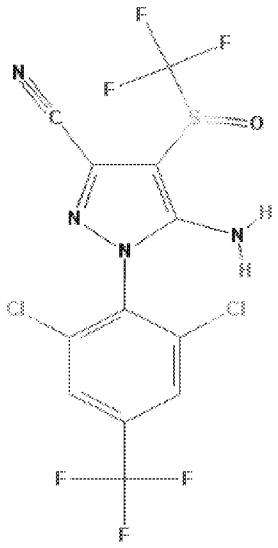
FIPRONIL

RISK CHARACTERIZATION DOCUMENT



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LIST OF ABBREVIATIONS

AADD	Annual average daily dose
ADI	Accepted daily intake
AFSSA	French Food Health Safety Agency
AFSSE	French Environmental Health Safety Agency
APVMA	Australian Pesticide and Veterinary Medicine Authority
aRfD	Acute reference dose
BMD	Benchmark dose
BMDL	Lower 95% confidence limit of the benchmark dose
BMDS	Benchmark Dose Software
BMR	Benchmark response level
BW	Body weight
CAR	Constitutive androstane receptor
CEC	Critical exposure commodity analysis
C_{max}	Maximum concentration
CNS	Central nervous system
CTA	Comparative Thyroid Assay
CYP	Cytochrome P450 enzyme
DEEM™	Dietary Exposure Evaluation Model
DNA	Deoxynucleic Acid
DNT	Developmental Neurotoxicity
DPR	Department of Pesticide Regulation
EAD	Exposure Assessment Document
FCID	Food Commodity Intake Database
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FOB	Functional Observational Battery
FQPA	Food Quality Protection Act
GABA	Gamma-aminobutyric acid
GD	Gestation day
HPT	Hypothalamic-pituitary-thyroid
IP	Intraperitoneal
LADD	Lifetime average daily dose
LD_{50}	Median lethal dose
LC_{50}	Median lethal concentration
LC	Liquid concentrate
LC-MS	Liquid chromatography mass spectrophotometry
LD	Lactation day
LOD	Limit of detection
LOAEL	Lowest-observed-adverse-effect-level

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LOEL	Lowest-observed-effect-level
MMAD	Median mass aerodynamic diameter
MOE	Margin of exposure
ND	Non-detected residues, non-detects
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect-level
PCT	Percent of crop treated
PDP	Pesticide Data Program
PISP	Pesticide Illness Surveillance Program
PND	Postnatal day
POD	Point of departure
ppm	Part per million
ppb	Part per billion
PPS	Preputial separation
PSN	Progressive senile nephropathy
RCD	Risk Characterization Document
RDL	Resistant to dieldrin GABA receptor
RfC	Reference concentration
RfD	Reference dose
SENSOR	Sentinel Event Notification System for Occupational Risk
SADD	Seasonal average daily dose
STADD	Short-term average daily dose
SULT	Sulfotransferase enzyme
$T_{1/2}$	Half-life
T3	Triiodothyronine
T4	Thyroxine
TH	Thyroid hormones
T_{max}	Time to maximum concentration
TOPE	Time to peak effect
ToxCast™	Toxicity Forecaster™
TR	Thyroid receptor
TSH	Thyroid stimulating hormone
UDP-GA	Uridine diphosphate glucuronic acid
UF	Uncertainty factors
UGT	Uridine diphospho-glucuronosyltransferase
USDA	United States Department of Agriculture
US EPA	United States Environmental Protection Agency
WOE	Weight-of-evidence

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I. EXECUTIVE SUMMARY

The purpose of this Risk Characterization Document (RCD) is to evaluate potential risks to human health that result from occupational and residential exposures to fipronil.

Fipronil (5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile) is a broad spectrum pesticide that is effective against various insect and arachnid pests. The pesticidal action is attributed to inhibition of the gamma-aminobutyric acid (GABA)-gated chloride channels in pests and in mammals.

Fipronil was first registered in the US in 1996 for use on golf courses and commercial turf. It was subsequently registered in California in 1997 to control termites, ants, and cockroaches in residential, industrial, and institutional sites. It is also used as the active ingredient in topical spot-on or spray anti-flea and tick formulations for companion animals (dogs, cats). There are no food uses of fipronil permitted in California.

Technical grade fipronil is a moderate to severe acute mammalian toxicant by the oral, dermal, and inhalation routes. Fipronil is designated as a Category II toxicant based on median lethal dose and concentration (LD_{50} and LC_{50}). It is a Category III eye irritant and a Category IV dermal irritant. Fipronil is classified as a Group C carcinogen, *i.e.*, a "Possible Human Carcinogen" by the US Environmental Protection Agency (US EPA). Fipronil was prioritized for risk assessment by the California Department of Pesticide Regulation (DPR) in 2009 for several reasons:

1. It is acutely neurotoxic in rats
2. It has low acute, subchronic, and chronic lowest-observed-effect levels and no-observed-effect levels (LOELs, NOELs) compared to other pesticides
3. It causes convulsions and other neurological disturbances in chronic toxicity studies in rats and dogs, and is oncogenic in rats (thyroid tumors), and
4. It is the source of a large number of adverse human health effects reports.

Sixty-eight cases of possible, probable, or definite illness in humans from fipronil exposure were submitted to the DPR Pesticide Illness Surveillance Program (PISP) between 1999 and 2017 (most current data available.[1]). More than 5000 possible adverse human health effects reports have been submitted to DPR by the pesticide registrants since 2008.

[1] California law requires physicians to report any known or suspected illness caused by a pesticide exposure. The DPR Pesticide Illness Surveillance Program (PISP) is tasked with collecting and evaluating these reports. Database queries and the latest reports are available at https://www.cdpr.ca.gov/docs/whs/pisp.htm

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Scope of Risk Assessment

The health effects and the risks of exposure to fipronil by both workers and the general public are detailed herein. Risks were calculated for occupational handlers, home users, and for adult and child residents following the use of flea and tick treatments, bait gels, dusts, and liquid concentrates approved for use in and around structures, and for turf applications. Fipronil does not have any approved food uses in California. However, because US EPA has established tolerances for several crops and because fipronil is approved for food use in other states, this RCD includes a dietary and drinking water assessment to characterize both acute and chronic risks for the general population and sensitive subpopulations. Toxicology data are available for fipronil as well as for its two main metabolites (fipronil-sulfone and fipronil-sulfide) and an environmental photodegradate (fipronil-desulfinyl). Data used in this assessment came from registrant-submitted studies, published scientific studies, and documents from other regulatory and scientific bodies. A systematic review of published literature was conducted through 1 October 2020, and is detailed in Appendix II. Qualitative data not useful for determining the points of departure were analyzed using a weight-of-evidence approach to understand modes of action and potential effects in humans.

Findings

Critical points of departure (PODs) were established for fipronil from acute, subchronic and chronic studies in laboratory rats for non-oncogenic effects by all routes of exposure. For purposes of this risk assessment, PODs are doses or air concentrations that do not produce toxicologically significant effects following a specific duration of exposure. Cancer risk was assessed by a threshold approach using an upstream marker of the relevant oncogenic process, instead of by linear extrapolation.

Acute Toxicity:

The critical acute oral POD of 0.87 mg/kg/day was based on effects seen in an acute oral neurotoxicity study in which a statistically significant dose-dependent reduction in hindlimb splay was observed in rats 7 hours after gavage administration (Hughes, 1997). This POD was calculated with the Benchmark Dose (BMD) modeling. It was the threshold dose $BMDL_{10}$, which caused 10% reduction in hindlimb splay. The acute oral POD was also used to evaluate the acute dermal and inhalation risk to humans.

Subchronic Toxicity:

The critical subchronic oral POD of 0.02 mg /kg/day was based on decreases in serum thyroxine (T4) levels, convulsions, and death in rats. It was the no observed effect level (NOEL) in a chronic toxicity study in which the effects were seen at the lowest observed effect level (LOEL) of 0.06 mg/kg/day within one year of exposure (Aughton, 1993). The subchronic oral POD was also used to evaluate the subchronic dermal and inhalation risk to humans.

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Chronic Toxicity:

The critical chronic oral POD of 0.02 mg/kg/day was based on convulsions and mortality, sustained decreases in T4, and increased progressive senile nephropathy in a chronic oral study in rats (Aughton, 1993). The POD was based on the study NOEL; the study LOEL was 0.06 mg/kg/day. The chronic oral POD was also used to evaluate dermal and inhalation risk to humans, as chronic inhalation and dermal toxicity studies were not available.

Oncogenicity:

Fipronil exposure resulted in statistically significant increases in thyroid follicular cell adenomas and carcinomas in male and female CD rats when compared to controls (Aughton, 1993). The weight-of-evidence suggests that fipronil-induced hepatic clearance of serum T4 is a necessary precursor (upstream effect) to the development of thyroid tumors in rats. The fipronil database meets all data requirements necessary to designate fipronil-induced thyroid tumors as arising from hypothalamic-pituitary-thyroid (HPT) axis disruption. The critical chronic POD (0.02 mg/kg/day) includes the upstream effect (decreased T4 levels), at much lower dose levels than where tumorigenesis occurred, and will therefore be protective of any possible tumor formation in humans. Thyroid tumor formation through this mode of action is well-understood in the rat, and is likely not relevant to humans due at least in part to more efficient serum thyroid buffering in humans.

Thyroid and Liver Toxicity:

Repeated exposures to fipronil caused increased thyroid weight and histopathology in adult and developing rats as well as thyroid tumors at the high dose in one study. However, fipronil did not act directly on the thyroid. Instead, it induced hepatic (liver) metabolism, which led to increased elimination of T4. Sustained T4 elimination is the required first step for all subsequent thyroid pathologies observed in rats. In humans, decreased T4 levels are generally not considered deleterious to adults in the short-term. During human development, however, thyroid hormone deficiencies of even a short duration during development can lead to irreversible brain damage. Analysis by DPR suggested that fipronil-induced thyroid effects occur at doses and exposure durations above the critical PODs.

Reference doses (RfDs) are target levels that are likely to be without appreciable risk of deleterious effects. These values are calculated by dividing the critical endpoint values by uncertainty factors. Commonly used default uncertainty factors are 10x to account for interspecies variability (UF_A) and 10x to account for intraspecies (human) sensitivity (UF_H). Both uncertainty factors are themselves products of two separate components, a pharmacokinetic uncertainty factor of 3x and a pharmacodynamic uncertainty factor of 3x. Default uncertainty factors are used in this draft assessment as the current database does not warrant alterations to these values.

Acute, subchronic, and chronic oral and dermal RfDs were generated using a total uncertainty factor of 100. RfDs were normalized for absorption using fipronil absorption rates established by

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DPR. The oral rate of 100% and the dermal rate of 4.3% were determined experimentally from registrant-submitted data. While inhalation exposure and risk were calculated for fipronil products, DPR found that the inhalation risk was minimal compared to the dermal risk for adults and compared to the dermal and incidental oral risk for children. In addition, when dermal and inhalation exposure occurred in tandem, dermal exposure drove risk. Therefore, a separate RfC was not calculated for inhalation. All values summarized in Summary Table 1, below, represent internal doses.

Summary Table 1. Points of Departure (PODs), Uncertainty Factors (UFs), and Reference Doses (RfDs) for Exposure to Fipronil

Duration	Route	POD (mg/kg/day)	% Abs.[a]	UF_{TOTAL}	RfD[a] (mg/kg/day)
Acute	Oral[b]	0.87	100	100	0.009
Acute	Dermal	0.87	4.3	100	0.2
Subchronic and chronic	Oral	0.02	100	100	0.0002
Subchronic and chronic	Dermal	0.02	4.3	100	0.005

POD: Point of Departure; % Abs: percent absorption; UF: Uncertainty factors: UF_{TOTAL}: total UF, includes 10x for intrahuman variability and 10x for interspecies extrapolation from animal to human; RfD: reference dose = (POD x % Abs)/UF_{TOTAL}.

[a]Oral percent absorption from (Powles, 1992); dermal percent absorption from (Cheng, 1995; DPR, 1999a). No data were available for inhalation percent absorption so DPR used 100% by default.

[b]Oral route is for incidental or non-dietary oral exposure.

The margin of exposure (MOE) is a quantitative tool used by DPR to determine the potential risk arising from exposure to a pesticide. A MOE is defined as the ratio of the critical POD value derived from the definitive acute, subchronic, or chronic studies to the estimated human exposure. The resulting value is compared to the acceptable or target MOE which, for purposes of this risk assessment, is equivalent to the total uncertainty factor (UF_{TOTAL}) of 100 that accounts in differences between lab animals and humans and between humans. Values at or above the target MOE are generally considered protective against the toxicity of fipronil.

$$\text{Margin of Exposure (MOE)} = \text{POD} / \text{Exposure concentration}$$

Risk was calculated for occupational handlers, home users, and for adult and child residents post-application. Exposure scenarios included pet spray and spot-on treatments, structural dust,

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structural liquid concentrate, turf granules, and structural bait gel uses. Exposure durations include short-term/acute (up to one week), seasonal/subchronic (7 days to one year) and annual/chronic (sum of monthly exposure values amortized over one year) (DPR, 2017a). Exposure calculations are described in the Exposure Assessment Document (EAD, Appendix 1). Exposures resulting in MOEs lower than the target of 100 indicate a potential health risk to humans.

Summary Table 2 details scenarios that resulted in MOEs lower than the target of 100. The table is organized by target population (the group of people expected to be exposed to fipronil), fipronil use scenario (specific person using a specific product), the duration (length) of exposure, the route of exposure, and the calculated MOE. Of these, the most common risk for occupational handlers was from dermal exposure to pet products and liquid concentrate over subchronic and chronic exposure durations. Inhalation of fipronil by occupational handlers of pet spray products also posed a subchronic and chronic risk, but the aggregate risk to these products was driven by dermal exposure. Pet spray posed an acute risk to home users (adults applying pet spray at home) from dermal exposure. Post-application dermal exposure to pet spray and spot-on posed a subchronic risk for both children and adults. Finally, children were expected to have oral (incidental or hand-to-mouth) exposure from three different products (pet spray, pet spot-on and turf granules). Overall, pet products accounted for 14 of 20 risk scenarios (9 pet spray scenarios and 5 spot-on scenarios) and dermal exposure accounted for 15 of 20 risk scenarios.

Summary Table 2. Fipronil Exposure Scenarios with Potential Risk to Humans

Target Population	Fipronil Use Scenario	Duration of Exposure	Route of Exposure	MOE
occupational	pet spray, groomer	acute	dermal	17
occupational	pet spot-on, groomer	subchronic	dermal	27
occupational	pet spray, groomer	subchronic	dermal	2
occupational	structural LC – no overhead	subchronic	dermal	40
occupational	structural LC – overhead	subchronic	dermal	15
occupational	turf granules	subchronic	dermal	83
occupational	pet spray, groomer	subchronic	inhalation	54
occupational	pet spot-on, groomer	chronic	dermal	27
occupational	pet spray, groomer	chronic	dermal	2
occupational	structural LC – no overhead	chronic	dermal	69
occupational	structural LC – overhead	chronic	dermal	26
occupational	pet spray, groomer	chronic	inhalation	54
home user, adult	pet spray, pet owner	acute	dermal	46
post-app, adult	pet spot-on	subchronic	dermal	36
post-app, adult	pet spray	subchronic	dermal	13
post-app, child	turf granules	acute	oral	38
post-app, child	pet spot-on	subchronic	oral	83
post-app, child	pet spray	subchronic	oral	29
post-app, child	pet spot-on	subchronic	dermal	20
post-app, child	pet spray	subchronic	dermal	7

Margin of Exposure (MOE) < 100 represents a potential health risk. MOE = point of departure/estimated exposure; LC: liquid concentrate; post-app: post-application

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Acute and chronic risk from combined exposures from fipronil residues in food and drinking water exposures was also calculated for the general population and sensitive subgroups including infants, children 1-2 years, and women of childbearing age (13 – 49). USDA's Pesticide Data Program database was used as a source for fipronil residues on food commodities. Food consumption data came from the National Health and Nutrition Examination Survey (NHANES, 2005 – 2010). All acute dietary MOEs at the 95th exposure percentile and all chronic dietary MOEs were above the target of 100, and therefore are not considered a health concern.

In addition, this assessment calculated aggregate MOEs for combined non-dietary incidental oral, dermal, and inhalation exposures. For adults, dermal exposure was the main contributor to total fipronil risk. For children, non-dietary incidental oral (hand-to-mouth) and dermal exposure contributed the most to the total risk.

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II. TECHNICAL SUMMARY

II.A. Toxicological Profile

II.A.1. Human Illness Reports and Epidemiology

Illnesses or injuries associated with exposure to fipronil were identified from DPR's Pesticide Illness Surveillance Program (PISP), the adverse human health effects reports submitted by fipronil registrants, the Sentinel Event Notification System for Occupational Risk (SENSOR) Pesticides program, published case studies on patients with purposeful or accidental fipronil ingestion, and human population-based studies. Over all, effects observed were consistent between data sources and were similar to effects seen in laboratory animals. Clinical signs in humans included red and irritated eyes and skin, vomiting, diarrhea and gastrointestinal upset, rash, vertigo, headache, disorientation, coughing, throat irritation, dizziness, tremors, and spinal pain. Two out of ~6000 adverse human health effects reports submitted to DPR by registrants identified people who died following fipronil exposure. In one case, the person died from allergic reaction to a pet spray product. Details were not available for the other case. Kidney and liver effects, seizures, and death were reported in published case studies on hospitalized patients.

Population-based studies monitoring human exposure to pesticides showed the main fipronil metabolite, fipronil-sulfone, in blood specimens in workers at a fipronil veterinary product factory, in neonate-parent groups, and in volunteers with no known pesticide exposure. The study on workers did not find a correlation between fipronil levels and levels of thyroid hormone (T4) in the blood. The study on newborns and their parents reported that increased fipronil-sulfone levels were associated with decreased triiodothyronine (T3) levels and neonate Apgar scores (measurement of well-being of the newborn). Two studies looked at potential exposure to fipronil in farm communities; in one, fipronil-sulfide was the most frequently detected pesticide in a wrist-band-based passive-sampling study of dermal and inhalation exposure of 1500 different chemicals. In the other study, no significant health risks due to inhalation of pesticides during spraying activities was found to rice farmers.

II.A.2. Toxicokinetics

Limited toxicokinetic data for humans were available. Oral ingestion showed variability as high as 46-fold in toxicokinetic parameters such as C_{max} and T_{max} (Mohamed *et al.*, 2004). C_{max} is the maximum or peak serum concentration that a xenobiotic achieves after dosing or exposure and the related pharmacokinetic parameter T_{max} is the time it takes to achieve C_{max}. Oral absorption in rats was assumed to be over 80%. Fipronil was extensively metabolized and distributed throughout the body. No unmetabolized fipronil was detected in the tissues or urine. The highest levels were found in the fat at 7 days after dosing. In both rats and humans, fipronil was metabolized mainly to its lipophilic sulfone-form. The feces were the major route of elimination for fipronil and its metabolites. About 20% of the radioactivity was excreted in feces within the first 24 hours of treatment as both unchanged fipronil and some metabolites, whereas only metabolites were seen at later time points. Bile cannulation experiments confirmed that a significant portion of the metabolites were eliminated in the bile enterohepatic circulation. In

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rats, the relatively slow elimination of fipronil and its metabolites (elimination half-life, $T_{1/2}$ of > 6 days) was proposed to be due to a partitioning onto fat. Dermal absorption was estimated to be 4.3%, based on studies conducted in rats. This value was also used to estimate dermal absorption in humans.

II.A.3. Acute Toxicity

Clinical signs of fipronil exposure in humans include seizures, dizziness, sweating, nausea and vomiting, agitation, high blood pressure, rash, tearing eyes, vertigo, headache, disorientation, coughing, throat irritation, burning eyes and lips, dizziness, tremors and spinal pain. The neurological symptomology is consistent with GABA receptor antagonism in the central nervous system (CNS). Published case studies showed acute kidney injury (retention of urine, high serum creatinine, kidney shutdown) and abnormal liver function following fipronil ingestion.

Fipronil caused clinical signs suggestive of excessive CNS stimulation (convulsions, seizures and tremors). Decreased coordination, gait abnormalities, hypoactivity, lethargy, diarrhea, decreased respiratory rate and prostration were also observed. Acute oral doses of fipronil which were lethal to 50% of the experimental animals (LD_{50}) ranged from 92 – 103 mg/kg. Acute inhalation exposures resulting in 50% mortality in rats (LC_{50}) ranged from 0.36 to 0.68 mg/L (equivalent to 41 to 53 mg/kg). Acute dermal LD_{50} values were > 2000 mg/kg in rats and 354 mg/kg in rabbits. Short-term effects in rats (*i.e.,* effects occurring after 1 - 7 days of exposure) included reduced weight gain, decreased triiodothyronine and thyroxine (T3 and T4) levels, and increased thyroid stimulating hormone (TSH) levels.

II.A.4. Subchronic Toxicity

Fipronil elicited a variety of responses under subchronic scenarios, including neurological disturbances, reductions in body weight, decreased litter survival, decreased pup viability, liver effects (increased liver weight, hypertrophy and fat deposition), thyroid effects (increased thyroid weight, hypertrophy and hyperplasia, decreased serum T4 and increased serum TSH) and delayed developmental signs (incisor eruption, vaginal patency and preputial separation). Increased oxidative stress also occurred under subchronic exposure conditions. Two human-based population studies showed altered thyroid-related hormones in humans.

II.A.5. Chronic Toxicity

Effects of chronic exposure included neurological disturbances, convulsions and tremors, mortality, changes in thyroid hormone levels, reductions in body weight, progressive senile nephropathy, and liver periacinar vacuolation.

II.A.6. Oncogenicity

In chronic toxicity/oncogenicity studies, fipronil induced thyroid follicular adenomas and carcinomas in male and female rats at the high dose. The weight of evidence indicates that the formation of thyroid follicular cell tumors in rat occurred by an anti-thyroidal mode of action via

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a process that disrupts the hypothalamo-pituitary-thyroid axis. Sustained elevations in TSH levels in turn cause follicular cell hypertrophy, hyperplasia and neoplasia. This mode of action is a well-recognized rat-specific mechanism for thyroid neoplasms and is not relevant to humans because humans have more efficient serum thyroid buffering.

II.A.7. Genotoxicity

Fipronil was negative in a battery of registrant-submitted genotoxicity tests, including *in vitro* gene mutation tests, *in vivo* chromosomal aberration tests, and tests for DNA damage and repair capabilities. One *in vitro* chromosomal aberration test in cultured Chinese lung cells was positive at exposure concentrations that were also cytotoxic. Studies in the published literature showed genotoxicity in mammalian tests *in vitro* and *in vivo*. *In vivo* genotoxicity occurred at high doses (e.g., 12 – 50 mg/kg/day) that are typically associated with overt toxicity. *In vitro* genotoxicity was often accompanied by cytotoxicity and oxidative stress, making it difficult to conclude that fipronil is directly genotoxic.

II.A.8. Developmental and Reproductive Toxicity

No developmental effects were attributed to treatment with fipronil in rats or in rabbits in standardized developmental toxicity studies. In a rat comparative thyroid assay (CTA), developmental toxicity was characterized by decreased T4 levels in fetuses and increased liver weight in pups. Reported effects of fipronil on rat reproduction included decreased body weights and convulsions in pups, decreased mating and fertility, reduced pup viability, decreased litter size, and pup developmental delays. Developmental neurotoxicity study in rats revealed dead/missing pups, decreases in body weight, decreased startle response, and developmental delays in male pups characterized by delays in preputial separation. Additional studies in the open literature indicate fipronil has other developmental and reproductive effects in rats, including delayed estrus and changes to sperm motility and morphology.

II.A.9. Thyroid Endocrinology

Repeated exposure to fipronil caused decreased T4 levels, increased thyroid weight and histopathology in adult and developing rats, and thyroid tumors at sufficiently high doses. Fipronil did not act directly on the thyroid. Rather, fipronil induced hepatic (liver) metabolism, which led to an increase in elimination of T4. Sustained T4 elimination is the required first step for all subsequent thyroid pathologies observed in rats. In humans, decreased T4 levels are unlikely to be deleterious to adults in the short-term. In the young, however, thyroid hormone deficiencies of even a short duration during development can lead to irreversible brain damage.

II.A.10. Neurotoxicity

Fipronil neurotoxic potential was measured under acute and subchronic exposure durations in rats. The principal effects included convulsions, tremors, gait abnormalities, absence of response to stimuli, decreased rearing and grip strength, and impaired righting reflex.

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II.A.11. Metabolite and Photodegradate Toxicity

The toxicological properties of fipronil depend on at least three chemical species: the parent compound, its sulfone form (the major metabolite in both vertebrates and insects) and the desulfinyl photoproduct. Fipronil itself is a toxicant for mammals even without oxidation to the sulfone. The available database for the sulfone form showed that its lethal potency is in the same range as the parent compound. Fipronil-desulfinyl is the principal photoproduct in plants and soils. Fipronil-desulfinyl had a lower oral LD_{50} in rats than fipronil, but other available data indicate that fipronil-desulfinyl has similar levels of toxicity compared to the parent. Fipronil-desulfinyl did not cause thyroid tumors following chronic administration. As such, all critical points of departure (POD) used in this assessment were established using the parent compound fipronil.

II.A.12. Toxicity Forecaster™ (ToxCast™)

The ToxCast™ analysis for fipronil resulted in 134 of 667 high-throughput screening assays, largely associated with metabolism, elimination, inflammation, cell cycle regulation, and fatty liver disease. Results from the ToxCast™ Endocrine Disruptor Screening Program showed that fipronil was negative in thyroid- and androgen-dependent assays and only positive in one of 15 estrogen-dependent assays.

II.B. Hazard Identification

II.B.1. Acute Toxicity

An acute oral point of departure (POD) of 0.87 mg/kg/day from an acute neurotoxicity study in rats was used to estimate the risk from the acute exposures to fipronil (PODs are described in Table 1). This POD was calculated with the Benchmark Dose (BMD) modeling. It represents the threshold dose $BMDL_{10}$, which caused 10% reduction in hindlimb splay in the rats at the BMD of 2.48 mg/kg. The critical acute oral POD of 0.87 mg/kg was used to evaluate the acute dermal and inhalation risk to humans

II.B.2. Subchronic Toxicity

The subchronic oral POD of 0.02 mg/kg/day was selected to characterize the risk of subchronic oral exposure of humans to fipronil. It was the no observed effect level (NOEL) in a chronic toxicity study in rats in which decreases in T4, convulsions, and mortality were seen at the lowest observed effect level (LOEL) of 0.06 mg/kg/day within one year of exposure. The critical POD of 0.02 mg/kg/day also was used to characterize human risks from subchronic dermal and inhalation exposures to fipronil.

II.B.3. Chronic Toxicity

The chronic oral POD of 0.02 mg/kg/day was selected to characterize the risk of chronic oral exposure of humans to fipronil. It was the NOEL in the chronic toxicity study in rats. Effects at

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the LOEL of 0.06 mg/kg/day included decreases in serum T4 in males at week 1 through week 50, convulsions, mortality, and progressive senile nephropathy. The critical POD of 0.02 mg/kg/day also was used to characterize human risks from chronic dermal and inhalation exposures to fipronil.

II.B.4. Oncogenic Risk

Cancer potency was not calculated for fipronil by linear extrapolation. Instead, cancer risk was assessed by a threshold approach using an upstream marker (T4) of the relevant oncogenic process.

Table 1. Critical Points of Departure (PODs) for Fipronil

Duration	Route	Critical Endpoint	POD (mg/kg/day)
Acute	Oral, Dermal and Inhalation	Decreased hindlimb splay in an acute oral neurotoxicity study in rats	0.87[a]
Subchronic	Oral, Dermal and Inhalation	Convulsions and mortality associated with convulsions and sustained decreases in T4 after subchronic oral exposure in a chronic study in rats	0.02[b]
Chronic	Oral, Dermal and Inhalation	Convulsions and mortality, sustained decreases in T4, and increased progressive senile nephropathy in a chronic oral study in rats	0.02[c]

T4: thyroxine thyroid hormone. POD: point of departure.
[a]Benchmark dose modeling (BMDS, version 2.6) of hindlimb splay data from acute neurotoxicity study in rat (Hughes, 1997).
[b]Combined chronic and oncogenic study in rat (Aughton, 1993). The critical subchronic POD was supported by POD established in three additional studies in rodents following subchronic exposure: 0.01 mg/kg/day based on increased incidence of urine in the FOB observation arena in rats (Driscoll and Hurley, 1993); 0.05 mg/kg/day based on delayed development and decreased startle response in rat pups (Broadmeadow, 1991; Aughton, 1993; Mandella, 1995); 0.06 mg/kg/day based on liver periacinar hypertrophy in mice (Mandella, 1995).
[c]Combined chronic and oncogenic study in rat (Aughton, 1993).

II.C. Exposure Assessment

II.C.1. Occupational Handler, Home User and Residential Post-application Exposures

Occupational handler, home user and residential post-application exposure assessments for fipronil were prepared as a separate document that included a complete description of the methods used (e.g., input data, formulae, assumptions, etc.). The exposure assessment includes estimates for short-term, seasonal, annual, and lifetime exposures for fipronil handler scenarios. Residential exposure was calculated for home users and for adults and children post-application (Appendix I).

II.C.2. Exposure from Diet and Drinking Water

Dietary exposure estimates to fipronil residues in food and in drinking water were calculated for the US population and sensitive subpopulations including infants, children 1-2 years old, and women of childbearing age (13-49 years) using a deterministic point estimate approach. Dietary

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exposure estimates were based on residues from monitoring databases or the maximum allowed residue level (tolerance).

Acute dietary exposure estimates

At the 95th exposure percentile, the estimated acute exposures to fipronil ranged from 0.097 µg/kg/day to 0.337 µg/kg/day. Children 1-2 years old were exposed to the highest dietary levels of fipronil when compared to other subpopulations. Eggs were the main contributor to the dietary exposure of children 1-2 years old (58% of the total exposure). Fipronil residues in drinking water were not a major contributor to dietary exposure.

Chronic dietary exposure estimates

Estimates for chronic exposure to fipronil from diet ranged from 0.005 µg/kg/day for nursing infants to 0.038 µg/kg/day for children aged 1-2 years.

II.D. Risk Characterization

Reference doses (RfDs) for fipronil were developed for the oral and dermal routes following DPR guidelines. RfDs were calculated using critical points of departure (PODs) for fipronil based on effects observed in oral toxicity studies in rats and mice divided by the total UF of 100 (10x for interspecies extrapolation, UF_A and 10x for intrahuman variability, UF_H). Reference concentrations were not calculated because inhalation exposure was minor compared to exposure by the non-dietary incidental oral and dermal route.

The acute oral RfD was 0.009 mg/kg. The acute dermal RfD was 0.2 mg/kg (adjusted for 4.3% absorption). The subchronic and chronic oral RfDs were 0.0002 mg/kg/day. The subchronic and chronic dermal RfDs were 0.005 mg/kg/day (adjusted for absorption).

The potential for non-oncogenic health effects resulting from exposure to fipronil was expressed as the margin of exposure (MOE). A MOE is the ratio of the critical POD derived from the definitive acute, subchronic, or chronic studies to the estimated human exposure. The resulting value is compared to the acceptable or target MOE which, for purposes of this risk assessment, is equivalent to the total uncertainty factor (UF_{TOTAL}) of 100 that accounts in differences between lab animals and humans and between different humans. Calculated MOE that are lower than the target MOE indicate a potential health concern.

$$\text{Margin of Exposure (MOE)} = \text{POD} / \text{Exposure Concentration}$$

Occupational Risk. Risk was characterized for each occupational exposure scenario. Aggregate MOEs that combined simultaneous dermal, inhalation, and oral (non-dietary incidental) exposure were also calculated (Table 2). Exposure from diet and drinking water were not included in the aggregate MOE calculations because the dietary exposure estimates had little impact on total exposure or on the overall aggregate MOE calculations. The aggregate risk was calculated using the hazard index approach:

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$$MOE_{aggregate} = 1/(\sum_{i=1}^{n} \frac{1}{MOEi} + \cdots + \frac{1}{MOEn})$$

Acute MOEs for occupational exposure to pet spray was lower than the target of 100, indicating a risk. All subchronic MOEs for occupational handlers, with the exception of the MOE for structural dust handlers, were below the target MOE of 100. All chronic MOEs except those for turf granule and structural dust handlers were also below the acceptable risk target. Dermal exposure was the predominant route of exposure for occupational handlers.

Table 2. Aggregate Margins of Exposure for Occupational Handlers

Product	Scenario	Acute MOE	Subchronic MOE	Chronic MOE
Pet spot-on	groomer	207	**27**	**27**
Pet spray	groomer	**16**	**2**	**2**
Structural dust	handler	8208	1176	1818
Structural LC	no overhead	451	**29**	**50**
Structural LC	overhead	134	**15**	**25**
Turf granules	handler	1229	**78**	155

MOE: margin of exposure. LC: Liquid concentrate. **Bold** text indicates MOE below target of 100.

Home User Risk. Risk was characterized for people who use fipronil at home. As for occupational risk calculations, aggregate MOEs that combined simultaneous dermal, inhalation and oral (non-dietary incidental) exposure were calculated (Table 3). Exposure from diet and drinking water were not included in the aggregate MOE calculations because the dietary exposure estimates had little impact on total exposure or on the overall aggregate MOE calculations. The aggregate risk was calculated using the hazard index approach, above.

Acute MOEs for home user exposure to pet spray were lower than the target of 100, indicating a risk. Subchronic and chronic risk was not calculated for home users, as exposure was not anticipated. The predominant route of exposure for home users was dermal.

Table 3. Aggregate Margins of Exposure for Home Users

Product	Scenario	Acute MOE	Subchronic MOE	Chronic MOE
Pet spot-on	adult pet owner	580	--	--
Pet spray	adult pet owner	**46**	--	--

MOE: margin of exposure. Note: Seasonal and annual exposure of residents to pet products is calculated in the post-application exposure scenarios. **Bold** text indicates MOE below target of 100.

Residential Post-Exposure Risk. Aggregate risk calculations for post-application exposure to adult and child residents are presented in Table 4. Aggregate values include exposure estimates for inhalation, dermal, and non-dietary incidental oral exposure, where applicable.

Table 4. Aggregate Margins of Exposure for Post-Application Exposure to Residents

Product	Scenario	Acute MOE	Subchronic MOE
Pet spot-on	adult	621	**36**

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Table 4. Aggregate Margins of Exposure for Post-Application Exposure to Residents

Product	Scenario	Acute MOE	Subchronic MOE
Pet spot-on	child	272	**16**
Pet spray	adult	363	**13**
Pet spray	child	153	**6**
Structural bait gel	adult	> 100,000	> 100,000
Structural bait gel	child	> 100,000	27211
Structural LC	adult	17755	2500
Structural LC	child	6259	1111
Turf granules	adult	> 100,000	NA
Turf granules	child	**38**	NA

LC: liquid concentrate. **Bold** text indicates MOE below target of 100. NA = calculation not applicable.

The only acute MOE below the target of 100 was for child exposure to turf granules. In that case, the risk value was driven by incidental oral (hand-to-mouth) exposure. Subchronic MOEs for exposure of adults and children to pet spray and pet spot-on products were all less than the target of 100, indicating a risk. The predominant route of exposure for residents post-application was by the dermal route. Longer term exposures to turf granules were not anticipated if the products were applied as per legal label use, and because of the very limited allowable use in California. Therefore subchronic risk for turf granules for post-application scenarios involving either adult or child residents were not calculated.

Dietary Risk. MOE were calculated for the combined exposures from fipronil residues in food and drinking water. The acute dietary MOE at the 95th exposure percentile were all above the target MOE of 100. Similarly, all chronic dietary MOE were above the target of 100.

II.E. Risk Appraisal

The main uncertainties with the toxicity of fipronil were associated with (*i*) the use of animal data to evaluate the toxic effects in humans (*ii*) the use of oral PODs to characterize dermal and inhalation risk, (*iii*) the critical acute POD was based on time to peak effect of 7 hours for convulsions and tremors that may not capture the actual peak effect for hindlimb splay, and (*iv*) the confidence in the thyroid hormone measurements in the comparative thyroid assay (CTA) was reduced due to uncertainties with non-guideline analytical quality control metrics.

The exposure assessment for fipronil used the best information available to evaluate exposure. However, defaults were used for some scenarios due to a lack of data. There were also several data gaps identified during the exposure assessment. These gaps and the discussion of how they were addressed is found in the Exposure Assessment Document (Appendix I).

Uncertainties in the dietary (food and drinking water) exposure assessment were introduced with the use of analytical limits of detection or tolerances used as surrogates for pesticide monitoring residue concentrations.

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III. INTRODUCTION

Fipronil is a broad spectrum insecticide that is toxic to numerous insects and arachnids including cockroaches, locusts, wire-worms, ticks and fleas (Aajoud *et al.*, 2003). It is a phenylpyrazole insecticide that blocks gamma-aminobutyric acid-gated (GABA-gated) chloride channels, leading to central nervous system excitation and to death at sufficient doses.

The first fipronil-containing products were registered in the US in 1996 for use on golf course and commercial turf. Fipronil was first registered for use in California in 1997. As of February 2020, 129 fipronil-containing products are registered in California. In California, fipronil is registered for non-food uses such as to control structural pests with public-health impacts. Fipronil is also used in to control ticks and fleas on companion animals in veterinary practices, pet grooming business, and in residential homes. Limited geographical and seasonal use is allowed on turf to control fire ants. Only licensed applicators can use turf granules, structural liquid concentrates, and structural dust or power products. None of these products are licensed in California for home consumer use, however residents can purchase bait gel and station products in retail stores to treat structural pests. There are no food uses of fipronil allowed in the state.

Fipronil was first prioritized for risk assessment by DPR in 2009 because:

- Acute neurotoxicity in rats (convulsions)
- Low acute, subchronic, and chronic NOELs in mammals compared to most pesticides
- Convulsions and neurological disturbances in chronic toxicity studies in rats and dogs
- Oncogenicity in rat thyroid
- Possible oncogenicity in mouse liver, and
- Thousands of adverse human health effects reports submitted to DPR detailing potential toxicity in human following fipronil exposure (adverse effects were first reported in 1999).

In 2013, DPR requested an independent peer review of its risk assessment practices by the National Research Council, an external committee of the National Academy of Sciences (NAS). As part of that review and audit, NRC recommended several improvements, including focusing on California-specific data, identifying relevant US EPA evaluations of the same pesticidal active ingredient, and identifying important sources of uncertainty and variability in the data. Fipronil is the first pesticide to enter risk assessment using the revised approach and this document is designed to incorporate and be responsive to the NRC recommendations.

This assessment evaluates potential human health risks associated with exposure to fipronil. The studies evaluated in this document include guideline studies submitted to fulfill pesticide registration data requirements and studies required under the California Birth Defect Prevention Act of 1984 (SB 950). DPR also reviewed relevant reports and risk assessments conducted by other regulatory agencies including US EPA, the National Toxicology Program (NTP), the European Food Safety Authority (EFSA), and the European Commission (EC). Studies available in the open literature were also reviewed using the National Center for Biotechnology

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Information (NCBI) electronic database. The most recent NCBI search was conducted on October 1, 2020.

III.A. Chemical Identification

III.A.1. Fipronil and Phenylpyrazoles

Fipronil is a phenylpyrazole insecticide discovered in 1987 by scientists at Rhône-Poulenc Agro laboratories (now Bayer CropScience) following experimental alteration of the core phenylpyrazole structure (Figure 1) (Moffat, 1993; Perrior, 1993). Phenylpyrazoles operate principally as herbicides. However, fipronil acts as an insecticide following contact or ingestion. It contains a unique trifluoromethylsulfinyl functional group not present in any other pesticide, which may contribute to its greater toxicity to insects over mammals (Hainzl and Casida, 1996).

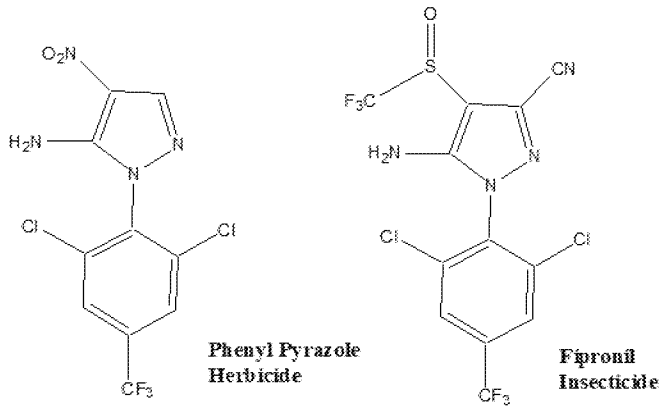

Figure 1. Chemical Structure of Fipronil and Phenyl Pyrazoles

III.A.2. GABA Receptor as Primary Fipronil Target

Fipronil (5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile) is a phenylpyrazole insecticide that blocks gamma-aminobutyric acid (GABA)-gated chloride channels, leading to excitation of the central nervous system (CNS) and to death at sufficient doses (US EPA, 2011b; Simon-Delso *et al.*, 2015). Fipronil represents the second generation of insecticidal chloride channel blockers. The selective toxicity for insects relative to mammals is more favorable for fipronil than for most of the first generation chloride channel blockers (chlorinated cyclodienes and polychlorinated cycloalkanes) (Hainzl and Casida, 1996). In addition, insects resistant to pyrethroid, cyclodiene, organophosphate and carbamate insecticides are not cross-resistant to fipronil (Simon-Delso *et al.*, 2015).

Initial functional studies showed that toxic signs elicited by fipronil in house flies and mice are similar to those of trioxabicyclooctanes, which block GABA-gated chloride channels (Cole *et al.*, 1993). GABA is a major inhibitory neurotransmitter in both vertebrates and invertebrates. It increases chloride conductance into cells, which results in decreased release of excitatory neurotransmitters and rapid inhibition of synaptic CNS signal transmission (McKernan and Whiting, 1996; Raymond and Sattelle, 2002). Compounds such as fipronil, which act as

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antagonists, stabilize non-conducting conformations of the chloride channel, reduce neuronal inhibition, and lead to hyper-excitation of the CNS, which can cause convulsions and death (Bloomquist, 2003).

Vertebrate GABA Receptor

GABA receptors are transmembrane glycoproteins consisting of five subunits that form a central pore. Many therapeutic drugs such as barbiturates, benzodiazepines and alcohols act as agonists or activators of the GABA receptor, and induce neuronal inhibition, sedation, anesthesia or coma (Eldefrawi and Eldefrawi, 1987; Kurata *et al.*, 1993; McKernan and Whiting, 1996). Electrophysiological and ligand binding studies confirm that fipronil reversibly and noncompetitively blocks passage of chloride ions through GABA receptors in the CNS (Millar *et al.*, 1994). Humans exposed to fipronil show symptoms such as headache, nausea and seizures, which are associated with antagonism of GABA receptors in the brain (Mohamed *et al.*, 2004).

Much of the knowledge about fipronil action as a chloride channel blocker comes from binding studies with radioligands, computational molecular modeling, site-mutation studies, and electrophysiological assays (Cole *et al.*, 1993; Kurata *et al.*, 1993; Hainzl *et al.*, 1998; Ikeda *et al.*, 2001; Ratra and Casida, 2001; Ikeda *et al.*, 2004). According to a proposed binding site model, fipronil and other antagonists interact at a single site in the GABA-gated chloride channel (Ratra and Casida, 2001; Chen *et al.*, 2006).

Insect GABA Receptor

Structure and operation of the GABA receptor and the GABA binding domain in insects are not well understood and subunit composition of the native GABA receptor is not known (Comitani *et al.*, 2014). The 'Resistant to Dieldrin' subunit (RDL) is used as an experimental model for the native receptor because it forms a functional GABA-gate chloride channel and exhibits many of the same toxicological properties as the native insect GABA receptor (Buckingham *et al.*, 2005). The *Drosophila* RDL subunit has high sequence homology to that of the human β_3 subunit (Ffrench-Constant *et al.*, 1991; Ffrench-Constant *et al.*, 1993; Sirisoma *et al.*, 2001).

The insect RDL GABA receptor mediates inhibitory neurotransmission (Ashby *et al.*, 2012; Comitani *et al.*, 2014). Blocking by fipronil occurs in the Cl^- channel, not at the GABA recognition site (Inoue and Akaike, 1988; Zhang *et al.*, 2016). This allosteric binding site is also known as the picrotoxin or noncompetitive blocking site (Sirisoma *et al.*, 2001). The binding site is best characterized in *Drosophila* (fruit fly), *Musca* (housefly) and *Periplaneta* (cockroach) (Ashby *et al.*, 2012; Comitani *et al.*, 2014). Evidence indicates that allosteric binding occurs with high affinity and selectivity (Comitani *et al.*, 2014).

III.A.4. Glutamate Receptors as Secondary Target for Fipronil in Insects

L-glutamate-activated chloride channels are a secondary fipronil target in invertebrates (Horoszok *et al.*, 2001; Ikeda *et al.*, 2003; Zhao *et al.*, 2004). Unlike mammals, where glutamate is an excitatory neurotransmitter, glutamate serves as an inhibitory neurotransmitter in

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invertebrates (Wolstenholme, 2012). They are closely related to GABA and glycine receptors, and to date have been found in invertebrate nerve and muscle cells (Cully *et al.*, 1996; Horoszok *et al.*, 2001; Raymond and Sattelle, 2002; Eguchi *et al.*, 2006). The selective toxicity of fipronil in insects over mammals could be influenced by its action on multiple target sites in insects.

III.B. Regulatory History

1995: US EPA established a temporary combined tolerance for fipronil and its sulfide metabolite on corn grain.

1996: Fipronil was registered in the US to control mole crickets on golf course and commercial turf (US EPA, 1996; US EPA, 2011a).

1997: US EPA established tolerances for combined residues of fipronil and its sulfone and sulfide metabolites on corn grain, stover and forage, eggs, milk, and animal fat, meat, organs and byproducts.

1997: Fipronil first registered in California by DPR.

1998: Fipronil spray and spot-on products first registered by the US EPA. The fipronil photo degradate, fipronil-desulfinyl, was added to the combined fipronil tolerances. Tolerances for fipronil on rice grain and straw were established.

1999: US EPA issued an Experimental Use Permit for fipronil on tuftgrass to evaluate the control of imported fire ants.

2001: US EPA approved fipronil use on wood structures to control Formosan termites.

2002: US EPA approved specific uses of fipronil to control fire ants and authorized limited use of fipronil in rodent bait boxes to control ticks.

2005: BASF petitioned US EPA to establish combined fipronil tolerances for raw agricultural commodity corm vegetables (potato, sweet potato), and indirect and inadvertent residues on wheat grain, forage, hay and straw.

2007: US EPA issued an amended human health risk assessment including an analysis of aggregate exposure to fipronil in workers, the US population, and for infants and children. That assessment included an updated dietary assessment included modeled values for fipronil levels in water. Tolerances were established for wheat forage, grain, hay and stray, potato and potato wet peel.

2009: BASF petitioned US EPA to reestablish combined tolerances for fipronil on rice. Use for fipronil for corn-in-furrow was cancelled.

2009: Fipronil enters the risk assessment process at DPR in California.

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2010. US EPA released a review of the large number of incident reports for pets (cats and dogs) treated with flea and tick spot-on products including two formulations containing fipronil.

2013: DPR starts monitoring fipronil in fresh produce sold in California through the California Pesticide Residue Monitoring Program.

2014: US EPA waived the requirement for an immunotoxicity study for fipronil because the weight-of-evidence indicated that potential immunology-related effects occurred only at doses above those used for points of departure (US EPA, 2014). US EPA also changed the critical short-term incidental oral study from the rabbit developmental study to the developmental neurotoxicity study in rat.

2015: US EPA requested a comparative thyroid assay be completed by the registrants because a determination that thyroid effects observed in adult rats were not measured in developing rats.

2015: DPR selects fipronil as pilot pesticide to incorporate recommendations by the National Academy of Sciences (NAS) National Research Council (NRC) for improving DPR's risk assessment process. In 2013, DPR contracted with NAS to conduct an independent peer review of DPR's risk assessment practices. An external committee of NAS, NRC completed its review and issued its report in April 2015.

2017: DPR released its Problem Formulation Document for fipronil. As part of the NAS NRC report mentioned above, NRC recommended that DPR conduct a Problem Formulation/Scoping phase prior to drafting the risk assessment. During this phase, risk managers and risk assessors met and discussed the scope of the risk assessment to determine scope. The problem formulation/scoping discussions resulted in a Problem Formulation Document and a diagram of exposure pathways, which were presented to the Pesticide Registration and Evaluation Committee and posted to DPR's website for public comment (DPR, 2017b).

2020: US EPA released a Draft Human Health Risk assessment which included among other things a comparative thyroid assay, revised points of departure, a reduction in the FQPA safety factor, and a reduction of the interspecies extrapolation factor from 10x to 3x when the POD was based solely on thyroid effects.

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IV. TOXICOLOGICAL PROFILE

The database used to develop the fipronil toxicological profile consisted of registrant-submitted studies, other regulatory documents, and scientific publications in the open literature. A systematic literature review was conducted to identify relevant studies in the open literature. The database search was most recently conducted on October 1, 2020 using the common name as the key word ("fipronil"). The resultant studies (1373) were screened for relevancy to this assessment. Results of the systematic literature review are included in Appendix II.

IV.A. Human Illness Reports and Epidemiology

Documented human exposure to fipronil has resulted in central nervous system effects (dizziness, sweating, vomiting, seizures), irritation at the contact site, agitation, high blood pressure, pneumonia, and death. Effects possibly caused by fipronil include hives, renal failure and allergic reaction. Fipronil metabolites were detected in serum in limited biomonitoring studies. Experiments in human cell lines showed increased cellular metabolism and oxidative stress. Humans exposed to fipronil show symptoms such as headache, nausea and seizures, which are associated with antagonism of GABA receptors in the brain (Mohamed *et al.*, 2004).

III.A.1. Acute Effects Observed in Humans

Five case studies were available concerning for patients who ingested fipronil and one was available for accidental dermal and inhalation exposure. The first study, which details a number of patients in Sri Lanka who ingested fipronil as a method of self-poisoning, is described in detail in the Toxicokinetics section of this RCD (Mohamed et al., 2004). To summarize, severe toxicity including CNS effects and death was observed in some of the patients. In contrast, the authors note that there were no obvious toxic signs in other patients who ingested similar doses. Body weights were not reported. Assuming a default adult weight of 71.8 kg, the dose of fipronil ingested by patients with severe symptoms (Patients 2 and 8) would be 70 mg/kg. Patients with little to no symptoms (Patients 3 and 7) would have ingested 35 mg/kg.

The other published case studies are briefly described below.

A 77-year-old woman in Hong Kong accidentally ingested a commercial ant bait (less than 0.14 mg fipronil ingested) (Fung *et al.*, 2003). Thirty minutes later she experienced mild impairment of senses. After admitting to the hospital, she had no other symptoms. At a follow up two weeks later she had raised serum creatinine of 93 mmol/L (reference range 58 to 91 mmol/L).

A 50-year-old male in Poland was admitted to a medical clinic after 5 hours of spraying his field with fipronil without protective equipment (Chodorowski and Anand, 2004). He experienced headache, nausea, vertigo and weakness, and went to the medical clinic. Physical examinations and biochemical results were normal, and all symptoms resolved spontaneously after about 5 hours. At follow-up appointments, he was asymptomatic.

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A 25-year-old male was brought to the emergency department for generalized tonic-clonic seizures and altered sensory faculties (Bharathraj *et al.*, 2015). Case study authors state that he had an "alleged history of fipronil compound consumption" and refer to the episode as "acute". The patient continued to have seizures, was unconscious for 10 hours, and was delirious for 3 days. He also had coarse tremors and incoordination and some retention of urine. All other tests were normal, and he was discharged on the 8th day.

A 45-year old female patient in India accidentally consumed 100 ml fipronil (Yadla *et al.*, 2017). The patient had four seizures and severe metabolic acidosis on the first day, followed on the second day by a shutdown of urine production. Her serum creatinine and urea levels, both measures of kidney function, were 4-8 times the normal range on the first and second days. Renal biopsy revealed acute tubular necrosis, vacuolation of tubular epithelial cells, and intratubular hemorrhages. After 10 days, fipronil levels were measured with mass spectrophotometry/ liquid chromatography at the National Institute of Nutrition, Hyderabad, India. Levels were described by the investigators as being 40 times the upper limit of quantification for screening methods used on produce. After 5 weeks, the patient's urine output and creatinine levels had improved. The report did not comment further on her general health.

A 32-year-old male in India consumed 150 mL of a 5% fipronil solution to self-harm (Gutta *et al.*, 2019). After two weeks of symptoms (altered sensory faculties with recurrent seizures, jaundice and pallor) the patient presented to the hospital. He had occurrences of generalized tonic–clonic seizures while at the hospital, and liver function tests were abnormal. His liver and neurological function resolved by the third week of managed care, and case study authors report that he was doing well at follow-up visits. The observed effects were consistent with fipronil-induced hepatic dysfunction and neurotoxicity.

IV.A.2. Illness Reports

Illnesses or injuries associated with exposure to fipronil were identified from three main sources: DPR's Pesticide Illness Surveillance Program (PISP), the adverse human health effects reports submitted by fipronil registrants, and the Sentinel Event Notification System for Occupational Risk (SENSOR) Pesticides program.

PISP maintains a database of pesticide-related illnesses and injuries reported in California. Case reports are received from physicians and workers' compensation records. The DPR database indicated that 68 cases of illness were linked to fipronil from 1999 to 2017 (the latest date data were available) (DPR, 2014; DPR, 2018; DPR, 2020). The health effects attributed to exposure to fipronil alone or in combination with other pesticides were rated as definite (3 cases), probable (18 cases) or possible (47 cases). Illnesses identified as "definite" included:

- A six-year-old female child who experienced red and irritated eyes after accidentally squirting a dog spot-on treatment into her eyes.
- A 60-year old woman who sustained eye irritation and pain after accidentally getting dog flea treatment in her eyes.

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- A 49-year old male professional pesticide applicator who touched his face with a glove contaminated with pesticide mixture and experienced itching and burning face and eyes.

Illnesses defined as "probably" due to fipronil exposure included reports on pest control operators and residents exposed at work or home to bait gels (3), termite or insect products (8), or pet products (8). Illness reports categorized as "possibly" due to fipronil exposure came from the use of pet products (5), ant or roach gel or bait (8), and structural liquid, dust, suspension or spray (33).

Clinical signs included vomiting, diarrhea and gastrointestinal upset, rash, tearing eyes, vertigo, headache, disorientation, coughing, throat irritation, burning eyes and lips, dizziness, tremors, and spinal pain. The number of illness reports has generally increased over time. A large number of incidents occurred in 2013 (10 incidents for up to 20 people) at a retirement community in Santa Barbara, California (Figure 2).

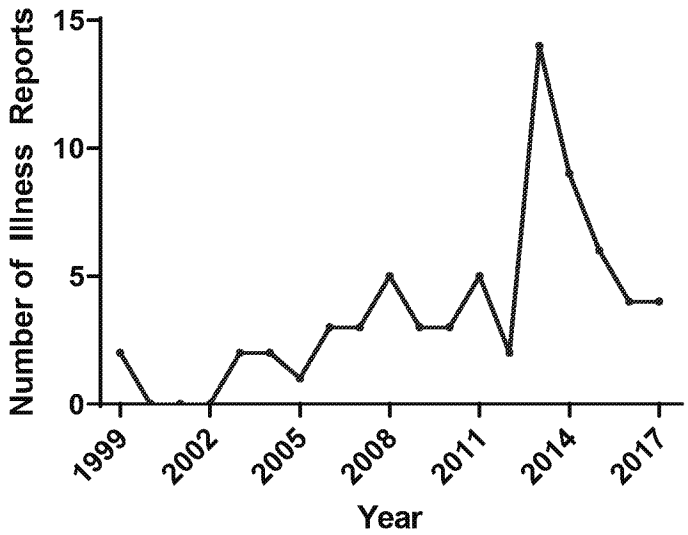

Figure 2. Yearly Incidence in California of Illness Reportedly Caused by Fipronil

IV.A.3. Adverse Human Health Effects Reports

Adverse Human Health Effects Reports are submitted to DPR by fipronil registrants as mandated under Section 12825.5 of the California Food and Agricultural Code. These include, but are not limited to information required under Section 6(a)(2) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The effects are mostly self-reported, and are graded as human fatality, major, moderate, minor or unspecified. The exposure level or duration is generally unknown, and the connection between exposure and symptoms is usually not verified. These reports are from across the entire United States and are not California-specific; actual location of the event is usually not available.

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DPR's databases for fipronil illness reports include cases submitted between 2009 and 2020. Earlier reports were also available from the US EPA. These reports were reviewed and summarized based on severity of effect and fipronil product type (Table 5).

Table 5. Adverse Effects Reports on Fipronil

Database	**US EPA (2011)[a]**	**DPR 2009 to 2015[b]**	**DPR 2016 to 2020**
Years	2002 to 2010	2009 to 2015	2016 to present
Number of incidents	4243 total	491 total*	1000 total
	- 1 death	- 0 deaths	- 1 death
	- 10 major	- 0 major	- 5 major
	- 377 moderate	- 16 moderate	- 111 moderate
	- 3815 minor	- 461 minor	- 750 minor
	- 40 unspecified	- 0 unspecified	- 127 unspecified
		- 14 other (no severity grading)	- 6 other (no severity grading)
Types of products reported[c]	Pet products, termite and insect products, ant and roach bait, fire ant control.	Pet products, roach bait, fire ant control.	Pet products, termite and insect products, roach bait, fire ant control, and area foggers.
Notes	75% of major and moderate incidents, including one death, due to pet products.	93% from use of pet products; 4% from unknown formulations; 2% from roach bait; 0.4% from fire ant products.	One death from termite product. 80% from use of pet products (70% spot-on, 8.5% spray, and 0.6% dog collars); 8.5% from roach bait; 7.6% from termite and insect products.

[a]Data published in (US EPA, 2011d) includes Adverse Effects Reports as well as incidents from other federal and state health and environmental agencies and individual consumers.
[b]These reports (and the reports in the DPR 2016 to 2020 database) are from incidents across the United States and are not California-specific. Because the timing of US EPA (2011d) and DPR (2008 to 2015) had overlap, it is possible some incidents were included twice.
[c]All databases included incidents where the specific fipronil product was not described (unknowns).
*Database included reports of effects in animals and wildlife and reports in which no species was mentioned. The total presented here represents incidents that clearly occurred in humans; reports where species was unclear were removed. This number could therefore omit human incidents.

Comprehensive data for fipronil reports prior to 2008 are only available in a publication (Fipronil: Review of Human Incidents) by the US EPA (US EPA, 2011d). This publication summarizes human health effects reported following fipronil use from January 1, 2002 to November 30, 2010.

Starting in 2009, DPR began documenting human health effects electronically for both humans and animals. Two databases are available. The first details reports from 2005 to 2015 (though a limited number of reports exist prior to 2009). The second includes reports from 2016 until early 2020. These databases contain human health effects reports and reports on effects in pets, wildlife and plants, for all pesticides registered in California. Both databases include registrant name, US EPA pesticide registration number, date the report was received, and US EPA chemical code. Some reports include the affected species and specific reported effects. Reports are for single incidents of exposure or aggregate reports with more than one incident.

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Following review of the three databases, DPR identified 5734 human health effects reported following fipronil use since 2002. Of these, 2 were deaths, 15 were major, 504 were moderate, 5026 were minor, 167 were unspecified, and 20 had no severity grading. In the first case of lethality, a 64-year-old female in Texas died following an allergic reaction to a pet spray product. In the second case, a person died in 2017 following exposure to a termiticide; additional details on the person or effects were not available.

Incidents with effects graded as major or moderate included neurological and cardiovascular effects, slurred speech, lethargy, allergic edema, neuropathy, breathing trouble, fatigue, coma, swelling, seizures and renal failure. The minor, unspecified and ungraded incidents generally do not include specific effects, but may indicate a pattern of, or potential for, exposure to fipronil.

A total of 3916 reports did not include information on product formulation. Of the 1818 reports for which formulation is known, 47% were for dog spot-on treatments, 17% were for pet products (not further described), 14% were for cat spot-on products and ~ 6% each were for roach bait, termite control and pet spray products. Taken together, pet products accounted for 84% of all adverse effects reports submitted to DPR.

Information on product type (formulation) was available for most (92%) of the major and moderate incidents (521 total incidents). Of these, 69% were from pet products (dog and cat spot-on, pet spray and dog collars), 16% were from termite or insect treatments, and 7% were from ant and roach bait stations.

In addition to effects in humans, tens of thousands of incidents were also reported in domestic animals following the use of fipronil in veterinary products.

IV.A.4. Sentinel Event Notification System for Occupational Risk (SENSOR) Pesticides Program

SENSOR, run by the National Institute for Occupational Safety and Health, collects pesticide illness surveillance data from 11 states and health departments. The SENSOR Pesticides Program reported 92 cases of illness from fipronil exposure from 2001 through 2007; an additional 11 cases were provided by DPR, for a total of 103 cases (Lee *et al.*, 2010). Most cases were identified through poison control centers. The majority involved exposure to a single product containing fipronil (as opposed to several products). Factors contributing to exposure included inadvertent splash, spray/spill, inadequate ventilation, and failure to leave a treated area during application. Two pest control operators experienced high-severity illnesses or seizure. Most cases were related to residential exposures. Nine cases were labeled as moderate severity and 92 were labeled as low severity. The most common symptoms were neurological, including dizziness, paresthesia and headache.

IV.A.5. Human Incidence Data from Other Countries

In their 2005 risk assessment, the French Food Health and Environmental Health Safety Agencies included data showing 458 cases of human effects resulting from exposure to

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veterinary products (307 cases), home insecticide use (95 cases) and professional application (53 cases) (Agence Francaise de Securite Sanitaire des Aliments, 2005). Ninety-five percent of the human cases were acute poisoning cases. Symptoms included erythema, persistent rash skin irritation, burning lips, blisters at the point of contact, hives, and edema of the eyelids. An additional 112 cases (105 accidental exposures and 7 cases of deliberate ingestion) were reported from January 1995 through March 2004. The report also included 8 cases over 3 years from the National Poison Control Center of the Netherlands (ingestion or dermal exposure in children) as well as 138 cases described by the World Health Organization from 1995 to May 2004. Symptoms include nausea, vomiting, transient dizziness and respiratory effects from oral exposure, and irritation following eye contact.

In 2003, the Australian Pesticide and Veterinary Medicine Authority (APVMA) initiated a risk assessment on fipronil due to "adverse experiences in humans and animals" involving fipronil veterinary products. During the time from initial registration in 1997 until 2006, 73 adverse experiences were reported. These included skin reactions in animals and humans, neurological signs, and death in pets and non-target animals (rabbits in particular). The APVMA preliminary review recommends revision to safety directions associated with some fipronil products and new re-handling intervals for fipronil veterinary spray products (APVMA, 2011).

Unintentional insecticide poisoning that occurred in young children (<5 years) in Queensland, Australia was assessed to determine mechanisms of acute poisoning and whether age affected poisoning patterns (English *et al.*, 2016). Fipronil was involved in 4.6% of calls for which medical attention was recommended for a young child. These involved ingestion of baits, ant liquids and veterinary products. Authors found a peak of exposure in one-year-olds, explained by mouthing (hand-to-mouth) behaviors.

IV.A.6. Population-Based Studies

Several population based studies sought to characterize exposure to pesticides and the resulting effects by quantifying biomarkers of exposure and effect.

In the first study, fipronil, fipronil-sulfone and thyroid hormones levels were measured in the blood specimens of 159 workers in a fipronil veterinary product manufacturing factory in France (Herin *et al.*, 2011). Blood fipronil concentrations averaged 7.79 ± 7.65 µg/L. Fipronil-sulfone levels increased with increasing employment time. There was a negative association between fipronil-sulfone levels and levels of TSH; free and total T4 levels had no association with fipronil levels. More explanation of the perturbation of thyroid hormones in animals is described in the Hazard Identification and Risk Appraisal sections of this document.

In the second study, levels of fipronil and fipronil-sulfone were measured in the blood specimens of 59 newborn infant-mother pairs and 51 fathers in South Korea (Kim *et al.*, 2019). Thyroid parameters were also measured. Fipronil-sulfone was detected in all patients. Fipronil was detected in one father only. The average fipronil-sulfone concentration in blood was 525 ± 240 µg/L in neonates, 744 ± 426 µg/L in mothers and 1163 ± 797 µg/L in fathers. These

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concentrations are similar to the median values in the Mohamed (2004) study. While T3 levels were considered to be within a normal range, infant cord blood T3 and free T3 levels were inversely associated with fipronil-sulfone levels. Fipronil-sulfone levels were also associated with decreased five-min Apgar scores[2] of newborn infants. This study showed placental transfer of fipronil-sulfone *in utero* and potential neurological effects on human development. Exposure is assumed to be subchronic or chronic duration, although sources of exposure and amount of exposure are unknown.

In another study, blood specimens from 96 human volunteers living in the Raleigh-Durham, North Carolina area were collected by the National Institute for Environmental Health Sciences between April and June 2001 (McMahen *et al.*, 2015). Fipronil-sulfone was detected in 25% of the samples, with concentrations ranging from 0.1 to 3.9 ng/mL. These levels were lower than those from other studies, and study subjects had no known pesticide exposure.

Levels of fipronil and the sulfone metabolite were measured postmortem in human liver and adipose tissues from patients with and without Alzheimer's disease (N=12, Arizona, US) (Manivannan *et al.*, 2019). Only fipronil, not the sulfone, was detected. Fipronil accumulated in both the liver and the adipose tissue. There was no evidence of tissue burden association with Alzheimer's disease.

In a study conducted in Latina females aged 14 – 26 living in an agricultural community (Salinas, California), fipronil-sulfide was the most frequently detected pesticide in a wrist-band-based passive-sampling study of dermal and inhalation exposure of 1500 different chemicals (Harley *et al.*, 2019). Fipronil-sulfide was measured in 87% of the 97 study participants. Measurements, reported as ng fipronil per gram silicone bracelet per day, averaged 34.5 ng/g/day with a median of 12.9 ng/g/day and a 95th percentile exposure level of 145 ng/g/day. Sulfide levels were statistically significantly lower ($p < 0.05$) in homes with door mats, and were higher in homes where a professional exterminator spray had been used in or around the home within the last six months (OR = 7.0; 95% CI: 1.4 – 35.7; $p < 0.05$). While this study did not measure fipronil levels in blood, it did establish the prevalence of fipronil exposure in a community in California.

Inhalation exposure was measured for 83 rice paddy farmers handling fipronil in Malaysia (Hamsan *et al.*, 2017). Authors found no significant health risks due to inhalation of pesticides during spraying activities.

IV.B. Toxicokinetics

Limited data were available for fipronil toxicokinetics in humans, including one hospital-based study. Several *in vitro* studies investigated changes in enzymatic activity or expression in human cell lines. In addition, 11 studies on metabolism and toxicokinetics in laboratory animals were

[2] The Apgar test is conducted at 1 and 5 minutes after birth to assess the well-being of a newborn. A low Apgar score can indicate that the neonate requires medical attention, and is considered a marker for developmental vulnerability.

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submitted to DPR by registrants. These included 7 oral studies (4 in rats and one each in laying hens, lactating goats and lactating cows), 2 comparative toxicokinetic studies and a whole body autoradiography study in rabbits, rats and mice, and 1 dermal study with rats. An *in vitro* dermal study was also available that measured the absorption of fipronil through human, rabbit and rat skin.

IV.B.1. Human Toxicokinetics

Case reports were described for 7 patients treated in hospitals in Sri Lanka in 2002 following fipronil self-poisoning (Mohamed *et al.*, 2004). The study also included a retrospective case review for one patient (Patient 8) who died 17 days following fipronil ingestion. All patients ingested Regent 50 SC® formulation (4.95% fipronil in propylene glycol). The estimated time from fipronil ingestion to hospital admission varied from 45 min to 18 hours (Table 6). Patient symptoms ranged from none to dizziness, sweating, nausea, agitation, seizures, high blood pressure, vomiting, mouth ulcers, pneumonia and death (Patient 8).

Blood specimens were taken from six patients on admission. Additional specimens were taken from five patients at later time points. The time from fipronil ingestion to the first blood sample varied from 75 min to 3.5 hours. Time between ingestion, admission and first blood sample is important when calculating half-life ($T_{1/2}$) estimates. The blood was analyzed for total fipronil with enzyme-linked immunosorbent assays (ELISA) or for fipronil and its sulfone and desulfinyl metabolites with liquid chromatography mass spectrometry (LC-MS). Toxicokinetic analysis was conducted when data were deemed sufficient by the investigators. Patient 3, who ingested 2.5 g fipronil, was the only patient with an increase in blood concentration over time; the C_{max} of 1040 µg/l was measured at an approximate time of 4.6 hours [DPR used GetData Graph Digitizer 2.26 to extract time from Figure 2 in (Mohamed *et al.*, 2004)]. Based on the C_{max} value, the authors note that Patient 3 likely ingested a larger amount of fipronil compared to Patients 2 and 4. The estimated C_{max} for Patients 2, 4 and 7 was based on the first and highest concentration measured after admittance. For these patients, fipronil levels in blood were similar, and leveled off after about 15 hours post ingestion. Patient 7 reportedly ingested the same amount of fipronil as Patient 3 (2.5 g), but his C_{max} of 82 µg/l at 1.3 hours was 46-fold lower than the other patients, and he did not show clinical signs.

The blood concentration for total fipronil (parent and metabolites) remained constant after 15 to 20 hours (the last time points tested), although the patients no longer exhibited symptoms. Study authors determined that for two of the patients (4 and 7), the fipronil-sulfone concentration increased, while there was a reduction in levels of the parent compound. The elimination $T_{1/2}$ of fipronil was estimated to be 36 hours (Patient 4) and 47 hours (Patient 7). However, the authors state that these times may not be conclusive as they were based on three measurements with no further follow up. In patients 2, 3 and 7, total fipronil concentration in blood started to increase over time after an initial decrease.

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Table 6. Summary of Toxicokinetic Data for Humans with Fipronil Self-Poisoning

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, gender	17, male	31, male	44, male	31, male	21, male	34, female	30, male	23, male
Other poisons	OP, imi.	none	none	none	OP	none	none	none
Fipronil (g)	unknown	5	2.5	unknown	unknown	unknown	2.5	5
Admission (min)	1100	100	225	190	180	150	45	180
Time to first sample (min)	NA[b]	200	170	210	210	180	75	NA
Peak (µg/L)	NA	1600	1040	3744	7	20	82	NA
$T_{1/2}$ elim (hr)	NA	> 70*	NA	36	NA	NA	47	NA
Symptoms	none	dizziness, sweating, nausea, vomiting, agitation, seizures	high blood pressure	vomiting, seizures, mouth ulcers	none	nausea, vomiting, heart burn	none	unconscious, seizures, pneumonia
Outcome after 12 hr	asympt.	asympt.	asympt.	asympt.	asympt.	asympt.	asympt.	died (day 17)

OP (organophosphate): dimethoate, fenthion; NA not available; Imi: imidacloprid; Peak: peak total fipronil in blood; Asympt = asymptomatic.

*Initial elimination half-life ($T_{1/2}$) estimate based on increases in total fipronil in blood over time; final measured time point was 70 hours. Data from Mohamed (2004).

IV.B.2. *In Vitro* Metabolism

Published studies with recombinant human isozymes of CYP450 and human liver microsomes suggest that CYP3A4 is the major isoform that oxidizes fipronil to fipronil-sulfone, the major metabolite (Tang *et al.*, 2004; Carrao *et al.*, 2019). This was confirmed in inhibition experiments using the irreversible, non-competitive inhibitor chlorpyrifos (Joo *et al.*, 2007). Chlorpyrifos, an organophosphorus pesticide that contains a P=S moiety, inhibited CYP3A4 and resulted in a 70-80% decrease in the production of fipronil-sulfone (Joo *et al.*, 2007). Testosterone, a CYP3A4 substrate, activated fipronil metabolism by human liver microsomes, while fipronil inhibited testosterone metabolism (Tang *et al.*, 2004). These activation/inhibition interactions were in agreement with a previously-proposed multisite kinetics model for CYP3A4 for the metabolism of testosterone (Tang *et al.*, 2004). These studies suggest that fipronil may interact with endogenous chemicals that are CYP3A4 substrates (Tang *et al.*, 2004; Joo *et al.*, 2007; Carrao *et al.*, 2019).

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Fipronil was a potent inducer of CYP isoforms in cultured human hepatocytes (Das *et al.*, 2006; Hodgson and Rose, 2007; Hodgson and Rose, 2008). Among 23 tested environmental chemicals, fipronil was the strongest inducer of CYP1A1 and CYP3A4 mRNA at concentrations between 0.5 µM -1 µM. Induction of CYP3A4 mRNA varied from 10-27-fold following 1 µM fipronil exposure. This induction level was similar to the level observed for a well-known CYP3A4 inducer, rifampicin (20 fold, n=3) (Das *et al.*, 2006). Changes were seen in CYP enzyme levels in human primary hepatocytes following fipronil exposure *in vitro* (Mitchell *et al.*, 2016). Exposure to 10 uM fipronil for 72 hours resulted in upregulation of mRNA (measured with qPCR) for CYPs 3A4, 3A5, 2A6, 1A1, 3A7, 2B6, 2B7 and 2C9. mRNAs for CYP4A11 and 4A22 were both down-regulated.

One study published in the scientific literature showed that fipronil binds *in vitro* and *in silico* to human serum albumin and competitively inhibits the binding of a heme-Fe(III) complex (Ascenzi *et al.*, 2018). This could reduce the direct toxicity of fipronil and/or impair binding of endogenous molecules.

IV.B.3. Rat Toxicokinetics

Powels, 1992

To investigate the oral absorption of fipronil, Crl:CD(SD)BR rats (5/sex/dose) received a single oral dose of 4 mg/kg or 150 mg/kg ^{14}C-fipronil (ring-labeled, 44.8 µCi/mg) (Powles, 1992). The radiolabeled fipronil was dissolved in 0.5% methylcellulose with 0.01% Tween 80. A parallel group included rats that were pre-administered non-radiolabeled fipronil for 14 days (4 mg/kg) before receiving a single oral dose of 4 mg/kg ^{14}C-fipronil. Whole blood was collected from the lateral tail vein at various intervals for up to one week after treatment to determine the concentration of radioactivity. Greater than 95% of the administered radioactivity was recovered at termination of the study at 168 hours (7 days) post-dose. No toxic signs were reported at 4 mg/kg, which is about 4% of the rat oral LD_{50} (92-103 mg/kg). Toxicity at 150 mg/kg, above the LD_{50}, included flushed and stressed faces, red staining, arched back while walking, and fluid around the nose. There were no deaths in this group up to 7 days following treatment.

Single dose of 4 mg/kg of [^{14}C]-fipronil. The plasma reached a maximum concentration (C_{max}) of 0.60-0.68 µg/g at 4 - 6 hours (T_{max}; Table 7). Adjusted for 100% mass balance, the average radioactivity recovered in the urine within 168 hours was 6% for both females and males. In the first 24 hours, 10-13% of the parent compound was detected in feces. Approximately 20% of the administered radioactivity was excreted in the feces within 24 hours with 3 to 6% of the dose recovered in feces at each remaining time point. An average of 46% radioactivity was recovered in the feces for both sexes within 168 hours. A similar portion of the dose, 46% (approximately 2 mg), was found in tissues (liver, adrenals, skin, pancreas, kidney, abdominal fat, ovaries, uterus and muscle) and in the carcass in both sexes at termination at 168 hours. The highest concentrations were measured in the abdominal fat (14.7-18.9 µg equivalents of ^{14}C-fipronil/g). The elimination $T_{1/2}$ was 149-200 hours. The authors concluded that absorption was relatively rapid, followed by slower elimination.

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Multiple doses of 4 mg/kg of [^{14}C]-fipronil. Pretreatment with non-radiolabeled doses of fipronil for 14 days (14 doses) resulted in a 2.5-fold greater renal excretion of labeled residues (14%-16% of total administered radioactivity) following a single dose of ^{14}C-fipronil. The 168-hour recovery of radioactivity in feces was 56% for males and 61% for females (~10% higher than in the single dose group), and ~20% radioactivity was measured in the tissues and carcass (about half that of the single dose group). The authors note body compartment saturation with fipronil or an increase in metabolism and excretion.

Single dose of 150 mg/kg [^{14}C]-fipronil. The absorption of fipronil at 150 mg/kg (T_{max} between 48-72 hr) was much slower than at the low dose (T_{max} 4 - 6 hr). The C_{max} for the high dose was 19.6-19.7 µg/g, about 30-fold higher than at the low dose (Table 7). The average radioactivity recovered in the urine within 168 hours was 22% for females and 29% for males. In feces, 67% and 75% was recovered in males and females, respectively. Between 2-5% (3-7.5 g) of the radioactivity was found in tissues and carcass at termination (1.5-4 times higher than the low dose exposure). The elimination $T_{1/2}$ at this dose (150 mg/kg) was 51-54 hours.

Intact fipronil was not detected in urine; the excreted radioactive compounds were mainly N-glucuronide conjugates. After deconjugation, up to 14 urinary metabolites were identified including fipronil (MB 46030), the sulfide metabolite (MB 45950), sulfone product (MB 46136), and fipronil-sulfone with the sulfonic acid removed (MB 45897), the amide metabolite RPA200766, and two pyrazole ring-opened metabolites (Figure 3). Based on the finding that conjugates, but not intact fipronil, were excreted in urine, the authors speculated that fipronil was largely metabolized prior to entering the systemic circulation.

At 24 hours, metabolites in the feces included the parent fipronil (MB 46030, 6-14%), the sulfide MB 45950 (1-3%), the sulfone MB 46136 (1-1.5%) and trace amounts of conjugates of the amide product RPA 200766 (< 1%). At later time points (73-120 h), the major metabolite was fipronil-sulfone (2-8%). Biliary excretion of fipronil was suggested based on the presence of metabolites in feces, but was not directly demonstrated.

Lipophilic metabolites were preferentially distributed and accumulated in tissues. Repeated low dosing or a single high dose of 150 mg/kg resulted in an overall decrease in the proportion of radioactivity in tissues, likely due to saturation (Powles, 1992). The only metabolite identified in all tissue samples was fipronil-sulfone. Trace radioactivity (< 0.25%) was recovered in expired air.

The study authors conclude that toxicokinetics of the 150 mg/kg dose was different from the 4 mg/kg dose. At 4 mg/kg, the T_{max} occurred within of 4 – 6 hours, compared to 48 – 72 hours at the high dose. The main route of excretion for both doses was the feces, although a higher percentage of the administered dose was excreted via the urine following the high-dose exposure. In the first 24 hours, 10 – 13 % of the parent compound was detected in feces following the low-dose exposure, while 8 – 14 % of the parent was detected following the high-dose exposure. Only metabolites were excreted after 72 hours. A lower limit of oral absorption in rats was assumed to be 80%.

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Totis and Fisher, 1994

A separate laboratory performed a second study on the kinetics of fipronil in rat (Totis and Fisher, 1994). In this study, Charles River CD rats (5/dose/sex) received [^{14}C-phenyl]-fipronil as a single oral dose of 4 or 40 mg/kg. Blood from the tail vein was collected at various intervals up to 2 weeks after treatment.

At 4 mg/kg, blood levels reached a maximum of 0.39-0.52 µg/g (C_{max}) at 4.8-6.2 hours (T_{max}). This was followed by a relatively slow elimination (135-171 hours). The C_{max}, T_{max} and $T_{1/2}$ were similar to values reported by Powles at the same dose (Powles, 1992). At 40 mg/kg, the T_{max} was 34-38 hours and the C_{max} was 6.7-7.6 µg/g, approximately 18-fold higher than the low-dose exposure. The elimination $T_{1/2}$ was 183-245 hours. However, the actual $T_{1/2}$ may exceed the study duration of 7 days, as radioactivity levels remained high at the last measured time point. DPR considered the absorption profile of the 40 mg/kg dose to be similar to that of the 150 mg/kg dose in the study by Powles (1992), but the elimination profile was more similar to that of the 4 mg/kg dose in Powles (1992).

Kemp, 1999

Biliary reabsorption of ^{14}C-fipronil was studied in male Sprague Dawley CD rats with cannulated bile ducts treated orally with 3.26 mg/kg (^{14}C) fipronil (Kemp, 1999). Absorption was 75%, with 3% of the administered dose recovered from urine, 12.7% from bile and 59% from the tissues and carcass at 72 hours post-dose. The fat and adrenal glands had the highest fipronil concentration. The pancreas, liver and thyroid gland represented a second tier of tissues with high fipronil concentrations. A second group of rats were treated with the bile product from the first exposed group. In this group, 73% of the administered radiolabel was recaptured in the urine, bile, and skin and carcass up to 96 hours after dosing. Approximately 38% of this dose was reintroduced via enterohepatic circulation.

Bile excretion was also studied in the rat (Totis, 1995). The predominant site of recovery 72 hours post-dose was in the tissues.

Cheng, 1995

In a dermal absorption study with ^{14}C-fipronil, a formulation containing 79% fipronil suspended in 1% aqueous carboxymethylcellulose was applied to the shaved backs of 4 male Crl:CDBR rats per dose at doses of 0.876 mg/rat (0.07 mg/cm^2), 8.35 mg/rat (0.67 mg/cm^2) and 48.5 mg/rat (3.9 mg/cm^2) (Cheng, 1995). Two control animals were treated with the vehicle alone. The site was covered with filter paper after fipronil application. The "directly" absorbed radioactivity was estimated from residues recovered in blood, carcass, cage wash and cage wipes and urine and feces at 0.5, 1, 2, 4, 10, and 24 hours after treatment. The amount of radioactivity "indirectly absorbed" (left in or on the skin after skin washing) was determined at the same time points. Over 94% of the applied radioactivity was washed off the rat skin. Absorption of the applied dose was linear at the low and intermediate doses but reached saturation at the highest dose.

