 7 hours post-dosing at the LOAEL of 7.0 mg/kg. These effects occurred following a single dose in the acute neurotoxicity study and therefore are appropriate for use in the acute dietary risk assessment. An UF of 100 was established for intraspecies variation (10x) and interspecies extrapolation (10x). The FQPA SFC determined that the SF of 1x is applicable for this acute dietary risk assessment. Thus, the aPAD for the general U.S. population (including infants and children) is equivalent to the acute RfD of 0.025 mg/kg.

Chronic Dietary Endpoint: The rat combined chronic toxicity/carcinogenicity study was used to derive the endpoint for establishing the chronic RfD of 0.0002 mg/kg/day. The NOAEL of 0.019 mg/kg/day was based on increased incidences of seizures and death, alterations in clinical chemistry (protein), and increased TSH and decreased T4 blood levels at the LOAEL of 0.059 mg/kg/day. An UF of 100 was established for intraspecies variation (10x) and interspecies extrapolation (10x). The FQPA SFC determined that the SF of 1x is applicable for chronic dietary risk assessment. Thus, the cPAD is equivalent to the chronic RfD of 0.0002 mg/kg/day.

Carcinogenicity: This chemical has been classified by the HED CPRC (document dated July 18, 1997) as a Group C - Possible Human Carcinogen. The RfD methodology should be used to estimate human risk because the thyroid tumors appear to be related to a disruption in the thyroid-pituitary status.

Short- and Intermediate-Term Incidental Oral: Short- and intermediate-term oral incidental

endpoints were selected from a rabbit developmental study. The LOAEL of 0.1 mg/kg/day was based on maternally toxic effects including decreased body weight gains, food consumption, and food efficiency. No NOAEL was established in this study.

Dermal Penetration: The dermal absorption factor is 1%.

Short- and Intermediate-Term Dermal Endpoint: A short- and intermediate-term dermal endpoint was selected from a rabbit 21-day dermal toxicity study. The NOAEL of 5 mg/kg/day was based on decreased body weight gain and food consumption in both sexes at the LOAEL of 10 mg/kg/day. This dose/endpoint is appropriate for short- and intermediate-term exposure risk assessment.

Long-term Dermal Endpoint: A long-term dermal endpoint was selected from a rat combined chronic toxicity/carcinogenicity study. The NOAEL of 0.019 mg/kg/day was based on an increased incidence of seizures and death, alterations in clinical chemistry (protein), and increased TSH and decreased T4 blood levels at the LOAEL of 0.059 mg/kg/day. This dose/endpoint is appropriate for long-term exposure risk assessment. Since an oral NOAEL was used for dermal risk assessment, the dermal absorption factor of 1% was used.

Short- and Intermediate-term Inhalation Endpoint: A short- and intermediate-term inhalation endpoint was chosen from a rat developmental neurotoxicity study. The NOAEL of 0.05 mg/kg/day was based on decreased group mean pup weights during lactation and increased preputial separation in males at the LOAEL of 0.90 mg/kg/day. This dose/endpoint is appropriate for short- and intermediate-term exposure risk assessment. An inhalation absorption factor of 100% was used.

Long-term Inhalation Endpoint: A long-term inhalation endpoint was selected from a rat combined chronic toxicity/carcinogenicity study. The NOAEL of 0.019 mg/kg/day was based on an increased incidence of seizures and death, alterations in clinical chemistry (protein), and increased TSH and decreased T4 blood levels at the LOAEL of 0.059 mg/kg/day. This dose/endpoint is appropriate for long-term exposure risk assessment. An inhalation absorption factor of 100% was used.

MOE for /Residential Risk Assessments: The level of concern for MOEs for short-and intermediate-term incidental oral risk assessment is 300. The level of concern for MOEs for dermal and inhalation occupational and non-occupational exposure risk assessment is 100. For long-term dermal and short-, intermediate-, and long-term inhalation exposures, the following route-to-route extrapolation was followed: the inhalation (using 100% absorption) and dermal (using 1% absorption) exposures were converted to equivalent oral doses, combined, and then compared to their respective oral NOAELs since one of the dermal and all of the inhalation endpoints are based on oral equivalents.

4.0. EXPOSURE ASSESSMENT

4.1. Summary of Proposed Uses

Table 4. Summary of Directions for Use of Fipronil.					
Applic. Timing, Type, and Equip.	Trade Name	Applic. Rate	Max. No. Applic. per Season	Max. Seasonal Applic. Rate	PHI (days)
Rice (Australia)					
Seed treatment (apply as a spray to seed prior to sowing)	Cosmos® Insecticidal Seed Treatment	20 mL/ 100 kg seed or 25 mL/ha	1	25 mL/ha	None
Use Directions and Limitations: No grazing restrictions for rice when used as directed.					
Rice (Brazil)					
Seed treatment (apply diluted insecticide over seeds, let seeds dry in shade prior to planting)	Standak	120-250 mL/ 100 kg seed [30.0-62.5 g ai/ 100 kg seed]	Not specified (NS)	NS	None
Spray application using a pulverizer adapted with a jet nozzle	KLAP	20-60 mL product/ ha [4-12 g ai/ha]	NS	NS	30 (safety interval)
Rice (box seedling; Japan)					
Mix uniformly with bed soil in seedling box, before sowing Broadcast uniformly from upside of seedling box, sowing time (before soil covering)	Prince ARASHI Granules	50 g ai/one box [seedling box 30x60x3 cm, approximately 5L soil]	1	50 g ai/one box [seedling box 30x60x3 cm, approximately 5L soil]	None

Conclusions. The submitted use directions information for Australia is not adequate to allow evaluation of the residue data relative to the proposed/registered uses as Section B does not include information on formulation type and a.i. percentages/product density so that applications rates could be converted from product to active ingredient. The submitted use information for Brazil (seed treatment) is adequate to allow evaluation of the residue data relative to the proposed uses; however, the submitted use information for Brazil (spray application) does not include maximum number of applications per season and/or maximum seasonal rate. The submitted use directions information for Japan is adequate to allow evaluation of the residue data relative to the proposed/registered uses. The petitioner should provide information pertaining to typical application patterns in the countries of use. In addition, the petitioner should provide assurance that the only countries in which their fipronil products will be used on rice destined for import into the U.S. are Australia, Brazil, and Japan.

4.2. Dietary Exposure

4.2.1. Food Exposure

Residue chemistry data pertaining to the proposed use of fipronil on imported rice were submitted and reviewed by HED (D368740, W. Donovan, 25-AUG-2009).

4.2.1.a. Nature of the Residue - Plants and Livestock

Residue Chemistry Memo (PP#7F4832): DP#s 235887, 239164, 239161, 239155, 239594, and 239006, 12/15/97, G.Kramer
HED Metabolism Committee Meeting of 5/28/97: DP# 236164, 6/5/97, R. Loranger

Plants

The qualitative nature of the residue in rice is adequately understood based on a metabolism study in which rice plants were separately treated with [phenyl-14C]fipronil as a granular application and a foliar application. The study was reviewed in support of PP#7F4832.

The HED Metabolism Committee, in a meeting held on 5/28/97, has determined that the fipronil residues of concern for the tolerance expression and dietary risk assessment in plants are the parent and its metabolites MB 46136 and MB 45950. The Committee also concluded that residue data for metabolite MB 46513 will be required for crops for which metabolism data indicate that this metabolite comprises a significant portion of the total radioactive residue (i.e., rice, potatoes, and rotational crops). Metabolite MB 46513 was identified as a significant component in/on rice commodities. HED concurs with the petitioner that the residues of concern for the proposed tolerances are fipronil and its metabolites MB 45950, MB 46136, and MB 46513.

Livestock

The nature of the residue in livestock is understood. Fipronil is metabolized by: 1) hydrolysis to the amide (RPA 200766), 2) oxidation to the sulfone MB 46136, or 3) reduction to MB 45950. The HED Metabolism Assessment Review Committee (MARC), in a meeting held on 5/28/97, has determined that the fipronil residues of concern for the tolerance expression and dietary risk assessment in livestock commodities are the parent, the metabolites MB 46136 and MB 45950, and photodegradate MB 46513 (D236164, R. Loranger, 05-JUN-1997). Even though the photodegradate MB 46513 is not an animal metabolite, it is included in the tolerance expression for livestock commodities in order to account for the transfer of secondary residues to livestock feed items and then to human consumption.

4.2.1.b. Residue Analytical Method - Plants and Livestock

Plants

An adequate enforcement method is available for determination of fipronil and its metabolites MB 45950 and MB 46136, and photodegradate MB 46513 in plants. The data-collection methods used in the Australian, Brazilian and Japanese rice studies were generally adequately validated in conjunction with the field trials. Although the Japanese studies did not include validation at the reported data-collection method LOQ (0.001 ppm for rice grain), validation data were provided at the LOQ of the enforcement method (0.01 ppm).

Livestock

A method for the determination of residues of fipronil and its metabolites MB 45950 and MB 46136 in livestock commodities was previously reviewed in conjunction with a petition for corn and livestock RACs (PP#5F04426). It has undergone a successful PMV and a revised method has been submitted. The requirements for analytical enforcement methodology are fulfilled. The livestock method has been forwarded to FDA for inclusion in PAM II.

4.2.1.c. Multiresidue Methods

A report on multiresidue testing of fipronil and its metabolites MB 45950 and MB 46136 has been received and forwarded to FDA. Acceptable recoveries of fipronil and its metabolites MB 45950 and MB 46136 were obtained in corn forage using Protocol E. Recoveries in forage were 38-65% using Protocol E. A report on Multiresidue testing of photodegradate MB 46513 has been received and forwarded to FDA. Acceptable recoveries of MB 46513 were obtained in corn forage using Protocol E and cottonseed using Protocol F. Recoveries were 98.6 ± 9.4% using Protocol E and 89 ± 6.2% using Protocol F.

4.2.1.d. Storage Stability Data

The available storage stability data for corn and cotton commodities are adequate and may be translated to validate the integrity of samples collected from the rice field trials. Ordinarily, HED would require submission of confirmatory information pertaining to sample storage and durations. However, for the current petition, such confirmatory data will not be requested for the following reasons: 1) the lack of stability issues observed with fipronil and its metabolites in corn and cotton matrices for 1-2 years of frozen storage, 2) the maximum storage duration in the rice field trials was approximately 9 months, and 3) the lack of any detectable residues in the rice field trials.

4.2.1.e. Crop Field Trials

Table 5. Summary of Residue Data from Rice Field Trials with Fipronil.										
Crop matrix	Analyte	Total Applic. Rate (lb ai/A) [g ai/ha]	PHI (days)	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Australia (proposed use: seed treatment at 20 mL product/100 kg seed or 25 mL product/ha)										
Rice, grain	Total [2]	0.011 [12.5]	144	2	<0.008	<0.008	<0.008	<0.008	<0.008	Not applicable
		0.022 [25]	144-215	7	<0.008	<0.008	<0.008	<0.008	<0.008	Not applicable
		0.045 [50]	144-215	7	<0.008	<0.008	<0.008	<0.008	<0.008	Not applicable
		0.089 [100]	167-215	5	<0.008	<0.008	<0.008	<0.008	<0.008	Not applicable
Brazil (proposed use: seed treatment at 120-250 mL product/100 kg seed or 30-62.5 g ai/100 kg seed)										
Rice, grain	Total [2]	75 g ai/ha/ 120 kg of seed	112-176	12	<0.04	<0.04	<0.04	<0.04	<0.04	Not applicable
		150 g ai/ha/ 120 kg of seed	112-176	12	<0.04	<0.04	<0.04	<0.04	<0.04	Not applicable
		250 g ai/ 100 kg of seed	167-189	9	<0.04	<0.04	<0.04	<0.04	<0.04	Not applicable
		500 g ai/ 100 kg of seed	167-189	9	<0.04	<0.04	<0.04	<0.04	<0.04	Not applicable
Brazil (proposed use: spray application at 4-12 g ai/ha, 30-day PHI)										
Rice, grain	Fipronil	0.089 [100]	30	4	<0.01	<0.01	<0.01	<0.01	<0.01	Not applicable
		0.178 [200]	30	4	<0.01	<0.01	<0.01	<0.01	<0.01	Not applicable
Japan (proposed use: 50 g ai/one box [seedling box 30x60x3 cm, approximately 5L soil])										
Rice, grain	Total [2]	50 g ai/ box	118-141	10	<0.004	<0.004	<0.004	<0.004	<0.004	Not applicable
Rice, straw	Total [2]	50 g ai/ box	118-141	10	<0.04	0.27	0.25	0.08	0.11	0.08