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IV.B.4. Comparative Toxicokinetics

In a comparative toxicokinetic study, female rabbits, rats and mice dosed orally by gavage for 14 days showed differences in the fipronil $T_{1/2}$ and T_{max} (Brockelsby *et al.*, 1991). Rabbits received 0.4 or 1.2 mg/kg/day while rats and mice received 0.4 or 4.0 mg/kg/day.

In a second comparative study, the percent recovery from a single dose of 5 mg/kg was determined (Lowden and Savage, 1999). In rats and mice, fipronil was not present in blood after 6 hours, whereas fipronil (sulfone) levels peaked on day 15 in rabbits. The maximum concentration was found in fat in all animals. Significant levels were also found in rabbit liver and thyroid. Fipronil-sulfone was the predominant metabolite for all species. The estimated elimination $T_{1/2}$ was longer in rabbit (11 and 10 days for blood and fat compared to 5 to 7 days in rodent). The $T_{1/2}$ in the thyroid of rodents was 5 days; data were too variable to calculate thyroid $T_{1/2}$ for rabbits.

The absorption of ^{14}C-fipronil through human, rabbit and rat skin was measured in vitro in horizontal glass diffusion cells (Walters and Brain, 1990). Rat and rabbit skin was obtained from dorsal and flank regions of euthanized animals. Human female abdominal skin was obtained from autopsy. Absorption rates were estimated for fipronil applied at doses of 0.2, 4 and 200 g/l in an aqueous formulation base (EP60145A). Fipronil at 4 g/l penetrated through the skin of all three species more slowly than either testosterone (a fast penetrant) or hydrocortisone (a slow penetrant). Based on this result, fipronil was considered a slow penetrant. The extent of fipronil absorption at 0.2 g/l was similar for human and rat skin (0.9 – 1.0%) at 8 hours, and was greater for rabbit skin (13.9%).

Whole body autoradiography performed in rat, mouse and rabbit following oral administration (5 mg/kg) of ^{14}C-fipronil showed rapid dispersion throughout the body with the highest level residing in the fat (Whitby, 1991). Moderate levels were in the adrenal and pituitary glands, mucosa of the gastrointestinal tract, kidneys, liver, lungs, pancreas and skin. The radioactivity was present in the central nervous system in the mouse only (Whitby, 1991).

IV.B.5. Metabolism

One major metabolic pathway was proposed in the rat based on metabolite profiles (Figure 3) (Powles, 1992). The Phase I metabolites found in rats (fipronil-sulfone; fipronil-sulfide and the amide product RPA200766) were also identified in goats (Stewart, 1994a). The fipronil metabolic profile (excretion and accumulation) in rats was similar to lactating goats, laying hens and lactating cows (Byrd, 1994; Stewart, 1994b). Sulfone was the predominant moiety detected in tissues of all animals tested.

Toxicologically, the formation of fipronil-desulfinyl (MB 46513) in mammals was of particular interest because desulfinyl is 9-times more potent than fipronil at the vertebrate GABA receptor (Hainzl *et al.*, 1998) and 2-fold more acutely toxic to mice (Cole *et al.*, 1993). However, fipronil-desulfinyl was not detected in tested animals.

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Rats administered 3 mg/kg/day fipronil by the oral route for 14 days exhibited an increase in elimination of antipyrine and glucuronidation of 4-nitrophenol, indicating increased cytochrome P450 (CYP) activity and increased UDP-glucuronosyltransferase (UGT) activity, respectively (Leghait *et al.*, 2009). Plasma concentrations of fipronil-sulfone were at least 20 times higher than concentrations of the parent compound, suggesting the metabolite may contribute to toxic effects.

A microarray mRNA study conducted on 2-3 month old female Wistar rats receiving 3 mg/kg/day oral fipronil (95.6% purity) for 14 days showed a significant increase in expression of hepatic enzyme mRNAs linked to the metabolism and transport of xenobiotics, hormones and endogenous compounds (Roques *et al.*, 2013). These included Phase I enzymes (CYP2b1, CYP2b2, CYP3a1), Phase II transporters (UGT1a1, SULT1b1), and Phase III ATP-binding cassette transporters (ABCc2, ABCc3, ABCg5, and ABCg8). CYP3a4, identified in other studies as the main enzyme responsible for fipronil metabolism, was not reported in this study. Plasma concentrations of fipronil-sulfone were 700-fold higher than the parent compound. In the same study, fipronil altered hepatic expression of genes involved in metabolism and excretion in male C57BL/6J mice administered 3 mg/kg/day fipronil orally for 14 days (Roques *et al.*, 2013).

A separate study conducted in the same laboratory measured increased UGT, SULT and CYP expression and activity and a decreased T4 C_{max}, evidence of increased hepatic metabolism, in thyroidectomized female Wistar rats (Roques *et al.*, 2012).

Fipronil also induced CYP activity in male rats after 6 days of exposure (the only time point tested) at 5 mg/kg/day, but not at 1 mg/kg/day (Caballero *et al.*, 2015).

In a study conducted with rat and human liver microsomes, the rat K_m and rat V_{max} were determined to be as 19.9 µM and 0.39 nmol/mg protein min, respectively (Tang *et al.*, 2004). CYP3A4 was identified as the major CYP isoform, and data suggested a higher intrinsic clearance of fipronil in rats than in humans.

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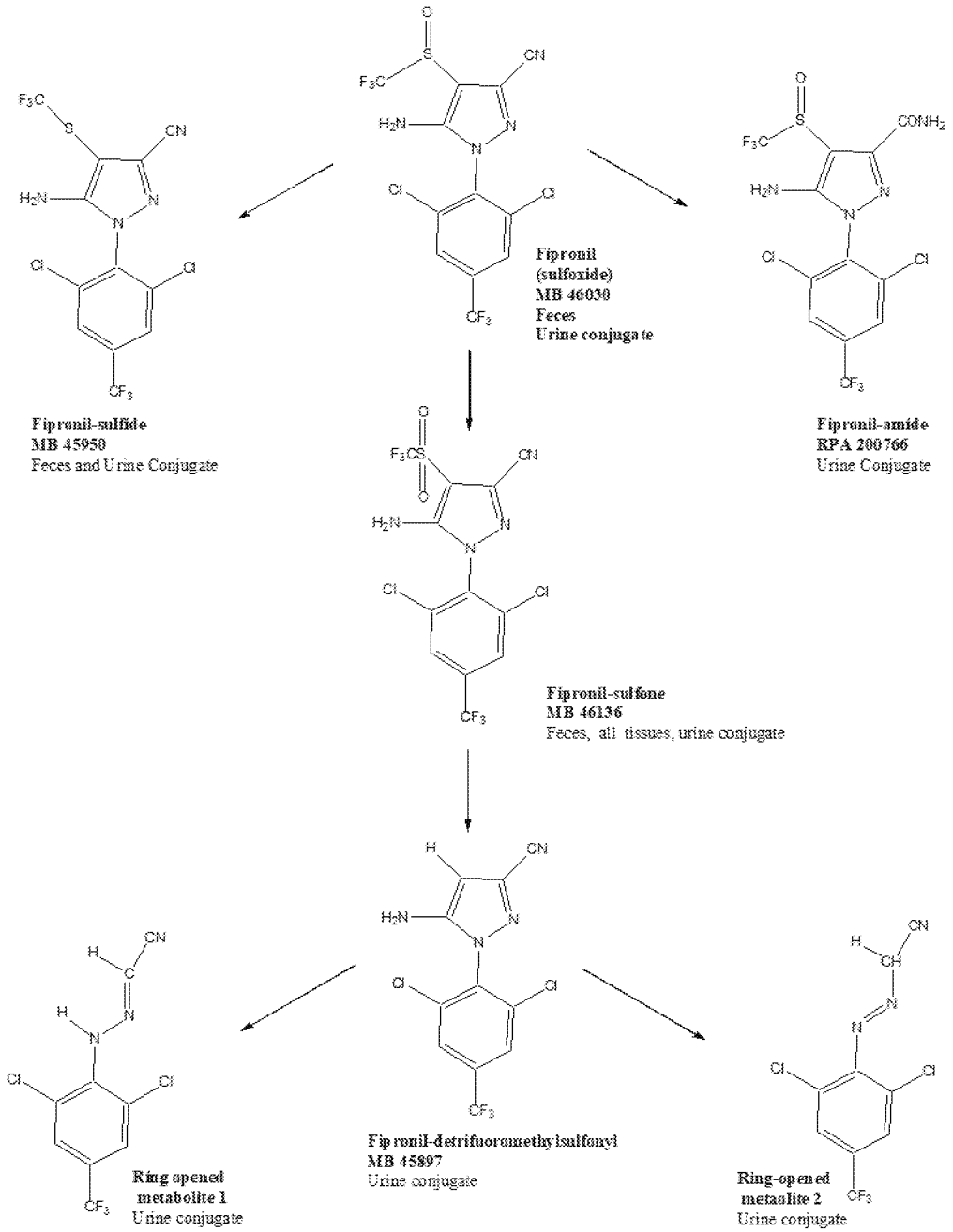

Figure 3. Biotransformation Pathways for Fipronil (sulfoxide) from Powell (1992).

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IV.B.6. Toxicokinetic and Metabolism Summary

Based on oral studies in rats, the oral absorption was assumed to be over 80% of the administered dose. For purposes of internal dose calculation, DPR considers oral absorption of > 80% to be complete (100%). Fipronil was extensively metabolized and distributed throughout the body. The parent compound was not detected in any tissues or in urine. At 7 days post dosing, fat tissue contained the highest metabolite levels. In both rats and humans, fipronil was metabolized primarily to the lipophilic sulfone metabolite. Other metabolites identified in rats included fipronil-sulfide and the amide product RPA 200766. The same or similar metabolites were found in goats and hens. Fipronil and its metabolites were eliminated mainly through the feces. In rats, the relatively slow elimination rate ($T_{1/2}$ > 6 days) was likely due to partitioning into fat and to enterohepatic recirculation.

The available toxicokinetic data for humans and rats was compared in Table 7. The data show that humans dosed at 35 mg/kg achieve peak blood concentrations of fipronil sooner (T_{max} of 1.3 – 4.6 hr) than rats dosed at 40 mg/kg (T_{max} 34-38 hr). The maximum blood concentration was 6 to 95-fold lower in humans. Elimination half-lives were calculated for rats and humans based on total fipronil concentrations in the blood (Table 7). However, substantial uncertainties were associated with these estimates. In rats, $T_{1/2}$ values were calculated to be 135-200 hours for a 4 mg/kg dose. For humans, an elimination $T_{1/2}$ of 47 hours was estimated for one individual (Patient 7, Table 6) who reportedly ingested 2.5 g of fipronil (estimated dose of 35 mg/kg using a default body weight of 71.8 kg). However, this $T_{1/2}$ estimate was based on only three time points with no measurements beyond 40 hours. A $T_{1/2}$ of 36 hours (also based on three time points) was estimated for Patient 4. Estimates for Patient 2, who ingested 5 g of fipronil (estimated dose of 70 mg/kg using a default body weight of 71.8 kg) indicate the $T_{1/2}$ in humans could be longer than 70 hours.

Additional toxicology data and toxicokinetics for the major fipronil metabolites and its environmental degradate are found in Appendix III.

Table 7. Comparison of Toxicokinetic Parameters for Fipronil in Rats and Humans

Exposure	Dose (mg/kg)	T_{max} (hours)	C_{max} (mg/ml)	$T_{1/2}$ (hours)
rats[a]	4	4.0-6.0	0.60-0.68	149-200
rats[b]	4	4.8-6.2	0.39-0.52	135-171
rats[b]	40	34-38	6.68-7.58	183-245
rats[a]	150	48-72	19.60-19.70	51-54
Patient 3[c]	35[d]	4.6	> 1.04	N/A
Patient 7[c]	35[d]	< 1.3	0.08	47
Patient 4[c]	UK	< 3.5	> 3.7	36
Patient 2[c]	70[d]	< 3.3	> 1.6	> 70[e]

C_{max}: maximum concentration in blood; T_{max}: time of C_{max} (absorption); $T_{1/2}$: elimination half-life.
[a]Powles (1992). [b]Totis (1994). [c]Mohamed (2004).
[d]Estimated dose using a default body weight of 71.8 kg.
[e]Last measured time point used as $T_{1/2}$.

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IV.C. Acute Toxicity

Acute toxicological studies with fipronil were conducted in rats, mice and rabbits to establish median lethal doses (LD_{50}) or concentrations (LC_{50}) necessary for determining the toxicity category of technical grade pesticides and formulations. In these studies, fipronil induced clinical signs suggestive of excessive CNS stimulation (convulsions, seizures and tremors). Other symptoms included incoordination and gait abnormalities, hypoactivity, lethargy, diarrhea, decreased respiratory rate and prostration. Fipronil caused eye irritation in rabbits, but did not produce skin irritation in rabbits or dermal sensitization in guinea pigs.

IV.C.1. Registrant-Submitted Acute Studies

One oral study was available in rat, with a median lethal dose (LD_{50}) of 92 mg/kg for males and 103 mg/kg for females (96.7% a.i., Table 8) (Gardner, 1988b). The LOEL for systemic effects was 50 mg/kg, the lowest dose tested, based on clinical signs (piloerection, hunched posture, gait abnormalities, and diarrhea; Table 9).

Two acute inhalation studies were available in the rat. In the first, fipronil was assessed in Sprague Dawley rats (Nachreiner, 1995) by nose-only exposure to fipronil dust (96.7% a.i.) for 4 hours. The LC_{50} was 0.36 mg/l for males and 0.42 mg/l for females (Table 8). The LOEL of 0.33 mg/l (lowest dose tested) was based on clinical signs and death (Table 9). This concentration was converted to a LOEL[3] of 53 mg/kg using a rat default breathing rate of 0.96 m^3/kg.

In the second acute inhalation study, fipronil (95.4% a.i.) was tested in CD rats via nose-only exposure for 4 hours (Cracknell, 1991). The LC_{50} for male and female rats, calculated with a log probit model, was 0.682 mg/l. The LOEL was 0.259 mg/l (lowest dose tested) or 41.4 mg/kg, based on mortality in females. Because particle size did not meet the US EPA requirements of 4 µm MMAD, the registrant submitted supplemental information regarding particle size (Cracknell, 1994).

Acute dermal toxicity studies were conducted in rat and in rabbit. In CD rats, fipronil (93% a.i.) in distilled water was applied to a shaved area on the back to 5/sex at a dose of 2000 mg/kg (Gardner, 1988a). The treatment sites were covered during the 24-hour exposure period. The pathological evaluation did not reveal treatment-related changes. The acute dermal LD_{50} of fipronil in rats was therefore > 2000 mg/kg (Table 8).

Fipronil (96.7% a.i.) was also tested for acute dermal toxicity (wetted in corn oil at 100, 250, 500, 1000 and 2000 mg/kg) in New Zealand White rabbits (Myers and Christopher, 1992), resulting in an acute dermal LD_{50} of 354 mg/kg for both sexes (Table 8). The LOEL for acute

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[3] Equivalent 1-day doses were calculated using the rat default breathing rate of 0.96 m^3/kg/day in the following equations: $\text{Dose (mg/kg/day)} = \text{Concentration (mg/m}^3\text{)} \times \frac{0.96\ m^3}{kg.day} \times \frac{4\ hours}{24\ hours}$

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dermal toxicity in rabbits was 100 mg/kg (lowest dose tested) based on hyperactivity in one male on days 5-7 and diarrhea in 2 females on days 1-2.

A primary dermal irritation study in New Zealand White rabbits resulted in a dermal Toxicity Category IV designation (Table 8) (Myers and Christopher, 1993b). A primary eye irritation study in New Zealand White rabbits resulted in a Category III designation (Myers and Christopher, 1993a). Delayed contact hypersensitivity was tested in guinea pigs (Smith, 1990). Based on results, the technical grade fipronil was regarded by DPR as "not a dermal sensitizer" in guinea pigs.

Acute oral, dermal and inhalation studies were also available for a 0.25% fipronil Frontline formulation (Clouzeau, 1994b; Clouzeau, 1994a; Robinson, 1994).

IV.C.2. Acute Studies from Published Literature

Two intraperitoneal studies in mice were available from the published literature. The studies were performed by the same group and utilized similar protocols (Cole *et al.*, 1993; Hainzl and Casida, 1996). The LD_{50} for fipronil was reported in Cole *et al.* to be 32 mg/kg and in Hainzl *et al.* to be 41 mg/kg. The LD_{50} for fipronil-desulfinyl was 23 mg/kg (Hainzl and Casida, 1996), *i.e.*, slightly more toxic than the parent compound. The LD_{50} was 80 mg/kg for fipronil-sulfone (Cole *et al.*, 1993). The IC_{50} at the GABA receptor was also measured. For fipronil-desulfinyl, the IC_{50} was less than one-tenth that of the parent compound, indicating a greater inhibitory potential at the mouse receptor (IC_{50} = 1010 nM for fipronil and 97 nM for fipronil-desulfinyl).

Acute toxicology, median lethality and irritation studies conducted with fipronil are summarized below and in Table 8. NOELs and Lowest-Observed-Effect-Levels (LOELs) from the appropriate studies are summarized in Table 9. NOELs and LOELs were based on clinical findings and were determined only from studies that employed a sufficient number of animals (e.g., at least 5 per dose group), included a range of doses, and provided experimental details on treatment protocol and experimental observations. Acute studies from the published literature were also reviewed. Studies relevant to the critical acute NOEL designation are described in the Hazard Identification section of this RCD.

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Table 8. Acute Lethal Doses (LD_{50}, mg/kg) and Lethal Concentrations (LC_{50}, mg/l) for Fipronil

Chemical	Animal Species	Route of Exposure	Males	Females	Toxicity Category	References
Fipronil technical (93-97%)	Rat – Crl:CD (SD)BR	Oral	92	103	II	Gardner (1988)
Fipronil technical (93-97%)	Rat – Sprague Dawley	Inhalation 4 hr dust	0.36[a,b]	0.42	II	Nachreiner (1995)
Fipronil technical (93-97%)	Rat – CD	Inhalation 4 hr dust	0.682[b]	0.682	--	Cracknell (1991)
Fipronil technical (93-97%)	Rat – CD	Dermal	>2000	>2000	III	Gardner (1988)
Fipronil technical (not described)	Mouse – Swiss-Webster	Intraperitoneal	32-41	--	--	Cole (1993), Hainzl (1996)
Fipronil technical (93-97%)	Rabbit – NZW	Dermal	354	354	II	Myers (1992)
Fipronil technical (93-97%)	Rabbit – NZW	Dermal Irritation	Not a dermal irritant, Category IV			Myers (1993)
Fipronil technical (93-97%)	Rabbit – NZW	Eye Irritation	Mild eye irritant[c], Category III			Myers (1993)
Fipronil technical (93-97%)	Guinea Pig	Dermal Sensitization	Not a dermal sensitizer			Smith (1990)
Fipronil-desulfinyl (MB 46513, 98.6%)	Rat	Oral	18	15	I	(Dange, 1993b)*
Fipronil-Desulfinyl (MB 46513, 98.6%)	Rat	Dermal	>2000	>2000	III	(Dange, 1993a)
Fipronil-Desulfinyl (MB 46513)	Mouse	Intraperitoneal	23	-	I	(Hainzl and Casida, 1996)
Fipronil-Sulfide (MB 45950)	Rat	Oral	83	83	II	(Dange, 1994)*
Fipronil-Sulfone (MB 46136)	Mouse	Intraperitoneal	80	-	II	(Cole *et al.*, 1993)
Fipronil formulation (0.25%)	Rat – Sprague Dawley	Oral[d]	>5000	>5000	--	Clouzeau (1994a)
Fipronil formulation (0.25%)	Rat – Sprague Dawley	Dermal[d]	>2000	>2000	--	Clouzeau (1994b)
Fipronil formulation (0.25%)	Rat – Sprague Dawley	Inhalation[d]	>5.0[b]	>5.0	--	Robinson (1994)

Toxicity category designation from US EPA (2020).

[a]More than 97% of the particles had an aerodynamic droplet size (MMAD) < 3 µm.

[b]The equivalent dose is calculated using the rat default breathing rate of 0.96 m^3/kg/day.

[c]Eye irritation cleared in 7 days.

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Table 9. NOELs and LOELs Derived from Acute Exposure Studies of Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, Wistar	oral acute LD_{50}, gavage	abnormal gait, hunched posture, diarrhea, piloerection	< 50	50	Gardner (1988)
Rat, Sprague Dawley	oral acute neurotox, gavage	reduced hindlimb splay, rearing	0.5	5	Gill (1993)
Rat, Crl:CD BR	oral acute neurotox, gavage	reduced hindlimb splay	2.5	7.5	Hughes (1997)
Rabbit, New Zealand White	dermal acute LD_{50}, 24-hr	hyperactivity, diarrhea, bloody kidney	< 100	100	Myers and Christopher (1992)
Rat, CD	inhalation acute LC_{50}, 4 hour nose-only	mortality in females	< 41.4[a]	41.4	Cracknell (1994)
Rat, Sprague Dawley	inhalation acute LC_{50}, 4 hour nose-only	death, clinical signs, gross pathology of stomach, lungs and brain	< 53[a]	53	Nachreiner (1995)

[a]Oral equivalent dose; calculated internal absorbed dose from external air concentrations by using a default rat breathing rate of 0.96 m^3/kg/day and 100% inhalation absorption.

IV.D. Subchronic Toxicity

Eight registrant-submitted subchronic toxicity studies were available in laboratory animals. These included oral studies in rat, mouse and dog, an inhalation study in rat, dermal studies in rat and rabbit, and an oral neurotoxicity study in rat.

The thyroid and the liver were the principle targets following subchronic exposure. Effects included decreased bodyweight and body weight gain; increased liver weight with enlarged hepatocytes, fat deposition and periacinar hypertrophy; changes in blood serum proteins indicative of liver injury; increased thyroid weights with follicular cell hypertrophy; clinical signs (including hyperactivity, convulsions, and body tremors); and death. Subchronic fipronil studies and NOELs are summarized below and in Table 12.

Additional subchronic studies were identified in the published literature, which monitored endpoints such as inflammation, genotoxicity or reproduction. These studies contributed to understanding mechanistic issues and are described in the Hazard Identification and Appraisal sections of this RCD, when appropriate.

ED_013611_00000016-00047

IV.D.1. Subchronic Oral Studies

Rat, 4 week (Peters, 1996)

Crl:DC (SD) BR rats (5/sex/dose) were exposed to fipronil (93%) over a 4-week period at dietary levels of 0, 25, 50, 100, 200 and 400 ppm. These concentrations corresponded to doses of to 0, 3.4, 6.9, 12.6, 24.5 and 45.3 mg/kg/day (males) and 0, 3.5, 6.7, 12.9, 24.9 and 54.9 mg/kg/day (females) (Peters, 1996).

One female from the 400 ppm group died after 4 days of treatment, with no evident clinical signs or pathological findings. While hair loss occurred in all exposure groups, all four of the surviving high-dose females displayed hair loss at termination, compared to 1/5 control animals.

Exposure to 100, 200 and 400 ppm caused a decrease in food consumption in both sexes (12-54% compared to control) during the first week of treatment. During this period, body weights were reduced up to 20% and remained 6-9% lower than controls until the end of the study. Body weight gain was significantly reduced compared to control during the first week ($p < 0.01$), but was not different for the remainder of the study, indicating that decreases in body weights were caused by reduction of food consumption. Food utilization was also reduced during the first week of exposure.

The absolute and relative liver weights were increased in all exposed groups in a dose-dependent manner. The increase in absolute liver weights ranged from 10 to 65% and was statistically significant in males at 200 ppm and higher and in females at all treated doses ($p < 0.05$). The increase in relative liver weights ranged from 8 to 81%.

Pathology examination revealed thyroid follicular hypertrophy in all treated groups. The severity of the effect was graded as minimal to moderate, and, in males, severity increased with dose. Histopathologic examination revealed hepatocyte enlargement in animals exposed to fipronil at doses higher than 50 ppm in males and at doses higher than 100 ppm in females. Enlarged livers were observed in males at the high dose (5/5 compared to 0/5 in controls) and in 3/5 females at the high dose (compared to 0.5 controls). Fat deposition was observed in the liver in 2 of 4 females examined in the 400 ppm group.

Changes in liver function in all treated groups were evident in the increased levels of globulin and total protein in serum (11-34%, $p < 0.01$). Particularly drastic was the increase in serum cholesterol, from 37% in the females at 25 ppm to 128% in the females at 400 ppm ($p < 0.01$). A decrease in aspartate aminotransferase was observed in both sexes above 50 ppm ($p < 0.05$).

The LOEL was set at the lowest tested dose of 25 ppm (3.4 mg/kg/day) based on increased absolute and relative liver weight in females, and liver and thyroid hypertrophy. A NOEL was not established.

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Rat, 13 week (Holmes, 1991a)

Fipronil (95.4% a.i.) was administered through the diet to 10 CD rats/sex/group at 0, 1, 5, 30 and 300 ppm (Holmes, 1991a). This corresponded to average daily doses of 0, 0.07, 0.3, 1.9 or 20 mg/kg/day for males and 0, 0.07, 0.4, 2.3 and 24 mg/kg/day for females. The main effects after 13 weeks of treatment included increased absolute and relative thyroid and liver weights, thyroid hypertrophy, and fat in the liver.

Mortality and clinical signs were not evident at any dietary level. Body weights were significantly reduced 15% in males at 300 ppm ($p \leq 0.01$) and 5% in females at 300 ppm ($p \leq 0.001$) during the first week of treatment; reductions in bodyweight persisted for three additional weeks. There was a 26% and 10% decrease in food intake in males during the first and second weeks of dosing, respectively, and a decrease of 14% in females during the first week. Authors note that the food utilization in males and females at the 300 ppm dose group were lower during week 1, indicating animals required more food to generate body mass.

The absolute weight of the thyroid was increased by 68% and 100% ($p < 0.01$) in the females and males, respectively, at 300 ppm. When expressed as thyroid/body weight ratio the increase was 75% for the females and 107% for the males ($p < 0.01$). The drastic increase in thyroid weight was likely due to both increased follicular cell size as well as to increased number of follicular cells. Hypertrophy of follicular cells was seen in all 10 females and in 8/10 males in the 300 ppm group. For comparison, only 1 female and 3 males in the control group had hypertrophic follicular cells. Six of 10 males and 2/10 females had follicular cell hyperplasia, whereas none of the control females and only 2 of the control males showed increased number of follicular cells.

Absolute liver weight was increased by 54% and 42% ($p < 0.01$) in females and males, respectively, at 300 ppm. The increase in relative (to bodyweight) weight was of similar magnitude (58% for females and 43% for the males, $p < 0.01$). Analysis of the serum chemistry of these animals revealed 15-30% ($p < 0.01$) increase in urea, glucose and α1-globulin in the blood, which could indicate changes in liver synthetic/metabolic function. Accumulation of fat in the liver was noted in both sexes at 300 ppm (20 mg/kg/day). The highest incidence was detected in liver sections of males (7/10 at 300 ppm *vs.*0/10 controls). Higher absolute and relative liver weight (14-24%, $p < 0.01$) was reported for the rats in the 30 ppm group.

The investigators proposed that fipronil affected the hypothalamic-pituitary-thyroid-liver axis. However, they did not measure thyroid hormone levels, pituitary hormones, or liver metabolic activity. The subchronic oral NOEL was 30 ppm (1.9 mg/kg/day). Effects at the LOEL of 300 ppm (20 mg/kg/day) included marked increases in the absolute and relative thyroid and liver weights, thyroid hypertrophy, fat accumulation the liver and altered serum proteins. DPR considered the increased relative liver weight in males and increased blood glucose in females seen at the NOEL not sufficiently robust for LOEL designation.

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Mouse, 13 week (Broadmeadow, 1991)

The toxicity of fipronil (95.4%) was evaluated in CD-1 mice (12/sex/dose) for a period of 13 weeks. The dietary levels of 0, 1, 3, 10 and 25 ppm corresponded to internal doses of 0, 0.13, 0.38, 1.27 and 3.2 mg/kg/day (males) and 0.17, 0.57, 1.72 and 4.53 mg/kg/day (females) (Broadmeadow, 1991). Hematology, clinical chemistry and ophthalmology were not evaluated. Thyroids were collected but not analyzed.

The liver was the principal target organ. The absolute weight of the liver was increased by 24% ($p < 0.01$) in males treated with 3.2 mg/kg/day fipronil (Table 10). Liver weights were also increased 5-14% in males at 1.27 mg/kg/day and in females at 1.72 mg/kg/day and higher, though statistical significance was not achieved. Relative to body weight, increases of up to 33% were statistically significant in both sexes at the high dose ($p < 0.05$) and were non-statistically increased up to 12% in the mid-high group in both sexes.

The increase in liver weight was in part due to increased hepatocyte size. Periacinar hypertrophy was reported for all male treatment groups, but not in controls. At the lowest dose, 2 of 12 males had liver hypertrophy. At 3 ppm, 3 of 12 males had hypertrophy. This effect became statistically significant at 10 and 25 ppm fipronil (6/12 and 10/12 males, respectively). One male treated at the highest tested dose had focal necrosis of liver cells. While liver hypertrophy was not detected in the females, fatty vacuolation occurred in hepatocytes in 2 female mice from the mid-high dose group and 1 from the high dose group.

The LOEL for this study was set at the lowest tested dose (0.13 mg/kg/day) based on the appearance of periacinar hypertrophy in the livers of male mice. The absence of statistical significance at 0.13 and 0.38 mg/kg/day is noted by DPR.

Table 10. Toxicity in CD-1 Mice Following 13-Weeks of Fipronil Dietary Exposure

	Males					**Females**				
ppm	**0**	**1**	**3**	**10**	**25**	**0**	**1**	**3**	**10**	**25**
mg/kg/day	**0**	**0.13**	**0.38**	**1.27**	**3.2**	**0**	**0.17**	**0.57**	**1.72**	**4.53**
N	12	12	12	12	12	12	12	12	12	12
BW gain (g)	14.6 ± 3.5	12.2 ± 4.9	13.9 ± 4.8	13.2 ± 4.2	11.4 ± 5.2	6.8 ± 3.1	5.8 ± 3.2	4.8 ± 2.3	7.6 ± 1.5	4.3 ± 3.0*
% of Control	100	84	95	90	78	100	85	71	112	63
Liver - Abs. Weight (g)	2.2 ± 0.3	2.2 ± 0.4	2.2 ± 0.4	2.4 ± 0.4	2.8 ± 0.3**	1.7 ± 0.2	1.6 ± 0.2	1.6 ± 0.3	0.9 ± 0.2	1.75 ± 0.2
Liver - Rel. Weight	5.0 ± 0.7	5.1 ± 0.4	4.9 ± 0.5	5.6 ± 0.5	6.6 ± 0.8**	5.6 ± 0.7	5.5 ± 0.6	5.8 ± 0.4	6.1 ± 0.6	6.3 ± 0.5**
Periacinar Hypertrophy	0	2	3	6*	10***	0	0	0	0	0

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Table 10. Toxicity in CD-1 Mice Following 13-Weeks of Fipronil Dietary Exposure

	Males					Females				
ppm	**0**	**1**	**3**	**10**	**25**	**0**	**1**	**3**	**10**	**25**
mg/kg/day	**0**	**0.13**	**0.38**	**1.27**	**3.2**	**0**	**0.17**	**0.57**	**1.72**	**4.53**
Fatty Vacuolation	0	0	0	0	0	0	0	0	2	1

*, ** and *** indicate p-values < 0.05, 0.01 and 0.001, respectively. BW: body weight; Abs: absolute weight; Rel: relative weight.
Data from Broadmeadow (1991)

Dog, 13 week (Holmes, 1991b)

The subchronic toxicity of fipronil (95.4%) was examined in Beagle dogs by daily gelatin capsule administration for a period of 13 weeks (Holmes, 1991b). The study included four groups of dogs, each containing four males and four females at doses of 0, 0.5, 2.0 and 10.0 mg/kg/day. Three females and one male in the 10 mg/kg/day dose group were sacrificed during the second week of treatment due to poor health. The subchronic oral NOEL of 2 mg/kg/day was based on severe toxicity (mortality, weight loss, clinical signs and neurological disturbances) at the LOEL of 10 mg/kg/day. However, reduced food intake (up to 11%) was reported for three of the females from the 2 mg/kg/day (NOEL) group during weeks 2-9.

IV.D.2. Subchronic Inhalation Studies

Rat, 4 week (Adamo-Trigiani, 1999)

Groups of 15 Sprague Dawley CD (Crl®(SD)BR) rats/sex/group were exposed by nose-only inhalation to micronized fipronil (95% purity) for 4 hours per day on 28 consecutive days (Adamo-Trigiani, 1999). Air concentrations were 0, 0.001, 0.005, or 0.03 mg/L fipronil, (MMAD 2.1 to 2.4 µm ± GSD 1.7 to 1.8). Oral equivalent doses were calculated using a rat default breathing rate[4].

Six females and 1 male at the high dose exhibited ungroomed fur on day 2. The male also showed decreased activity, and two of the females showed salivation and decreased activity on day 2 (Table 11). Two additional high dose females displayed sustained convulsions (in one case, with handling) on day 2 (Table 11). Mortality was not observed.

Decreased body weight in males (9%, $p < 0.01$) and decreased food consumption in both sexes were seen at day 8. Body weights remained statistically significantly decreased in high dose males until the end of the study. In females at the mid- and high-dose groups, body weights were statistically significantly reduced (~6%) from day 22 to day 28.

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[4] Rat default breathing rate of 0.96 m^3/kg/day:

$$\text{Dose (mg/kg/day)} = \text{Concentration (mg/m}^3\text{)} \times \frac{0.96\ \text{m}^3}{\text{kg.day}} \times \frac{4\ \text{hours}}{24\ \text{hours}} \quad \text{(1 day exposure)}$$

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Altered liver function was indicated by the clinical chemistry data, including: significantly elevated globulin in the mid- and high-dose males and the high-dose females; decreased bilirubin in males at all doses and in females at the mid- and high-doses; increased cholesterol in females at the mid- and high-dose; and increased prothrombin (PT) times ($p < 0.001$) and activated partial thromboplastin time in males at the mid- and high-doses (Table 11).

At study termination, absolute and relative liver weights were elevated by 11-22% in mid- and high-dose males, and 16-24 % in high dose females.

The subchronic NOEL was 0.001 mg/L, based on decreased body weights in females, increased relative liver weights in both sexes, increased absolute liver weights in males, and changes in blood chemistry parameters in males and females at the LOEL of 0.005 mg/L (Table 11). Oral equivalent doses were calculated using a rat default breathing rate, making the subchronic NOEL and LOEL equal to 0.16 and 0.8 mg/kg/day, respectively.

Although this was a repeated exposure study, clinical signs were noted on day 2 in the rats at the high dose (0.03 mg/L), indicating an acute response. These animals also had significant decreases in body weight and food consumption after 1 week of exposure. Therefore, the NOEL of 0.005 mg/L (0.8 mg/kg/day) for these effects can be used to characterize acute and short-term inhalation exposures to fipronil.

Table 11. Toxicity in Sprague Dawley Rats following 28-days of Inhalation Exposure to Fipronil

	Males				**Females**			
Dose (mg/l)	**0**	**0.001**	**0.005**	**0.03**	**0**	**0.001**	**0.005**	**0.03**
Dose (mg/kg/day)	**0**	**0.16**	**0.8**	**4.8**	**0**	**0.16**	**0.8**	**4.8**
N	15	15	15	15	15	15	15	15
Day 1 BW	197 ± 10.5	202 ± 9.0	201 ± 8.5	196 ± 10.0	149 ± 7.1	151 ± 5.3	151 ± 5.9	150 ± 5.7
% of control	100%	103%	102%	99%	100%	101%	101%	101%
Day 8 BW	243 ± 14.0	238 ± 14.5	242 ± 14.6	221 ± 14.2**	171 ± 9.1	170 ± 8.3	167 ± 9.7	166 ± 9.2
% of control	100%	98%	100%	91%	100%	99%	98%	97%
Day 22 BW	320 ± 18.7	303 ± 22.5	312 ± 26.6	290 ± 20.3**	212 ± 12.4	202 ± 13.4	200 ± 12.8*	199 ± 12.5*
% of control	100%	95%	98%	91%	100%	95%	94%	94%
Day 28 BW	341 ± 18.1	331 ± 29.0	332 ± 32.3	311 ± 22.7**	228 ± 14.2	221 ± 15.5	213 ± 14.1*	215 ± 13.2*
% of control	100%	97%	97%	91%	100%	97%	93%	94%
Fur, ungroomed - day 2	0	0	0	1	0	0	0	6
Slight salivation - day 2	0	0	0	0	0	0	0	1
Moderate salivation - day 2	0	0	0	0	0	0	0	1
Activity, decreased - day 2	0	0	0	1	0	0	0	2

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Table 11. Toxicity in Sprague Dawley Rats following 28-days of Inhalation Exposure to Fipronil

	Males				Females			
Dose (mg/l)	**0**	**0.001**	**0.005**	**0.03**	**0**	**0.001**	**0.005**	**0.03**
Dose (mg/kg/day)	**0**	**0.16**	**0.8**	**4.8**	**0**	**0.16**	**0.8**	**4.8**
Convulsions - day 2[a]	0	0	0	0	0	0	0	1
Sustained convulsions	0	0	0	0	0	0	0	1
Absolute Liver (g)	8.6 ± 0.8	8.7 ± 1.0	9.63 ± 1.3*	9.57 ± 0.7*	6.32 ± 0.6	6.36 ± 0.7	6.31 ± 0.6	7.34 ± 0.6**
% of control	100%	101%	112%	111%	100%	101%	100%	116%
Relative Liver (g)	2.8 ± 0.1	2.95 ± 0.2	3.32 ± 0.5***	3.42 ± 0.1***	3.14 ± 0.2	3.25 ± 0.2	3.34 ± 0.2*	3.90 ± 0.3**
% of control	100%	105%	119%	122%	100%	104%	106%	124%
Cholesterol (mg/dl)	52.6 ± 9.3	55.1 ± 12.7	56.0 ± 5.8	62.0 ± 11.9	58.9 ± 12.2	62.7 ± 11.6	72.1 ± 9.1*	90.6 ± 16.0**
% of control	100%	105%	106%	118%	100%	106%	122%	154%
Globulin (g/dl)	2.8 ± 0.2	2.9 ± 0.2	3.1 ± 0.2**	3.1 ± 0.2**	2.9 ± 0.2	2.9 ± 0.2	2.9 ± 0.1	3.1 ± 0.2**
% of control	100%	104%	111%	111%	100%	100%	100%	107%
Total Bilirubin (mg/dl)	0.15 ± 0.03	0.13 ± 0.03*	0.11 ± 0.02**	0.10 ± 0.02**	0.16 ± 0.03	0.14 ± 0.04	0.11 ± 0.03**	0.11 ± 0.03**
% of control	100%	87%	73%	67%	100%	88%	69%	69%
Prothrombin Time (sec)	15.2 ± 0.5	15.9 ± 1.4	16.3 ± 1.8*	17.4 ± 2.5***	15.2 ± 0.6	14.8 ± 0.8	15.1 ± 0.5	14.9 ± 0.5
% of control	100%	105%	107%	114%	100%	97%	99%	98%
Activated Partial Thromboplastin Time (sec)	18.7 ± 1.9	20.7 ± 1.8	21.9 ± 2.3**	25.2 ± 4.7***	16.8 ± 1.5	16.6 ± 2.4	16.6 ± 2.2	16.7 ± 2.0
% of control	100%	111%	117%	135%	100%	99%	99%	99%

[a]Sustained convulsions when handling - day 2

*, ** and *** indicate p-values < 0.05, 0.01 and 0.001, respectively. BW: body weight.

Data from Adamo-Trigiani (1999)

IV.D.3. Subchronic Dermal Studies

Rat, 4 week (Henwood, 1997)

Fipronil (94.95% a.i.) mixed with 1% methylcellulose in reverse osmosis water was applied to a porous gauze dressing and administered to the clipped, intact dorsal skin on the trunk of 10 Crl:CD(SD)BR rats/sex/dose. Doses were 0, 100, 500, or 1000 mg/kg/day (Henwood, 1997). Animals were exposed for 6 to 7 hours per day, 5 days per week, for 4 consecutive weeks.

One male at the high dose displayed excessive salivation on day 22 of treatment. No other clinical signs were observed. The incidence of erythema was sporadically increased in the 500 and 1000 mg/kg/day dose groups after 18 to 29 days (males) and 18-31 days (females).

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Body weight gains of males were reduced by 20-36% in the 500 and 1000 mg/kg/day dose groups from days 1-8 (statistically significant in high-dose only, $p < 0.05$). Food consumption was statistically significant decreased by 14% in females at the high dose during days 1-8.

Increased total protein levels were observed in all exposed male groups (up to 7%, $p < 0.05$) and in the two higher doses in females (7%, $p < 0.05$). Globulin levels were increased by at least 8% in all treated groups; the increase of 17% in the high-dose males and 20% in the mid- and high-dose females was statistically significant ($p < 0.05$). The albumin:globulin ratio was decreased in all exposed males by 10-15% and females by 5-15%. The decrease was statistically significantly in the high-dose males (15%, $p < 0.05$) and in females at the mid- and high-doses (15%, $p < 0.05$).

Increased absolute liver weights were observed in all treated groups (14-22% in males, 9-20% in females). The increases were statistically significant in the mid- and high-dose females only ($p < 0.05$). The relative liver weights were also increased in all treated groups in both sexes (10-22% in males and 7-20% in females). Relative liver weights were statistically significantly increased at the mid- and high-doses in both sexes ($p < 0.05$).

The dermal LOEL was 100 mg/kg/day (lowest dose tested) based on altered clinical chemistry and increased relative liver weights.

Rabbit, 3 week (Hermansky and Wagner, 1993)

In a 21-day dermal toxicity study, fipronil (96.7%) was applied as a paste under a semi-occlusive cover to a shaved area of the back of 6 New Zealand white rabbits/sex/dose at doses. Doses were 0, 0.5, 1.0, 5.0 or 10.0 mg/kg (Hermansky and Wagner, 1993) in 0.5% carboxymethylcellulose in water (vehicle). Treatment was for 6 hours/day, 5 days/week over 3 weeks (15 applications).

Toxic effects were reported for animals at the 10 mg/kg/day dose. These included "extreme" hyperactivity in 1 male and 1 female on days 20-21, decreased food consumption (44% in males and 21% in females) during the last week of treatment that was statistically significant in males only ($p < 0.05$), decreased bodyweight gain in from days 1 to 15 and 1 to 22, which was statistically significant at day 21 ($p < 0.01$), and weight loss in males at the end of the study (7%, $p < 0.05$).

The subchronic NOEL for fipronil was 5 mg/kg/day, based on "extreme" hyperactivity, reduced body weight gain and decreased food consumption at the LOEL of 10 mg/kg/day.

Table 12. NOELs and LOELs Derived from Subchronic Exposure Studies

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, Crl:CD(SD)BR	oral, dietary, 4 weeks	increased liver weight, thyroid hypertrophy	< 3.4	3.4	Peters (1996)
Rat, CD	oral, dietary, 13 weeks	increased relative and absolute liver and	1.9	20	Holmes (1991)

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Table 12. NOELs and LOELs Derived from Subchronic Exposure Studies

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
		thyroid weights, thyroid hypertrophy, and fat accumulation in liver			
Rat, Sprague Dawley	oral, neurotox, dietary, 13 weeks	autonomic nervous system effects	0.03	0.3	Driscoll and Hurley(1993)
Mouse, CD-1	oral, dietary, 13 weeks	hepatocyte periacinar hypertrophy	< 0.13	0.13	Broadmeadow (1991)
Dog, Beagle	oral, gelatin capsule, 13 weeks	mortality, weight loss, clinical signs and neurological disturbances	2	10	Holmes (1991)
Rabbit, New Zealand White	dermal, 3 wk, 5 day/wk, 6 hr/day	extreme hyperactivity, reduced BW gain and food consumption	5	10	Hermansky and Wagner (1993)
Rat, Crl:CD(SD)BR	dermal, 4 wk, 5 day/wk, 6-7 hr/day	increased total protein and globulin levels and increased relative liver weights	< 100	100	Henwood (1997)
Rat, Sprague Dawley	inhalation, 4 weeks, 4 h/day, nose-only	decreased BW and food consumption, increased relative liver weights in males, changes in blood chemistry	0.16[a]	0.8	Adamo-Trigiani (1999)

[a]Oral equivalent dose; calculated internal absorbed dose from external air concentrations by using a default rat breathing rate of 0.96 m^3/kg/day and 100% inhalation absorption.

IV.E. Chronic Toxicity

Four chronic toxicity studies were available to characterize fipronil's chronic effects and potential to cause cancer in laboratory animals. These included two-year dietary studies in rats and mice and two one-year oral studies in dogs, Studies are summarized in Table 15.

The most common effects following chronic exposure were convulsions and tremors in rats and dogs. Morphologic effects included liver and kidney lesions in rats and mice and thyroid lesions in rats. Thyroid disruption in rats was suggested by increased thyroid weights and changes in serum thyroid hormones (decreased T4 and increased TSH). Liver effects in mice included hypertrophy and periacinar vacuolation. Progressive senile nephropathy was seen in rats. In addition, thyroid follicular cell tumors were reported in rats at levels that caused clinical signs and death. Fipronil action on an extrathyroidal site was suggested as the cause of thyroid neoplasia, but was not directly demonstrated. An extrathyroidal cancer model was proposed based on evidence that fipronil does not interfere with the incorporation of iodide in the thyroid, but does increase the clearance of T4 from the blood. The chronic exposure studies are summarized below.

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IV.E.1. Chronic Oral – Rat (Aughton, 1993)

In a chronic toxicity/oncogenicity study, fipronil (95.4% a.i.) was administered to CD rats at dietary levels of 0, 0.5, 1.5, 30 and 300 ppm (Aughton, 1993). The study was divided into three phases. The Oncogenicity Phase consisted of 50 rats/sex/dose that received fipronil for 89-91 weeks. In the Toxicity Phase, an additional 15 rats/sex/dose were examined for effects after 53 weeks of treatment. In the Reversibility Phase, 15 more rats/sex/dose received fipronil for 52 weeks, then given untreated food for 13 weeks to assess the reversibility of any toxicity. The average daily doses were 0.02, 0.06, 1.3 and 13 mg/kg/day for males and 0.03, 0.08, 1.6 and 17 mg/kg/day for females. The Oncogenicity Phase was shortened from 104 weeks to 89 weeks (males) or 91 weeks (females) due to poor survival of both controls and treated rats.

At the conclusion of the study, no dose-dependent difference in mortality were observed. However, death in males treated with fipronil was observed sooner than the control males. The first control male died at week 42. In contrast, the first male in the 0.5, 1.5, 30 and 300 ppm groups died at weeks 27, 23, 25 and 1, respectively (Table 13). Convulsions lasting up to 25 min were reported in 3 males exposed to 1.5 ppm fipronil and in a total of 24 animals from both sexes in the 30 and 300 ppm groups (Table 13). Convulsions were frequently observed during the first few weeks of treatment and sporadically throughout the entire exposure duration in both sexes at the high dose. Convulsions occurred at the LOEL (1.5 ppm, 0.06 mg/kg/day) during weeks 23, 61 and 69 in males and at 30 ppm (1.6 mg/kg/day) in females from weeks 1 through 55. One out of 3 males from the 1.5 ppm group and 8 out of 24 animals from the 30 and 300 ppm groups died following convulsions. Other clinical signs in rats treated with 1.5 ppm fipronil and higher included irritability, vocalization, salivation, aggressive behavior, grinding teeth and a higher number of thin animals.

Chronic exposure to 300 ppm fipronil resulted in a substantial reduction in body weights (up to 18 % for the males and 25% for the females, $p \leq 0.01$, one-way ANOVA by DPR) at all times. Decreases in body weight of same magnitude (15 – 22% ($p \leq 0.05$) was also observed in males and females at the 30 ppm dietary level toward the end of the treatment (weeks 68 – 88 of the study). The reduction in the body weight was clearly treatment-related, because food intake of these animals was similar to the control. Body weight data indicate that the maximum tolerated dose was reached or exceeded in this study at the high dose. Body weights of the animals receiving 30 and 300 ppm fipronil did not recover to the control level during the 13 week reversibility period (Table 13). Other effects occurring from exposure at or above 1.5 ppm included decreased hemoglobin concentrations and erythrocyte counts, increased platelet numbers, increased plasma cholesterol and calcium concentrations, increased alpha- and beta-globulins and decreased albumin levels, and shorter prothrombin time.

Thyroid and pituitary function were affected by altered serum levels of thyroid hormones. Triiodothyronine (T3) was statistically significantly reduced (13%) in males from the 300 ppm group after 1 week of treatment ($p < 0.05$). It was sporadically decreased and increased at other doses and time points. Thyroxine (T4) was markedly lower in all treated male groups at most time points (week 1 to week 50) and was not detectable in the serum of male or female rats

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exposed at 300 ppm after 1 week of treatment ($p < 0.001$). At week 1, a dose-dependent and statistically significant decrease in T4 occurred in males at 1.5 ppm and higher (24 – 100% decrease, $p < 0.05$). From weeks 4-12, a statistically significant and dose-dependent decrease occurred in all exposed males (14 – 88% decrease, $p < 0.05$). T4 levels were decreased in females by 46 and 100% at the mid- and high-dose at week one ($p < 0.01$) and at the high-dose were by 49 – 74% for the duration of the study ($p < 0.001$). The T4 levels in females were statistically significantly decreased at lower doses at various times. Correspondingly, TSH was 292 to 441% of controls ($p < 0.001$) for males and 197 to 265% of controls for females treated at 300 ppm ($p < 0.001$). TSH was also increased (205 to 251% of control) in males at 30 ppm at week 1, 4 and 50 ($p < 0.05$). After 11 weeks of recovery, the TSH level remained at 221% of controls in the 300 ppm males, ($p < 0.01$, Table 13). At the time, TSH was 21-121% higher in all exposed male groups and was sporadically 15% higher in the high-dose females.

The absolute and relative-to-body weights of several organs from rats exposed to 1.5-300 ppm fipronil were consistently higher than controls at 52 and 88 – 91 weeks of treatment. These organs included liver (up to a 43% and 58% increase in absolute and relative weights, respectively, $p < 0.05$), thyroid (up to a 123% and 163% increase in absolute and relative weights, respectively, $p < 0.05$); adrenals (up to a 48% and 55% increase in absolute and relative weights, respectively, $p < 0.05$) and kidney (up to a 56% and 84% increase in absolute and relative weights, respectively, $p < 0.05$). The absolute weight of the thyroid gland increased significantly in all male treatment groups at terminal examination (88 weeks, Table 13).

Pathological examination revealed an increase in incidence and severity of progressive senile nephropathy (PSN) that was not reversible at the high dose in females. PNS in rats is characterized by enlarged and pale kidneys with cystic spaces caused by thickening and dysfunction of the basement membrane, possibly due to increased content of collagen-like polypeptides(Greaves and Faccini, 1984; Abrass, 2000). PSN was seen as early as 23 weeks in treated males and 52 weeks in treated females, compared to 62 weeks (male) and 66 weeks (female) for controls. In animals that survived until the end of treatment, the effect was statistically significant for males in all treatment groups (Table 13). Changes were most dramatic in males treated with 30 and 300 ppm exposed for 89 weeks. When decedents are included, incidence was statistically significantly increased in the 30 ppm females and 300 ppm males and females. Also, there was an increase in PSN in animals at the interim (52 week) sacrifice, which was statistically significant in high dose females. Decreased albumin and increased α-globulins and cholesterol have been described in rats with PSN (Barthold, 1979), and were observed in this study in rats at 30 and 300 ppm. PSN is common in aging rats, but fipronil increased the rate at which PSN occurred.

The chronic NOEL was 0.5 ppm (0.02 mg/kg/day) based on convulsions, clinical signs, increased incidence of progressive senile nephropathy, and thyroid hormone alterations at the LOEL of 1.5 ppm (0.06 mg/kg/day). Some of the effects at the LOEL were first seen within the first week of treatment (altered T4 levels) or within six months (convulsions) and continued until the end of the study. Thyroid tumors observed in males and females at the high dose are described in the oncogenicity section, below.

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Table 13. Toxicity in CD Rats following Chronic Dietary Exposure to Fipronil

	Males					Females				
Dose (ppm)	**0**	**0.5**	**1.5**	**30**	**300**	**0**	**0.5**	**1.5**	**30**	**300**
Dose (mg/kg/day)	**0**	**0.02**	**0.06**	**1.3**	**13**	**0**	**0.03**	**0.08**	**1.6**	**17**
N[a]	80	80	80	80	80	80	80	80	80	80
Total mortality (weeks 88-91)	30	36	28	30	36	28	29	28	37	28
Week of first mortality	42	26	23	25	1	44	37	58	42	1
Convulsions[b]	0	0	3	1	8	0	0	0	3	12
Death after convulsions	0	0	1	0	4	0	0	0	1	3
Total mortality (88-91 weeks)	30	36	28	30	36	28	29	28	37	28
BW (g) week 1	253 ± 22	253 ± 21	250 ± 20	249 ± 19	216 ± 19†††	190 ± 16	187 ± 16	186 ± 15	183 ± 14†	171 ± 12††††
% of con	100%	100%	99%	98%	85%	100%	98%	98%	96%	90%
BW (g) week 52	904 ± 164	918 ± 145	896 ± 119	861 ± 145	792 ± 114††††	500 ± 97	508 ± 100	498 ± 95	488 ± 86	435 ± 76
% of con	100%	102%	99%	95%	88%	100%	102%	100%	98%	87%
BW (g) week 13 reverse[c]	880 ± 243	855 ± 168	965 ± 142	853 ± 116	703 ± 115†	546 ± 144	537 ± 124	507 ± 81	547 ± 118	428 ± 64††††
% of con	100%	97%	110%	97%	80%	100%	98%	93%	100%	78%
BW (g) week 88-91	881 ± 138	964 ± 206	963 ± 138	836 ± 222	758 ± 76	612 ± 126	565 ± 135	599 ± 117	480 ± 135††	486 ± 96†††
% of con	100%	109%	109%	95%	86%	100%	92%	98%	78%	79%
N (hormone measurements)	10	10	10	10	10	10	10	10	10	10
T4 week 1 (µg/dL)	2.93 ± 0.5	3.02 ± 0.6	2.23 ± 0.74*	1.16 ± 0.7***	0.00 ± 0***	2.23 ± 1.0	1.86 ± 0.5	2.58 ± 1.15	1.26 ± 0.6**	0.0 ± 0***
% of con	100%	103%	76%	40%	0%	100%	83%	116%	57%	0%
T4 week 50 (µg/dL)	5.95 ± 1.1	5.51 ± 1.0	4.83 ± 0.6**	3.90 ± 0.7***	2.07 ± 0.4***	3.31 ± 1.1	3.46 ± 0.7	3.0 ± 0.6	2.06 ± 0.6***	1.38 ± 0.4***
% of con	100%	93%	81%	66%	35%	100%	105%	91%	62%	42%
T4 week 11 reverse (µg/dL)[c]	3.7 ± 0.8	3.58 ± 0.7	3.25 ± 0.6	3.29 ± 0.6	3.52 ± 0.6	2.95 ± 0.6	3.6 ± 0.7	3.27 ± 0.4	3.65 ± 0.7*	3.09 ± 1.0
% of con	100%	97%	88%	89%	95%	100%	122%	111%	124%	105%
T3 week 1 (ng/mL)	0.61 ± 0.09	0.59 ± 0.07	0.61 ± 0.10	0.58 ± 0.06	0.53 ± 0.06*	0.78 ± 0.16	0.75 ± 0.14	0.77 ± 0.12	0.75 ± 0.13	0.8 ± 0.23
% of con	100%	83%	100%	83%	83%	100%	100%	100%	100%	114%

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Table 13. Toxicity in CD Rats following Chronic Dietary Exposure to Fipronil

	Males					Females				
Dose (ppm)	**0**	**0.5**	**1.5**	**30**	**300**	**0**	**0.5**	**1.5**	**30**	**300**
Dose (mg/kg/day)	**0**	**0.02**	**0.06**	**1.3**	**13**	**0**	**0.03**	**0.08**	**1.6**	**17**
T3 week 50 (ng/mL)	0.7 ± 0.13	0.67 ± 0.12	0.84 ± 0.14*	0.82 ± 0.13*	0.69 ± 0.14	0.87 ± 0.12	0.88 ± 0.12	0.83 ± 0.21	0.84 ± 0.08	0.87 ± 0.21
% of con	100%	86%	114%	114%	86%	100%	100%	100%	100%	100%
T3 week 11 reverse (ng/mL)[c]	0.56 ± 0.15	0.52 ± 0.09	0.59 ± 0.10	0.62 ± 0.10	0.64 ± 0.43	0.75 ± 0.14	0.81 ± 0.12	0.83 ± 0.06	0.95 ± 0.18**	1.11 ± 0.21***
% of con	100%	93%	105%	111%	114%	100%	108%	111%	127%	148%
TSH week 1 (ng/mL)	4.7 ± 0.9	7.1 ± 2.7	6.2 ± 2.5	11.8 ± 5.6***	20.3 ± 7.4***	3.5 ± 1.1	3.5 ± 0.7	3.2 ± 1.2	3.6 ± 0.9	7.6 ± 4.2***
% of con	100%	151%	132%	251%	432%	100%	100%	91%	103%	217%
TSH week 50 (ng/mL)	13.0 ± 7.2	17.1 ± 5..6	12.4 ± 5.5	26.6 ± 18.9*	57.3 ± 21.7***	6.2 ± 1.4	8.0 ± 4.0	5.5 ± 2.1	6.1 ± 1.3	13.5 ± 5.0***
% of con	100%	132%	95%	205%	441%	100%	129%	89%	98%	218%
TSH week 11 reverse (ng/mL)c	3.8 ± 1.4	4.6 ± 2.3	4.6 ± 1.2	5.1 ± 2.5	8.4 ± 6.0**	2.7 ± 0.5	3.1 ± 1.2	2.9 ± 0.8	2.7 ± 0.5	3.1 ± 1.0
% of con	100%	121%	121%	134%	221%	100%	115%	107%	100%	115%
N (52 weeks)	12	14	14	15	12	14	14	14	14	13
52 week absolute liver wt (g)	29.5 ± 5.5	30.0 ± 7.8	29.1 ± 6.2	34.3 ± 8.0	40.5 ± 5.2**	16.4 ± 3.6	17.3 ± 4.3	17.1 ± 3.1	19.1 ± 4.3	23.4 ± 4.6**
% of con	100%	102%	99%	116%	137%	100%	105%	104%	116%	143%
52 week relative liver wt	3.53 ± 0.55	3.44 ± 0.37	3.40 ± 0.35	4.32 ± 0.61**	5.26 ± 0.40**	3.56 ± 0.51	3.62 ± 0.60	3.7 ± 0.51	4.31 ± 0.53**	5.49 ± 0.68**
% of con	100%	97%	96%	122%	149%	100%	102%	104%	121%	154%
52 week absolute thyroid wt (mg)	39 ± 7	35 ± 12	42 ± 8	47 ± 15	56 ± 11**	27 ± 9	31 ± 7	30 ± 6	32 ± 7	45 ± 11**
% of con	100%	90%	108%	121%	144%	100%	115%	111%	119%	167%
52 week relative thyroid wt[d]	4.7 ± 1.1	4.0 ± 1.0	5.0 ± 0.6	5.8 ± 1.4*	7.3 ± 1.5**	5.9 ± 1.7	6.4 ± 0.8	6.5 ± 1.3	7.3 ± 1.6*	10.7 ± 3.1**
% of con	100%	85%	106%	123%	155%	100%	108%	110%	124%	181%
N (13 week reverse)[c]	13	15	13	13	10	13	13	11	15	10

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Table 13. Toxicity in CD Rats following Chronic Dietary Exposure to Fipronil

	Males					Females				
Dose (ppm)	**0**	**0.5**	**1.5**	**30**	**300**	**0**	**0.5**	**1.5**	**30**	**300**
Dose (mg/kg/day)	**0**	**0.02**	**0.06**	**1.3**	**13**	**0**	**0.03**	**0.08**	**1.6**	**17**
13 week reverse absolute liver wt (g)[c]	30.3 ± 7.0	30.3 ± 10.2	32.9 ± 6.4	30.9 ± 5.2	30.6 ± 5.9	18.5 ± 4.8	19.4 ± 5.2	17.8 ± 3.8	21.0 ± 5.7	19.7 ± 4.6
% of con	100%	100%	109%	102%	101%	100%	105%	96%	114%	106%
13 week reverse relative liver wt[c,d]	3.5 ± 0.7	3.7 ± 1.2	3.4 ± 0.5	3.7 ± 0.4	4.6 ± 1.1*	3.4 ± 0.3	3.6 ± 0.4	3.5 ± 0.3	3.8 ± 0.5*	4.7 ± 1.2**
% of con	100%	106%	97%	106%	131%	100%	106%	103%	112%	138%
13 week reverse absolute thyroid wt (mg)[c]	38 ± 13	39 ± 7	43 ± 11	45 ± 11	45 ± 6	31 ± 5	31 ± 8	30 ± 5	34 ± 10	35 ± 6
% of con	100%	103%	113%	118%	118%	100%	100%	97%	110%	113%
13 week reverse relative thyroid wt[c,d]	4.5 ± 1.3	4.7 ± 0.6	4.5 ± 1.0	5.4 ± 1.5	6.7 ± 1.7*	5.9 ± 1.1	5.8 ± 1.2	6.1 ± 0.9	6.3 ± 1.1	8.0 ± 0.7**
% of con	100%	104%	100%	120%	149%	100%	98%	103%	107%	136%
N (89-91 weeks)	20	14	22	20	12	22	22	21	13	22
90 week absolute liver wt (g)	28.3 ± 10.6	32.4 ± 6.2	32.1 ± 4.9	33.9 ± 6.4	39.4 ± 5.3**	23.0 ± 6.8	22.0 ± 5.4	21.5 ± 5.0	25.0 ± 6.4	27.9 ± 5.0*
% of con	100%	114%	113%	120%	139%	100%	96%	93%	109%	121%
90 week relative liver wt	3.30 ± 1.18	3.24 ± 0.52	3.48 ± 0.89	4.4 ± 1.14**	5.41 ± 0.64**	3.88 ± 0.90	3.98 ± 0.67	3.82 ± 0.65	5.12 ± 1.08**	6.14 ± 1.06**
% of con	100%	98%	105%	133%	164%	100%	103%	98%	132%	158%
90 week absolute thyroid wt (mg)	42 ± 13	51 ± 10*	53 ± 13*	63 ± 20**	94 ± 24**	36 ± 11	38 ± 17	36 ± 8	44 ± 14	72 ± 79*
% of con	100%	121%	126%	150%	224%	100%	106%	100%	122%	200%

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Table 13. Toxicity in CD Rats following Chronic Dietary Exposure to Fipronil

	Males					Females				
Dose (ppm)	**0**	**0.5**	**1.5**	**30**	**300**	**0**	**0.5**	**1.5**	**30**	**300**
Dose (mg/kg/day)	**0**	**0.02**	**0.06**	**1.3**	**13**	**0**	**0.03**	**0.08**	**1.6**	**17**
90 week relative thyroid wt[d]	4.9 ± 1.4	5.2 ± 1.2	5.6 ± 1.5	8.2 ± 2.8**	12.9 ± 2.9**	6.0 ± 1.9	7.0 ± 2.9	6.5 ± 1.4	9.0 ± 2.8**	15.6 ± 16.2*
% of con	100%	106%	114%	167%	263%	100%	117%	108%	150%	260%
PSN at 52 weeks -- scheduled[e]	42	21	36	47	75	29	36	21	43	54
PSN at 52 weeks -- all	40	20	33	47	73	27	40	27	40	53
PSN at 13-week reversibility	54	47	54	62	60	38	31	45	73	90*
PSN at 89-91 weeks -- scheduled	40	79*	77*	85**	92**	26	57	24	69*	55
PSN at 89-91 weeks -- all	52	56	64	84	88*	28	42	34	62*	48**

BW: body weight; wt: weight; PSN: progressive senile nephropathy.
[a]Animals included 50 rats/sex/dose from the Oncogenicity Phase, 15 rats/sex/dose from the Toxicity Phase and 15 rats/sex/dose from the Reversibility Phase.
[b]Animals from all phases were examined for convulsions.
[c]After fipronil administration for 52 weeks, animals were fed diet without fipronil for 13 weeks to assess the reversibility of fipronil-induced toxicity. Thyroid hormones were measured after 11 weeks on the fipronil-free diet (study week 63).
[d]Relative thyroid weight multiplied by 1000.
[e]"Scheduled" includes animals that survived to schedule sacrifice date; "all" includes animals that died prior to the scheduled sacrifice date.
†, ††, †††Statistically significant different from controls at $p \leq 0.05$, 0.01 or 0.001 (calculated by DPR with one-way ANOVA and Dunnett's test for multiple comparisons in GraphPad Prism 7).
*, **, ***Statistically significant different from controls at $p \leq 0.05$, $p \leq 0.01$ or $p \leq 0.001$ (one-tailed Fisher's Exact test, Mann Whitney U Test, Behrens-Fisher test or Dunnet's test for pairwise comparisons with Bartlett's test for variance homogeneity performed by study authors)
Data from Aughton (1993).

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IV.E.2. Chronic Oral – Mouse (Broadmeadow, 1993)

In a chronic toxicity/oncogenicity study, fipronil (95.4% a.i.) was administered via the diet to CD-1 mice (Broadmeadow, 1993). Mice in the Oncogenicity Phase (52/sex/dose) received fipronil for 78 weeks. Mice in the Toxicity Phase (20/sex/dose) received fipronil for 53 weeks. The dietary levels of fipronil were 0, 0.1, 0.5, 10, 30 or 60 ppm. The reported average daily doses were 0, 0.011, 0.055, 1.181 and 3.430 mg/kg/day for males and 0, 0.012, 0.063, 1.230 and 3.616 mg/kg/day for females. Control animals received untreated diet.

Convulsions in 3 males and a marked decline in weight gain and food intake in both sexes were noted at 60 ppm. Fourteen 60-ppm males and 7 females died during the first 9 weeks of treatment (19% of the males and 10% of the females), indicating that the maximum tolerated dose was exceeded. The decedents had higher relative liver weights at necropsy. Due to marked toxicity at 60 ppm, all surviving mice in this dose group were sacrificed without necropsy at week 10. The highest tested dose in the study thereafter was 30 ppm.

Animals treated at 30 ppm exhibited reduced body weight gains (14-19%, $p < 0.05$) and body weights (up to 13%) compared to controls. Food consumption was consistently low at 30 ppm, but was not statistically significantly affected by treatment. The data were insufficient to conclude that there was a treatment effect on food consumption.

At 76 weeks, females showed a lower proportion of neutrophils and higher proportion of lymphocytes at 30 ppm, compared to controls. This was not apparent at 50 weeks nor was it observed in males, but the effect exhibited dose responsiveness.

Absolute and relative liver weights were increased in both sexes at 53 and 78 weeks (Table 14). Absolute spleen weight also decreased in both sexes in a dose-dependent manner, achieving statistical significance at the high dose ($p < 0.05$). Increased spleen weights were also seen in female rats (Aughton, 1993).

Histopathology findings at 53 and 78 weeks included an increased incidence of microvesicular periacinar vacuolation of hepatocytes in the liver. Males from all treated groups exhibited hepatocyte vacuolation at levels higher than the control; the effect became statistically significant at 10 and 30 ppm (incidence of 7/16 and 12/18, respectively; 0/14 for control) at both durations. In females, the effect was increased at 30 ppm at 53 weeks, and was statistically significantly increased at 0.5 and 30 ppm at 78 weeks. The severity of effect was graded as slight to marked. There was evidence of an increase in severity at the high dose in males: 3/7 of the scores in the high dose were marked as opposed to all slight in the controls. This effect was also seen in mice following subchronic (13-week) dietary exposure (Broadmeadow, 1991).

The chronic NOEL for non-oncogenic effects following chronic exposure in mice was 0.5 ppm (0.06 mg/kg/day), based on significantly increased liver weights (absolute and relative) and liver pathology (periacinar vacuolation) at the LOEL of 10 ppm (1.18 mg/kg/day). Possible oncogenic effects are described in the Oncogenicity section of this RCD, below.

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Table 14. Effects in CD-1 Mice after Chronic Dietary Exposure to Fipronil

	Males					Females				
Dose (ppm)	**0**	**0.1**	**0.5**	**10**	**30**	**0**	**0.1**	**0.5**	**10**	**30**
Dose (mg/kg/day)	**0**	**0.01**	**0.06**	**1.18**	**3.43**	**0**	**0.01**	**0.06**	**1.23**	**3.62**
N (week 78)	24	31	26	26	26	33	35	27	41	38
Bodyweight gain (g) week 0-78	23.1 ± 5.9	21.9 ± 5.7	23.7 ± 4.9	21.3 ± 6.6	19.9 ± 4.8	25.4 ± 10.0	21.7 ± 8.1	25.8 ± 11.2	22.1 ± 8.6	20.6 ± 6.6*
% of Control	100%	95%	103%	92%	86%	100%	85%	102%	87%	81%
N (livers, week 53)	14	15	19	16	18	18	19	15	17	13
Abs. liver wt (g) week 53	2.6 ± 0.4	2.6 ± 0.5	2.7 ± 0.7	3.0 ± 0.8	3.4 ± 0.6**	1.7 ± 0.2	1.8 ± 0.4	1.9 ± 0.2	1.8 ± 0.2*	2.0 ± 0.4**
% of Control	100%	100%	104%	115%	131%	100%	106%	112%	106%	118%
Rel. liver wt week 53	5.1 ± 0.5	5.6 ± 1.1	5.7 ± 1.1*	6.1 ± 1.5*	7.7 ± 1.4**	4.4 ± 0.8	4.4 ± 0.6	4.5 ± 0.7	4.7 ± 0.6	5.4 ± 0.9**
% of Control	100%	110%	112%	120%	151%	100%	100%	102%	107%	123%
N (livers, week 78)	24	31	26	26	26	32	32	26	37	38
Abs. liver wt (g) week 78	2.8 ± 0.7	2.8 ± 1.0	2.9 ± 1.6	3.3 ± 1.5	3.8 ± 1.1**	2.0 ± 0.3	1.9 ± 0.4	2.0 ± 0.5	2.0 ± 0.3	2.1 ± 0.4
% of Control	100%	100%	104%	118%	136%	100%	95%	100%	100%	105%
Rel. liver wt week 78	5.6 ± 1.1	5.7 ± 1.9	6.0 ± 3.4	7.0 ± 2.8*	8.3 ± 2.5**	4.5 ± 0.9	4.6 ± 1.0	4.5 ± 0.8	4.8 ± 0.8	5.3 ± 0.9**
% of Control	100%	102%	107%	125%	148%	100%	102%	100%	107%	118%
Periacinar vacuolation week 53	0/14	2/15	2/19	7/16**	12/18***	1/18	1/19	4/15	1/17	4/13
% Periacinar vacuolation week 53	0	13%	11%	44%	67%	6%	5%	27%	6%	31%
Periacinar vacuolation week 78	5/24	7/31	7/26	13/26*	13/26*	0/32	0/32	4/26*	3/37	7/38*
% Periacinar vacuolation week 78	21%	23%	27%	50%	50%	0%	0%	15%	8%	18%

Abs: absolute; Rel: relative; wt: weight; Vacuol: vacuolation.
*, **, *** Statistically significant different from controls (one-tailed Fisher's Exact test, performed by study authors) at $p \leq 0.05$, $p \leq 0.01$ or $p \leq 0.001$.
Data from Broadmeadow (1993).

IV.E.3. Chronic Oral – Dog

Two chronic toxicity studies with fipronil in Beagle dogs were submitted to DPR. Both studies were performed in the Pharmaco-Life Science Research Laboratory for a period of 52 weeks. In the first study, fipronil was administered to the dogs in gelatin capsule (Holmes, 1992). In the second study, fipronil was incorporated into ground diet (Holmes, 1993).

Capsule (Holmes, 1992)

A chronic study in Beagle dogs was conducted with fipronil (95.4%) administered in gelatin capsules (Holmes, 1992). Six dogs/sex/dose were given 0, 0.2, 2.0 or 5.0 mg/kg/day for 52

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weeks. The principal treatment-related effects were neurological. All animals treated at 5 mg/kg/day, as well as most at 2 mg/kg/day, exhibited tremors, muscular twitching and leg rigidity, nervous behavior, gait abnormalities, and excessive salivation. The most serious neurological sign was convulsions, with 1 male and 1 female from the 2 mg/kg/day group and 2 males and 1 female from the 5 mg/kg/day dose group showing this sign during weeks 2-51. Convulsions typically lasted from 30 sec to 2 min and occurred as soon as 15 min after dosing. Most of the dogs had a series of convulsive episodes, which were graded from severe to epileptiform petit-mal seizures. Following the convulsions, the dogs appeared dazed, unsteady and unaware of their surroundings. They were also sensitive to sudden noise or touch and had rigid legs. One male in the 2 mg/kg/day group and 2 males in the 5 mg/kg/day group were sacrificed during weeks 11, 31 and 34, respectively, due to health deterioration following convulsions. Other signs included blindness, weight loss, severe ataxia and blood stained saliva around the mouth. The females receiving the lowest dose of fipronil (0.2 mg/kg/day) showed a higher incidence of salivation (2 out of 6 dogs) on several occasions during weeks 34-51 compared to controls (0/30). Females treated at the mid-dose also showed a higher incidence of salivation (3/6), while females at the high dose did not (1/6). There were also sporadic effects on hemoglobin, platelet and plasma protein levels.

Based on severe toxicity (convulsions and other neurological effects) observed at the LOEL of 2 mg/kg/day, the chronic oral NOEL for dogs was 0.2 mg/kg/day.

Dietary (Holmes, 1993)

A second chronic study in Beagle dogs was performed with fipronil (95.4%) incorporated into the diet (Holmes, 1993). This study included 5 dogs/sex/dose fed at target doses of 0, 0.075, 0.3, 1.0 or 3.0 mg/kg/day for 52 weeks. Achieved doses were 0.074, 0.299, 0.998 and 1.992 mg/kg/day for males and 0.074, 0.295, 0.996 and 1.995 mg/kg/day for females. The highest tested dose (3 mg/kg/day) was given to the dogs for 38 days, but was reduced thereafter to 2 mg/kg/day due to significant toxicity (death); 3 mg/kg/day therefore exceeded the maximum tolerated dose for dogs.

The main effects of fipronil exposure occurred in the central nervous system. One high-dose male suffered convulsions during weeks 6 and 45, and one female had severe convulsions during week 5. Convulsions lasted from 30 sec to 10 min and were usually followed by tremors and whole body twitching. Convulsive dogs showed excessive chewing behavior, extensor limb rigidity, head nodding and urine stains on limbs and tail. After the convulsive episodes in week 5, the female dog was sacrificed *in extremis*. Rigidity in limbs occurred in both sexes at 3 mg/kg/day and in 1 female at 1 mg/kg/day. It also occurred in 1 male at 0.3 mg/kg/day, but did not occur in males at the next higher dose. Tremors were observed in three males at the high dose during week 4, weeks 4-6 and, for one male, at numerous times during the first 10 weeks of treatment. Tremors and convulsions were observed in one female at the high dose (sacrificed on day 32 due to poor health), and twitching was observed in one female at 1 mg/kg/day during week 13. Higher absolute and relative spleen weight were noted in high dose males, along with

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higher incidence of swollen or large spleens and hyperplasia of the red pulp in the spleen under microscopic examination.

The chronic oral NOEL for dogs receiving fipronil in the diet was 0.3 mg/kg/day based on CNS effects (twitching of muscles and rigidity of limbs) at the LOEL of 1 mg/kg/day.

Table 15. Chronic No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, CD	combined chronic/onco, dietary, 91 weeks	convulsions and mortality in males, decreases in thyroid hormones weeks 1 to 50, progressive senile nephropathy	0.02	0.06	Aughton (1993)
Mouse, CD-1	combined chronic/onco, dietary, 78 weeks	increased relative liver weights and periacinar vacuolation	0.06	1.18	Broadmeadow (1993)
Dog, Beagle	gelatin capsule, 53 weeks	convulsions, neurological effects	0.2	2	Holmes (1992)
Dog, Beagle	dietary, 52 weeks	muscle rigidity and tremors	0.3	1	Holmes (1993)

IV.F. Oncogenicity

IV.F.1. Rat (Aughton, 1993)

In a chronic toxicity/oncogenicity study, fipronil (95.4% a.i.) was administered to CD rats at dietary levels of 0, 0.5, 1.5, 30 and 300 ppm (Aughton, 1993). The Oncogenicity Phase consisted of 50 rats/sex/dose that received fipronil for 89-91 weeks. The average daily doses were 0.02, 0.06, 1.3 and 13 mg/kg/day for males and 0.03, 0.08, 1.6 and 17 mg/kg/day for females. The Oncogenicity Phase was shortened from 104 weeks to 89 weeks (males) or 91 weeks (females) due to poor survival of both controls and treated rats.

Various types of tumors were reported in a total of 28 organ or tissue sites. There was an increase in rat liver neoplasms in the high dose male group only. Notably, thyroid follicular cell tumors were found in fipronil-treated rats, but not in controls (Table 16). These included follicular cell adenomas in male rats treated with 1.5 to 300 ppm and in females at 300 ppm, and carcinomas in males at 300 ppm and females at 30 and 300 ppm. The first tumor was detected at week 42 in the high dose group. Historical control data from the conducting laboratory (Pharmaco-LSR Ltd) between 1989 and 1992 showed 26 of 359 (7.2%) control males and 10 of 365 (2.7%) control females had follicular cell tumors. Based on these data, the incidence of thyroid follicular tumors at the high dose of 300 ppm (17/50 males and 10/50 females) was outside the historical control ranges.

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A Cochran-Armitage trend test conducted by DPR on the adenoma-plus-carcinoma data found a significant trend with and without continuity correction for males and females ($p < 0.001$). DPR also conducted a Poly-3 test using MCPAN R-Package to assess the neoplastic prevalence in males. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account (Portier and Bailer, 1989; Bieler and Williams, 1993) Results indicated a trend for increased tumor incidence with increasing dose ($p < 0.001$). Despite being within the historical control range, tumor incidence increased with concomitant increases in fipronil exposure (1.5 and 30 ppm) based on pairwise and trend statistics.

Table 16. Thyroid Tumor Incidence in CD Rats Exposed to Fipronil for 89 to 91 Weeks via Diet and Historical Control Data

	Males					**Females**				
Dose (ppm)	**0**	**0.5**	**1.5**	**30**	**300**	**0**	**0.5**	**1.5**	**30**	**300**
Dose (mg/kg/day)	**0**	**0.02**	**0.06**	**1.3**	**13**	**0**	**0.03**	**0.08**	**1.6**	**17**
N (thyroids)	49	48	50	50	50	50	50	50	50	50
Follicular Cell Adenoma	0	1	5*	3	12***	0	0	0	0	8**
Follicular Cell Carcinoma	0	0	0	0	5*	0	1	0	1	2
Adenoma + Carcinoma	0	1	5*	3	17***	0	1	0	1	10***
Percent Occurrence (%)	0%	2%	10%	6%	34%	0%	2%	0%	2%	20%
N (historical control)	359					365				
Adenoma + Carcinoma	26					10				
Percent Occurrence (range)	7.2 (3.6-16)%					2.7 (0-12)%				
N (liver)	49	48	50	50	50	50	50	50	50	50
Hepatocellular Carcinoma	2	2	0	1	0	0	0	0	0	0
Hepatocellular Adenoma	1	0	2	0	4	0	0	1	0	0

Historical control data from the conducting laboratory were supplied in the combined chronic and oncogenic study data volume. Controls included 7 combined chronic toxicity and oncogenicity or oncogenicity studies conducted in the four years prior to the present study. Statistics performed by study authors.
Data from Aughton (1993).

IV.F.2. Mouse (Broadmeadow, 1993)

In a chronic toxicity/oncogenicity study, fipronil (95.4% a.i.) was administered via the diet to CD-1 mice (Broadmeadow, 1993). Mice in the Oncogenicity Phase (52/sex/dose) received fipronil for 78 weeks at 0, 0.1, 0.5, 10, 30 or 60 ppm. The reported average daily doses were 0, 0.011, 0.055, 1.181 and 3.430 mg/kg/day for males and 0, 0.012, 0.063, 1.230 and 3.616 mg/kg/day for females. Control animals received untreated diet.

Various tumor types were reported in 17 organ/tissue sites. There was no treatment-dependent increase in neoplasms at any site except, possibly, the liver (Table 17). Male mice treated with 10 and 30 ppm fipronil showed an increase in incidence of liver tumors (6/26 hepatocellular adenomas and 1/26 hepatocellular carcinoma in the 10 ppm group; 5/26 adenomas and 3/26

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carcinomas in the 30 ppm group). None of the control males showed liver carcinomas, but these animals had a higher incidence of hepatocellular adenomas (7/24; 29%) than the historical control from the same lab during the two years encompassing the study (0 to 17% with an average of 4.7%) (Broadmedow, 1993). It also exceeded the historical control range of 0 to 23.1% for adenomas in CD-1 mice in a separate report (Doi, 2008), and exceeded published reports of 10.5% or less, with a single study maximum of 28% (Carmichael *et al.*, 1997; Giknis and Clifford, 2005). See Table 18 for incidence of liver tumors in historical controls. In addition, the survival rate of the control mice (46%) in the study appeared low for this strain compared to the 61 to 66% survival rate for historical controls (Carmichael *et al.*, 1997).