[1] HAFT = Highest average field trial result.
[2] Includes fipronil, MB 45950, MB 46136, and MB 46513.

Conclusions. The submitted residue data reflecting seed treatment generally appear to reflect the proposed use pattern in Australia, Brazil, and Japan. The results showed that following preplant seed treatment at rates approximating the proposed rates for each country, the maximum fipronil residues of concern (fipronil, MB 45950, MB 46136, and MB 46513) in/on treated rice grain samples were below the respective combined LOQs (<0.008 ppm from Australia, <0.04 ppm from Brazil, and <0.004 ppm from Japan). The submitted residue data reflecting foliar treatment in Brazil are inadequate because samples were only analyzed for fipronil *per se*. Residues of fipronil *per se* were below the LOQ (<0.01 ppm) in/on rice grain harvested 30 days following a single foliar application of a suspension concentrate formulation at 100 g ai/ha (0.089 lb ai/A) or 200 g ai/ha (0.178 lb ai/A). HED concludes that the proposed seed treatment uses are supported by adequate residue data pending submission of confirmatory information pertaining to typical application patterns as well as field trial parameters. The proposed foliar use pattern for rice grown in Brazil is inadequate, and additional data reflecting this use pattern are required.

4.2.1.f. Processed Food/Feed

An adequate rice processing study was submitted in conjunction with a previous petition (PP#7F04832). The available data indicate that total residues of fipronil and its metabolites MB 45950, MB 46136, MB 46513, and RPA 200766 are less than the LOQ (<0.01 ppm) in/on rice grain harvested at maturity following preplant incorporated broadcast application of the 80% WDG formulation at ~0.25 lb ai/A (5x the maximum previously established U.S. seasonal rate) or seed treatment with a 10% liquid formulation equivalent to ~0.30 lb ai/A at the stated seeding rate (6x). Because treatment at the exaggerated rate did not result in quantifiable levels of fipronil residues of concern in rice grain, all further requirements for the processing study are waived, and no tolerances are required for the processed commodities of rice.

4.2.1.g. Meat, Milk, Poultry and Eggs

Secondary residues are expected in livestock commodities associated with registered and proposed uses. Meat/milk/poultry/egg tolerances have been established as a result of other fipronil uses (40 CFR §180.517a: fat of cattle, goat, horse and sheep, 0.40 ppm; liver of cattle, goat, horse and sheep, 0.10 ppm; meat byproducts (except liver) of cattle, goat, horse and sheep, 0.04 ppm; meat of cattle, goat, horse and sheep, 0.04 ppm; hog fat, 0.04 ppm; hog liver, 0.02 ppm; hog meat, 0.01 ppm; hog meat byproducts (except liver), 0.01 ppm; milk, fat (reflecting 0.05 ppm in whole milk), 1.50 ppm; poultry fat, 0.05 ppm; poultry meat, 0.02 ppm; poultry meat byproducts, 0.02 ppm; and eggs, 0.03 ppm). HED estimates indicate that no increases in theoretical dietary burden for livestock are expected from the levels used to establish the existing levels for MMPE. Therefore, HED recommends that existing tolerances on livestock be maintained.

4.2.1.h. Confined Accumulation in Rotational Crops

No data pertaining to rotational crops are required for an imported crop.

4.2.1.i. International Harmonization of Tolerances

A Codex MRL (CXL) has been established for fipronil residues in rice at 0.01 mg/kg. The proposed import tolerance is not harmonized with the established MRL, a fact attributable to the difference in tolerance expression between Codex and the U.S. There are currently no established Canadian MRLs for fipronil and there are currently no established Mexican MRLs for fipronil in rice.

4.2.2. Drinking Water

The HED Metabolism Committee determined that the residues of concern in drinking water are fipronil + metabolites MB46136 and MB45950 + photodegredate MB46513. Through the cultivation of crop commodities, residues of the insecticide fipronil may become evident in water sources as a result of these prescribed uses. For this reason, a drinking water exposure

assessment of fipronil was carried out by the Environmental Fate and Effects Division (EFED) with their most recent determination being incorporated directly into this evaluation (DP No. 322415, J. Hetrick, 06/19/2007). This comparative drinking water assessment was made assuming that 100% of fipronil for registered uses would be available for degradation, runoff, and leaching into the environment. It is based upon screening level models that incorporate data representative of all exiting uses, new registrations for treatment scenarios such as onion seed, and cancelled uses on applications made to rice. In doing so, an analysis was made by adding the one in ten year peak concentrations for fipronil to determine an acute surface water estimate of 0.002654 ppm. Similarly, by adding the one in ten year average concentrations for fipronil, a chronic surface water estimate of 0.000318 ppm was concluded. Groundwater EECs are much lower than for surface water.

4.2.2.a. Environmental Fate Assessment

Fipronil is stable ($t_{1/2}$ >30 days) in pH 5 and pH 7 buffer solution and hydrolyzes slowly ($t_{1/2}$=28 days) in pH 9 buffer solution. The major hydrolysis degradate is RPA200766 (5-amino-3-carbamoyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoro-methanesulfinyl pyrazole. Photodegradation of fipronil is a major route of degradation (photodegradation in water half-life=3.63 hours) in aquatic environment. In contrast, fipronil photodegradation on soil surfaces (dark control corrected half-life=149 days) does not appear to be a major degradation pathway. Major photolysis products of fipronil are MB46513 and RPA104615 (5-amino-3-cyano-1-(2,6-dichloro-4-trifluoro methyl phenyl) pyrazole-4-sulfonic acid). The chemical degradation of fipronil appears to be dependent predominately on photodegradation in water and, to a lesser extent, on alkaline-catalyzed hydrolysis.

Fipronil degradation in terrestrial and aquatic systems appears to be controlled by slow microbially-mediated processes. In aerobic mineral soil, fipronil is moderately persistent to persistent ($t_{1/2}$= 128 to 300 days). Major aerobic soil degradates (>10% of applied of fipronil) are RPA200766 and MB46136. Minor degradates (<10% of applied fipronil) are MB45950 and MB46513. Fipronil also is moderately persistent (anaerobic aquatic $t_{1/2}$ = 116-130 days) in anoxic aquatic environments. Major anaerobic aquatic degradates are MB45950 and RPA200766. Supplemental aerobic aquatic metabolism data indicate that fipronil degradation ($t_{1/2}$=14 days) is rapid in aquatic environments with stratified redox potentials. These data contradict the longer fipronil persistence reported in anaerobic aquatic and aerobic soil environments.

Conclusions regarding the environmental fate of fipronil degradates, except MB46513, are more tentative because they are based on a preliminary review of interim data not a formal evaluation of a fully documented study report. Since discernable decline patterns for the fipronil degradates were not observed in metabolism studies, the degradates are assumed to be persistent ($t_{1/2}$≈700 days) to microbially mediated degradation in terrestrial and aquatic environments. However, the fipronil degradate, MB46136, rapidly photodegrades ($t_{1/2}$=7 days) in water.

Fipronil degradates have relatively low potential mobility because of a moderate to high sorption affinity to soil. The high sorption affinity of fipronil degradates is expected to limit movement into ground and surface water.

Table 6: Environmental Fate Data for Fipronil Degradation Products

Fate Parameter	MB 46136	MB 46513	MB 45950
Mean Koc	4208 mL/g	1290 mL/g	2719 mL/g
Aerobic Soil Metabolism Half-life	700 days	660 days	700 days
Aqueous Photolysis Half-life	7 days	Stable	Stable
Hydrolysis Half-life	Stable	Stable	Stable
Aquatic Metabolism Half-lives	1400 days	1320 days	1400 days
Water Solubility	0.16 mg/L	0.95 mg/L	0.1 mg/L
% of Fipronil Application Rate	23.9	0.96	4.9
References	RP# 201555 ACD/EAS/Im/255 Theissen 10/97	MRID 44262831 44262830 Theissen 10/97	RP 201578 Theissen 10/97

4.2.2.b. Surface Water Assessment

PRZM (3.12 beta) and EXAM (2.97.5) using PE4V01.pl (August 13, 2003) modeling was conducted using standard scenarios which are representative of high runoff areas or specific use areas. EFED also conducted surface water modeling for the individual degradation products including MB 46513, MB 46136 and MB45950. The modeling was conducted assuming the maximum daily conversion efficiency for the compound was represented by the maximum percentage formed in the environmental fate laboratory studies. Because the fipronil degradation products are formed through abiotic or biotic degradation pathways in soil and water, the degradation products were assumed to have 100% application efficiency on the soil surface. There was no correction for molecular weight because the molecular weights of fipronil and degradation products are similar. Application rates are based on a fipronil equivalence basis. By adding the 1 in 10 year peak concentration for fipronil and it's metabolites and the 1 in 10 year

annual average concentrations for the onion seed treatment scenario, the acute value is 0.002654 ppm and the chronic is 0.000318 ppm (D322415, J. Hetrick, 06/19/2007).

4.2.2.c. Ground Water Assessment

Ground water concentrations for fipronil were estimated using SC2.3 (July 29, 2003). Aerobic soil metabolism rate, Koc, and application rate (lbs/A) for fipronil and its degradation products were derived from PRZM/EXAMS inputs. The highest ground water concentrations for fipronil and its degradation products are for in-furrow corn and rutabags/turnip uses. Peak and chronic concentrations in shallow, source ground water are not expected to exceed 0.000021 mg/L for fipronil. Low concentrations of degradation products were estimated because of their high soil carbon sorption coefficients and low formation efficiencies (D322415, D319940, 328892, J. Hetrick, 06/26/2006).

4.2.2.d Drinking Water Assessment

PRZM/EXAMS simulations of the various registered and proposed uses of fipronil show a range of estimated concentrations in drinking water. From the registered and proposed uses for fipronil, the highest concentrations of fipronil and its degradation products in surface source drinking water are expected to be from the use on onion seeds. Fipronil concentrations in surface source water are not expected to exceed **0.002654 ppm** in acute scenarios and **0.000318 ppm** in chronic scenarios (D322415, J. Hetrick, 06/19/2007).

4.2.3. Dietary Exposure and Risk Analyses

HED conducts dietary (food only) risk assessments using DEEM™, which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population subgroup of interest. The consumption distribution can be multiplied by a residue point estimate for a deterministic exposure/risk assessment, or be used with a residue distribution in a probabilistic type risk assessment. Acute exposure estimates are expressed in mg/kg bw/day and as a percent of the aPAD. For chronic risk assessments, residue estimates for foods or food-forms of interest are multiplied by the average consumption estimate of each food/food-form of each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the cPAD.