DPR conducted a Cochran-Armitage trend test on the adenoma-plus-carcinoma data and found a statistically significant trend with and without continuity correction for males and females ($p < 0.05$). However, a Fisher Exact test and a Poly-3 test (Portier and Bailer, 1989; Bieler and Williams, 1993) conducted by DPR showed that tumor incidence in treated groups was not statistically different from controls.

Table 17. Liver Tumor Incidence in CD-1 Mice Exposed to Fipronil for 78 Weeks via Diet

	Males					**Females**				
Dose (ppm)	**0**	**0.1**	**0.5**	**10**	**30**	**0**	**0.1**	**0.5**	**10**	**30**
Dose (mg/kg/day)	**0**	**0.01**	**0.06**	**1.18**	**3.43**	**0**	**0.01**	**0.06**	**1.23**	**3.62**
Adenomas	7	2	0	6	5	0	0	0	0	1
Percent Adenoma	29%	7%	0%	23%	19%	0%	0%	0%	0%	3%
Carcinomas	0	1	2	1	3	0	0	0	0	0
Percent Carcinoma	0%	3%	8%	4%	12%	0%	0%	0%	0%	0%
Adenoma + Carcinoma	7	3	2	7	8	0	0	0	0	1
Percent Adenoma + Carcinoma	29%	10%	8%	27%	31%	0%	0%	0%	0%	3%

Data from Broadmeadow (1993).

Table 18. Historical Control Liver Tumor Data for CD-1 Mice

	Males	**Females**
N	212[a]	--
Percent Adenoma (range)	4.7 (0 - 17.2)%	--
Percent Carcinoma (range)	10.4 (2.9 - 25)%	--
Percent Adenoma + Carcinoma (range)	15.7 (2.9 - 25)%	--
N	426[b]	425
Adenoma (range)	11.27 (0 - 23.1)%	0.24 (0 - 2)%
Carcinoma (range)	7 (2 - 11.5)%	0.47 (0 - 2)%
Percent Adenoma + Carcinoma (range)	18.27 (2 - 34.6)%	0.71 (0 - 4)%

[a]Historical male tumor incidence data from in the same lab during the two years blanketing the study (Broadmedow (1993).
[b]Historical control data from published literature for CD-1 mice from Doi (2008). Includes data for all animals (including decedents); oral gavage and dietary administration.

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IV.G. Genotoxicity

Six genotoxicity studies were submitted to DPR to fulfill the pesticide registration data requirements for the State of California (Table 19). These included 2 *in vitro* point mutation studies and four chromosome aberration studies (two *in vivo* and two *in vitro*) at fipronil concentrations up to its toxicity or solubility limits. Fipronil was negative for gene mutations or cytogenetic damage under the experimental conditions of these tests, with the exception that positive results occurred sporadically in one of the *in vitro* chromosome aberration tests at concentrations where cytotoxicity was also observed.

Additional genotoxicity studies were identified in the published literature. *In vitro* studies included a comet assay in primary human tonsil epithelial cells, sister chromatid exchange in human lymphocytes, micronucleus and comet assays in human lymphocytes, and micronuclei assays in human hepatic HepaRG cells. One of these studies reported genotoxicity without corresponding cytotoxicity to human epithelial mucosal cells isolated from human tonsils (Tisch *et al.*, 2007). DPR concluded that the study did not demonstrate DNA breakage from genotoxicity as opposed to cell death (necrosis and/or apoptosis).

In vivo published studies included chromosome aberration and comet assays in Holtzman rats, Swiss mice, and Wistar rat spermatozoa, a mutation frequency study in *Drosophila*, and a micronucleus assay and genomic stability assay in plants.

While fipronil was positive for chromosomal aberrations and DNA damage, those effects were often accompanied by cytotoxicity both *in vitro* and *in vivo*. A total of 20 published studies provide evidence that fipronil induces oxidative stress at doses higher than the critical POD, which leads to oxidative damage, increased cell death and genotoxicity.

Table 19. Genotoxicity Studies conducted with Fipronil

Test Type, System	Species or Culture	Exposure Regime	S9[a]	Results	Cytotoxicity	Reference
Ames Test	*S. typhimurium* TA98, TA100, TA1535, TA1537	0 (DMSO), 0.8, 2, 20, 100, 400 or 500 µg/plate, 48 hr	±	Negative	No	Clare (1988)[b]
HGPRT Forward Mutation	Chinese hamster lung cell line V79	0 (DMSO), 0.8, 4, 20, 100 or 500 µg/mL, 3 hr	±	Negative	No	Lloyd (1993)[b]
In vitro Chromosome Aberration	Human lymphocytes	0 (DMSO), 75, 150 or 300 µg/ml, 3 hr	±	Negative	Decreased cell viability	Marshall (1988)[b]
In vitro Chromosome Aberration	Chinese hamster lung cell line CHL	0, (DMSO), 30, 45, or 60 µg/ml for 6, 24 or 48 hr	±	Positive at 60 µg/ml after 6 hrs only, no S9	Yes	Wright, (1995)[b]
In vivo Bone Marrow Micronucleus Test	CD-1 mouse bone marrow erythrocytes	0 (0.5% methylcellulose), 1, 5 or 25 mg/kg, gavage, single dose	n/a	Negative	No	Edwards (1993)[b]

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Table 19. Genotoxicity Studies conducted with Fipronil

Test Type, System	Species or Culture	Exposure Regime	S9[a]	Results	Cytotoxicity	Reference
In vivo Bone Marrow Micronucleus Test	CD-1 mouse bone marrow erythrocytes	0 (0.5% methyl cellulose), 1, 12.5, 25 or 50 mg/kg, gavage, single dose	n/a	Negative	No	Edwards[b] (1995)
In vitro Comet Assay	Human laryngeal mucosal cells	0, 0.05, 0.1, 0.5, 0.75 or 1 mM, 1 hr	n/a	Positive at all doses	Likely	Tisch (2007)
In vivo Comet Assay and Micronucleus Test	Swiss mice	0 (water), 15, 25 or 50 mg/kg, IP, 1 dose; blood taken after 24 (Comet) or 24, 48 or 72 hr (MN)	n/a	Positive at 50 mg/kg	Not measured; authors indicate apoptotic cells not included in analysis.	de Oliveira (2012)
In vitro Sister Chromiatid Exchange and Micronucleus Test	Human lymphocytes	0, 0.1, 0.3 or 0.7 µg/ml, 72 hr	n/a	SCE and Comet positive at all doses; MN positive at two higher doses; unknown formulation and % purity, improper controls	Decreased mitotic index, indicating high cellular toxicity, at all dose levels	Celik (2014)
In vivo Comet Assay and Chromatin Assay	Wistar rat (spermatozoa)	0 (corn oil), 2.5, 5 or 10 mg/kg/day, gavage, 28 days	n/a	Comet positive at 2.5 mg/kg/day and higher; damage to sperm chromatin at 5 mg/kg/day and higher	Apoptosis at all doses.	Khan (2015)
In vitro Micronucleus Test and γH2AX marker	Human HepaRG cells	0, 15 or 25 µM for 7 days or 0, 15 or 20 µM for 15 d	n/a	MN test positive at 15 and 25 µM after 7 days; γH2AX marker positive at 20 µM after 7 and 15 days	Increased cytotoxicity (MTT assay) observed at all positive doses and time points	Quesnot (2016)
In vivo Comet Assay and Micronucleus Test	Holtzman rat (Comet) and Swiss albino mice (MN)	0 (corn oil), 2.5, 12.5 or 25 mg/kg, gavage, 1 dose	n/a	Positive at 12.5 and 25 mg/kg	Not measured; indirect evidence of oxidative stress.	Badgujar (2016)
In vivo Mammalian Bone Marrow Chromosome Aberration Test and Comet Assay	BALB/cYwal mice	4.75, 9.5, 19, 31.7 mg/kg, IP, 1 dose (Comet) 19 mg/kg, IP, 1 dose or 10 days (CA)	n/a	Comet consistently positive at 9.5 mg/kg and higher after 6 and 24 hr; CA test positive at 9.5 mg/kg; fipronil source and purity unknown	Not described.	Lovinskaya (2016)

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Table 19. Genotoxicity Studies conducted with Fipronil

Test Type, System	Species or Culture	Exposure Regime	S9[a]	Results	Cytotoxicity	Reference
In vivo Somatic Mutation and Recombination Test	Drosophila melanogaster third instar larvae	0.3, 0.7, 1.5 or 3.0 × 10^{-5} mM, 48 hours	n/a	Increased mutagenicity at 0.3 x 10^{-5} mM and higher, Increased recombination that was not dose-responsive. Increased tumor frequency (numbers of warts)	Dose-responsiveness not seen in mutagenic or recombination studies. Cytotoxicity observed at 0.7 x10^{-5} mM and higher.	de Morais (2016)
In vivo Random Amplified Polymorphic DNA (RAPD)	*Vicia faba* seedlings	0, 0.5, 1, 2, 3 or 4 ppm for 7 days.	n/a	Genomic template stability (GTS) was decreased in a dose-dependent manner for most of the 15 primers tested. The average GTS (for all 15 primers) was also decreased in a dose-dependent manner. Fipronil source and purity unknown; negative control is unknown.	Unknown.	Yildrim (2016)
In vivo Micronucleus Test	*Tradescantia pallida* flowering plant stems	0.025, 0.05, 0.1, 0.2, 0.4, 0.8 and 1.6 g/L solution for 8 hr, with 24-hr recovery phase	n/a	Increased formation of MN at ≥ 0.2 g/L compared to the negative control	Unknown.	de Morais (2019)

[a]S9 is liver homogenate used for biological activation of xenobiotics in DNA damage testing. ± indicates the test was done in the absence (-) or presence (+) of S9. ROS: reactive oxygen species.
[b]Registrant-submitted studies.

IV.H. Developmental Toxicity

IV.H.1. Developmental Toxicity – Rat

Fipronil (93% a.i.) was administered daily by gavage to mated female CRL:CD(SD)BR VAF/Plus rats from gestation day (GD) 6 through 15 (Brooker and John, 1991). Each dose group consisted of 25 rats. The doses were 0, 1, 4 or 20 mg/kg/day. Control animals were treated with vehicle (0.5% methylcellulose). On GD 20, fetuses were delivered by cesarean section and examined for developmental abnormalities.

Maternal effects at 20 mg/kg/day included reduced body weight (up to 8%) and reduced body weight gain (up to 61%) from the second day of treatment until study termination. Food

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consumption also decreased – up to 24% – during GD 6-11 with a significant decrease from GD 8-9 ($p \leq 0.001$, one-way ANOVA by DPR).

The maternal NOEL of 4 mg/kg/day was based on reduced body weight at the LOEL of 20 mg/kg/day. The developmental NOEL was 20 mg/kg/day, based on no effects detected at the high dose.

IV.H.2. Developmental Toxicity – Rabbit

The developmental toxicity of fipronil was examined in the rabbit. Artificially inseminated New Zealand White rabbits (22/dose level) were treated by gavage for a total of 14 days, from GD 6 through GD 19, with daily doses of 0.1, 0.2, 0.5 or 1 mg/kg/day (King, 1990). Cesarean section and examination of the dams and fetuses were performed on GD 29. Histological examination was performed on reproductive organs from the controls and high dose group animals and on the thyroid glands and liver from all adult animals in all groups.

No developmental effects were seen in the fetuses at any dose level. Food consumption in dams treated with 0.5 and 1 mg/kg/day was significantly reduced by up to 33% ($p \leq 0.01$) compared to controls during the treatment period (Table 20). In turn, the mean body weight gain of these rabbits was decreased by 50-70% ($p < 0.01$) from the second day of treatment (GD 8) until the end of the study at GD 24 (e.g., five days after the last dose). After two doses, the body weight gain of the dams at and above 0.2 mg/kg/day was reduced by 50% ($p < 0.01$) on GD 8. The decreased body weight gain of these dams was statistically significant until the end of the treatment (GD 19). The rabbits in the lowest tested group (0.1 mg/kg/day) exhibited statistically significant reductions (54%, $p < 0.01$) on GD 10; however, a dose-response was not observed as the reduction in body weight gain at 0.2, 0.5 and 1 mg/kg/day was 36%, 45% and 45%, respectively.

The NOEL for maternal toxicity was 0.1 mg/kg/day, based on reduced weight gain at the LOEL of 0.2 mg/kg/day.

Table 20. Toxicity Observed in Rabbit Dams following Oral Fipronil Exposure in a Developmental Toxicity Study

Dose (mg/kg/day)	**0**	**0.1**	**0.2**	**0.5**	**1**
# Females inseminated	22	22	22	22	22
# Females pregnant	20	21	21	18	19
# Females surviving treatment	19	21	21	18	19
Total titter loss	1	1	0	0	1
Food consumption (%) GD 1-5	100	91	98	100	96
Food consumption (%) GD 6-12	100	91	90	96	88**
Food consumption (%) GD 13-19	100	85	90	79*	67**
BW gain (g) GD 6-8	60 ± 40	40 ± 40	30 ± 40*	30 ± 40**	30 ± 30*
% of control	100%	67%	50%*	50%**	50%*
BW gain (g) GD 6-10	110 ± 50	50 ± 40***	70 ± 60*	60 ± 50***	60 ± 50**

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Table 20. Toxicity Observed in Rabbit Dams following Oral Fipronil Exposure in a Developmental Toxicity Study

Dose (mg/kg/day)	**0**	**0.1**	**0.2**	**0.5**	**1**
% of control	100%	45%***	64%*	55%***	55%**
BW gain (g) GD 6-12	150 ± 60	100 ± 70	70 ± 150	90 ± 70*	80 ± 60*
% of control	100%	67%	47%	60%*	53%*
BW gain (g) GD 6-18	300 ± 70	240 ± 100	210 ± 190*	170 ± 140*	120 ± 150***
% of control	100%	80%	70%*	57%*	40%***
BW gain (g) GD 6-20	300 ± 100	220 ± 120	220 ± 230	150 ± 150**	90 ± 170***
% of control	100%	73%	73%	50%**	30%***
BW gain (g) GD 6-24	370 ± 90	290 ± 130	310 ± 190	250 ± 150*	170 ± 120***
% of control	100%	78%	84%	68%*	46%***

GD: gestation day; BW: body weight. Data from King (1990).

III.H.3. Developmental Studies Published in the Open Literature

The ability of fipronil to impair the development and quality of mouse preimplantation embryos was assessed *in vitro* and *in vivo* in ICR (CD-1 IGS) mice (Sefcikova et al., 2018). Two-day old embryos were removed from dams, pooled and exposed to 0, 0.1, 1, 10 or 100 µM fipronil for 72 hours. A significant decrease in embryos reaching the blastocyst state and an increase in dead cells occurred at 1 µM and higher. Dams were also exposed *in vivo* by gavage to 0, 0.9 or 0.009 mg/kg/day from GD 1 to GD 3. Controls received the vehicle (water with 0.01% DMSO). A decrease in the number of isolated cells, slower transition from oviduct to uterus, increased degraded embryos, and a decrease in the number of blastocysts were observed at 0.9 mg/kg/day. A tendency toward decreased average embryo number (not statistically significant) and increased number of blastocysts with dead cells was seen at 0.009 mg/kg/day. However, this dose did not affect the ability of embryos to reach the blastocyst state. The biological meaning of these data are unclear, as the animals were not followed through birth or into postnatal development.

An additional study that examined developmental endpoints *in vivo* were not useful for establishing critical POD because the appropriate controls were not used (Eisa *et al.*, 2017).

Table 21. Developmental NOELs and LOELs for Fipronil

Species, Strain	**Study Type and Exposure**	**Effects at LOEL**	**NOEL (mg/kg/day)**	**LOEL (mg/kg/day)**	**Reference**
Rat, CRL:CD(SD)BR VAF/Plus	gavage, GD 6 - GD 15	maternal: reduced bodyweight	4	20	Brooker (1991) [a]
		developmental: no effects at high dose	20	> 20	
Rabbit, New Zealand White	gavage, GD 6 - GD 19	maternal: decreased BW gain	0.1	0.2	King (1990) [a]
		developmental: no effects at high dose	1	> 1	
Rat, Sprague Dawley	DNT, dietary, GD 6 - LD 10	maternal: death, alopecia, dead/missing pups, decreased BW, BW gain and food consumption	0.9	15	Mandella (1995) [a]

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Table 21. Developmental NOELs and LOELs for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
		developmental: delayed preputial separation in males, decreased maximum startle response, and decreased BW during lactation	0.05	0.9	
Rat, Sprague Dawley	CTA, dietary, GD 6 - LD 21	maternal: decreased T4, increased TSH, histopathology	1	3	Coder (2018)[a]
		developmental: decreased T4, increased liver weight	0.3	1	
Rat, CD	gavage, GD 6 - GD 15	maternal: decreased BW	0.2	1	Foulon (1997)[b]
	fipronil-desulfinyl	developmental: decreased BW and delayed bone ossification	1	2.5	
Mouse, ICR (CD-1 IGS)	gavage, GD 1 - GD 3	increased percentage of dead cells in blastocysts and more blastocysts with dead cells; altered development of embryos	< 0.009	0.009	Sefcikova (2019)

[a]Registrant-submitted study.
[b]Registrant-submitted study with fipronil-desulfinyl.
GD: gestation day; BW: body weight; DNT: developmental neurotoxicity study; CTA: comparative thyroid assay.

IV.I. Reproductive Toxicity

IV.I.1. Two-Generation Study (King, 1992)

The effects of fipronil (95.4%) on reproduction and development were examined in a two-generation study (2 litters/generation) in CD rats (30/sex/dose in the parental generation, F0) (King, 1992). Animals received dietary doses containing 0, 3, 30 or 300 ppm fipronil. The F0 generation was exposed for 10 weeks prior to mating and then during mating, gestation and lactation for both the F1A and F1B litters. The F0 animals were sacrificed after the F1B animals were weaned. For the second generation, F1A parental animals (30/sex/dose) were treated similarly to the F0 animals. Clinical signs and mortality were monitored daily. Animals were weighed at least weekly for the duration of the study. Mating and gestational time, litter size, mortality, sex ratio, body weight, physical development, macroscopic pathology and histology were recorded. Fipronil intake was determined based on food consumption during each week of the 10-week pre-mating period. Food intake was lower in the high-dose group than in controls for both sexes. Animals generally had a decreased fipronil intake over time; the intake of fipronil was lowest for both sexes and both generations at week 10 of treatment. The ranges of daily fipronil intake during the 10-week treatment period prior to mating were as follows:

Fipronil intake was determined based on food consumption during each week of the 10-week pre-mating period. Food intake was lower in the high-dose group than in controls for both sexes. Animals generally had a decreased fipronil intake over time; the intake of fipronil was lowest for both sexes and both generations at week 10 of treatment. The ranges of daily fipronil intake during the 10-week treatment period prior to mating were as follows:

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- F0 generation: 3 ppm: 0.16-0.46 mg/kg/day (males) and 0.20-0.47 mg/kg/day (females); 30 ppm: 1.68-4.48 mg/kg/day (males) and 2.00-4.56 mg/kg/day (females); 300 ppm: 16.97-33.96 (males) and 20.76-36.39 mg/kg/day (females).
- F1 generation: 3 ppm: 0.16-0.40 mg/kg/day (males) and 0.20-0.39 mg/kg/day (females); 30: ppm 1.69-4.14 mg/kg/day (males) and 2.09-4.06 mg/kg/day (females); 300: ppm 17.72-45.60 (males) and 22.92-44.94 mg/kg/day (females).

A total of 9 rats died or were sacrificed due to ill health during weeks 1- 24 of treatment in the parental generation (F0). This included one male from the 30 ppm group, 2 males and 5 females from the 300 ppm groups, and 1 control female. Two females treated with 300 ppm had convulsions but survived until the end of the study. The major clinical signs were convulsions lasting 15 to 20 minutes, loss of muscular control, limited use of limbs, irregular breathing, pupil dilation, and blood and urine stains.

Compared to controls, the F0 females treated with 300 ppm fipronil had a substantial reduction in body weight during gestation (up to 10%, $p < 0.001$) and during lactation (up to 13%, $p \leq 0.001$). Decreased food consumption (29-32%, $p < 0.001$) and premating body weights (up to 16%, $p \leq 0.001$) were reported for the F0 and F1 males and females.

The thyroid and the liver were the principal target organs in the F0-F1 rats with treated with 30 ppm and 300 ppm fipronil. The liver weight was increased up to 9% ($p < 0.05$, absolute and relative weight) in the rats exposed to 30 ppm fipronil and up to 37% (absolute weight, $p < 0.01$) and 49% (relative $p < 0.01$) in the rats from the highest dose group (300 ppm). Pathology examination revealed fatty vacuolation of hepatocytes in the 300 ppm females (19 out of 26; 0/30 for control). Investigators graded the severity of this effect as slight to marked.

The absolute weight of the thyroid gland was increased by 15% -51% ($p < 0.01$) in the females and males in the 30 and 300 ppm dose groups. When expressed as thyroid/body weight ratio the increase was about 20% ($p < 0.01$) for both sexes treated with 30 ppm fipronil; and up to 60% ($p < 0.01$) for the 300 ppm group. Pathology examinations revealed thyroid follicular hypertrophy in 30-ppm males (2/29 *vs.* 0/30 controls). In the 300 ppm group follicular hypertrophy rose to 10/ 29 males ($p<0.001$) and 6/26 ($p< 0.01$) females. Investigators graded the severity of this effect as minimal to slight.

Fipronil at 300 ppm affected the mating, fertility, pre- and postnatal viability, litter size, body weight and the development of the F1 and F2 generations.

Following pairing, only 25 of 30 F1 animals from the 300 ppm group mated (83%, $p < 0.01$), compared to 30/30 controls. The fertility index[5] of these rats was reduced (80% for the 300 ppm group *vs.* 90% for the control). The live birth index[6] was 83% ($p < 0.01$) for the F1 offspring and

[5] Fertility index: (number of animals that achieved a pregnancy)/(animals paired) x 100
[6] Live birth index[6]: (number of live offspring on day 1 *postpartum*/total number of offspring on day 1 *postpartum*) x 100.

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78% ($p < 0.001$) for the F2 offspring in the 300 ppm pups; this index was 98%for the controls. The F1 and F2 pup viability index[7] were 89% ($p < 0.05$) and 73% ($p < 0.001$), respectively, in the 300 ppm group, compared to 97-98% for the control pups. The F1 and F2 mean litter size was significantly lower in the 300 ppm group, with 10 F1 pups/litter and 10.5 F2 pups/litter on PND 1, respectively. For comparison, the control litter sizes on PND 1 were 14.5 F1 pups/litter and 13.6 F2 pups/litter. F1 pups litter size at 300 ppm remained decreased until litter size adjustment on PND 4 (9.6 pups/litter compared to 14 pups/litter in the control, $p < 0.001$).

The offspring of the F0 and F1 dams treated with 300 ppm fipronil had a markedly lower body weight (up to 22%, $p \leq 0.001$) compared to controls from PND 1-25. Thirteen F1 pups from 9 litters had convulsions between PND 14-20 in the 300 ppm group. Four F2 pups in 3 litters had convulsions on PND 15 and 18 in the 300 ppm group. F1 and F2 pups from the 300 ppm groups exhibited slower development compared to the control, as evidenced by the delays in tooth eruption (0.7 days, $p<0.05$; F1 pups) and pinna unfolding (0.5 days delay, F2 offspring).

In summary, toxicity was observed at doses of 30 ppm fipronil and higher. The main effects included mortality, convulsions, decreased body weight, thyroid hypertrophy, fat accumulation in the liver, decreased mating and fertility, decreased offspring viability, decreased pup body weight and delays in pups development. The parental NOEL was 3 ppm (0.16 mg/kg/day), based on mortality, increased absolute and relative weights of liver and thyroid, and hypertrophy of thyroid follicular cells at the LOEL of 30 ppm. The reproductive and developmental NOELs were 30 ppm (1.7 mg/kg/day), based on decreased body weights and convulsions in F0-F1 adults and F1-F2 pups, decreased mating and fertility of F0-F1 adults, reduced pup viability, decreased litter size, and developmental delays of pups of both generations at 300 ppm.

IV.I.2. Reproductive Studies Published in Literature

Several reproduction and/or development studies with rat were available in the published literature. Endpoints assayed included sperm quality, reproduction, estrus cycling, sperm structural integrity and DNA damage. Effects occurred at similar doses to those seen in the registrant submitted data.

In a 14-day oral (gavage) study, Wistar rat dams were exposed to 0, 0.03, 0.3 or 3 mg/kg/day fipronil from GD 15 to PND 7 (*i.e.*, between the final week of pregnancy and the first week of lactation) (de Barros *et al.*, 2016b). Study authors report a significant decrease in absolute and relative pituitary weights in Wistar rat dams. However, while the results were statistically significant, DPR notes that dose-dependence was not evident. Exposure to the highest dose of fipronil (3 mg/kg) delayed vaginal opening and first estrus. The duration of the estrus cycle was increased at 0.3 mg/kg/day (but not at other doses). At PND 80, a significant decrease in absolute and relative weight of the thyroid was seen in high dose animals. The LOEL for this study was 3

[7] Pup viability index was calculated as: (total pups alive on day 4 before culling/total pups born alive on day 1 *postpartum*) x 100.

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mg/kg/day based on delayed vaginal opening and first estrus, resulting in a NOEL of 0.3 mg/kg/day.

In a study conducted in the same laboratory following the two-week treatment described above, statistically significant decrease in sperm Type A (sperm that were mobile and had a progressive path) was detected in male pups at puberty at all doses ($p < 0.05$) (de Barros *et al.*, 2016a). There was also an increase in abnormal sperm Type C (non-mobile) at the highest dose 3 mg/kg/day ($p < 0.05$). Thyroid weights, fertility, and time of preputial separation were not affected. The lack of dose-response for the Sperm Type A data over the 100-fold dose range combined with no effect on subsequent reproduction parameters and small sample sizes make these findings unsuitable for human hazard assessment.

Another study examined the effects of fipronil (98%) on adult male Wistar rat reproductive health (Khan *et al.*, 2015). Fipronil doses of 0, 2.5, 5 or 10 mg/kg/day were administered by oral gavage for 28 consecutive days. After 4 weeks, there was a decrease in sperm density, motility, viability and acrosome integrity at 5 and 10 mg/kg/day ($p < 0.05$) as well as a change in sperm morphology at 2.5 mg/kg/day and higher. An increase in reactive oxygen species and DNA fragmentation (sperm chromatin structure assay) and lipid peroxidation occurred at all doses. The investigators proposed that fipronil causes male reproductive toxicity through oxidative stress-induced DNA damage and apoptosis in spermatozoa. A LOEL was set at the lowest dose of 2.5 mg/kg/day, based on changes in sperm morphology, DNA damage, lipid peroxidation, loss of spermatozoa, change in mitochondrial membrane potential, and increased cell death.

Fipronil (Frontline® TopSpot™, 10% a.i.) or saline was applied to 3-month old female Wistar rats (Ohi *et al.*, 2004). For analysis of hormone levels, 6 animals/group were treated with a single topical dose of 70 mg/kg fipronil (treatment group) or with saline (control group) during the proestrous cycle. Plasma progesterone and estradiol levels were determined 0, 24, 48, 72 and 96 hours after treatment. To study estrous cycle, regular-cycling females were treated with 0 (20 rats), 70 mg/kg (12 rats) or 280 mg/kg (10 rats) fipronil. The estrous cycle was monitored daily at the same time by examining the cytology vaginal smears for 20 days. To understand the effects on mating, pregnancy, and outcome, pregnant female rats (10-12/dose) received a single dermal dose of fipronil on day 0 of pregnancy (the day of sperm detection in vaginal smears) at doses of 0, 70, 140 or 280 mg/kg. Rats were observed daily for clinical signs. Maternal weight was measured on days 1, 4, 8, 13, 18 and 21 of pregnancy. Litter size, sex ratio and number of viable pups were assessed and the body weights of the newborn pups were measured on PND 1, 7, 14 and 21. The dams were sacrificed after weaning and examined postmortem for uterus and ovary weights and for number of implantation sites. At 70 mg/kg, fipronil caused a statistically significant 2.2-fold increase in plasma progesterone levels and a 2-fold decrease in estradiol levels 96 hours after treatment. The estrous cycle of animals treated with 70 and 280 mg/kg fipronil was dramatically lengthened by 4.9 days and 10.7 days, respectively, compared to controls. Females treated with 140 and 280 mg/kg fipronil showed statistically significant decreases in body weight gain and a significantly lower (17% and 33%) pregnancy index (ratio of pregnant to sperm-positive females). The authors proposed that fipronil interferes with reproductive behavior by blocking the inhibitory GABAergic hypothalamic processes (Ohi *et al.*,

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2004). The LOEL for acute dermal toxicity in rats was 70 mg/kg/day based on statistically significant alterations in the progesterone and estradiol levels and lengthening of the estrous cycle in female rats. The fipronil used in this study was a commercial formulation available in Brazil but not in California. DPR was not able to confirm the solvents or adjuvants used in the commercial preparation as the information is proprietary. As such, it is unclear if the reported effects in the study were caused solely by fipronil, as control animals were treated with saline and not with the formulation vehicle.

Table 22. Reproductive NOELs and LOELs for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, CD	2-generation, 2-litter repro, dietary, 10 weeks prior to mating through lactation for both liters	paternal: mortality, increased absolute and relative liver and thyroid weights, hypertrophy of thyroid follicular cells	0.16	1.7	King (1992)[a]
		developmental: convulsions, decreased bodyweights, mating and fertility, pup viability and litter size and developmental delays	1.7	17.7	
Rat, Wistar, female	gavage, GD 15 to PND 7	female pups: delay in vaginal opening and first estrus, increased duration of estrus, decreased pituitary weight all doses that was not dose-dependent	0.3	3	de Barros (2016a)
	gavage, GD 15 to PND 7	male pups: increase in non-mobile sperm	0.3	3	de Barros (2016b)
Rat, Wistar, male	gavage, 28-day	changes in sperm morphology, DNA damage, lipid peroxidation, loss of spermatozoa mitochondria membrane potential and increased cell death	< 2.5	2.5	Khan (2015)
Rat, Wistar, female	single dermal application to cervical spine	increased progesterone and decreased estrogen levels, lengthening of estrous cycle (did not include proper controls)	< 70	70	Ohi (2004)

[a]Registrant-submitted study.
GD: gestation day; PND: postnatal day. Repro: reproduction

IV.J. Thyroid Endocrinology

IV.J.1. Rat Thyroid-Pituitary Function

Two studies were submitted to DPR that investigated mechanisms that may contribute to fipronil's effects on thyroid-pituitary function. These were submitted because thyroid hormone levels were altered following fipronil exposure in the chronic study in rat, described above (Aughton, 1993). Despite not being chronic studies, their placement here reflects our view that the studies clarify effects noted by Aughton (1993).

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Perchlorate Discharge (Peters et al., 1991)

The first study utilized the Perchlorate Discharge Test, designed to detect chemicals that act directly on the thyroid gland (Peters *et al.*, 1991a). Perchlorate is an ion that inhibits the transport of iodide into the thyroid, causing free, non-organified cytoplasmic iodide to "discharge" back into the bloodstream. If a compound interferes with the incorporation of iodide into thyroglobulin (iodide organification), the perchlorate discharge test detects a loss of radioactive iodine from the thyroid and an increase of radioactive iodide in the blood. In this study, male Crl:CD (SD) BR rats were exposed for 14 days to fipronil (10 mg/kg/day), propylthiouracil (200 mg/kg/day) or Noxyflex (50 mg/kg/day). Propylthiouracil blocks the incorporation of iodide to thyroglobulin by inhibiting the enzyme thyroperoxidase. Noxyflex inhibits iodide organification *in vitro*. Both of these compounds represent positive controls. On day 15, all animals were injected IP with ^{125}I. Six hours later, all animals received 10 or 25 mg/kg potassium perchlorate.

Rats receiving fipronil for 14 days did not show increased ^{125}I efflux into blood following potassium perchlorate treatment when compared to the control. This indicated that fipronil did not inhibit iodide organification. However, fipronil treatment increased accumulation of radioactive iodine in the thyroid and increased thyroid weight (8%), indicating increased thyroid follicular cell stimulation. Noxyflex increased accumulation of ^{125}I and increased thyroid weight similar to fipronil, suggesting Noxyflex stimulated thyroid follicular cells but did not block iodide organification *in vivo*. In contrast, propylthiouracil acted as a potent inhibitor of iodide organification, evidenced by a 75% increase in radioactive iodine in whole blood compared to controls, a drastic increase in thyroid weight (174% of control), and a decrease in the ratio of radioactivity found in the thyroid versus the blood (12% of control). To conclude, fipronil increased thyroid follicular cell stimulation but did not affect iodide organification.

Thyroxine Clearance (Peters et al., 1991b)

The second study investigated whether fipronil causes thyroid-pituitary disruption by altering thyroid hormone clearance from the blood. Fipronil (10 mg/kg/day) was given via gavage to two groups of 6 male Crl:CD (SD) BR rats for 1 or 14 days. Four hours after dosing, the rats received ^{125}I-thyroxine (Peters *et al.*, 1991b). The radioactivity was monitored in whole blood for 30 hours to calculate thyroxine (T4) half-life ($T_{1/2}$), clearance, and volume of distribution. Phenobarbital, known to enhance T4 clearance via induction of liver microsomal enzymes, was used as a reference compound.

After one day of treatment, the fipronil-treated group showed no statistically significant effects on toxicokinetic parameters compared to controls. The phenobarbital-treated group, however, showed statistically significantly ($p < 0.01$) decreased thyroxine clearance (18%) and increases in the volume of distribution (9%) and clearance (32%). Rats treated with fipronil for 14 days showed statistically significant ($p < 0.01$) changes: the T4 $T_{1/2}$ was decreased by 48%, the clearance was increased by 161% (261% of control) and the volume of distribution was increased by 37% (137% of control). Phenobarbital (80 mg/kg/day) treatment for 14 days

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resulted in similar changes, but was less potent than fipronil (T4 $T_{1/2}$ was decreased by 31%, clearance was increased by 84%, and volume of distribution increased 25%, $p < 0.01$).

In conclusion, fipronil decreased the T4 $T_{1/2}$ and increased clearance of T4 from the blood in rats. The study authors proposed a mechanism for thyroid neoplasia in which the decreased level of serum T4 leads to increased secretion of thyroid stimulating hormone (TSH), consequently stimulating the thyroid gland and increasing thyroid weight. This proposal is discussed further in the Risk Appraisal section below.

IV.J.2. Comparative Thyroid Assay

The potential for impacts on thyroid function in pregnant adult female Sprague-Dawley Crl:CD (SD) rats and their offspring was assessed prenatally and postnatally during gestation and lactation (Coder, 2019). Pregnant adult females (45 per dose group) were exposed daily to fipronil (99.9%) via the diet from implantation (GD 6) through weaning of the offspring (PND 21). The pups were indirectly exposed to fipronil for a total of 35 days (15 days *in utero* and 20 days via lactation). Doses were 0, 0.1, 0.3, 1 or 3 mg/kg/day. Study authors reported that the dietary formulations contained 82.6% to 113% of the target test substance concentration, which was within the protocol-specified range of 85% to 115%. Dietary administration of 6-propyl-2-thiouracil in a separate group acted as a positive control, which demonstrated the ability of the assay system to detect changes in thyroid weight and thyroid hormone levels. Animals in the negative control group were exposed to acetone (carrier).

Dams were monitored for viability, BW, food consumption, compound consumption, and parturition (ease of birth, mean litter survival, survival index, etc.). One cohort of F0 dams (21 per dose group) was terminated on GD 20. Blood samples were taken from the jugular vein of the dams and from the umbilical vein of each fetus on that day for thyroid hormone analysis. Fetal blood was pooled by litter, regardless of sex. F0 animals were sacrificed for necropsy, tissue collection, organ weights (liver and thyroid), and thyroid histology / histopathology. The same parameters, including thyroid hormones, were measured at necropsy on the remaining dams on LD 21. The F1 litters were observed for viability, clinical signs, and gender and body weight. Pup blood was collected by cardiac puncture for thyroid hormone determinations on PND 4 and PND 21. Litters (N = 20 – 24 per group) were euthanized and endpoints were measured on PND 21.

Fipronil exposure at these doses did not affect gestation length or parturition. Lower food consumption was recorded at the high dose for GD 6 – 9 (18 g/day vs. 20 g/day in controls, $p < 0.05$). This corresponded to a decrease in BW gain noted for the same period at the same dose.

In dams, statistically significant increases in absolute and relative liver weight (11%) were seen on GD 20 at 3 mg/kg/day (Table 23). On LD 21, relative liver weights were marginally increased (7%, $p \leq 05$) at 1 and 3 mg/kg/day. On LD 21, histopathology of the thyroid showed an increase in follicular cell height and a decrease in colloid area in dams at the high dose. Follicular cell height measurements were scored as Grade 1-5, with higher grade indicating a higher follicular

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cell height. Controls included 4 dams at Grade 1 and 18 dams at Grade 2. In the 3 mg/kg/day group, 1 dam was at Grade 1, 12 dams were at Grade 2 and 11 dams were at Grade 3. Colloid area measurements was also scored from Grade 1-5, with higher grade indicating a larger colloid area. Control dams included 1 dam at Grade 3, 18 at Grade 4, and 5 at Grade 5. In the 3 mg/kg/day group, 11 dams were Grade 3, 12 dams were Grade 4 and 1 dam was Grade 5; colloid area decreased with dose. On GD 20, there was a 28% ($p \leq 0.01$) decrease in T4 levels in dams, with a corresponding 44% increase in TSH ($p \leq 0.05$) at 3 mg/kg/day (Table 23).

In pups on PND 4, statistically significant increases (20% and 13%) were noted in the absolute liver weights in males at 1 mg/kg/day and 3 mg/kg/day, respectively (Table 24). On PND 21, increased absolute liver weights were seen in males and females at 0.3, 1 and 3 mg/kg/day. The increases ranged from 11 to 16% and were statistically significant in all male treatment groups and in the 1 mg/kg/day female treatment group. Relative-to-body liver weights in fetuses and pups (calculated by DPR) were increased by 13 – 20% at 3 mg/kg/day, 9 – 20% at 1 mg/kg/day and 5 – 11% at 0.3 mg/kg/day on PND 4 and PND 21. In PND 21 male and female pups, thyroid follicular cell height and colloid area were affected at 3 mg/kg/day. In GD 20 fetuses, statistically reduced T4 levels (19 – 30%) were observed at 1 and 3 mg/kg/day (Table 24). On PND 4, reduced T3 and T4 (26 – 33%) were observed in male and female pups at 3 mg/kg/day ($p < 0.01$). In PND 21 pups, there were no clear effects on thyroid hormones.

The maternal NOEL of 1 mg/kg/day was based on reduced T4, increased TSH, increased thyroid follicular cell height and decreased colloid area, and increased liver weight on GD 20-21 at the LOEL of 3 mg/kg/day. The developmental NOEL of 0.3 mg/kg/day was based on decreased T4 in fetuses on GD 20 and increased absolute liver weights in males on PND 4 and in both sexes on PND 21 at the LOEL of 1 mg/kg/day. Effects seen at the study NOEL (increased absolute liver weights in pups at 0.3 mg/kg/day on PND 21 and increased relative liver weight in dams at 1 mg/kg/day on PND 21) were not considered sufficiently robust for LOEL determination because they were relatively small and were not associated with liver histopathology.

Table 23. Effects in Rat Dams following Fipronil Exposure in Comparative Thyroid Assay

	0 (acetone)	**positive control[a]**	**Dose (mg/kg/day)**			
			0.1	**0.3**	**1**	**3**
GD 20 liver wt (abs, g)	15.7 ± 2.0	16.0 ± 1.5	16.0 ± 1.5	16.6 ± 1.2	16.8 ± 1.4	17.6 ± 1.8**
%	100	102	101	105	106	111
GD 20 liver wt (rel x 100)	4.3 ± 0.30	4.4 ± 0.33	4.4 ± 0.32	4.5 ± 0.35	4.6 ± 0.35*	4.8 ± 0.34**
%	100	103	102	104	107	112
LD 21 liver wt (abs, g)	16.7 ± 1.9	17.7 ± 2.0	17.0 ± 1.9	17.4 ± 2.4	17.9 ± 2.4	17.8 ± 1.9
%	100%	106	102	104	107	106

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Table 23. Effects in Rat Dams following Fipronil Exposure in Comparative Thyroid Assay

	0 (acetone)	positive control[a]	Dose (mg/kg/day)			
			0.1	0.3	1	3
LD 21 liver wt (rel x 100)	5.1 ± 0.4	5.5 ± 0.4**	5.2 ± 0.4	5.4 ± 0.5	5.5 ± 0.5*	5.4 ± 0.4*
%	100	108	103	106	107	107
T4, GD 20 (pg/ml)	19407±6527	8337±2756	17236±4790	21448±4733	17625±5353	14046±3678**
%	100%	43%	89%	111%	91%	72%
TSH, GD 20 (pg/ml)	3383.4±1224	7085.3±2249**	3878.4±1450	3837.4±1450	4038.7±1576	4869.7±2068*
%	100%	209%	115%	113%	119%	144%
TSH, LD 21 (pg/ml)	3758.6±3219	8765.3±3970**	4419.1±2416	3190.9±1257	4608.0±2865	4934.9±4435
%	100%	233%	118%	85%	123%	131%

[a]Positive control 6-propyl-2-thiouracil (6-PTU) was administered at 3 ppm, which equaled 0.23 mg/kg/day during pregnancy and 0.5 mg/kg/day during lactation.
*, **: Statistically significant different from controls (determined by study authors) at $p \leq 0.05$ or $p \leq 0.01$, respectively.
GD: gestation day; wt: weight; abs: absolute; rel: relative; wt: weight; LD: lactation day; T4: thyroxine; TSH: thyroid stimulating hormone.
Data from Coder (2019).

Table 24. Effects in Rat Fetuses and Pups following Fipronil Exposure in Comparative Thyroid Assay

	0 (acetone)	positive control[a]	Dose (mg/kg/day)			
			0.1	0.3	1	3
PND 4 male liver wt (abs, g)	0.37 ± 0.05	0.36 ± 0.04	0.38 ± 0.05	0.40 ± 0.03	0.440 ± 0.04**	0.41 ± 0.04*
%	100	99	103	109	120	113
PND 4 male liver wt (rel)	3.27	3.24	3.55	3.57	3.93	3.94
%	100	99	109	109	120	120
PND 4 female liver wt (abs, g)	0.38 ± 0.05	0.35 ± 0.04*	0.37 ± 0.04	0.39 ± 0.05	0.41 ± 0.05	0.41 ± 0.06
%	100	92	95	103	108	106
PND 4 female liver wt (rel)	3.49	3.37	3.66	3.64	3.8	4.1
%	100	97	105	105	109	118
PND 21 male lver wt (abs, g)	2.42 ± 0.4	2.23 ± 0.3	2.45 ± 0.4	2.77 ± 0.3*	2.77 ± 0.5*	2.79 ± 0.5**
%	100	93	101	115	115	116

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Table 24. Effects in Rat Fetuses and Pups following Fipronil Exposure in Comparative Thyroid Assay

	0 (acetone)	positive control[a]	Dose (mg/kg/day)			
			0.1	0.3	1	3
PND 21 male liver wt (rel)	4.61	4.39	4.71	5.09	5.11	5.36
%	100	95	102	111	111	116
PND 21 female liver wt (abs, g)	2.38 ± 0.4	2.13 ± 0.3**	2.42 ± 0.5	2.68 ± 0.4	2.74 ± 0.4*	2.65 ± 0.5
%	100	89	102	113	115	111
PND 21 female liver wt (rel)	4.64	4.41	4.75	5.05	5.06	5.22
%	100	95	102	109	109	113
T4, GD 20 fetuses (pg/ml)	5064 ± 1613	1337 ± 599**	4233 ± 893	4658 ± 1309	4122 ± 988*	3569 ± 855**
%	100%	26%	84%	92%	81%	70%
T3, PND 4 males (pg/ml)	172.9 ± 57	212.7 ± 77	204.0 ± 61	187.9 ± 30	163.4 ± 44	116.6 ± 33**
%	100%	123%	119%	109%	95%	67%
T4, PND 4 males (pg/ml)	20653 ± 4600	10814 ± 2776**	24265 ± 5656	22781 ± 2222	18979 ± 4376	14706 ± 3962**
%	100%	52%	117%	110%	92%	71%
T3, PND 4 females (pg/ml)	186.2 ± 51	202.1 ± 87	208.3 ± 58	187.1 ± 37	176.3 ± 50	133.2 ± 48*
%	100%	109%	112%	101%	95%	72%
T4, PND 4 females (pg/ml)	21600 ± 4065	10517 ± 2666**	23822 ± 5794	23553 ± 3664	19544 ± 3214	15945 ± 3473**
%	100%	49%	110%	109%	90%	74%

[a]Positive control 6-propyl-2-thiouracil (6-PTU) was administered at 3 ppm, which equaled 0.23 mg/kg/day during pregnancy and 0.5 mg/kg/day during lactation.
*, **: Statistically significant different from controls (determined by study authors) at $p \leq 0.05$ or $p \leq 0.01$, respectively.
PND: postnatal day; GD: gestation day; g: grams; rel: relative weight; abs: absolute weight; T4: thyroxine; T3: triiodothyronine; TSH: thyroid stimulating hormone.
Data from Coder (2019).

IV.K. Neurotoxicity

The potential for fipronil to result in neurotoxicity under acute and subchronic exposure regimens was addressed in three studies conducted in rats. The principal effects documented in these studies included convulsions, tremors, gait abnormalities, absence of response to stimuli, decreased rearing and grip strength, decreased hindlimb splay and motor activity, impaired righting reflex, exaggerated tail pinch and startle responses and increased urine in the observation arena.

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III.K.1. Acute Neurotoxicity

Gill et al., 1993

Fipronil (96.7%) was administered as a single gavage dose to Sprague-Dawley rats, 15/sex/dose at 0 (corn oil) at 0.5, 5 or 50 mg/kg/day (Gill *et al.*, 1993). Neurobehavioral signs were evaluated using the functional observational battery (FOB). As part of the study protocol, authors determined the time to peak effect (TOPE) in a dose range-finding probe study. An abbreviated FOB was performed every hour for 7 hours and 24 hours after dosing. The TOPE of 7 hours was based on the results of the probe study. In the current study, the FOB evaluations were performed pretest, at the TOPE (7 hours after treatment) and on days 7 and 14. Changes in motor activity were assessed pretest, at 8 hours post-treatment and on days 7 and 14 using an automated recording apparatus. Ten rats/sex/group were subjected to pathological evaluation of brain, spinal cord, peripheral nerves (sciatic, peroneal, sural and tibial), dorsal root, and gasserian ganglia.

The high dose (50 mg/kg/day) produced severe toxicity including death. Five males and 1 female died within 2-6 days of treatment (Table 25). Brain hemorrhage was detected at necropsy in the five animals found dead within 2 days of dosing. Major clinical signs included convulsions and tremors. Convulsions were clonic or clonic and tonic[8], and were seen in 4 males and 1 female within the first day of treatment. Three of these animals died within 24 hours of the convulsive episodes. Other clinical signs within 2-14 days of treatment at 50 mg/kg included dehydration, emaciation, unkempt appearance, urine stains, perioral encrustation, and cold extremities. Decreased body weights in males (up to 10%, $p < 0.01$) were observed at the 7- and 14-day evaluations.

The FOB findings at the TOPE from the 50 mg/kg/day group were indicative of CNS stimulation (convulsions, tremors, head bobbing, myoclonic movements and a decrease in landing hindlimb splay by up to 29%, $p \leq 0.01$). In contrast, neurological depression was evident in the decreased rearing (95-97%, $p \leq 0.01$), decreased arousal, tail-pinch and approach responses, and decreased muscle tone. Some of the acute effects on neuromuscular function were persistent, as they were also seen in FOB conducted on days 7 and 14 (e.g., ~20% decreased hindlimb landing splay in females). Both males and females treated with 50 mg/kg fipronil showed 90-93% decreases in motor activity at the TOPE ($p \leq 0.01$).

FOB effects at the TOPE at the intermediate dose (5 mg/kg/day) included decreased hindlimb splay in both sexes (12-13% compared to controls, $p \leq 0.05$), reduction in the number of rears in females (42%, $p \leq 0.01$), and absence of an approach response (2/15 males). Significant

[8] Clonic convulsions involve myoclonic jerks, running fits or explosive jumps; tonic convulsions involve rigorous extension of the head and body; clonic and tonic convulsions alternate convulsion types.

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decreases in rearing at the TOPE (50%, $p \leq 0.01$) were also reported for the females treated with 0.5 mg/kg/day.

Fipronil caused acute neurotoxicity in rats ranging from neuromuscular effects at 5 mg/kg to convulsions and mortalities at 50 mg/kg. The NOEL of 0.5 mg/kg/day was based on neurobehavioral signs (decreased hindlimb splay, rearing and approach response) at the LOEL of 5 mg/kg/day. At the NOEL of 0.5 mg/kg, there was a statistically significant but not dose-dependent decrease (50%) in rearing in females and a decrease in hindlimb splay (9%, not statistically significant) in males.

Table 25. Neurological Effects in Sprague-Dawley Rats following a Single Gavage Dose with Fipronil

	Males				**Females**			
Dose (mg/kg)	**0**	**0.5**	**5**	**50**	**0**	**0.5**	**5**	**50**
Mortality	**0/15**	**0/15**	**0/15**	**5/15**	**0/15**	**0/15**	**0/15**	**1/15**
Clonic convulsions	0/15	0/15	0/15	4/15	0/15	0/15	0/15	1/15
Tonic convulsions	0/15	0/15	0/15	2/15	0/15	0/15	0/15	0/15
Dehydration	0/15	0/15	0/15	6/15	0/15	0/15	0/15	6/15
Urine stains	0/15	0/15	0/15	4/15	0/15	0/15	0/15	6/15
Perioral encrustation	0/15	0/15	0/15	13/15	0/15	0/15	0/15	9/15
Body weight (% of control)								
7-hr post tx	100	99	100	99	100	100	101	99
7-day post tx	100	99	99	90**	100	101	102	97
14-day post tx	100	99	98	94**	100	100	103	99
FOB observations at 7-hr post tx								
Fine tremors	0/15	0/15	0/15	6/15*	0/15	0/15	0/15	6/15*
Coarse tremors	0/15	0/15	0/15	5/15*	0/15	0/15	0/15	1/15
Altered gait	0/15	0/15	0/15	10/15*	0/15	0/15	0/15	8/15
Palpebral closure (drooping)	0/15	0/15	0/15	4/15	0/15	0/15	0/15	3/15
Tail pinch (no response)	2/15	1/15	1/15	6/15	0/15	0/15	0/15	3/15
Pupil size (decreased)	1/15	0/15	0/15	9/15**	5/15	4/15	2/15	8/15
Muscle tone (decreased)	0/15	0/15	0/15	5/15*	1/15	0/15	1/15	10/15**
Air righting reflex (uncoordinated)	1/15	0/15	0/15	8/15*	0/15	0/15	0/15	0/15
Approach (no response)	0/15	0/15	2/15	6/15*	0/15	0/15	0/15	0/15
Hindlimb splay (% of control)	100	91	88*	72**	100	101	87*	71**
Urination								
7-hr post tx	0/15	0/15	1/15	8/15**	2/15	1/15	2/15	6/15
7-day post tx	0/15	0/15	1/15	3/10	0/15	2/15	1/15	1/14
14-day post tx	0/15	2/15	2/15	6/10**	1/15	2/15	2/15	1/14
Rearing (% of control)								
7-hr post tx	100	178	107	5.4*	100	50**	58**	3**
7-day post tx	100	89	187	289**	100	72	87	104

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Table 25. Neurological Effects in Sprague-Dawley Rats following a Single Gavage Dose with Fipronil

	Males				Females			
Dose (mg/kg)	**0**	**0.5**	**5**	**50**	**0**	**0.5**	**5**	**50**
14-day post tx	100	105	153	123	100	66	84	89

FOB: functional observational battery; TOPE: time of peak effect (7 hours); tx: treatment.
*, ** Statistically significant difference from controls at $p < 0.05$ or $p < 0.01$. Study authors analyzed data variance and used ANOVA (heterogeneous variance) or t-test (unequal variance).
Data from Gill (1993).

Hughes et al., 1997

Fipronil (97.9%) was administered by gavage in a single dose to 10 Crl:CD BR rats/sex/dose at 0 (corn oil), 2.5, 7.5 or 25 mg/kg (Hughes, 1997). This study was intended to provide a more accurate NOEL for acute neurotoxicity, as the earlier study by Gill 1993 had a 10-fold difference between the LOEL and the NOEL (5 and 0.5 mg/kg/day, respectively).The rats were evaluated for neurotoxicity using FOB testing. A time to peak effect (TOPE) of 7 hours was based on neurobehavioral changes observed in a preliminary study conducted by study authors and described in an appendix. FOB evaluations were performed pretest at the TOPE and on days 7 and 14. Changes in motor activity were assessed at the same time points using an activity monitoring system equipped with an infrared detector to determine time spent in no movement, locomotor activity, and non-locomotor activity. Histopathological evaluations of brain, spinal cord, peripheral nerves (sciatic, peroneal, sural and tibial), dorsal root, and ganglia were conducted in 5 rats/sex/dose.

Males and females in the 25 mg/kg/day group displayed reduced body temperature on day 0 ($p < 0.05$). Clinical signs at the high dose that were not seen in the controls included staining of head regions in males (5/10) and females (6/10) and soiled angiogenital region in males (3/10). There were no deaths during the study. Rats treated with 7.5 and 25 mg/kg/day fipronil had statistically significant decreased body weight gains (47%-75%, $p < 0.01$) and decreased food consumption (7-26%, $p < 0.01$) during the first week after exposure (Table 26). Markedly impaired food conversion (grams food consumed per week per kilogram body weight gain) was observed after one week in females at 7.5 and 25 mg/kg and in males at the high dose.

FOB findings at the TOPE for the 25 mg/kg/day group included increased forelimb grip strength in males (21%, $p < 0.01$) and decreased landing hindlimb splay in both sexes (21-28%, $p < 0.01$). Significantly decreased hindlimb landing foot splay (up to 23%, $p < 0.01$) was also reported for males treated with 7.5 mg/kg/day fipronil. Motor activity at 25 mg/kg was reduced by 42-51% compared to control levels ($p < 0.01$).

The study NOEL of 2.5 mg/kg/day was based on neurobehavioral signs (decreased hindlimb splay) in males and decreased body weight gain and decreased food consumption in females at the LOEL of 7.5 mg/kg/day. At the NOEL, hindlimb splay was decreased by 10% in males, though statistical significance was not achieved.

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Table 26. Neurotoxicity in Crl:CD BR Rats Following a Single Gavage Dose

	Males				Females			
Dose (mg/kg)	**0**	**2.5**	**7.5**	**25**	**0**	**2.5**	**7.5**	**25**
Body temperature Day 0	37.9	38	37.9	37.6*	38.2	38.1	38.2	37.6**
Unusual behavior/posture	0/10	0/10	0/10	1/10	0/10	0/10	0/10	1/10
Food consump. week 1 (% con)	100	95	93	74**	100	92	84**	76**
Food consump. week 2 (% con)	100	97	93*	90**	100	97	90	99
BW gain week 1 (% con)	100	88	84	53**	100	94	44**	25**
BW gain week 2 (% con)	100	89	74	94	100	106	71	112
BW 7 h post-tx (% con)	100	98	98	96	100	98	98	99
BW 7 d post-tx (% con)	100	97	97	92	100	98	94	93
BW 14 d post-tx (% con)	100	96	95	92	100	99	92	95
Food conversion, week 1	7	7.4	7.7	9.7	10.2	9.9	20.2	30.8
% control	100	106	110	139	100	97	198	302
Food conversion, week 2	6.2	6.8	7.8	6	9.1	8.3	11.3	8
% control	100	110	126	97	100	91	124	88
Hindlimb splay at 7 h (% con)	100	90	77**	72**	100	100	86	79*
Forelimb grip strength 7 h (% con)	100	108	106	122**	100	100	104	108
Motor activity 8 h (% con)	100	94	92	49**	100	104	94	58**

Food consumpt: food consumption; con: control; BW: body weight; tx: treatment.
*, ** Statistically significant difference from controls at $p < 0.05$ or $p < 0.01$. Data were analyzed by study authors with Bartlett's test for variance, one-way ANOVA or Student's t-test, and William's test for dose-response.
Data from Hughes (1997).

III.K.2. Subchronic Neurotoxicity

Driscoll and Hurley, 1993

In a subchronic neurotoxicity study, fipronil (96.7% a.i.) was administered to Sprague-Dawley rats (15/sex/dose) at dietary levels of 0, 0.5, 5 or 150 ppm for 13 weeks (Driscoll and Hurley, 1993). The average daily doses based on food consumption corresponded to 0, 0.03, 0.3 and 9 mg/kg/day for males and 0, 0.03 0.4 and 11 mg/kg/day for females. Animals were examined for mortality and clinical signs twice per day, 7 days per week. The FOB and motor activity tests were performed 1 week pretest and at weeks 4, 9 and 13 of treatment. Six rats/sex were subjected to pathological evaluation in brain, spinal cord, trigeminal nerve, dorsal root, and gasserian ganglion in the controls and high dose animals, only.

Mortality was not observed in this study. Periocular encrustation (2/15) was observed in high-dose males.

During the first week of exposure, fipronil caused a reduction in body weights in both sexes at 150 ppm (up to 6%, females; 8%, males; $p \leq 0.05$) and a decrease in body weight gain of up to 70% (Table 27). The effect persisted in male rats through the second week ($p < 0.01$) and may have resulted, at least partially, from a decrease in food consumption (23-24%) during week 1. By the end of the study, body weights in males were significantly higher than controls in the 5

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and 150 ppm groups (7-8% higher, $p < 0.01$). Absolute brain weights were also increased in high-dose males (5%, $p < 0.05$), but relative brain weights were not.

In FOB tests, males treated with 5 and 150 ppm fipronil showed increased incidence of urine in the observation area during weeks 4 and 9 (7-10/10 in treated groups versus 5/10 in controls); the increase was significant at the high-dose during week 4 ($p < 0.05$). Males in the 150 ppm groups also showed exaggerated tail pinch response during weeks 4 and 9 (2-4/10 versus 0/10 in controls) and exaggerated startle response at weeks 4, 9 and 13 (2-4/10 versus 0/10 in controls). One female showed "unusual behavior" during week 4.

At study termination, 1/15 males at the high dose showed scar or abscess on the skin, a dilated kidney pelvis or calculus in the kidney. 1/15 females at the high dose showed oral malocclusion, alopecia, scabbing of skin, or nose fracture. Microscopic analysis showed minimal myelin sheath swelling in 1/6 high dose males and 2/6 high dose females (compared to 0/6 controls). Tissues from the 0.5 and 5 ppm groups were not assayed.

The NOEL for the subchronic neurotoxicity of fipronil in rats was 0.5 ppm (0.03 mg/kg/day), based on the LOEL of 5 ppm (0.3 mg/kg/day) for effects on the autonomic nervous system (presence of urine in the observation area and exaggerated tail pinch response).

Table 27. Effects seen in subchronic neurotoxicity study following oral fipronil exposure in rats

	Males				**Females**			
Dose (ppm)	**0**	**0.5**	**5**	**150**	**0**	**0.5**	**5**	**150**
Dose (mg/kg/day)	**0**	**0.03**	**0.3**	**9**	**0**	**0.03**	**0.4**	**11**
N	15	15	15	15	15	15	15	15
BW (g) week 1	295.4 ± 9.4	300.9 ± 7.8	296.9 ± 12.0	277.4 ± 10.5**	191.3 ± 7.6	193.1 ± 8.0	192.5 ±7.5	179.9 ± 7.5**
% of con	100	102	101	94	100	101	101	94
BW gain (g) week 1	28.9 ± 5.2	32.8 ± 4.7	30.4 ± 5.0	11 ± 5.1**	14.2 ± 4.0	16.2 ± 5.1	14.3 ± 4.6	4.2 ± 4.3**
% of con	100	113	105	38	100	114	101	30
BW (g) week 2	315.5 ± 12	325.2 ± 10.8	319.2 ± 15.4	307.3 ± 12.2	203.2 ± 9.8	204.1 ± 9.0	204.8 ± 11.9	197.7 ± 10.7
% of con	100	103	101	97	100	100	101	97
BW gain (g) week 2	49.1 ± 7.3	57.1 ± 7.5	52.6 ± 9.1	40.9 ± 6.3**	26 ± 8.7	27.2 ± 5.9	26.7 ± 5.5	22.1 ± 6.5
% of con	100	116	107	83	100	105	103	85
Final BW (g)	426.6 ± 19.9	441.5 ± 21.5	454.6 ± 22.3**	458.6 ± 22.4**	265.1 12.9±	263.9 ± 14.9	264.3 ± 10.6	266.7 ± 23.7
% of con	100	103	107	108	100	100	100	101

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Table 27. Effects seen in subchronic neurotoxicity study following oral fipronil exposure in rats

	Males				Females			
Dose (ppm)	**0**	**0.5**	**5**	**150**	**0**	**0.5**	**5**	**150**
Dose (mg/kg/day)	**0**	**0.03**	**0.3**	**9**	**0**	**0.03**	**0.4**	**11**
food consum.[a] week 1	22.4 ± 1.3	22.7 ± 1.4	22.6 ± 1.1	17.2 ± 1.2**	16.5 ± 0.9	16.8 ± 1.2	16.1 ± 1.3	12.5 ± 1.2**
% of con	100	101	101	77	100	102	98	76
food consum. week 2	22.1 ± 1.4	22.5 ± 1.6	22.5 ± 1.2	22.8 ± 1.1	16.7 ± 1.2	16.4 ± 1.2	16.3 ± 1.8	17.1 ± 1.3
% of con	100	102	102	103	100	98	98	102
brain weight (g)	2.1 ± 0.07	2.1 ± 0.08	2.1 ± 0.1	2.2 ± 0.07*	1.9 ± 0.08	1.9 ± 0.07	1.9 ± 0.07	2 ± 0.1
% of con	100	100	100	105	100	100	100	105
unusual behavior week 4	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10
Urine in Observation Arena								
week 4	5/10	6/10	9/10	10/10*	4/10	6/10	0/10	4/10
week 9	5/10	4/10	7/10	9/10	2/10	6/10	5/10	6/10
week 13	5/10	5/10	4/10	9/10	7/10	8/10	7/10	6/10
Exaggerated Startle Response								
week 4	0/10	0/10	0/10	4/10	0/10	0/10	0/10	0/10
week 9	0/10	0/10	1/10	2/10	0/10	0/10	0/10	0/10
week 13	0/10	0/10	0/10	2/10	0/10	0/10	0/10	0/10
Exaggerated Tail Pinch Response								
week 4	0/10	0/10	0/10	4/10	1/10	2/10	0/10	1/10
week 9	0/10	0/10	1/10	2/10	0/10	0/10	0/10	0/10
week 13	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10

BW: body weight; Food consum: food consumption (g/animal/day).
*,** Statistically significant difference from controls at $p < 0.05$ or $p < 0.01$..
Data from Driscoll and Hurley (1993).

IV.L. Developmental Neurotoxicity

IV.L.1. Mandella et al., 1995

Developmental neurotoxicity of fipronil (96.1%) was evaluated in a developmental neurotoxicity study in which 30 mated female Sprague Dawley rats were administered fipronil in the diet (Mandella, 1995). The dams were treated from gestation day (GD) 6 through lactation day (LD) 10 at doses of 0, 0.5, 10 and 200 ppm fipronil in acetone. The average daily intake of fipronil calculated from food consumption was 0, 0.05, 0.9 and 15 mg/kg/day. Twenty-seven control rats

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and 29 rats in each of the three treatment groups produced litters. The pups were indirectly exposed to fipronil for a total of 25 days (15 days *in utero* and 10 days via lactation). The dams and pups (4 males and 4 females/litter after culling on LD 4) were observed for signs of general toxicity throughout the treatment period. All dams were sacrificed on LD 21, following weaning. One male and 1 female/litter were evaluated for developmental toxicity until ~65 days of age. Parameters included timing of developmental landmarks such as pinna detachment, incisor (tooth) eruption, eye opening, vaginal patency and preputial separation. Motor activity was assessed on 4 separate occasions between PND 13-60. Auditory startle habituation was tested on PND 22 and 60. Swimming ability was examined on 5 different occasions between PND 6 and 14. Learning and memory (short and long-term) were evaluated in using a water "Y maze" in 6 tests between PND 24 and 65. Brain tissues, spinal cord and peripheral nerves (sciatic, sural and tibial) from PND 60 rats (six/sex/group) were examined for neuropathology.

Dams

Two females in the 200 ppm group died on lactation days 6 and 9. Both decedents showed discolored lungs at necropsy. Compared to controls, fewer 200 ppm dams were described as "normal within limits" (17/30 at GD 21 and 11/27 at LD 21 for the 200 ppm dams *vs.* 25/30 and 21/27 for controls). The description "normal within limits" was based on physical observations during the gestation and lactation period (though the examined parameters were not provided in the study). The 200 ppm dams had a total of 41 dead/missing pups from LD 1 through the end of the lactation period; 4 litters lost all pups (Table 28). Control dams had no dead or missing pups. In addition, the 200 ppm dams showed a significantly higher alopecia incidence through the treatment period (13/30 in the 200 ppm group *vs.* 4/30 for controls on GD 21, $p < 0.05$, Fisher's exact test performed by DPR). Other abnormal findings for the 200 ppm dams during the physical observations included broken/maloccluded incisors and scabs.

Offspring

All 27 control litters survived until weaning. In contrast, 4 of 29 litters from the 200 ppm group lost all of the pups by LD 4 (85.2% survival). Pup viability was statistically significantly reduced in the 200 ppm group ($p < 0.01$). The number of pups in the 200 ppm group dying or missing between LD 0 and LD 21 was 170 (out of 428 born alive; 40%). For comparison, 35 control pups were dead or missing by LD 21 (out of 398 born alive; 9%). Most of the pups died between LD 0-4. The viability index on day 4 (total pups born alive) was 75.5% in the 200 ppm group versus 98.9% for the control pups. There were no significant pathological findings for the dead pups.

Male and female pups in the 10 and 200 ppm groups exhibited reduced body weights at all examinations during lactation (7 – 41%, $p \leq 0.01$, Table 29). Difference in weight at the high dose persisted even when fipronil was removed from the dam's diet (LD 10). At the end of the study the body weight of these rats was about 12 – 14% ($p \leq 0.01$) less than the control. Absolute brain weights were substantially decreased for both sexes (7 – 20 % decrease, $p < 0.01$) at the two evaluations on postnatal day (PND) 11 and PND 60. This effect may be, at least in part, due to the reduction of 12 – 41% of the body weights of these animals.

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Males and females treated with 200 ppm fipronil had slower development compared to the control, evidenced by the statistically significant delays in pinna detachment (0.5 days delay) and delays in upper and lower incisor eruption (0.6 – 1.5 days delay, Table 30). In addition, vaginal patency, a landmark for female puberty, was delayed by 1.5 days. The number of days to preputial separation, an indicator of male puberty, were significantly increased by 1.4 and 4.8 days at 10 and 200 ppm, respectively, compared to concurrent controls. The mean days to preputial separation (range) were: 44.0 (40.7 – 46.7); 44.7 (41.7 – 53.5); 45.4 (42.0 – 53.3, $p < 0.01$); and 48.8 (45.0 – 54.0, $p < 0.001$) for ascending doses, respectively. Furthermore, the mean values for the 10 ppm and 200 pm groups exceeded historical control means in the same rat strain from 4 studies conducted in the same laboratory between 1989 and 1995 (Mandella and Rodwell, 2005): 43.6 (40.0 – 47.0); 42.8 (39.0 – 46.90); 43.6 (41.0 – 48.0); and 45.0 (41.8 – 49.7).

Pups in the 200 ppm dose group showed decreased maximum response (23 – 27%; $p \leq 0.0001$) and decreased average response (25 – 26%; $p < 0.001$) in auditory startle evaluations on PND 22. This could be due to a general depression of the nervous system or a loss of hearing. A significant decrease in maximal response was also seen in males at 10 ppm (13%; $p \leq 0.05$) (Table 31).

On PND 6, a significantly higher number of pups in the 200 ppm group were unable to stay afloat or swim in straight line, compared to controls. By PND 14, nearly all of the control pups could maintain their ears, nose of head tops above water, whereas 62 – 63% ($p < 0.04$) of the 200 ppm pups could not hold their heads above the surface. The 200 ppm pups also had a significant delay in swimming development on PND 22 (Table 31).

The maternal NOEL was 10 ppm (0.9 mg/kg/day) based on death, alopecia, dead/missing pups, and decreased body weight, body weight gain and food consumption at the LOEL of 200 ppm fipronil (15 mg/kg/day). The NOEL for developmental neurotoxicity was 0.5 ppm (0.05 mg/kg/day) based on statistically significant delays in preputial separation in male pups, decreased maximum startle response in male pups, and decreases in body weight in both sexes at the LOEL of 10 ppm (0.9 mg/kg/day).

Table 28. Body Weight and Litter Effects on Sprague Dawley Rat Dams

Dose (ppm)	**0**	**0.5**	**10**	**200**
Dose (mg/kg/day)	**0**	**0.05**	**0.9**	**15**
Dam BW GD 0-6 (g)	40 ± 8	43 ± 8	39 ± 9	40 ± 8
Dam BW GD 6-10 (g)	19 ± 7	19 ± 3	18 ± 8	-29 ± 10**
Dam BW GD 10-15 (g)	35 ± 6	33 ± 6	35 ± 5	49 ± 9**
Total Number of Litters on PND 0	27	29	29	29
Surviving Litters on PND 21	27	29	29	23**
Pup Live Birth Index[a] (%)	99.1	98.9	98.4	93
Pup Viability Index[b] (%)	98.9	95.7	98.3	75.5**

Number of dams: 26-28 per dose group; 23-29 pups per dose group.

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[a]Pup Live Birth Index: (total pups born alive/total pups born) x 100
[b]Pup Viability Index: (total pups alive on PND $4_{pre\text{-}cull}$ /total pups born alive) x 100
*, ** Statistically significant difference from controls at $p < 0.05$ or $p < 0.01$, respectively
BW: body weight; GD: gestation day. PND: postnatal day.
Data from Mandella (1993)

Table 29. Body Weight of Sprague Dawley Rat Pups Exposed During Gestation and Lactation

	Male Pups				Female Pups			
Dose (ppm)	**0**	**0.5**	**10**	**200**	**0**	**0.5**	**10**	**200**
Dose (mg/kg/day)	**0**	**0.05**	**0.9**	**15**	**0**	**0.05**	**0.9**	**15**
PND 0	100	100	97	91**	100	98	95*	92**
PND 4 post cull	100	96	93*	73**	100	94*	91**	73**
PND 11	100	96	93	66**	100	95	92*	66**
PND 17	100	99	93*	75**	100	97	91**	73**
PND 60	100	96	96	88**	100	102	99	87**

Numbers are percent of control. PND: postnatal day. Data from Mandella (1993).
*, **, and **** are equal to $p \leq 0.05$, 0.01, and 0.0001, determined by DPR with one-way ANOVA and Dunnett's multiple comparison test post hoc.

Table 30. Developmental Landmarks in Sprague Dawley Rat Pups Exposed During Gestation and Lactation

Dose (ppm)	**0**	**0.5**	**10**	**200**
Dose (mg/kg/day)	**0**	**0.05**	**0.9**	**15**
N (all animals)	394	426	436	323
Pinna (ear) attachment	2.5 (0.6)	2.6 (0.6)*	2.5 (0.6)	3.0 (1)****
Lower incisor eruption	11.4 (0.9)	11.6 (0.9)*	11.4 (0.9)	12.1 (0.1)****
Upper incisor eruption	10.3 (0.9)	10.5 (0.9)	10.4 (1.0)	10.9 (1.2)****
N (females)	96	96	100	78
Vaginal patency (days)	31.4 (1.1)	32.0 (1.4)**	31.6 (1.3)	32.9 (1.7)****
N (males)	89	103	100	70
Preputial separation (days)	44 (2.5)	44.7 (1.03)	45.4 (2.9)**	48.8 (3.3)****

Data presented as mean (standard deviation).
*, **, and **** are equal to $p \leq 0.05$, 0.01, and 0.0001. Significance determined by DPR with one-way ANOVA and Dunnett's multiple comparison test post hoc.
Data from Mandella (1993).

Table 31. Neurological Effects on Sprague Dawley Rat Pups Exposed during Gestation and Lactation

	Males				Females			
Dose (ppm)	**0**	**0.5**	**10**	**200**	**0**	**0.5**	**10**	**200**
Dose (mg/kg/day)	**0**	**0.05**	**0.9**	**15**	**0**	**0.05**	**0.9**	**15**
N	26	28	29	20	26	27	29	21
Maximum Startle Response (% of control)	100	106	87*	73****	100	108	99	77****
Average Startle Response (% of control)	100	111	92	74***	100	107	97	75***

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Unable to Stay Afloat PND 6	12%	7%	7%	50%**	8%	7%	4%	35%
Unable to Swim in Straight Line PND 6	50%	32%	41%	73%**	39%	37%	25%	57%
Unable to Keep Head out of Water PND 6	64%	82%	79%	96%	77%	63%	64%	91%*
Unable to Keep Head out of Water PND 14	8%	18%	28%	63%	8%	30%	18%	46%

PND: postnatal day.
*, ***, ** and **** are equal to $p \leq 0.05$, 0.01, 0.001 or 0.0001 by DPR with one-way ANOVA and Dunnett's multiple comparison test post hoc.
Number of pups ranged from 19 to 28 per sex, per exposure group, per time point.
Startle response was measured on PND 22 and PND 60. Data are from PND 22.
Data from Mandella (1993).

IV.L.2. Lassiter et al., 2009

The *in vitro* neurotoxicity of fipronil were assayed in undifferentiated and differentiating PC12 cells (Lassiter *et al.*, 2009). Authors also investigated the effects of chlorpyrifos, an insecticide that is neurotoxic to mammals, as well as a mixture of fipronil and chlorpyrifos. Endpoints included cell replication, cell number, differentiation, and viability after short-term (1 hour) and long-term (6 day) exposures. Fipronil elicited a greater effect during replication and differentiation, was more potent and caused more widespread effects than chlorpyrifos. Effects were seen as low as 1 μM. These included decreased cell number, reduction in DNA synthesis, impairment of protein synthesis, and increased oxidative stress without decreased cell viability, all suggesting neuro-developmental alterations. Fipronil was also more potent on differentiating cells, inducing a switch in transmitter phenotype that can cause mis-wiring of neural circuits. The investigators concluded that fipronil is inherently a more potent disruptor of neuronal cell development than is chlorpyrifos in this system. The authors concluded that neurodevelopmental effects were not dependent on GABAα antagonist properties as PC12 cells lack that receptor.

IV.M. Toxicity of the Metabolites and Photodegradate of Fipronil

Fipronil (parent), its sulfone and sulfide metabolites, and the desulfinyl environmental degradate (a product of UV decomposition) all block GABA-gated chloride channels to greater or lesser degrees. Fipronil-sulfone is the major metabolite in both vertebrates and insects, while fipronil-desulfinyl is the principal photoproduct on plants and soils (Hamon *et al.*, 1996).

The registrant-submitted fipronil-desulfinyl database included: Oral toxicokinetic studies in rat, goat and laying hen, and a dermal toxicokinetic study in rat; Acute oral and dermal toxicity studies in rat; Subchronic 14-day, 28-day and 90-day oral studies in rat, 28-day and 90-day oral studies in mouse and 28-day and 90-day oral studies in dog; Combined chronic and oncogenic study in rat; Gene mutation studies in *S. typhimurium* and Chinese hamster ovary cells; Chromosome aberration studies in human lymphocytes and mice; Developmental toxicity study in rat; and, Acute neurotoxicity study in rat. In addition, a published study with in rat was available on oxidative stress. Registrant-submitted studies for fipronil-sulfide included an acute toxicity study in rat and a gene mutation study in *S. typhimurium.* Registrant-submitted studies for fipronil-sulfone included a gene mutation study in *S. typhimurium* and a chromosome aberration study in human lymphocytes. A published study with in rat was available on oxidative

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stress. The toxicity of other identified fipronil metabolites (detrifluoromethylsulfonyl-fipronil and the amide RPA200766) have not been evaluated in mammals.

DPR considers critical values for the parent fipronil protective for the other moieties. The toxicity of the metabolites and the environmental photodegradate are more fully described in Appendix III.

IV.N. Toxicity Forecaster (ToxCast™)

Toxicity Forecaster (ToxCast™) is a federal program that aims to reduce the number of animals used in toxicity testing by validating high-throughput screening technologies and toxicity data (US EPA, 2016). The multi-phase ToxCast™ program consists of over 700 unique high-throughput screening assays that measure more than 1000 endpoints in 300 signaling pathways. ToxCast™ data can potentially elucidate biochemical interactions or identify adverse outcome pathways (AOPs). It used by the US EPA to prioritize chemicals for animal toxicity testing. DPR includes ToxCast™ data in its RCDs to help inform its analysis of potential chemical hazards. ToxCast™ version 2 was used for this analysis (analyses performed August, 2018).

A total of 11 target families were impacted by exposure to fipronil. The highest frequency of active hits occurred in the transferase, CYP, cell cycle, cytokine and cell adhesion families. These results are interesting in the context of fipronil exposure because transferase and CYP enzymes are involved in xenobiotic metabolism and support the evidence that fipronil increases clearance of thyroid hormone in rat. The five assays with the most potent response following fipronil exposure were all related to regulation of the constitutive androstane (CAR) nuclear receptor, which is important in hepatic metabolism (Assem *et al.*, 2004; Roques *et al.*, 2013). These results are in concordance with liver effects seen in laboratory animals. Endocrine-specific assays showed limited effects at the thyroid, androgen and estrogen receptors. Fipronil was not positive in ToxCast™ assays for GABA receptor interaction. This is likely because fipronil acts at an allosteric binding – it does not bind at the same site on the GABA receptor as the neurotransmitter GABA (Ratra and Casida, 2001; Zhang *et al.*, 2016). GABA receptor-based effects seen in *in vivo* studies therefore were not identified by the ToxCast™ *in vitro* assays.

DPR performed gene ontology analyses on the fipronil ToxCast™ dataset with the online bioinformatics functional annotation tool DAVID (Huang da *et al.*, 2009a; Huang da *et al.*, 2009b). The use of gene ontology with ToxCast™ is an emerging field in predictive toxicology. Such ontological analyses determine whether biological pathways or molecular functional categories are significantly enriched in a data set. DPR used gene ontology results to determine concordance between ToxCast™ data and effects seen *in vivo* and the analysis identified pathways and functional categories that were statistically significantly enriched. Of interest is that some gene ontology results were related to liver effects observed *in vivo*. For example, steroid binding domains, transcription pathways, steroid hormone mediated signaling and type II diabetes are all induced by fipronil through its ability to induce hepatic metabolism.

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V. RISK ASSESSMENT

V.A. Hazard Identification

For purposes of this risk assessment, points of departure (PODs) are internal doses that did not produce toxicologically significant effects following oral, dermal or inhalation exposure. Critical PODs are the most toxicologically-robust study PODs established for particular exposure durations and routes, and represent the threshold doses for non-oncogenic effects. Cancer risk was assessed by a threshold approach using an upstream marker of the relevant oncogenic process, instead of by linear extrapolation (see discussion below). For reasons delineated in the following paragraphs, the critical PODs by the dermal and inhalation routes were set at the same oral values for the corresponding exposure duration.

Data from toxicity studies submitted by the registrant were used to establish critical PODs. None of the studies identified through a systematic review of the published literature produced a critical POD. The PODs were either experimentally determined (i.e. NOELs) or data-derived. Data-derived POD values for fipronil were calculated using dose extrapolation factors. Benchmark dose (BMD) modeling was used to derive PODs from datasets that were amenable to modeling. BMD modeling, also called low-dose extrapolation, was performed using US EPA's Benchmark Dose Software (BMDS; versions 2.6 and 2.7). In this approach, the dose-response data for each endpoint were analyzed to generate a family of mathematically-based models (US EPA, 2012a). Each model resulted in the generation of a BMD and a corresponding BMDL value for a predetermined benchmark response level. A BMDL represents the 95% lower bound of a BMD and is considered equivalent to the POD for the observed effect. BMD analyses are available in Appendix IV. A detailed description of the hierarchical examination DPR conducts for BMDL goodness-of-fit is described in Appendix IV.

The critical PODs were used to estimate the risks posed by fipronil exposures. PODs were evaluated as critical based on their corresponding route and duration, relative value, and toxicological considerations. All critical PODs used in this assessment were based on the parent compound fipronil and the effects observed in laboratory animals exposed to technical grade fipronil (93 – 99.9%) (summarized in Table 32).

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Table 32. Summary of Critical Points of Departure for Fipronil

Duration	Route	Critical Endpoint	POD (mg/kg/day)
Acute	Oral, Dermal and Inhalation	Decreased hindlimb splay in an acute oral neurotoxicity study in rats	0.87[a]
Subchronic	Oral, Dermal and Inhalation	Convulsions and mortality associated with convulsions and sustained decreases in T4 after subchronic oral exposure in a chronic study in rats	0.02[b]
Chronic	Oral, Dermal and Inhalation	Convulsions and mortality, sustained decreases in T4, and increased progressive senile nephropathy in a chronic oral study in rats	0.02[c]

T4: thyroxine thyroid hormone. POD: point of departure.
[a]Benchmark dose modeling (BMDS, version 2.6) of hindlimb splay data from acute neurotoxicity study in rat (Hughes, 1997).
[b]Combined chronic and oncogenic study in rat (Aughton, 1993). The critical subchronic POD was supported by POD established in three additional studies in rodents following subchronic exposure: 0.01 mg/kg/day based on increased incidence of urine in the FOB observation arena in rats (Driscoll and Hurley, 1993); 0.05 mg/kg/day based on delayed development and decreased startle response in rat pups (Mandella, 1995); 0.06 mg/kg/day based on liver periacinar hypertrophy in mice (Broadmeadow, 1991).
[c]Combined chronic and oncogenic study in rat (Aughton, 1993).

V.A.1. Points of Departure for Acute Toxicity

Six registrant-submitted acute studies were evaluated for POD. These included one oral LD_{50} study in rats, two oral neurotoxicity studies in rats, one dermal study in rabbits, and two inhalation studies in rats. Studies that employed repeated exposures were also considered for acute POD determinations if the effects were observed during the first week of treatment (e.g., with short-term exposure duration). Studies with acute and short-term exposure durations were also available in the published literature. The critical acute PODs and relevant studies and endpoints are described in Table 33. Acute and short-term symptoms included neurological disturbances, changes in serum thyroid hormone concentrations, decreased maternal and offspring body weights, and delayed development. Acute intraperitoneal injection caused hepatocyte vacuolation, hypertrophy and lipid accumulation, changes in plasma membrane morphology, and increased oxidative stress in rodents. However, this atypical dosing route limited the utility of this study for establishing a critical NOEL.

Acute Oral Toxicity

The lowest acute oral NOEL was established in an acute neurotoxicity study in rats (Gill *et al.*, 1993). In this study, the rats received a single dose of fipronil (0, 0.5, 5 or 50 mg/kg/day) by gavage. The NOEL of 0.5 mg/kg/day was based on neurobehavioral signs (decreased hindlimb landing splay, rearing and approach response) at the LOEL of 5 mg/kg/day. There was a significant but non dose-dependent decrease (50%) in rearing in females and a decrease in hindlimb splay (9%, not significant) in males at the study NOEL. Attempts to model the hindlimb spay and rearing data using the BMDS approach were unsuccessful as the models did

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not pass goodness-of-fit tests. Moreover, the decrease in rearing could have been due to biological variation. The likelihood that rearing was a true response to fipronil was minimized by the absence of such an effect at a similar dose range in the Hughes (1997) study (described below). Because there was a 10-fold difference between the LOEL and NOEL doses in this study, the registrant conducted a second acute neurotoxicity study in rats designed to provide a more precise POD for acute neurotoxicity (Hughes, 1997).

In contrast to Gill *et al.*, Hughes (1997) used exposure doses that were spaced 3-fold (0, 2.5, 7.5 and 25 mg/kg/day) (Hughes, 1997). A statistically significant, dose-dependent reduction in hindlimb splay was observed 7 hours after gavage administration of at the LOEL of 7.5 mg/kg, resulting in a study NOEL of 2.5 mg/kg/day. A 10% decrease in hindlimb splay that was non-statistically significant was also observed at the study NOEL of 2.5 mg/kg/day. It should be noted that a similar decrease (9%) was also observed at the NOEL of 0.5 mg/kg/day in the earlier acute neurotoxicity study (Gill *et al.*, 1993). Because this effect did not increase in magnitude or reach statistical significance over a 5-fold dose increase (0.5 to 2.5 mg/kg/day), DPR considered it to be within the observed range of variation. Therefore, a 10% benchmark response level (BMR) was selected by DPR to model hindlimb splay. Application of BMDS modeling, which provides a statistically rigorous approach to the dataset and a better characterization of the dose-response relation at the low-end of the observable dose range, resulted in a $BMDL_{10}$ of 0.87 mg/kg/day (BMD = 2.48 mg/kg/day) (Exponential 4 model).The $BMDL_{10}$ of 0.87 mg/kg/day was therefore selected as the critical POD to characterize the acute risk due to oral exposure. BMDS outputs are provided in Appendix IV.

Published studies identified acute or short-term NOELs in the range of 1-5 mg/kg/day. Effects included neurotoxicity (Martins, 2009), increased hepatic metabolism (Caballero *et al.*, 2015), decreased T3 and T4 and altered metabolic profiles (Moser *et al.*, 2015) in rats at 5 – 10 mg/kg/day. A 3-day study in mice showed an increased number of blastocysts containing dead cells in embryos extracted from dams exposed to 0.009 mg/kg/day (Sefcikova et al., 2018). This observation was difficult to interpret, as noted is described in the Appraisal section of this RCD.

Acute Inhalation Toxicity

Three registrant-submitted inhalation toxicity studies with acute or short-term endpoints were available for fipronil. These included two acute LC_{50} studies and one subchronic study, all in rats. Of these, the lowest NOEL was established in the subchronic inhalation study for effects seen as early as 2 days of exposure (Adamo-Trigiani, 1999). In this study, animals were subjected to nose-only exposure at 0, 0.001, 0.005, or 0.03 mg/L aerosolized fipronil for 4 hours per day, 7 days per week, for 4 weeks. Clinical signs (salivation, decreased activity, and convulsions) in females on day 2, and decreased body weight in males and decreased food consumption in both sexes were observed at week 1 at the LOEL of 0.005 mg/L. The NOEL was 0.001 mg/L. Oral equivalent doses were calculated using a rat default breathing rate, making the acute inhalation NOEL and LOEL equal to 0.8 mg/kg/day and 0.16 mg/kg/day, respectively.

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Both acute inhalation LC_{50} studies exposed rats for 4 hours (nose-only). In the first study, mortality in females occurred at the LOEL of 0.259 mg/L (oral equivalent dose of 41.4 mg/mg/day) (Cracknell, 1994). In the second study, death, clinical signs, gross pathology of stomach, lungs and brain were seen at the LOEL of 0.33 mg/l, with an oral equivalent dose of 53 mg/kg/day (Nachreiner, 1995).

The lowest acute inhalation POD of 0.8 mg/kg/day was based on clinical signs and decreased body weight and food consumption in rats. This value was very similar to the critical acute oral POD of 0.87 mg/kg/day, which was based on decreased hindlimb splay in rats. A route-specific inhalation POD is generally preferable for characterizing risks to humans from inhalation exposure. However, in this case the critical oral POD was used for risk calculation. DPR felt that less uncertainty was associated with the oral value because it was obtained by a statistically robust process of BMD modeling. In contrast, calculation of an absorbed, internal dose from an air concentration value in the inhalation study required use of a default value for a normalized rat inhalation rate (in mg/kg-BW/day). In addition, toxicokinetic data were not available for the inhalation route and the inhalation study did not perform an FOB. Therefore, the acute inhalation POD of 0.87 mg/kg/day was based on significant dose-dependent reduction in hindlimb splay observed in rats 7 hours after gavage administration of fipronil in an acute neurotoxicity study (Hughes, 1997).

Acute Dermal Toxicity

Two registrant-submitted dermal studies, an acute LD_{50} dermal study in rabbits and a subchronic (4-week) dermal study in rats, were available for analysis. In the acute study, rabbits were treated with a single dermal dose of fipronil wetted in corn oil at 100, 250, 500, 1000 or 2000 mg/kg/day for 24 hours (Myers and Christopher, 1992). Hyperactivity in one male on days 5 – 7, diarrhea in two females on days 1 – 2, and a dark purple kidney in one female at necropsy were observed at the LOEL of 100 mg/kg/day.

Two acute dermal studies were available in published in literature. However, neither study utilized proper controls (Ohi *et al.*, 2004; Terçariol and Godinho, 2011).

In the subchronic dermal study, fipronil was applied to the skin on the trunks of rats for 6 – 7 hours per day, 5 days per week, for 4 consecutive weeks at doses of 0, 100, 500, or 1000 mg/kg/day (Henwood, 1997). Body weight and food consumption were statistically significantly decreased by 5% and 14%, respectively at the LOEL of 1000 mg/kg/day during days 1 – 8. The acute/short-term dermal NOEL was 500 mg/kg/day.

The lowest acute dermal LOEL was 100 mg/kg/day for hyperactivity, diarrhea, and bloody kidney in rabbits (NOEL not determined). However, hindlimb splay, the most sensitive endpoint seen following acute oral fipronil exposure, was not measured in either dermal study. Therefore, the critical acute oral POD of 0.87 mg/kg was used to evaluate the acute dermal risk to humans (Hughes, 1997).

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DPR used a dermal absorption study in rat (Cheng, 1995) to estimate a dermal fipronil absorption rate of 4.3% (DPR, 1999a).

Table 33. Summary of Acute Points of Departure (PODs) for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, Wistar	oral acute LD_{50}, gavage	abnormal gait, hunched posture, diarrhea, piloerection	< 50	50	Gardner (1988)
Rat, Crl:CD BR	**oral acute neurotox, gavage**	**reduced hindlimb splay**	**0.87[a]**	**7.5**	**Hughes (1997)**
Rat, Sprague Dawley	oral acute neurotox, gavage	reduced hindlimb splay, rearing	0.5	5	Gill (1993)
Rat, Wistar	single dose, gavage, 6 days	increased hepatic metabolism	1	5	Caballero (2015)†
Rat, Long-Evans	single dose, gavage	decreased T3 and T4 and altered metabolic profiles	5	10	Moser (2015)†
Rat, male, Wistar	single dose, gavage	decreased rearing and movement time in the open maze and decreased time in the closed arm of the elevated cross maze	1	10	Martins (2009)†
Rabbit, New Zealand White	dermal acute LD_{50}, 24-hr	hyperactivity, diarrhea, bloody kidney	< 100	100	Myers and Christopher (1992)
Rat, Crl:CD(SD)BR	dermal subchronic, 4 wk, 5 day/wk, 6-7 hr/day	decreased BW, decreased food consumption within one week	500	1000	Henwood (1997)
Rat, Sprague Dawley	inhalation subchronic, 4 weeks, 4 h/day, nose-only	clinical signs on day 2, decreased BW and decreased food consumption during week 1	0.8[b]	4.8	Adamo-Trigiani (1999)
Rat, CD	inhalation acute LC_{50}, 4 hour nose-only	mortality in females	< 41.4[b]	41.4	Cracknell (1994)
Rat, Sprague Dawley	inhalation acute LC_{50}, 4 hour nose-only	death, clinical signs, gross pathology of stomach, lungs and brain	< 53[b]	53	Nachreiner (1995)

Note: The shaded and bolded row indicates the critical acute study and POD (Hughes, 1997).
[a]Benchmark Dose Software (BMDS, version 2.6) modeling – derived NOEL (BMDL).
[b]Oral equivalent dose; calculated internal absorbed dose from external air concentrations by using a default rat breathing rate of 0.96 m^3/kg/day and 100% inhalation absorption.

V.A.2. Points of Departure for Subchronic Toxicity

Subchronic toxicity studies were available via the oral, inhalation and dermal routes. Subchronic exposure to fipronil elicited a variety of responses including neurological disturbances,

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autonomic dysregulation, reductions in body weight, decreased litter survival and pup viability, liver effects (increased liver weight, hypertrophy and hepatocytic fat deposition), thyroid effects (decreased T4, increased thyroid weight, hypertrophy and hyperplasia) and delayed developmental signs (incisor eruption, decreased vaginal patency and delayed preputial separation).

Subchronic Oral Toxicity

Subchronic oral toxicity endpoints for fipronil were analyzed in registrant-submitted studies in rat, mouse, rabbit and dog, and in studies obtained from the published literature. The subchronic oral POD of 0.02 mg/kg/day was based on decreases in T4, convulsions and mortality in rats within one year in a combined chronic and oncogenic study (Aughton, 1993). A significant dose-dependent decrease in T4 was observed in male rats from week 1 through week 50 at the LOEL of 0.6 mg/kg/day. In addition one male had convulsions and died at 23 weeks at the LOEL.

Several studies showed effects at similar dose levels, resulting in subchronic PODs ranging from 0.01 to 0.06 mg/kg/day. The PODs were based on the following effects:

1. Significant delays in preputial separation and altered startle response in rat pups at the LOEL of 0.9 mg/kg/day with a NOEL of 0.05 mg/kg/day in a developmental neurotoxicity study (Mandella, 1995).

2. Autonomic dysregulation in rats evidenced by presence of urine in the FOB observation area at the LOEL of 0.3 mg/kg/day in a subchronic neurotoxicity study (Driscoll and Hurley, 1993). Benchmark dose modeling resulted in a $BMDL_{10}$ of 0.01 mg/kg/day (10% effect, Multistage 3 model).

3. A significant and dose-dependent increase in the incidence of hepatocyte periacinar hypertrophy in male mice at the LOEL and lowest dose tested (0.13 mg/kg/day) in a 13-week subchronic oral toxicity study in CD-1 mice (Broadmeadow, 1991). Benchmark dose modeling resulted in a $BMDL_{10}$ of 0.06 mg/kg/day (10% effect, Quantal-Linear model).

The oral POD of 0.02 mg/kg/day, based on decreases in T4, convulsions and mortality (Aughton, 1993), was selected as the critical value to characterize the human risk from subchronic oral exposure to fipronil. This POD was chosen over the lowest subchronic oral POD of 0.01 mg/kg/day, for presence of urine in the observation area (Driscoll and Hurley, 1993). This is because the Aughton (1993) POD was based on several endpoint measurements in animals (T4 levels, convulsions and mortality) versus the single, indirect parameter measured in the Driscoll and Hurley (1993) study (urine in arena).

One published study showed effects in the liver and spleen in mice at 0.475 mg/kg/day (Bano and Mohanty, 2020). The observed effects were ameliorated with T4 supplementation. An estimated NOEL of 0.05 mg/kg/day is similar to the critical subchronic POD of 0.02 mg/kg/day. Eight additional published studies with subchronic exposure durations were identified through

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systematic literature review. These studies showed sporadic or non-linear toxicity, or did not use proper controls (Gill and Dumka, 2013; Udo *et al.*, 2014; Magalhaes *et al.*, 2015; Mossa *et al.*, 2015; de Barros *et al.*, 2016a; de Barros *et al.*, 2016b; Gill and Dumka, 2016; Eisa *et al.*, 2017).

Subchronic Inhalation Toxicity

One registrant-submitted study in rats was available to evaluate subchronic inhalation toxicity (Adamo-Trigiani, 1999). Animals were subjected to aerosolized fipronil (0, 0.001, 0.005, or 0.03 mg/L) in nose-only chambers for four hours per day, seven days per week, for four weeks. Decreased body weight and food consumption in females, increased relative and absolute liver weights in males, and altered blood chemistry parameters indicating liver effects in both sexes were observed at the LOEL of 0.005 mg/l. The NOEL was 0.001 mg/l or 0.16 mg/kg/day when converted to an oral equivalent dose using a rat default breathing rate. Because thyroid hormones and development were not monitored in this study, the critical subchronic oral POD of 0.02 mg/kg/day was used to characterize human risks from subchronic inhalation exposures to fipronil.

Subchronic Dermal Toxicity

Two registrant-submitted studies were available to evaluate the potential for fipronil to results in subchronic dermal toxicity (Table 34). Of these, the lower subchronic dermal NOEL of 5 mg/kg/day came from a study in rabbits (Hermansky and Wagner, 1993). Animals were administered dermal doses for six hours per day, five days per week, for three weeks. Extreme hyperactivity in both sexes, reduced body weight gain (days 1-22) and decreased food consumption (days 15-21) in males were observed at the LOEL of 10 mg/kg/day. Because thyroid-related and developmental endpoints were not monitored in either subchronic dermal study, the subchronic dermal risk evaluation was based on the critical subchronic oral POD of 0.02 mg/kg/day.

Table 34. Summary of Subchronic Points of Departure (PODs) for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, Crl:CD(SD)BR	oral, dietary, 4 weeks	increased liver weight, thyroid hypertrophy	< 3.4	3.4	Peters (1996)
Rat, CD	oral, dietary, 13 weeks	increased relative and absolute liver and thyroid weights, thyroid hypertrophy, and fat accumulation in liver	1.9	20	Holmes (1991)
Rat, Sprague Dawley, ♀	oral, DNT, dietary, GD 6 - LD 10	maternal: death, alopecia, dead/missing pups and decreased BW, weight gain and food consumption	0.9	15	Mandella (1995)
		developmental: delayed preputial separation and	0.05	0.9	

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Table 34. Summary of Subchronic Points of Departure (PODs) for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
		decreased startle response			
Rat, Sprague Dawley	oral, neurotox, dietary, 13 weeks	reduced BW, autonomic nervous system effects	0.01[a]	0.02	Driscoll and Hurley (1993)
Rat, CD	**oral, combined chronic, dietary, 52-91 weeks**	**convulsions, death and decreased thyroid hormones**	**0.02**	**0.06**	**Aughton (1993)**
Mouse, CD-1	oral, dietary, 13 weeks	hepatocyte periacinar hypertrophy	0.06[b]	0.13	Broadmeadow (1991)
Dog, Beagle	oral, gelatin capsule, 13 weeks	mortality, weight loss, clinical signs and neurological disturbances	2	10	Holmes (1991)
Mouse, Swiss Albino	oral, gavage, PND 31 to PND 60	Reduced relative thymus weight, number of splenocytes and thymocytes, and proliferative index in splenocytes and thymocytes. Effects reversed with T4 supplementation	< 0.475	0.475	Bano and Mohanty (2020)*
Rabbit, New Zealand White	dermal, 3 wk, 5 day/wk, 6 hr/day	extreme hyperactivity, reduced BW gain and food consumption	5	10	Hermansky and Wagner (1993)
Rat, Crl:CD(SD)BR	dermal, 4 wk, 5 day/wk, 6-7 hr/day	increased total protein and globulin levels and increased relative liver weights	< 100	100	Henwood (1997)
Rat, Sprague Dawley	inhalation, 4 weeks, 4 h/day, nose-only	decreased BW and food consumption, increased relative liver weights in males, changes in blood chemistry	0.16	0.8	Adamo-Trigiani (1999)
Rat, CD	2-generation, 2-litter repro, dietary, 10 weeks prior to mating through lactation for both liters	paternal: mortality, increased absolute and relative liver and thyroid weights, hypertrophy of thyroid follicular cells	0.16	1.7	King (1992)
		developmental: convulsions, decreased bodyweights, mating and fertility, pup viability and litter size and developmental delays	1.7	17.7	

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Table 34. Summary of Subchronic Points of Departure (PODs) for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, Wistar, ♀	repro, gavage, GD 15 to PND 7	female pups: delay in vaginal opening and first estrus, increased duration of estrus, decreased pituitary weight all doses that was not dose-dependent	0.3	3	de Barros (2016a)*
	repro, gavage, GD 15 to PND 7	male pups: increase in non-mobile sperm	0.3	3	de Barros (2016b)*
Rat, Wistar, ♂	repro, gavage, 28-day	changes in sperm morphology, DNA damage, lipid peroxidation, loss of spermatozoa mitochondria membrane potential and increased cell death	< 2.5	2.5	Khan (2015)*
Rat, CRL:CD(SD)BR VAF/Plus	developmental, gavage, GD 6 - GD 15	maternal: reduced bodyweight	4	20	Brooker (1991)
		developmental: no effects at high dose	20	> 20	
Rabbit, New Zealand White	developmental, gavage, GD 6 - GD 19	maternal: decreased BW gain	0.1	0.2	King (1990)
		developmental: no effects at high dose	1	> 1	
Rat, Sprague Dawley, ♀	DNT, dietary, GD 6 - LD 10	maternal: death, alopecia, dead/missing pups, decreased BW, BW gain and food consumption	0.9	15	Mandella (1995)
		developmental: delayed preputial separation in males, decreased maximum startle response, and decreased BW during lactation	0.05	0.9	
Rat, Sprague Dawley, ♀	CTA, dietary, GD 6 - LD 21	maternal: decreased T4, increased TSH, histopathology	1	3	Coder (2018)
		developmental: decreased T4, increased liver weight	0.3	1	
Rat, CD	developmental, gavage, GD 6 - GD 15	maternal: decreased BW	0.2	1	Foulon (1997)
	fipronil-desulfinyl	developmental: decreased BW and delayed bone ossification	1	2.5	

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Table 34. Summary of Subchronic Points of Departure (PODs) for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Mouse, ICR (CD-1 IGS), ♀	developmental, gavage, GD 1 - GD 3	increased percentage of dead cells in blastocysts and more blastocysts with dead cells; altered development of embryos	< 0.009	0.009	Sefcikova* (2019)

Note: The shaded and bolded row indicates the critical subchronic study and POD (Aughton, 1993).
* Published study.
[a]Benchmark Dose Software (BMDS, version 2.7) modeling of data resulted in a $BMDL_{10}$ of 0.01 mg/kg/day and BMD of 0.02 mg/kg/day with the Quantal-Linear model.
[b]Benchmark Dose Software (BMDS, version 2.6) modeling of data resulted in a $BMDL_{10}$ of 0.06 mg/kg/day and BMD of 0.13 mg/kg/day with the Log Logistic model.
[b]Oral equivalent dose; calculated internal absorbed dose from external air concentrations by using a default rat breathing rate of 0.96 m^3/kg/day and 100% inhalation absorption.

V.A.3. Points of Departure for Chronic Toxicity

Chronic toxicity studies on fipronil were available by the oral route in rat, mouse, and dog. Effects of chronic exposure to fipronil included neurological disturbances, convulsions and tremors, mortality, changes in thyroid hormone levels, reductions in body weight, progressive senile nephropathy in rats, and liver periacinar vacuolation in mice. Chronic studies are summarized in Table 35.

The chronic oral POD of 0.02 mg/kg/day was established in chronic toxicity study in rats, which was the lowest chronic oral NOEL (Aughton, 1993). Effects at the LOEL of 0.06 mg/kg/day included a statistically significant, dose-dependent decrease in serum T4 in males at week 1 that was sustained through week 50, an increase in convulsions and mortality compared to controls, and a statistically significant increase in progressive senile nephropathy. Support for the critical chronic POD came from a chronic dietary study in mice administered fipronil for 78 weeks (Broadmeadow, 1993). The NOEL of 0.06 mg/kg/day was based on increased relative liver weights in males and females and increased liver periacinar vacuolation in males at 52 and 78 weeks at the LOEL of 1.18 mg/kg/day.

In the absence of a chronic inhalation or dermal toxicity study, risk by both routes was evaluated using the chronic oral POD of 0.02 mg/kg/day.

Table 35. Summary of Chronic Points of Departure (PODs) for Fipronil

Species, Strain	Study Type and Exposure	Effects at LOEL	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Reference
Rat, CD	**combined chronic/onco, dietary, 52-91 weeks**	**convulsions and mortality, decreases in thyroid hormones weeks 1 to 50, progressive senile nephropathy**	**0.02**	**0.06**	**Aughton (1993)**

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Mouse, CD-1	combined chronic/onco, dietary 53-78 weeks	increased relative liver weights and periacinar vacuolation	0.06	1.18	Broadmeadow (1993)
Dog, Beagle	gelatin capsule, 53 weeks	convulsions, neurological effects	0.2	2	Holmes (1992)
Dog, Beagle	dietary, 52 weeks	muscle rigidity and tremors	0.3	1	Holmes (1993)

Note: The shaded and bolded row indicates the critical subchronic study and POD (Aughton, 1993).

V.A.4. Oncogenicity

Carcinogenicity studies conducted with fipronil were available in rats and mice. A statistically significant increase in thyroid follicular cell adenomas and carcinomas was seen in male and female rats at the highest administered doses (13 and 17 mg/kg/day, respectively) after 89 and 91 weeks of daily dietary exposure (Table 36) (Aughton, 1993). The induction of thyroid follicular cell tumors in rats following exposure to xenobiotics is based on a well-characterized, non-mutagenic "extra-thyroidal" mechanism considered not to be relevant to humans (US EPA, 1998; International Agency for Research on Cancer, 1999).

Table 36. Thyroid Tumor Incidence in CD Rats Exposed to Fipronil for 89 to 91 Weeks via Diet and Historical Control Data

	Males					**Females**				
Dose (ppm)	**0**	**0.5**	**1.5**	**30**	**300**	**0**	**0.5**	**1.5**	**30**	**300**
Dose (mg/kg/day)	**0**	**0.02**	**0.06**	**1.3**	**13**	**0**	**0.03**	**0.08**	**1.6**	**17**
N (thyroids)	49	48	50	50	50	50	50	50	50	50
Follicular Cell Adenoma	0	1	5*	3	12***	0	0	0	0	8**
Follicular Cell Carcinoma	0	0	0	0	5*	0	1	0	1	2
Adenoma + Carcinoma	0	1	5*	3	17***	0	1	0	1	10***
Percent Occurrence (%)	0%	2%	10%	6%	34%	0%	2%	0%	2%	20%
N (historical control)	359					365				
Adenoma + Carcinoma	26					10				
Percent Occurrence (range)	7.2 (3.6-16)%					2.7 (0-12)%				

Data from Aughton (1993).
*, **, *** Statistically significant different from controls (one-tailed Fisher's Exact test, performed by study authors) at $p \leq 0.05$, $p \leq 0.01$ or $p \leq 0.001$.
Historical control data from the conducting laboratory were supplied in the data volume. Controls included 7 combined chronic toxicity and oncogenicity or oncogenicity studies conducted in the four years prior to the present study.

In addition to neoplasms in rats, there was an indication that chronic exposure to fipronil may induce hepatocellular tumors in male CD-1 mice at two high doses (Broadmeadow, 1993). The combined incidences of liver adenomas and carcinomas were as follows: 7/24, 3/31, 2/26. 7/26 and 8/26 at 0, 0.01, 0.06, 1.18 and 3.43 mg/kg/day, respectively. However, because of the high incidence of hepatocellular adenomas in concurrent controls (7/24, 29%) and the low number of mice surviving to terminal sacrifice (24 males and 31 females out of 52 mice per sex), the incidence of liver tumors was not statistically significantly increased compared to concurrent

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controls. In conclusion, data suggested that chronic treatment with fipronil induced hepatocellular tumors in male mice. However, the statistical analysis of the data was compromised due to the high incidence of adenomas and low survival of the control males.

Data indicating oncogenicity usually trigger a quantitative cancer potency analysis using the multistage linear extrapolation algorithm. This approach assumes that the lesions in question were generated by genotoxic mechanisms. However, the evidence for fipronil-induced genotoxicity was limited. Furthermore, rat thyroid follicular cell tumor data are often not subject to linear extrapolation because tumorgenesis is thought to be driven by an anti-thyroidal mechanism (US EPA, 2005). This is discussed in detail in the Risk Appraisal section of this document. Finally, because non-oncogenic effects seen following fipronil exposure (particularly decreased T4 and increased TSH) have a lower toxicity threshold than the thyroid tumors, protection against their occurrence is expected to prevent fipronil-mediated oncogenicity (US EPA, 1998).

V.A.5. Genotoxicity

Six genotoxicity studies were submitted to DPR to fulfill pesticide registration data requirements. With one exception, all studies for genotoxicity were negative. The one positive result was an increase in chromosomal aberrations in Chinese hamster ovary cells at 45 and 60 µg/ml after a 6-hour exposure without S9 microsomes (used for metabolic activation). Results were negative with S9 microsomes and at later time points (12 hours, 24 hours). Results were also negative in other assays with human lymphocytes up to 300 µg/ml and in mice up to 50 mg/kg. Studies published in the open literature showed genotoxic effects both *in vitro* and *in vivo*, usually coincident with cytotoxicity and oxidative stress.

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V.B. Exposure Assessment

V.B.1. Pesticide Handler, Home User and Residential Post-Application Exposures

Fipronil is the active ingredient of many products used for structural pest control, pet flea/tick control, and lawn maintenance. Currently, no fipronil product is registered for food use in California. The exposure assessment evaluated a total of 26 exposure scenarios based the label-approved uses of the above products. Of these 26 scenarios, low human exposure is expected for eight scenarios. Fipronil exposure was estimated for the remaining 18 scenarios over short-term, seasonal, annual and life-time durations.

For handlers, exposure may occur during mixing and loading of liquid concentrate and granular products as well as application of all products (all formulations). Fipronil has a low vapor pressure (2.8×10^{-9} mmHg at 25 °C), so risk of inhalation is expected to be low from liquid concentrate or application of pet spot-on products. However, inhalation exposure from aerosolized pet spray products may occur at the time of application, largely because of the application method. This is reflected in Tables 17 and 18 in the exposure assessment (Appendix 1). There may also be minimal exposure to aerosols from mixing or applying granular products, and this is reflected in Tables 33 and 34 of Appendix 1.

Exposures for home users are largely driven by the dermal route for pet spot-on and spray products, although there is some potential for inhalation exposure to the spray products during application, much like for the handlers (see Table 19 in Appendix 1). Exposures for post-application scenarios for residential adults and children were evaluated for bait products, turf granules, structural liquid concentrate, and the pet products. For adults, exposures were highest via the dermal route for pet products. For children, exposures were largest via the dermal route for pet products and incidental oral routes for both turf granules and pet products. All exposure estimates for scenarios involving occupational handlers, home users, and adult and child residents are detailed in Appendix I. The exposure estimates are also used in the calculation of the margins of exposure in the Risk Characterization section, below.

V.B.2. Dietary and Drinking Water Exposure

The dietary exposure from food and drinking water was estimated from residues of the parent fipronil. Monitoring data on food commodities were available for the metabolites fipronil-sulfide and fipronil-sulfone but not for photodegradate fipronil-desulfinyl. Monitoring data for residues in drinking water are discussed in the EAD (Appendix I).

Introduction

DPR conducts acute and chronic dietary exposure assessments to evaluate the potential risk of human exposure to pesticide residues on food (Bronzan and Jones, 1989). These analyses are performed per DPR guidance for the total dietary exposure based on residues on all commodities with established fipronil tolerances, as well as residues in drinking water (DPR, 2009). A tolerance is the legal maximum residue concentration of a pesticide, which may exist in or on a

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raw agricultural commodity or processed food. Tolerances are set by US EPA and are published in the Code of Federal Regulations (Title 40, part 180).

Dietary exposure is a product of food consumption and the corresponding residue concentration of a given pesticide. The total dietary exposure for an individual during a defined period of time (e.g., a day) is the sum of dietary exposures for all foods (in various forms and as ingredients in food items) consumed within that time-period:

$$\text{Exposure} = \sum_{i=1}^{n}(\text{residue}_i \text{ x consumption}_i)$$

where n is the number of food items in the diet.

Data on the amount of the pesticide residue on food and food consumption provide dietary exposure estimates for various population subgroups based on age, gender, ethnicity, season, and pregnancy/lactation status. In this document, exposure estimates were calculated for the US population and sensitive subpopulations including infants, children aged 1 – 2, and women of childbearing age (13 – 49 years old).

For estimating acute exposure, the highest residue values at or below the tolerance, or distribution of residues are considered. Acute exposure is calculated on a per-user basis including in the distribution of exposures only the days of survey that at least one commodity with potential pesticide residues is consumed. Chronic exposure to pesticides is calculated using per-capita, mean consumption estimates that include the entire population (DPR, 2009).

The acute and chronic dietary exposure assessments for fipronil were conducted for all combined food uses and included drinking water. As of October, 2020, US EPA has established tolerances for the combined residues of the parent fipronil and its metabolites fipronil-sulfone and fipronil-sulfide, and its photodegradate fipronil-desulfinyl. The published tolerances for fipronil are listed in 40 CFR 180.517 and are expressed for plant and animal commodities as follows: milk fat (1.5 ppm), milk (0.05 ppm), animal fat (0.05 – 0.4 ppm), meat (0.01 – 0.04 ppm), meat byproducts (0.01 – 0.04 ppm), liver (0.02 – 0.1 ppm), eggs (0.03 ppm), wheat (0.005 ppm), corn (0.02 ppm), rice (0.04 ppm), and potato (0.03 ppm) (Code of Federal Regulations, 2015).

On the date of publication of this document, no products containing fipronil were registered for use on agricultural commodities in California. However, as legal uses exist at the federal level, the possibility of dietary exposure to fipronil was considered. Corn was not included in this analysis because fipronil is only registered for use on seed corn for export. Wheat and rice were also excluded, as there was no reported use of fipronil on wheat or rice in in the US in the last 10 years (US EPA, 2018).

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Consumption Data and Dietary Exposure

The US EPA's Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM-FCID™, version 4.02)[9] was used to calculate the dietary exposure and risk. DEEM-FCID™ incorporates food consumption data from the National Health and Nutrition Examination Survey)/"What We Eat in America" (NHANES/WWEIA) dietary survey for the years 2005-2010[10]. The WWEIA survey collected food consumption data from 24,673 respondents. Each WWEIA respondent provided two days of food consumption data, which leads to a total of 49,346 food diaries. WWEIA-FCID translates food consumption as reported eaten in WWEIA (2005 – 2010 survey cycles) into consumption of DEEM-FCID™-defined food commodities.

Acute exposure was calculated on a per-user basis (i.e., the days included in the exposure distribution were those in which a specific commodity was consumed). Chronic exposure to pesticides was calculated using per-capita mean consumption estimates to include the entire population. The estimates for both acute and chronic exposure were expressed as a dosage in µg/kg/day.

Residue Data Sources

The residue data for fipronil used in the current risk assessment were based on the USDA Pesticide Data Program (PDP). The PDP (www.ams.usda.gov/science/pdp/download.htm) is the most representative monitoring residue database, because it is designed to obtain pesticide residue data for risk assessments. The PDP samples are collected in ten states, including California.

PDP monitoring data for fipronil were available for potato, beef muscle and adipose, egg, butter, infant formula, milk, pork muscle and adipose, and chicken meat. There were a total of 59,972 samples screened for fipronil from 2003 through 2019. Standard protocol dictates the use of data spanning the last five years. Because fipronil detections in food were rare (92 detects out of 59,972 samples, 0.12% detection rate), additional years (data from 2003 to 2019) were used to increase the sample number and incidence of detects.

PDP data also included monitoring of fipronil-sulfone (19,393 samples since 2016) and fipronil-sulfide (315 samples, all in 2017), for which there were no detections. The range of the limit of detection (LOD) for sulfone was 0.0025 to 0.05 ppm; the sulfide LOD was 0.01 ppm. No data were available for fipronil-desulfinyl, the photodegradate.

Residue data on fipronil were also available from other databases such as the US FDA Total Diet Study[11], DPR's California Pesticide Residue Monitoring Program (California Food and Agricultural Code §12532)[12] and registrant submitted field trail data. These databases did not

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[9] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/deem-fcidcalendex-software-installer
[10] http://fcid.foodrisk.org/
[11] https://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/default.htm
[12] https://www.cdpr.ca.gov/docs/enforce/residue/rsmonmnu.htm

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monitor commodities that were not screened by PDP. Fipronil residues in drinking water were evaluated based on surface water monitoring data collected by DPR and other state and federal agencies (see EAD, Appendix I). The residues used in acute and chronic dietary exposure assessments are shown in Table 37.

Acute Dietary Exposure Assessment

DPR estimates the acute dietary exposure to a pesticide using the tiered approach in the selection of the appropriate pesticide residue values (DPR, 2009). The tiered approach begins with the point estimate (deterministic) analyses (Tiers 1 and 2) that employ the tolerance or the upper bound value or the mean residue value. The Monte Carlo probabilistic approach (Tier 3) can subsequently be used to refine the assessment by taking into account the occurrence and distribution of residue levels, and providing the probability distribution of exposure.

DPR uses two thresholds to indicate if the next tier of assessment is needed. The thresholds are based on the dietary risk expressed as margin of exposure (MOE, defined as the POD divided by the estimated exposure). The two possible screening thresholds are:

(1) the MOE at the 99th percentile exposure is within 5-fold of the target MOE, or
(2) the MOE at the 95th percentile exposure is within 10-fold of the target MOE.

For fipronil, the target MOE is 100 (described in the Risk Characterization section of this RCD). Therefore, the screening threshold for the next tier of assessment would be an MOE of 500 at the 99th percentile or an MOE of 1000 at the 95th percentile. If the MOE do not reach the threshold (e.g., are lower than the target), the next tier of exposure assessment may be needed. These thresholds provide room for exposures from other potential routes during exposure aggregation; the 5-and 10-fold distance from the target MOE ensures the likelihood that dietary exposure will not be a major contributor to the aggregate risk.

Tier 1 Acute Deterministic (Point Estimate) Dietary Exposure Assessment

The acute dietary exposure to fipronil of the US population and various population subgroups was assessed using the deterministic approach (Tiers 1 and 2). In this approach, a single value (referred to as a point estimate) was selected to represent the concentration of fipronil on each of the registered commodities.

This assessment assumed that all foods consumed in a given day contain pesticide residues at the tolerance level. For fipronil, this analysis produced exposures that resulted in MOEs below the thresholds of 1000 and 500 at the 95th or 99th percentiles, respectively, for all of the population subgroups. Therefore, Tier 2 point estimate assessment was used to refine the dietary exposure calculation.

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Table 37. Fipronil Residues used for Acute and Chronic Dietary Exposure Assessments

Commodity	Source of Data	Year	Number of Samples	Number of Fipronil Detects	Detected Residues (ppm)	Range LOD (ppm)	Acute Point Estimate (ppm)	Chronic Average Residue (ppm)
Beef, goat, pork and sheep fat and baby food fat and skin	Beef PDP LOD (adipose)	2008-2009	292	0	NDR	0.0012	0.0012	0.006
Beef, goat, horse, and sheep meat, meat byproducts, kidney, and baby food meat and meat byproducts[a]	Beef PDP LOD (muscle)	2008-2009	292	0	NDR	0.0012	0.0012	0.006
Pork, meat, meat byproducts, kidney, and baby food meat and meat byproducts	Pork PDP LOD (muscle)	2005	352	0	NDR	0.0006	0.0006	0.0003
Pork, fat and baby food fat and skin	Pork PDP LOD (adipose)	2005	352	0	NDR	0.0021	0.0021	0.00105
Beef, liver, baby food	Tolerance	2015	--	--	--	--	0.1	0.05
Pork, liver	Tolerance	2015	--	--	--	--	0.02	0.01
Sheep, liver	Tolerance	2015	--	--	--	--	0.1	0.05
Poultry, chicken and turkey fat, skin and baby food fat and skin	Tolerance (poultry fat)	2015	--	--	--	--	0.05	0.025
Poultry, chicken and turkey meat, meat byproducts, and baby food meat and meat byproducts	PDP residue (poultry meat)	2006	1309	3	0.001-0.0012	0.0006	0.0012	0.0003
Egg white, whole, yolk and baby food white (solids), whole and yolk	PDP LOD (egg)	2010-2016	1036	0	NDR	0.003-0.04	0.003	0.0015
Milk fat and baby food/infant formula fat	PDP LOD (butter)	2003-2012	736	0	NDR	0.0027-0.02	0.02	0.00238
Milk, nonfat water and solids	CA-specific PDP LOD (milk)	2015 to 2019	598	0	NDR	0.0025	0.0025	0.00125
Milk, sugar, nonfat water and solids-baby food and formula	PDP LOD (infant formula)	2013-2014	705	0	NDR	0.0018	0.0018	0.0009
Potato tuber with and without peel, flour, dried and chips and baby food	PDP residue	2015-2016	1723	36	0.003-0.0096	0.0018-0.005	0.0096	0.00419

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Table 37. Fipronil Residues used for Acute and Chronic Dietary Exposure Assessments

Commodity	Source of Data	Year	Number of Samples	Number of Fipronil Detects	Detected Residues (ppm)	Range LOD (ppm)	Acute Point Estimate (ppm)	Chronic Average Residue (ppm)
Water, direct and indirect	SURF	2002 to 2017	3371	303*	0.0017-0.275 ppb	n/a	0.000275	0.000033

LOD: Limit of detection; PDP: Pesticide Data Program (USDA); NDR no detectable residues; SURF: Surface Water Database at DPR.
[a]adjustment factor of 1.92 used for dried beef.
*only includes positive fipronil detections from waters that could reasonably be used as drinking water.

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Tier 2 Acute Deterministic (Point Estimate) Dietary Exposure Assessment

The typical assumptions in the Tier 2 are: (*i*) all consumed foods contain the highest reported residue at or below the tolerance, (*ii*) pesticide residues below the LOD are equal to that limit, (*iii*) all crops are treated with the pesticide, and (*iv*) residue concentrations do not vary from the time of sampling to the time of consumption (DPR, 2009).

For the fipronil acute Tier 2 analysis, the highest detected residue or the highest LOD from PDP were used for potato, beef muscle and adipose, egg, butter, infant formula, milk, pork muscle and adipose, and chicken meat. For milk, no residues were detected from 2003 to 2019. The California-specific range of LODs for the last five years (2015 to 2019) were selected to refine the fipronil residue level for this commodity. For egg, the lowest LOD was used as the highest LOD was higher than the tolerance. PDP data were not were not available for horse, goat, or sheep. For these commodities, residues measured by PDP on beef meat and fat were used as a surrogate. Beef meat was also used as a surrogate for meat byproducts, which lacked monitoring data, when the byproduct and meat tolerances were the same. In cases where the byproduct tolerance was different than the meat tolerance, the byproduct tolerance was used. For drinking water, the residue was the highest reasonable detection (e.g., in water that people might reasonably be expected to consume).

The acute Tier 2 dietary exposure assessment resulted in 95th percentile of user-day exposures that ranged from 0.067 µg/kg/day for women of childbearing age (13-49 years old) to 0.347 µg/kg/day for children ages 1-2 (Table 38). Exposure at the 99th percentile level ranged from 0.104 µg/kg/day (women of childbearing age) to 0.478 µg/kg/day (children 1-2). Because additional exposure data for fipronil were not available, Tier 3 refinement was not performed.

Table 38. Acute Tier 2 Dietary Exposure Estimates for Fipronil

Population Subgroup (Users)	**95th Percentile**	**99th Percentile**
	µg/kg/day	**µg/kg/day**
Total US Population	0.116	0.226
Nursing Infants	0.109	0.232
Non-Nursing Infants	0.260	0.397
All Infants	0.24	0.391
Children 1-2 years old	**0.347**	**0.478**
Women of childbearing age (13-49 years old)	0.067	0.104

DEEM-FCID™, version 4.02 was used for the analysis.
The acute point estimate dietary exposure from all commodities with fipronil registrations was calculated at the 95th and 99th percentiles of user-days for all population subgroups. The highest exposures are indicated in bold.
95th and 99th percentile exposure estimates are in µg fipronil/kg body weight/day.

A critical exposure contribution analysis was performed using DEEM-FCID to determine which food commodities contributed most to the total dietary exposure. Milk contributed to 71% of the estimated dietary exposure for children age 1-2. Potato, chicken fat, milk and water were the high contributors for other population subgroups. Exposure estimates for water and potato were

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based on the single highest detect, while estimates for the other commodities were derived from the analytical LOD or from the tolerance, not from actual measured values.

Chronic Dietary Exposure Assessment

The fipronil chronic dietary exposure analysis was assessed using a deterministic approach. In this approach, a single value (referred to as a point estimate) was selected to represent the concentration of fipronil on each registered commodity. The value is either the arithmetic mean of measured residue values from monitoring data or ½ the LOD, when available. For commodities for which monitoring data were not available, the chronic residue concentration was set equal to ½ of the tolerance (Table 37).

The chronic dietary exposure assessment resulted in exposures estimates that ranged from 0.007 µg/kg/day for nursing infants to 0.070 µg/kg/day for children aged 1-2 (Table 39).

Table 39. Tier 2 Chronic Dietary Exposure Analysis

Population Subgroup	Exposure (µg /kg/day)
Total US Population	0.015
Nursing Infants	0.007
Non-Nursing Infants	0.025
All Infants	0.019
Children 1-2	**0.070**
Women of childbearing age (13-49 years old)	0.011

DEEM-FCID™, version 4.02 was used for the analysis. Exposure estimates are in µg fipronil/kg body weight/day.

A critical exposure contribution analysis performed in DEEM-FCID determined that milk (fat, sugar, solids and water), potato, chicken fat and skin, and indirect sources of water contributed the most to chronic exposure through diet. Milk contributed to 78% of the estimated dietary exposure for children aged 1-2, and to 45 – 54% of the dietary exposure for the other subpopulations. With the exception of potato and water, exposure estimates for high-contributor crop groups were derived from the tolerance (chicken skin and fat) or from the LOD values (milk products).

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V.C. Risk Characterization

The margin of exposure (MOE) is a quantitative tool used by DPR to determine the potential risk arising from exposure to a pesticidal active ingredient. The potential for non-oncogenic health effects resulting from fipronil exposure was estimated from critical POD for a specific exposure duration and route divided by the estimate of human exposure for that duration and route:

$$MOE = \frac{POD}{Exposure\ Dosage}$$

The resulting value is compared to the acceptable or target MOE which, for purposes of this risk assessment, is equivalent to the total uncertainty factor (UF_{TOTAL}) of 100. Values at or above the target MOE are generally considered protective against the toxicity of fipronil when the POD is derived from an animal study. This reflects the default assumption that (1) humans are 10-fold more sensitive than animals, and (2) a 10-fold range of sensitivity exists within the human population (Dourson *et al.*, 2002).

The critical acute, subchronic, and chronic PODs for fipronil are summarized in the Hazard Identification section in Table 32. DPR used these values to calculate risks from short-term, seasonal and annual exposures to handlers and residents. Handler and residential exposure estimates are detailed in the EAD (Appendix I). Dietary exposure is described in the Exposure Assessment section of this document.

This risk assessment estimated exposures by both route-specific pathways and by aggregate exposures. Aggregate exposure is defined as the exposure to a single chemical (i.e., a pesticide) through multiple pathways and routes (US EPA, 2001). When using an aggregate exposure approach, DPR assumes that a pesticidal active ingredient can enter the human body from multiple pathways including those related to occupational applications and through dermal exposure, air, food, and drinking water. Exposures by different routes are then combined (aggregated) when exposure durations and toxic effects of the pesticide correspond. For fipronil, the predominant routes of exposure are incidental oral (children) and dermal (children and adults). While DPR analyzed inhalation exposure scenarios, and aggregate exposures include inhalation exposure values, exposure via the inhalation route does not drive fipronil risk.

Risk was estimated for the following population subgroups:

(a) Occupational Handlers: Includes those who are licensed or certified to apply fipronil and professional pet groomers. Risk was estimated for separately for dermal and inhalation scenarios, and for aggregated exposures where both dermal and inhalation exposures were expected to occur simultaneously.

(b) Home Users: Individuals who apply pet products at home. Risk was estimated separately for dermal and inhalation scenarios, and for aggregated exposures where both dermal and inhalation exposure were expected to occur simultaneously.

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(c) Residential Post-Application Exposure, Adult: Adults who are potentially exposed to fipronil following professional residential treatment or applications of pet products at home. Risk was estimated separately for dermal and inhalation scenarios, and for aggregated exposures where both dermal and inhalation exposure were expected to occur simultaneously.

(d) Residential Post-Application Exposure, Child: Children (1-2 years old) who are potentially exposed to fipronil following professional residential treatment or applications of pet products at home. Risk was estimated separately for incidental oral, dermal, inhalation scenarios, and for aggregated exposures where each route of exposure is expected to occur simultaneously.

Aggregate MOEs were estimated by using a hazard index approach, that is:

- Aggregate MOE for Occupational Handlers = $1/(1/MOE_D + 1/MOE_I)$
- Aggregate MOE for Home Users = $1/(1/MOE_D + 1/MOE_I)$
- Aggregate MOE for Adults Post-Application = $1/(1/MOE_D + 1/MOE_I)$
- Aggregate MOE for Children Post-Application = $1/(1/MOE_D + 1/MOE_O + 1/MOE_I)$

Where,

D: dermal exposure (i.e., short-term absorbed daily dose, STADD)
I: inhalation exposure
O: non-dietary incidental (hand-to-mouth) oral exposure

MOE aggregation was conducted in a sequential, additive manner in order to obtain information on the relative contribution of each exposure scenario to overall risk. Oral exposures were not anticipated in handler or home user scenarios. Dietary and drinking water values were not included in calculating the aggregate MOE values because they did not impact the final risk values (see below).

V.C.1. Occupational Handler Margins of Exposure

Dermal and inhalation MOEs for occupational exposure to fipronil are summarized in Table 40. The exposure estimates used to calculate MOEs are found in the EAD (Appendix I). Acute inhalation MOEs for all occupational categories were greater than 100. Acute dermal MOEs for groomers applying pet spray were less than the target value of 100, indicating a concern. The only aggregated acute MOE for handler exposure below the target value of 100 was that for groomers applying pet spray (aggregate MOE of 16). In this case, risk was driven by dermal exposure, which alone was less than the target MOE.

The subchronic dermal MOEs for all handler categories were below 100 with the exception of handlers of structural dust (dermal MOE of 1429). The groomer subchronic inhalation MOE for pet spray was also below 100 (MOE of 54). Aggregated subchronic MOEs were all below 100 (driven by dermal exposure) with the exception of the MOE for structural dust handlers.

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The chronic dermal MOEs for all occupational settings were below 100, except for handlers of turf granules and structural dust. The chronic inhalation MOE for pet spray groomers was also below 100. Aggregated chronic MOEs were below the target of 100 (driven by dermal exposure) for all occupational exposure scenarios except for handlers of structural dust and turf granules.

Table 40. Risk Estimates for Occupational Handlers Exposed to Fipronil

Product	Scenario	Acute MOE[a]			Subchronic MOE[b]			Chronic MOE[c]		
		Dermal	Inhal.	Agg.[d]	Dermal	Inhal.	Agg.	Dermal	Inhal.	Agg.
pet spot-on	groomer	207	NA	207	**27**	NA	**27**	**27**	NA	**27**
pet spray	groomer	**17**	725	**16**	**2**	**54**	**2**	**2**	**54**	**2**
structural dust	handler	10235	41429	8208	1429	6667	1176	2222	10000	1818
structural LC	no overhead	621	1642	451	**40**	105	**29**	**69**	182	**50**
structural LC	overhead	138	5118	134	**15**	286	**15**	**26**	500	**25**
turf granules	handler	1318	18125	1229	**83**	1176	**78**	167	2222	155

MOE: margin of exposure (POD/exposure). Acute POD was 0.87 mg/kg/day (Hughes, 1997); subchronic and chronic POD were 0.02 mg/kg/day (Aughton, 1993). NA: Inhalation exposure is negligible considering the product formulation and the application method (US EPA, 2012b); LC: liquid concentrate; Inhal: inhalation; Agg: aggregate.
[a]Acute risk calculated with short-term absorbed daily dose (STADD; See EAD, Appendix I). The STADD = exposure (µg/lb) × fipronil handled (lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg).
[b]Subchronic risk calculated with the seasonal average daily dose (SADD; see EAD, Appendix I). SADD = exposure (µg/lb) × fipronil handled (lb/d) × absorption rate ÷ body weight.
[c]Chronic risk calculated with the annual average daily dose (AADD; see EAD, Appendix I). Annual Average Daily Dose = AADD × (annual use months ÷ 12).
[d]Aggregate risk = $1(1/MOE_D + 1/MOE_I)$ where D = dermal and I = inhalation exposures.
Bold text indicates MOE below the target of 100.

V.C.2. Home Users Margins of Exposure

Acute dermal and inhalation MOEs were calculated for home users exposed to fipronil through pet spray or pet spot-on formulations (Table 41). Non-dietary incidental oral (hand-to-mouth) MOEs were not calculated for home users, as oral exposure was not anticipated. Seasonal and annual exposures were not anticipated for home users by any route. The acute dermal and aggregated MOEs for users of pet spray were less than the target MOE of 100 (driven by dermal exposure), thus indicating a risk.

Table 41. Risk Estimates for Home Users Exposed to Fipronil

Product	Scenario	Acute[a] Dermal MOE	Acute Inhalation MOE	Acute Aggregate MOE
pet spot-on	adult pet owner	580	NA	580
pet spray	adult pet owner	**46**	2175	**45**

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MOE: margin of exposure (POD/exposure). Acute POD was 0.87 mg/kg/day (Hughes, 1997). NA: Inhalation exposure is not anticipated with pet spot-on products; Inhal: inhalation; Agg: aggregate.
[a]Acute risk calculated with short-term absorbed daily dose (STADD; See EAD, Appendix I). The STADD = exposure (µg/lb) × fipronil handled (lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg).
[d]Aggregate risk = $1(1/MOE_D + 1/MOE_I)$ where D = dermal and I = inhalation exposures.
Bold text indicates MOE below the target of 100.

V.C.3. Residential Post-Application Margins of Exposure

Adults

MOEs for residential post-application exposure of adults appear in Table 42. Non-dietary incidental (hand-to-mouth) oral MOEs were not calculated for adults, nor were chronic MOEs for any exposure scenarios. Acute dermal MOEs were calculated for five exposure scenarios. Acute inhalation MOEs were calculate for one exposure scenario. All acute MOEs (singular and aggregated) were above the target MOE of 100.

Subchronic MOEs were calculated for four dermal exposure scenarios and one inhalation exposure scenario. Subchronic dermal and aggregate MOE calculations for pet spray and for pet spot-on users were less than the target of 100, indicating a risk. Aggregate risk was driven by dermal exposure, and the lowest MOE was for pet spray.

Table 42. Risk Estimates for Adult Residential Post-Application Exposure to Fipronil

Product	Acute[a] MOE			Subchronic[b] MOE		
	Dermal	Inhal.	Agg.	Dermal	Inhal.	Agg.
pet spot-on	621	NA	621	**36**	NA	**36**
pet spray	363	NA	363	**13**	NA	**13**
structural bait gel	>100,000	NA	>100,000	>100,000	NA	>100,000
structural LC	33462	37826	17755	10000	3333	2500
turf granules	>100,000	NA	>100,000	NA	NA	NA

MOE: margin of exposure (POD/exposure). Acute POD was 0.87 mg/kg/day (Hughes, 1997); subchronic chronic POD was 0.02 mg/kg/day (Aughton, 1993). NA: Inhalation exposure is not anticipated with pet products, bait gel or turf granules; subchronic dermal exposure not anticipated for turf granules; LC: liquid concentrate; Inhal: inhalation; Agg: aggregate.
[a]Acute risk calculated with short-term absorbed daily dose (STADD; See EAD, Appendix I). The STADD = exposure (µg/lb) × fipronil handled (lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg).
[b]Subchronic risk calculated with the seasonal average daily dose (SADD; see EAD, Appendix I). SADD = exposure (µg/lb) × fipronil handled (lb/d) × absorption rate ÷ body weight.
[d]Aggregate risk = $1(1/MOE_D + 1/MOE_I)$ where D = dermal and I = inhalation exposures.
Bold text indicates MOE below the target of 100.

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Children

MOEs for residential post-application exposure of children (age 1 - 2 years) to fipronil appear in Table 43. Annual MOEs were not calculated for these scenarios. Unlike with adults, post-application exposure to children included non-dietary incidental (hand-to-mouth) oral exposures for some scenarios.

Acute oral MOEs were calculated for five exposure scenarios. The only acute MOE below the target were those for oral and aggregate exposure resulting from usage of turf granules. Risk was driven by the oral route.

Subchronic MOEs were calculated for four subchronic exposure scenarios. Oral and dermal exposure to pet spot-on products and to pet spray products resulted in MOEs lower than the target for both dermal and inhalation exposure. Aggregate MOEs for these scenarios were also below the target value of 100 (driven primarily by the dermal route), thus indicating a risk.

Table 43. Risk Estimates for Child Residential Post-Application Exposure to Fipronil

Product	Acute[a] MOE				Subchronic[b] MOE			
	Oral	Dermal	Inhal.	Agg.	Oral	Dermal	Inhal.	Agg.
pet spot-on	1450	335	NA	272	**83**	**20**	NA	**16**
pet spray	791	189	NA	153	**29**	**7**	NA	**6**
structural bait gel	>100,000	>100,000	NA	>100,000	27778	>100,000	NA	27211
structural LC	11918	48333	18125	6259	4000	20000	1667	1111
turf granules	**38**	88776	NA	**38**	NA	NA	NA	NA

MOE: margin of exposure (POD/exposure). Acute POD was 0.87 mg/kg/day (Hughes, 1997); subchronic POD was 0.02 mg/kg/day (Aughton, 1993). NA: Inhalation exposure is not anticipated with pet products, bait gel or turf granules; subchronic dermal exposure not anticipated for turf granules; LC: liquid concentrate; Inhal: inhalation; Agg: aggregate.
[a]Acute risk calculated with short-term absorbed daily dose (STADD; See EAD, Appendix I). The STADD = exposure (µg/lb) × fipronil handled (lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg).
[b]Subchronic risk calculated with the seasonal average daily dose (SADD; see EAD, Appendix I). SADD = exposure (µg/lb) × fipronil handled (lb/d) × absorption rate ÷ body weight.
[c]Chronic risk calculated with the annual average daily dose (AADD; see EAD, Appendix I). Annual Average Daily Dose = AADD × (annual use months ÷ 12).
[d]Aggregate risk = $1(1/MOE_D + 1/MOE_I + 1/MOE_O)$ where D = dermal, I = inhalation and O = incidental oral exposures.
Bold text indicates MOE below the target of 100.

V.C.4. Diet and Drinking Water Margins of Exposure

The MOEs for the combined exposures from fipronil residues in food and drinking water exposures in various subpopulations are summarized in Table 44. The acute MOEs were calculated using the critical oral POD of 0.87 mg/kg, based on decreased hindlimb splay in rats following a single dietary dose of fipronil (Hughes, 1997). The chronic dietary MOEs were

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calculated using the critical oral POD of 0.02 mg/kg/day, based on sustained decreases in T4 in male rats, convulsions and death, and progressive senile nephropathy in male rats (Aughton, 1993). Exposure values from diet and drinking water were calculated as described above in the Dietary and Drinking Water Exposure section. Acute (Tier 2) MOEs at the 95th exposure percentile were all above the target MOE of 100, thus not of potential health concern. Similarly, all chronic (Tier 2) MOEs were above the target of 100.

Table 44. Risk Estimates for Exposure from Fipronil Residues in Food and Drinking Water

Population Subgroup	Acute MOE 95th Percentile	Chronic MOE
Total US Population	6779	1231
Nursing Infants	6014	3751
Non-Nursing Infants	4174	1230
All Infants	4432	1559
Children 1-2 years old	2583	523
Females 13-49 years old	8936	1571

DEEM-FCID™, version 4.02 was used for the analysis. Acute and chronic point estimate dietary exposures were calculated from residues in all commodities with fipronil registrations and in drinking water.
MOE: margin of exposure = point of departure/exposure. Acute POD was 0.87 mg/kg/day (Hughes, 1997); chronic POD was 0.02 mg/kg/day (Aughton, 1993).
Acute (Tier 2) dietary exposure was calculated at the 95th and 99th percentiles of user-days for all population subgroups.

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VI. REFERENCE DOSES (RfD)

Reference doses (RfDs) are an estimate of the concentration or dose of a substance (with uncertainty spanning perhaps an order of magnitude) to which a human population can be exposed (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (US EPA, 2011f). RfDs are calculated by dividing the critical POD by the total uncertainty factors (UF_{Total}). DPR uses a default UF_{Total} of 100, which reflects the default assumption that (1) humans are 10-fold more sensitive than animals (UF_A of 10), and (2) a 10-fold range of sensitivity exists within the human population (UF_H of 10). The UF_A and UF_H both consist of pharmacokinetic and pharmacodynamic variables.

RfDs were calculated for acute, subchronic, and chronic oral and dermal exposure to fipronil. Oral and dermal RfDs were calculated because significant exposure and risk was identified for adults and children through these routes. While inhalation exposure and risk were calculated for fipronil products, DPR found that the inhalation risk was minimal compared to the dermal risk for adults and compared to the dermal and incidental oral risk for children. In addition, inhalation exposure always occurred simultaneously with dermal exposure. Therefore, a separate RfC was not calculated for inhalation.

Dermal and oral RfDs both considered the percent absorbed and the concentration of active ingredient. The concentration of the technical grade fipronil was > 95% by volume. DPR estimated the percent absorbed orally as > 80%, which DPR considers complete (100%). The percent absorbed through the skin was estimated to be 4.3% in rats and in humans (Cheng, 1995; DPR, 1999a). As the most sensitive endpoints were not measured in the available dermal studies, the acute, subchronic and chronic critical dermal RfDs were derived from the oral PODs.

$$RfD = (NOEL/\ \%\ absorbed)/UF_{TOTAL}$$

VI.A. Acute RfDs

The acute oral POD of 0.87 mg/kg/day was derived from an acute neurotoxicity study in rat (Hughes, 1997). The acute dermal POD was derived from the same study. Acute oral and dermal RfDs are listed in Table 45.

Table 45. Acute Oral and Dermal RfDs Derived with Default UF

Route	POD (mg/kg)	% Abs.	UF	UF_{TOTAL}	RfD (mg/kg)
Oral	0.87[a]	100	10_A	100	0.009
			10_H		
Dermal	0.87[a]	4.3	10_A	100	0.2
			10_H		

POD: Point of Departure; % Abs: percent absorption; UF: Uncertainty factors: UF_{TOTAL}: total UF, includes 10x for intrahuman variability (UF_H) and 10x for interspecies extrapolation from animal to human (UF_A); RfD: reference dose.

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[a]Benchmark dose modeling (BMDS, version 2.6) of hindlimb splay data from acute neurotoxicity study in rat (Hughes, 1997).

VI.B. Subchronic and Chronic RfDs

The subchronic POD of 0.02 mg/kg/day was based on convulsion-associated mortality and a statistically significant, dose-dependent decrease in T4 in males at week 1 through week 50 (Aughton, 1993).

The chronic POD of 0.02 mg/kg/day was based on sustained decreases in T4, increased incidence of convulsions, convulsion-associated mortality and mortality, and progressive senile nephropathy in rats in the combined chronic / oncogenicity study (Aughton, 1993).

Subchronic and chronic oral and dermal RfDs are listed in Table 46.

Table 46. Subchronic and Chronic Oral and Dermal RfDs Derived with Default UF

Duration	Route	POD (mg/kg)	% Abs.	UF	UF_{TOTAL}	RfD (mg/kg)
Subchronic and Chronic	Oral	0.02	NA	10_A	100	0.0002
				10_H		
Subchronic and Chronic	Dermal	0.02	4.3	10_A	100	0.005
				10_H		

POD: Point of Departure; % Abs: percent absorption (dermal route only);
Uncertainty factors: UF_{TOTAL}: total UF, includes 10x for intrahuman variability (UF_H) and 10x for interspecies extrapolation from animal to human (UF_A); RfD: reference dose.
Subchronic POD based on effects seen following subchronic exposure in chronic study in rat (Aughton, 1993).
Chronic POD from combined chronic and oncogenic study in rat (Aughton, 1993).

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VII. RISK APPRAISAL

Risk assessment is the process by which the toxicity of a chemical is compared to its potential for human exposure under specific conditions in order to estimate the risk to human health. This assessment evaluates the health risks associated with handler, residential, dietary, and aggregate exposures to fipronil. All risk assessments have limitations in the basic assumptions and the data on which they are based. These limitations contribute to uncertainties in the hazard identification, dose-response assessment, and exposure assessment processes, resulting ultimately in uncertainty in the final the estimation of human risk. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, their magnitude varies with the availability and quality of the relevant data, and with the types of exposure scenarios assessed. Prominent areas of risk assessment uncertainty involve assumptions about inter- and intraspecies sensitivity, the effectiveness of dose and route extrapolations, and the quality of the available experimental data. Specific uncertainties associated with this fipronil risk assessment are detailed in the following paragraphs.

VII.A. Uncertainties Associated with Fipronil Toxicity and Critical Points of Departure

VII.A.1. Acute Point of Departure

DPR uses route-specific critical endpoints whenever appropriate. However, if a POD is based on target organ or tissue toxicity monitored by one exposure route (usually oral) but not another (dermal or inhalation), that endpoint may be used to establish critical values for the other routes, as recommended by the US EPA (Rowland, 2008). For fipronil, a single POD was used to characterize acute oral, dermal and inhalation toxicity. As stated previously, both dermal and inhalation studies with acute or short-term duration endpoints were available. However, the route-specific studies did not measure the most sensitive endpoints, and, in the case of inhalation, calculation of an internal dose relied on default values that are associated with additional uncertainty. Therefore, the oral POD was used to calculate risk for all routes.

Regardless of the endpoints chosen, DPR recognizes that toxicokinetics is likely different by the different routes, which creates another source of uncertainty. For example, chemicals do not undergo hepatic first pass metabolism by the inhalation and dermal routes, which increases the possibility that inhalation or dermal exposure creates a different set of metabolites. Absorption and distribution can also be different by different routes.

The acute POD was based on effects seen in an acute oral study ($BMDL_{10}$ of 0.87 mg/kg based on decreased hindlimb splay in rats after a single dose). Benchmark dose (BMD) modeling incorporated the entire data set, including variability and uncertainty due to sampling and measurement error (US EPA, 2012a). The use of the $BMDL_{10}$ of 0.87 mg/kg as the critical acute POD is supported by several lines of evidence, as described in the paragraphs below.

The critical oral POD ($BMDL_{10}$) of 0.87 mg/kg/day was based on decreased hindlimb splay at the time to peak effect (TOPE) in male rats after a single gavage dose (Hughes, 1997). In this study, the experimental NOEL was 2.5 mg/kg/day and the LOEL was 7.5 mg/kg/day. Decreased

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hindlimb splay is consistent with a CNS effect, expected with a GABA receptor antagonist. However, there is uncertainty regarding the TOPE, which for fipronil was defined as the time after the administration of the dose when the highest incidence of convulsions and tremors were measured in the rats. The TOPE for hindlimb splay, however, could be different than that for convulsions and tremors.

The lowest acute oral NOEL was established in an acute neurotoxicity study that reported reduced hindlimb splay and rearing at 5 mg/kg/day, resulting in a NOEL of 0.5 mg/kg/day (Gill *et al.*, 1993). This NOEL was 10-fold lower than the LOEL (5 mg/kg/day), creating uncertainty with respect to the actual NOEL level. In addition, a 9% non-statistically significant decrease in hindlimb splay was observed at the NOEL of 0.5 mg/kg/day, suggesting that the experimental NOEL may not have captured this effect. In cases like this, BMD modeling, which takes into account all of the data for a particular effect, is the preferred approach to resolve the statistical uncertainties and identify the threshold level. However, data from this study did not produce an acceptable BMD model (failed the goodness-of-fit tests).

Because of the large dose gap separating the LOEL and NOEL in Gill *et al* (1993), the registrant conducted a second acute neurotoxicity (Hughes, 1997) that utilized more closely-spaced (3x) doses spanning the dose-gap range in the Gill study. Hughes (1997) confirmed that reduced hindlimb splay was the most sensitive effect caused by fipronil and set the study LOEL at 7.5 mg/kg/day and the NOEL at 2.5 mg/kg/day. At the NOEL, a 10% decrease in hindlimb splay was reported in male rats, a non-statistically significant level similar to that measured at the NOEL of 0.5 mg/kg/day in Gill *et al* (1993). Because this effect did not increase in magnitude or achieve statistical significance over a 5-fold dose increase in the two studies (0.5 to 2.5 mg/kg/day), DPR considered the 9 – 10% decrease in hindlimb splay to be within the observed range of variation. DPR also concluded that a 10% benchmark response level (BMR) was appropriate for modeling this effect based on the data from Hughes (1997). The exponential model passed the goodness-of-fit tests and produced a $BMLD_{10}$ of 0.87 mg/kg/day. This value was lower than the experimental NOEL of 2.5 mg/kg/day, indicating that the model recognized some level of decreased hindlimb splay at the NOEL was treatment-related (*i.e.*, above the normal variation). Because the data in Hughes (1997) was amenable to modeling, the use of BMD reduced the uncertainty in the acute POD designation. Hughes *et al* (1997) was therefore selected as the critical acute study.

Support for the critical acute oral POD came from the results of the subchronic inhalation toxicity study by Adamo-Trigiani (1999). Clinical signs (ungroomed fur, decreased activity, salivation and convulsions) on day 2 and decreased body weight and food consumption during week 1 at the LOEL of 4.8 mg/kg/day resulted in a short-term study NOEL of 0.8 mg/kg/day. Even though this value is lower than the acute oral POD of 0.87 mg/kg/day, more confidence in the modeled value was warranted because it evaluated all data in the observed dose range. In addition, the proximity of this value to the critical oral value of 0.87 mg/kg/day is noteworthy; experimental data confirm the model. Finally, BMD modeling gives a more precise estimate of POD than route-to-route extrapolation, which requires conversion from an air concentration (0.005 mg/L) to an internal dose (0.8 mg/kg/day) using a default rat breathing rate. Therefore,

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DPR used the $BMDL_{10}$ of 0.87 mg/kg/day as the critical acute value to characterize inhalation risk rather than the inhalation NOEL of 0.8 mg/kg/day.

Two studies reported effects at lower doses following short-term exposure to fipronil, raising the possibility that the critical NOEL underestimated the acute toxicity of fipronil. A published study conducted in adult female ICR (CD-1 IGS) mice exposed to fipronil from gestation day (GD) 1 to GD 3 showed an increased number of blastocysts with dead cells in embryos extracted from dams exposed at 0.009 mg/kg/day (Sefcikova *et al.*, 2018). The toxicological significance of these data are unknown, as the animals were not followed to parturition. Furthermore, a basal level of cell death is normative in rodent and human blastocysts, and a level that might affect reproductive outcomes or development is unknown (Hardy and Spanos, 2001; Sefcikova *et al.*, 2018). In the second study, decreased T4 levels were observed at 1.6 mg/kg/day and 0.06 mg/kg/day in female and male rats, respectively, after one week of exposure (Aughton, 1993). DPR conducted extensive weight-of-evidence analysis related to thyroid hormone perturbations, and concluded that the critical acute oral POD of 0.87 mg/kg/day is protective of acute, treatment-related changes in thyroid hormone. This is described in detail in the Thyroid Toxicity section of this appraisal, below.

VII.A.2. Subchronic Point of Departure

The subchronic critical POD of 0.02 mg/kg/day was based on decreases in serum T4 levels, convulsions, and death in adult male rats within one year of exposure to 0.06 mg/kg/day fipronil (Aughton, 1993). Confidence in this determination was based on the following factors:

- The T4 decreases were sustained, dose-dependent and carried pairwise statistical significance at the LOEL dose and above. Short-term thyroid hormone deficiencies in adults are unlikely to be harmful. However, sustained decreases in T4 in adult rats are toxicologically relevant to humans as they can generate clinical manifestations of hypothyroidism including lethargy, hyporeflexia, poor motor coordination and memory impairment (Bernal, 2015).

- Convulsions occurred at the LOEL in one male at week 23. Two more males experienced convulsions at weeks 61 and 69 at that dose. While not within a subchronic timeframe, the post one-year incidences strongly suggested that the occurrence at week 23 was due to fipronil exposure and that the subchronic timeframe was relevant. Moreover, convulsions at the high dose (13 mg/kg/day) were frequently observed in both sexes within the subchronic timeframe.

- One male died during week 26 at the LOEL (0.06 mg/kg/day) after experiencing convulsions at week 23. Because of this, we judged the death to be due to fipronil.

As noted in the Hazard Identification section, three other studies generated subchronic PODs of similar magnitude to the critical value, increasing the strength of the critical POD determination.

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- A subchronic NOEL of 0.05 mg/kg/day based on delayed preputial separation and decreased startle response in rats at 0.9 mg/kg/day was established in the developmental neurotoxicity study (Mandella, 1995). However, the significant dose gap between the NOEL and LOEL may be consistent with a higher NOEL value.

- A subchronic $BMDL_{10}$ of 0.06 mg/kg/day based on hepatic periacinar hypertrophy was set in the 13-week mouse study (Broadmeadow, 1991). Although the primary function of liver is to respond to xenobiotic load, this effect was constantly observed in repeat-dose studies with fipronil.

- Benchmark dose modeling of urine found in the FOB observation area (suggestive of autonomic dysfunction) resulted in a POD of 0.01 mg/kg/day in rats (Driscoll and Hurley, 1993). However, this value was based on an indirect observation rather than a direct observation in the experimental animals. Furthermore, the high incidence of this apparent effect in controls calls into question the appropriateness of the default 10% benchmark response rate for this parameter.

Finally, uncertainty accompanied the use of an oral study to characterize dermal and inhalation risks. The subchronic oral value was used because the subchronic dermal and inhalation studies did not measure the most sensitive endpoints detected in the oral studies.

VII.A.3. Chronic Point of Departure

The critical chronic oral POD of 0.02 mg/kg/day was derived from the rat chronic dietary study based on convulsions and mortality, sustained decreases in T4, and increased progressive senile nephropathy at 0.06 mg/kg/day (Aughton, 1993). We note, however, that several effects were observed at the study NOEL. These effects included decreased serum albumin, increased absolute liver, thyroid and spleen weights, and increased incidence of progressive senile nephropathy. The data underlying these observations were insufficiently robust to support critical LOEL designation. For example, the relative weights of these organs were unaffected, the small increases in relative spleen and thyroid weight did not achieve statistical significance, and the incidence of progressive senile nephropathy did not exhibit dose-responsiveness at this dose.

Because inhalation and dermal toxicity studies with chronic duration were not available, the chronic dermal and inhalation toxicity were gauged using the chronic oral POD. This decision carries uncertainties similar to those accompanying the acute and subchronic route extrapolation.

VII.A.4. Developmental Toxicity Endpoints

Five registrant-submitted studies evaluated the potential effects of fipronil on development. These included developmental studies in rats and rabbits, a reproductive toxicity study in rats, a DNT study in rats and a CTA in rats (Mandella, 1995; Coder, 2019). The effects reported in these studies included decreased T4 levels in fetuses and increased liver weight in pups, decreased body weights and convulsions in pups, reduced pup viability, decreased litter size, dead/missing pups, decreased startle response and developmental delays.

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In studies from the published literature, effects that could be considered developmental or reproductive in nature (i.e., sperm with altered motility, increased incidence of dead cells in blastocysts) had unclear toxicological meaning (de Barros *et al.*, 2016a; Sefcikova *et al.*, 2018), Skeletal abnormalities in pups observed in a published study in rats were not clearly attributable to fipronil, as the exposures were conducted without appropriate controls (Eisa *et al.*, 2017).

The DNT and CTA studies evidenced developmental effects at doses lower than maternal effect. Delayed preputial separation was observed after 25 doses *in utero* and via lactation (LOEL of 0.9 mg/kg/day and NOEL of 0.05 mg/kg/day) (Mandella, 1995). This effect was likely related to the reduced body weights of the male pups, and thus required repated exposues. In the CTA study, decreased thyroid hormone levels were measured in GD 20 fetuses after 15 days of *in utero* exposure (LOEL of 1 mg/kg/day and NOEL of 0.3 mg/kg/day (Mandella, 1995; Coder, 2019). The critical subchronic NOEL of 0.02 mg/kg/day for decreases in T4, convulsions and convulsion-associated deaths in adult rats will be protective against the developmental toxicities seen after repeated exposures in the DNT study (NOEL of 0.05 mg/kg/day) and in the CTA (NOEL of 0.3 mg/kg/day). However, fetal T4 levels were first measured in the CTA on GD 20. It is conceivable that hormone decreases could have occurred after a single or a few *in utero* doses thus making the NOEL of 0.3 mg/kg/day also applicable to acute exposures. This value is lower than the critical acute oral POD of 0.87 mg/kg/day based on decreased hindlimb splay in rats. DPR did not select the NOEL of 0.3 mg/kg/day as the critical acute oral POD due to uncertainties regarding the reliability of the measured thyroid hormone levels in the CTA (see discussion below in the Thyroid Hormone Measurements section).

VII.A.5. Thyroid Toxicity

Decreased Thyroxine in Male Rats after Short-term Exposure

Decreased thyroxine (T4) levels were observed at 1.6 mg/kg/day and 0.06 mg/kg/day in female and male rats respectively after one week of exposure in a combined chronic and oncogenic study (Aughton, 1993). Because the exposure duration was short-term, DPR considered the effect for the critical acute POD.

The decreased T4 in male rats (LOEL of 0.06 mg/kg/day) occurred at a treatment level 40x lower than the BMD_{10} (2.48 mg/kg/day, equivalent to the LOEL) for decreased hindlimb splay from the acute neurotoxicity study. This is concerning because neurological and developmental effects can result from prenatal (maternal) or perinatal hypothyroidism during critical developmental periods (DeLong and Adams, 1991). Thyroid hormone deficiency, even of short duration, during specific timing in development can lead to irreversible brain damage (Bernal, 2015). Numerous studies have reported deficits in cognition (decreased IQ scores or similar measures) in children with decreased neonatal thyroid hormone levels, despite maternal levels that are within the traditional "normal" reference ranges (OEHHA, 2015). Therefore, short-term changes in circulating thyroid hormone levels can be used in risk assessment to serve as an upstream indicator of possible developmental effects in humans (Woodruff *et al.*, 2008). However, a careful weight-of-evidence analysis indicated that the decreased T4 levels seen in adult male rats at 0.06 mg/kg/day were

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unlikely to be deleterious in the short term and were not an appropriate surrogate for decreased T4 levels in pregnant females or developing animals. The decision was justified by the following considerations:

- Reductions in T4 levels were measured in pregnant females after 15 days of fipronil administration and after one week in non-pregnant females. This effect occurred at similar dose levels: the LOEL for pregnant dams was 3 mg/kg/day (Coder, 2019) and the LOEL for non-pregnant females was 1.6 mg/kg/day (Aughton, 1993).

- In the comparative thyroid assay (CTA), reductions in T4 levels were measured in GD 20 rat fetuses and PND 4 pups at 1 and 3 mg/kg/day, respectively, after 15 to 20 days of exposure (Coder, 2019). These doses are similar to those that caused T4 decreases in pregnant and non-pregnant females (3 mg/kg/day and 1.6 mg/kg/day, respectively) (Aughton, 1993; Coder, 2019).

- An acute study in male Long-Evans rats showed decreased T4 following a single gavage dose of 10 mg/kg fipronil, with no effect measured at 5 mg/kg (Moser *et al.*, 2015). In contrast, adult male CD rats appeared to be more sensitive to fipronil with a LOEL for T4 decreases of 0.06 mg/kg/day (Aughton, 1993). Regardless, short-term thyroid hormone deficiencies in adults are unlikely to be harmful (Bernal, 2015).

- Humans are likely to be less sensitive to changes in circulating thyroid hormone levels than rats, as they possess better thyroid hormone storage and buffering capabilities (US EPA, 1998; International Agency for Research on Cancer, 1999).

In conclusion, the critical acute oral POD of 0.87 mg/kg/day is considered protective of acute, treatment-related changes in thyroid hormone.

Thyroid Hormone Measurements

Because thyroid hormone levels play an important role in the hazard identification for fipronil, metrics used to assess the quality of thyroid hormone data are described herein. To be considered adequate for risk assessment, thyroid hormone effects must be dose-dependent and statistically significant. In addition, the presence or absence of related effects, including changes in thyroid organ weight or histopathology, is considered. The magnitude of change in thyroid hormones should be ≥ 20% in either direction to be considered a robust effect, as this would be outside the range of normal variation (US EPA, 2011e). In addition, the coefficient of variation (the standard deviation divided by the mean) for each exposure group should be less than 25 – 30% for T3 and T4 (US EPA, 2011e; Li *et al.*, 2019). Finally, the mode of action by which thyroid parameters are altered and the biological significance of those alterations are also considered.

A dose-dependent and statistically significant 24% decrease in T4 levels occurred in male CD rats following one week of daily (oral) fipronil exposure at 0.06 mg/kg/day in the combined chronic and oncogenicity study in rat (Aughton, 1993). The coefficient of variation for this dose

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was 33%, which was just outside the recommended range of 25 – 30%. Because this effect was observed after just one week of fipronil exposure, it could be considered an acute effect. However, the results were not ultimately used in determining the acute critical POD because decreased T4 levels in adult rats and humans are unlikely to be deleterious in the short term.

In the comparative thyroid assay, decreased T4 levels were measured in dams on GD 20 at 3 mg/kg/day and in fetuses on GD 20 at 1 mg/kg/day, generating NOELs of 1 mg/kg/day (dams) and 0.3 mg/kg/day (fetuses) (Coder, 2019). These effects were statistically significant ($p < 0.05$) and dose-dependent. T4 levels decreased by 19% in the pups and 26% in the dams. The coefficient of variation was 24% for pup data and 26% for dam data. These results provided confirmation that neither toxicologically significant thyroid hormone decreases nor thyroid-dependent overt developmental impacts were likely to occur in rats at or below the fetal NOEL of 0.3 mg/kg/day. Because T4 levels were first measured after 15 consecutive in utero doses, the exact timeline of the hormone decreases in fetuses is not known. Therefore, the results from the CTA study could be used for setting an acute critical POD to protect against possible developmental effects in humans.

DPR's analysis unveiled issues with the reliability of the measured thyroid hormone levels in the CTA. Importantly, many of the individual data points for hormone values were not within the ion ratio tolerance established by the investigator. The T3 or T4 ion ratio is equivalent to the primary ion peak divided by a second, confirmatory ion peak. The study-calculated ion ratios labeled as sample were not within the tolerance. In addition, a total of 286/855 T4 measurements (33%) were not within the tolerance with the rate ranging from 0 to 88.2% for T4 measurements in different exposure groups. The highest percent fail in T4 data was in negative control samples. Numerous T3 measurements also failed.

While the methods and data were certified by the study quality assurance representative, the failed ion ratio observations were not mentioned in the study report. DPR later learned that US EPA requested an additional thyroid hormone quality measure for this study which was not part of the CTA protocol. The conducting laboratory performed the ion ratio analyses in which primary and confirmatory samples were both analyzed and the resultant data were compared. The conducting laboratory used an analytical calibration curve plot to derive a curve mean and ± 20% tolerance. Sample ion ratios that fell outside that range were not within tolerance. It is possible that this method was too stringent, as the tolerable range was derived from a calibration curve instead of biological specimens that tend to be more variable than standards. Many of the failed samples were just outside of the tolerable range (e.g., 20.3% instead of 20%). There was no apparent correlation between percent fail and population (dams or fetuses) or exposure groups.