4.2.3.a. Acute Dietary Exposure Analysis

A Tier 1 acute dietary risk assessment was performed assuming tolerance-level residues, 100% CT and a drinking water (acute) modeled concentration of 0.002654 ppm. Default processing factors were used for all commodities except for potato, flakes and potato, chips, both of which are dried potato commodities. These are usually given the default processing factor of 6.5. HED determined, via residue data, that the processing factors for these commodities are actually <1. Using a processing factor of 1 allows for a more refined estimate of the acute dietary exposure and risk. For acute dietary risk, HED's level of concern is >100% aPAD. Dietary

exposure estimates for the U.S. population and other representative subgroups are presented in Table 7.

Table 7. Summary of Results from Acute DEEM™ Analysis at 95th Percentile

Subgroups [1]	Exposure (mg/kg/day)	% aPAD
U.S. Population	0.002389	9.6
All infants (<1 year old)	0.003279	13
Children (1-2 years old)	**0.006209**	**25**
Children (3-5 years old)	0.004455	18
Children (6-12 years old)	0.002913	12
Youth (13-19 years old)	0.001822	7.3
Adults 20-49 years old.	0.001384	5.5
Females (13-49 years old)	0.001142	4.6
Adults (50+ years old)	0.001308	5.2

[1] HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., non-nursing infants, etc.). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants, females, 13-50 years, etc.).

The results of the acute analysis indicate that the estimated acute dietary risk associated with the existing U.S registered uses and proposed foreign use on rice is below HED's level of concern (<100% aPAD). (D368732, P. Savoia, 09/17/2009)

4.2.3.b. Chronic Dietary Exposure Analysis

A refined analysis was performed using ARs from field trial data and processing factors for existing uses and a drinking water (chronic) modeled concentration of 0.000318 ppm. It includes a new AR level of 0.017 ppm determined for imported rice grain using residue data recently provided by the registrant compiled from fipronil field trials undertaken in several countries abroad (D368740, W. H. Donovan, 08/25/09). For the other crop commodities used in this assessment, the relevant ARs are taken from residue data generated for crop field trial studies made to support prior fipronil actions. New fipronil screening level usage analyses were provided by BEAD for determining %CT data on corn and potato (Usage Reports from A. Grube, 07/23/2009 and 08/27/2009). The relevant %CT data on imported rice grain which would merit consideration as a result of this action were also determined by BEAD (from email, D. Brassard, 07/21/2009). For all other crops, 100%CT assumptions were used respectively for the purpose of carrying out this assessment. To provide an overview of these inputs, the pertinent ARs and current %CT information of each plant commodity used to form the chronic dietary model for fipronil are summarized below.

Crop Commodity	Chronic Anticipated Residue (AR) Level[1]	% Crop Treated (CT) usage for fipronil
Corm Vegetables (crop group 1C)	0.0120 ppm	100%[2]
Corn Grain	0.0150 ppm[3]	2.5%[4]
Field Corn, forage	0.0360 ppm[3]	2.5%[4]
Onion (dry bulb)	0.0210 ppm	100%[3]
Shallot (dry bulb)	0.0210 ppm	100%[3]
Potatoes (tuber)	0.0120 ppm	43%[5]
Potatoes (chip)	0.0048 ppm[6]	43%[5]
Potatoes (flake)	0.0056 ppm[6]	43%[5]
Potatoes (wet peel)	0.0480 ppm[6]	43%[5]
Rice Grain (imported)	0.0170 ppm[7]	15%[8]
Rutabaga	1.0000 ppm[9]	100%[3]
Sweet Potatoes	0.0120 ppm	100%[3]
Turnip	1.0000 ppm[9]	100%[3]
Wheat Grain	0.0050 ppm[10]	100%[3]

[1] Chronic ARs for all crop commodities except corn, rice, rutabaga, turnip and wheat are based upon the corresponding mean residue crop field trial result derived in DP Nos. D313293, D318283, D319854 & D318677, M. Sahafeyan, 08/05/2005.

[2] Default 100% CT assumption.

[3] Corn ARs are derived from the Anticipated Residue calculations supporting the Section 18 Exemption for fipronil use in/on cottonseed in Mississippi found in DP No. D255833, S. Chun, 05/19/1999.

[4] %CT information determined in a Usage Report Package in Support of Registration for the Insecticide Fipronil from A. H. Grube of BEAD, 07/23/2009.

[5] %CT information determined in a Draft Usage Report/Package in Support of Registration/Reregistration for the Insecticide Fipronil from A. Grube and D. Brassard of BEAD, 08/27/2009.

[6] Chronic AR is based upon the potato tuber mean residue crop field trial result adjusted by its corresponding processing factor derived in DP Nos. D313293, D318283, D319854 & D318677, M. Sahafeyan, 08/05/2005.

[7] Chronic AR for imported rice grain is derived in DP No. D368740, W. H. Donovan, 08/25/2009.

[8] %CT information determined in a usage analysis provided as an email from D. Brassard of BEAD, 07/21/2009. %CT information determined in a Usage Report Package in Support of Registration for the Insecticide Fipronil from A. H. Grube of BEAD, 07/23/2009.

[9] Chronic AR is the tolerance level established in support of the section 18 emergency exemption registration action for rutabaga and turnip derived in DP Nos. D316795, D322527 & D322529, B. Hanson, 11/07/2005.

[10] Chronic AR for wheat is the tolerance level established to support the registration action for indirect or inadvertent residues derived in DP Nos. D313293, D318283, D319854 & D318677, M. Sahafeyan, 08/05/2005.

In addition, following the prior fipronil dietary assessment for onion seed, shallot seed, tuber and corm vegetables, HED has since updated Table 1 (Table 1 Feedstuffs June 2008) to reflect more reasonable livestock diets. Using this update, the dietary burdens of fipronil for the pertinent animal commodities were therefore recalculated using practical livestock diets constructed according to the current guidelines (private communication, J. Stokes). Final determination of the AR inputs for animal products are then made based upon the livestock feedstuff contributions to diet. This determination followed the prior calculation of AR inputs derived for dietary exposure analyses previously made to support the registration of fipronil on cottonseed (DP No. D271641, S. J. Levy, 02/14/2001). Using a ratio of the maximum feeding study dose and contribution to diet, the total residues observed in the tissues and products of livestock found at the maximum dosing level are normalized to 1x. The normalized residue values derived below are in turn used as the chronic ARs for livestock commodities.