Despite the uncertainty regarding the reliability of the measured thyroid hormone levels in the CTA, effects such as increased thyroid weight and histopathology observed at higher doses suggested that the changes in blood thyroid hormone levels were representative of potential physiologic or pathologic change. For purposes of this assessment, data flagged as outside of tolerance increased the level of uncertainty of the toxicological significance of the data.

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Therefore, while there was qualitative value to the study results, the analytical integrity precluded the use of the acute results from the CTA to derive a quantitative acute POD.

Hepatic-Induced Thyroid Toxicity

Fipronil caused thyroid toxicity but did not act directly on the thyroid. Rather, it induced hepatic (liver) metabolism, which led to an increase in elimination of T4. This caused hyper-stimulation of the thyroid, increased thyroid weight, hypertrophy and hyperplasia, and, at sufficiently high doses, thyroid tumors (Peters *et al.*, 1991b; Peters *et al.*, 1991a; King, 1992; Aughton, 1993; Coder, 2019).

Direct toxicity to the liver was observed in registrant-submitted and published studies in rat, mouse, and dog and in one published case study with a human who ingested fipronil to self-harm (Bharathraj *et al.*, 2015). The effects (hepatocyte damage, lipid accumulation, increased oxidative stress, increased absolute and relative liver weights, changes in blood chemistry parameters, altered transport and metabolism, and mitochondria dysfunction) are similar to symptoms that characterize nonalcoholic steatohepatitis or fatty liver disease in humans. Fatty liver disease compromises liver function and can result in additional disease and death (McCullough, 2006; Fisher *et al.*, 2008; Hardwick *et al.*, 2010; Canet *et al.*, 2014; National Institute for Health and U.S. National Library of Medicine, 2015).

Using the predictive toxicology bioinformatics tool DAVID, DPR assessed concordance between *in vitro* data and effects seen *in vivo* (Huang da et al., 2009a; Huang da et al., 2009b). Gene ontology identified enriched pathways and functional categories in the ToxCast™ dataset. It is of interest that some ontological results were related to the liver pathologies described above. Specific examples include enriched steroid binding domains, transcription pathways, steroid hormone mediated signaling and type II diabetes.

VII.A.6. Oncogenicity

Fipronil induced thyroid follicular cell adenomas and carcinomas in male and female CD rats (Aughton, 1993). Because tumor incidence rates at the high dose (13 – 17 mg/kg/day) were higher than controls by significant margins in both males and females, a fipronil-based etiology is likely.

Data indicating oncogenesis usually trigger a quantitative cancer analysis in which potency, defined as the slope of the dose versus tumor incidence curve, is determined using multistage linear extrapolation. This is a process with implicit biological assumptions, including that the dose-response can be extrapolated in linear fashion back to zero dose. However, in all likelihood, fipronil induced thyroid tumors in rats through a process of hypothalamic-pituitary-thyroid axis disruption. This mode of action (MOA) is well-recognized in the rat, and is not likely to be relevant to humans due at least in part to more efficient serum thyroid buffering in humans. Various chemicals including phenobarbital and propyzamide operate by this MOA in rats. The process starts with hepatic enzyme induction, followed by enhanced T4 metabolism and clearance, decreased negative feedback on the hypothalamus, and consequent increased TSH

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secretion by the pituitary gland. Sustained elevations in TSH in turn causes follicular cell hypertrophy, hyperplasia and, ultimately, neoplasia (Papineni *et al.*, 2015).

To determine if chemically-induced thyroid tumorigenesis operates through this pathway, fulfillment of a specific set of requirements is recommended (US EPA, 1998). These are enumerated below along with the evidence for their fulfillment by fipronil in the rat.

1. Increased cellular growth: Increased liver weights occurred in at least nine registrant-submitted studies at doses as low as 0.3 mg/kg/day in rat pups in the CTA (Coder, 2019) and at 0.06 mg/kg/day in adult rats in the chronic mouse study (Broadmeadow, 1993). Thyroid cell hypertrophy was detected in rats at as low as 1.7 mg/kg/day (Holmes, 1991a; Aughton, 1993; Peters, 1996). In published studies, Kupffer cell hyperplasia was observed in mouse livers following IP administration of 15 mg/kg fipronil (Ferreira *et al.*, 2012a), and hypertrophy of mouse thyroid cells was observed at 50 mg/kg (IP) (Ferreira *et al.*, 2012b).

2. Hormonal changes: Decreased T4 levels were the most sensitive endpoint in the two registrant-submitted studies that measured thyroid endpoints (Aughton, 1993; Coder, 2019). Decreased T4 was also observed in rats in several published studies (Leghait *et al.*, 2010; Moser *et al.*, 2015; Ehsan *et al.*, 2016; Martin *et al.*, 2020). Increased TSH levels were observed in rat (Roques *et al.*, 2013), and increased T4 clearance was observed in rats and sheep (Leghait *et al.*, 2010; Roques *et al.*, 2012).

3. Site of action: Increased hepatic metabolism leading to increased T4 clearance from blood plasma was observed in rats following fipronil administration (Peters *et al.*, 1991b; Leghait *et al.*, 2009). These observations indicated strong liver involvement. In addition, fipronil induced hepatic enzymes involved in thyroid hormone clearance, including UDP-GT, CYPs, carboxylesterases, and membrane transport proteins in rats (Roques *et al.*, 2012; Roques *et al.*, 2013) and in human cell cultures (Das *et al.*, 2006). Fipronil also induced hepatic cytochrome P450 levels and activity in rats and in human cells (Tang *et al.*, 2004; Caballero *et al.*, 2015) and upregulated CYP mRNA and long non-coding RNA in human cell cultures (Mitchell *et al.*, 2016; Mitchell *et al.*, 2017). Both human and rat liver microsomes metabolize fipronil, although the evidence suggests that rats have a higher intrinsic clearance of fipronil than humans (Tang *et al.*, 2004). High fipronil clearance would decrease the negative feedback on the pituitary through the hypothalamus, leading to sustained TSH stimulation of the thyroid and consequent tumor formation. Thus, the weight-of-evidence suggests that with its enzyme induction and increased metabolism, the liver is the primary target organ. Altered thyroid function is secondary to the primary effects on the liver.

4. Dose correlations: Induction of rat thyroid tumors occurred at doses also associated with the primary liver-mediated effects noted above (*i.e.*, 13 to 17 mg/kg/day for males and females, respectively) (Aughton, 1993). While liver effects also occurred at a lower dose,

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the data suggest that consequent changes in thyroid hormone concentrations were likely insufficient to support tumorigenesis.

5. Reversibility: Effects on thyroid hormone levels in the rat combined chronic/ oncogenicity study were reversible; T4 levels rose and TSH levels declined after fipronil was removed from the diet (Aughton, 1993). If a chemical works through hypothalamic-pituitary-thyroid axis disruption, levels of thyroid-pituitary hormones return to normal after cessation of chemical dosing, decreasing the possibility of tumor induction.

In conclusion, the weight of evidence suggests that fipronil-induced hepatic clearance of serum T4 is a necessary precursor to the development of thyroid tumors in rats. Such a process is unlikely to be operative in humans, in part because humans buffer thyroid hormone changes more efficiently. Nevertheless, the critical chronic POD of 0.02 mg/kg/day based partly on the precursor event for tumors at 0.06 mg/kg/day will be protective of any possible tumor formation in humans.

VII.A.7. Estimate of Oral Absorption

This assessment assumes that the great majority of orally administered fipronil is absorbed though the gut and reaches the general circulation. The consequence of this assumption is that the administered dose is equivalent to the internal dose. However, the observation that ~50% of the dose is actually excreted in the feces over long period of time (7 days), combined with the confirmation of enterohepatic recirculation, suggests that the systemic absorption could be lower because a major fraction of the dose may not reach the general circulation. Were this the case, then the actual oral POD would be lower than the critical POD cited in this document (*i.e.*, fipronil would be more toxic) by a factor determined by the absorption rate. In calculating human risk from oral exposure, as long as the assumed oral absorption rate assumption (100%) is the same as that used for calculating human exposure by this route, oral MOE would not be affected. Similarly, the dermal MOE would accurately represent dermal risk because the human dermal exposure reflected an experimentally verified 4.3% absorption rate. However, uncertainty exists for risk calculations by the inhalation route, since the assumption of 100% inhalation absorption in human populations (See EAD, Appendix I) has not been experimentally verified.

VII.A.8. Fipronil Derivative Toxicity

This assessment evaluated the human risk from exposure to the parent compound fipronil only. However, the toxicological properties of fipronil depend not only on the parent, but also on its bioactive sulfone and sulfide metabolites, and the desulfinyl photoproduct. The effects of the fipronil derivatives are particularly relevant in cases when exposure to these compounds occurs independent of exposure to the parent. This is the case for exposure from drinking water where the sulfone, sulfide and amide metabolites, and the photodegradate were detected separately in the surface water in California (Appendix I). Therefore, a complete picture of the potential health risks of fipronil would include not only toxicity data on fipronil and its derivatives, but also their potential for human exposure, especially as dietary tolerances include those derivatives. But

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because exposure estimates for the derivatives are limited, total risk from exposure to fipronil-plus-derivatives may be underestimated in this assessment.

VI.B. Exposure Appraisal

VI.B.1. Handler, Home User, and Residential Post-Application Exposure Appraisal

The exposure assessment used the best information available at the time of this assessment. When possible, fipronil specific data were used to analyze identified exposure scenarios using registered fipronil products, specific application methods, and specific user groups. However, for scenarios that lacked fipronil specific information, either default values suggested by standard U.S. EPA or DPR practices (Beauvais *et al.*, 2007; US EPA, 2012b) or surrogate data from pesticides with physiochemical properties and application methods similar to fipronil were used. Scenarios which employed surrogate data included handler scenarios for structural liquid concentrate and turf products, post-application scenarios for structural bait gel and bait strip products, and applicator scenarios for structural dust products. In so doing, uncertainties may have been introduced into the analysis including the potential for overestimation of certain handler exposures. However, steps were taken to provide reasonable worst-case scenarios based only on legal use to provide a conservative, and therefore protective, approach to the exposure estimations.

Of the almost 5800 human health illness reports analyzed, approximately 80% were associated with the use of pet products. DPR only evaluates legal label uses for its exposure scenarios. It is not known how many of the illnesses may have been due to illegal use or use that did not adhere to label instructions. It is important to follow all manufacturers' instructions on the label in order to reduce potential exposure. However, because of the large number of illness reports associated with pet products, the exposure and risk from home use of these products were carefully evaluated.

Home use of pet products can potentially lead to inhalation exposure, dermal exposure, and/or incidental oral exposure. In regards to inhalation exposure, the low vapor pressure of fipronil (2.8×10^{-9} mmHg at 25 °C) reduces the risk of inhalation of spot-on products for home users and reduces inhalation risk for children and adults following use of either spot-on or spray products. In regards to dermal and incidental hand-to mouth exposures associated with home use, DPR notes that pet product suggest regular monthly application to companion animals. A significant level of radiolabeled fipronil was detected in the stratum corneum and viable epidermis of the application zone (neck) of beagle dogs up to 56 days post-application (Cochet *et al.*, 1997). This persistence combined with regular 30-day applications may underestimate dermal and incidental hand-to-mouth exposures. However, since the transferable (e.g. available) amount of fipronil on companion animals rapidly decreases within 28 days after treatment, there is a lowered risk of longer term exposure (see Appendix 1 for additional details). Even so, estimates of post-application object-to-mouth exposures can be further refined to reflect more accurate multi-day or multi-episode exposure profiles to reflect product-specific retreatment intervals (US EPA, 2012b).

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Additional information on how specific data gaps were addressed and the confidence in the exposure analysis and methodologies for fipronil are found in the Exposure Assessment Document (Appendix I).

VI.B.2. Dietary Exposure Assessment Appraisal

Uncertainties in the exposure to fipronil residues in food were introduced with the use of analytical limits of detection (LOD) or tolerances as surrogates for pesticide monitoring residue concentrations. While thousands of food commodity samples have been screened for fipronil residues, only a small number showed positive detections (0.35% of PDP samples; 2007 – 2017). Importantly, the input residue values for all commodities identified as major contributors to the acute dietary exposure were based on LOD values. Additional uncertainty arose from the assumption that fipronil exposure only results from the consumption of foods based on commodities with tolerances. That is, no illegal uses of fipronil in food crops were included in this analysis.

Uncertainties were also associated with the consumption database embedded in the current DEEM-FCID™ (version 4.02), which is based on the NHANES 2-day food consumption survey data for 2005 through 2010. A consumption survey from recent years would more accurately represent the population's consumption patterns.

Finally, the acute dietary exposure was estimated using a Tier 2 point-estimate analysis, which employs tolerance or upper bound measured residues. These assumptions are conservative, as it is unlikely that all of the commodities consumed in a given day will contain fipronil residues at the highest legally-allowed or measured level. Since the resulting exposures produced MOE levels above the DPR screening MOE targets (500 and 1000 at the 95th and 99th percentiles, respectively), further refinements were not performed.

VI.C. Other Regulatory Agencies

United States Environmental Protection Agency (US EPA)

The US EPA completed a Draft Risk Assessment for Registration Review in 2020 (US EPA, 2020). It revised and updated regulatory values from a previous 2015 memorandum, 2011 scoping document, and 2007 human health risk assessment (US EPA, 2007; US EPA, 2011c; US EPA, 2015). The most significant changes include:

- Removal of an FQPA safety factor applied to short- and intermediate-term oral exposure for lack of thyroid hormone data.
- Reduction of the interspecies extrapolation factor from 10 to 3 for short- and intermediate- duration exposures that were based on thyroid hormone endpoints.
- Revised short- and intermediate-term POD.
- An increase in the POD value for the developmental neurotoxicity study in rat.

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The US EPA (2020) acute reference dose (aRfD) for acute dietary exposure was 0.025 mg/kg/day, based on effects in the acute neurotoxicity study in rat with total uncertainty/safety factors of 100x (US EPA, 2020). The chronic reference dose (cRfD) for chronic dietary exposure was 0.0002 mg/kg/day, for effects in the combined/oncogenicity study in rat, with total safety factors of 100x. US EPA also developed levels of concern for short-, intermediate-and long-term incidental oral, dermal and inhalation exposure (US EPA, 2020).

European Food Safety Authority (EFSA)

In 2006 the European Food Safety Authority (EFSA) published their conclusions on a draft human health risk assessment prepared for proposed uses of fipronil (EFSA, 2006). The Acceptable Daily Intake (ADI) of 0.0002 mg/kg/day was based on the NOAEL of 0.02 mg/kg/day in the rat oncogenicity study with the EFSA standard safety factor of 100. An aRfD of 0.009 mg/kg/day was derived from the developmental neurotoxicity study in rat with a developmental NOAEL of 0.9 mg/kg/day, with the EFSA standard safety factor of 100. The assessment concluded that no genotoxic or oncogenic potential was demonstrated, and that the induction of thyroid follicular cell tumors is specific to rat and not considered relevant to humans.

French Food Health Safety Agency (AFSSA)/ French Environmental Health Safety Agency (AFSSE)

In 2005 the French Food Health Safety Agency (AFSSA) and French Environmental Health Safety Agency (AFSSE) completed a human health risk assessment on fipronil (Agence Francaise de Securite Sanitaire des Aliments, 2005). The ADI of 0.0002 mg/kg/day was based on the NOAEL of 0.02 mg/kg/kg/day in the chronic rat study with 100x safety factors. An aRfD of 0.009 mg/kg/day was based on a NOAEL of 0.9 mg/kg/day for neurobehavioral effects in offspring and reduced body weights and food consumption in dams in a developmental neurotoxicity study in rat, with safety factors of 100x. This aRfD replaced a previous aRfD of 0.003 mg/kg/day. The assessment concluded that the available experimental data do not give reason to suspect oncogenic risk from fipronil in humans, as the thyroid follicular tumorigenesis observed in rats can be explained by a rat-specific biological mechanism.

Australian Pesticide and Veterinary Medicine Authority (APVMA)

In 2003, the Australian Pesticide and Veterinary Medicine Authority (APVMA) initiated a risk assessment for fipronil following receipt of 73 adverse reports in humans and animals involving fipronil veterinary products from 1997 to 2006 (APVMA, 2011). The current Australian ADI for fipronil is 0.0002 mg/kg/day (set in June 1994). It was derived from the NOEL of 0.02 mg/kg/day in the chronic/oncogenicity rat study with safety factors of 100x. The ADI includes the parent compound and metabolites. The Australian aRfD of 0.02 mg/kg is based on a NOEL of 2.5 mg/kg for decreased landing foot splay in an acute oral neurotoxicity study in rats (APVMA, 2011). The aRfD incorporates a safety factor of 100x.

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VIII. CONCLUSION

The purpose of this risk characterization document was to evaluate the human health risks associated with fipronil exposure.

Data submitted by registrants, published in scientific journals, or reported by other regulatory or scientific bodies were reviewed for toxicological endpoints in mammals. Critical acute, subchronic, and chronic points of departure determined from these studies were combined with human exposure estimates to characterize risks from handler and residential exposure, as well as from food and drinking water. Oral and dermal acute and chronic reference doses were also developed as target exposure levels for adults and children.

All of the critical points of departure for fipronil were based on effects observed in oral toxicity studies in rats and mice. Non-oncogenic risks were calculated as margins of exposure, a ratio of the critical points of departure to the estimates of exposure. An analysis of the uncertainties inherent in this risk characterization resulted in designation of 100 as the target for all scenarios evaluated. The target margin of exposure is the product of an interspecies uncertainty factor (UF_A) of 10 and an intraspecies uncertainty factor (UF_H) of 10. Values falling below the target of 100 are considered to pose a potential health risk.

Individual and aggregate risks were calculated for both handler and home use exposure scenarios. Although considered a contributor in certain scenarios, DPR did not include food or drinking water exposures in the aggregate risk calculations because of the inconsequential change to overall risk. Likewise, oncogenic risk was not calculated. Because the chronic POD is based on an upstream oncogenic effect (decreased T4) at a dose level that is much lower than the level where tumors occurred in rats (0.02 mg/kg/day versus 13 mg/kg/day), and because oncogenesis is likely caused by an extra thyroidal mechanism that is not relevant to humans, the chronic POD is considered protective of cancer in humans.

Handler margins of exposure considered to pose a potential health risk include:

- Short-term dermal exposure to pet spray products
- Seasonal exposure to pet spray and spot-on products as well as structural liquid concentrate and turf granules
- Annual dermal exposure scenarios for pet products and liquid concentrate

Scenarios that pose a potential risk to home users include:

- Acute dermal exposure for users who apply pet spray at home

Post-application residential exposures for adults considered to pose a potential health risk include:

- Seasonal exposure to pet spray and pet spot-on products

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Post-application residential exposure for children considered to pose a potential health risk include:

- Short-term oral exposure to turf granules
- Seasonal oral exposure to pet products
- Seasonal dermal exposure to pet products

Reference doses (RfDs) were calculated using total uncertainty factors (UF) of 100, which included 10x for interspecies extrapolation and 10x for intrahuman variability. The acute oral RfD was 0.009 mg/kg. The acute dermal RfD was 0.2 mg/kg (adjusted for 4.3% absorption). The subchronic and chronic oral RfDs were 0.0002 mg/kg/day. The subchronic and chronic dermal RfDs were 0.005 mg/kg/day (adjusted for absorption).

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APPENDIX I. ASSESSMENT OF HUMAN EXPOSURE TO FIPRONIL (70 pages)

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ASSESSMENT OF HUMAN EXPOSURE TO FIPRONIL

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ACRONYMS

AADD	annual average daily dose
AVMA	American Veterinary Medical Association
DAF	dermal absorption factor
DPR	Department of Pesticide Regulation
FAC	Food and Agricultural Code
HHA	Human Health Assessment Branch
HPLC	high-performance liquid chromatography
HUD	US Department of Housing and Urban Development
LADD	lifetime average daily dose
LC	liquid concentrate
LPM	liter per minute
LSC	liquid scintillation counter
M/L/A	mixer/loader/applicator
MOE	margin of exposure
MQL	minimum quantifiable level
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NOEL	no-observed effect level
NRC	National Research Council
PCOC	Pest Control Operators of California
PHED	Pesticide Handlers Exposure Database
PISP	Pesticide Illness Surveillance Program
PPE	personal protective equipment
REI	restricted entry interval
PUR	Pesticide Use Reporting
RCD	risk characterization document
RTU	Ready-to-use
SENSOR	Sentinel Event Notification System for Occupational Risks
SOP	standard operating procedure
SADD	seasonal average daily dose
STADD	short-term absorbed daily dose
SURF	Surface Water Database
SWIMODEL	Swimmer Exposure Assessment Model
SWP	Surface Water Program
TTR	transferable turf residue
TWA	time-weighted average
US EPA	US Environmental Protection Agency
USGS	US Geological Survey

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EXECUTIVE SUMMARY

Fipronil is a phenylpyrazole insecticide discovered by Rhône-Poulenc in 1987 and first registered in California in 1997. Fipronil is the active ingredient of many products used for structural pest control, pet flea/tick control, and lawn maintenance. Currently, no fipronil product is registered for agricultural produce use in California.

The Human Health Assessment (HHA) Branch of the California Department of Pesticide Regulation (DPR) initiated the comprehensive human health risk assessment for fipronil due to potential mammalian toxicity from both acute and chronic exposure. Surveillance networks in California and nationwide have reported human illness incidents associated with fipronil use.

In 2013, the National Academy of Sciences (NAS) reviewed the risk assessment practices of DPR. Following the recommendations from NAS, DPR risk assessment process was improved with increased transparency and involvement of all stakeholders. Fipronil was selected as the first active ingredient to follow the revised process.

This assessment identified 25 exposure scenarios during the problem formulation phase. One additional scenario was suggested by the Pest Control Operators of California (PCOC). Of these 26 scenarios, low human exposure is expected for eight scenarios. Fipronil exposure was estimated for the remaining 18 scenarios. For these 18 scenarios, short-term absorbed daily dose (STADD) via individual exposure pathway, which represents short-term fipronil exposure, is summarized in Table E1. Seasonal, annual and life-time average daily doses (SADD, AADD and LADD), which represent intermediate and long-term exposure, are less than the STADDs and are listed under individual exposure sections. Anticipated fipronil concentrations in the surface water for use in dietary exposure assessment were also developed: 0.275 ppb for the acute and 0.033 ppb for the chronic dietary risk assessments.

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Table E1. Fipronil exposure summary for evaluated use scenarios

Product	Handler/ Post-application	Human receptor	Exposure pathway	STADD[a] (µg/kg/d)
Turf granule	Handler	Adult	Dermal	0.66
			Inhalation	0.048
	Post-application, resident	Adult	Dermal	0.0069
		Child	Dermal	0.0098
			Oral	23
Pet spray	Applicator, groomer	Adult	Dermal	52
			Inhalation	1.2
	Applicator, home user	Adult	Dermal	19
			Inhalation	0.4
	Post-application, resident	Adult	Dermal	2.4
		Child	Dermal	4.6
			Oral	1.1
Pet spot-on	Applicator, groomer	Adult	Dermal	4.2
	Applicator, home user	Adult	Dermal	1.5
	Post-application, resident	Adult	Dermal	1.4
		Child	Dermal	2.6
			Oral	0.60
Structural dust	Applicator	Adult	Dermal	0.085
			Inhalation	0.021
Structural LC[b]	Handler, no overhead	Adult	Dermal	1.4
			Inhalation	0.53
	Handler, with overhead	Adult	Dermal	6.3
			Inhalation	0.17
	Post-application, resident	Adult	Dermal	0.026
			Inhalation	0.023
		Child	Dermal	0.018
			Inhalation	0.048
			Oral	0.073
Structural bait gel	Post-application, resident	Adult	Dermal	0.000076
		Child	Dermal	0.000054
			Oral	0.0025

a: short-term absorbed daily dose; b: liquid concentrate.

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I. INTRODUCTION

Fipronil, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile, is a phenylpyrazole insecticide discovered by Rhône-Poulenc in 1987 and first registered in California in 1997. Fipronil is the active ingredient in many home-use and commercial pesticide products. In California, these products are used for various purposes including controlling structural pests, treating parasites on dogs/cats, and performing landscape maintenance. Although fipronil products are registered to control agricultural crop pests in some US states, no fipronil product is registered for use on agricultural produce in California (USEPA, 1998).

In 2013, the California Department of Pesticide Regulation (DPR) requested the National Academy of Sciences (NAS) independently peer review DPR risk assessment practices. In April 2015, the National Research Council (NRC), an external committee of NAS, completed its review and issued recommendations to improve DPR risk assessment process and risk characterization documents (RCDs). NRC recommended that for each specific pesticide, DPR conducts a problem formulation/scoping phase prior to drafting the RCD, during which DPR risk managers and risk assessors discuss the scope of the risk assessment. Information and data relevant to each pesticide are evaluated to determine the scope of the risk assessment. These data may include toxicology, pesticide use reports, pesticide sales, illness reports including adverse effects reports, primary uses of the pesticide, exposure scenarios identified on product labels, relevant US Environmental Protection Agency (US EPA) risk assessments, important sources of uncertainty and variability in the data, potential exposure pathways, and mitigation options that could address these potential exposure pathways. NRC also emphasized the importance of incorporating California-specific information into the risk assessment process when available and encouraged DPR to use more of such data, including the DPR Pesticide Use Reporting (PUR) database and reports from the Pesticide Illness Surveillance Program (PISP).

In response to NRC recommendations, the Human Health Assessment Branch (HHA) of DPR revised its human health risk assessment process and selected fipronil as the first pesticide to enter the new process. DPR initiated a comprehensive human health risk assessment for fipronil due to potential adverse human health effects associated with registered fipronil uses. This human exposure assessment document was prepared as part of the risk assessment. All fipronil products registered in California were considered and all label-described uses of these products were assessed for fipronil exposure, including occupational and non-occupational scenarios.

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II. FACTORS CONSIDERED TO DEVELOP EXPOSURE SCENARIOS

Based on the NRC recommendations, this assessment includes a problem formulation/scoping step in the risk assessment process. NRC envisions the problem formulation as a phase when risk managers, risk assessors, and stakeholders are brought together to determine "the major factors to be considered, the decision-making context, and the timeline and depth needed to ensure that the right questions are being asked in the context of the assessment" (NRC, 2009).

HHA incorporated this recommendation into the risk assessment process. During the problem formulation stage, HHA reviewed information and data relevant to fipronil, especially the California-specific data. This section describes factors considered in developing the exposure scenarios. HHA focused on exposure to products with significant use in California and the scenarios with greatest exposure potential.

A. Physiochemical properties

The two-dimensional chemical structure of fipronil is shown in Figure 1. Some key physiochemical properties that affect fipronil environmental fate and human exposure potential are summarized below (Tomlin, 1996). Fipronil is considered a non-ionic hydrophobic compound based on its low water solubility and high octanol/water partition coefficient (K_{ow}). Fipronil also has very low vapor pressure (2.8 x 10^{-9} mmHg at 25 °C), indicating the inhalation exposure from gas phase fipronil is expected to be low (Teerlink, 2017). However, fipronil inhalation is still possible if humans are exposed to air containing fipronil aerosols.

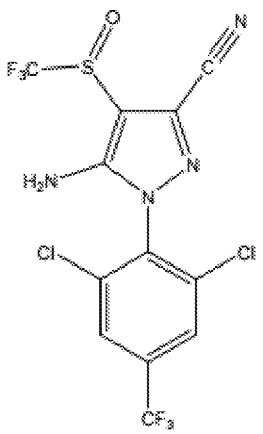

Figure 1. Chemical structure of fipronil

- Molecular formula: $C_{12}H_4Cl_2F_6N_4OS$
- Molecular weight: 437.2 g·mol^{-1}
- Octanol-water partition coefficient (Log K_{ow}): 4.0
- Henry's law constant: 3.7x10^{-5} Pa·m^3·mol^{-1}
- Solubility (g·L^{-1}, 20°C): 0.002 in distilled water, 545.9 in acetone, 3.0 in toluene

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B. Fipronil use and sales in California

Fipronil is used for structural, lawn, and pet treatments. There are no fipronil products registered for agricultural produce use in California. Some fipronil products have use restricted to licensed applicators, while many products can be used by both licensed applicators and the general public.

The DPR PUR database records fipronil use by licensed applicators. Title 3 of the California Code of Regulation (CCR) requires licensed applicators, either individuals, companies, or agencies in the business of pest control, to report their pesticide use to the agricultural commissioner of the county in which the application was made (3 CCR § 6627(a)). Fipronil use by licensed applicators in 2011-2015 is summarized in Table 1. Structural pest control accounted for almost all (>99%) fipronil use by licensed applicators.

Table 1. Fipronil use (lbs) by licensed applicators in 2011-2015

Commodity	2011	2012	2013	2014	2015
Structural Pest Control	63,345	53,156	70,928	79,245	91,339
Landscape Maintenance	113	109	57	68	136
Other	2	13	479	337	954
Total Use	63,460	53,278	71,464	79,650	71,464

The top five counties for fipronil use in 2015 are Orange, Los Angeles, Santa Clara, Sacramento and Riverside, which together accounted for 63% of total fipronil used by licensed applicators (Figure 2). Orange County alone had around 20,000 lbs of fipronil applied by licensed applicators in 2015, accounting for over 20% of total use by licensed applicators in California. In 2012-2015, the counties of Los Angeles, Orange, San Diego, Riverside and San Bernardino accounted for over 50% of annual fipronil use in California, indicating significant fipronil use by licensed applicators in southern California.

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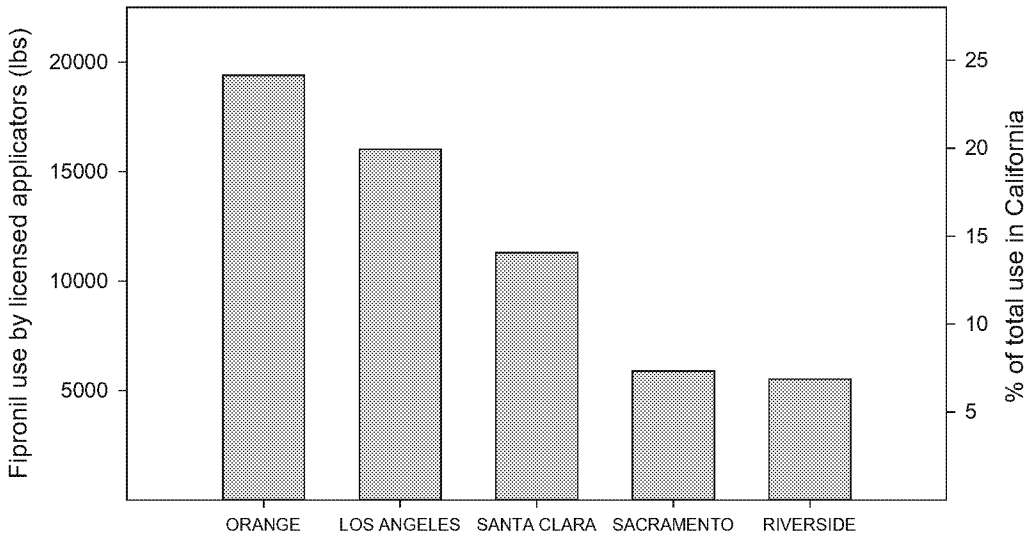

Figure 2. Fipronil use by licensed applicators in 2015: top five Counties

PUR data also showed licensed applicators used more fipronil during the warm, dry months (e.g., April to October, Figure 3). As shown in Figure 4, more fipronil was used during April-October than in other time of a year in both southern and northern California. For instance, in Orange County in 2015, months with >5% of annual fipronil use are all in the dry season.

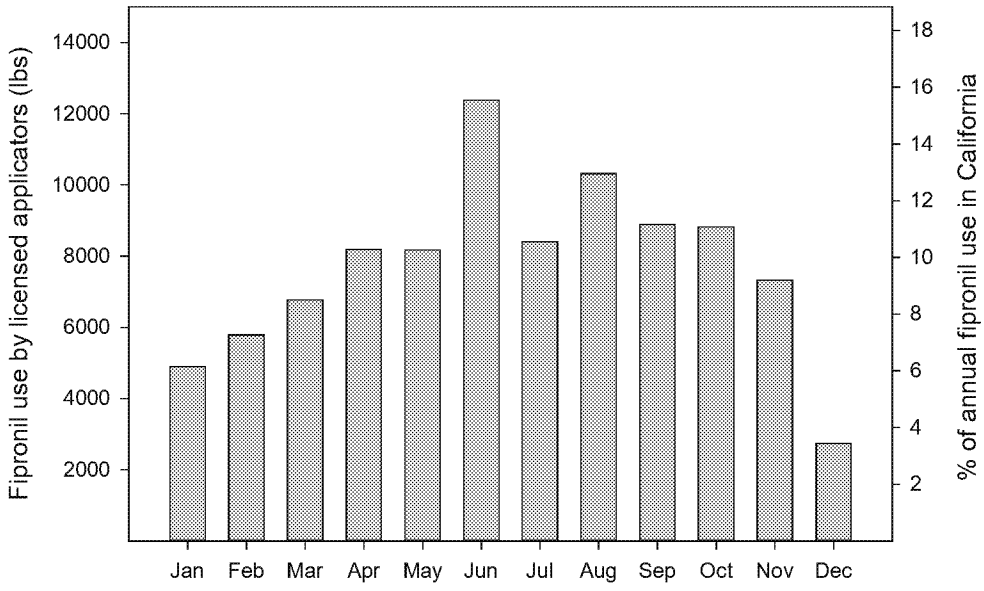

Figure 3. Monthly fipronil use by licensed applicators in California in 2015

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Fipronil products are also sold at retail stores and can be used by home users, such as pet owners who use spot-on and spray products on their dogs/cats and bait gel and station products used by homeowners to treat structural pests. Fipronil pet spot-on products that are commonly used to treat ectoparastic pests represent the largest number of fipronil products registered in California (DPR, 2020). However, their use by home users are not recorded in the PUR database.

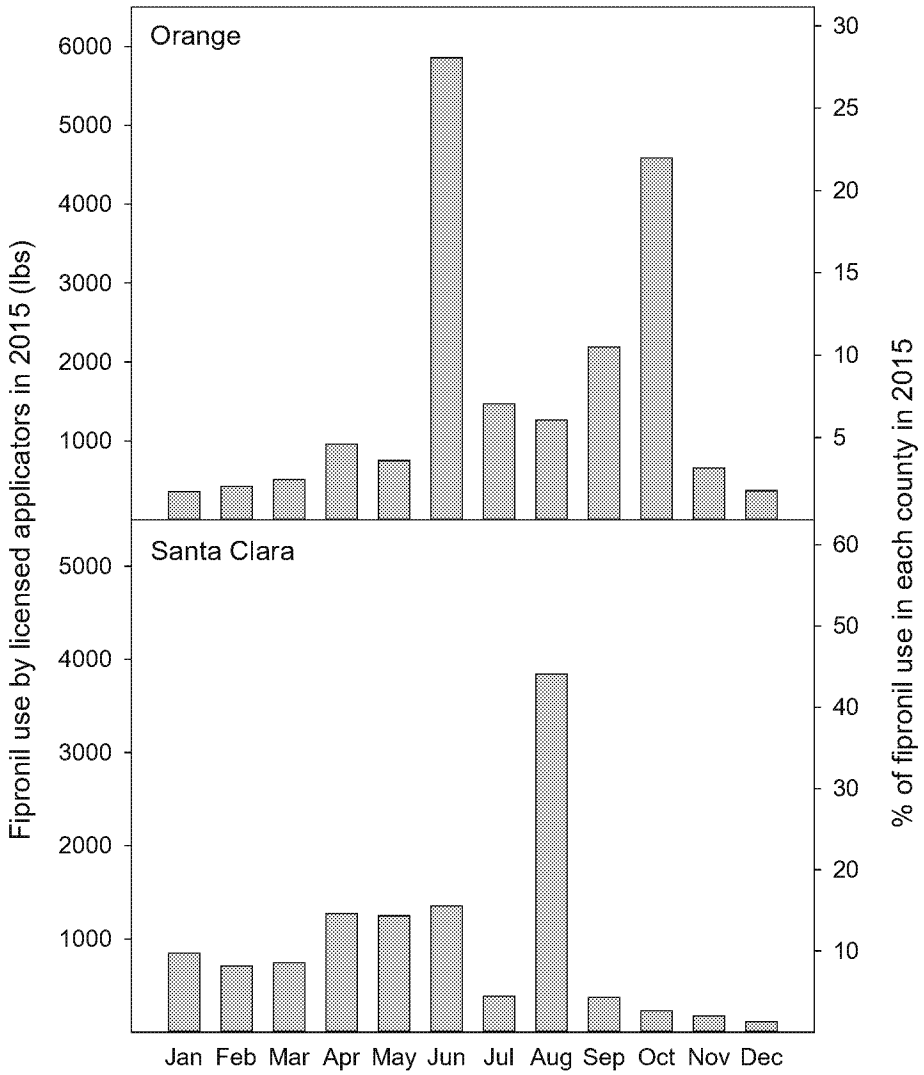

Figure 4. Monthly fipronil use by licensed applicators in Orange County and Santa Clara County in 2015

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C. Registered products in California and labeled uses

As of January 2016, 124 products containing fipronil have active registrations in California. Registered products represent various formulation types, including dust, pressurized spray, liquid concentrate, ready-to-use (RTU) liquid, gel, baits, and granules and contain fipronil at 0.00045-9.8%. Based on the use purpose and formulation, these products were categorized into seven groups, as summarized in Table 2.

Table 2. Summary of fipronil products registered in California as of January 2016

Target site	Formulation	Application	Licensed user only	PPE[b] required	Use in indoor living space
Turf	RTU[c] granule	Broadcast	Yes	Yes	No
Dog/cat	RTU solution	Spot-on	No	No	N/A[a]
Dog/cat	RTU solution	Spray	No	Yes	N/A[a]
Structure	RTU dust/powder	Injection	Yes	No	No
Structure	LC[d]	Spray	Yes	Yes	No
Structure	RTU bait station	Placement	No	No	Yes
Structure	RTU gel/strip	Spots along cracks/crevices	No	No	Yes

a: not applicable as use locations was only included on the turf and structural product labels; b: personal protective equipment; c: ready-to-use; d: liquid concentrate.

Turf products. These include ready to use (RTU) granule products to control imported fire ants (*Solenopsis spp.*). In California, the use is limited to the Coachella Valley and the months of April to September.

Dog/Cat spot-on products. These products represent the largest number of fipronil products registered in California and can be used by both professional groomers and home users to treat ticks, fleas, and lice on cats and dogs. The product is applied by squeezing a full tube of liquid onto the skin between the shoulder blades of a dog or cat. There is one tube size for cats and four tubes sizes for dogs based on the body weight ranges (i.e., ≤22 lbs, 23-44 lbs, 45-88 lbs and 89-132 lbs). Gloves and other personal protective equipment (PPE) are not required when applying the spot-on products.

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Dog/Cat spray products. This includes RTU liquid formulation products in pressurized or hand-trigger container. The applicator is required to put on gloves before application. The applicator ruffles the dog or cat hair with one hand while holding and applying a spray product with the other hand. For head and eye areas, the applicator sprays the product on one gloved hand and then gently rubs the product onto the treated area.

Structural LC products. These are LC formulations used to control structural pests such as termites. The products must be diluted with water prior to application. They can be applied for termite control during pre-construction (e.g., broadcast spray on surface to be covered beneath the concrete slab) and post-construction (e.g., trenching and rodding along exterior perimeter and in accessible crawl space) phases. They can also be applied along exterior foundation perimeters to control invasive insects such as ants and spiders. Broadcast application of these products to indoor living spaces is restricted.

Structural dust/powder products. This formulation is a RTU solid in a non-refillable package exclusively used with specially designed application equipment. The product label does not require PPE during application.

Structural bait station products. This formulation is a RTU in a secure reservoir. The products can be applied in both indoor and outdoor areas by placing these stations in spots with known or suspected pest activities. PPE is not required during application.

Structural bait gel/strip products. This formulation is RTU packed in syringes or strips and applied for spot treatments in both indoor and outdoor areas. PPE is not required during application.

D. Reported Illnesses

Pesticide illness data are evaluated to determine the exposure-specific data associated with the human illnesses, including the product type, formulation, and exposure routes. Descriptive data from the most recent five years of reports available at the time were used to develop relevant exposure scenarios used in this exposure assessment. Pesticide-related illness cases in California are recorded by DPR's Pesticide Illness Surveillance Program (PISP). Case reports are received throughout the state from poison control centers, the Department of Industrial Relations, local health officers, emergency departments, and medical doctors. The PISP scientists review the cases and the information is logged into a database where it can be used for future assessments of worker protection standards and evaluation of illness trends. Analysis of the PISP data has been included in the problem formulation document and also discussed below (DPR, 2017).

Between 2009 and 2013, PISP recorded 27 illness cases that are associated with the potential exposure to fipronil. Three of these cases occurred during structural and pet pest control applications and 20 cases occurred during post-application. Four cases resulted from product

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misuse or unidentified causes. Six cases were categorized as "Probable", indicating the illness was most likely caused by fipronil use, but the evidence was limited or circumstantial. One case was categorized as "Definite", meaning the exposure and consequent illness were supported by both physical and medical evidence. In this "Definite" case, a home user was exposed to fipronil while the pet spot-on product broke and a portion of the content splashed into the eye. Seven cases included exposure to other pesticides in addition to fipronil, so it is not possible to assign an illness to fipronil alone.

The National Institute of Occupational Safety and Health (NIOSH) maintains the SENSOR database and records pesticide illnesses in some US states. Acute illnesses related to fipronil exposure in 11 states from 2001-2007 were summarized by Lee et al. (Lee *et al.*, 2010). The most illness cases reported were associated with structural applications of LC product Termidor® suspended concentrate (SC), followed by the pet spot-on product Frontline® Plus. Pesticide handlers accounted for less than 40% of total illnesses. Pet care products, including both spray and spot-on formulations, were associated approximately 40% of total illnesses recorded by SENSOR.

E. Occurrence in Environmental Media with Human Exposure Potential

Air. The DPR Air Monitoring Network (AMN) measures airborne pesticides in agricultural communities (Vidrio *et al.*, 2017). Fipronil is not monitored as part of the AMN and air concentration data are scarce. Given its low volatility and no agricultural produce use in California, non-occupational human exposure to fipronil from outdoor air is expected to be low.

Residential areas. Fipronil is used in residential areas by both licensed applicators and home users for controlling home-invading pests and treating dogs/cats. Residues of fipronil and fipronil degradates have been detected in both residential indoor and outdoor areas. In 2009, US EPA and the US Department of Housing and Urban Development (HUD) published findings on pesticide occurrence inside residential homes (Stout *et al.*, 2009). This study sampled 500 public and private housing units across the US between June 2005 and March 2006. Indoor hard surfaces were sampled by isopropanol wipes. Fipronil was one of the most detected pesticides, with a detection frequency of 40% and an arithmetic mean concentration of 0.16 ng/cm^2. In another study, Mahler et al. (2009) collected indoor and outdoor floor dust from 24 apartments in Austin, TX from April-July, 2008 (Mahler *et al.*, 2009). Fipronil was measured by collecting floor dust using a high-volume surface sampler. The median and maximum concentration in the indoor dust was 89 and 9800 ng/g, and the median and maximum concentration in the outdoor dust was 4.81 and 300 ng/g, respectively. The authors found that the indoor and outdoor concentrations were not correlated, suggesting that the fipronil residues found in these two areas originated from different applications.

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Fipronil residues in residential indoor areas in California have not been well quantified. However, Jiang et al. recently published data on fipronil occurrence in residential outdoor areas in California (Jiang *et al.*, 2016a). In this study, Jiang et al. used a commercial vacuum cleaner to sample three outdoor surfaces adjacent to residential homes. The houses were located in two neighborhoods in Riverside, CA and were sampled three times from May to September 2011. Dust samples (*N*=360) were analyzed for fipronil and three fipronil degradates (i.e., desulfinyl, sulfide and sulfone). The detection frequency and concentrations of fipronil and degradates are summarized in Table 3. Outdoor concentrations of fipronil and degradates in this study were similar to those found in Mahler et al. (Mahler *et al.*, 2009). Fipronil concentrations increased from May to September, suggesting that fipronil and its degradates accumulate on residential outdoor surfaces during the dry summer months (Jiang *et al.*, 2016a).

Table 3. Detection frequency and concentration (ng/g) of fipronil and degradates on residential outdoor surfaces

Pesticide[a]	May		July		September	
	D%[b]	*C*[c]	D%	*C*	D%	*C*
Neighborhood 1						
fipronil	15.0	<RL[d] (3.1)	51.7	1.0 (100.3)	71.7	2.5 (59.2)
desulfinyl fipronil	20.0	<RL (14.2)	75.0	2.3 (90.1)	78.3	1.8 (18.6)
fipronil sulfide	0.0	<RL	13.3	<RL (21.3)	11.6	<RL (3.0)
fipronil sulfone	36.7	<RL (15.2)	91.7	4.6 (184.1)	90.0	4.9 (105.1)
Neighborhood 2						
fipronil	10.0	<RL (29.1)	25.0	<RL (58.4)	55.0	1.2 (858.9)
desulfinyl fipronil	18.3	<RL (14.2)	58.3	2.0 (128.9)	68.3	3.0 (34.6)
fipronil sulfide	1.7	<RL (2.5)	10.0	<RL (12.8)	8.3	<RL (16.8)
fipronil sulfone	28.3	<RL (23.0)	71.7	4.5 (380.7)	95.0	6.9 (85.7)

a: Data is obtained from Jiang et al., 2016; b: percent of detection, N=60; c: the median concentration value (ng/g) in all the samples analyzed (N=60). Values in brackets are the maximum concentration value; d: less than reporting limit (RL), which equals to 1 ng/g.

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A similar study was conducted in Orange County, CA in which gutters, driveways, and street surfaces were sampled around twenty homes (Richard, 2013). The same homes were sampled three times, in August and October 2013 and in February 2014. Fipronil detection frequency was 36.3% and the median and maximum concentrations were <1.0 and 3663.9 ng/g, respectively. Dust on driveways contained higher fipronil concentrations than either the gutter or the street, which the authors attributed to the closer proximity of driveway to the perimeter of houses where fipronil was usually applied.

Urban surface water. The product labels prohibit fipronil applications directly to surface water. However, outdoor surface runoff and indoor drainage transfer of fipronil from urban and residential areas into receiving water bodies contribute to fipronil contamination in urban surface waters in California. Fipronil occurrence in California surface water has been measured in several studies. A summary of these studies is found in Jiang et al. (2016b).

DPR's Surface Water Protection Program (SWPP) maintains the Surface Water Database (SURF) that catalogues pesticide occurrence data from California surface waters. Table 4 summarizes data on fipronil and fipronil degradates as of June 2015. Fipronil and its degradates are among the most frequently detected insecticides in urban surface water in both southern and northern California (Ensminger, 2015; Budd, 2016).

Table 4. Occurrence of fipronil and degradates in California surface water

Pesticide	N^a	Mean[b]	Max
	Surface water (µg/L)		
fipronil	1075	0.031	2.11
desulfinyl	981	0.012	0.305
sulfide	1011	0.001	0.102
sulfone	1011	0.02	0.546
amide	552	0.007	0.246
	Sediment (µg/kg)		
fipronil	217	0.002	0.046
sulfide	164	0.011	0.091
sulfone	123	0.038	0.189

a: number of samples; b: The quantification levels varied among different sampling sites. To calculate the mean, for all the samples, non-quantifiable values were treated as zero.

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F. Label precautions and regulations

Pesticide labels use three signal words, i.e., Danger, Warning, or Caution, to categorize how dangerous a product can be to humans. All fipronil product labels carry the signal word "Caution", meaning the products are generally less dangerous than products with "Danger" or "Warning" signs if handled following label instructions. Fipronil product labels also state "harmful if swallowed, absorbed through skin or inhaled", "keep out of reach of children", and "wash thoroughly with soap and water after handling and before eating and drinking".

Only licensed applicators can use turf, structural LC, and structural dust/powder products. Different groups of fipronil products also have different PPE requirements. Applicators are required to wear long sleeved shirt, long pants, waterproof gloves, shoes and socks when applying turf and structural LC products. The labels of structural LC products also require applicators to wear respirator when working in a non-ventilated area. Dog/cat spray products require applicators to wear gloves.

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III. EXPOSURE SCENARIOS AND CONCEPTUAL MODELS

Based on the information discussed above, nine handler and sixteen post-application exposure scenarios were selected during the problem formulation phase to enter into exposure assessment. These scenarios are summarized in Table 5 and 6 and were categorized as "High", "Medium" or "Low" priority based on criteria detailed in the table footnotes. Briefly, this assessment first ranked individual scenarios based on the fipronil exposure potential and then increased the priority of scenarios with significant use/sales in California or with recorded illnesses. This assessment evaluated all the identified scenarios but prioritized assessment of exposures with a "High" priority assigned.

Conceptual models illustrate sources, exposure pathways and human receptors for the exposure scenarios, and are recommended by NRC as they "*serve as a guide for determining what types, amount, and quality of data are needed for the assessment to address the issues and concerns of interest to decision-makers*" (NRC, 2009). The conceptual model for fipronil was initially developed during the problem formulation phase of exposure assessment (Figure 5). The exposure assessment document followed each of the scenarios identified in the conceptual model to assess human exposures via different exposure routes. Dermal contact and inhalation are the primary routes of fipronil exposure during application. Exposure may occur during mixing and loading of LC and granular products as well as application of all products (all formulations). Because fipronil has a low vapor pressure, inhalation exposure from gas phase fipronil is anticipated to be low. However, inhalation of aerosols during loading of granular products and during mixing and application of liquid formulation products may constitute a non-negligible fipronil exposure route.

Two handler and four post-application exposure scenarios were categorized as "Low" priority. These scenarios were not assessed in this document with the reasons summarized below.

Structural bait station products. These are a group of RTU products contained in a secure reservoir. The fipronil content in these products ranges from 0.01% to 0.03%. The product is applied by placing the stations near ant trails or where ant activities are frequently seen. No replacement stations are needed for at least three months. The primary exposure route for the handler is dermal contact. As the applicator does not directly contact the fipronil formulation, HHA determined the exposure was negligible; this determination is consistent with the US EPA assessment (USEPA, 2012; USEPA, 2020). Post-application exposure is also negligible because the fipronil formulation is securely contained. Therefore, both applicator and post-application exposures were not assessed for bait station products.

Structural bait gel/strip products. This contains a group of RTU products with fipronil formulation packed as syringe tubes or strips. Fipronil content of these products ranges from 0.001% to 0.01%. The bait gel product is applied by touching the tip of the syringe to the target

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surface and depressing the syringe plunger. The strip product is applied by peeling off the cover film and placing the strip to the target surface. Both types of products are applied to areas with suspect pest activities, such as cracks and crevices, and are effective up to one month. The primary exposure route for applicator is dermal contact. As the handler does not directly contact the formulation, handler exposure is minimal, which is consistent with the US EPA assessment (USEPA, 2012; USEPA, 2020). Therefore, applicator exposure was not assessed for the bait gel/strip products.

Swimmer. Direct application of fipronil into surface water is prohibited. However, fipronil is detected in California surface water samples (Zhang, 2016). Thus, human (adult and child) exposure from swimming in contaminated water may be a potential exposure pathway. Primary exposure routes are dermal contact, inhalation, and incidental oral ingestion. A preliminary assessment following US EPA guidelines indicates that fipronil exposure was low for both adult and child swimmers (USEPA, 2003). Therefore, swimmer exposure was not assessment in this document.

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Table 5. Fipronil handler exposure scenarios

Exposure Scenario	Human receptor	Exposure based evidence					Use and illness based adjustment								Final priority decision
		Exposure estimate			Amount handled[d]	Preliminary priority decision[e]	Use restricted to licensed applicator[f]?	PUR data (Licensed use)		Sales data (if exempt from PUR)		Illnesses within CA (CalPISP)		Increase from preliminary priority decision?	
		Source of exposure estimate[a]	Label-required PPE deviated from default PPE[b]?	Exposure estimate[c]				Priority[g]	Source	Priority[h]	Source	% of Cases in 5 yrs[i]	Highest association[j]		
Turf, Granule	Handler	DPR Scenario 27	No	High	Low	Medium	Yes	Low (< 10% of use)	2010-2014 PUR					No	Medium
Pet, Spray	Applicator, home user	EPA C-113	Yes (gloves)	High	Low	Medium	No			Low	Internal database, 2015	7% (1 / 15)	Probable	Yes	High
	Applicator, groomer	EPA C-113	Yes (gloves)	High	Low	Medium								Yes[l]	High
Pet, Spot-on	Applicator, home user	EPA C-130	No	High	Low	Medium	No			Low[k]	Internal database, 2015	27% (4 / 15)	Definite	Yes	High
	Applicator, groomer	EPA C-130	No	High	Low	Medium								Yes	High
Structural, Dust	Applicator	EPA C-32	No	High	Low	Medium	Yes	Low (< 10% of use)	2010-2014 PUR			7% (1 / 15)	Possible	No	Medium
Structural, Liquid concentrate	Handler	DPR Scenario 23	No	High	Medium	High	Yes	High (> 90% of use)	2010-2014 PUR			7% (1 / 15)	Possible	No	High
Structural, Bait gel	Applicator	EPA 7-4	No	Low	Low	Low	No			Low	Internal database, 2015			No	Low
Structural, Bait station	Applicator	EPA 7-4	No	Low	Low	Low	No			Low	Internal database, 2015			No	Low

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a: Two reference was used to determine exposure estimate: DPR, which represents DPR Memo HS-1826 (http://www.cdpr.ca.gov/docs/whs/pdf/hs1826.pdf), and EPA, which represents US EPA Standard Operation Procedure (SOP) for Residential Pesticide Exposure Assessment (https://www.epa.gov/sites/production/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf).

b: Exposure estimates provided in DPR and US EPA SOP include description of PPE used (i.e., default PPE) when the exposure estimates were obtained. If the actual PPE of this specific scenario and specific pesticide is different from the default PPE, the exposure estimate will be lower (for actual PPE is more protective than default PPE) or higher (for actual PPE is less protective than default PPE) than default that with default PPE.

c: Exposure estimate of >5000, 500-5000 and <500 μg/lb active ingredient was categorized as "High", "Medium" or "Low" respectively.

d: "High" represents handling of >100 ac area or >100 gallons of finished solution; "Medium" represents handling of 1-100 ac area or 1-100 gallons of finished solution; "Low" represents handling of <1 ac area or <1 gallon of finished solution.

e: Preliminary decision was made based on "Exposure estimate" and "Amount handled" (DPR, 2017).

f: If yes (i.e., products with use restricted to licensed applicators), use "PUR data"; If no (i.e., use of products not restricted to licensed applicators), use "Sales data".

g: High, Medium or Low is assigned to a category that account for >50%, 10-50% or <10% use of the active ingredient. A "High" in "PUR data" will increase "Final priority decision" from "Preliminary priority decision" by one level.

h: High, Medium or Low was assigned to a category that account for >50%, 10-50%, or <10% sale of the active ingredient. A "High" in "Sales data" will increase "Final priority decision" from "Preliminary decision on exposure priority" by one level.

i: Intentional pesticide ingestion (e.g., suicide commitment) and any other illegal exposure are suggested to be removed. The percentage sum of "% of cases" may not equal to 100% because some illness cases were not possible to determine the exposure scenario.

j: Observation of California PISP case(s) with "Definite" or "Probable" association will increase "Final decision on exposure priority" by one level.

k: Pet groomer handlers more pets per day than pet owner. Therefore, even though use and illness evidence did not suggest adjustments, we gave groomer exposure scenario the same priority decision as pet owner scenario.

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Table 6. Fipronil post-application exposure scenarios

Category	Human receptor	Exposure based evidence					Use and illness based adjustment								Final priority decision
		Transfer coefficient			Child involved?[d]	Preliminary priority decision[e]	Use restricted to licensed applicator?[f]	PUR data (Licensed Use)		Sales data (if exempt from PUR)		Illnesses within CA (CalPISP)[i]		Increase from preliminary decision?[j]	
		Source of transfer coefficient[a]	Transfer coefficient[b]	Exposure duration[c]				Priority[g]	Source	Priority[h]	Source	% of Cases in 5 yrs[i]	Highest Association[j]		
Turf, Granule	Reentry, Adult	EPA 3-9	High	Medium	No	High	Yes	Low (< 10% of use)	2010-2014 PUR					No	High
	Reentry, Child	EPA 3-9	High	Medium	Yes	High								No	High
Pet, Spray	Reentry, Adult	EPA 8-7	High	Low	No	Medium	No			Low	Internal database, 2015			No	Medium
	Reentry, Child	EPA 8-7	Medium	Medium	Yes	High						13% (2 / 15)	Probable	Yes	High
Pet, Spot-on	Reentry, Adult	EPA 8-7	High	Low	No	Medium	No			Low	Internal database, 2015			No	Medium
	Reentry, Child	EPA 8-7	Medium	Medium	Yes	High						20% (3 / 15)	Probable	Yes	High
Structural, Dust	Reentry, Adult	Professional judgement	Low	Low	No	Low	Yes	Low (< 10% of use)	2010-2014 PUR			13% (2 / 15)	Probable	Yes	Medium
	Reentry, Child	Professional judgement	Low	Low	Yes	Medium								No	Medium
Structural, Liquid concentrate	Reentry, Adult	EPA 7-24[k]	High	Low	No	Medium	Yes	High (> 90% of use)	2010-2014 PUR			40% (6 / 15)	Probable	Yes	High
	Reentry, Child	EPA 7-24	Medium	Low	Yes	High								No	High
Structural, Bait gel	Reentry, Adult	EPA 7-24	High	Medium	No	High	No			Low	Internal database, 2015			No	High
	Reentry, Child	EPA 7-24	Medium	Medium	Yes	High								No	High
Structural, Bait station	Reentry, Adult	Professional judgement	Low	Low	No	Low	No			Low	Internal database, 2015	7% (1 / 15)	Possible	No	Low
	Reentry, Child	Professional judgement	Low	Low	Yes	Low								No	Low
Public	Swimmer, Adult	N/A	N/A	N/A	No	Low[l]								No	Low
	Swimmer, Child	N/A	N/A	N/A	Yes	Low								No	Low

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a: Transfer coefficient was obtained primarily from US EPA Standard Operation Procedure for Residential Pesticide Exposure Assessment (https://www.epa.gov/sites/production/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf).

b: Transfer coefficient of >5000, 1000-5000, and <1000 cm^2/hr was respectively categorized as "High", "Medium" and "Low".

c: Exposure time of >4, 1-4 and <1 h was respectively categorized as "High", "Medium" and "Low".

d: If the human receptor is a child/toddler, the preliminary priority decision will be increased by one level from the decision based on transfer coefficient and exposure duration (e.g., increase from "Medium" to "High"). The only exception is when the pesticide is in a closed container, such as bait station.

e: Preliminary decision was made based on both "Transfer coefficient" and "Amount handled" (DPR, 2017).

f: If yes (i.e., products with use restricted to licensed applicators), use "PUR data"; If no (i.e., use of products not restricted to licensed applicators), use "Sales data".

g: High, Medium or Low is assigned to a category that account for >50%, 10-50% or <10% use of the active ingredient. A "High" in "PUR data" will increase "Final priority decision" from "Preliminary priority decision" by one level.

h: High, Medium or Low was assigned to a category that account for >50%, 10-50%, or <10% sale of the active ingredient. A "High" in "Sales data" will increase "Final priority decision" from "Preliminary priority decision" by one level.

i: Intentional pesticide ingestion (e.g., suicide commitment) and any other illegal exposure are suggested to be removed. The percentage sum of "% of cases" may not equal to 100% because some illness cases were not possible to determine the exposure scenario.

j: Observation of California PISP case(s) with "Definite" or "Probable" association will increase "Final priority decision" from "Preliminary priority decision" by one level.

k: No reference is available. Indoor hard surface was used as surrogate. The exposure duration was determined as low because of less time spent in outdoor areas than indoor areas.

l: Swimmer exposure will be categorized as "High" or "Low" based on whether this pesticide is allowed to be applied directly to natural water bodies. Also child shares the same exposure routes (dermal and oral) as adult, so child exposure scenario will not be offered a higher priority.

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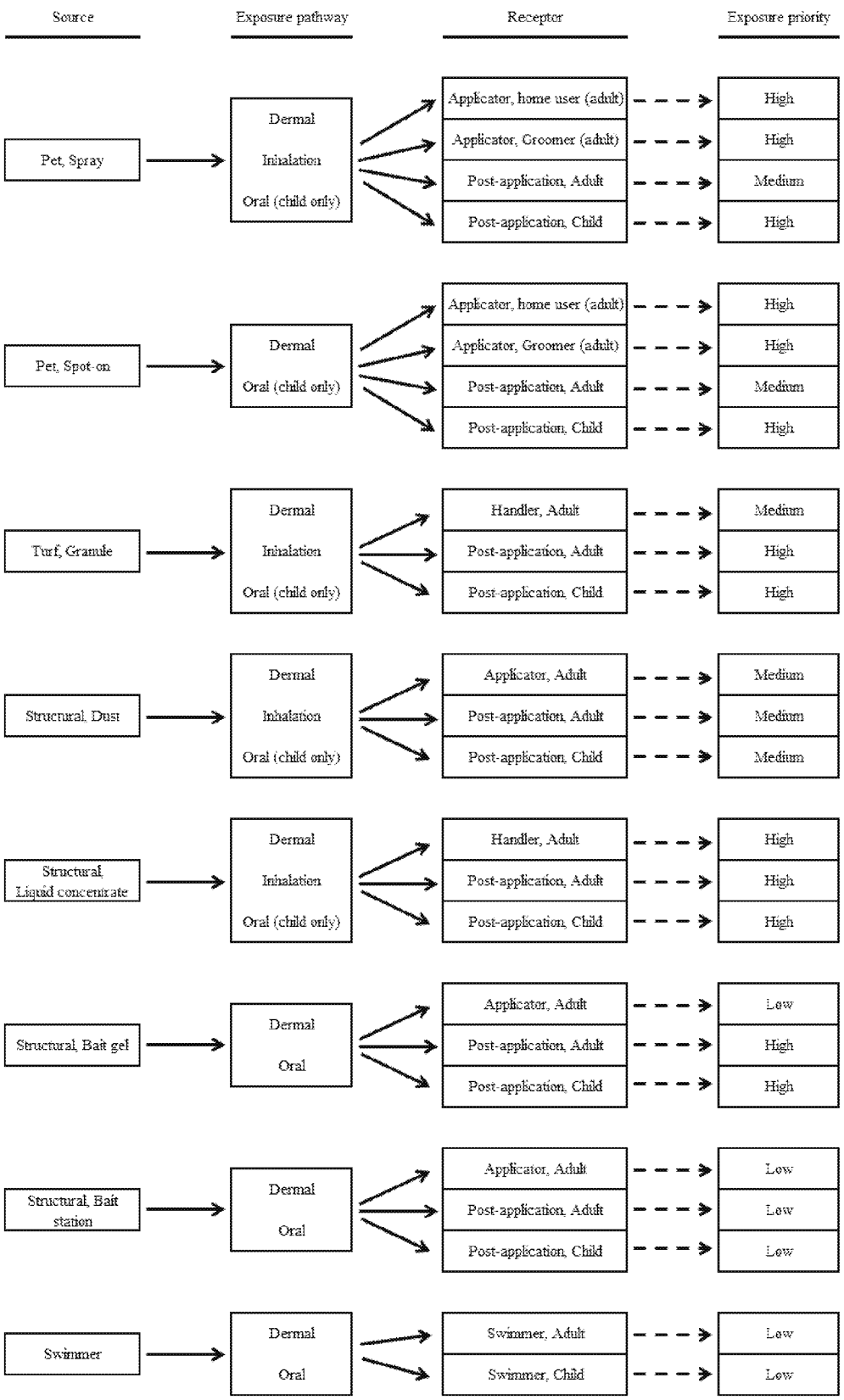

Figure 5. Conceptual models for fipronil exposure scenarios

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IV. EXPOSURE ASSESSMENT

A. Exposure duration

Handler and post-application scenarios are assessed for short-, intermediate- and long-term exposures. Short-term exposure, expressed as short-term absorbed daily dose (STADD), represents the highest exposure an individual may realistically experience while performing a label-permitted activity. An upper-bound estimate (e.g., the estimated 95th percentile of exposure) is used to calculate the daily exposure (Powell, 2002; Beauvais *et al.*, 2007; Kwok, 2017). In addition, for post-application STADD, this assessment assumes a human subject (adult or child) enters the treated areas or contacts the treated objects immediately after the expiration of the "no-contact" post-application interval as specified on the product label. Intermediate-term exposure is assessed using seasonal average daily dose (SADD), and long-term exposure is assessed using annual average daily dose (AADD) and lifetime average daily dose (LADD). For SADD, AADD and LADD, the average daily exposure instead of the upper-bound estimate is used, assuming for an extended period, continuous daily exposure at the "upper-bound" level is unlikely and average daily exposure is received (Kwok, 2017).

B. Absorption rate

Dermal. Dermal absorption factor (DAF) of fipronil (i.e., 4.3%) was derived by Thongsinthusak (1999) based on a registrant submitted study (Cheng, 1995; Thongsinthusak, 1999). This DAF of 4.3% is used in this document.

Inhalation. Absorption rate of fipronil through inhalation is not available. When no inhalation absorption rate estimate is available, this assessment uses a default rate of 100% (Frank, 2008).

Oral. This document uses 100% as the fipronil oral absorption rate, which is the same as determined in the RCD.

C. Structural LC products

These are concentrated formulations used by licensed applicators for both pre- and post-construction pest controls. Fipronil content in these products is 9.1%. Unlike other fipronil products, structural LC products need to be diluted to the desired concentration (e.g., 0.06%, 0.09% or 0.125%) before application. The product labels do not specify the application frequency, but Pest Control Operators of California (PCOC) indicates the typical above-ground perimeter application is twice per year per product, but more than two applications per year are possible if multiple products are used (Van Steenwyk, 2016).

Handler. Handlers apply structural LC products in both pre- and post-construction stages to control termites. During pre-construction treatments (i.e., construction phases prior to the final grade installation), diluted LC products may be applied to various areas, for example beneath concrete slabs, in trenches along foundation walls, or to achieve a thorough horizontal and

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vertical barrier around the structural site. Structural LC products are also applied during the post-construction phase to protect the structure from termite infestation or control existing termite populations through trenching around the foundation, or drilling and injecting at areas where trenching is not permissible (e.g., surface with concrete pavement). In California, LC products are also used on outdoor surfaces and along structural foundation perimeters to control other home invasive pests, especially ants. PPE required on the product labels include long-sleeve shirt, long pants, socks, shoes, and chemical-resistant gloves. A respirator is also required if the handler works in a non-ventilated space such as crawl space and basement. The handler exposure for a licensed applicator was categorized as High priority in the Problem Formulation Document, and this assessment evaluated exposures from both dermal contact and inhalation (DPR, 2017).

A registrant submitted study monitored fipronil handler inhalation exposure during the application of a structural LC product, i.e., Termidor® 80 WG (Honeycutt and Kennedy, 2001). However, the submitted study lacked critical information for use in handler exposure calculations including information on the amount of fipronil applied by each handler. This study specified the application rates at 4 gallons finished solution per 10 linear feet on outer and interior walls and 2 gallons finished solution per 10 linear feet injected into foundation walls. However, the treated lengths of outer, interior, and foundation walls were not reported. Therefore, it was difficult to calculate the normalized exposure rate based on the amount of fipronil handled. In addition, this study used a product called Termidor® 80 WG, a dry powder formulation sealed in a water soluble package which is not registered in California. Termidor® 80 WG is expected to have lower handler exposure than fipronil LC product, as the formulation is securely sealed in a water-soluble bag and less likely to contact with a handler. Lastly, this study did not monitor handler dermal exposure.

Accordingly, the handler exposure was assessed using Pesticide Handlers Exposure Database (PHED) Scenario 22: Low pressure handwand mixer/loader/applicator (M/L/A) using liquid formulation (open pour) (Beauvais *et al.*, 2007). PPE of pesticide handlers in this scenario include long pants, long-sleeve shirt, and gloves, which are the same as the PPE requirements on fipronil structural LC product labels.

This assessment assumed each handler prepares and applies 40 gallons of the finished solution, which is the default pesticide volume that a low-pressure handwand M/L/A handles during a work day (USEPA, 2001). Fipronil concentration in the finished solution was assumed at 0.125%, which was the highest rate instructed on product labels. With the information above, the calculated dermal and inhalation STADDs are summarized in Table 8.

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Table 8. Inhalation and dermal fipronil exposure for handlers applying structural LC products

Exposure pathway	STADD[a] (µg/kg/d)	SADD[b] (µg/kg/d)	AADD[c] (µg/kg/d)	LADD[d] (µg/kg/d)
Dermal contact	1.4	0.50	0.29	0.17
Inhalation	0.53	0.19	0.11	0.06

a: short-term absorbed daily dose (STADD) = exposure (88.9 and 5360 µg/lb for inhalation and dermal respectively) × fipronil handled (0.42 lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
b: seasonal average daily dose (SADD) = exposure (31.9 and 1930 µg/lb for inhalation and dermal respectively) × fipronil handled (0.42 lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
c: annual average daily dose (AADD) = SADD × annual use months (7, April-October) ÷ 12;
d: lifetime average daily dose (LADD) = AADD × 40 years of work in a lifetime ÷ 70.

During the problem formulation phase, DPR invited all stakeholders to provide input relevant to fipronil risk assessment, including purposes of fipronil use in California and potential exposure scenarios. PCOC responded to the DPR request by describing an application of fipronil SC products to overhead spaces, such as under the eaves, that may result in high fipronil exposure (Van Steenwyk, 2016).

Handler fipronil exposure from overhead application may be higher due to aerosols generated from the spray. After reviewing relevant studies, no appropriate data was found to establish the assumptions for a structural overhead scenario. Therefore, the handler scenario for tree application was used as a surrogate, and because fipronil is not registered for tree applications, this assessment used a study that measured handler exposure during application of carbaryl to trees using hand-held pump (Merricks, 1998). The US EPA SOP for tree handler exposure assessment uses the same data set, and this assessment also considered this study as the best information available for this scenario (USEPA, 2012).

In Merricks (1998), 20 non-professional volunteers were recruited and asked to mix, load, and apply a carbaryl liquid concentrate product to citrus (around 8 ft tall) and ornamental (around 4 ft tall) trees. The volunteers were suited in long-sleeve shirts and long pants as working apparel. They also wore another set of long-sleeve shirts and long pants beneath the working apparel as dermal dosimeters to monitor carbaryl exposure on the body, legs and arms. Face/neck wipe and handwash samples were taken as well to monitor the exposure on face/neck and hands. This study also monitored inhalation exposure by attaching a personal pump to each volunteer. The pump was collected to a XAD-2 sorbent tube and the pump speed was set at 2 liters per minute (LPM).

This assessment used the raw data instead of the directly presented study results. First, handlers in this study did not wear gloves, while the fipronil LC product label requires gloves for handlers. Therefore, the monitored hand exposure was adjusted assuming gloves provided 90% exposure reduction. Second, the calculated 95th percentile exposure rates were smaller than the

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highest monitored values, thus the latter was used for STADD calculations (Table 9) (Frank, 2009). Same as above, each handler was assumed to apply 40 gallons 0.125% solution per day. A statistical summary of dermal and inhalation exposure rates is shown in Table 9 and the calculated exposure is provided in Table 10.

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Table 9. Dermal and inhalation exposure rates (µg/g) for handlers who mix, load, and apply carbaryl pesticides to trees using hand-held pump[a]

	Dermal									Inhalation[b]
	Forearm	Upper arm	Front torso	Back torso	Lower leg	Upper leg	Hand	Face/Neck	Total	
Mean	0.57	0.064	0.23	0.075	0.096	0.15	9.9	0.19	11	0.024
STD[c]	0.51	0.0086	0.43	0.032	0.092	0.13	12	0.46	12	0.014
Max.[d]	2.0	0.087	2.1	0.17	0.46	0.58	53	2.2	54	0.063
95th percentile[e]	2.1	0.078	0.53	0.12	0.19	0.36	25	0.38	28	0.045

a: The raw data is from Merricks (1998); b: breathing rate at 1.6 m^3/h; c: standard deviation; d: maximum; e: 95th percentile value was calculated based on the method described elsewhere (Frank, 2009).

Table 10. Inhalation and dermal fipronil exposure for handlers applying structural LC products to overhead areas

Exposure pathway	STADD[a] (µg/kg/d)	SADD[b] (µg/kg/d)	AADD[c] (µg/kg/d)	LADD[d] (µg/kg/d)
Dermal contact	6.3	1.3	0.76	0.43
Inhalation	0.17	0.07	0.04	0.02

a: short-term absorbed daily dose (STADD) = exposure (28 and 24642 µg/lb for inhalation and dermal respectively) × fipronil handled (0.42 lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
b: seasonal absorbed SADD = exposure (11 and 5020 µg/lb for inhalation and dermal respectively) × fipronil handled (0.42 lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
c: annual average daily dose (AADD) = SADD × annual use months (7, April-October) ÷ 12;
d: lifetime average daily dose (LADD) = AADD × 40 years of work in a lifetime ÷ 70.

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Post-application, resident. This scenario estimates exposure of a resident, either an adult or a child, entering a treated structure. Product labels state that contact with contaminated areas is prohibited. The labels also state that residents should not enter a treated structure before cleanup is completed and the spray is dried. However, there is no clear "restricted entry interval (REI)-equivalent" language on product labels. This assessment assumes a resident enters the treated structure immediately after the application is complete. For adults, this assessment evaluated exposures from dermal contact and inhalation, and for children, this assessed exposures were dermal contact, inhalation, and incidental oral ingestion. In the Problem Formulation document, the post-application exposure was categorized as High priority for both adults and children.

Post-application inhalation exposure occurs while aerosols from spraying remain in the air after application. Therefore, the highest air concentration is expected shortly after the application. Only one registrant submitted study that measured post-application fipronil air concentrations (Honeycutt and Kennedy, 2001). This study treated 16 houses in nine US states for termites. These houses have a range of characteristics, including size, floor number, foundation type, and were treated with solutions containing different percentage of fipronil (Table 11). The applied product was Termidor® 80 WG, which is a dry powder formulation sealed in a water soluble package. The product is applied by diluting into water. The application rate of the spraying solution was: 4 gallons finished solution per 10 linear feet on outer and interior walls, and 2 gallons finished solution per 10 linear feet injected into foundation walls.

Table 11. Characteristics of houses treated with Termidor® 80 WG

House No.	App. month[a]	Base. type[b]	State located	Story[c]	Size (sq. ft.)	Linear ft. treated	% Fipronil[d]	App. psi[e]
1	May	BA	KY	2	3193	363	0.08	25
2	June	CS	NC	2	2402	498	0.08	10-15
3	Jun.	CS	NC	2	2637	460	0.07	10-15
4	Jun.	CS	NC	N/A[f]	N/A	344	0.07-0.08	~25
5	Jun.	CS	NC	1	2048	360	0.07-0.08	15
6	Jun.	BA	MO	1	2280	443	0.08	50
7	Jul.	BA	NY	2	1586	420	0.05	25
8	Jul.	CS	SC	1	1164[g]	142	0.08	30-40
13	Aug.	SL	FL	N/A[h]	N/A	440[i]	0.08	40
14	Aug.	SL	FL	N/A	N/A	440	0.08	40
15	Aug.	SL	FL	N/A	N/A	440	0.08	40

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16	Aug.	SL	FL	N/A	N/A	440	0.08	40
17	Aug.	SL	LA	N/A[f]	N/A	142	0.125	50-70
25	Nov.	BA	KY	1	4114	312	0.08	60
26	Nov.	BA	KY	1	1320[d]	NR[j]	0.08	100
27	Dec.	BA	VA	N/A[f]	N/A	300	0.08	60

a: application month; b: basement type, including full basement (BA), crawl space (CS) and slab (SL); c: information on house story number and size was obtained from Trulia, Zillow, or Redfin, and may not be accurate; d: fipronil percent in the finished solution; e: application pressure (psi); f: Not available, this location could not be found; g: The information on story and size may not be accurate, as the zip code does not match; h: Houses 13-16 are apartments in the same community and the house information is unknown; i: This includes entire building treatment and House 13-16 are individual units within this building; j: not recorded.

Fipronil indoor air concentrations were monitored by placing sampling equipment in the kitchen, den, and bedroom. The sampling equipment consisted of an air pump run at 2.0 LPM and an attached XAD air sorbent tube positioned approximately 2 ft above the floor. The pump started collecting air samples immediately after the beginning of the fipronil application and sampled for 24 hours. Duplicate samples were collected in each room. A statistical summary of the highest concentration found at each house is provided in Table 12. For post-application exposure, this document used the highest measured 24-h time weighted average (TWA) concentration and assumed a breathing rate of 0.59 and 0.28 m^3/kg/d for child and adult respectively (Andrews, 2000). Calculated inhalation STADD and SADD values for adult and child are summarized in Table 13.

Table 12. Statistical summary of indoor air fipronil concentrations.

	24-h TWA concentration (ng/L)
Mean	0.021
Standard Deviation	0.020
Minimum	< 25 ng per sample[a]
Maximum	0.081
95th percentile[b]	0.050

a: The volume of air pumped varied among samples. This is approximately 0.0087 ng/L; b: 95th percentile value was calculated based on the method described elsewhere (Frank, 2009).

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Table 13. Fipronil inhalation exposure in a post-application indoor environment.

Human receptor	Exposure pathway	STADD[a] (µg/kg/d)	SADD[b] (µg/kg/d)
Adult	Inhalation	0.023	0.006
Child	Inhalation	0.048	0.012

a: short-term absorbed daily dose (STADD) = maximum 24-h TWA concentration (0.081 ng/L) × inhalation rate (0.59 and 0.28 m^3/kg/d for child and adult respectively);
b: seasonal average daily dose (SADD) = average 24-h TWA concentration (0.021 ng/L) × inhalation rate (0.59 and 0.28 m^3/kg/d for child and adult respectively).

This assessment considers fipronil treated in outdoor areas may be transferred into indoor surfaces through various ways, including spray drift, or by wind or foot track, and post-application dermal and oral exposure occurs when a resident is in contact with fipronil contaminated indoor surfaces. This assessment reviewed available information including registrant submitted studies and open literature and did not find data on indoor deposition of fipronil following outdoor treatments with structural LC product. In addition, no study has measured fipronil occurrence in indoor areas in California. This assessment used a study conducted by US Geological Survey (USGS) in Austin, TX as it is considered as the best information available (Mahler *et al.*, 2009).

The USGS study collected dust samples from 24 apartments using a high-volume surface sampler. Eighteen of the 24 sampled surfaces were carpeted and 16 surfaces were hard floor (concrete, wood, linoleum or tile). The collected dust was analyzed for fipronil and two degradates, i.e., fipronil desulfinyl and fipronil sulfone.

The raw data was obtained from the author by permission and further analyzed. The USGS study did not collect information on the number of days that elapsed between fipronil treatments and the sampling. Therefore, for purposes of this assessment, HHA assumed all fipronil degradates were formed from the same application event and the total concentration of all three fipronil compounds (parent fipronil and two measured degradates) was used to represent the maximum amount of fipronil deposited on indoor surfaces. Second, the USGS study fractionated the collected dust and analyzed the <0.05 mm fraction. To extrapolate the total surface concentration, it was assumed all particles had the same fipronil concentration. Third, the measured fipronil amount was divided by the surface area sampled to calculate the surface area-normalized concentration. A statistical summary of the recalculated data is provided in Table 14.

Table 14. Statistical summary of total fipronil compound concentrations on indoor surfaces[a]

	Concentration of total fipronil[b] (ng/m^2)
Mean	9622
Standard Deviation	28253

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Minimum	2.8
Maximum	128931
95th percentile	20296

a: Raw data is cited from Mahler et al. (2009); b: Total concentration of fipronil and 2 measured degradates; b: 95th percentile value was calculated based on the method described elsewhere (Frank, 2009).

Dermal and oral exposure was assessed following the US EPA SOP (USEPA, 2012) and the maximum concentration in Table 14 was used for the calculations (Frank, 2009). Calculated STADDs and SADDs are summarized in Table 15.

Table 15. Post-application dermal and oral exposure from fipronil in indoor space

Human receptor	Exposure pathway	STADD[a] (µg/kg/d)	SADD[b] (µg/kg/d)
Adult	Dermal contact[c]	0.026	0.002
Child	Dermal contact	0.018	0.001
	Oral, hand-to-mouth[d]	0.064	0.005
	Oral, object-to-mouth	0.0086	0.001
	Oral, total	0.073	0.005

a: short-term absorbed daily dose (STADD) was calculated using the maximum value of fipronil on indoor space in Table 14;
b: seasonal average daily dose (SADD) was calculated using the mean value of fipronil on indoor space in Table 14;
c: STADD and SADD (dermal) = fipronil concentration (0.013 and 0.001 µg/cm^2 for STADD and SADD respectively) × transferable fraction (0.06) × transfer coefficient (6800 and 1800 cm^2/hr for adult and child respectively) × exposure time (8 and 4 hr for adult and child respectively) × dermal absorption rate (0.043) ÷ body weight (70 and 13 kg for adult and child respectively);
d: STADD and SADD (oral, hand-to-mouth and object-to-mouth) calculation equations can be found on USEPA SOP page 7-39 and 7-44 (USEPA, 2012).

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D. Pet spray products

Fipronil spray products are used by both professional groomers and home users to treat ticks and fleas on dogs and cats. The products are packaged in aerosol or triggered spray cans. The fipronil concentration is 0.29%. For products in trigger spray cans, labels suggest one to two pumps per pound of dog and/or cat body weight. For products in aerosol cans, labels suggest spraying one to two seconds per pound of dog and/or cat body weight (pets with long or dense coats may need a higher application rate). The label language directs that dog or cat head and eye areas should be treated by spraying the product onto a gloved hand and then rubbing the product into the hair. The spray product labels suggest monthly application for effective tick/flea controls. The only PPE required on the product labels is gloves (e.g., latex or nitrile gloves).

Applicator, pet groomer. Professional groomers, including commercial and veterinary groomers, were selected as the representative of frequent fipronil handlers. Professional groomers treat dogs and/or cats on a daily basis and handle more pets than pet owners. Their fipronil exposure was categorized as High priority in the Problem Formulation document. This assessment evaluated exposures from both inhalation and dermal contact.

This assessment reviewed relevant studies and only found one registrant submitted study that measured dermal and inhalation exposure of professional groomers from using fipronil spray products (Meo *et al.*, 1997). This study recruited sixteen groomers and each groomer treated eight dogs (except one groomer that treated nine dogs) using Frontline® spray. The groomers followed the label instructions by applying two pumps (~3 mL) of the product per pound of the dogs. The amount of fipronil used by each groomer was estimated by counting the number of pumps of the product applied (Table 16). All the groomers in this study wore latex gloves, short-sleeved cotton shirt, long-cotton pants, long-sleeved ribbed cuff smock, socks and shoes.

Table 16. Time and total amount of fipronil used by individual professional groomer when treating dogs using Frontline® spray[a]

Groomer No.	Length of treatment (min)	Dog weight[b] (lbs)	Fipronil applied (mg)
1	52	39 (7-70)	1505
2	55	23 (6-67)	1077
3	48	29 (12-70)	1483
4	49	28 (8-72)	1581
5	70	31 (11-75)	2118
6[c]	68	57 (13-122)	2907
7	59	28 (5-86)	1657

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8	48	18 (11-33)	1147
9	60	25 (7-48)	1643
10	48	45 (12-78)	2959
11	63	25 (7-37)	1717
12	49	21 (12-45)	1115
13	49	28 (8-46)	1484
14	61	36 (13-75)	2389
15	38	21 (7-45)	859
16	72	58 (13-89)	2733

a: The raw data is cited from Meo et al. (1997); b: mean (minimum-maximum); c: this groomer treated nine dogs.

Each groomer was asked to wear a long whole-body suit as the dosimeter to monitor body dermal exposure. The suit was worn underneath the work clothing and PPE, but over the undergarments. Hand exposure was measured by asking each groomer to wear a pair of cotton gloves underneath the latex gloves when treating dogs. Face and neck exposure was measured by wiping the groomer's face and neck with ethanol cloth patches after the dog treatment.

Inhalation exposure was monitored by attaching an air-sampling pump to each groomer and the pump ran at 1.5 LPM during the entire dog treatment period. The pump was attached to a cassette that contained a glass fiber filter (1 µm pore size) and a cellulose support pad to retain fipronil in aerosol phase, and a Chromosorb 102 tube to retain fipronil in vapor phase.

This assessment used raw data provided in the report appendix and work apparel adjustments were made before the data being used for exposure assessment. A whole-body suit was used as the dermal dosimeter and each groomer also wore a long-sleeved smock, a short-sleeved shirt and long pants over the suit. The groomers also wore latex gloves over the cotton gloves that were used to monitor hand exposure. These PPE and apparel are not required by the label and, so, are not required to be used by the groomers in California. A registrant submitted survey showed professional groomers often do not wear a uniform or PPE (other than gloves) while treating dogs and/or cats (Irwin, 1997). This assessment assumes the working apparel for groomers include short-sleeved shirt and long pants. Calculated dermal exposure on different body parts assumes one layer of clothes provides a 90% exposure reduction. A statistical summary of the re-calculated dermal and inhalation exposure measures are provided in Table 17.

Table 17. Dermal and inhalation exposure (μg/g) of professional groomers who used a pet spray product to treat dogs[a]

	Dermal[b]								Inhalation[c]		
	Forearm	Upper arm	Chest	Back	Lower body	Face/Neck	Hand	Total	Aerosol	Vapor	Total
Mean	6740	902	259	7.0	105	4.1	8.3	8024	9.5	0.84	10
STD[d]	6350	1331	430	4.2	367	3.1	10	6611	7.6	0.49	7.6
Max.[e]	25840	4457	1735	15	1527	10	34	26347	29	2.3	30
95th percentile[f]	27629	5555	1305	16	158	13	31	31788	32	1.7	33

a: The raw data is obtained from Meo et al. (1997); b: Exposure on forearm, upper arm, chest, back and lower body was multiplied by 10 as one extra layer of work apparel was used in the study and the protection factor was assumed at 90%; c: breathing rate at 1.6 m^3/h; d: standard deviation; e: maximum; f: 95th percentile value was calculated based on the method described elsewhere (Frank, 2009).

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The amount of fipronil applied daily depends on the number of dogs and/or cats treated by a groomer and the size of treated dogs and/or cats. A registrant submitted survey indicates a commercial groomer treated an average of 9.62 dogs and/or cats per day, and a veterinary groomer treated an average of 4.1 dogs and/or cats per day (Irwin, 1997). This assessment assumed a pet groomer treats 10 dogs per day. This assessment also assumed the number of small (14 lbs), medium (33 lbs) and large (66 lbs) dogs treated is four, three, and three respectively, which is based on a national survey conducted by American Veterinary Medical Association (AVMA) in 2012 that showed 39.2%, 33.4 % and 27.3 % of US dogs are in small, medium and large size, respectively (AVMA, 2012). The calculated dermal and inhalation exposure are summarized in Table 18.

Table 18. Dermal and inhalation exposure for pet groomers using a spray product

Exposure pathway	STADD[a] (µg/kg/d)	SADD[b] (µg/kg/d)	AADD[c] (µg/kg/d)	LADD[d] (µg/kg/d)
Dermal contact	52	12	12	7.3
Inhalation	1.2	0.37	0.37	0.21

a: short-term absorbed daily dose (STADD) = exposure (33 and 31788 µg/g for inhalation and dermal respectively) × fipronil handled (2.6 g/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
b: seasonal average daily dose (SADD) = exposure (10 and 8024 µg/g for inhalation and dermal respectively) × fipronil handled (2.6 g/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
c: annual average daily dose (AADD) is the same as SADD. There is no data to analyze use pattern of pet spray products over a year, so this assessment assumes year round use;
d: lifetime average daily dose (LADD) = AADD × 40 years of work in a lifetime ÷ 70.

Applicator, home user. Spray products can also be used by pet owners to treat their own dogs and/or cats. The exposure estimates, i.e., dermal and inhalation exposure per gram of fipronil handled, are expected similar to pet groomers, but the pet owner is assumed to treated fewer dogs and/or cats per day. In the Problem Formulation document, pet owner exposure as spray product handler is categorized as High priority (DPR, 2016).

This assessment used the same registrant study above to assess pet owner exposure (Meo et al., 1997). This assessment assumes a pet owner has two dogs. This is based on the AVMA survey which showed 62.9% households own one or two pets, and the average number of pets per household is 1.5 (AVMA, 2012). The same survey also showed the average number of dogs in dog-owning households in California is 1.6. This assessment assumes a pet owner treats two large size (66 lbs) dogs per month, and the calculated dermal and inhalation STADDs are summarized in Table 19. Only STADDs are calculated, as the pet owners are expected to use these products once per month as suggested on the labels.

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Table 19. Dermal and inhalation exposure for a home user using a spray product

Exposure pathway	STADD (µg/kg/d)
Dermal contact	19
Inhalation	0.4

a: 95th percentile values in Table 17 are used to calculate STADDs (Frank, 2009);
b: short-term absorbed daily dose (STADD) = exposure × fipronil handled (0.74 g/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg).

Post-application, resident. This is the exposure scenario for a pet owner, either an adult or a child, contacting dogs and/or cats treated with spray products. In the Problem Formulation document, the post-application exposure was categorized as Medium and High priority for adult and child, respectively, for this exposure scenario (DPR, 2016). For adults, this assessment evaluated post-application exposures from dermal contact, and for children, the assessed exposure pathways were dermal contact and incidental oral ingestion. Considering the low volatility of fipronil and the small amount applied for pet products, this assessment determined the post-application inhalation exposures were negligible. This agrees with US EPA guidelines, and in the latest US EPA fipronil risk assessment, post-application inhalation exposures were not assessed either for pet product (USEPA, 2012; USEPA, 2020).

Post-application exposure is determined by dislodgeable fipronil residue on treated dogs and/or cats that is readily transferable to humans. This assessment reviewed all four registrant submitted studies and used them to determine the dislodgeable fipronil residue (de Fontenay *et al.*, 1997c; de Fontenay *et al.*, 1997d; Hughes, 1997a; Hughes, 1997b). These four studies have similar study design and sampling strategies. In one study, six Beagle dogs were weighed and treated with Frontline® spray (fipronil content: 0.29%, w/w) at the label rate (i.e., 6 ml/kg dog weight) (de Fontenay *et al.*, 1997c). After treatment, the study investigator wore a cotton glove and petted the whole-body surface of the dog with the glove-wearing hand by stroking five times from the head to the tail, i.e., one stroke each on the back, right and left flank, and right and left side of the ventral zone. Fipronil amount collected on the glove was measured as the dislodgeable fipronil residue on the dog. The same dogs were petted in the same way at different post-treatment intervals, i.e., 0 d (before treatment), 1 hour, 4 hours, 8 hours, and post-application days 1, 2, 4, 7, 14, 21, and 28 to determine the dissipation of dislodgeable fipronil residue.

A summary of findings from these four studies is provided in Table 20. In de Fontenay et al. (1997a), each dog was treated with 125,671 to 148,491 µg fipronil. At 1 h (the sampling interval closest to the treatment), the measured dislodgeable fipronil residue was 653-2674 µg, which is equivalent to 0.52-1.06 % of the application rate. The highest dislodgeable residue (1053-2674 µg or 0.83-2.06 % of application rate) was seen at 4 h following application of fipronil. Two

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fipronil degradates, i.e., fipronil sulfide and sulfone, were also detected on the gloves, but their total concentrations were <5% of fipronil at both 1 and 4 h post treatment.

The 95th percentile dislodgeable fipronil residue was calculated from these studies (Frank, 2009). The highest value was 2.2% of the application rate (Table 20). This value is slightly higher than the US EPA SOP default value of 2% of applied rate dislodgeable fraction. This assessment assumes 2.20% of the applied fipronil is available to transfer. It is also assuming the treated dog is large in size (66 lbs) and has the body surface area of 11000 cm^2. According to US EPA SOP, a large-size dog has the largest body weight-surface area ratio and hence the highest transferable residue per dog surface area (USEPA, 2012). The calculated dermal and oral STADDs are summarized in Table 21.

Table 20. Summary of fipronil dislodgeable residues on pets treated with pet spray products

Source	Dislodgeable fipronil residue			Comment
	Range	Mean ± STD.[b]	95th percentile[c]	
de Fontenay et al., 1997a	0.83-2.06%	1.37±0.44 %	2.20%	Six Beagle dogs. Highest dislodgeable residues were seen at 4 h.
Hughes, 1997a	Short-haired: 0.44-1.37%	Short-haired: 0.84±0.36 %	Short-haired: 1.58 %	Five short-haired dogs. Highest dislodgeable residues were seen mostly at 12 h.
	Long-haired: 0.43-0.84%	Long-haired: 0.67±0.13 %	Long-haired: 0.95 %	Five long-haired dogs. Highest dislodgeable residues were seen mostly at 4 h.
de Fontenay et al., 1997b	0.49-0.91 %	0.68±0.15 %	0.95 %	Six cats. Highest dislodgeable residues were seen mostly at 4 h.
Hughes, 1997b	0.20-0.54 %	0.43±0.12 %	0.73 %	Five cats. Highest dislodgeable residues were seen mostly at 4 h.

a: highest dislodgeable fipronil residue on each dog, and expressed as % of the application rate; b: mean ± standard deviation; c: 95th percentile value was calculated based on measured concentrations (Frank, 2009).

Table 21. Post-application dermal and oral exposure for pet spray products

Human receptor	Exposure pathway	STADD[a] (µg/kg/d)	SADD[b] (µg/kg/d)
Adult	Dermal contact[c]	2.4	1.5
Child	Dermal contact	4.6	2.9
	Oral, hand-to-mouth	1.1	0.7

a: short-term absorbed daily dose (STADD)s were calculated using the maximum dislodgeable fipronil percentile (2.2%) in Table 20;

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b: seasonal average daily dose (SADD)s were calculated using the mean value of dislodgeable fipronil percentile (1.37%) in Table 20 from de Fontenay et al., 1997a;
c: short-term absorbed daily dose (STADD) and SADD (dermal) = applied fipronil amount (495 mg) × dislodgeable fraction (0.022 and 0.0137 for STADD and SADD respectively) ÷ pet surface area (11000 cm^2) × transfer coefficient (5200 and 1400 cm^2/h for adult and child respectively) × exposure time (0.77 and 1 h for adult and child respectively) ÷ body weight (70 and 13 kg for adult and child respectively) × dermal absorption rate (0.043);
b: short-term absorbed daily dose (STADD) and SADD (oral, hand-to-mouth) calculation equations can be found on USEPA SOP page 7-39 and 7-44 (USEPA, 2012).

E. Pet spot-on products

Fipronil is also formulated as spot-on products and used by professional groomers and pet owners to treat dogs and/or cats. The products are contained in small pre-measured tubes and contain fipronil up to 9.8 %. During each application, the applicator selects a tube with the size appropriate to the treated the dog or cat and applies the entire tube contents onto the skin between the shoulder blades of the dog or cat (Table 22). The treated area should not be contacted until dry, and a dog or cat should not be treated more than once per month.

Table 22. Selection of tube size according to the treated pet size

Weight range	Tube size (mL)	Application rate (mg)
Cat	0.50	5.0
Dog, 5-22 lbs	0.67	6.7
Dog, 23-44 lbs	1.34	13.4
Dog, 45-88 lbs	2.68	26.8
Dog, 89-132 lbs	4.02	40.2

This chart is based on Frontline® Top Spot® for dogs and cats. The weight range, tube size, and application rates may be slightly different for other spot-on products.

Applicator, pet groomer. Professional groomers were selected as the representative of frequent handlers of fipronil spot-on products. Their fipronil exposure was categorized as High priority in the Problem Formulation document. As the products are in liquid formulation and applied by squeezing a tube of contents onto a pet, the inhalation exposure is considered negligible (USEPA, 2012). This assessment only evaluated applicator exposure from dermal contact.

This assessment reviewed available data, including registrant submitted studies and open literature, and selected a registrant submitted study based on the data quality and completeness (Meo *et al.*, 1997). This study measured dermal exposure of professional groomers during the application of fipronil spot-on product. Sixteen commercial pet groomers were recruited and each groomer was asked to treat eight dogs using Frontline® Top Spot™. The working apparel and PPE of these groomers include long-cotton pants, long-sleeved smock, short-sleeved shirt, latex gloves, socks and shoes. The average amount of fipronil applied by each groomer during the day was 1047 mg fipronil, with a range of 670-1809 mg (Table 23).

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Table 23. Time and total amount of fipronil used by individual professional groomer when treating dogs using Frontline® Top Spot™

Groomer	Length of treatment (min)	Fipronil applied (mg)	Weight range of treated dogs (lbs)
1	26	1072	7-79
2	25	938	8-83
3	32	1139	11-72
4	14	737	7-30
5	26	1474	13-96
6	21	737	9-50
7	21	1809	12-170
8	17	804	3-55
9	17	1139	12-115
10	17	670	8-37
11	22	938	11-75
12	19	871	8-62
13	17	871	6-71
14	17	1206	4-80
15	18	1139	13-75
16	15	1206	9-68

The raw data is cited from Meo et al., 1997.

The fipronil dermal exposure was monitored using the same method described above for groomers using the spray product. Briefly, each groomer wore a long whole-body suit to monitor body exposure except for the face, neck and hands. The suit was worn underneath the work apparel, but over the undergarments. Hand exposure was measured by asking each groomer to wear a pair of cotton gloves underneath the latex gloves when treating dogs. Face and neck exposure was measured by wiping the groomer's face and neck with ethanol-wetted cotton patches after the dog treatment.

This assessment used the raw data provided in the appendix instead of the summary of results presented directly in the report. In this study, a whole-body suit was used as the dermal

dosimeter and each groomer wore a long-sleeved smock, a short-sleeved shirt, and long pants over the suit. The cotton gloves were worn underneath latex gloves. However, long-sleeved smock and gloves are not required by the label and so, are not required to be used by the groomers in California. This assessment assumes the working apparel for groomers include short-sleeved shirt, long pants, socks and shoes, and recalculated the dermal exposure by assuming one layer of clothes provides 90% exposure reduction. A statistical summary of the re-calculated dermal exposure on different body parts are provided in Table 24.

As the maximum observed exposure value is greater than the estimated 95th percentile value, the maximum value in Table 24 was used to calculate the dermal exposure (Powell, 2002). Similar to the spray product, this assessment assumes a pet groomer treats 10 dogs per day, including four small-size (14 lbs) dogs, three medium-size (33 lbs) dogs and three large-size (66 lbs) dogs. Accordingly, the pet groomer uses four 0.67 mL tubes, three 1.34 mL tubes and three 2.68 mL tubes, and total applied fipronil is 1474 mg. The calculated dermal exposure is shown in Table 25.

Table 24. Dermal exposure of professional groomers who used a pet spot-on product to treat dogs

	Dermal[b] (µg/g)							
	Forearm	Upper arm	Chest	Back	Lower body	Face/ Neck	Hand	Total
Mean	130	157	383	14	8.1	14	80	787
STD[c]	251	430	1107	33	22	42	153	1270
Max.[d]	781	1693	4533	142	94	175	528	4591
95th %ile[e]	407	272	660	31	17.5	33.8	349.1	3579

a: The raw data is cited from Meo et al. (1997); b: Exposure on forearm, upper arm, chest, back and lower body was multiplied by 10 as one extra layer of work apparel was used in the study and the protection factor was assumed at 90%; c: standard deviation; d: maximum.; e: estimated 95th percentile of the distribution of concentrations based upon measured concentrations (Frank, 2009).

Table 25. Dermal exposure for groomers using pet spot-on products.

Human receptor	Exposure pathway	STADD[a] (µg/kg/d)	SADD[b] (µg/kg/d)	AADD[c] (µg/kg/d)	LADD[d] (µg/kg/d)
Adult	Dermal contact	4.2	0.73	0.73	0.41

a: short-term absorbed daily dose (STADD) = exposure (4591 µg/g) × fipronil handled (1.5 g/d) × absorption rate (0.043) ÷ body weight (70kg);
b: seasonal average daily dose (SADD) = exposure (787 µg/g) × fipronil handled (1.5 g/d) × absorption rate (0.043) ÷ body weight (70kg);
c: annual average daily dose (AADD) is the same as SADD. There is no data to analyze use pattern of pet spot-on products over a year;
d: lifetime average daily dose (LADD) = AADD × 40 years of work in a lifetime ÷ 70.

Applicator, home user. Pet owners may use spot-on products to treat their own dogs and/or cats. Dermal exposure per gram of fipronil handled is expected the same as pet groomers, but the pet owner is assumed to treat the dogs/ cats once per month. Product labels do not require pet owners to use gloves, or wash hands after application. In the Problem Formulation, pet owner exposure as spot-on product handler is categorized as High priority.

This assessment assumed dermal exposure estimate for pet owner is the same as professional groomer, and the same registrant study was used for assessment (Meo et al., 1997). This assessment also assumes a pet owner has two large size (66 lbs) dogs. Accordingly, the pet groomer uses two 2.68 mL tubes, and total applied fipronil is 536 mg. The calculated dermal exposure is shown in Table 26. Only STADDs are calculated, as the pet owners are expected to use these products once per month as suggested on the labels.

Table 26. Dermal exposure for a home user using pet spot-on products.

Human receptor	Exposure pathway	STADD[a] (µg/kg/d)
Adult	Dermal contact	1.5

a: short-term absorbed daily dose (STADD) = exposure (4591 µg/g) × fipronil handled (0.54 g/d) × absorption rate (0.043) ÷ body weight (70kg).

Post-application, resident. This is the exposure scenario for a pet owner, either an adult or a child, contacting dogs/cats treated with spot-on products. In the Problem Formulation, the post-application exposure was categorized as Medium and High priority for adult and child, respectively. As stated earlier for pet spray products, the post-application inhalation exposures were determined negligible (USEPA, 2012; USEPA, 2020). For adults, this assessment evaluated exposures from dermal contact, and for children, the assessed exposure pathways were dermal contact and incidental oral ingestion.

This assessment reviewed all four studies submitted by registrants that measured dislodgeable fipronil residues on spot-on treated dogs and/or cats (de Fontenay *et al.*, 1997b; de Fontenay *et al.*, 1997a; Hughes, 1997c; Hughes, 1997d). These studies had similar design and sampling strategies as the pet spray product. For instance, in one study from de Fontenay et al., six Beagle dogs, weighing approximately 10 kg each, were treated with Frontline (fipronil content: 9.83%) (de Fontenay *et al.*, 1997b). The applied fipronil amount for each dog was 172 mg. The study investigator measured dislodgeable fipronil residues on each treated dog by wearing a cotton glove and stroking the whole body surface of the dog. The amount of fipronil transferred onto the glove was used to represent the dislodgeable residue.

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A summary of findings from these four studies is provided in Table 27. Among these four studies, the highest fipronil dislodgeable residue was seen on fipronil-treated cats in de Fontenay et al. (1997c). The 95th percentile value was 16.77 % of the application rate.

Table 27. Summary of dislodgeable fipronil residue on dogs or cats after treatments with Frontline® spot-on

Source	Dislodgeable fipronil residue[a]			Comment
	Range	Ave. ± Stdev.[b]	95th percentile[c]	
de Fontenay et al., 1997c	2.13-13.63%	6.46±4.91%	16.77%	Six cats. Highest dislodgeable residues were seen at 1 h.
de Fontenay et al., 1997d	0.38-3.12%	1.21±0.91%	2.84%	Six Beagle dogs. Highest dislodgeable residues were mostly seen at 4 h.
Hughes, 1997c	0.40-1.65%	1.02±0.51%	2.20%	Five cats. Highest dislodgeable residues were seen mostly at 4 h.
Hughes, 1997d	Short-haired: 0.36-1.16%	Short-haired: 0.80±0.28 %	Short-haired: 1.47 %	Five short-haired dogs. Highest dislodgeable residues were seen mostly within 2 d after treatment.
	Long-haired: 0.45-1.29%	Long-haired: 0.67±0.31	Long-haired: 1.16%	Five long-haired dogs. Highest dislodgeable residues were seen mostly at 4 h.

a: highest dislodgeable fipronil residue on each dog or cat, and expressed as % of the application rate; b: mean ± standard deviation; c: 95th percentile value was calculated based on measured concentrations (Frank, 2009).

The calculated 95th percentile value (16.77%) was selected as the fraction of application rate that is readily transferable to humans (Powell, 2002). The pet selected was a small-size cat with 1500 cm^2 body surface area. According to the US EPA SOP, a small size cat has the largest body weight-surface area ratio for spot-on products and hence the highest transferable residue per pet surface area (US EPA, 2012). The post-application exposure was calculated in the same way as described above for spray product, and the calculated short- (STADD) and intermediate-term (SADD) dermal and oral exposures were summarized in Table 28.

Table 28. Post-application dermal and oral exposure for pet spot-on products

Human receptor	Exposure pathway	STADD[a] (µg/kg/d)	SADD (µg/kg/d)
Adult	Dermal contact[c]	1.4	0.55
Child	Dermal contact	2.6	1.0
	Oral, hand-to-mouth[d]	0.60	0.24

a: short-term absorbed daily dose (STADD) was calculated using the maximum dislodgeable fipronil percentile (16.77%) in Table 27;
b: seasonal average daily dose (SADD) was calculated using the mean value of dislodgeable fipronil percentile (6.46%) in Table 27 from de Fontenay et al., 1997c;
c: STADD and SADD (dermal) = Applied fipronil amount (5 mg) × Dislodgeable fraction (0.17 and 0.06 for STADD and SADD respectively) ÷ Pet surface area (1500 cm^2) × Transfer coefficient (5200 and 1400 cm^2/h for adult and child respectively) × Exposure time (0.77 and 1 h for adult and child respectively) ÷ Body weight (70 and 13 kg for adult and child respectively) × Dermal absorption rate (0.043);
d: STADD and AADD (oral, hand-to-mouth) calculation equations can be found on US EPA SOP page 7-39 and 7-44 (USEPA, 2012).

F. Turf granule products

These products are formulated as granules and used to treat fire ants on turf. Turf product use is restricted to licensed applicators and applications can only be made in Coachella Valley from April through September. The highest fipronil content in this group of products is 0.1 %. The maximum application rate is 0.0125 lbs fipronil per acre, and the product may not be applied more than once per year. The label also suggests irrigating the treated turf after application for best fire ant control.

Handler. This exposure scenario is for licensed applicators using broadcast equipment to apply fipronil turf granule products Applicators are required to wear long sleeved shirt, long pants, waterproof gloves, socks, and shoes while handling the product. In the Problem Formulation Document (DPR, 2016), handler exposure was categorized as Medium priority. This assessment evaluated exposures from dermal contact and inhalation.

As there is no fipronil-specific data on turf granule products handler exposure. Therefore, the PHED database was used as a surrogate to calculate handler exposure. The calculation is based on HS-1826 Scenario 27, i.e., a mixer/loader/applicator (M/L/A) applying granular formulation with a belly grinder (Beauvais *et al.*, 2007). This scenario includes data for an M/L/A wearing long pants, long-sleeves shirt and gloves, which is consistent with the requirements on the fipronil turf granule product labels. This assessment also assumed each applicator can treat one acre per day using belly grinder, and the application rate is 0.0125 lbs fipronil per acre (USEPA, 2001). The calculated dermal and inhalation exposure are summarized in Table 29.

Table 29. Handler dermal and inhalation exposure for turf granule products.

Human receptor	Exposure pathway	STADD[a] (µg/kg/d)	SADD[b] (µg/kg/d)	AADD[c] (µg/kg/d)	LADD[d] (µg/kg/d)
Adult	Dermal contact	0.66	0.24	0.12	0.068
	Inhalation	0.048	0.017	0.009	0.005

a: short-term absorbed daily dose (STADD) = Exposure (86400 and 266 µg/lb for dermal and inhalation respectively) × fipronil handled (0.0125 lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
b: seasonal average daily dose (SADD) = Exposure (31100 and 95.5 µg/lb for dermal and inhalation respectively) × fipronil handled (0.0125 lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
c: annual average daily dose (AADD) = SADD × annual use months (6, April-September) ÷ 12

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d: lifetime average daily dose (LADD) = AADD × 40 years of work in a lifetime ÷ 70

Post-Application, resident. This exposure scenario is for an adult or a child entering a treated turf area. In the Problem Formulation, the post-application exposure was categorized as High priority for both adult and child. For adults, this assessment evaluated post-application exposures from dermal contact, and for children, the assessed exposure pathways were dermal contact and incidental oral ingestion. The post-application inhalation exposures from turf products were considered minimal, due to the low vapor pressure of fipronil and dilution in outdoor air (USEPA, 2012; USEPA, 2020).

The post-application exposure is determined by transferable turf residue (TTR), which is the portion of applied pesticide readily transferable to humans. There was a registrant submitted study that measured fipronil TTR after granular formulation treatment and is used in this assessment to determine TTR (Macy, 1998).

This study was conducted in California and North Carolina. Turf plots at each location were treated with a 0.1% fipronil granular formulation at 0.025 lbs A.I. per acre (140.1 ng/cm^2). The treated plots were then irrigated with approximately 0.25 in water, either within four hours or 48 hours after the application at different post-application intervals, fipronil TTR was measured using the "California Roller" method. Fipronil TTRs were below the 0.0736 ng/cm^2 at all post-application intervals at the California site.

As the fipronil application rate in this study is twice of the maximum rate allowed in California (0.0125 lbs A.I. per acre.), this assessment expected the TTR at the California maximum application rate to be <0.0736 ng/cm^2. This assessment used 1/2 of the value, i.e., 0.0368 ng/cm^2, as the TTR value to calculate adult and child post-application exposure. Following the US EPA SOP, this assessment also assumes an adult receives dermal exposure through normal physical activities and when mowing the treated turf. This assessment assumes a child will receive non-dietary oral exposure through hand-to-mouth, object-to-mouth, incidental soil ingestion and episodic granular ingestion. The calculated dermal and oral STADDs for adult and child are summarized in Table 30.

Table 30. Post-application dermal and oral exposure for turf granule product.

Human receptor	Exposure pathway	STADD[a] (µg/kg/d)
Adult	Dermal, normal physical activity[b]	0.0068
	Dermal, Mowing[c]	0.00012
	Total dermal	0.0069

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Child	Dermal, normal physical activity	0.0098
	Oral, hand-to-mouth	0.0021
	Oral, object-to-mouth	0.00013
	Oral, incidental soil ingestion	0.00036
	Oral, episodic granular ingestion	23
	Total oral	23

a: short-term absorbed daily dose (STADD) (dermal, normal physical activity) = TTR (0.0368 ng/cm^2) × transfer coefficient (200000 and 54000 cm^2/h for adult and child respectively) × exposure time (1.5 h) ÷ body weight (70 and 13 kg for adult and child respectively) × dermal absorption rate (0.043);
b: short-term absorbed daily dose (STADD) (dermal, mowing) = TTR (0.0368 ng/cm^2) × transfer coefficient (5500 cm^2/h) × exposure time (1 h) ÷ body weight (70 kg) × dermal absorption rate (0.043);
c: short-term absorbed daily dose (STADD) (oral, hand-to-mouth, object-to-mouth and incidental soil ingestion and episodic granular ingestion) calculation equations can be found on USEPA SOP page 3-14, 3-18, 3-22 and 3-24 (USEPA, 2012); the exposure time is 1.5 h.

G. Structural bait gel/strip products

This contains a group of RTU products with fipronil formulation packed as syringe tubes or strips. Fipronil content ranges from 0.001% to 0.01% (w/w). The bait gel product is applied by depressing the syringe plunger and applying appropriate amount (e.g., dime-size) to the target surface. The strip product is applied by peeling off the cover film and placing the strip on the target surface. The products can be applied to both indoor and outdoor areas with suspected pest activities, such as cracks and crevices. Each application is effective for up to a month.

Post-application, resident. This exposure scenario is for an adult or a child in contact with indoor surfaces of a treated structure. These products do not have a REI-equivalent statement, therefore a resident may enter the treated indoor areas immediately after fipronil treatment. For adults, this assessment evaluated post-application exposures from dermal contact, and for children, the assessed exposure pathways were dermal contact and incidental oral ingestion. The post-application inhalation exposures were determined minimal considering the low vapor pressure of fipronil and low amount applied.

There is no fipronil-specific study measuring post-application exposure for the bait gel/strip products. Exposure information on structural bait gel/strip products is also scarce. There is no exposure scenario directly corresponding to bait gel/strip products in the US EPA SOP. This assessment followed the US EPA guidelines for indoor crack and crevice post-application and used monitoring data from a surrogate pesticide with application method similar to fipronil bait gel/strip products (USEPA, 2012). Details of the assessment method are provided below.

This assessment did not use the default 0.3 μg/cm as surface deposited residue in the US EPA SOP because this value is too high for fipronil bait products and might significantly overestimate

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the exposure (USEPA, 2012). In the US EPA SOP, crack and crevice application is defined as "an application of pesticides with the use of a pin stream nozzle, into cracks and crevices in which pests hide or through which they may enter a building" (USEPA, 2012). Crack and crevice application was considered similar to perimeter pin stream application, but with a smaller treated area. For crack and crevice application, the US EPA SOP assumes the default deposition rate for untreated area is 10 % of the application rate, which is expected to be higher than bait products.

Structural bait gel/strip products are applied to similar areas as crack and crevice applications. However, these products are applied in a non-continuous fashion. The application rates for structural bait gel/strip products are also lower. Using the default 0.3 $\mu g/cm^2$ surface deposition rate and the product with the highest fipronil content (i.e., 30 g with 0.01% fipronil), it was determined that a 10 m^2 area will need 10 gel/strip products to be sufficient. Therefore, this assessment only followed the US EPA's method for crack and crevice application for post-application exposure assessment, but determined the surface deposition residue using a separate registrant submitted study (Rosenheck and Schuster, 1995). The pesticide used in this study is abamectin, which is also a non-volatile, hydrophobic compound with use similar as fipronil.

This study used two abamectin products: 1) a flowable dust formulation (abamectin content: 0.05%; density: 0.67 g/cm^3) packed in a squeeze tube with a long, narrow spout; and, 2) a pressurized gel formulation (abamectin content: 0.05%, density: 1.05 g/cm^3) in a non-aerosol spray pump bottle fitted with a plastic extension tube. These products were applied in hotel rooms behind tile, behind bed headboards, into wall voids, into heaters, into cracks next to cabinets, and spaces behind baseboards. Approximately 0.15 g of the product was dispensed at each testing location and approximately 24 baits were placed per 100 square feet. The applied abamectin amount in each room is summarized in Table 31.

Abamectin surface depositions were measured by placing two pieces of 100% cotton cloth (29×59 cm) in the treated room. One piece of cloth was placed on the floor and the other was placed on the bed. Each set of cloths was at placed and retrieved at different times to monitor abamectin deposition during different post-application intervals, i.e., -2-0 h (pre-treatment), 0-0.5 h, 0.5-2 h, 2-12 h, 12-24 h and 24-48 h. The abamectin levels were below the minimum quantifiable level (MQL) (102 ng, or 0.06 ng/cm^2) for all cloth samples.

Avert® Prescription Treatment® contains abamectin in flowable dust formulation, which is different from fipronil in bait strip/gel products. Flowable dust formulation is expected to be more easily transferable to untreated surfaces, resulting in higher deposition residues. Monitoring results for this product were also included for exposure assessment, as there were only two gel formulation applications. This assessment used ½ MQL, i.e., 0.03 ng/cm^2, as the abamectin surface deposition residue and normalized this value to the application rate in each room (Table

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31). The 95th percentile application rate-normalized surface deposition residue was calculated at 13 ng/g/cm^2 and was used to assess post-application exposure (Frank, 2009).

This assessment also assumed that the entire content of a product package was applied during each application. The largest size of bait gel products in California is 30 g and the highest fipronil concentration is 0.01%. The calculated dermal and oral are summarized in Table 32.

Table 31. Summary of abamectin surface deposition after crack and crevice treatments

Formulation	Abamectin applied (mg)	Abamectin deposition (ng/m^2)	Normalized deposition[b] (ng/g/cm^2)
Flowable dust	5.3	<MQL	5.6
Flowable dust	8.2	<MQL	3.6
Flowable dust	4.8	<MQL	6.2
Flowable dust	5.6	<MQL	5.3
Pressured gel	28	<MQL	1.1
Pressured gel	59	<MQL	0.51
Mean:			3.7
95th percentile[c]:			13

a: The raw data is cited from Rosenheck and Schuster (1995); b: Assuming the surface deposition residue at ½ minimum quantifiable level (MQL), i.e., 0.03 ng/cm^2, and divided this value by the abamectin application rate in each room; c: Estimated 95th percentile of the distribution of concentrations based upon measured concentrations (Frank, 2009).

Table 32. Post-application dermal and oral exposure for structural bait gel product

Human receptor	Exposure pathway	STADD (µg/kg/d)	SADD (µg/kg/d)
Adult	Dermal	0.000076	0.000022
Child	Dermal	0.000054	0.000015
	Oral, hand-to-mouth	0.0025	0.00071
	Oral, object-to-mouth	0.000025	0.0000071
	Oral, Total	0.0025	0.00072

a: short-term absorbed daily dose (STADD) and seasonal average daily dose (SADD) of dermal exposure = deposition residue (381 and 111 ng/m^2 for STADD and SADD respectively) × dislodgeable fraction (0.06) × transfer coefficient (6800 and 1800 cm^2/h for adult and child respectively) × exposure time (8 and 4 h for adult and child respectively) ÷ body weight (70 and 13 kg for adult and child respectively) × dermal absorption rate (0.043);
b: STADD and SADD (oral, hand-to-mouth) calculation equations can be found on USEPA SOP page 7-39 and 7-44 (USEPA, 2012).

H. Structural dust products

This group contains only one active registered product, Termidor® Dry California. This product contains 0.5% fipronil and is used only by licensed applicators to control subterranean and drywood termites. The product is packed as a RTU formulation, and is applied by a specially designed bulb duster to areas such as structural voids, galleries, utility poles, etc. There is no PPE requirement while handling this product. Re-application to the same areas is allowed after 30 days.

Applicator. This represents exposure scenario of a licensed applicator during the application of the dust product. The exposure was categorized as Medium Priority in the Problem Formulation Document (DPR, 2016). This assessment evaluated applicator exposures from dermal contact and inhalation.

There is no fipronil-specific study quantifying handler exposure for the structural dust product, and exposure monitoring data for handlers that inject dust/powder formulations into structural voids is also not available. This assessment used the US EPA SOP plunger duster handler scenario as a surrogate. However, instead of using the default exposure values directly provided by the USEPA SOP, this assessment instead used the raw data from the study specifically supporting the plunger duster handler scenario (Merricks, 1997).

Apparel adjustment was made to the raw data before use in the exposure calculations. In this study, each handler wore a long-sleeve shirt and long pants to monitor dermal exposure, and a second layer of long-sleeve shirt and long pants over the inner set. However, the fipronil dust product label does not require PPE. This assessment assumed a handler wears a short-sleeve shirt and long pants. Correspondingly, this assessment used pesticide on the forearm outer layer plus on upper arm, front and back torso, and upper and lower leg parts of the inner layer to calculate total body exposure. A statistical summary of the recalculated dermal and inhalation exposure on different body parts is provided in Table 33.

This assessment also assumed each handler applied 2 cans of the product. This is the default value in US EPA SOP (USEPA, 2012) and also agrees with DPR PUR data. In 2012-2014 in California, the median amount of dust-formulated fipronil used in one application was 0.04 g, which is equivalent to 1.6 cans of the product. The calculated dermal and inhalation exposures are summarized in Table 34.

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Table 33. Statistical summary of applicator dermal and inhalation exposure for structural dust product

	Dermal[e] (µg/g)									Inhalation[f] (µg/g)
	Forearm	Upper arm	Front torso	Back torso	Lower leg	Upper leg	Hand	Face/ Neck	Total	
Mean	84	0.95	2.1	1.4	1.8	2.6	348	1.8	443	4.4
STD[b]	101	0.90	1.8	1.4	2.4	3.6	571	1.6	604	6.6
Max.[c]	428	4	7.8	6.2	10	15	2546	6.5	2765	29
95th percentile[d]	250	3	5.9	4.5	5.1	8.3	1211	6.1	1447	22

a: The raw data is cited from Merricks (1997); b: standard deviation; c: maximum; d: 95th percentile value was calculated based on the method described elsewhere (Frank, 2009);
e: Forearm data is from the outer layer dosimeter, and other body part data is from the inner layer dosimeter; f: breathing rate at 1.6 m^3/h.

Table 34. Applicator dermal and inhalation exposure for structural dust product

Human receptor	Exposure pathway	STADD[b] (µg/kg/d)	SADD[b] (µg/kg/d)	AADD (µg/kg/d)	LADD (µg/kg/d)
Adult	Dermal	0.085	0.014	0.009	0.005
	Inhalation	0.021	0.003	0.002	0.001

a: short-term absorbed daily dose (STADD) = exposure (2765 and 29 µg/g for dermal and inhalation respectively) × fipronil handled (0.00011 lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
b: seasonal average daily dose (SADD) = exposure (443 and 4.4 µg/g for dermal and inhalation respectively) × fipronil handled (0.00011 lb/d) × absorption rate (0.043 for dermal and 1 for inhalation) ÷ body weight (70kg);
c: annual average daily dose (AADD) = SADD × annual use months (8) ÷ 12. The number of annual use months is based on 2012-2014 PUR;
d: lifetime average daily dose (LADD) = AADD × 40 years of work in a lifetime ÷ 70

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Post-application, resident. These are exposure scenarios for residents, either an adult or a child, entering a treated structure. The exposure was categorized as Medium priority in the Problem Formulation Document for both adults and children (DPR, 2016). The primary exposure routes are dermal contact and inhalation for adult, and dermal contact, inhalation, and incidental oral ingestion for child.

There were no fipronil-specific studies quantifying post-application exposure following structural dust product treatment. Information on similar exposure scenarios for other pesticides is also lacking. In the Problem Formulation Document (DPR, 2016), the priority was first determined as Low because the product is applied to areas that are inaccessible to residents during normal activities. The Problem Formulation Document later increased the priority from Low to Medium because there is one illness case identified (Table 6). This assessment further reviewed this illness case and found that it might be caused by other fipronil products. Therefore, HHA determined the post-application exposure for structural dust product is low and did not warrant inclusion in this assessment.

I. Anticipated residue in drinking water

Fipronil is used widely across the state, although the data are spatial and temporally limited to county and month (Figure 6). Non-commercial, retail use of fipronil is not tracked, but is likely a significant portion of total statewide use. Lacking accurate spatial location of use precludes the option of identifying specific drinking water extraction sites that are downstream of fipronil use.

The Environmental Monitoring Branch (EM) at DPR curates a database of surface water testing results conducted in California by DPR, USGS, and other state, local, and federal agencies (SURF). There are 404 SURF surface water sampling sites where fipronil was tested for at least once, with 103 of those having at least one positive detection above the limit of quantitation (mean LOQ of 0.021 ppb, standard deviation 0.017 ppb) for a total of 576 positive detections. The location of SURF sites covers high use counties and thus likely accurately represents the range of concentrations that could be found in surface water (Figure 6).

Because the majority of use is for structural pest control or retail household use, many SURF sampling sites were located at storm drains near residential housing complexes. These storm drain samples are expectedly of much higher concentrations than those from natural waterways (Figure 7). Since no drinking water is taken directly from neighborhood storm drains, these samples should be excluded from further human risk assessment calculations. Similarly, it is unlikely that sloughs are used for drinking water and their lack of flow could result in higher concentrations. Therefore, these data sets should also be excluded from further analysis. Once the storm drain and slough samples are removed from the analysis (Figure 8), the remaining fipronil detections (n = 303) ranged from 0.0017 ppb to 0.275 ppb (mean 0.033 ppb). Therefore,

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the recommended concentrations for use in drinking water exposure assessment are 0.275 ppb for the acute dietary and 0.033 ppb for the chronic dietary.

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Fipronil use (2015) and surface water sampling (all years)

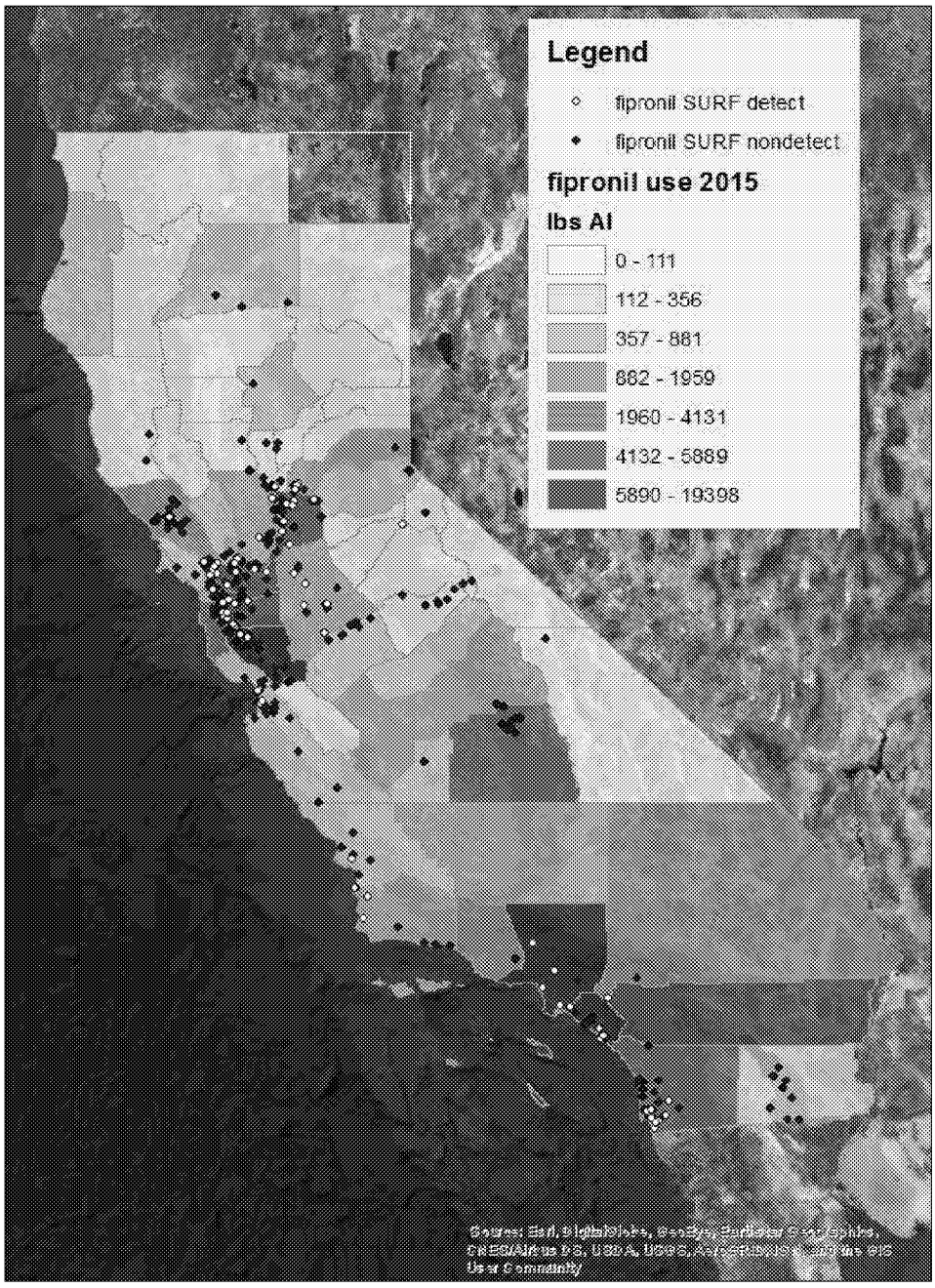

Figure 6. Statewide fipronil use for 2015 and all SURF sites that tested for fipronil at any time

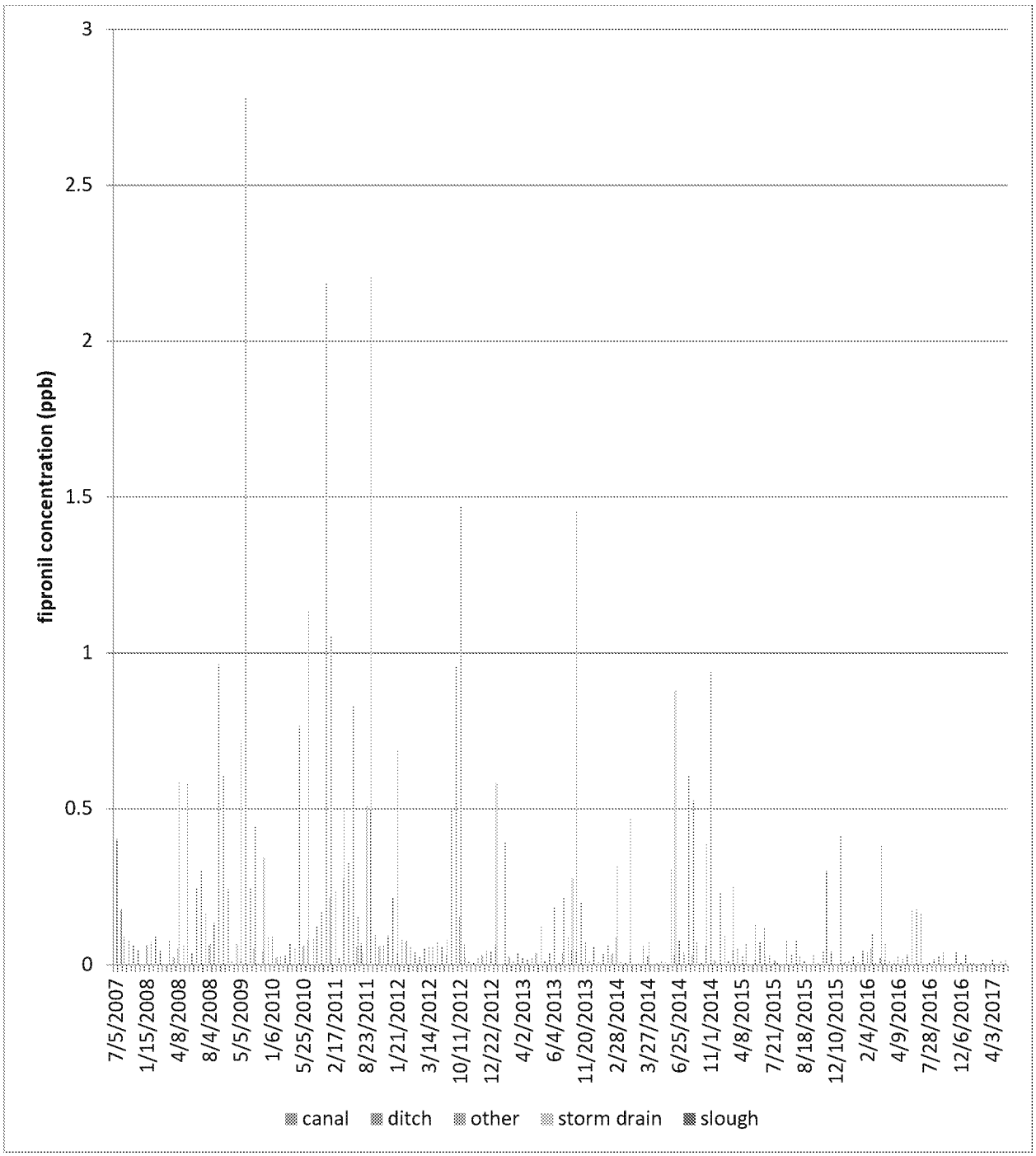

Figure 7. Fipronil SURF detections in surface water by waterway type

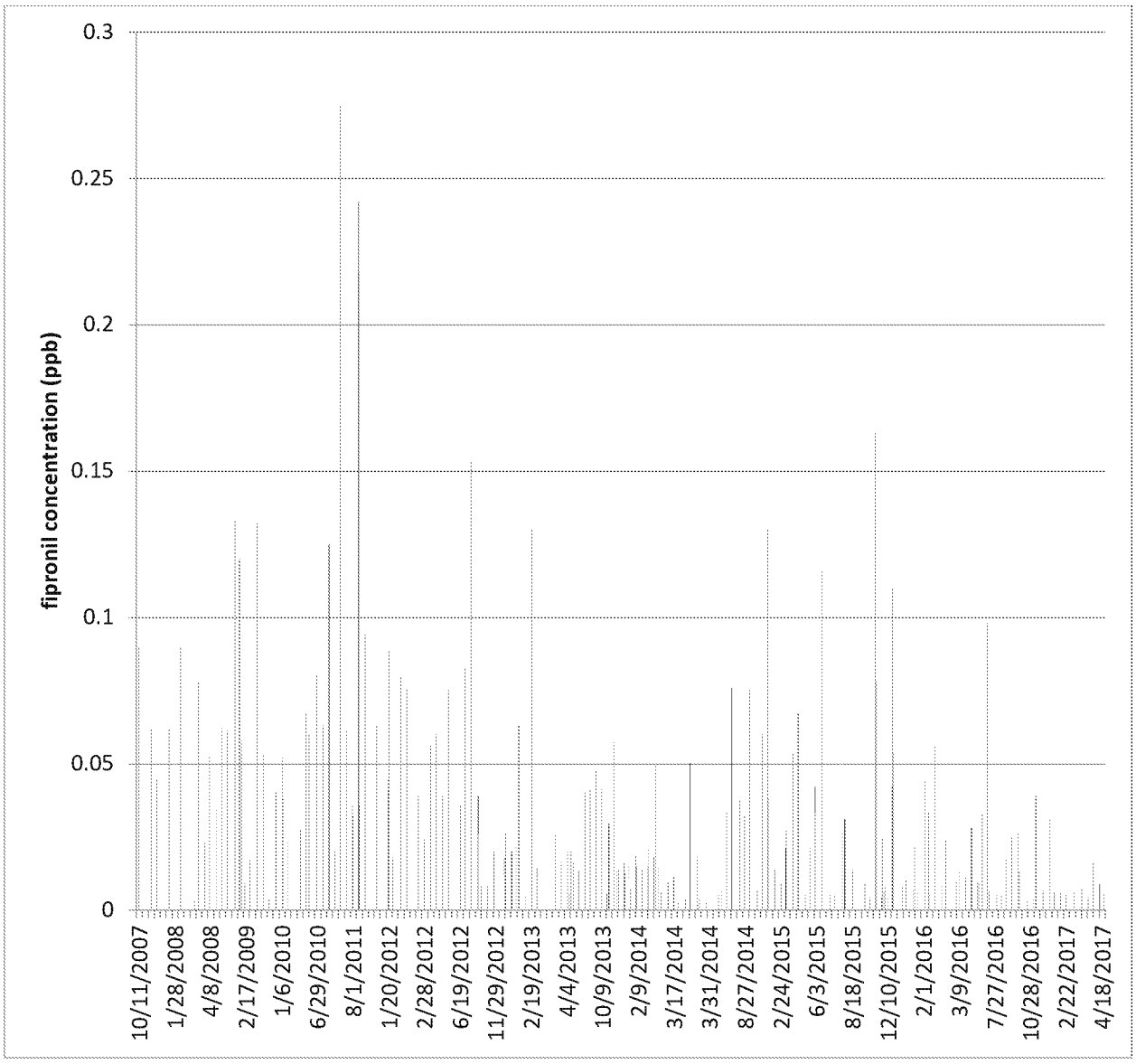

Figure 8. Fipronil SURF detections in surface water by waterway type, no storm drains (colored by site)

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V. EXPOSURE APPRAISAL

This section evaluates the uncertainties that may occur in this assessment. This assessment used the best information available to evaluate fipronil exposure. However, defaults were used for some scenarios due to a lack of data. This appraisal section also discusses these data gaps identified during the exposure assessment and how they were addressed.

A. Structural LC products

Handler. Handler exposure was assessed using PHED Scenario 22, which contains low pressure handwand M/L/A data for liquid formulations (open pour) (Beauvais *et al.*, 2007). Detailed discussions on the PHED data can be found elsewhere (Beauvais *et al.*, 2007). To assess fipronil handler exposure, this assessment also assumed each handler uses 40 gallons solution that contains 0.125% fipronil, which is the highest rate allowed per the product label. This rate is equivalent to 0.42 lb fipronil per application. This is in comparison to 2012-2014 PUR data showing the median amount of fipronil per application was 0.094 lb, and that 75.7% of the applications used <0.42 lb fipronil. Therefore, the application rate selected for this assessment is higher than that used for most application events, ensuring that the calculated STADD provides the maximum reasonable protections under scenarios permitted on the product labels.

Exposure of handlers applying LC products to overhead areas was based on a registrant submitted study that measured handler exposure during pesticide application to trees (8ft tall) using hand-held pumps (Merricks, 1998). This study was the only registrant submitted study that measured handler exposure using a hand-held pump to treat trees and no other handler data were available to assess exposure from structural overhead applications. Using these data likely overestimated the STADDs for several reasons. First, although Merricks (1998) did not state the amount of pesticide applied to trees, it is assumed greater than for structural overhead applications. Second, the active ingredient used in this study, i.e., carbaryl, is more volatile than fipronil, so the inhalation exposure may be overestimated (Gunasekara and Troung, 2007; Teerlink, 2017). Third, this assessment is based on highest application rate permitted on fipronil labels.

Post-application, resident. Post-application inhalation exposure was assessed using a registrant submitted study (Honeycutt and Kennedy, 2001). As stated above, this study was not acceptable for use in handler exposure assessment because it did not provide information on the total amount of fipronil applied to each house. However, the application rate in this study was similar to rates used in California. Also, houses in this study had a wide range of characteristics, including size, foundation type and number of stories. Although the product used, Termidor® 80 WG, is not registered in California, it requires mixing with water before use, so the application method is similar to the LC products. This study represents typical fipronil applications in

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California and findings from this study could be used for post-application inhalation exposure assessment.

There were no available data to characterize indoor fipronil deposition after structural pest control. Instead, post-application dermal and oral exposures were based on a USGS study that monitored fipronil occurrence on residential indoor surfaces (Mahler *et al.*, 2009). This study did not specify the individual fipronil sources, so it is possible that indoor contamination resulted from multiple products (including both structural and pet products) applied at different times. Correspondingly, the calculated post-application exposure represents combined exposure from both structural and pet product use. For this reason, this assessment did not evaluate fipronil transfer from pet spray and spot-on products from treated animals to indoor surfaces.

This assessment used the total analyzed fipronil compounds (fipronil and two degradates) from Mahler et al. (2009) to represent the highest possible fipronil amount on indoor surface dust. However, it is unknown whether these two degradates were formed in indoor environment. If the degradates were formed elsewhere and transferred into indoor areas afterward, using the total combined concentrations will overestimate the actual fipronil exposure. Mahler et al. (2009) also did not analyze one common fipronil degradate, i.e., fipronil sulfone, which is formed through oxidation process (Gunasekara and Troung, 2007; Teerlink, 2017). Although there is no study analyzing its occurrence in residential indoor areas, evidence has shown its common detections on residential outdoor surfaces, at levels comparable or even higher than parent fipronil (Jiang *et al.*, 2016a; Jiang *et al.*, 2016b). Therefore, the calculated exposure did not account for the portion of fipronil transformed to fipronil sulfone and may underestimate indoor exposure.

There was no available data to characterize post-application outdoor air concentrations. To control termites, fipronil is injected into structural inaccessible areas through small holes. To control other pests such as ants, fipronil is applied onto exterior structural surfaces. US EPA considers the post-application inhalation exposure in similar settings, i.e., application on outdoor lawn/turf, to be minimal due to pesticide low vapor pressure and dilution effect in outdoor air (USEPA, 2012). As such, this assessment assumes that outdoor air concentration of fipronil from either termite or ant control to be minimal.

Exposure to fipronil from contaminated outdoor surfaces was also considered for this assessment. Mahler et al. (2009) sampled 24 residences in Austin, TX. Researchers found that for every residence tested, the total concentration of fipronil compounds (fipronil and two degradates) on indoor surfaces exceeded that in outdoor dust (Mahler *et al.*, 2009). The median indoor concentration was 100 µg/kg, which is approximately 20 times the outdoor concentration. The maximum indoor concentration was 14200 µg/kg, which was 32 times higher than the maximum outdoor concentration. As detailed earlier in this document, Jiang et al. (2016a) determined that the concentration of fipronil and its degradate were similar to the outdoor concentrations found in Austin, TX (Jiang *et al.*, 2016a). For exterior surface treatment, fipronil is applied in crack-and-crevice fashion, usually around structural perimeter and along pest crawl

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and hide trails. It is likely that the treated surface area is much smaller than the areas an adult or child may play on. Because this assessment assumes that fipronil levels on outdoor surfaces are lower than on indoor surfaces, the potential exposure from contaminated surfaces can be adequately covered by the indoor scenario.

B. Pet spray and spot-on products

Fipronil products for cats and dogs are available in two formulations, i.e., spray and spot-on. Because pesticide exposure potential is associated with the product formulation (Beauvais *et al.*, 2007), groomer, home user and post-application exposures for adults and children were assessed for each of the formulations.

Applicator, groomer. The number and size of dogs/cats treated by each handler per day is expected to vary greatly among different handlers. This assessment assumed each groomer treated 10 dogs per day, which is the average number of dogs and cats treated by a commercial groomer based on a registrant submitted survey (Irwin, 1997). Irwin (1997) also found that veterinary groomers treated fewer dogs/cats per day than commercial groomers (Irwin, 1997). Therefore, this assessment used 10 dogs/cats for professional groomers per day as well as two dogs once per month for pet owners. This agrees with findings from the most recent AVMA survey (AVMA, 2012) and the number of treated dogs/cats selected in the US EPA SOP (AVMA, 2012; USEPA, 2012).

Applicator, home user. The product labels suggest repeated applications of fipronil on pets to maintain satisfactory tick and flea controls. The suggested application frequency is monthly, i.e., home users only need to apply fipronil once every month. Accordingly, the intermediate- and long-term home user exposures were not assessed because the once-a-month use pattern is not consistent with the definitions of intermediate and long-term exposures as defined in Kwok (2017).

Post-application, resident. As stated earlier, this assessment did not evaluate fipronil transfer from treated pet to indoor surfaces and the associated human exposure, rather relying on an indoor monitoring study that evaluated various residential fipronil uses. One study attempted to quantify fipronil transfer after pet treatment (Bigelow-Dyk *et al.*, 2012). Researchers placed cotton cloths in areas frequently visited by the treated dogs/cats (beds, furniture, play areas, and cat trees), collecting them after 2 weeks to measure the concentrations of fipronil and three degradates (desulfinyl, sulfone and sulfide). This study also measured fipronil transfer to humans by asking pet owners to wear cotton socks 2 hours per night for seven consecutive days.

There were several reasons results from Bigelow-Dyk, et al., were not used, most of which center on the location and duration of the testing and the representativeness of indoor fipronil levels. For example, the levels of fipronil transferred to socks was 0.18-16 μg per hour of

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activity. Because the socks were worn for one week, it is difficult to calculate fipronil daily transferable amount. In addition, only transfer rates per hour can be calculated, but not the amount deposited per unit of indoor surface area; the latter is needed for this assessment.

Another potential post-application exposure scenario considered in this assessment is exposure from bathing treated dogs/cats. No data were available to evaluate fipronil exposure during bathing dogs/cats for either groomers or owners. The US EPA SOP recommends using handler exposure studies as surrogate scenarios, as handlers are expected having more vigorous contact with the treated animals (USEPA, 2012).

This assessment conducted a preliminary evaluation of fipronil exposure during dog bathing using US EPA's Swimmer Exposure Assessment Model as the surrogate scenario, but only considered dermal exposure on hands and forearms, assuming that these two body parts contact the bathing water (USEPA, 2003). Dermal permeability coefficient required by this model was calculated following the US EPA summary on dermal exposure assessment (USEPA, 2007). Fipronil concentration in the bathing water of a treated dog was based on data from Teerlink *et al.* (2017). This study recruited 34 dogs weighing 2.2-41.6 kg, and each dog was treated with fipronil spot-on products appropriate to its weight. Applied fipronil ranged from 67.1 to 410 mg. Each dog was washed once at 2, 7, or 28 days after fipronil treatment and the bathing water was analyzed for fipronil and four fipronil degradates (amide, sulfide, sulfone and desulfinyl). The maximum amount of total five fipronil compounds in the bathing water was 230.6 mg, which represented 86.0% of total applied fipronil. The authors indicate that the approximate time to bathe a dog (i.e., exposure time) is 20 minutes and as stated earlier in this document, it is assumed that a groomer bathes 10 dogs a day and a pet owner bathes 2 dogs in a day. The resulting dermal STADDs are summarized in Table 35. This assessment is in agreement with US EPA in that the STADDs from bathing dogs are lower than handler STADDs.

Table 35. Post-application dermal STADDs for pet owner and groomer from bathing treated dogs

Occupation	Human receptor	STADD[a] (µg/kg/d)
Professional groomer	Adult	2.3
Pet owner	Child, 7-10 years old	0.58
	Teen, 11-14 years old	0.66
	Adult	0.45

a: short-term absorbed daily dose (STADD) = Exposure time (200 and 40 minutes for groomer and pet owner respectively) × Surface area of exposed skin (0.10, 0.19 and 0.19 m^2 for child, teen and adult respectively) × Dermal permeability coefficient (0.0028 cm/h) × Water concentration (8.9 µg/mL) ÷ Body weight (30, 48 and 72 kg for child, teen and adult respectively) (USEPA, 2003; USEPA, 2007; Frank, 2009);

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The calculated STADDs in Table 35 might overestimate fipronil exposure from dog bathing. Fipronil water concentrations used in the calculation (8.9 µg/mL) was the maximum measured concentration of total fipronil compounds in the bathing water, but this value already exceeded fipronil water solubility (2 µg/mL) (Teerlink *et al.*, 2017). As discussed in this paper, dog bathing water contained 1.6-76.2 g/L suspended solids. Therefore, the water concentration used in the calculation includes fipronil amount associated with suspended solids, which does not have the same dermal uptake as the freely soluble fipronil. This assessment did not evaluate post-application inhalation exposures for pet products, and there is no study that monitored fipronil air concentrations shortly after pet product use. As stated previously in the Exposure Assessment section, due to the low volatility of fipronil and the small amount applied, the inhalation exposures were determined minimal. Using the ideal gas law, the maximum concentration dictated by the saturation vapor pressure of fipronil after application is 0.065 $\mu g/m^3$ at 25 °C. However, using this concentration will significantly overestimate the inhalation exposures because of the assumptions of immediate volatilization loss after application and no mass transfer limitations (e.g., surface-to-air) during the volatilization. In fact, in a study from Honeycutt and Kennedy (2001) that monitored fipronil air concentrations during and after applications of structural LC products, the 24-hr average air concentration was 0.021 $\mu g/m^3$ (Table 12). Given the lower use rates and frequencies of pet products than structural LC products, the post-application inhalation exposures for pet products is expected to be low.

This assessment also did not evaluate post-application incidental oral exposure for long-term exposure duration. Data revealed detections of radiolabeled fipronil in the stratum corneum and viable epidermis of the application zone (neck) of beagle dogs up to 56 days post-application (Cochet et al., 1997). The persistence of the active ingredient combined with regular 30-day applications indicates the possibility of long-term fipronil exposures, but the exposure levels are expected to be much lower than the short- and intermediate-term exposures estimated in this assessment, since the transferable amount of fipronil on cats and dogs rapidly decreased within 28 days after treatments (de Fontenay et al., 1997a; de Fontenay et al., 1997b; de Fontenay et al., 1997c; de Fontenay et al., 1997d; Hughes, 1997a; Hughes, 1997b; Hughes, 1997c; Hughes, 1997d). Post-application object-to-mouth exposure following indoor applications is generally considered short-term in duration (US EPA, 2012). Refinement of product-specific dose estimate to reflect a more accurate multi-day or multi-episode exposure profile can be accomplished when more information becomes available, such as long-term monitoring data of transferable residues on pets after repeated fipronil treatments.

C. Turf granule products

Post-application, resident. Exposure monitoring data is usually considered as the best information to assess post-application exposure from treated-turf for a particular pesticide and formulation. No monitoring data were available for post-application fipronil exposure from

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treated turf. Therefore, this assessment followed US EPA SOP (2012) to assess post-application turf exposure, and assumed the dermal exposure is proportional to the TTR value (USEPA, 2012).

Besides TTR, DPR may also use monitoring of other pesticides as surrogate data when exposure monitoring data are not available. For instance, carbaryl post-application exposure on treated turf was estimated using a study that monitored exposure instead of TTR (Beauvais, 2014). In another example, dithiopyr exposure was monitored after turf treatment with a granular formulation product (Baugher *et al.*, 2004). The application rate was 0.5 lbs/ac, which was 40 times of the maximum on turf. Within 24 hours after application, study participants were asked to wear long, 100% cotton coverall and long cotton underwear as outer and inner dermal dosimeters, and perform Jazzercise® exercise on treated turf for 20 minutes. Handwash, face/neck wipes, and socks were also collected after the exercise to monitor dithiopyr exposure on corresponding body parts. Adult and child dermal STADDs were calculated based on surrogate dithiopyr exposure monitoring. As shown in Table 36, the calculated fipronil exposure using both methods is the same order of magnitude, but STADDs from the TTR method are about three times higher than STADDs from monitoring data for both the adult and child.

Table 36. Comparison of adult and child dermal STADD calculated using TTR method or exposure monitoring data

STADD (µg/kg/d)	USEPA SOP TTR[a]	Exposure monitoring study
Adult	0.0068	0.0017[b]
Child	0.0098	0.0024[c]

a: short-term absorbed daily dose (STADD) (dermal, normal physical activity) = TTR (0.0368 ng/cm^2) × transfer coefficient (200000 and 54000 cm^2/h for adult and child respectively) × exposure time (1.5 h) ÷ Body weight (70 and 13 kg for adult and child respectively) × dermal absorption rate (0.043);
b: short-term absorbed daily dose (STADD) (adult dermal, monitoring data) = monitored exposure (24.1 µg/20-min) × exposure time (1.5 h) ÷ application rate ratio (40) ÷ body weight (70 kg) × dermal absorption rate (0.043);
c: short-term absorbed daily dose (STADD) (child dermal, monitoring data) = monitored adult exposure (24.1 µg/20-min) × exposure time (1.5 h) ÷ adult body surface area (1.95 m^2) × child body surface area (0.53 m^2) ÷ application rate ratio (40) ÷ child body weight (13 kg) × dermal absorption rate (0.043);

For a 1-2 year old child, the calculated oral exposure through episodic granular ingestion was 4-5 orders of magnitude higher than the exposure through other oral routes. This assessment calculated episodic granular ingestion exposure assuming fipronil concentration on the ingested granules equals the concentration in the product. The product labels suggest the lawn be irrigated after the treatment, so the actual exposure may be lower due to loss of fipronil from granules. However, there is no information on fipronil residue remaining on the formulation granules after irrigation. This assessment assumed 100% fipronil remained on granules after irrigation, based on the hydrophobic property of fipronil.

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For similar reasons as for pet products, post-application inhalation exposures were not assessed for turf products and are expected low.

D. Structural bait gel/strip products

Post-application, resident. As there is no fipronil-specific study, this assessment used a registrant submitted abamectin study as a surrogate to calculate fipronil deposition (Rosenheck and Schuster, 1995). Abamectin was applied in two formulations, i.e. flowable dust and gel. Flowable dust applications were used to calculate 95th percentile value of surface deposition because there were only two gel applications. This may overestimate the surface deposition as flower dust formulation is more prone to transfer off-site and generate higher indoor deposition.

In this study from (Rosenheck and Schuster, 1995), abamectin application rate at each room was vastly different (Rosenheck and Schuster, 1995). This assessment assumed abamectin deposition level was proportional to the application rate, but factors other than application rates also affect indoor deposition levels, and pesticide concentrations on indoor surfaces are often found not correlated to application rates. For instance, in US EPA SOP it has already mentioned that for crack and crevice applications there was no correlation between application rate and post-application indoor residue (USEPA, 2012).

E. Structural dust products

Applicator. Handler exposure was assessed using the US EPA SOP scenario for a handler using the plunger dust application method. Instead of using the SOP default values directly, this assessment used the raw data on which this scenario relies (Merricks, 1997). This assessment considered this study as the best available information to assess the dust handler exposure scenario. However, it is also acknowledged that this study might yield results that overestimate the handler exposure. First, the package of fipronil dust product is directly connected to a specially designed duster, so the exposure during loading and unloading the product from the duster is expected to be lower than that measured in the study. Second, fipronil is applied by inserting duster outlet tip into a pre-drilled hole, therefore drift during the application is less likely and inhalation exposure is expected to be lower than measured in the study. Third, the fipronil dust product was applied into structural voids, and air flow generated in each pump is unlikely to cause additional handler exposure through re-suspension of already-applied product.

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F. Drinking water

Confidence in this assessment is moderate. Since all fipronil use data lacks any spatial component less than a county level, it is difficult, if not impossible, to accurately identify the surface water derived drinking water sources at highest risk of being contaminated. This assessment identifies a large number of sampling points that span both space and time and includes heavy fipronil use regions, so the sampling values should be representative. It is possible that there are drinking water extraction sites that might have a higher fipronil concentration than the highest sampled value from free flowing waterways. Nevertheless, insufficient information exists to determine if such sites exist or to determine the exact fipronil concentration would be. Since sampling in storm drains in neighborhoods of high use showed fipronil concentrations less than an order of magnitude greater than the highest samples in free flowing waterways, this assessment assumes that any drinking water contamination would be much less than the storm drain samples and thus closer to the recommended concentration values.

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APPENDIX II. FIPRONIL SYSTEMATIC REVIEW (4 pages)

Specific Aims

- Conduct literature searches and use systematic review methods to identify studies published until October 2020 that are relevant to understanding the potential human health hazards of fipronil as outlined in the PECO (population, exposure, comparator, and outcome) criteria.
- Track potentially relevant supplemental material, including mechanistic evidence informative of mode of action (MOA), potential genotoxicity, human illness reports, epidemiology studies, and ADME information. Studies conducted in non-mammalian model systems (*i.e.*, nematodes and fish) are not included at this time.

Methods and Results

Database Searches

Prior to 2017, the Human Health Assessment (HHA) branch conducted literature searches on fipronil using the key word "fipronil," both in PubMed (www.ncbi.nlm.nih.gov) and in the Google.com search engine. Information for articles deemed relevant to risk assessment (either for critical endpoints or as supplemental data) was compiled into Microsoft Word documents or Microsoft Excel files, and full article texts were obtained and reviewed. In 2017, HHA identified relevant articles in the PubMed database, exported the information as a .csv file and imported the file into Microsoft Excel. A total of 117 articles were identified as potentially relevant to the fipronil RCD. This process was repeated in 2018 a total of 171 potentially-relevant articles were identified. In 2019, the search was repeated, and the resulting database was screened for studies with acute and short-term exposure duration; 21 potentially-relevant articles were identified.

On October 1, 2020 a database search was conducted in PubMed (www.ncbi.nlm.nih.gov) using the common pesticide name "fipronil" as the key word (because the fipronil derivative names all include the word "fipronil", this search also found publications on metabolites and on the photodegradate). The resultant studies (1373) were exported from PubMed as a .csv file and imported into Microsoft Excel. Thirteen additional papers not referenced in PubMed were identified in the fipronil references and were added to the list.

Level 1. Title and abstract screen

Article titles and abstracts were screened for relevance to the fipronil human health Risk Characterization Document (RCD). Of the initial 1386 studies, 139 were identified as potentially relevant for human health risk assessment.

Level 2: Full text screening for PECO criteria and supplemental material

Full texts were screened for the fulfillment of all PECO criteria listed in Table 1. Dates of screening decisions and results were recorded. Studies that did not meet PECO criteria were tagged with a reason for exclusion as indicated in Table 2. Studies containing data that were

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potentially relevant as supplemental material were tagged with appropriate supplemental information tags (Table 3).

Table 1. PECO Criteria Used for the Fipronil Systematic Literature Review

PECO Element	Evidence
P (population)	**Human:** Any population and lifestage (occupational or general population, including children and other sensitive populations). **Animal:** Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).
E (exposure)	**Relevant forms and synonyms:** Fipronil-sulfone Fipronil-sulfide Fipronil-desulfinyl **Routes:** I. Oral (gavage or dietary) A. Acute or short-term (up to one week): LOEL under 7.5 mg/kg-day or NOEL under 3 mg/kg-day B. Subchronic or chronic: LOEL under 0.5 mg/kg-day or NOEL under 0.1 mg/kg-day II. Inhalation: Any III. Dermal: Any
C (comparator)	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits), or exposure for shorter periods of time. *Case reports and case series will be tracked as "potentially relevant supplemental information."*
	Animal and Other: A concurrent control group exposed to vehicle-only treatment or untreated control.
O (outcome)	All health outcomes.

Note: Because DPR had already reviewed registrant-submitted and published data, the final PECO criteria were focused to find articles with effects below a certain exposure level in order to inform the selection of critical points of departure. Articles not captured with the PECO were included in the weight-of-evidence analysis.

Table 2. Reasons for Exclusion Used for the Fipronil Systematic Literature Review

Reason for Exclusion	Description of reason
Environmental Fate/Risk	Studies focused on environmental fate or environmental risk of fipronil
No Exposure	Exposure data were not provided
Foreign Language	Study was not available in English

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Table 2. Reasons for Exclusion Used for the Fipronil Systematic Literature Review

Reason for Exclusion	Description of reason
Application/Efficacy	Study was focused on efficiency of fipronil for anti-flea and tick treatment, or for application methods
Derivatives	Compound studied was not fipronil or relevant derivatives
Removal	The study focused on methods of fipronil removal from waste/surface water
Non-Mammalian	Model organism was not mammalian (*i.e.*, birds, fish, amphibians, crustaceans, reptiles, worms)
Review/Editorial/Commentary	Publication without original data or analysis
Target Organism	Study of effects on target organisms (*i.e.*, insects, arachnids, or fungi)
Detection	The study focused on methods of fipronil detection
Other	Other categories do not apply

Of the initial 1386 studies, 14 were identified as meeting all PECO criteria. An additional 12 studies were identified as potentially relevant to ADME/PBPK, 10 as potentially relevant to genotoxicity, 6 to epidemiology, 7 to illness reports, and 91 were identified as potentially relevant supplemental mechanistic studies (Table 3). All 14 PECO studies and 1 genotoxicity study were included in the mechanism review. Relevant information from articles deemed important for weight-of-evidence was recorded.

Table 3. Supplemental Information tags for Fipronil Publications

Supplemental Material Tag	Number of Publications	Studies Reported
Mechanistic	91	Studies were performed in human or nonhuman mammalian animal species of any lifestage (including preconception, *in utero*, lactation, peripubertal, and adult stages), or in cell lines, primary cultures or protein extracts derived from those species, or in a relevant *in vivo* model; do not meet PECO criteria
ADME/PBPK	12	Studies describing physiologically-based pharmacokinetic (PBPK) models and/or metabolic products
Genotoxicity	10	Studies describing genotoxicity or mutagenicity
Epidemiology	6	Studies describing health-related sequelae in exposed populations
Illness reports	7	Studies describing illnesses or fatalities in humans following fipronil exposure

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Level 3: In-depth review and analysis for Point of Departure (POD) designation or support

Studies identified though PECO screening were reviewed in-depth for methodologies and findings. This included the creation of study summaries that described the study design (i.e. animal model, sex, exposure route, doses tested, key endpoints, results, and NOEL/LOEL values (where applicable). Studies found to not meet PECO criteria were noted and tagged with reason for exclusion. Data analyses were performed when appropriate, and data suitable for Benchmark Dose (BMD) modeling were identified.

None of the articles identified through PECO screening contributed a POD for the fipronil RCD. However, several were useful for weight-of-evidence analysis and subchronic POD support.

Summary

A summary of the systematic review process used for fipronil and the corresponding results is provided in Table 4.

Table 4. Overview of Systematic Literature Review Results for Fipronil

Level review	Criteria	Objective(s)	Number of Publications
Initial search	Key word "fipronil"	NCBI database search	1386
Level 1	Title and abstract reviewed to identify relevance to critical endpoint determinations, mechanism, ADME-PBPK, illnesses, genotoxicity or epidemiology	Review of full texts	140
Level 2	Full texts reviewed for PECO criteria relevance	Review of full text, relevant selected	14
Level 3	In-depth review and data analysis	Develop POD	0

Quality Control

Following the completion of screening review phases, the data and conclusions expressed in prepared review documents were subjected to quality control review to ensure fidelity to the original publications.

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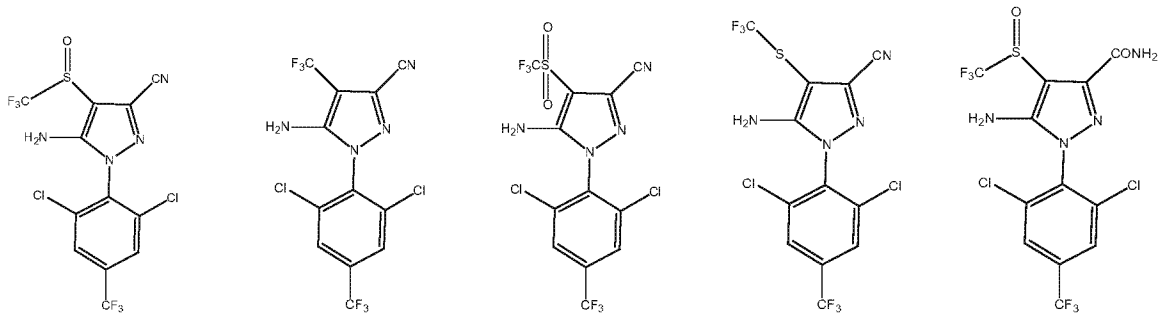
APPENDIX III. FIPRONIL METABOLITE AND PHOTODEGRADATE TOXICOLOGY PROFILE (19 pages)

The overall toxicological properties of fipronil depend on the parent compound and on its derivatives (metabolites and photoproduct, see Figure 1.) (Hainzl *et al.*, 1998). The effects of the fipronil derivatives are particularly relevant in cases where exposure to a derivative occurs independently of exposure to parental fipronil, such as occurs with the environmental photodegradate. A complete picture of the potential health risks resulting from fipronil exposure would include toxicity data on its derivatives and their potential for human exposure, especially considering that the dietary fipronil tolerances are established for the combined residues of fipronil and three derivatives (two metabolites and a photodegradate). Because exposure estimates for the derivatives are limited, total risks from exposure to fipronil may be underestimated in this assessment.