Tissue	Observed Feeding Study Maximum Residue Levels[2]	Normalized Residue Level[3]
Ruminants[4] (Cattle, Goats, Horses and Sheep)		
Milk, fat[5]	0.062 ppm	0.06627 ppm[6]
Liver	0.180 ppm	0.01800 ppm[7]
Kidney	0.042 ppm	0.00420 ppm[7]
Muscle	0.066 ppm	0.00660 ppm[7]
Fat	0.610 ppm	0.06100 ppm[7]
Swine[8]		
Liver	0.180 ppm	0.00016 ppm
Kidney	0.042 ppm	0.00004 ppm
Muscle	0.066 ppm	0.00006 ppm
Fat	0.610 ppm	0.00057 ppm
Poultry[9]		
Eggs	0.120 ppm	0.00035 ppm
Liver	0.079 ppm	0.00023 ppm
Muscle	0.017 ppm	0.00005 ppm
Skin/Fat	0.220 ppm	0.00064 ppm

[1] Normalized residue value is used as the chronic AR.
[2] Total residues observed at the feeding study maximum dosing level.
[3] Maximum residues of livestock tissues normalized to 1x (Observed Max Residue / [Feeding Study Max Dose / Table 3 Cont. to Diet]).
[4] The fipronil cattle feeding study was administered at a maximum dose of 0.43 ppm (10x for beef cattle and 29x for dairy cattle). Dairy cattle dosed daily for 35 consecutive days with fipronil; at levels of 0 ppm, 0.04 ppm, 0.13 ppm and 0.43 ppm in the diet (DP Nos. D222541 & D222350, G. F. Kramer, 04/01/1996).
[5] Derived from the maximum residues in whole milk and a theoretical concentration factor of 31x ([0.062 ppm/29x]x 31x = 0.06627 ppm). (DP No. D271641, S. J. Levy, 02/14/2001).
[6] Normalized to 1x for dairy cattle.
[7] Normalized to 1x for beef cattle.
[8] Swine determinations are made using the residue totals observed in cattle tissues at the 0.43 ppm maximum dosing level (1075x).
[9] The fipronil poultry feeding study was administered at a maximum dose of 0.103 ppm (343x). Leghorn hens dosed daily for 42 consecutive days with fipronil; at levels of 0 ppm, 0.01 ppm, 0.031 ppm and 0.103 ppm in the diet (DP No. D214376, G. F. Kramer, 07/25/1995).

To complete the chronic dietary evaluation made herein, DEEM 7.81 processing factors were appropriately used to reflect the possible altering of residue levels through the manufacture of other applicable food forms. The corresponding processing factors were therefore applied accordingly to the chonic fipronil dietary model except for those values specified for the dried potato commodities (flakes and potato, chips, etc.). As previously noted, dried potato food forms are usually given a default processing factor of 6.5 but residue data are available which indicate that it is actually <1 for these commodities. For all other commodities included in this assessment, the default adjustment factor of 1.0 was used to weight the processing affects of alternate food forms. It is important to note that the established tolerance for ruminant meat byproducts does in fact exclude the liver of cattle, goat, horse and sheep in its expression. As a result, the chronic dietary model put forward is constructed using the AR derived for muscle which is the highest residue value for tissue in comparison to kidney to be specified for ruminant meat byproducts. A chronic drinking water estimate of 0.000318 ppm was likewise included in this assessment to reflect a possible concentration for fipronil so that this evaluation is protective of such exposures.

For chronic dietary risk, HED's level of concern is > 100% cPAD. Dietary exposure estimates for the U.S. population and other representative subgroups are presented in Table 8.

Table 8. Summary of Results from Chronic DEEM™ Analysis.

Subgroups [1]	Exposure (mg/kg/day)	% cPAD
U.S. Population	0.000073	36
All infants (<1 year old)	0.000066	33
Children (1-2 years old)	**0.000190**	**95**
Children (3-5 years old)	0.000157	78
Children (6-12 years old)	0.000100	50
Youth (13-19 years old)	0.000063	32
Adults (20-49 years old)	0.000056	28
Females (13-49 years old)	0.000051	26
Adults (50+ years old)	0.000064	32

[1] HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., non-nursing infants, etc.). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants, females, 13-49 years, etc.).

The results of the chronic analysis indicate that the estimated **chronic dietary risk associated with the existing U.S. uses and proposed foreign uses of fipronil are below HED's level of concern** (<100% cPAD) (D368732, P. Savoia, 09/17/2009).

4.2.3.c. Cancer Dietary Exposure Analysis

Fipronil has been classified as a "Group C" chemical (possible human carcinogen) by the HED CPRC (document dated 7/18/95). The HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the DEEM™ chronic exposure analysis using the RfD; therefore, a cancer dietary exposure analysis was not performed.

4.3. Residential Exposure

Fipronil is registered for a variety of home-use products, including those to treat outdoor ant pests, as well as to treat fleas and ticks on pets. Exposure and risks from currently registered residential uses have previously been assessed (ref: D246176, G. Kramer *et al.*, 05/22/1998; D269725, M. Dow, 10/18/2000; D244048, M. Dow, 10/24/2000; D331890, B. Hanson, 06/19/2007). While residential exposures are considered to be at least short-term in duration, others are also considered to have intermediate-term duration potential. However, for fipronil the toxicity route-specific endpoint effects and points of departure are the same for both short- and intermediate-term exposure durations.