Fipronil	Fipronil-desulfinyl	Fipronil-sulfone	Fipronil-sulfide	Fipronil-amide
MB 46030	MB 46513	MB 46136	MB 45950	RPA 200766

Figure 1. Chemical Structure of Fipronil, Metabolites and Photoproduct

Fipronil-desulfinyl is the principal photoproduct in plants and soils (Hamon *et al.*, 1996). The database for fipronil-desulfinyl is extensive, consisting of toxicokinetic studies in rats, goats and laying hens, acute studies in rats and mice, subchronic studies in rats, mice and dogs, a combined chronic and oncogenic study in rats, developmental toxicity and acute neurotoxicity studies in rats, a gene mutation study in *Salmonella typhimurium*, an *in vitro* chromosomal aberration study in human lymphocytes, an *in vivo* chromosome aberration study in mice, and a oxidative stress study on mitochondria isolated from rat livers.

Limited toxicity data were available for two of the major Phase I metabolites (fipronil-sulfone and fipronil-sulfide). These metabolites are formed through oxidation. Fipronil-sulfone is the major metabolite in both vertebrates and insects (Hamon *et al.*, 1996). It has been detected in humans as well as rats, goats, hens, rabbits and cows (Powles, 1992; Byrd, 1994; Stewart, 1994a; Stewart, 1994b; Mohamed *et al.*, 2004). Studies available on fipronil-sulfone included an acute study in mice, a gene mutation study in *Salmonella typhimurium*, an *in vitro* chromosomal aberration study in human lymphocytes, and an oxidative stress study on mitochondria isolated from rat livers. For fipronil-sulfide, the database included an acute study in rat and a gene mutation study in *Salmonella typhimurium*.

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In addition, a report was submitted by the registrants that compared the toxicity of fipronil to its derivatives (Blacker, 1997).

The toxicology profiles for fipronil-desulfinyl, fipronil-sulfide and fipronil-sulfone are detailed below.

I. Fipronil-Desulfinyl

I.A. Toxicokinetics

I.A.1. Oral – Rat

A study on the kinetics of fipronil-desulfinyl was performed on six different groups of Sprague Dawley rats (Totis and Fisher, 1994). In Groups 1, 2 and 4, 5 rats/sex/group received a single oral gavage dose of [phenyl-U-^{14}C]-fipronil-desulfinyl at 1 or 10 mg/kg. In Group 3, 8 rats/sex received 14 consecutive non-radiolabeled daily doses followed by administration of a single ^{14}C labelled oral dose of 1 mg/kg to 5 rats/sex/group. In Group 5, 7 rats/sex/group received a single oral dose of radiolabeled fipronil-desulfinyl of 1 mg/kg. In Group 6, 3 male rats received a single radiolabeled oral dose at 1 mg/kg.

Recovery of fipronil-desulfinyl was 96.86 ± 3.73%. Elimination was greater in the feces than in the urine. The highest mean fecal excretion rate was in the high-dose (10 mg/kg) animals (70 and 56% in males and females, respectively). In the 1 mg/kg groups, 61 and 46% of elimination occurred via the feces in males and females treated with a single dose, respectively, and 61 and 53% was recovered in feces from males and females, respectively, treated with multiple doses. Mean recovery in urine was 8.8 and 10.7% in single high-dose males and females, 6 and 4% in single low-dose males and females, and 10 and 11% in repeated low-dose males and females.

Mean recovery of radioactivity in tissues after 168 hours post dosing was 20% and 30% in the high-dose males and females, 27 and 41% for the single low-dose males and females and 22 and 32% for the repeated low-dose males and females, respectively. The highest concentrations of radioactivity were present in fat. At the high dose, all tissues had detectable radioactivity. Radioactivity levels were dose-dependent and appeared in relatively high levels in liver, adrenals, skin, fur, intestine and ovaries.

In the blood, the mean C_{max} in the high-dose group was 2.03 ± 0.47 and 2.31 ± 0.90 µg radioactivity equivalents/g in males and females at a T_{max} of 72.53 ± 9.08 and 70.52 ± 8.30 hours, respectively. The elimination half-life was 170.10 ± 21.20 hours and 220.60 ± 55.71 hours in males and females, respectively, with estimated areas under the curve (AUC) of 503.40 and 539.86 µg equivalents/g, indicating comparable bioavailability in both sexes. The C_{max} mean values at the low-dose were 0.14 ± 0.02 and 0.15 ± 0.03 µg equivalents/g, with T_{max} mean values of 45.93 ± 13.63 and 60.65 ± 17.14 hours in males and females, respectively. Elimination half-life mean values were 156.26 ± 17.89 and 209.90 ± 13.75 hours for males and females, respectively, with an AUC of 33.18 ± 5.13 and 49.45 ± 7.33 µg equivalent/g, indicating a slightly lower bioavailability in males than in females.

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Up to 17 different radiolabeled entities were detected in urine and up to 13 different compounds in feces. Trace levels of intact compound were detected in urine, whereas parental fipronil-desulfinyl was the main compound in feces. Fipronil-desulfinyl subject to intensive metabolism by Phase I enzymes *in vivo*. Elimination occurred mostly via the fecal route, indicating either poor oral bioavailability, enterohepatic recirculation, or both. Small differences were seen between the single- and repeated-dose experiments. Presence of radioactivity in the carcass and the relatively long half-life indicate partitioning into a deep compartment, *e.g.,* fat.

I.A.2. Oral – Goat:

Three lactating goats, one per dose level, received oral doses of [^{14}C]-phenyl-labeled fipronil-desulfinyl twice daily by gelatin capsule for 7 days at dietary concentrations of 0.05, 2, or 10 ppm (Johnson *et al.*, 1996). Radiolabel was followed in urine, feces, whole blood, plasma, and milk during exposure, and fat (peri-renal and omental) liver, kidneys, and skeletal muscle at termination.

Fecal excretion accounted for 20 – 50% of the administered label, constituting the major route of excretion at each concentration. Urinary excretion ranged from 3% to 7% of the total exposure. Tissue accumulation was significant: 7 – 26% was found in total body fat. No difference between specific activities in renal fat and omental fat was detected. Liver had the second highest specific activity, comprising 2.2 – 4.4% of the administered dose. Skeletal muscle had lower specific activity than liver, but represented a much larger proportion of body mass, accounting for a larger proportion of total recovered radioactivity (4 – 9% of administered dose). Milk accounted for 1 – 5% of total administered dose. Exhaled CO_2 was not measured in this study, but a rat disposition study (Totis and Fisher, 1994) determined that CO_2 residue was trivial.

About 50% of the administered 0.05 ppm radiolabel was absorbed. Accumulation of residues in milk reached steady state at ~100 hours. This is consistent with the relatively long retention time previously observed in rat, both for the parent fipronil and for the photodegradate. Quantitative distribution in organs and excreta was evaluated only in the goat exposed to 10 ppm. In urine samples, a sulfate conjugation product of the pyrazole amine group was the most significant metabolite [21 – 31% of the total recovered residues (TRR)], with a glucuronide of that same amino group comprising 5 – 6% of the TRR. The only other identified metabolite was MB 46400, where the trifluoromethyl carbon was replaced by a carboxylic acid (6 – 8% of the TRR). Fipronil-desulfinyl comprised 1 – 2% of the urinary TRR and 72 – 77% of the TRR in feces. Liver radiolabel was dominated by fipronil-desulfinyl (58% of TRR), with no other single residue exceeding 3.4% of the TRR. Fipronil-desulfinyl comprised 49%, 70%, 86%, 82% and 94% of the kidney muscle, renal fat, omental fate and milk TRRs, respectively.

I.A.3. Oral – Laying Hen

^{14}C-phenyl-labeled fipronil-desulfinyl was given orally by capsule to groups of 5 laying hens at dietary concentrations of 0.05, 2, or 10 ppm for 14 days (McCorquodale *et al.*, 1996). Eggs were collected throughout the study days and were separated into whites and yolks. Excreta was

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collected prior to the first dose administration and at 24 hours intervals thereafter. Animals were killed approximately 23 hours following the final dose. A total of 68.0 – 81.4% of the total administered radiolabel was recovered: 53 – 71% was recovered in excreta, with recovery percentage declining with increased dose; 4.2 – 6.7% was recovered in eggs, with 2 – 3 fold higher levels detected in yolks than in whites; and 3.99 – 6.34% was recovered in tissues. The highest tissue residue levels were in omental fat, partially formed eggs, liver and skin fat.

I.A.4. Dermal – Rat

The extent of dermal absorption of ^{14}C-fipronil-desulfinyl was examined in male rats (Cheng, 1996). Twenty four rats per dose (4 rats per time point) were exposed to 0.08, 0.8 or 8 mg fipronil-desulfinyl in 1.0% carboxymethylcellulose. Two animals received vehicle only. The skin was washed and animals sacrificed at 0.5, 1, 2, 4 10 or 24 hours post dose, when blood, urine and feces were also collected. Mean recovery of total radioactivity ranged from 93 to 103%, with the majority (90 to 102%) occurring in the skin wash. Radioactivity in blood, excreta and carcass accounted for less than 3% of the total applied radioactivity. DPR estimated that the dermal absorption of fipronil-desulfinyl (3.2%) is similar to that of fipronil (4.3%) (DPR, 1999b).

I.B. Acute Toxicity

I.B.1. Oral – Rat

Fipronil-desulfinyl (98.6%) was administered by gavage to 5 Sprague Dawley rats/sex/group at 3, 10, 20, or 30 mg/kg (Dange, 1993b). Rats were monitored for 14 days thereafter. Mortality occurred in 0/5, 0/5, 3/5, and 5/5 males and 0/5, 0/5, 4/5, and 5/5 females at ascending doses. Animals displayed dyspnea, bradypnea, hunched posture, and tonic and clonic convulsions at 30 mg/kg. Reduced motor activity and nasal discharge was observed at 10 to 30 mg/kg. An apparent hyper-reaction to noise appeared at all dose levels without a clear dose-response. Treatment-related pathological findings occurred at 30 mg/kg and included enlarged livers with marked lobular pattern (2/5 in males), pale livers (2/5 in females), and hyper-salivation (1/5 males and 5/5 females). The investigators calculated LD_{50} values of 18 mg/kg for males and 15 mg/kg for females. Fipronil-desulfinyl is a Toxicity Category I oral toxicant.

I.B.2. Dermal – Rat

A single dose of 2000 mg/kg fipronil-desulfinyl (98.6%) was applied to the clipped dorsal skin of 5 Sprague Dawley rats/sex for 24 hours to investigate acute toxicity following dermal exposure (Dange, 1993a). Two females died; one death was attributed to the test substance. Clinical observations in males included subdued behavior, piloerection, chromodachryorrhea in nose and eyes, and polypnea (rapid or panting respiration). In females, lacrymation, reduced motor activity, piloerection, bradypnea, palpebral ptosis, tremors, soiled fur, curled up at handling and increased motor activity were noted. Slight body weight loss occurred during the first week, but body weight gain occurred during the subsequent week in all animals. The terminal weights of surviving animals exceeded their initial weights. Autolysis was observed in the two rats that died during the study. White areas in the liver were observed in 1 of the

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decedents, and red areas in the liver were observed in 1 surviving female rat at terminal necropsy. The LD_{50} for males and females was > 2000 mg/kg, making it a Toxicity Category III toxicant.

I.B.3. Intraperitoneal – Mouse

A published study in mice was available from literature with administration via intraperitoneal injection (Hainzl and Casida, 1996). Male Swiss-Webster mice were treated via intraperitoneal injection with fipronil or fipronil-desulfinyl. All compounds were dissolved in DMSO. Eight to 17 mice were used for each LD_{50} determination. Toxicity was evaluated 24 hours after treatment. Further experimental details such as doses and the treatment protocol were not provided. The LD_{50} for desulfinyl-fipronil was 23 mg/kg (Hainzl and Casida, 1996), which was approximately 2-fold more toxic than the parent (41 mg/kg). The study also measured the mouse GABA receptor IC_{50} for fipronil and fipronil-desulfinyl. The IC_{50} for fipronil-desulfinyl was less than one-tenth that of the parent, indicating its greater inhibitory potential at the mouse receptor (IC_{50} = 1010 nM for fipronil and 97 nM for fipronil-desulfinyl).

I.C. Subchronic Toxicity

I.C.1. Oral 14-day – Rat

An exploratory 14-day toxicity study was conducted in the rat by oral gavage (Dange, 1994c). Fipronil-desulfinyl (98.6%) was administered to 5 Sprague Dawley rats/sex/dose at 0.3, 1, 3 or 10 mg/kg/day for 14 days. Between days 5 and 8, 1 female died at 3 mg/kg/day and all animals died at 10 mg/kg/day. Clinical signs including piloerection, chromodachryorrhea, prostration, excessive reaction to noise, curled up at handling, hunched posture, nasal discharge, and few feces were observed at 3 and 10 mg/kg/day. Convulsions preceding death occurred in 3 males and 2 females at 10 mg/kg/day. Decreased body weights were observed at 10 mg/kg/day in males and females at day 5. Decreased body weight gain was observed at 3 mg/kg/day and 10 mg/kg/day in males and females. Average feed consumption rates decreased at 3 mg/kg/day in females and at 10 mg/kg/day in males and females. Neutrophils increased in a dose-dependent manner up to 240%, achieving statistical significance at 3 mg/kg/day ($p < 0.01$). A dose-dependent decrease in total bilirubin occurred in males and females, achieving statistical significance at 3 mg/kg/day dose ($p < 0.05$). Increased serum total protein was observed in females at 3 mg/kg/day ($p < 0.05$). Brain congestion was noted in all decedents. There was an increase in severity and occurrence of thyroid cell atrophy in males but not in females. The investigators considered the effect treatment-related at 3 mg/kg/day.

The NOEL was 1 mg/kg/day, based on blood chemistry effects and mortality seen at 3 mg/kg/day.

I.C.2. Oral 28-day – Rat

Fipronil-desulfinyl (97.5%) was administered to 10 Sprague-Dawley rats/sex/group in the diet at 0, 0.5, 3, 30, or 100 ppm for 28 consecutive days (Dange, 1995b). All rats at 100 ppm died

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between days 5 and 15. One male at 30 ppm died on day 6. Mean dose levels were 0, 0.04, 0.23, and 2.2 mg/kg/day in males and 0, 0.04, 0.24, and 2.32 mg/kg/day in females (mean doses at 100 ppm were not included due to total mortality). Clinical signs included curling up on handling, thin appearance, crusty skin, and piloerection. There were dose-related body weight and food consumption decrements. A sharp reduction in thyroid hormones was detected at 30 and 100 ppm: On day 7, Triiodothyronine (T3) was 46% lower in surviving females ($p < 0.001$) and Thyroxine (T4) was lower by 63% in males ($p < 0.05$) and by 50% in females ($p< 0.01$) at 100 ppm. In animals dosed at 30 ppm, T4 was lower by 33% in males ($p < 0.001$); on day 23, both sexes had reduced T4 (49% in males and 61% in females, $p < 0.01$) and T3 was 33% lower in males ($p < 0.01$).

The NOEL was 3 ppm (0.23 mg/kg/day) based on mortality and reductions in thyroid hormones at 30 ppm.

I.C.3. Oral 90-day – Rat

Fipronil-desulfinyl (97.5%) was administered to 10 Sprague Dawley rats/sex/group via diet at 0, 0.5, 3, 10, or 30 ppm, equivalent to 0, 0.029, 0.177, 0.594, and 1.772 mg/kg/day for males and 0, 0.035, 0.210, 0.709, and 2.101 mg/kg/day for females (Dange, 1994b). In addition to standard subchronic study parameters, measurements of T3, T4, and thyroid stimulating hormone (TSH) were taken at study weeks 2 and 10.

Clinical signs including irritability to touch in both sexes at 10 ppm and 30 ppm and in 1 male at 3 ppm. Increased motor activity was seen in 1 female at 10 ppm and in 9/10 females at 30 ppm. Five out of 10 males at 30 ppm curled up on handling. Mortality occurred at 30 ppm in 1 male and in 3 females on days 11 and 13. Treatment at 30 ppm significantly reduced body weight in females from day 8 to 36 and in males by 8 – 15% from days 8 to 71 ($p < 0.05$). At 10 ppm, body weight was significantly decreased in males by 7 – 5% from day 57 to 78 ($p < 0.05$). Food consumption was transiently reduced at 30 ppm in males and females; decrement was significant through day 15 in males ($p < 0.01$) and through day 8 in females ($p < 0.05$).

Significant changes in clinical chemistry parameters occurred in females treated with 30 ppm fipronil-desulfinyl. These include reduced cholesterol ($p < 0.05$), reduced triglycerides ($p < 0.05$), and reduced bilirubin ($p < 0.01$). Treatment-related histopathology was limited to decedents, and showed lymphoid depletion in the spleen, pulmonary edema in lungs, and hypertrophy of the zona fasciculata of the adrenal cortex. Increased relative brain weight was seen in males at 10 and 30 ppm ($p < 0.05$). Increased liver weight relative to body weight was observed in females at 10 ppm only ($p < 0.05$).

There was a 29% reduction of T3 at week 10 ($p < 0.05$) and a 48% reduction of T4 at week 2 ($p < 0.01$) in 30 ppm males.

The 90-day NOEL for fipronil-desulfinyl in rats is 0.5 ppm (~0.03 mg/kg/day) based on clinical signs in males at 3 ppm (~0.18 mg/kg/day).

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I.C.4. Oral 28-day – Mouse

Ten OF-1 mice/sex/group were dosed with fipronil-desulfinyl (97.5%) via the diet at 0, 0.5, 3, 30, or 60 ppm, equating to mean dose levels of 0.08, 0.49, and 5.0 mg/kg/day for the lowest 3 dose levels in males, and 0.10, 0.61, 5.6, and 12.1 mg/kg/day in females (Dange, 1994d). All males at 60 ppm died by the end of week 2. Six females at 60 ppm died and 7 males and 2 females at 30 ppm died. Clinical signs at 30 and 60 ppm included increased motor activity, excessive jumping, and compulsive biting. Body weights of males treated at 60 ppm were significantly decreased by 27% after 1 week of exposure ($p < 0.05$); no males survived to the next weight measurement. Males treated at 30 ppm had significantly decreased body weight of up to 17% for the duration of the treatment period ($p < 0.05$). Females at 60 ppm also saw a 10% decrease in body weight after 1 week ($p < 0.05$). Body weight gain was significantly reduced in males at 30 ppm for all time points and at 60 ppm for the one time point measured ($p < 0.05$). Food consumption was decreased in males at 30 ppm for the first two weeks and in males and females at 60 ppm for the first week. Relative liver weights were elevated by 19% in males at 30 ppm and by 22% in females at 60 ppm ($p < 0.05$). Centrilobular hypertrophy was remarkably increased in males at 30 ppm.

The NOEL for fipronil-desulfinyl in mouse is 3 ppm or 0.49 mg/kg/day based on clinical signs, mortality and liver changes at 30 ppm.

I.C.5. Oral 90-day – Mouse

Ten OF1 mice/sex/group received 0, 0.5, 2 or 10 ppm fipronil-desulfinyl (96%) in the diet for 13 weeks (Bigot, 1996). The mean achieved doses were 0, 0.08, 0.32 and 1.74 mg/kg/day in males and 0, 0.11, 0.43 and 2.15 mg/kg/day in females. All 10 males and 1 female from the 10 ppm group died or were euthanized in moribund condition before study termination. Death occurred in males on days 20, 28, 39, 48, 52, 62 and 84 and in the females on day 5. The only clinical signs noted for these animals were excessive jumpiness and/or irritability in 3 males, indicating possible neurological effects. There were no treatment effects on mean body weight or food consumption.

The mean serum alkaline phosphatase level in 10 ppm females was 61% higher than that of the control ($p < 0.05$) and was increased in a dose-dependent manner. Conversely, the alkaline phosphatase level in males decreased with increasing dose, and differences were not significantly different from control. There were no treatment related effects on the absolute or relative organ weights, although liver enlargement was seen in 3/10 and small thymus was seen in 4/10 male decedents at 10 ppm. The incidence of centrilobular hypertrophy in the liver increased in 10 ppm male decedents (0/10 at 0 ppm vs. 6/10 at 10 ppm).

The subchronic dietary NOEL for mice is 2 ppm or 0.32 mg/kg/day, based on mortality in both sexes and increased alkaline phosphatase levels in females at 10 ppm.

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I.C.6. Oral 28-day – Dog

Two Beagle dogs/sex/dose received fipronil-desulfinyl (97.5%) in the diet at 0, 27, 80 or 270 ppm for 28 days (Dange, 1995a). This study was a preliminary, range-finding study. The mean intake levels were 0, 1, 1.9 and 2.3 mg/kg/day in males and 0, 1, 1.7 and 2.3 mg/kg/day in females. Mortality (2/2) occurred at both 80 and 270 ppm.

At 80 ppm, 1 dog/sex was sacrificed moribund on day 10 and the remaining dogs were sacrificed on day 15. Animals displayed reduced motor activity, staggering steps, irritability, increased salivation, absent or few feces and emaciation. All animals at 270 ppm were sacrificed on day 10 due to moribundity caused by a lack of food consumption beginning on day 5. Few or no feces and emaciation were noted at 270 ppm. Soft feces were occasionally observed in males at 27 ppm. One male in the 27 ppm group vomited on day 20, and the other male displayed fear and convulsions on day 29.

Body weights and food consumption at 27 ppm were comparable to controls. All animals lost weight at 80 ppm (0.3 to 1.2 kg) and at 270 ppm (0.3 to 1.8 kg). At 80 ppm, food consumption was decreased starting on day 4. At 270 ppm, all animals had a marked decrease in food consumption beginning on day 2 and were generally not eating from day 6 to 10. There was a dose-dependent decrease in weight gain in both males and females.

At terminal necropsy, one female at 27 ppm had a pale liver and both males had lower relative thymus weights compared to controls. The 80 ppm animals sacrificed on day 10 revealed pale abnormal liver color in one male and multifocal whitish areas on the liver, small thymus, and multifocal red areas on the lung in one female. Sacrifice of the remaining 2 animals at 80 ppm on day 15 revealed small thymus in both male and female with mottled appearance of the liver in the male and pinpoint black spots on the gastric mucosa in the female. At 80 ppm, there was marked thymus atrophy, diffuse sinusoidal leukocytosis in liver, and centrilobular hepatocytic enlargement in all dogs. Additionally, mild multifocal hydropic degeneration of the hepatocytes and chronic hepatitis with periportal fibrosis were noted in one male and one female.

The NOEL was < 27 ppm (< 1 mg/kg/day) based on convulsions and incidence of pale liver at 27 ppm.

I.C.7. Oral 90-day – Dog

Five Beagle dogs/sex/dose received fipronil-desulfinyl (96%) in the diet at 0, 3.5, 9.5, or 35 ppm for 90 days (Dange, 1996). The mean fipronil-desulfinyl intake was 0, 0.10, 0.27, and 0.95 mg/kg/day for males and 0, 0.10, 0.29, and 1.05 mg/kg/day for females.

One 35-ppm female was sacrificed on day 28 with increased salivation, prostration, writhing and tremors, noisy breathing, and dyspnea. Microscopy revealed marked coronary arteritis and myocardial necrosis. The investigators considered these effects common to dogs of this age and did not attribute the death to treatment.

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Body weight, food consumption, and hematology were comparable to controls at all dose levels. Excessive barking and aggressive behavior were noted on day 84 and increased salivation, irritability, and tremors were noted on day 86 in one female at 35 ppm. At week 13, a male in the 9.5 ppm dose group displayed increased alanine aminotransferase and alkaline phosphatase activities relative to controls. A significant increase in group mean urine pH was noted for males at 35 ppm ($p < 0.01$). A low incidence of mild to moderate coronary arteritis and slight to moderate thymus involution was observed across all groups (including controls) and both sexes. Gross necropsy, organ weights, and histopathology were unremarkable.

The NOEL of 9.5 ppm (0.29 mg/kg/day) was based on aggressive behavior and increased salivation, irritability, and tremors in one high dose female.

I.D. Chronic Toxicity and Oncogenicity - Rat

Fipronil-desulfinyl (96%) was administered via the diet at 0, 0.5, 2 or 10 ppm to 10 Sprague-Dawley rats/sex/group for sacrifice after 53 weeks (interim group) and to 60 rats/sex/group for sacrifice after 104 weeks (terminal sacrifice group) (Bigot, 1998). Animals were observed daily for clinical signs. Body weights and food consumption were measured weekly for the first 13 weeks and once every 4 weeks thereafter. Hematology was performed on the interim group at 26 and 52 weeks and clinical chemistry was performed at weeks 25 and 51. Hematology was performed in the terminal sacrifice group at weeks 26, 52, 78 and 104, and clinical chemistry was performed at weeks 25, 51, 77 and 103. The mean fipronil-desulfinyl intake during the treatment period from week 1-53 was 0, 0.028, 0.113 and 0.563 mg/kg/day in males and 0, 0.039, 0.143 and 0.733 mg/kg/day in females. The mean fipronil-desulfinyl intake during the treatment period from week 1-101 was 0, 0.025, 0.098 and 0.497 mg/kg/day in males and 0, 0.032, 0.127 and 0.546 in females.

By 26 weeks of treatment at 10 ppm there was an increase in the mortality rate in females. Investigators subsequently reduced the dietary level from 10 to 6 ppm for females only. The authors state that the survival rates of all control and treated groups were in the same range as the survival rates from historical controls in the conducting laboratory. Survival rates were provided for 4 historical control studies, but no details were given on the strain or number of animals or the date range of these studies.

Chronic exposure to fipronil-desulfinyl resulted in chromodachryorrhea (bloody tears due to excessive secretion of porphyrins) that was dose-responsive and significantly increased in the high-dose females ($p < 0.05$). Aggressive behavior and irritability to the touch were increased in high dose males and females ($p < 0.05$ for males, $p < 0.001$ for females). Convulsions were observed in all exposed groups and in control males and were statistically significantly increased relative to controls in females at 2 and 10 ppm ($p < 0.05$ and $p < 0.01$, respectively). Males exposed to 2 ppm experienced convulsions before any other group (day 85). In females, the onset of convulsions occurred earlier with increasing dose, in a dose-dependent manner. No changes were observed in body weight, food consumption, urinalysis, organ weights, or histopathological findings at necropsy.

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The high dose group males had statistically significant increases of sub-epithelial mixed cell infiltration in the stomach ($p < 0.05$). A dose-dependent increase in incidences of lung congestion/hemorrhage occurred in females, which was statistically significant at the high dose ($p < 0.05$). There was a statistically significant decrease in bilirubin and in triglycerides and an increase in glucose in females at high dose during week 26 only.

The chronic NOEL for fipronil-desulfinyl in the rat was 0.5 ppm or 0.025 mg/kg/day due to mortality in males and increased convulsions in females at the LOEL of 2 ppm.

I.E. Genotoxicity

The below table (Table 1) describes genotoxicity studies for fipronil-desulfinyl and for fipronil metabolites fipronil-sulfide and fipronil-sulfone.

Table 1. Genotoxicity Studies Conducted with Fipronil Photodegradate or Metabolites

Chemical	Test Type	System	Species, Strain or Culture	Dose or Concentration	S9	Result	Reference/Study Status
Fipronil-Desulfinyl	Gene Mutation	Ames Reverse Mutation Assay	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA138	10, 25, 50, 100, 250 µg/plate, 60 hr	±	Negative	(Percy, 1993)
Fipronil-Desulfinyl	Gene Mutation	HGPRT Forward Mutation	Chinese hamster lung V79 cell line	15, 30, 60, 80 or 100 µg/ml	±	Negative	(Adams, 1996a)
Fipronil-Desulfinyl	Chromosomal Aberration	*In vitro* Chromosome Aberration	Human lymphocytes (♂)	5, 15, 30, 60, 125, 250, 500 or 625 µg/ml for 18 or 32 hr	±	Negative	(Adams, 1996b)
Fipronil-Desulfinyl	Chromosomal Aberration	*In vivo* Chromosome Abberation	CD-1 Swiss mouse bone marrow erythrocytes (♀ + ♂)	2, 4, 8 or 16 mg/kg for 24, 48 or 72 hr	n/a	Negative	(Proudlock, 1996)
Fipronil-Sulfide	Gene Mutation	Ames Reverse Mutation Assay	*S. typhimurium* TA98, TA100, TA1535, TA1537	10, 25, 50, 100 and 250 µg/plate, 72 hr	±	Negative	(Percy, 1994)
Fipronil-Sulfone	Gene Mutation	Ames Reverse Mutation Assay	*S. typhimurium* TA98, TA100, TA1535, TA1537	0.32, to 500 µg/plate, 48 hr	±	Negative	(Clare, 1988)
Fipronil-Sulfone	Chromosomal Aberration	*In vitro* Chromosome Aberration	Human lymphocytes (♀ + ♂)	75, 100 or 300 µg/ml for 3 hr	±	Negative	(Marshall, 1988)

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Table 1. Genotoxicity Studies Conducted with Fipronil Photodegradate or Metabolites

Chemical	Test Type	System	Species, Strain or Culture	Dose or Concentration	S9	Result	Reference/Study Status
Fipronil-Desulfinyl and Fipronil-Sulfone	Oxidative Stress In Vitro	Mitochondrial respiration, ATP synthesis, mitochondrial membrane potential, Ca^{2+} efflux	Wistar rat liver cells	0.5- 25 µM	n/a	Positive	(Tavares *et al.*, 2015)

I.G. Developmental Toxicity - Rat

Fipronil-desulfinyl (99.2%) was administered to sperm-positive female CD rats (25 per group) by oral gavage from gestation days (GD) 6 to 15 at doses of 0.2, 1.0 or 2.5 mg/kg/day (Foulon, 1997). Dams were examined daily for signs of illness. Body weights were recorded on GD 0, GD 6-16 and on GD 20. Dams were sacrificed on GD 20 and the reproductive tract and fetuses were examined.

No mortality occurred in the dams. A significant decrease in weight gain occurred in dams at 1.0 and 2.5 mg/kg/day from GD 6-12 and at 2.5 mg/kg/day from GD 6-26 ($p < 0.01$). Reduced food consumption was seen at 2.5 mg/kg/day from GD 9-12 and GD 12-16 ($p < 0.01$). A significant increase in hair loss and scabbing in dams occurred at 2.5 mg/kg/day ($p < 0.05$).

At 2.5 mg/kg/day, there was a dose-dependent, significant increase in non-ossification of the 5th and 6th sternebrae in fetuses ($p < 0.01$). In addition, there was an increase in ossification delay of pubic bones and the caudal vertebrae at 2.5 mg/kg/day. Fetal body weights were statistically significantly decreased by 2.4% in females ($p < 0.01$) and 2.5% in males ($p < 0.05$).

The maternal NOEL is 0.2 mg/kg/day due to statistically significant decreases in body weight during the dosing period at 1.0 mg/kg/day. The developmental NOEL is 1.0 mg/kg/day due to fetal body weight change and ossification delays at 2.5 mg/kg/day.

I.H. Acute Neurotoxicity - Rat

Fipronil-desulfinyl (99.5%) was administered as a single oral gavage dose to 12 Crl: CD BR rats/sex/dose at 0.5, 2 or 12 mg/kg in corn oil (Hughes, 1996). Animals were observed for 14 days following treatment. FOBs were performed before treatment, at time of peak effect (TOPE, determined to be 6 hours in a range-finding experiment conducted in the same laboratory) and at days 7 and 14 post-dosing. All animals from the control and high dose groups were subjected to pathological evaluation. Brain, spinal cord, peripheral nerves (sciatic, sural and tibial), dorsal root and gasserian ganglia were examined for pathology.

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No mortality was observed. Significant decreases in body weight gains were observed at 12 mg/kg in males and females during week 1 (22 – 25%, $p < 0.01$) and a 30% increase in weight gain was seen in males during week 2 ($p < 0.05$). Food consumption decreased in 12 mg/kg males and females during week 1 ($p < 0.01$) with no effect on food utilization/conversion. Clinical signs (soft stool and change in appearance of the fur) were also seen in the controls and were attributed to the corn oil vehicle.

Significant changes were observed in the FOBs conducted in animals dosed at 12 mg/kg group, compared with the control group, in both sexes. At the 6-hour TOPE, there was an increase in forelimb strength in females, a decrease in hindlimb splay in males and females, and a decrease in rectal temperature in males and females ($p < 0.01$). On day 7, a significantly decreased forelimb grip strength in males and an increase in mean activity counts in females at 12 mg/kg were observed ($p < 0.05$). There was also a significant increase in mean activity counts in females at 2 mg/kg on day 7 ($p < 0.05$). However, the mean activity counts were the same for all three fipronil treatment doses; a lack of dose-response over the 24-fold range lacks plausibility as a treatment effect. At day 14, there was a significant increase in mean rearing events in females and a decrease in immediate righting reflex in males at 12 mg/kg (both $p < 0.05$), which were highly variable and may not have been due to treatment.

A total of 4/12 control males had axonal degeneration in nerve tissues compared to 6/10 males in the high-dose group; the increase was not statistically significant. One of 5 female controls and 2/5 high-dose females displayed axonal degeneration. The report authors suggest that axon degeneration is not treatment related. However, the modest increase combined with the fact that authors did not evaluate tissues from the low- or mid-doses made it impossible to determine if this was due to treatment.

The acute neurotoxicity study NOEL for rats was 2 mg/kg due to decreased body weight gain and food consumption and observations in the functional observational battery in the 12 mg/kg group.

II. Fipronil-Sulfone

II.A. Acute Toxicity - Mouse

A published study in mice was available from open literature with administration via intraperitoneal injection (Cole *et al.*, 1993). Male Swiss-Webster mice were treated via intraperitoneal injection with fipronil and its metabolite fipronil-sulfone. All compounds were dissolved in DMSO. Eight to seventeen mice were used for each LD_{50} determination. Toxicity was evaluated 24 hr after treatment. Further experimental details such as doses and the treatment protocol were not provided. The LD_{50} for fipronil was reported as 32 mg/kg and the LD_{50} was reported as 80 mg/kg for fipronil-sulfone.

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II.B. Genotoxicity

A gene mutation study, a chromosome aberration study, and an oxidative stress study with fipronil-sulfone are described in the genotoxicity Table 1 in the fipronil-desulfinyl section, above.

III. Fipronil-Sulfide

III.A. Acute Toxicity - Rat

Fipronil-sulfide was orally administered to 5 Sprague Dawley rats/sex/dose at 50, 65, 90 or 120 mg/kg (Dange, 1994a). Mortality was observed in both sexes at doses higher than 50 mg/kg within the first week following treatment. Body weight gains were observed in all surviving rats except 1 female at 50 mg/kg during the two-week post-exposure period. Common clinical signs include excessive jumps at 50 mg/kg in males and females. Subdued behavior, fear, mucoid feces, clonic convulsions, slight tremor, curls up at handling, piloerection, hunched posture, reduced motor activity, soiled fur and excessive vocalization were observed at the higher doses. Stomach distended with gas and moderately enlarged liver were observed in rats at terminal autopsies and at autopsy of decedents. The LD_{50} for males and females is 83 mg/kg. Fipronil-sulfide is a Toxicity Category II acute oral toxicant. The LOEL of 50 mg/kg is based on excessive jumping in both sexes and failure to gain weight in one female.

III.B. Genotoxicity

A gene mutation study with fipronil-sulfide is described in the genotoxicity Table 1 in the fipronil-desulfinyl section, above.

IV. Comparative Toxicity of Fipronil, Metabolites and Photodegradate

Fipronil and fipronil-desulfinyl share a similar pharmacokinetic profile and mode of action (interaction with the GABA receptor). The pharmacokinetic profiles for absorption, distribution, elimination, and blood kinetics in rats were similar for fipronil and desulfinyl, with feces being the main route of elimination. Acute studies for fipronil-desulfinyl showed the photodegradate to be more toxic than fipronil by the oral route but similarly toxic by dermal and IP administration. The toxicity profile for fipronil-desulfinyl was characterized by mortality and clinical signs of neurotoxicity (increased/decreased motor activity in rats, convulsions) while fipronil showed selective organ toxicity (liver and thyroid) in addition to neurotoxic effects. Unlike the parent fipronil, chronic exposure of rats to fipronil-desulfinyl did not result in thyroid toxicity or tumors. Fipronil and fipronil-desulfinyl may differ in their ability to affect the thyroid gland. It has been suggested that the sulfoxide group of fipronil, which the photodegradate lacks, may be responsible for the thyroid effects (US EPA, 2000).

The limited acute toxicity studies in rats and mice indicate that the sulfide and the sulfone have mammalian toxicity similar to the parent compound, but the sulfone may be a stronger inhibitor of the GABA receptor. Chronic toxicity studies were not available for the sulfone or the sulfide

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metabolites to evaluate their effects on the liver or thyroid function. The toxicity of other identified fipronil metabolites (detrifluoromethylsulfonyl-fipronil and the amide RPA200766) have not been evaluated in mammals.

Neither the metabolites nor the photodegradate caused mutations or chromosome aberrations. However, fipronil-desulfinyl and fipronil-sulfone caused increased oxidative stress *in vitro*.

V. Conclusions

Based on the limited data available for the metabolites fipronil-sulfone and fipronil-sulfide, toxicity is comparable to the parent. However, the lack of subchronic, chronic, developmental and neurotoxic data preclude further comparison. Based on the acute LD_{50} values in rat and mice, oral and dermal desulfinyl is more toxic than the parent. However, the points of departure (POD) established in the available studies are comparable, and the critical POD for fipronil will be protective of desulfinyl exposure.

An important consideration is a lack of exposure data for the metabolites and for fipronil-desulfinyl. As such, characterizing risk from total exposure to fipronil and its derivatives cannot be conducted at this time.

In conclusion, the critical POD established for fipronil in this risk assessment are assumed to be protective against the toxicity of fipronil-desulfinyl. Table 2 compares the critical points of departure (POD) for fipronil to the POD established in the respective studies with fipronil-desulfinyl.

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Table 2. Fipronil Critical POD compared to Toxicity of Fipronil-Desulfinyl

Duration	Fipronil	Fipronil POD	Fipronil-desulfinyl	Fipronil-desulfinyl POD
	Critical Endpoint	**(mg/kg/day)**	**Endpoints**	**(mg/kg/day)**
Acute	Decreased hindlimb splay in an acute oral neurotoxicity study in rats	0.87[a]	Altered forelimb grip strength, decreased hindlimb splay, decreased rectal temperature and decreased body weight gain and food consumption in an acute oral neurotoxicity study in rats	2.0[d]
Subchronic	Convulsions and mortality and sustained decreases in T4 after subchronic oral exposure in a chronic study in rats	0.02[b]	Irritability to touch and aggressive behavior in a 90-day subchronic oral study in rats	0.029[e]
Chronic	Convulsions and mortality, sustained decreases in T4, and increased progressive senile nephropathy in a chronic oral study in rats	0.02[c]	Mortality in males and increased convulsions in females in a chronic oral study in rats	0.025[f]

POD: point of departure; T4: thyroxine thyroid hormone.
[a]Benchmark dose modeling (BMDS, version 2.6) of hindlimb splay data from acute neurotoxicity study in rat (Hughes, 1997). NOEL of 2.5 mg/kg/day.
[b]Combined chronic and oncogenic study in rat (Aughton, 1993).
[c]Combined chronic and oncogenic study in rat (Aughton, 1993).
[d]Acute neurotoxicity study in rat (Hughes, 1996).
[e]Subchronic 90-day oral study in rat (Dange, 1994b).
[f]Combined chronic and oncogenic study in rat (Bigot, 1998).

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APPENDIX IV. FIPRONIL BENCHMARK DOSE MODELING OF ENDPOINT DATA FOR FIPRONIL (13 pages)

The Department of Pesticide Regulation (DPR) used a benchmark dose (BMD) approach to derive points of departure (PODs) for all data amenable to modeling. The US EPA's Benchmark Dose Software (BMDS; versions 2.6 and 2.7) was used to estimate the threshold of toxicity for each endpoint. For this risk assessment, modeled data included quantal data (dichotomous incidence response) and continuous data (exact values and standard deviations from reported measurements). The threshold or Benchmark Response (BMR) level for a given effect was 10% for quantal or continuous data, and 5% for developmental effects (US EPA, 2012a). BMDS converted the data for each endpoint into a family of related mathematical models. Each model provided a benchmark dose (BMD) value as well as a value representing the 95% lower bound of the BMD (BMDL), which was considered the POD for the observed effect.

In the BMD approach, the data for each endpoint were used to generate a family of models. Each model was evaluated over the full dose range to select a "best" model for each data set. The evaluation process was based on a hierarchical examination of:

- the results from statistical tests for goodness-of-fit,
- the lowest Akaike Information Criteria (AIC) score for relative goodness-of-fit,
- closeness of BMD and BMDL to each other and to the nearest dose levels for goodness-of-fit and model dependence,
- visual inspection of lines over data points for goodness-of-fit and toxicological plausibility,
- the magnitude of residuals for goodness-of-fit, and
- considerations of sample size, variability, and whether there is a maximum response at the high dose.

The most appropriate models for each endpoint were next evaluated as part of the hazard identification process for their fitness to provide PODs for risk assessment. This evaluation reconsidered factors that included the toxicological plausibility of the effect and the quality of the data, as well as the relative magnitude of the threshold of toxicity represented by the BMDL. Models and PODs that were considered in the fipronil risk assessment are described in this appendix.

I. Acute Point of Departure

Continuous hindlimb splay data from male Crl:CD BR rats in an acute neurotoxicity study (Hughes, 1997) were modeled with a 10% effect level (BMR_{10}).

Exponential4 was the best-fit model, with a BMD_{10} of 2.48 mg/kg and a $BMDL_{10}$ of 0.87 mg/kg. Raw data are shown in Table 1. BMDS analysis results are shown in Table 2, and the best-fit model plot is shown in Figure 1.

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Table 1. Hindlimb splay data in male Crl:CD BR rats, 7 hours post-treatment with fipronil, in acute neurotoxicity study

Dose (mg/kg)	N	Mean (cm)	SD
0	10	8.7	1.58
2.5	10	7.8	1.38
7.5	10	6.7**	1.07
25	10	6.3**	2.08

** Indicates p-value < 0.01; SD: standard deviation.
Data from Hughes (1997).

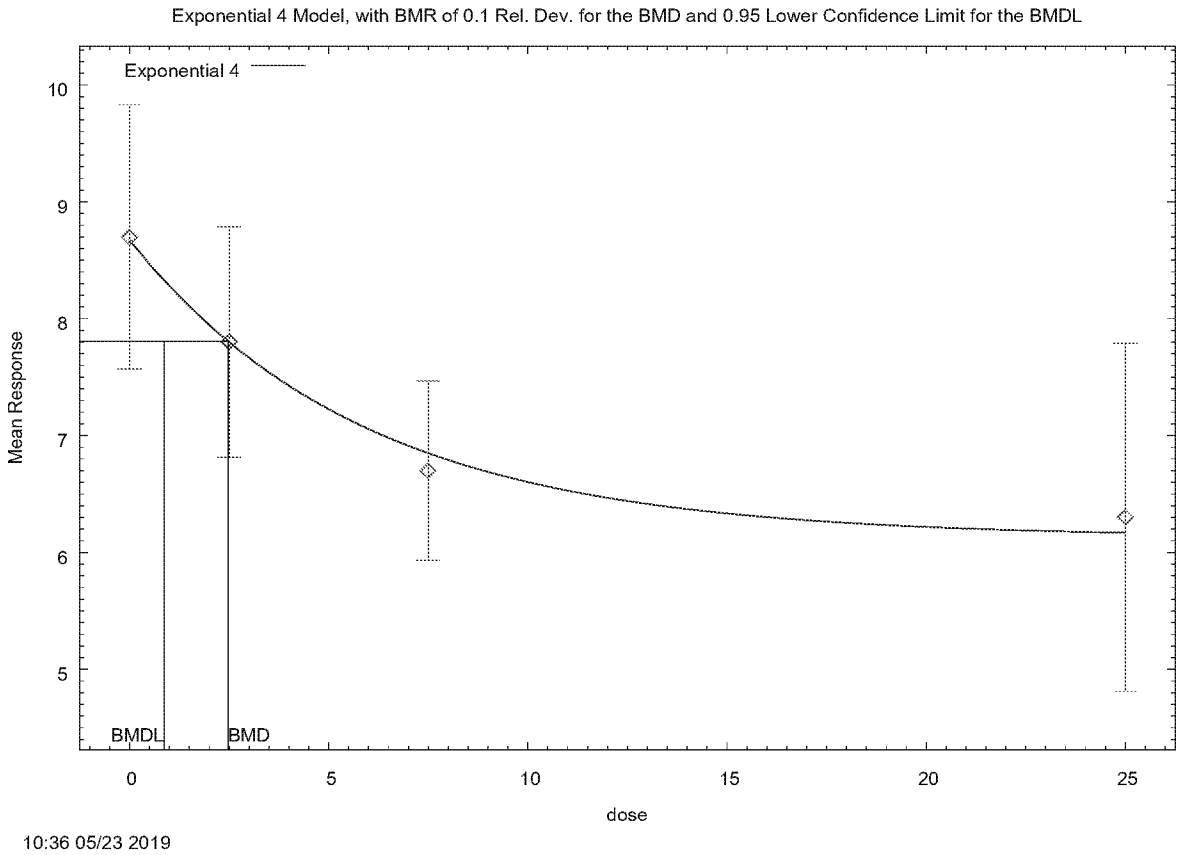

Figure 1. Plot of best-fit (Exponential 4) model of hindlimb splay in male Crl:CD BR rats following exposure to fipronil in acute neurotoxicity study (Hughes, 1997)

ED_013611_00000016-00249

Table 2. BMDS analysis of hindlimb splay data in male Crl:CD BR rats after fipronil exposure in acute neurotoxicity study

Model Name	Expo 2	Expo 3	Expo 4	Expo 5	Hill	Linear	Polynomial	Polynomial	Power
Data File Name	Hughes 1997 male splay.dax	Hughes 1997 male splay.dax	Hughes 1997 male splay.dax	Hughes 1997 male splay.dax	Hughes 1997 male splay.dax	Hughes 1997 male splay.dax	Hughes 1997 male splay.dax	Hughes 1997 male splay.dax	Hughes 1997 male splay.dax
Option File Name	Exp-ConstantVariance-BMR10-Down.opt	Exp-ConstantVariance-BMR10-Down.opt	Exp-ConstantVariance-BMR10-Down.opt	Exp-ConstantVariance-BMR10-Down.opt	Hil-ConstantVariance-BMR10-Restrict.opt	Lin-ConstantVariance-BMR10.opt	Ply2-ConstantVariance-BMR10-RestrictDown.opt	Ply3-ConstantVariance-BMR10-RestrictDown.opt	Pow-ConstantVariance-BMR10-Restrict.opt
Estimated Values of Interest	Array	Array	Array	Array					
Table of Data and Estimated Values of Interest					Array	Array	Array	Array	Array
Specified Effect	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Risk Type	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation
BMD	7.62838	7.62838	2.47559	2.58684	2.57724	9.02931	9.02931	9.02931	9.02931
BMDL	4.42852	4.42852	0.874684	0.875941	0.567152	5.77249	5.77249	5.77249	5.77249
p-value Test 1: Lack dose response?	0.006272	0.006272	0.006272	0.006272	0.006272	0.006272	0.006272	0.006272	0.006272

ED_013611_00000016-00250

Table 2. BMDS analysis of hindlimb splay data in male Crl:CD BR rats after fipronil exposure in acute neurotoxicity study

Model Name	Expo 2	Expo 3	Expo 4	Expo 5	Hill	Linear	Polynomial	Polynomial	Power
p-value Test 2: Constant variance?	0.2082	0.2082	0.2082	0.2082	0.2082	0.2082	0.2082	0.2082	0.2082
p-value Test 3: Good variance model?	0.1333	0.1333	0.1333	0.1333	0.1333	0.1333	0.1333	0.1333	0.1333
p-value for fit: Does the model for the mean fit?	0.2311	0.2311	0.9358	N/A	NA	0.1791	0.1791	0.1791	0.1791
AIC	82.33704	82.33704	81.41376	83.40727	83.40727	82.846991	82.846991	82.846991	82.846991
Scaled residual for dose group nearest the BMD	-1.491	-1.491	0.001198	-0.05359	-0.0536	-1.62	-1.62	-1.62	-1.62
Scaled residual for control group	1.115	1.115	0.06263	0.08217	0.0822	1.27	1.27	1.27	1.27

Expo: Exponential model; BMD: benchmark dose; BMDL: lower 95th percentile limit of BMD; AIC: Akaike Information Criteria score for relative goodness-of-fit. Blue highlighting and bold text: Final BMD and BMDL.
Data from Hughes (1997).

ED_013611_00000016-00251

II. Pup Body Weight in Developmental Neurotoxicity Study

Fipronil registrants analyzed pup body weight data from this study and from the two-generation reproductive study in rat (King, 1992) to determine a potential POD (Fipronil Task Force, 2015). Four continuous BMD models were tested to fit pup body weight data at 1 standard deviation (SD) and at 5% and 10% extra risk levels. They determined that the most conservative BMDL was derived from the developmental neurotoxicity (DNT) study, with 5% extra risk, on female pup body weight at PND 21, with a $BMDL_{05}$ of 0.39 mg/kg/day. DPR was able to replicate the registrant's model, which failed Test 2. In addition, the analysts did not describe why data from PND 4 pre-cull, 11, 17 and 60 were not modeled. DPR modeled male and female pup BW data from all time points. The model shown below was considered the best for assessing risk to decreased BW in rat pups.

Continuous pup body weight data from post-natal day (PND) 17 male Sprague Dawley rat pups in the DNT study (Mandella, 1995) were modeled using a 5% effect level (BMR_{05}).

The Hill model provided the best-fit, with a BMD_{05} of 0.67 mg/kg and a $BMDL_{05}$ of 0.33 mg/kg. Raw data are shown in Table 3. Analysis results are shown in Table 4, and the best-fit model plot is shown in Figure 2. DPR considers this BMDL appropriate for use as an endpoint for decreased pup weight in the DNT study, but not for other effects seen in the DNT study.

Table 3. Body weight data for PND 17 male Sprague Dawley rat pups following fipronil exposure *in utero* and during lactation in developmental neurotoxicity study

Dose (mg/kg/day)	N	Mean (grams)	SD
0	27	40.3	3
0.05	29	39.2	4.7
0.9	29	36.7	4.9
15	23	29.5	4.6

SD: standard deviation. Data from Mandella (1995).

ED_013611_00000016-00252

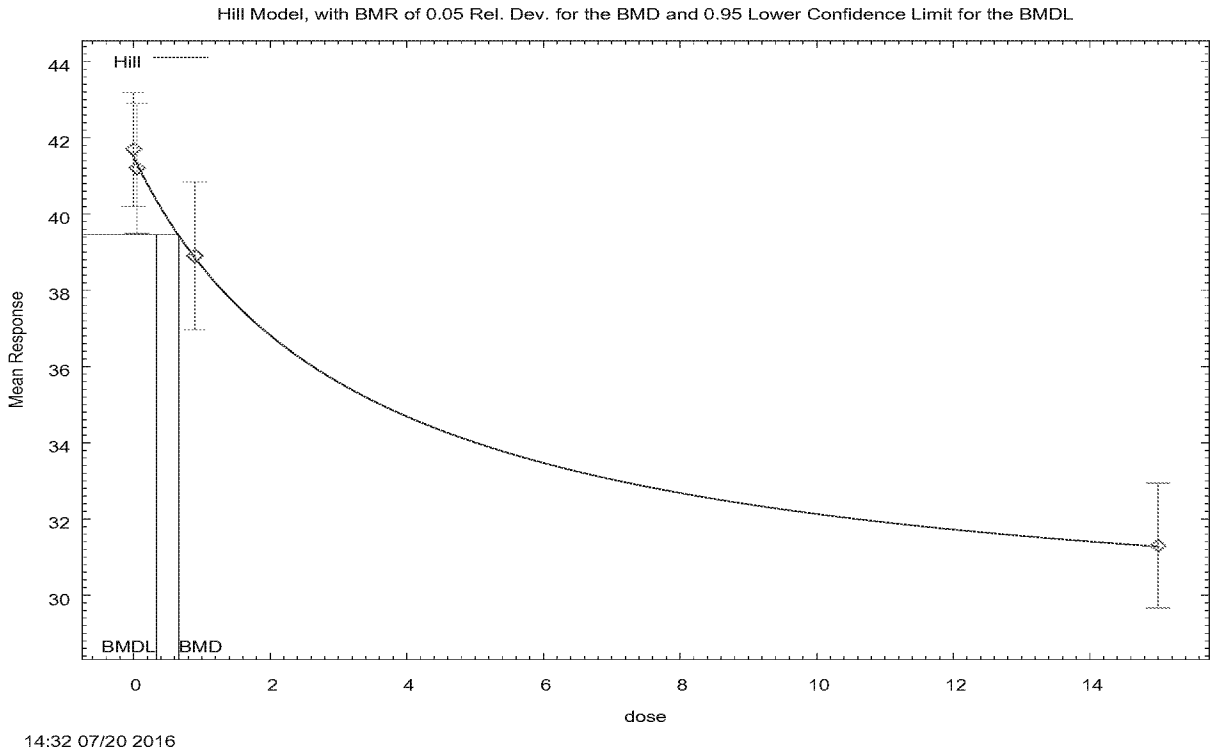

Figure 2. Plot of best-fit (Hill) model of pup body weight in male Sprague Dawley rats following fipronil exposure *in utero* and during lactation from Mandella (1995) developmental neurotoxicity study

ED_013611_00000016-00253

Table 4. BMDS analysis of PND 17 body weight data in Sprague Dawley rat pups following fipronil exposure *in utero* and during lactation in developmental neurotoxicity study

Model Name	Expo 2	Expo 3	Expo 4	Expo 5	Hill	Linear	Polynomial	Polynomial	Power
Data File Name	pup BW day 17.dax	pup BW day 17.dax	pup BW day 17.dax	pup BW day 17.dax	pup BW day 17.dax	pup BW day 17.dax	pup BW day 17.dax	pup BW day 17.dax	pup BW day 17.dax
Option File Name	Exp-ConstantVariance-BMR05-Down.opt	Exp-ConstantVariance-BMR05-Down.opt	Exp-ConstantVariance-BMR05-Down.opt	Exp-ConstantVariance-BMR05-Down.opt	Hil-ConstantVariance-BMR05-Restrict.opt	Lin-ConstantVariance-BMR05.opt	Ply2-ConstantVariance-BMR05-RestrictDown.opt	Ply3-ConstantVariance-BMR05-RestrictDown.opt	Pow-ConstantVariance-BMR05-Restrict.opt
Estimated Values of Interest	Array	Array	Array	Array					
Table of Data and Estimated Values of Interest					Array	Array	Array	Array	Array
Specified Effect	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Risk Type	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation	Relative deviation
BMD	2.84807	2.84807	0.683316	0.683316	0.665089	3.18563	3.18563	3.18563	3.18563
BMDL	2.35878	2.35878	0.381344	0.381344	0.334217	2.70886	2.70886	2.70886	2.70886
p-value Test 1: Lack dose response?	< 0.0001	< 0.0001	< 0.0001	< 0.0001	<.0001	<.0001	<.0001	<.0001	<.0001

ED_013611_00000016-00254

Table 4. BMDS analysis of PND 17 body weight data in Sprague Dawley rat pups following fipronil exposure *in utero* and during lactation in developmental neurotoxicity study

Model Name	Expo 2	Expo 3	Expo 4	Expo 5	Hill	Linear	Polynomial	Polynomial	Power
p-value Test 2: Constant variance?	0.2235	0.2235	0.2235	0.2235	0.2235	0.2235	0.2235	0.2235	0.2235
p-value Test 3: Good variance model?	0.2235	0.2235	0.2235	0.2235	0.2235	0.2235	0.2235	0.2235	0.2235
p-value for fit: Does the model for the mean fit?	0.1418	0.1418	0.7722	0.7722	0.7827	0.1221	0.1221	0.1221	0.1221
AIC	418.7689	418.7689	416.9461	416.9461	416.938292	419.068093	419.068093	419.068093	419.068093
Scaled residual for dose group nearest the BMD	-1.587	-1.587	0.01526	0.01526	0.0182	-1.64	-1.64	-1.64	-1.64
Scaled residual for control group	1.022	1.022	0.2024	0.2024	0.191	1.06	1.06	1.06	1.06

PND: postnatal day; Expo: Exponential model; Poly: polynomial model. BMD: benchmark dose; BMDL: lower 95th percentile limit of BMD; AIC: Akaike Information Criteria score for relative goodness-of-fit. Blue highlighting: Final BMD and BMDL.
Data from Mandella (1995).

ED_013611_00000016-00255

III. Support for Subchronic Point of Departure

III.A. 13-week oral mouse study

Dichotomous periacinar hypertrophy data in male CD-1 mice exposed via the diet for 13 weeks (Broadmeadow, 1991) were modeled with a 10% effect level (BMR_{10}).

The Log Logistic model was the best-fit, with a BMD_{10} of 0.11 mg/kg/day and a $BMDL_{10}$ of 0.06 mg/kg/day. Raw data are shown in Table 5. Analysis results are shown in Table 6, and the plot of the best-fit model is shown in Figure 3.

Table 5. Incidence of periacinar hypertrophy in male CD-1 mice after 13-weeks of daily fipronil exposure

Dose (mg/kg/day)	N	Effect
0	12	0
0.13	12	2
0.38	12	3
1.27	12	6
3.2	12	10

Data from Broadmeadow (1991).

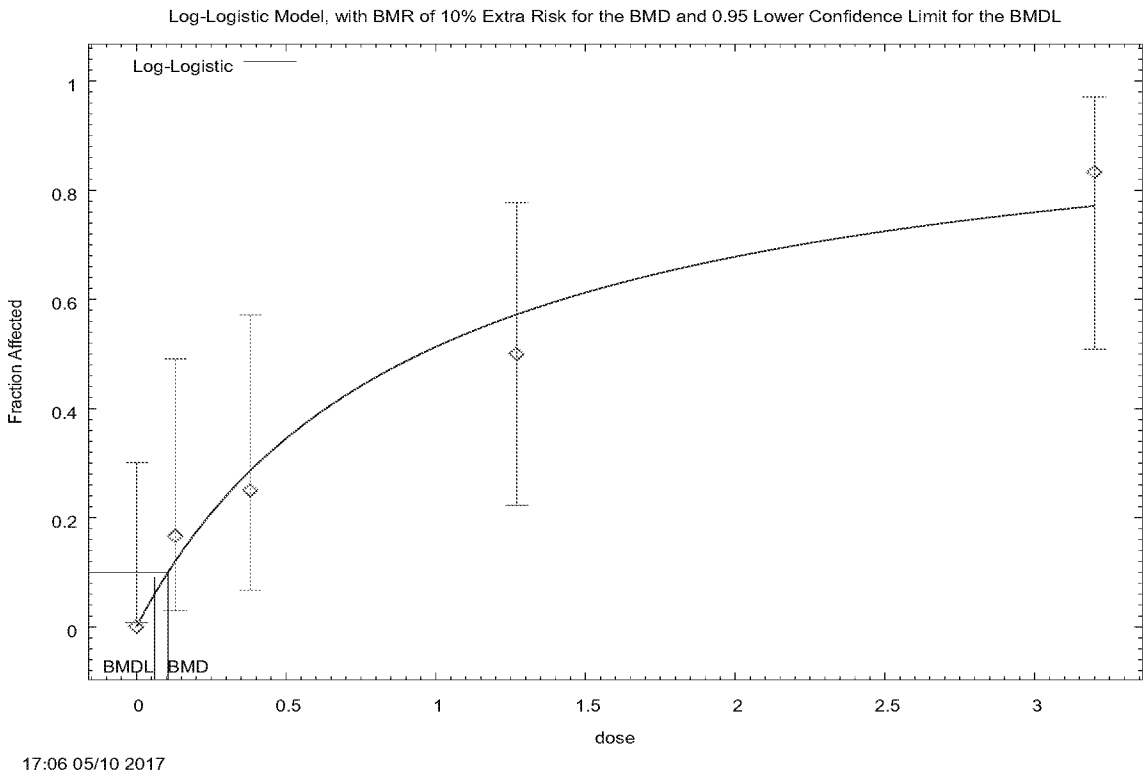

Figure 3. Plot of best-fit (LogLogistic) model of periacinar hypertrophy incidence in male CD-1 mice following 13-weeks of daily fipronil exposure (Broadmeadow, 1991)

ED_013611_00000016-00256

Table 6. BMDS analysis of periacinar hypertrophy data in CD-1 male mice following 13 weeks of daily fipronil exposure

Model Name	Gamma	Logistic	LogLogistic	LogProbit	Multistage	Multistage	Probit	Weibull	Quantal-Linear
Data File Name	Braodmeadow 1991 mouse periacinar male.dax	Braodmeadow 1991 mouse periacinar male.dax	Braodmeadow 1991 mouse periacinar male.dax	Braodmeadow 1991 mouse periacinar male.dax	Braodmeadow 1991 mouse periacinar male.dax	Braodmeadow 1991 mouse periacinar male.dax	Braodmeadow 1991 mouse periacinar male.dax	Braodmeadow 1991 mouse periacinar male.dax	Braodmeadow 1991 mouse periacinar male.dax
Option File Name	Gam-BMR10-Restrict.opt	Log-BMR10.opt	Lnl-BMR10-Restrict.opt	Lnp-BMR10-Restrict.opt	Mst2-BMR10-Restrict.opt	Mst3-BMR10-Restrict.opt	Pro-BMR10.opt	Wei-BMR10-Restrict.opt	Qln-BMR10.opt
BMD	0.174321	0.513478	0.105446	0.342033	0.17432	0.174321	0.494133	0.174322	0.174321
BMDL	0.116961	0.353945	0.0605984	0.205462	0.116961	0.116961	0.355383	0.116961	0.116961
P-value	0.7155	0.4341	0.9336	0.5216	0.7155	0.7155	0.442	0.7155	0.7155
AIC	57.052	59.9741	54.5911	58.8308	57.052	57.052	59.868	57.052	57.052
Scaled residual for dose group nearest the BMD	0.996	0.538	0.492	0.517	0.996	0.996	0.552	0.996	0.996
Scaled residual for control group	-0.371	-1.328	0	-1.031	-0.371	-0.371	-1.298	-0.371	-0.371

BMD: benchmark dose; BMDL: lower 95th percentile limit of BMD; AIC: Akaike Information Criteria score for relative goodness-of-fit. Blue highlighting: Final BMD and BMDL.

ED_013611_00000016-00257

III.B. 13-week oral rat neurotoxicity study

Dichotomous incidence data for urine in the observation arena from male Sprague-Dawley rats exposed via the diet for 13 weeks (Driscoll and Hurley, 1993) were modeled with a 10% effect level ($BMDL_{10}$).

The Multistage 3 model was the best-fit, with a BMD_{10} of 0.02 mg/kg/day and a $BMDL_{10}$ of 0.008 mg/kg/day. Several other models (Gamma, Weibul and Quantal-Linear) also resulted in the same BMD, BMDL and AIC. Raw data are shown in Table 7. Analysis results are shown in Table 8, and the plot of the best-fit model is shown in Figure 4.

Table 7. Incidence of urine in the observation arena in male Sprague-Dawley rats following 13-weeks of fipronil exposure in subchronic neurotoxicity study

Dose (mg/kg/day)	N	Effect
0	10	5
0.03	10	6
0.3	10	9
9	10	10

Data from Driscoll and Hurley (1993).

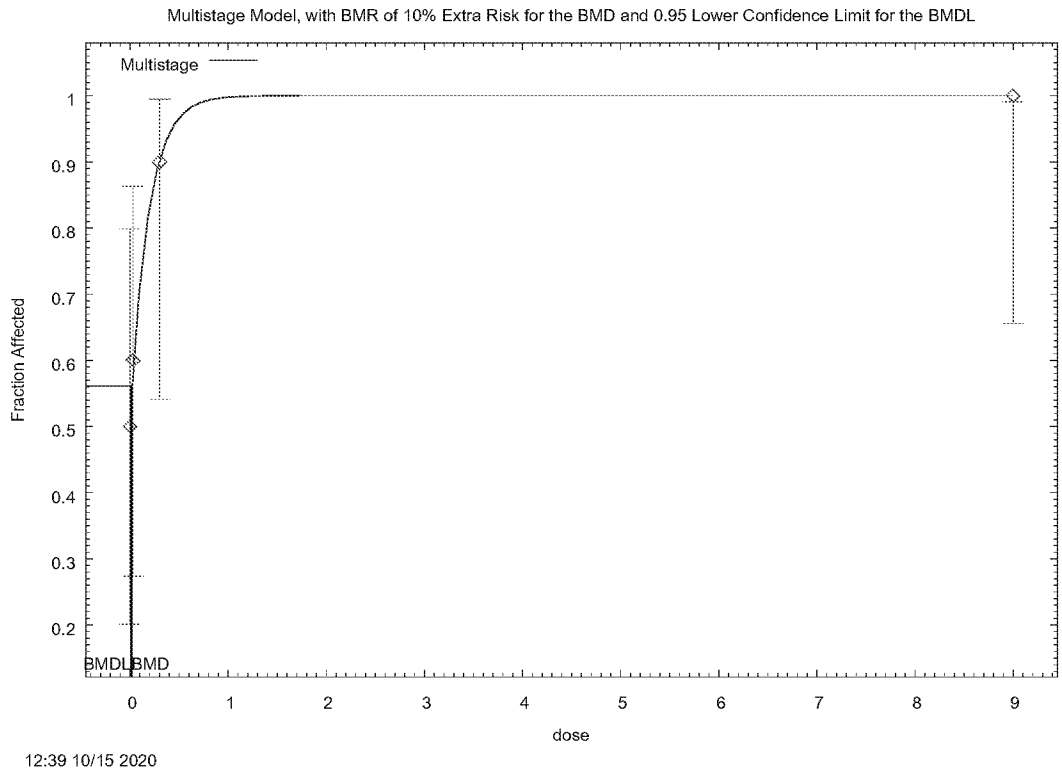

Figure 4. Plot of best-fit (Multistage 3) model of urine in the observation arena in male Sprague-Dawley rats following 13-weeks of fipronil exposure in subchronic neurotoxicity study by Driscoll and Hurley (1993)

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Table 8. BMDS analysis of urine in the observation arena in male Sprague-Dawley rats following 13-weeks of fipronil exposure in subchronic neurotoxicity study

Model Name	Gamma	Logistic	LogLogistic	LogProbit	Multistage	Multistage	Probit	Weibull	Quantal-Linear
Data File Name	Week4Male.dax	Week4Male.dax	Week4Male.dax	Week4Male.dax	Week4Male.dax	Week4Male.dax	Week4Male.dax	Week4Male.dax	Week4Male.dax
Option File Name	Gam-BMR10-Restrict.opt	Log-BMR10.opt	Lnl-BMR10-Restrict.opt	Lnp-BMR10-Restrict.opt	Mst2-BMR10-Restrict.opt	Mst3-BMR10-Restrict.opt	Pro-BMR10.opt	Wei-BMR10-Restrict.opt	Qln-BMR10.opt
BMD	0.0196456	0.0270913	0.017898	0.0358746	0.0196456	0.0196457	0.0292368	0.0196454	0.0196454
BMDL	0.0082223	0.0131233	0.002051	0.0110934	0.0082223	0.0082223	0.0160695	0.0082223	0.0082223
BMDU	0.258875	0.120677	0.283394	0.291216	0.186036	0.217748	0.122391	0.284517	0.113105
P-value	0.9919	0.9773	0.8873	0.9543	0.9919	0.9919	0.9735	0.9919	0.9919
AIC	37.8411	37.8709	39.8599	37.9187	37.8411	37.8411	37.8788	37.8411	37.8411
Scaled residual for dose group nearest the BMD	0.099	0.159	0.047	0.229	0.099	0.099	0.172	0.099	0.099
Scaled residual for control group	-0.077	-0.141	-0.03	-0.191	-0.077	-0.077	-0.154	-0.077	-0.077

BMD: benchmark dose; BMDL: lower 95th percentile limit of BMD; AIC: Akaike Information Criteria score for relative goodness-of-fit. Blue highlighting: Final BMD and BMDL.
Data from Driscoll and Hurley (1993).

ED_013611_00000016-00259

IV. References

Broadmeadow, A. 1991. M&B 46,030: Preliminary Toxicity Study by Dietary Administration to CD-1 Mice for 13 Weeks. Life Science Research Limited Eye. Suffolk, UK. LSR Report 90/RHA364/0860 In *Life Science Research Limited Eye. Suffolk, UK. LSR Report 90/RHA364/0860.*

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Hughes, E. 1997. Fipronil: Neurotoxicity to rats by acute oral administration (including a time to peak effect study). Huntingdon Life Sciences Ltd., Cambridgeshire, PE18 6ES, U.K., RNP 536/973345. (DPR Vol. No. 52062-0387, Record No. 235557).

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APPENDIX V. FIPRONIL DIETARY EXPOSURE ASSESSMENT -- DEEM OUTPUT FILES (81 pages)

ED_013611_00000016-00261

Acute Tier 2 Results

Ver. 4.02, 05-10-c

DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

==========

Summary calculations--per capita:

	95th Percentile Exposure	95th Percentile MOE	99th Percentile Exposure	99th Percentile MOE	99.9th Percentile Exposure	99.9th Percentile MOE
Total US Population:	0.000128	6784	0.000230	3790	0.000428	2032
Nursing Infants:	0.000089	9735	0.000243	3576	0.000524	1660
Non-Nursing Infants:	0.000208	4190	0.000466	1866	0.000688	1264
All Infants:	0.000180	4831	0.000450	1935	0.000688	1265
Children 1-2:	0.000337	2584	0.000489	1780	0.000664	1309
Children 3-5:	0.000264	3291	0.000376	2311	0.000532	1634
Children 6-12:	0.000177	4928	0.000259	3359	0.000412	2111
Female 13-49:	0.000097	8936	0.000151	5778	0.000224	3880

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""
==========

Summary calculations--users:

	95th Percentile Exposure	95th Percentile MOE	99th Percentile Exposure	99th Percentile MOE	99.9th Percentile Exposure	99.9th Percentile MOE
Total US Population:	0.000128	6779	0.000230	3786	0.000428	2031
Nursing Infants:	0.000145	6014	0.000352	2469	0.000525	1658
Non-Nursing Infants:	0.000208	4174	0.000466	1865	0.000688	1264
All Infants:	0.000196	4432	0.000463	1879	0.000688	1265
Children 1-2:	0.000337	2583	0.000489	1780	0.000664	1309
Children 3-5:	0.000264	3290	0.000376	2310	0.000532	1634
Children 6-12:	0.000177	4928	0.000259	3359	0.000412	2111
Female 13-49:	0.000097	8936	0.000151	5778	0.000224	3880

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

Total US Population /a

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000049	0.000049
Standard Deviation	0.000046	0.000046
Standard Error of mean	0.000000	0.000000
Margin of Exposure 2/	17,649	17,610

Percent of Person-Days that are User-Days = 99.78%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000013	65,573	90.00	0.000097	9,010
20.00	0.000019	44,841	95.00	0.000128	6,779
30.00	0.000025	35,169	97.50	0.000169	5,136
40.00	0.000030	28,718	99.00	0.000230	3,786
50.00	0.000037	23,715	99.50	0.000287	3,029
60.00	0.000045	19,420	99.75	0.000350	2,486
70.00	0.000055	15,779	99.90	0.000428	2,031
80.00	0.000070	12,409			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000013	66,279	90.00	0.000096	9,017
20.00	0.000019	45,115	95.00	0.000128	6,784
30.00	0.000025	35,292	97.50	0.000169	5,140
40.00	0.000030	28,795	99.00	0.000230	3,790
50.00	0.000037	23,761	99.50	0.000287	3,031
60.00	0.000045	19,455	99.75	0.000350	2,488
70.00	0.000055	15,801	99.90	0.000428	2,032
80.00	0.000070	12,424			

a/ Analysis based on all two-day participant records in NHANES 2005-2010 2-Day with 2 days of valid drinking water records.
2/ Margin of Exposure = NOEL/ Dietary Exposure.