For the purposes of performing the short- and intermediate-term aggregate risk assessments, the residential uses/scenarios with the highest exposure potential have been combined with appropriate food and drinking water exposures (Section 5.0). For adults, the aggregate

assessment was performed with exposures resulting from fipronil use to control fire ants, and for toddlers, with exposures resulting from use on pets. Exposures and risks from these residential use scenarios are described below.

4.3.1 Residential Exposure and Risk - Fire Ant Products

Table 9 below contains assessments of homeowner exposure from the registered fipronil products used to control fire ants. Margins of exposure (MOE) for dermal (1700) and inhalation (1500) resulting from the ready-to-use (RTU) product, while not of concern to HED, represent the worst case adult scenario among fire ant uses, as well as all other previously assessed residential use products.

Table 9. Adult Handler Exposure from Fire-Ant Uses.

Job Function and Formulation	Unit Exposure [1] mg ai/lb ai handled	Data Confidence	Units per Day [2]	AR [3] lb ai/unit	ADD [4] (mg/kg/day) derm	ADD [4] (mg/kg/day) inhal	MOE [5] derm	MOE [5] inhal
Homeowner Granular dispersed/hand	430 derm 0.467 inhal	med med	0.5 A[a]	0.000023 lb ai/A	8.6^{-5}	9.3^{-8}	>58K	>500K
Homeowner Belly-grinder open pour MLA	110 derm 0.062 inhal	med high	0.5A [a]	0.000023 lb ai/A	2.2^{-5}	1.24^{-8}	>200K	>4M
Homeowner Drop Spreader open pour MLA	3.0 derm 0.0063 inhal	low high	0.5 A[a]	0.000023 lb ai/A	5.7^{-7}	1.2^{-9}	>8M	>41M
Homeowner 0.0143% G Drop Spreader	3.0 derm 0.0063 inhal	low high	0.5 A[a]	0.024 lb ai/A	6.0^{-4}	1.3^{-6}	>8K	>38K
Homeowner 0.05% RTU	220 derm 2.4 inhal	med med	24 fl[b] oz/day	3.3^{-5} lb ai/fl oz	2.9^{-3}	3.2^{-5}	**>1.7K**	**>1.5K**

1 Unit Exposures for homeowner applications are taken from "DRAFT Standard Operating Procedures (SOPs) for Residential Exposure Assessments," Dec. 18, 1997, p B-3, B-4, B-5, B-6 and B-16.
2 a. Draft SOPs for Residential Exposure Assessments, 18/DEC/97, p 12; b. Proposed label for H&G 61748A fipronil insecticide RTU Spray.
3 Proposed labels for Chipco Banish File Symb. 264-LIG; Chipco Choice File Symb. 264-LLN; Chipco 61748; End User Fipronil File Symb 264-LOE; Chipco 61748A Service Fipronil File Symb 264-LON; H&G 61748A; Fipronil Insecticide File Symb. 264-LOL; H&G 61743A RTU Insecticide Spray File Symb. 264-LOT; Chipco 61442A Imported Fire-ant Bait.
4 ADD = Unit Exposure x AR x Unit/Day x 1/BW (60 kg for homeowner).
5 MOE = NOAEL/ADD

4.3.2 Residential Exposure and Risks - Pet Products

Table 10 below summarizes the risk estimates for toddler postapplication exposure to fipronil following treatment of pets with Frontline® pet spray products. The MOEs were calculated from the exposure estimates obtained from the review of previously submitted studies (D246176, G. Kramer, *et. al.*, 05/22/1998). MOEs for dermal (5000) and non-dietary oral (3300) resulting from the spray product, while not of concern to HED, represent the worst case child scenario among registered pet uses, as well as all other previously assessed residential use products.

Table 10. Child Postapplication Exposure from Treated Pets

Dermal Dose (mg/kg/day)	Non-Dietary Dose (mg/kg/day)	Dermal MOE[1]	Non-Dietary MOE[1]
0.001	0.00003	5000	3300

[1] MOE = NOAEL(or LOAEL)/Exposure (dermal NOAEL = 5 mg/kg/day, inhalation NOAEL = 0.05 mg/kg/day, short- and intermediate-term incidental oral LOAEL = 0.1 mg/kg/day).

Note that residential standard operating procedures (SOPs) for all residential use scenarios are undergoing revision. Upon completion of this process, assessments of residential use scenarios, including pet use scenarios may be revisited and updated.

4.3.4. Aggregate Residential Exposure

Based on existing uses, the worst case aggregate exposure for adults is represented by their combined estimated handler dermal and inhalation exposures resulting from applying a fipronil product to control fire ants. The worst case aggregate exposure for toddlers is represented by their combined estimated postapplication dermal and incidental oral exposures resulting from contact with fipronil-treated pets. These combined exposures/risks are used with average food and drinking water exposure estimates to determine short- and intermediate aggregate risks below.

5.0. RISK ASSESSMENTS AND RISK CHARACTERIZATION

Risk assessments were performed for acute and chronic aggregate exposure (food + drinking water) and short-/intermediate-term aggregate exposure (food + drinking water + residential use. A cancer aggregate risk assessment was *not* performed because HIARC determined that cancer dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the chronic exposure assessment.

5.1. Acute Aggregate Risk (food + drinking water)

An unrefined acute analysis was performed assuming tolerance level residues and that 100% of each crop was treated and included an anticipated concentration in water (acute) at 0.002654 ppm. Default processing factors were used for all commodities except for potato, flakes and potato, chips, both of which are dried potato commodities. These are usually given the default processing factor of 6.5. HED determined, via residue data, that the processing factors for these commodities are actually <1. Using a processing factor of 1 allows for a more refined estimate

of the acute dietary exposure and risk. Acute dietary risk estimates were 9.6% of the aPAD at the 95th percentile for the general U.S. population and 25% of the aPAD for the highest exposure group, children 1-2 years old. The results of the acute analysis indicate that the **acute dietary risk estimates associated with the currently registered and proposed uses of fipronil do not exceed HED's level of concern** (Table 7). Additional refinement by incorporating %CT information may result in even lower exposure estimates.

5.2 Short/Intermediate-Term Aggregate Risk (food + drinking water + residential)

Adults

The short- and intermediate-term aggregate risk assessments takes into account average (chronic) exposure estimates from dietary consumption of fipronil (food and drinking water) and non-occupational exposures. A short-/intermediate-term aggregate risk assessment for adults was conducted using combined dermal and inhalation exposures from fire ant use as a worst case. For food and drinking water, dietary exposures values for the U.S. Population, which includes adults, were used to represent the worst case dietary exposure for adults. Table 11 summarizes the results. Since the level of concern (LOC) is different for dermal/inhalation exposures and food, 100 and 300, respectively, the Aggregate Risk Index method was used to determine aggregate risk. The aggregate ARI from food, water, and non-occupational exposures is 3.1 for adults. Therefore, **short-/intermediate-term aggregate risk estimate for adults does not exceed HED's level of concern** (i.e. ARIs are greater than or equal to 1).

Table 11. Short-/Intermediate-term Aggregate Risk for Adults

Population	food + water				dermal			Inhalation			ARI Aggregate
	LOAEL	EXP	LOC	MOE	LOAEL	LOC	MOE	NOAEL	LOC	MOE	
Adults (U.S. Population)	0.1	0.000073	300	1370	5	100	1700	0.05	100	1500	2.9

LOC=Level of Concern
MOE= NOAEL (or LOAEL)/exp
$ARI=MOE_{Calculated}/MOE_{LOC}$
$ARI_{Aggregate}= 1/((1/ARI_{food})+(1/ARI_{oral})+(1/ARI_{inhalation}))$

Children

The short- and intermediate-term aggregate risk assessments takes into account average exposure estimates from dietary consumption of fipronil (food and drinking water) and non-occupational exposures. A short-/intermediate-term aggregate risk assessment was conducted, using children with combined dermal and oral exposures from pet uses as a worst case scenario. Table 12 summarizes the results. Since the level of concern (LOC) is different for oral and dermal exposures, 300 and 100, respectively, the Aggregate Risk Index method was used to determine

short-term aggregate risk. The aggregate ARI from food, water, and non-occupational exposures is 1.5. Therefore, **short-/intermediate-term aggregate risk estimate for children does not exceed HED's level of concern** (i.e. ARIs greater than or equal to 1).

Table 12. Short-/Intermediate-term Aggregate Risk for Children

Population	food + water				oral			Dermal			ARI Aggregate
	LOAEL	EXP	LOC	MOE	LOAEL	LOC	MOE	NOAEL	LOC	MOE	
Children (1-2 years old)	0.1	0.000190	300	526	0.1	300	3300	5	100	5000	1.5

LOC=Level of Concern
MOE= NOAEL (or LOAEL)/exp
$ARI=MOE_{Calculated}/MOE_{LOC}$
$ARI_{Aggregate}= 1/((1/ARI_{food})+(1/ARI_{oral})+(1/ARI_{dermal}))$

5.3. Chronic Aggregate Risk (food + drinking water)

Chronic aggregate risk estimates are below HED's level of concern. A refined analysis was performed using ARs from field trial data and processing factors for existing uses from the last fipronil dietary analysis (D368732, P. Savoia, 09/17/2009) and a new drinking water (chronic) modeled concentration of 0.000318 ppm. Slightly refined ARs are taken from residue data generated for crop field trial studies made to support prior fipronil actions. HED also determined that existing tolerances on livestock should be maintained. The dietary burdens of fipronil for the pertinent animal commodities were however recalculated according to current guidelines. Final determination of the AR inputs for animal products are then made based upon the livestock feedstuff contributions to diet. The results of the chronic analysis indicate that the **Tier 2 chronic dietary risk estimates associated with the U.S. registered and proposed foreign uses of fipronil are below HED's level of concern** (Table 8).

6.0. DATA GAPS/LABEL CHANGES

6.1. Chemistry

860.1200 Directions for Use

- The petitioner should provide additional information pertaining to typical application patterns in the countries of use. The submitted use directions information for Australia does not include information on formulation type and a.i. percentages/product density so that applications rates could be converted from product to active ingredient. The submitted use information for Brazil (spray application) does not include maximum number of applications per season and/or maximum seasonal rate. In addition, the petitioner should provide assurance that the only countries in which their fipronil products will be used on rice destined for import into the U.S. are Australia, Brazil, and Japan.

860.1500 Crop Field Trials

- For the Japanese trials (MRIDs 47530301, 47530302, and 47530303), information concerning the field portion of the study (including application data, field conditions, and sample handling and storage) and the analytical portion of the study (including supporting method validation data and raw data with example calculations and chromatograms) must be submitted. English translations of all information and data should be included as necessary.

- To support the proposed foliar use in Brazil, data are required which depict magnitude of the residues of fipronil and its metabolites MB 45950, MB 46136, and MB 46513 in/on rice grain harvested 30 days following postemergence foliar treatment of the proposed formulated product (KLAP) at 12 g ai/ha. The petitioner should consult the December 2005 *NAFTA Guidance Document on Data Requirements for Tolerances on Imported Commodities in the Unites States and Canada* to determine the required number of trials.

6.2. Toxicology

870.3465. 28-day inhalation toxicity study in the rat.

Note to RD: Other than the immunotoxicity study requirement, there are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158 for fipronil and the hazard endpoints have been identified. However, this toxicity study in the rat is requested to further characterize the inhalation risk for use in the risk assessment of fipronil. The protocol for the existing 90-day inhalation toxicity study (OPPTS Guideline 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.

APPENDIX 1

870.7800. Immunotoxicity testing

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies assessing functional immunotoxic endpoints are helpful in fully characterizing a pesticide's potential immunotoxicity. These data will be used in combination with data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies to characterize potential immunotoxic effects.
Practical Utility of the Data
How will the data be used? These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

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