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

Nursing Infants

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000022	0.000035
Standard Deviation	0.000053	0.000063
Standard Error of mean	0.000002	0.000003
Margin of Exposure	40,394	25,074

Percent of Person-Days that are User-Days = 62.07%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000002	576,435	90.00	0.000071	12,191
20.00	0.000005	185,231	95.00	0.000145	6,014
30.00	0.000007	121,203	97.50	0.000212	4,104
40.00	0.000012	71,117	99.00	0.000352	2,469
50.00	0.000017	50,174	99.50	0.000439	1,983
60.00	0.000023	38,297	99.75	0.000523	1,664
70.00	0.000030	29,107	99.90	0.000525	1,658
80.00	0.000039	22,126			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000049	17,700
20.00	0.000000	>1,000,000	95.00	0.000089	9,735
30.00	0.000000	>1,000,000	97.50	0.000183	4,754
40.00	0.000000	>1,000,000	99.00	0.000243	3,576
50.00	0.000005	193,012	99.50	0.000436	1,997
60.00	0.000010	88,178	99.75	0.000521	1,670
70.00	0.000018	47,339	99.90	0.000524	1,660
80.00	0.000028	30,949			

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

Non-Nursing Infants

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000065	0.000066
Standard Deviation	0.000079	0.000079
Standard Error of mean	0.000002	0.000002
Margin of Exposure	13,345	13,233

Percent of Person-Days that are User-Days = 99.16%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000023	37,808	90.00	0.000127	6,860
20.00	0.000027	31,998	95.00	0.000208	4,174
30.00	0.000032	27,409	97.50	0.000308	2,822
40.00	0.000036	24,144	99.00	0.000466	1,865
50.00	0.000041	21,040	99.50	0.000560	1,553
60.00	0.000047	18,339	99.75	0.000688	1,264
70.00	0.000057	15,239	99.90	0.000688	1,264
80.00	0.000078	11,188			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000023	38,653	90.00	0.000124	7,001
20.00	0.000027	32,377	95.00	0.000208	4,190
30.00	0.000032	27,600	97.50	0.000308	2,824
40.00	0.000036	24,300	99.00	0.000466	1,866
50.00	0.000041	21,172	99.50	0.000560	1,554
60.00	0.000047	18,409	99.75	0.000688	1,264
70.00	0.000056	15,432	99.90	0.000688	1,264
80.00	0.000078	11,216			

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

All Infants

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000051	0.000059
Standard Deviation	0.000075	0.000077
Standard Error of mean	0.000002	0.000002
Margin of Exposure	16,906	14,792

Percent of Person-Days that are User-Days = 87.50%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000012	72,658	90.00	0.000113	7,704
20.00	0.000022	39,051	95.00	0.000196	4,432
30.00	0.000027	32,270	97.50	0.000279	3,120
40.00	0.000032	27,052	99.00	0.000463	1,879
50.00	0.000037	23,512	99.50	0.000530	1,640
60.00	0.000043	20,062	99.75	0.000630	1,380
70.00	0.000052	16,656	99.90	0.000688	1,265
80.00	0.000071	12,256			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000000	>1,000,000	90.00	0.000106	8,246
20.00	0.000009	95,057	95.00	0.000180	4,831
30.00	0.000022	39,054	97.50	0.000259	3,362
40.00	0.000028	31,321	99.00	0.000450	1,935
50.00	0.000033	26,146	99.50	0.000525	1,657
60.00	0.000039	22,164	99.75	0.000616	1,412
70.00	0.000048	18,278	99.90	0.000688	1,265
80.00	0.000063	13,852			

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

Children 1-2

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000130	0.000131
Standard Deviation	0.000102	0.000101
Standard Error of mean	0.000002	0.000002
Margin of Exposure	6,669	6,646

Percent of Person-Days that are User-Days = 99.65%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000038	22,627	90.00	0.000267	3,257
20.00	0.000056	15,614	95.00	0.000337	2,583
30.00	0.000069	12,520	97.50	0.000418	2,083
40.00	0.000083	10,513	99.00	0.000489	1,780
50.00	0.000099	8,786	99.50	0.000535	1,624
60.00	0.000121	7,166	99.75	0.000609	1,427
70.00	0.000149	5,838	99.90	0.000664	1,309
80.00	0.000190	4,586			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000038	22,994	90.00	0.000267	3,262
20.00	0.000055	15,730	95.00	0.000337	2,584
30.00	0.000069	12,564	97.50	0.000417	2,084
40.00	0.000082	10,565	99.00	0.000489	1,780
50.00	0.000099	8,814	99.50	0.000535	1,625
60.00	0.000121	7,187	99.75	0.000609	1,427
70.00	0.000148	5,863	99.90	0.000664	1,309
80.00	0.000189	4,599			

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

Children 3-5

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000101	0.000101
Standard Deviation	0.000079	0.000079
Standard Error of mean	0.000001	0.000001
Margin of Exposure	8,615	8,606

Percent of Person-Days that are User-Days = 99.89%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000032	26,872	90.00	0.000208	4,178
20.00	0.000042	20,485	95.00	0.000264	3,290
30.00	0.000054	16,081	97.50	0.000325	2,679
40.00	0.000066	13,261	99.00	0.000376	2,310
50.00	0.000077	11,338	99.50	0.000410	2,122
60.00	0.000092	9,424	99.75	0.000460	1,889
70.00	0.000112	7,759	99.90	0.000532	1,634
80.00	0.000147	5,921			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000032	27,052	90.00	0.000208	4,180
20.00	0.000042	20,527	95.00	0.000264	3,291
30.00	0.000054	16,105	97.50	0.000325	2,679
40.00	0.000066	13,276	99.00	0.000376	2,311
50.00	0.000077	11,345	99.50	0.000410	2,123
60.00	0.000092	9,433	99.75	0.000460	1,889
70.00	0.000112	7,768	99.90	0.000532	1,634
80.00	0.000147	5,926			

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

Children 6-12

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000068	0.000068
Standard Deviation	0.000053	0.000053
Standard Error of mean	0.000001	0.000001
Margin of Exposure	12,816	12,815

Percent of Person-Days that are User-Days = 99.99%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000021	42,223	90.00	0.000138	6,294
20.00	0.000029	30,041	95.00	0.000177	4,928
30.00	0.000036	23,993	97.50	0.000212	4,109
40.00	0.000046	19,037	99.00	0.000259	3,359
50.00	0.000053	16,340	99.50	0.000294	2,963
60.00	0.000063	13,721	99.75	0.000320	2,719
70.00	0.000076	11,452	99.90	0.000412	2,111
80.00	0.000096	9,062			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000021	42,242	90.00	0.000138	6,294
20.00	0.000029	30,048	95.00	0.000177	4,928
30.00	0.000036	23,997	97.50	0.000212	4,109
40.00	0.000046	19,039	99.00	0.000259	3,359
50.00	0.000053	16,341	99.50	0.000294	2,963
60.00	0.000063	13,721	99.75	0.000320	2,719
70.00	0.000076	11,453	99.90	0.000412	2,111
80.00	0.000096	9,062			

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for FIPRONIL NHANES 2005-2010 2-Day
Residue file: fipronil acute tier 2 26Aug19.R10 Adjustment factor #2 NOT used.
Analysis Date: 09-28-2020/15:20:22 Residue file dated: 08-26-2019/15:49:41
NOEL (Acute) = 0.870000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

Female 13-49

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000039	0.000039
Standard Deviation	0.000030	0.000030
Standard Error of mean	0.000000	0.000000
Margin of Exposure	22,402	22,402

Percent of Person-Days that are User-Days = 100.00%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000011	76,026	90.00	0.000077	11,282
20.00	0.000017	52,657	95.00	0.000097	8,936
30.00	0.000021	40,984	97.50	0.000118	7,349
40.00	0.000026	34,007	99.00	0.000151	5,778
50.00	0.000031	28,509	99.50	0.000176	4,935
60.00	0.000037	23,734	99.75	0.000192	4,525
70.00	0.000044	19,636	99.90	0.000224	3,880
80.00	0.000056	15,453			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

Percentile	Exposure	MOE	Percentile	Exposure	MOE
10.00	0.000011	76,035	90.00	0.000077	11,282
20.00	0.000017	52,660	95.00	0.000097	8,936
30.00	0.000021	40,986	97.50	0.000118	7,349
40.00	0.000026	34,008	99.00	0.000151	5,778
50.00	0.000031	28,510	99.50	0.000176	4,935
60.00	0.000037	23,734	99.75	0.000192	4,525
70.00	0.000044	19,637	99.90	0.000224	3,880
80.00	0.000056	15,453			

DEEM-FCID Acute analysis for FIPRONIL
Residue file name: C:\Users\lscanlan\Documents\Fipronil\Dietary\new POD\fipronil acute tier 2 26Aug19.R10
Analysis Date 09-28-2020 Residue file dated: 08-26-2019/15:49:41
Reference dose (NOEL) = 0.87 mg/kg bw/day

Acute Tier 2 Residue File

EPA Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
3100044000	31	Beef, meat	0.012000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3100044001	31	Beef, meat-babyfood	0.012000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3100045000	31	Beef, meat, dried	0.012000	1.920	1.000	PDP LO
		Full comment: PDP LOD				
3100046000	31	Beef, meat byproducts	0.012000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3100046001	31	Beef, meat byproducts-babyfood	0.012000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3100047000	31	Beef, fat	0.012000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3100047001	31	Beef, fat-babyfood	0.012000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3100048000	31	Beef, kidney	0.012000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3100049000	31	Beef, liver	0.100000	1.000	1.000	Tolera
		Full comment: Tolerance				
3100049001	31	Beef, liver-babyfood	0.100000	1.000	1.000	Tolera
		Full comment: Tolerance				
4000093000	40	Chicken, meat	0.001200	1.000	1.000	PDP re
		Full comment: PDP residue (meat)				
4000093001	40	Chicken, meat-babyfood	0.001200	1.000	1.000	PDP re
		Full comment: PDP residue (meat)				
4000094000	40	Chicken, liver	0.001200	1.000	1.000	PDP re
		Full comment: PDP residue (meat)				
4000095000	40	Chicken, meat byproducts	0.001200	1.000	1.000	PDP re
		Full comment: PDP residue (meat)				
4000095001	40	Chicken, meat byproducts-babyfoo	0.001200	1.000	1.000	PDP re
		Full comment: PDP residue (meat)				
4000096000	40	Chicken, fat	0.050000	1.000	1.000	Tolera
		Full comment: Tolerance				
4000096001	40	Chicken, fat-babyfood	0.050000	1.000	1.000	Tolera
		Full comment: Tolerance				
4000097000	40	Chicken, skin	0.050000	1.000	1.000	Tolera
		Full comment: Tolerance				
4000097001	40	Chicken, skin-babyfood	0.050000	1.000	1.000	Tolera
		Full comment: Tolerance				
7000145000	70	Egg, whole	0.040000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
7000145001	70	Egg, whole-babyfood	0.040000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
7000146000	70	Egg, white	0.040000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
7000146001	70	Egg, white (solids)-babyfood	0.040000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
7000147000	70	Egg, yolk	0.040000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
7000147001	70	Egg, yolk-babyfood	0.040000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3200169000	32	Goat, meat	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3200170000	32	Goat, meat byproducts	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3200171000	32	Goat, fat	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3200172000	32	Goat, kidney	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3200173000	32	Goat, liver	0.100000	1.000	1.000	Cattle
		Full comment: Cattle Tolerance				
3300189000	33	Horse, meat	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3600222000	36	Milk, fat	0.020000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3600222001	36	Milk, fat-baby food/infant formu	0.020000	1.000	1.000	PDP LO
		Full comment: PDP LOD				
3400290000	34	Pork, meat	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3400290001	34	Pork, meat-babyfood	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3400291000	34	Pork, skin	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3400292000	34	Pork, meat byproducts	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3400292001	34	Pork, meat byproducts-babyfood	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3400293000	34	Pork, fat	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3400293001	34	Pork, fat-babyfood	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3400294000	34	Pork, kidney	0.012000	1.000	1.000	Cattle
		Full comment: Cattle PDP LOD				
3400295000	34	Pork, liver	0.020000	1.000	1.000	Tolera

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          Full comment: Tolerance
0103296000 1C   Potato, chips                      0.003000   1.000  1.000PDP re
          Full comment: PDP residue
0103297000 1C   Potato, dry (granules/ flakes)     0.003000   1.000  1.000PDP re
          Full comment: PDP residue
0103297001 1C   Potato, dry (granules/ flakes)-b   0.003000   1.000  1.000PDP re
          Full comment: PDP residue
0103298000 1C   Potato, flour                      0.003000   1.000  1.000PDP re
          Full comment: PDP residue
0103298001 1C   Potato, flour-babyfood             0.003000   1.000  1.000PDP re
          Full comment: PDP residue
0103299000 1C   Potato, tuber, w/peel              0.003000   1.000  1.000PDP re
          Full comment: PDP residue
0103299001 1C   Potato, tuber, w/peel-babyfood     0.003000   1.000  1.000PDP re
          Full comment: PDP residue
0103300000 1C   Potato, tuber, w/o peel            0.003000   1.000  1.000PDP re
          Full comment: PDP residue
0103300001 1C   Potato, tuber, w/o peel-babyfood   0.003000   1.000  1.000PDP re
          Full comment: PDP residue
6000301000 60   Poultry, other, meat               0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
6000302000 60   Poultry, other, liver              0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
6000303000 60   Poultry, other, meat byproducts    0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
6000304000 60   Poultry, other, fat                0.050000   1.000  1.000tolera
          Full comment: tolerance
6000305000 60   Poultry, other, skin               0.050000   1.000  1.000tolera
          Full comment: tolerance (fat)
3500339000 35   Sheep, meat                        0.012000   1.000  1.000Cattle
          Full comment: Cattle PDP LOD
3500339001 35   Sheep, meat-babyfood               0.012000   1.000  1.000Cattle
          Full comment: Cattle PDP LOD
3500340000 35   Sheep, meat byproducts             0.012000   1.000  1.000Cattle
          Full comment: Cattle PDP LOD
3500341000 35   Sheep, fat                         0.012000   1.000  1.000Cattle
          Full comment: Cattle PDP LOD
3500341001 35   Sheep, fat-babyfood                0.012000   1.000  1.000Cattle
          Full comment: Cattle PDP LOD
3500342000 35   Sheep, kidney                      0.012000   1.000  1.000Cattle
          Full comment: Cattle PDP LOD
3500343000 35   Sheep, liver                       0.100000   1.000  1.000Tolera
          Full comment: Tolerance
5000382000 50   Turkey, meat                       0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
5000382001 50   Turkey, meat-babyfood              0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
5000383000 50   Turkey, liver                      0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
5000383001 50   Turkey, liver-babyfood             0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
5000384000 50   Turkey, meat byproducts            0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
5000384001 50   Turkey, meat byproducts-babyfood   0.001200   1.000  1.000PDP re
          Full comment: PDP residue (chicken meat)
5000385000 50   Turkey, fat                        0.050000   1.000  1.000Tolera
          Full comment: Tolerance
5000385001 50   Turkey, fat-babyfood               0.050000   1.000  1.000Tolera
          Full comment: Tolerance
5000386000 50   Turkey, skin                       0.050000   1.000  1.000Tolera
          Full comment: Tolerance
5000386001 50   Turkey, skin-babyfood              0.050000   1.000  1.000Tolera
          Full comment: Tolerance
8601000000 86A  Water, direct, all sources         0.000275   1.000  1.000EAD hi
          Full comment: EAD highest detect
8602000000 86B  Water, indirect, all sources       0.000275   1.000  1.000EAD hi
          Full comment: EAD highest detect
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DEEM-FCID Acute Critical Exposure Contribution Analysis (Ver. 4.02, 05-10-c)
NHANES 2005-2010 2-Day
Residue file = C:\Users\lscanlan\Documents\Fipronil\Dietary\new POD\fipronil acute tier 2 26Aug19.R10
Acute report = C:\Users\lscanlan\Documents\Fipronil\Dietary\new POD\fipronil_acute_tier2_28Sept2020.AC10
Date and time of analysis: 09-28-2020 15:19:58
Daily totals for food and foodform consumption used.
Adjustment factor #2 not used.
Minimum exposure contribution = 10%
Exposures divided by body weight

Acute Tier 2 CEC

Subpopulations:
1 Total US Population
2 Nursing Infants
3 Non-Nursing Infants
4 All Infants
5 Children 1-2
6 Children 3-5
7 Children 6-12
8 Female 13-49

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Total US Population
Low percentile for CEC records: 95 Exposure (mg/day) = 0.000128
High percentile for CEC records: 99 Exposure (mg/day) = 0.000230
Number of actual records in this interval: 2719

Critical foods with foodforms for this population (as derived from these records):
N=number of appearances in all records (including duplicates)
%=percent of total exposure for all records (including duplicates)

Food,	FF,	N ,	Percent,	Food Name
7000145000,	213,	1499,	33.33%,	Egg, whole-Cooked; Fresh or N/S; Fried
3600222000,	110,	814,	6.59%,	Milk, fat-Uncooked; Fresh or N/S; Cook Meth N/S
3100044000,	210,	438,	3.82%,	Beef, meat-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,	212,	202,	3.59%,	Egg, whole-Cooked; Fresh or N/S; Boiled
3100044000,	211,	241,	2.65%,	Beef, meat-Cooked; Fresh or N/S; Baked
3100044000,	213,	237,	2.08%,	Beef, meat-Cooked; Fresh or N/S; Fried
7000145000,	211,	213,	1.62%,	Egg, whole-Cooked; Fresh or N/S; Baked
4000096000,	210,	195,	1.53%,	Chicken, fat-Cooked; Fresh or N/S; Cook Meth N/S
7000146000,	213,	61,	1.37%,	Egg, white-Cooked; Fresh or N/S; Fried
3400290000,	250,	164,	1.30%,	Pork, meat-Cooked; Cured, etc; Cook Meth N/S
4000096000,	213,	145,	1.13%,	Chicken, fat-Cooked; Fresh or N/S; Fried
3100044000,	212,	97,	0.99%,	Beef, meat-Cooked; Fresh or N/S; Boiled
3400290000,	210,	116,	0.97%,	Pork, meat-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,	210,	133,	0.91%,	Egg, whole-Cooked; Fresh or N/S; Cook Meth N/S
4000097000,	213,	112,	0.83%,	Chicken, skin-Cooked; Fresh or N/S; Fried
4000097000,	210,	99,	0.70%,	Chicken, skin-Cooked; Fresh or N/S; Cook Meth N/S
8601000000,	110,	120,	0.68%,	Water, direct, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
7000145000,	110,	48,	0.66%,	Egg, whole-Uncooked; Fresh or N/S; Cook Meth N/S
4000096000,	211,	81,	0.62%,	Chicken, fat-Cooked; Fresh or N/S; Baked
0103300000,	212,	88,	0.56%,	Potato, tuber, w/o peel-Cooked; Fresh or N/S; Boiled
3400290000,	213,	64,	0.54%,	Pork, meat-Cooked; Fresh or N/S; Fried
3400290000,	211,	57,	0.52%,	Pork, meat-Cooked; Fresh or N/S; Baked
4000097000,	211,	66,	0.51%,	Chicken, skin-Cooked; Fresh or N/S; Baked
5000385000,	210,	61,	0.39%,	Turkey, fat-Cooked; Fresh or N/S; Cook Meth N/S
7000146000,	211,	39,	0.33%,	Egg, white-Cooked; Fresh or N/S; Baked
3100047000,	210,	66,	0.31%,	Beef, fat-Cooked; Fresh or N/S; Cook Meth N/S
3100044001,	240,	23,	0.29%,	Beef, meat-babyfood-Cooked; Canned; Cook Meth N/S
3100049000,	214,	9,	0.22%,	Beef, liver-Cooked; Fresh or N/S; Fried/baked
3100049000,	210,	8,	0.21%,	Beef, liver-Cooked; Fresh or N/S; Cook Meth N/S
3600222000,	120,	43,	0.21%,	Milk, fat-Uncooked; Frozen; Cook Meth N/S
4000096000,	212,	31,	0.21%,	Chicken, fat-Cooked; Fresh or N/S; Boiled
7000145000,	214,	34,	0.21%,	Egg, whole-Cooked; Fresh or N/S; Fried/baked
3600222000,	210,	37,	0.20%,	Milk, fat-Cooked; Fresh or N/S; Cook Meth N/S
8602000000,	130,	29,	0.16%,	Water, indirect, all sources-Uncooked; Dried; Cook Meth N/S
3600222000,	211,	31,	0.14%,	Milk, fat-Cooked; Fresh or N/S; Baked
7000147000,	213,	11,	0.13%,	Egg, yolk-Cooked; Fresh or N/S; Fried
5000386000,	210,	17,	0.12%,	Turkey, skin-Cooked; Fresh or N/S; Cook Meth N/S
7000146000,	223,	7,	0.12%,	Egg, white-Cooked; Frozen; Fried
0103300000,	211,	17,	0.12%,	Potato, tuber, w/o peel-Cooked; Fresh or N/S; Baked
4000097000,	212,	17,	0.12%,	Chicken, skin-Cooked; Fresh or N/S; Boiled
8602000000,	110,	23,	0.11%,	Water, indirect, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
3100047000,	213,	23,	0.11%,	Beef, fat-Cooked; Fresh or N/S; Fried
3100045000,	230,	8,	0.11%,	Beef, meat, dried-Cooked; Dried; Cook Meth N/S
3100044000,	250,	9,	0.11%,	Beef, meat-Cooked; Cured, etc; Cook Meth N/S
0103300000,	223,	24,	0.11%,	Potato, tuber, w/o peel-Cooked; Frozen; Fried
7000145000,	232,	15,	0.10%,	Egg, whole-Cooked; Dried; Boiled
3600222000,	232,	14,	0.10%,	Milk, fat-Cooked; Dried; Boiled
3400293000,	213,	15,	0.09%,	Pork, fat-Cooked; Fresh or N/S; Fried
3400290001,	240,	6,	0.09%,	Pork, meat-babyfood-Cooked; Canned; Cook Meth N/S
3400292000,	210,	10,	0.09%,	Pork, meat byproducts-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,	214,	9,	0.08%,	Beef, meat-Cooked; Fresh or N/S; Fried/baked
3400290000,	212,	9,	0.08%,	Pork, meat-Cooked; Fresh or N/S; Boiled
7000145000,	230,	5,	0.08%,	Egg, whole-Cooked; Dried; Cook Meth N/S
0103300000,	210,	13,	0.08%,	Potato, tuber, w/o peel-Cooked; Fresh or N/S; Cook Meth N/S
3600222000,	215,	13,	0.08%,	Milk, fat-Cooked; Fresh or N/S; Boiled/baked
4000096001,	240,	13,	0.07%,	Chicken, fat-babyfood-Cooked; Canned; Cook Meth N/S
3400293000,	210,	13,	0.07%,	Pork, fat-Cooked; Fresh or N/S; Cook Meth N/S

3100044000,	240,	12,	0.07%,	Beef, meat-Cooked; Canned; Cook Meth N/S
5000385000,	211,	9,	0.07%,	Turkey, fat-Cooked; Fresh or N/S; Baked
0103299000,	211,	9,	0.06%,	Potato, tuber, w/peel-Cooked; Fresh or N/S; Baked
3600222000,	212,	12,	0.06%,	Milk, fat-Cooked; Fresh or N/S; Boiled
4000097001,	240,	10,	0.06%,	Chicken, skin-babyfood-Cooked; Canned; Cook Meth N/S
3400290000,	253,	6,	0.05%,	Pork, meat-Cooked; Cured, etc; Fried
8602000000,	232,	11,	0.05%,	Water, indirect, all sources-Cooked; Dried; Boiled
5000385000,	213,	10,	0.05%,	Turkey, fat-Cooked; Fresh or N/S; Fried
3100046000,	210,	6,	0.05%,	Beef, meat byproducts-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,	233,	8,	0.04%,	Egg, whole-Cooked; Dried; Fried
3600222000,	214,	7,	0.04%,	Milk, fat-Cooked; Fresh or N/S; Fried/baked
0103299000,	213,	9,	0.04%,	Potato, tuber, w/peel-Cooked; Fresh or N/S; Fried
3500339000,	210,	4,	0.04%,	Sheep, meat-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,	221,	4,	0.04%,	Beef, meat-Cooked; Frozen; Baked
7000145000,	221,	4,	0.03%,	Egg, whole-Cooked; Frozen; Baked
0103299000,	212,	8,	0.03%,	Potato, tuber, w/peel-Cooked; Fresh or N/S; Boiled
3100049000,	212,	1,	0.03%,	Beef, liver-Cooked; Fresh or N/S; Boiled
0103300000,	213,	6,	0.03%,	Potato, tuber, w/o peel-Cooked; Fresh or N/S; Fried
7000146000,	214,	5,	0.03%,	Egg, white-Cooked; Fresh or N/S; Fried/baked
3100047000,	212,	6,	0.03%,	Beef, fat-Cooked; Fresh or N/S; Boiled
3400293000,	250,	7,	0.03%,	Pork, fat-Cooked; Cured, etc; Cook Meth N/S
3600222000,	130,	2,	0.03%,	Milk, fat-Uncooked; Dried; Cook Meth N/S
3100047000,	211,	7,	0.03%,	Beef, fat-Cooked; Fresh or N/S; Baked
5000386000,	211,	3,	0.03%,	Turkey, skin-Cooked; Fresh or N/S; Baked
7000145000,	252,	1,	0.02%,	Egg, whole-Cooked; Cured, etc; Boiled
7000147000,	210,	4,	0.02%,	Egg, yolk-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,	110,	1,	0.02%,	Beef, meat-Uncooked; Fresh or N/S; Cook Meth N/S
3200169000,	211,	1,	0.02%,	Goat, meat-Cooked; Fresh or N/S; Baked
0103296000,	213,	3,	0.02%,	Potato, chips-Cooked; Fresh or N/S; Fried
8602000000,	230,	3,	0.01%,	Water, indirect, all sources-Cooked; Dried; Cook Meth N/S
3100047000,	250,	3,	0.01%,	Beef, fat-Cooked; Cured, etc; Cook Meth N/S
4000096000,	221,	2,	0.01%,	Chicken, fat-Cooked; Frozen; Baked
3400290000,	240,	2,	0.01%,	Pork, meat-Cooked; Canned; Cook Meth N/S
3600222000,	213,	2,	0.01%,	Milk, fat-Cooked; Fresh or N/S; Fried
7000147000,	211,	2,	0.01%,	Egg, yolk-Cooked; Fresh or N/S; Baked
4000096000,	240,	1,	0.01%,	Chicken, fat-Cooked; Canned; Cook Meth N/S
3400293000,	211,	2,	0.01%,	Pork, fat-Cooked; Fresh or N/S; Baked
7000147000,	110,	2,	0.01%,	Egg, yolk-Uncooked; Fresh or N/S; Cook Meth N/S
5000385000,	253,	2,	0.01%,	Turkey, fat-Cooked; Cured, etc; Fried
7000145001,	240,	2,	0.01%,	Egg, whole-babyfood-Cooked; Canned; Cook Meth N/S
6000304000,	210,	1,	0.01%,	Poultry, other, fat-Cooked; Fresh or N/S; Cook Meth N/S
4000097000,	221,	2,	0.01%,	Chicken, skin-Cooked; Frozen; Baked
3100046000,	212,	2,	0.01%,	Beef, meat byproducts-Cooked; Fresh or N/S; Boiled
3400291000,	213,	1,	0.01%,	Pork, skin-Cooked; Fresh or N/S; Fried
4000093000,	211,	1,	0.01%,	Chicken, meat-Cooked; Fresh or N/S; Baked
3500339000,	212,	1,	0.01%,	Sheep, meat-Cooked; Fresh or N/S; Boiled
4000096000,	214,	1,	0.01%,	Chicken, fat-Cooked; Fresh or N/S; Fried/baked
8602000000,	212,	1,	0.01%,	Water, indirect, all sources-Cooked; Fresh or N/S; Boiled
3600222000,	230,	1,	0.01%,	Milk, fat-Cooked; Dried; Cook Meth N/S
3600222000,	240,	1,	0.01%,	Milk, fat-Cooked; Canned; Cook Meth N/S
3400293000,	100,	1,	0.01%,	Pork, fat-Uncooked; FF N/A; Cook Meth N/S
5000386001,	240,	1,	0.01%,	Turkey, skin-babyfood-Cooked; Canned; Cook Meth N/S
5000382000,	211,	1,	0.01%,	Turkey, meat-Cooked; Fresh or N/S; Baked
3600222000,	220,	1,	0.01%,	Milk, fat-Cooked; Frozen; Cook Meth N/S
5000386000,	250,	1,	0.00%,	Turkey, skin-Cooked; Cured, etc; Cook Meth N/S
5000385000,	250,	1,	0.00%,	Turkey, fat-Cooked; Cured, etc; Cook Meth N/S
4000096000,	250,	1,	0.00%,	Chicken, fat-Cooked; Cured, etc; Cook Meth N/S
4000097000,	250,	1,	0.00%,	Chicken, skin-Cooked; Cured, etc; Cook Meth N/S
6000305000,	210,	1,	0.00%,	Poultry, other, skin-Cooked; Fresh or N/S; Cook Meth N/S
5000385001,	240,	1,	0.00%,	Turkey, fat-babyfood-Cooked; Canned; Cook Meth N/S
3100047000,	110,	1,	0.00%,	Beef, fat-Uncooked; Fresh or N/S; Cook Meth N/S
5000384000,	210,	1,	0.00%,	Turkey, meat byproducts-Cooked; Fresh or N/S; Cook Meth N/S
0103300001,	240,	1,	0.00%,	Potato, tuber, w/o peel-babyfood-Cooked; Canned; Cook Meth N/S
7000146000,	120,	1,	0.00%,	Egg, white-Uncooked; Frozen; Cook Meth N/S
4000093000,	213,	1,	0.00%,	Chicken, meat-Cooked; Fresh or N/S; Fried
5000382000,	210,	1,	0.00%,	Turkey, meat-Cooked; Fresh or N/S; Cook Meth N/S
3600222000,	221,	1,	0.00%,	Milk, fat-Cooked; Frozen; Baked
8602000000,	240,	1,	0.00%,	Water, indirect, all sources-Cooked; Canned; Cook Meth N/S
4000093000,	214,	1,	0.00%,	Chicken, meat-Cooked; Fresh or N/S; Fried/baked
3100044000,	242,	1,	0.00%,	Beef, meat-Cooked; Canned; Boiled

Critical foods (without foodforms) for this population (as derived from these records):
N=number of appearances in all records (including duplicates)
%=percent of total exposure for all records (including duplicates)

Food ,	N ,	Percent,	Food Name
7000145000,	2162,	40.59%,	Egg, whole
3100044000,	1049,	9.86%,	Beef, meat
3600222000,	979,	7.49%,	Milk, fat
4000096000,	457,	3.52%,	Chicken, fat
3400290000,	418,	3.47%,	Pork, meat
4000097000,	297,	2.17%,	Chicken, skin
7000146000,	113,	1.85%,	Egg, white
0103300000,	148,	0.90%,	Potato, tuber, w/o peel
8601000000,	120,	0.68%,	Water, direct, all sources
5000385000,	83,	0.52%,	Turkey, fat
3100047000,	106,	0.49%,	Beef, fat
3100049000,	18,	0.46%,	Beef, liver
8602000000,	68,	0.34%,	Water, indirect, all sources
3100044001,	23,	0.29%,	Beef, meat-babyfood

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3400293000,      38,     0.21%,   Pork, fat
7000147000,      19,     0.17%,   Egg, yolk
5000386000,      21,     0.15%,   Turkey, skin
0103299000,      26,     0.13%,   Potato, tuber, w/peel
3100045000,       8,     0.11%,   Beef, meat, dried
3400290001,       6,     0.09%,   Pork, meat-babyfood
3400292000,      10,     0.09%,   Pork, meat byproducts
4000096001,      13,     0.07%,   Chicken, fat-babyfood
3100046000,       8,     0.06%,   Beef, meat byproducts
4000097001,      10,     0.06%,   Chicken, skin-babyfood
3500339000,       5,     0.05%,   Sheep, meat
0103296000,       3,     0.02%,   Potato, chips
3200169000,       1,     0.02%,   Goat, meat
7000145001,       2,     0.01%,   Egg, whole-babyfood
3400291000,       1,     0.01%,   Pork, skin
4000093000,       3,     0.01%,   Chicken, meat
6000304000,       1,     0.01%,   Poultry, other, fat
5000382000,       2,     0.01%,   Turkey, meat
5000386001,       1,     0.01%,   Turkey, skin-babyfood

Number of printed records = 25
Number of records represented = 25
 (nf = number of foods/ff reported for this daily exposure amount (exceeding minimum contribution)
 (nx = number of times this exposure amount was computed for the same person on the same day.)

Demographic data for each record:                                   Exposure contribution data by food/ff consumed (NF lines):
  PID,  SEQN,     Day,Sex,  Age,   BW-kg,  Nf,  Nx,   Tot Expos,  Samplwt,  Food,    FF, Amt(g),   Residue , Adj#1, Adj#2,  Contr
 -----, --------, ---,---,  ---,  ------,  --, ----, -----------, -------,--------, --, ------, ----------, -----, -----,  -----

 17056 ,52622    , 2  ,F   ,2Y   , 13.00 , 2  ,   1 ,  0.0002295 ,  5503 ,7000145000 ,213,  40.9 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3400290000 ,250,  37.5 ,  0.012000 , 1.00 , 1.00 ,  0.

 18275 ,54126    , 2  ,M   ,1Y   ,  9.90 , 2  ,   1 ,  0.0002295 ,  8432 ,3100044000 ,211,  63.7 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  55.0 ,  0.020000 , 1.00 , 1.00 ,  0.

 20689 ,57172    , 2  ,F   ,13Y  , 46.00 , 4  ,   1 ,  0.0002289 ,  1637 ,4000096000 ,210,  50.5 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,4000097000 ,210,  30.6 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,211,  53.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,213,  72.6 ,  0.040000 , 1.00 , 1.00 ,  0.

 10867 ,44620    , 2  ,F   ,31Y  , 53.10 , 1  ,   1 ,  0.0002288 ,  8620 ,7000145000 ,213, 219.5 ,  0.040000 , 1.00 , 1.00 ,  0.

   166 ,31322    , 2  ,M   ,4Y   , 18.50 , 1  ,   1 ,  0.0002288 ,  1688 ,7000145000 ,213,  76.1 ,  0.040000 , 1.00 , 1.00 ,  0.

  3908 ,35949    , 2  ,M   ,7Y   , 27.10 , 2  ,   1 ,  0.0002287 ,  1890 ,7000145000 ,213,  78.8 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,5000385000 ,210,  20.7 ,  0.050000 , 1.00 , 1.00 ,  0.

 12311 ,46439    , 1  ,M   ,4Y   , 30.20 , 1  ,   1 ,  0.0002286 ,  9949 ,7000145000 ,213, 133.5 ,  0.040000 , 1.00 , 1.00 ,  0.

  7973 ,40894    , 1  ,F   ,4Y   , 14.80 , 3  ,   1 ,  0.0002285 ,  2126 ,3100044000 ,210,  42.2 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,212,  44.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  27.8 ,  0.020000 , 1.00 , 1.00 ,  0.

  5947 ,38441    , 1  ,F   ,4Y   , 15.40 , 2  ,   1 ,  0.0002285 ,  1703 ,4000096000 ,213,   9.4 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,213,  41.0 ,  0.040000 , 1.00 , 1.00 ,  0.

  5791 ,38256    , 1  ,M   ,1Y   , 12.10 , 2  ,   1 ,  0.0002285 ,  1646 ,7000145000 ,213,  30.8 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  45.6 ,  0.020000 , 1.00 , 1.00 ,  0.

  9025 ,42247    , 2  ,F   ,6Y   , 24.50 , 3  ,   1 ,  0.0002284 , 11167 ,7000145000 ,230,  56.9 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,230,  37.1 ,  0.020000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3400290000 ,211, 125.9 ,  0.012000 , 1.00 , 1.00 ,  0.

 20108 ,56433    , 1  ,F   ,3Y   , 18.30 , 2  ,   1 ,  0.0002284 ,  9748 ,7000145000 ,213,  45.3 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3400290000 ,210,  39.1 ,  0.012000 , 1.00 , 1.00 ,  0.

 15783 ,50981    , 2  ,F   ,8Y   , 25.10 , 2  ,   1 ,  0.0002284 ,  3019 ,3100044000 ,214, 126.3 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,213,  83.8 ,  0.040000 , 1.00 , 1.00 ,  0.

 22164 ,59032    , 2  ,M   ,67Y  , 67.10 , 2  ,   1 ,  0.0002283 ,  2301 ,3100044000 ,210,1039.9 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3100047000 ,210, 184.1 ,  0.012000 , 1.00 , 1.00 ,  0.

 21609 ,58336    , 2  ,M   ,7Y   , 23.80 , 1  ,   1 ,  0.0002282 ,  1287 ,7000145000 ,213,  92.9 ,  0.040000 , 1.00 , 1.00 ,  0.

 21456 ,58145    , 1  ,M   ,19Y  , 79.50 , 3  ,   1 ,  0.0002281 ,  1555 ,3100044000 ,211, 598.5 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,4000096000 ,213,  47.9 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,211,  66.3 ,  0.040000 , 1.00 , 1.00 ,  0.

  4303 ,36425    , 1  ,F   ,10M  ,  8.90 , 1  ,   1 ,  0.0002279 ,  1200 ,7000145000 ,213,  42.4 ,  0.040000 , 1.00 , 1.00 ,  0.

  3196 ,35057    , 1  ,M   ,7Y   , 21.20 , 1  ,   1 ,  0.0002277 ,  1475 ,7000145000 ,213,  87.7 ,  0.040000 , 1.00 , 1.00 ,  0.

 11983 ,46030    , 2  ,F   ,10M  , 10.00 , 3  ,   1 ,  0.0002277 , 15137 ,3100044000 ,212,  76.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,4000093000 ,211, 314.3 ,  0.001200 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,4000096000 ,211,  11.6 ,  0.050000 , 1.00 , 1.00 ,  0.

  6154 ,38692    , 2  ,F   ,2Y   , 17.20 , 2  ,   1 ,  0.0002277 ,  1304 ,7000145000 ,213,  64.5 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  24.6 ,  0.020000 , 1.00 , 1.00 ,  0.

 19173 ,55262    , 2  ,F   ,1Y   , 11.50 , 1  ,   1 ,  0.0002277 ,  1932 ,7000145000 ,213,  38.6 ,  0.040000 , 1.00 , 1.00 ,  0.

 24140 ,61502    , 2  ,F   ,1Y   , 10.60 , 1  ,   1 ,  0.0002277 ,  8882 ,7000145000 ,213,  38.4 ,  0.040000 , 1.00 , 1.00 ,  0.
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  7598 ,40449    , 2  ,M   ,1Y   , 11.30 , 1  ,   1 ,  0.0002275 ,  2570 ,7000145000 ,213,  49.1 ,  0.040000 , 1.00 , 1.00 ,  0.
 17010 ,52568    , 2  ,F   ,4Y   , 19.60 , 3  ,   1 ,  0.0002275 ,  4200 ,4000096000 ,212,  16.2 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,4000097000 ,212,  14.5 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,7000145000 ,213,  58.0 ,  0.040000 , 1.00 , 1.00 ,  0.
 10226 ,43783    , 2  ,F   ,3Y   , 16.10 , 1  ,   1 ,  0.0002271 ,  8828 ,7000145000 ,213,  53.6 ,  0.040000 , 1.00 , 1.00 ,  0.


================================================================================
Nursing Infants
Low percentile for CEC records: 95     Exposure (mg/day) =    0.000089
High percentile for CEC records: 99    Exposure (mg/day) =    0.000243
Number of actual records in this interval: 31


Critical foods with foodforms for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food,         FF,      N  ,  Percent,  Food Name
----------,  ---,    -----,  -------,  -------------
7000145000,  213,      12,   33.07%,  Egg, whole-Cooked; Fresh or N/S; Fried
7000147000,  213,       3,    5.58%,  Egg, yolk-Cooked; Fresh or N/S; Fried
3600222000,  110,       7,    4.51%,  Milk, fat-Uncooked; Fresh or N/S; Cook Meth N/S
8602000000,  130,       5,    3.63%,  Water, indirect, all sources-Uncooked; Dried; Cook Meth N/S
3100044001,  240,       2,    3.53%,  Beef, meat-babyfood-Cooked; Canned; Cook Meth N/S
3100044000,  213,       1,    2.39%,  Beef, meat-Cooked; Fresh or N/S; Fried
4000096001,  240,       3,    2.34%,  Chicken, fat-babyfood-Cooked; Canned; Cook Meth N/S
7000145000,  212,       1,    2.18%,  Egg, whole-Cooked; Fresh or N/S; Boiled
4000097001,  240,       2,    2.11%,  Chicken, skin-babyfood-Cooked; Canned; Cook Meth N/S
7000146000,  213,       1,    1.95%,  Egg, white-Cooked; Fresh or N/S; Fried
3100044000,  211,       2,    1.58%,  Beef, meat-Cooked; Fresh or N/S; Baked
3400290000,  250,       2,    1.52%,  Pork, meat-Cooked; Cured, etc; Cook Meth N/S
3400290001,  240,       1,    1.43%,  Pork, meat-babyfood-Cooked; Canned; Cook Meth N/S
4000096000,  212,       2,    1.29%,  Chicken, fat-Cooked; Fresh or N/S; Boiled
7000146000,  211,       1,    1.28%,  Egg, white-Cooked; Fresh or N/S; Baked
8602000000,  110,       3,    1.18%,  Water, indirect, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
3100044000,  210,       2,    1.07%,  Beef, meat-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,  211,       1,    0.99%,  Egg, whole-Cooked; Fresh or N/S; Baked
0103300000,  212,       2,    0.98%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Boiled
7000145000,  230,       1,    0.90%,  Egg, whole-Cooked; Dried; Cook Meth N/S
3100044000,  240,       2,    0.82%,  Beef, meat-Cooked; Canned; Cook Meth N/S
3600222000,  240,       1,    0.65%,  Milk, fat-Cooked; Canned; Cook Meth N/S
4000097000,  212,       1,    0.60%,  Chicken, skin-Cooked; Fresh or N/S; Boiled
3100047000,  213,       1,    0.56%,  Beef, fat-Cooked; Fresh or N/S; Fried
7000145000,  210,       2,    0.54%,  Egg, whole-Cooked; Fresh or N/S; Cook Meth N/S
8602000000,  230,       1,    0.51%,  Water, indirect, all sources-Cooked; Dried; Cook Meth N/S
3600222000,  211,       1,    0.47%,  Milk, fat-Cooked; Fresh or N/S; Baked
5000385000,  210,       1,    0.46%,  Turkey, fat-Cooked; Fresh or N/S; Cook Meth N/S
5000385001,  240,       1,    0.34%,  Turkey, fat-babyfood-Cooked; Canned; Cook Meth N/S
4000096000,  211,       1,    0.30%,  Chicken, fat-Cooked; Fresh or N/S; Baked
8601000000,  110,       1,    0.26%,  Water, direct, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
3100047000,  210,       1,    0.20%,  Beef, fat-Cooked; Fresh or N/S; Cook Meth N/S


Critical foods (without foodforms) for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food      ,      N ,  Percent,   Food Name
----------,  -----,  -------,  -------------
7000145000,     17,   37.68%,   Egg, whole
3100044000,      7,    5.86%,   Beef, meat
3600222000,      9,    5.63%,   Milk, fat
7000147000,      3,    5.58%,   Egg, yolk
8602000000,      9,    5.32%,   Water, indirect, all sources
3100044001,      2,    3.53%,   Beef, meat-babyfood
7000146000,      2,    3.23%,   Egg, white
4000096001,      3,    2.34%,   Chicken, fat-babyfood
4000097001,      2,    2.11%,   Chicken, skin-babyfood
4000096000,      3,    1.59%,   Chicken, fat
3400290000,      2,    1.52%,   Pork, meat
3400290001,      1,    1.43%,   Pork, meat-babyfood
0103300000,      2,    0.98%,   Potato, tuber, w/o peel
3100047000,      2,    0.76%,   Beef, fat
4000097000,      1,    0.60%,   Chicken, skin
5000385000,      1,    0.46%,   Turkey, fat
5000385001,      1,    0.34%,   Turkey, fat-babyfood
8601000000,      1,    0.26%,   Water, direct, all sources

Number of printed records = 25
Number of records represented = 25
 (nf = number of foods/ff reported for this daily exposure amount (exceeding minimum contribution)
 (nx = number of times this exposure amount was computed for the same person on the same day.)

Demographic data for each record:                                  Exposure contribution data by food/ff consumed (NF lines):
  PID,  SEQN,     Day,Sex,  Age,   BW-kg,  Nf,  Nx,   Tot Expos,  Samplwt,  Food,    FF, Amt(g),   Residue , Adj#1, Adj#2,  Contr
 -----, --------, ---,---,  ---,  ------,  --, ----, -----------, -------,--------, --, ------, ----------, -----, -----,  -----
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 20613 ,57076    , 2  ,F   ,9M   ,  8.60 , 1  ,   1 ,  0.0002419 ,  3080 ,7000145000 ,213,  41.5 ,  0.040000 , 1.00 , 1.00 ,  0.
  2475 ,34149    , 1  ,F   ,9M   ,  8.50 , 4  ,   1 ,  0.0002394 ,  1005 ,3100044000 ,211,  24.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,7000145000 ,211,   9.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3600222000 ,110,  12.1 ,  0.020000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3400290000 ,250,  25.0 ,  0.012000 , 1.00 , 1.00 ,  0.
  6099 ,38620    , 2  ,F   ,11M  ,  7.40 , 2  ,   1 ,  0.0002169 ,  7420 ,7000145000 ,213,  21.2 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3600222000 ,110,  11.9 ,  0.020000 , 1.00 , 1.00 ,  0.
 13252 ,47680    , 2  ,M   ,9M   ,  9.80 , 1  ,   1 ,  0.0002140 ,  1966 ,7000145000 ,213,  39.8 ,  0.040000 , 1.00 , 1.00 ,  0.
 21001 ,57567    , 2  ,M   ,10M  , 11.20 , 1  ,   1 ,  0.0002109 , 20369 ,7000145000 ,213,  51.4 ,  0.040000 , 1.00 , 1.00 ,  0.
  2475 ,34149    , 2  ,F   ,9M   ,  8.50 , 5  ,   1 ,  0.0002026 ,  1005 ,3100044000 ,211,  27.6 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3100044000 ,240,  16.6 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3600222000 ,110,  22.3 ,  0.020000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3400290000 ,250,  25.0 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,5000385000 ,210,   3.6 ,  0.050000 , 1.00 , 1.00 ,  0.
  1064 ,32412    , 1  ,M   ,6M   ,  9.00 , 1  ,   1 ,  0.0001953 ,  1113 ,7000145000 ,213,  42.4 ,  0.040000 , 1.00 , 1.00 ,  0.
 20752 ,57241    , 2  ,F   ,9M   ,  9.50 , 1  ,   1 ,  0.0001862 ,  3951 ,7000145000 ,213,  39.8 ,  0.040000 , 1.00 , 1.00 ,  0.
 14408 ,49183    , 1  ,F   ,10M  ,  7.40 , 2  ,   1 ,  0.0001839 ,  4138 ,3100044001 ,240,  76.2 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,8602000000 ,230, 639.2 ,  0.000275 , 1.00 , 1.00 ,  0.
 14718 ,49582    , 1  ,M   ,8M   ,  8.10 , 2  ,   1 ,  0.0001802 ,  1085 ,3100044000 ,213,  74.8 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3100047000 ,213,  17.4 ,  0.012000 , 1.00 , 1.00 ,  0.
 13085 ,47467    , 2  ,F   ,5M   ,  5.10 , 3  ,   1 ,  0.0001694 ,   950 ,4000096001 ,240,   4.0 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,4000097001 ,240,   4.3 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3400290001 ,240,  28.3 ,  0.012000 , 1.00 , 1.00 ,  0.
 21719 ,58475    , 2  ,M   ,10M  ,  8.70 , 2  ,   1 ,  0.0001557 ,  8469 ,7000145000 ,213,  25.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3600222000 ,240,  13.1 ,  0.020000 , 1.00 , 1.00 ,  0.
  8306 ,41323    , 1  ,M   ,10M  ,  8.70 , 2  ,   1 ,  0.0001494 ,  1710 ,7000145000 ,212,  22.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,8602000000 ,130, 478.7 ,  0.000275 , 1.00 , 1.00 ,  0.
  7669 ,40529    , 2  ,M   ,11M  ,  9.10 , 3  ,   1 ,  0.0001449 ,  7613 ,7000145000 ,230,   9.5 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3600222000 ,110,  14.6 ,  0.020000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,0103300000 ,212,  63.1 ,  0.003000 , 1.00 , 1.00 ,  0.
 16509 ,51947    , 1  ,F   ,10M  ,  8.30 , 2  ,   1 ,  0.0001443 ,  1971 ,7000145000 ,213,  23.1 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,8602000000 ,130, 510.8 ,  0.000275 , 1.00 , 1.00 ,  0.
 15498 ,50616    , 2  ,F   ,11M  , 10.40 , 1  ,   1 ,  0.0001439 ,  3993 ,7000145000 ,213,  23.1 ,  0.040000 , 1.00 , 1.00 ,  0.
 16839 ,52353    , 1  ,F   ,10M  , 11.50 , 2  ,   1 ,  0.0001427 ,  1064 ,7000146000 ,213,  26.1 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,8602000000 ,110,1034.5 ,  0.000275 , 1.00 , 1.00 ,  0.
  3422 ,35347    , 1  ,F   ,9M   ,  8.20 , 2  ,   1 ,  0.0001336 ,   511 ,7000145000 ,213,  21.2 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,8602000000 ,110, 472.0 ,  0.000275 , 1.00 , 1.00 ,  0.
 12275 ,46396    , 2  ,M   ,5M   ,  7.80 , 2  ,   1 ,  0.0001282 ,   783 ,7000145000 ,210,   3.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,7000147000 ,213,  17.0 ,  0.040000 , 1.00 , 1.00 ,  0.
  1829 ,33354    , 1  ,M   ,11M  ,  7.90 , 2  ,   1 ,  0.0001278 ,   311 ,7000147000 ,213,  17.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,8602000000 ,130, 372.3 ,  0.000275 , 1.00 , 1.00 ,  0.
 24440 ,61888    , 2  ,M   ,7M   ,  8.50 , 2  ,   1 ,  0.0001254 ,  1213 ,4000096001 ,240,   8.1 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,4000097001 ,240,   9.5 ,  0.050000 , 1.00 , 1.00 ,  0.
 13252 ,47680    , 1  ,M   ,9M   ,  9.80 , 4  ,   1 ,  0.0001169 ,  1966 ,4000096000 ,212,   6.3 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3600222000 ,110,   7.9 ,  0.020000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,0103300000 ,212,  80.0 ,  0.003000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,8602000000 ,130, 856.0 ,  0.000275 , 1.00 , 1.00 ,  0.
  1829 ,33354    , 2  ,M   ,11M  ,  7.90 , 2  ,   1 ,  0.0001154 ,   311 ,7000147000 ,213,  17.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,3600222000 ,110,   9.3 ,  0.020000 , 1.00 , 1.00 ,  0.
  5621 ,38041    , 1  ,M   ,10M  ,  8.70 , 3  ,   1 ,  0.0001086 ,  3092 ,3100044000 ,240,  10.6 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,4000096000 ,211,   2.4 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,8601000000 ,110, 385.1 ,  0.000275 , 1.00 , 1.00 ,  0.
 14408 ,49183    , 2  ,F   ,10M  ,  7.40 , 1  ,   1 ,  0.0001048 ,  4138 ,7000145000 ,213,  16.0 ,  0.040000 , 1.00 , 1.00 ,  0.


==============================================================================
Non-Nursing Infants
Low percentile for CEC records: 95     Exposure (mg/day) =    0.000208
High percentile for CEC records: 99    Exposure (mg/day) =    0.000466
Number of actual records in this interval: 68


Critical foods with foodforms for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food,        FF,      N  ,  Percent,  Food Name
```

7000145000,	213,	49,	50.44%,	Egg, whole-Cooked; Fresh or N/S; Fried
7000145000,	212,	8,	8.58%,	Egg, whole-Cooked; Fresh or N/S; Boiled
3600222000,	110,	25,	7.83%,	Milk, fat-Uncooked; Fresh or N/S; Cook Meth N/S
3100044000,	210,	9,	2.83%,	Beef, meat-Cooked; Fresh or N/S; Cook Meth N/S
3400290000,	210,	3,	1.43%,	Pork, meat-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,	211,	2,	1.13%,	Beef, meat-Cooked; Fresh or N/S; Baked
0103300000,	212,	4,	0.96%,	Potato, tuber, w/o peel-Cooked; Fresh or N/S; Boiled
7000147000,	213,	2,	0.90%,	Egg, yolk-Cooked; Fresh or N/S; Fried
7000145000,	211,	4,	0.84%,	Egg, whole-Cooked; Fresh or N/S; Baked
8602000000,	110,	5,	0.80%,	Water, indirect, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
8602000000,	130,	4,	0.69%,	Water, indirect, all sources-Uncooked; Dried; Cook Meth N/S
7000146000,	213,	1,	0.66%,	Egg, white-Cooked; Fresh or N/S; Fried
4000096000,	211,	3,	0.62%,	Chicken, fat-Cooked; Fresh or N/S; Baked
4000097000,	211,	3,	0.57%,	Chicken, skin-Cooked; Fresh or N/S; Baked
3100044000,	213,	2,	0.56%,	Beef, meat-Cooked; Fresh or N/S; Fried
4000096000,	210,	3,	0.50%,	Chicken, fat-Cooked; Fresh or N/S; Cook Meth N/S
3100047000,	210,	2,	0.50%,	Beef, fat-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,	212,	1,	0.46%,	Beef, meat-Cooked; Fresh or N/S; Boiled
3100044001,	240,	2,	0.40%,	Beef, meat-babyfood-Cooked; Canned; Cook Meth N/S
3400290000,	213,	1,	0.37%,	Pork, meat-Cooked; Fresh or N/S; Fried
3100046000,	210,	1,	0.21%,	Beef, meat byproducts-Cooked; Fresh or N/S; Cook Meth N/S
4000093000,	211,	1,	0.19%,	Chicken, meat-Cooked; Fresh or N/S; Baked
3400293000,	213,	1,	0.18%,	Pork, fat-Cooked; Fresh or N/S; Fried
3400290000,	250,	1,	0.14%,	Pork, meat-Cooked; Cured, etc; Cook Meth N/S
7000146000,	214,	1,	0.14%,	Egg, white-Cooked; Fresh or N/S; Fried/baked
7000145000,	210,	1,	0.14%,	Egg, whole-Cooked; Fresh or N/S; Cook Meth N/S
4000097001,	240,	1,	0.13%,	Chicken, skin-babyfood-Cooked; Canned; Cook Meth N/S
0103300000,	210,	1,	0.12%,	Potato, tuber, w/o peel-Cooked; Fresh or N/S; Cook Meth N/S

Critical foods (without foodforms) for this population (as derived from these records):
N=number of appearances in all records (including duplicates)
%=percent of total exposure for all records (including duplicates)

Food ,	N ,	Percent,	Food Name
7000145000,	62,	60.00%,	Egg, whole
3600222000,	25,	7.83%,	Milk, fat
3100044000,	14,	4.98%,	Beef, meat
3400290000,	5,	1.94%,	Pork, meat
8602000000,	9,	1.49%,	Water, indirect, all sources
4000096000,	6,	1.12%,	Chicken, fat
0103300000,	5,	1.08%,	Potato, tuber, w/o peel
7000147000,	2,	0.90%,	Egg, yolk
7000146000,	2,	0.80%,	Egg, white
4000097000,	3,	0.57%,	Chicken, skin
3100047000,	2,	0.50%,	Beef, fat
3100044001,	2,	0.40%,	Beef, meat-babyfood
3100046000,	1,	0.21%,	Beef, meat byproducts
4000093000,	1,	0.19%,	Chicken, meat
3400293000,	1,	0.18%,	Pork, fat
4000097001,	1,	0.13%,	Chicken, skin-babyfood

Number of printed records = 25
Number of records represented = 25
(nf = number of foods/ff reported for this daily exposure amount (exceeding minimum contribution)
(nx = number of times this exposure amount was computed for the same person on the same day.)

Demographic data for each record: Exposure contribution data by food/ff consumed (NF lines):

PID,	SEQN,	Day,	Sex,	Age,	BW-kg,	Nf,	Nx,	Tot Expos,	Samplwt,	Food,	FF,	Amt(g),	Residue ,	Adj#1,	Adj#2,	Contr
16151 ,	51468 ,	1 ,	M ,	11M ,	8.80 ,	2 ,	1 ,	0.0004641 ,	16422 ,	7000145000 ,	213,	79.7 ,	0.040000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										8602000000 ,	110,	1500.9 ,	0.000275 ,	1.00 ,	1.00 ,	0.
4588 ,	36780 ,	1 ,	M ,	11M ,	9.70 ,	1 ,	1 ,	0.0004559 ,	2413 ,	7000145000 ,	213,	87.8 ,	0.040000 ,	1.00 ,	1.00 ,	0.
18210 ,	54045 ,	1 ,	F ,	10M ,	11.30 ,	1 ,	1 ,	0.0004504 ,	5841 ,	7000145000 ,	213,	92.3 ,	0.040000 ,	1.00 ,	1.00 ,	0.
15528 ,	50653 ,	1 ,	M ,	10M ,	10.10 ,	1 ,	1 ,	0.0004443 ,	3315 ,	7000145000 ,	213,	96.5 ,	0.040000 ,	1.00 ,	1.00 ,	0.
19768 ,	56027 ,	2 ,	F ,	9M ,	10.70 ,	1 ,	1 ,	0.0004428 ,	1400 ,	7000145000 ,	213,	92.9 ,	0.040000 ,	1.00 ,	1.00 ,	0.
21374 ,	58050 ,	2 ,	M ,	10M ,	9.20 ,	1 ,	1 ,	0.0004223 ,	2068 ,	7000145000 ,	213,	91.0 ,	0.040000 ,	1.00 ,	1.00 ,	0.
23781 ,	61045 ,	1 ,	M ,	10M ,	8.80 ,	1 ,	1 ,	0.0003872 ,	4434 ,	7000145000 ,	213,	45.3 ,	0.040000 ,	1.00 ,	1.00 ,	0.
14767 ,	49650 ,	2 ,	F ,	9M ,	9.60 ,	1 ,	1 ,	0.0003834 ,	1288 ,	7000145000 ,	213,	74.4 ,	0.040000 ,	1.00 ,	1.00 ,	0.
678 ,	31938 ,	1 ,	F ,	10M ,	10.00 ,	3 ,	1 ,	0.0003788 ,	1813 ,	3100044000 ,	213,	45.7 ,	0.012000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										7000145000 ,	211,	10.7 ,	0.040000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										7000145000 ,	213,	49.3 ,	0.040000 ,	1.00 ,	1.00 ,	0.
17686 ,	53399 ,	1 ,	F ,	11M ,	10.50 ,	2 ,	1 ,	0.0003674 ,	3349 ,	7000145000 ,	213,	81.0 ,	0.040000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										3600222000 ,	110,	24.7 ,	0.020000 ,	1.00 ,	1.00 ,	0.
4440 ,	36599 ,	2 ,	F ,	11M ,	9.70 ,	2 ,	1 ,	0.0003644 ,	2006 ,	7000145000 ,	213,	42.2 ,	0.040000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										3600222000 ,	110,	59.6 ,	0.020000 ,	1.00 ,	1.00 ,	0.
12618 ,	46858 ,	2 ,	F ,	8M ,	6.00 ,	2 ,	1 ,	0.0003607 ,	1050 ,	7000145000 ,	212,	44.0 ,	0.040000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										3600222000 ,	110,	17.8 ,	0.020000 ,	1.00 ,	1.00 ,	0.

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  9541 ,42899    , 1  ,M   ,11M  , 10.80 , 1  ,   1 ,  0.0003598 ,   800 ,7000145000 ,213,  80.9 ,  0.040000 , 1.00 , 1.00 ,  0.
    37 ,31168    , 1  ,M   ,11M  ,  9.30 , 5  ,   1 ,  0.0003592 , 11318 ,3100044000 ,210,  77.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3100046000 ,210,  32.1 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3100047000 ,210,  54.9 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3600222000 ,110,  17.3 ,  0.020000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3400290000 ,210,  31.0 ,  0.012000 , 1.00 , 1.00 ,  0.
 11490 ,45399    , 2  ,F   ,8M   ,  8.20 , 2  ,   1 ,  0.0003495 ,  2623 ,3100044000 ,210,  45.8 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  39.8 ,  0.040000 , 1.00 , 1.00 ,  0.
  6459 ,39067    , 2  ,F   ,11M  , 10.00 , 3  ,   1 ,  0.0003437 ,  1670 ,3100044000 ,210,  32.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000146000 ,213,  33.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3600222000 ,110,  48.9 ,  0.020000 , 1.00 , 1.00 ,  0.
  2546 ,34242    , 1  ,M   ,11M  , 10.00 , 1  ,   1 ,  0.0003411 ,   501 ,7000145000 ,212,  74.0 ,  0.040000 , 1.00 , 1.00 ,  0.
     1 ,31127    , 1  ,M   ,11M  , 10.20 , 3  ,   1 ,  0.0003369 ,  1969 ,7000145000 ,212,  10.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  46.9 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3600222000 ,110,  28.5 ,  0.020000 , 1.00 , 1.00 ,  0.
 24213 ,61597    , 1  ,F   ,11M  , 12.50 , 1  ,   1 ,  0.0003312 ,  1785 ,7000145000 ,213,  92.2 ,  0.040000 , 1.00 , 1.00 ,  0.
 11364 ,45244    , 2  ,M   ,9M   , 11.50 , 1  ,   1 ,  0.0003289 ,  3941 ,7000145000 ,212,  88.0 ,  0.040000 , 1.00 , 1.00 ,  0.
  1702 ,33199    , 2  ,F   ,7M   ,  7.40 , 3  ,   1 ,  0.0003264 ,  1431 ,3100044000 ,210,  22.9 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  32.1 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,8602000000 ,130,1325.4 ,  0.000275 , 1.00 , 1.00 ,  0.
 12668 ,46921    , 1  ,F   ,8M   ,  7.80 , 4  ,   1 ,  0.0003254 ,  1915 ,3100044000 ,213,  36.8 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,4000096000 ,211,   5.8 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,4000097000 ,211,   6.9 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000147000 ,213,  25.3 ,  0.040000 , 1.00 , 1.00 ,  0.
 10443 ,44076    , 2  ,F   ,8M   ,  9.60 , 2  ,   1 ,  0.0003252 ,  6084 ,3100044000 ,211, 121.0 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,211,  13.3 ,  0.040000 , 1.00 , 1.00 ,  0.
 16181 ,51508    , 2  ,F   ,11M  ,  9.80 , 4  ,   1 ,  0.0003181 ,  1801 ,4000097000 ,211,   7.0 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,211,  10.4 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  22.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3600222000 ,110,  22.0 ,  0.020000 , 1.00 , 1.00 ,  0.
  9109 ,42355    , 2  ,M   ,11M  , 10.00 , 3  ,   1 ,  0.0003109 ,   770 ,7000145000 ,213,  39.8 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3600222000 ,110,  17.5 ,  0.020000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,0103300000 ,212, 257.8 ,  0.003000 , 1.00 , 1.00 ,  0.


================================================================================
All Infants
Low percentile for CEC records: 95     Exposure (mg/day) =    0.000180
High percentile for CEC records: 99    Exposure (mg/day) =    0.000450
Number of actual records in this interval: 101


Critical foods with foodforms for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food,         FF,      N  ,  Percent,  Food Name
----------,  ---,    -----,  -------,  -------------
7000145000,  213,      71,   49.08%,  Egg, whole-Cooked; Fresh or N/S; Fried
3600222000,  110,      41,    8.68%,  Milk, fat-Uncooked; Fresh or N/S; Cook Meth N/S
7000145000,  212,      12,    8.41%,  Egg, whole-Cooked; Fresh or N/S; Boiled
3100044000,  210,      13,    2.79%,  Beef, meat-Cooked; Fresh or N/S; Cook Meth N/S
3100044001,  240,       4,    1.19%,  Beef, meat-babyfood-Cooked; Canned; Cook Meth N/S
3400290000,  210,       4,    1.16%,  Pork, meat-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,  211,       4,    1.13%,  Beef, meat-Cooked; Fresh or N/S; Baked
8602000000,  130,       9,    0.94%,  Water, indirect, all sources-Uncooked; Dried; Cook Meth N/S
7000145000,  211,       6,    0.89%,  Egg, whole-Cooked; Fresh or N/S; Baked
3100044000,  213,       3,    0.83%,  Beef, meat-Cooked; Fresh or N/S; Fried
0103300000,  212,       4,    0.72%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Boiled
8602000000,  110,       6,    0.71%,  Water, indirect, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
7000147000,  213,       2,    0.67%,  Egg, yolk-Cooked; Fresh or N/S; Fried
4000096000,  211,       4,    0.56%,  Chicken, fat-Cooked; Fresh or N/S; Baked
4000097000,  211,       4,    0.51%,  Chicken, skin-Cooked; Fresh or N/S; Baked
7000146000,  213,       1,    0.49%,  Egg, white-Cooked; Fresh or N/S; Fried
4000096000,  210,       3,    0.38%,  Chicken, fat-Cooked; Fresh or N/S; Cook Meth N/S
3100047000,  210,       2,    0.37%,  Beef, fat-Cooked; Fresh or N/S; Cook Meth N/S
3400290000,  250,       3,    0.37%,  Pork, meat-Cooked; Cured, etc; Cook Meth N/S
3100044000,  212,       1,    0.34%,  Beef, meat-Cooked; Fresh or N/S; Boiled
7000145000,  210,       2,    0.30%,  Egg, whole-Cooked; Fresh or N/S; Cook Meth N/S
3400290000,  213,       1,    0.27%,  Pork, meat-Cooked; Fresh or N/S; Fried
3600222000,  130,       1,    0.20%,  Milk, fat-Uncooked; Dried; Cook Meth N/S
8602000000,  230,       2,    0.17%,  Water, indirect, all sources-Cooked; Dried; Cook Meth N/S
3100046000,  210,       1,    0.15%,  Beef, meat byproducts-Cooked; Fresh or N/S; Cook Meth N/S
4000093000,  211,       1,    0.14%,  Chicken, meat-Cooked; Fresh or N/S; Baked
3400293000,  213,       1,    0.14%,  Pork, fat-Cooked; Fresh or N/S; Fried
7000146000,  214,       1,    0.10%,  Egg, white-Cooked; Fresh or N/S; Fried/baked
3100047000,  213,       1,    0.10%,  Beef, fat-Cooked; Fresh or N/S; Fried
4000097001,  240,       1,    0.10%,  Chicken, skin-babyfood-Cooked; Canned; Cook Meth N/S
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0103300000,  210,       1,    0.09%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,  240,       1,    0.09%,  Beef, meat-Cooked; Canned; Cook Meth N/S
7000146000,  211,       1,    0.09%,  Egg, white-Cooked; Fresh or N/S; Baked
5000385000,  210,       1,    0.08%,  Turkey, fat-Cooked; Fresh or N/S; Cook Meth N/S
4000096000,  213,       1,    0.07%,  Chicken, fat-Cooked; Fresh or N/S; Fried


Critical foods (without foodforms) for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food       ,     N ,  Percent,   Food Name
----------,  -----,  -------,  -------------
7000145000,     91,   58.68%,   Egg, whole
3600222000,     42,    8.88%,   Milk, fat
3100044000,     22,    5.18%,   Beef, meat
8602000000,     17,    1.82%,   Water, indirect, all sources
3400290000,      8,    1.80%,   Pork, meat
3100044001,      4,    1.19%,   Beef, meat-babyfood
4000096000,      8,    1.01%,   Chicken, fat
0103300000,      5,    0.81%,   Potato, tuber, w/o peel
7000146000,      3,    0.68%,   Egg, white
7000147000,      2,    0.67%,   Egg, yolk
4000097000,      4,    0.51%,   Chicken, skin
3100047000,      3,    0.47%,   Beef, fat
3100046000,      1,    0.15%,   Beef, meat byproducts
4000093000,      1,    0.14%,   Chicken, meat
3400293000,      1,    0.14%,   Pork, fat
4000097001,      1,    0.10%,   Chicken, skin-babyfood
5000385000,      1,    0.08%,   Turkey, fat

Number of printed records = 25
Number of records represented = 25
 (nf = number of foods/ff reported for this daily exposure amount (exceeding minimum contribution)
 (nx = number of times this exposure amount was computed for the same person on the same day.)

Demographic data for each record:                                   Exposure contribution data by food/ff consumed (NF lines):
  PID,  SEQN,     Day,Sex,  Age,   BW-kg,  Nf,  Nx,   Tot Expos,  Samplwt,  Food,    FF, Amt(g),   Residue , Adj#1, Adj#2,  Contr
 -----, --------, ---,---,  ---,  ------,  --, ----, -----------, -------,--------, --, ------, ----------, -----, -----,  -----

 15528 ,50653    , 1  ,M   ,10M  , 10.10 , 1  ,   1 ,  0.0004443 ,  3315 ,7000145000 ,213,  96.5 ,  0.040000 , 1.00 , 1.00 ,  0.
 19768 ,56027    , 2  ,F   ,9M   , 10.70 , 1  ,   1 ,  0.0004428 ,  1400 ,7000145000 ,213,  92.9 ,  0.040000 , 1.00 , 1.00 ,  0.
  7669 ,40529    , 1  ,M   ,11M  ,  9.10 , 2  ,   1 ,  0.0004375 ,  7613 ,7000145000 ,213,  75.6 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  38.3 ,  0.020000 , 1.00 , 1.00 ,  0.
 21374 ,58050    , 2  ,M   ,10M  ,  9.20 , 1  ,   1 ,  0.0004223 ,  2068 ,7000145000 ,213,  91.0 ,  0.040000 , 1.00 , 1.00 ,  0.
 23781 ,61045    , 1  ,M   ,10M  ,  8.80 , 1  ,   1 ,  0.0003872 ,  4434 ,7000145000 ,213,  45.3 ,  0.040000 , 1.00 , 1.00 ,  0.
 14767 ,49650    , 2  ,F   ,9M   ,  9.60 , 1  ,   1 ,  0.0003834 ,  1288 ,7000145000 ,213,  74.4 ,  0.040000 , 1.00 , 1.00 ,  0.
   678 ,31938    , 1  ,F   ,10M  , 10.00 , 3  ,   1 ,  0.0003788 ,  1813 ,3100044000 ,213,  45.7 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,211,  10.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,213,  49.3 ,  0.040000 , 1.00 , 1.00 ,  0.
 17686 ,53399    , 1  ,F   ,11M  , 10.50 , 2  ,   1 ,  0.0003674 ,  3349 ,7000145000 ,213,  81.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  24.7 ,  0.020000 , 1.00 , 1.00 ,  0.
  4440 ,36599    , 2  ,F   ,11M  ,  9.70 , 2  ,   1 ,  0.0003644 ,  2006 ,7000145000 ,213,  42.2 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  59.6 ,  0.020000 , 1.00 , 1.00 ,  0.
 12618 ,46858    , 2  ,F   ,8M   ,  6.00 , 2  ,   1 ,  0.0003607 ,  1050 ,7000145000 ,212,  44.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  17.8 ,  0.020000 , 1.00 , 1.00 ,  0.
  9541 ,42899    , 1  ,M   ,11M  , 10.80 , 1  ,   1 ,  0.0003598 ,   800 ,7000145000 ,213,  80.9 ,  0.040000 , 1.00 , 1.00 ,  0.
    37 ,31168    , 1  ,M   ,11M  ,  9.30 , 5  ,   1 ,  0.0003592 , 11318 ,3100044000 ,210,  77.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3100046000 ,210,  32.1 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3100047000 ,210,  54.9 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  17.3 ,  0.020000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3400290000 ,210,  31.0 ,  0.012000 , 1.00 , 1.00 ,  0.
  7539 ,40376    , 1  ,F   ,11M  ,  9.30 , 2  ,   1 ,  0.0003565 ,  1461 ,7000145000 ,213,  59.8 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  23.3 ,  0.020000 , 1.00 , 1.00 ,  0.
 10122 ,43652    , 2  ,F   ,9M   ,  7.70 , 1  ,   1 ,  0.0003502 ,  2558 ,7000145000 ,213,  53.8 ,  0.040000 , 1.00 , 1.00 ,  0.
 11490 ,45399    , 2  ,F   ,8M   ,  8.20 , 2  ,   1 ,  0.0003495 ,  2623 ,3100044000 ,210,  45.8 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,213,  39.8 ,  0.040000 , 1.00 , 1.00 ,  0.
  6459 ,39067    , 2  ,F   ,11M  , 10.00 , 3  ,   1 ,  0.0003437 ,  1670 ,3100044000 ,210,  32.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000146000 ,213,  33.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  48.9 ,  0.020000 , 1.00 , 1.00 ,  0.
  2546 ,34242    , 1  ,M   ,11M  , 10.00 , 1  ,   1 ,  0.0003411 ,   501 ,7000145000 ,212,  74.0 ,  0.040000 , 1.00 , 1.00 ,  0.
     1 ,31127    , 1  ,M   ,11M  , 10.20 , 3  ,   1 ,  0.0003369 ,  1969 ,7000145000 ,212,  10.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,7000145000 ,213,  46.9 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  28.5 ,  0.020000 , 1.00 , 1.00 ,  0.
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 24213 ,61597    , 1  ,F   ,11M  , 12.50 , 1  ,   1 ,  0.0003312 ,  1785 ,7000145000 ,213,  92.2 ,  0.040000 , 1.00 , 1.00 ,  0.
 11364 ,45244    , 2  ,M   ,9M   , 11.50 , 1  ,   1 ,  0.0003289 ,  3941 ,7000145000 ,212,  88.0 ,  0.040000 , 1.00 , 1.00 ,  0.
  1702 ,33199    , 2  ,F   ,7M   ,  7.40 , 3  ,   1 ,  0.0003264 ,  1431 ,3100044000 ,210,  22.9 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  32.1 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,8602000000 ,130,1325.4 ,  0.000275 , 1.00 , 1.00 ,  0.
 12668 ,46921    , 1  ,F   ,8M   ,  7.80 , 4  ,   1 ,  0.0003254 ,  1915 ,3100044000 ,213,  36.8 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,4000096000 ,211,   5.8 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,4000097000 ,211,   6.9 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000147000 ,213,  25.3 ,  0.040000 , 1.00 , 1.00 ,  0.
 10443 ,44076    , 2  ,F   ,8M   ,  9.60 , 2  ,   1 ,  0.0003252 ,  6084 ,3100044000 ,211, 121.0 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,211,  13.3 ,  0.040000 , 1.00 , 1.00 ,  0.
 16509 ,51947    , 2  ,F   ,10M  ,  8.30 , 2  ,   1 ,  0.0003249 ,  1971 ,7000145000 ,212,  44.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  18.6 ,  0.040000 , 1.00 , 1.00 ,  0.
 16181 ,51508    , 2  ,F   ,11M  ,  9.80 , 4  ,   1 ,  0.0003181 ,  1801 ,4000097000 ,211,   7.0 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,211,  10.4 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  22.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3600222000 ,110,  22.0 ,  0.020000 , 1.00 , 1.00 ,  0.


================================================================================
Children 1-2
Low percentile for CEC records: 95     Exposure (mg/day) =    0.000337
High percentile for CEC records: 99    Exposure (mg/day) =    0.000489
Number of actual records in this interval: 158


Critical foods with foodforms for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food,         FF,       N  ,  Percent,  Food Name
----------,  ---,    -----,  -------,  -------------
7000145000,  213,     137,   57.83%,  Egg, whole-Cooked; Fresh or N/S; Fried
3600222000,  110,      46,    4.14%,  Milk, fat-Uncooked; Fresh or N/S; Cook Meth N/S
7000145000,  212,       9,    3.75%,  Egg, whole-Cooked; Fresh or N/S; Boiled
7000145000,  110,       7,    2.98%,  Egg, whole-Uncooked; Fresh or N/S; Cook Meth N/S
3100044000,  210,      16,    1.82%,  Beef, meat-Cooked; Fresh or N/S; Cook Meth N/S
3100049000,  214,       3,    1.36%,  Beef, liver-Cooked; Fresh or N/S; Fried/baked
7000146000,  213,       4,    1.32%,  Egg, white-Cooked; Fresh or N/S; Fried
3100044000,  213,       7,    0.88%,  Beef, meat-Cooked; Fresh or N/S; Fried
3100049000,  212,       1,    0.48%,  Beef, liver-Cooked; Fresh or N/S; Boiled
4000096000,  210,       5,    0.45%,  Chicken, fat-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,  212,       3,    0.45%,  Beef, meat-Cooked; Fresh or N/S; Boiled
3100044000,  211,       3,    0.42%,  Beef, meat-Cooked; Fresh or N/S; Baked
3400290000,  213,       4,    0.41%,  Pork, meat-Cooked; Fresh or N/S; Fried
4000097000,  210,       3,    0.26%,  Chicken, skin-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,  211,       2,    0.25%,  Egg, whole-Cooked; Fresh or N/S; Baked
5000385000,  210,       2,    0.17%,  Turkey, fat-Cooked; Fresh or N/S; Cook Meth N/S
0103300000,  212,       2,    0.17%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Boiled
3600222000,  232,       2,    0.15%,  Milk, fat-Cooked; Dried; Boiled
3400290000,  250,       2,    0.14%,  Pork, meat-Cooked; Cured, etc; Cook Meth N/S
3400290000,  253,       1,    0.12%,  Pork, meat-Cooked; Cured, etc; Fried
7000145000,  210,       1,    0.09%,  Egg, whole-Cooked; Fresh or N/S; Cook Meth N/S
3400290000,  251,       1,    0.08%,  Pork, meat-Cooked; Cured, etc; Baked
0103299000,  211,       1,    0.07%,  Potato, tuber, w/peel-Cooked; Fresh or N/S; Baked
3400291000,  213,       1,    0.07%,  Pork, skin-Cooked; Fresh or N/S; Fried
3100047000,  210,       1,    0.07%,  Beef, fat-Cooked; Fresh or N/S; Cook Meth N/S
3100047000,  213,       1,    0.07%,  Beef, fat-Cooked; Fresh or N/S; Fried
7000145000,  232,       1,    0.07%,  Egg, whole-Cooked; Dried; Boiled
7000146000,  211,       1,    0.06%,  Egg, white-Cooked; Fresh or N/S; Baked
0103300000,  211,       1,    0.06%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Baked


Critical foods (without foodforms) for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food      ,      N ,  Percent,   Food Name
----------,  -----,  -------,  -------------
7000145000,    157,   64.97%,   Egg, whole
3600222000,     48,    4.29%,   Milk, fat
3100044000,     29,    3.57%,   Beef, meat
3100049000,      4,    1.84%,   Beef, liver
7000146000,      5,    1.38%,   Egg, white
3400290000,      8,    0.75%,   Pork, meat
4000096000,      5,    0.45%,   Chicken, fat
4000097000,      3,    0.26%,   Chicken, skin
0103300000,      3,    0.23%,   Potato, tuber, w/o peel
5000385000,      2,    0.17%,   Turkey, fat
3100047000,      2,    0.14%,   Beef, fat
0103299000,      1,    0.07%,   Potato, tuber, w/peel
3400291000,      1,    0.07%,   Pork, skin

Number of printed records = 25
Number of records represented = 25
```

(nf = number of foods/ff reported for this daily exposure amount (exceeding minimum contribution)
(nx = number of times this exposure amount was computed for the same person on the same day.)

Demographic data for each record: Exposure contribution data by food/ff consumed (NF lines):

PID,	SEQN,	Day,	Sex,	Age,	BW-kg,	Nf,	Nx,	Tot Expos,	Samplwt,	Food,	FF,	Amt(g),	Residue ,	Adj#1,	Adj#2,	Contr
23194	60282	2	F	2Y	10.90	1	1	0.0004882	2659	7000145000	213	121.3	0.040000	1.00	1.00	0.
18014	53804	2	F	1Y	10.30	3	1	0.0004880	17846	3100044000	210	56.7	0.012000	1.00	1.00	0.
,,,,,,,,,										7000145000	213	64.3	0.040000	1.00	1.00	0.
,,,,,,,,,										3600222000	110	25.5	0.020000	1.00	1.00	0.
18019	53810	1	F	2Y	11.90	1	1	0.0004879	6275	7000145000	213	93.0	0.040000	1.00	1.00	0.
11257	45108	2	M	1Y	10.00	2	1	0.0004879	2996	4000096000	210	10.8	0.050000	1.00	1.00	0.
,,,,,,,,,										7000146000	213	81.8	0.040000	1.00	1.00	0.
11637	45582	1	M	2Y	13.00	2	1	0.0004868	1975	3100044000	213	56.1	0.012000	1.00	1.00	0.
,,,,,,,,,										7000145000	213	92.2	0.040000	1.00	1.00	0.
12955	47288	1	M	1Y	10.40	1	1	0.0004850	2005	7000145000	213	92.3	0.040000	1.00	1.00	0.
18532	54462	2	F	1Y	9.30	1	1	0.0004849	9519	7000145000	213	95.5	0.040000	1.00	1.00	0.
18158	53986	2	M	2Y	14.30	1	1	0.0004799	2751	7000145000	213	136.0	0.040000	1.00	1.00	0.
12681	46937	1	F	2Y	15.00	1	1	0.0004757	11671	7000145000	213	138.3	0.040000	1.00	1.00	0.
2343	33996	2	M	1Y	10.40	2	1	0.0004722	1398	7000145000	213	93.9	0.040000	1.00	1.00	0.
,,,,,,,,,										3600222000	110	28.6	0.020000	1.00	1.00	0.
9266	42555	1	F	2Y	14.60	1	1	0.0004698	7668	7000145000	213	130.9	0.040000	1.00	1.00	0.
13144	47542	1	F	2Y	11.60	1	1	0.0004696	1598	7000145000	213	83.9	0.040000	1.00	1.00	0.
16018	51289	2	M	2Y	14.50	2	1	0.0004682	4511	7000145000	110	76.0	0.040000	1.00	1.00	0.
,,,,,,,,,										7000145000	213	87.0	0.040000	1.00	1.00	0.
5429	37796	1	F	2Y	12.80	1	1	0.0004674	3861	7000145000	110	116.1	0.040000	1.00	1.00	0.
70	31209	2	F	2Y	13.20	2	1	0.0004654	1274	7000145000	213	99.8	0.040000	1.00	1.00	0.
,,,,,,,,,										3600222000	110	39.7	0.020000	1.00	1.00	0.
24362	61783	1	M	1Y	10.70	2	1	0.0004587	8195	7000145000	213	87.0	0.040000	1.00	1.00	0.
,,,,,,,,,										3600222000	110	52.5	0.020000	1.00	1.00	0.
14365	49132	2	M	2Y	17.00	2	1	0.0004576	1386	3100049000	214	45.9	0.100000	1.00	1.00	0.
,,,,,,,,,										7000145000	213	58.3	0.040000	1.00	1.00	0.
14208	48931	2	M	1Y	14.10	1	1	0.0004563	6302	7000145000	213	92.3	0.040000	1.00	1.00	0.
15160	50164	1	F	1Y	11.00	2	1	0.0004557	6122	7000145000	213	91.0	0.040000	1.00	1.00	0.
,,,,,,,,,										3600222000	110	46.8	0.020000	1.00	1.00	0.
5841	38316	1	F	2Y	10.50	1	1	0.0004544	7919	7000145000	213	93.9	0.040000	1.00	1.00	0.
3969	36022	2	M	2Y	14.40	1	1	0.0004518	7386	7000145000	212	132.0	0.040000	1.00	1.00	0.
16609	52070	2	M	1Y	10.30	3	1	0.0004516	5505	3100044000	212	117.2	0.012000	1.00	1.00	0.
,,,,,,,,,										7000145000	213	58.3	0.040000	1.00	1.00	0.
,,,,,,,,,										3600222000	110	32.6	0.020000	1.00	1.00	0.
16776	52277	1	F	1Y	10.50	2	1	0.0004510	7913	3100049000	214	33.6	0.100000	1.00	1.00	0.
,,,,,,,,,										7000146000	213	26.1	0.040000	1.00	1.00	0.
655	31910	2	M	1Y	11.70	2	1	0.0004509	1239	3100049000	214	30.6	0.100000	1.00	1.00	0.
,,,,,,,,,										7000145000	213	37.7	0.040000	1.00	1.00	0.
22430	59363	2	F	2Y	12.20	2	1	0.0004488	7326	3100044000	211	79.2	0.012000	1.00	1.00	0.
,,,,,,,,,										7000145000	213	61.1	0.040000	1.00	1.00	0.

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Children 3-5
Low percentile for CEC records: 95 Exposure (mg/day) = 0.000264
High percentile for CEC records: 99 Exposure (mg/day) = 0.000376
Number of actual records in this interval: 133

Critical foods with foodforms for this population (as derived from these records):
N=number of appearances in all records (including duplicates)
%=percent of total exposure for all records (including duplicates)

Food,	FF,	N ,	Percent,	Food Name
7000145000,	213,	104,	50.33%,	Egg, whole-Cooked; Fresh or N/S; Fried
7000145000,	212,	14,	5.20%,	Egg, whole-Cooked; Fresh or N/S; Boiled
3100044000,	210,	16,	3.05%,	Beef, meat-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,	110,	4,	2.09%,	Egg, whole-Uncooked; Fresh or N/S; Cook Meth N/S
3600222000,	110,	16,	1.85%,	Milk, fat-Uncooked; Fresh or N/S; Cook Meth N/S

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7000145000,  211,       8,    0.93%,  Egg, whole-Cooked; Fresh or N/S; Baked
3100044000,  212,       5,    0.88%,  Beef, meat-Cooked; Fresh or N/S; Boiled
4000096000,  210,       7,    0.86%,  Chicken, fat-Cooked; Fresh or N/S; Cook Meth N/S
4000096000,  213,       7,    0.80%,  Chicken, fat-Cooked; Fresh or N/S; Fried
3400290000,  250,       7,    0.74%,  Pork, meat-Cooked; Cured, etc; Cook Meth N/S
7000146000,  213,       1,    0.74%,  Egg, white-Cooked; Fresh or N/S; Fried
3100044000,  213,       4,    0.68%,  Beef, meat-Cooked; Fresh or N/S; Fried
3100044000,  211,       4,    0.61%,  Beef, meat-Cooked; Fresh or N/S; Baked
7000145000,  210,       2,    0.56%,  Egg, whole-Cooked; Fresh or N/S; Cook Meth N/S
3400290000,  210,       3,    0.53%,  Pork, meat-Cooked; Fresh or N/S; Cook Meth N/S
4000097000,  213,       4,    0.52%,  Chicken, skin-Cooked; Fresh or N/S; Fried
3100047000,  210,       5,    0.44%,  Beef, fat-Cooked; Fresh or N/S; Cook Meth N/S
4000096000,  211,       4,    0.41%,  Chicken, fat-Cooked; Fresh or N/S; Baked
4000097000,  211,       3,    0.40%,  Chicken, skin-Cooked; Fresh or N/S; Baked
3100045000,  230,       2,    0.34%,  Beef, meat, dried-Cooked; Dried; Cook Meth N/S
8601000000,  110,       4,    0.33%,  Water, direct, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
3400290000,  211,       2,    0.25%,  Pork, meat-Cooked; Fresh or N/S; Baked
5000385000,  210,       2,    0.21%,  Turkey, fat-Cooked; Fresh or N/S; Cook Meth N/S
3200169000,  210,       1,    0.17%,  Goat, meat-Cooked; Fresh or N/S; Cook Meth N/S
3400290000,  213,       1,    0.17%,  Pork, meat-Cooked; Fresh or N/S; Fried
7000145000,  214,       1,    0.16%,  Egg, whole-Cooked; Fresh or N/S; Fried/baked
3400290000,  240,       1,    0.16%,  Pork, meat-Cooked; Canned; Cook Meth N/S
7000145000,  232,       1,    0.15%,  Egg, whole-Cooked; Dried; Boiled
0103299000,  211,       1,    0.13%,  Potato, tuber, w/peel-Cooked; Fresh or N/S; Baked
4000097000,  212,       1,    0.12%,  Chicken, skin-Cooked; Fresh or N/S; Boiled
3400290000,  212,       1,    0.12%,  Pork, meat-Cooked; Fresh or N/S; Boiled
4000096000,  212,       1,    0.10%,  Chicken, fat-Cooked; Fresh or N/S; Boiled
3600222000,  212,       1,    0.10%,  Milk, fat-Cooked; Fresh or N/S; Boiled
3100044000,  214,       1,    0.09%,  Beef, meat-Cooked; Fresh or N/S; Fried/baked
3400291000,  213,       1,    0.08%,  Pork, skin-Cooked; Fresh or N/S; Fried
3400293000,  240,       1,    0.08%,  Pork, fat-Cooked; Canned; Cook Meth N/S
3600222000,  215,       1,    0.07%,  Milk, fat-Cooked; Fresh or N/S; Boiled/baked
5000385000,  213,       1,    0.07%,  Turkey, fat-Cooked; Fresh or N/S; Fried


Critical foods (without foodforms) for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food      ,     N ,  Percent,   Food Name
----------,  -----,  -------,  -------------
7000145000,    134,   59.42%,   Egg, whole
3100044000,     30,    5.31%,   Beef, meat
4000096000,     19,    2.17%,   Chicken, fat
3600222000,     18,    2.02%,   Milk, fat
3400290000,     15,    1.97%,   Pork, meat
4000097000,      8,    1.04%,   Chicken, skin
7000146000,      1,    0.74%,   Egg, white
3100047000,      5,    0.44%,   Beef, fat
3100045000,      2,    0.34%,   Beef, meat, dried
8601000000,      4,    0.33%,   Water, direct, all sources
5000385000,      3,    0.28%,   Turkey, fat
3200169000,      1,    0.17%,   Goat, meat
0103299000,      1,    0.13%,   Potato, tuber, w/peel
3400291000,      1,    0.08%,   Pork, skin
3400293000,      1,    0.08%,   Pork, fat

Number of printed records = 25
Number of records represented = 25
 (nf = number of foods/ff reported for this daily exposure amount (exceeding minimum contribution)
 (nx = number of times this exposure amount was computed for the same person on the same day.)

Demographic data for each record:                                   Exposure contribution data by food/ff consumed (NF lines):
  PID,  SEQN,     Day,Sex,  Age,   BW-kg,  Nf,  Nx,   Tot Expos,  Samplwt,  Food,    FF, Amt(g),   Residue , Adj#1, Adj#2,  Contr
 -----, --------, ---,---,  ---,  ------,  --, ----, -----------, -------,--------, --, ------, ----------, -----, -----,  -----

  2235 ,33862    , 2  ,M   ,3Y   , 13.90 , 2  ,   1 ,  0.0003757 ,  3224 ,7000145000 ,213,  93.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3600222000 ,110,  40.5 ,  0.020000 , 1.00 , 1.00 ,  0.

 17142 ,52735    , 2  ,F   ,5Y   , 16.70 , 1  ,   1 ,  0.0003751 ,  5676 ,7000145000 ,213, 116.4 ,  0.040000 , 1.00 , 1.00 ,  0.

  2029 ,33599    , 2  ,M   ,4Y   , 19.30 , 3  ,   1 ,  0.0003748 ,  9975 ,7000145000 ,213,  87.8 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3400290000 ,250, 100.0 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,0103299000 ,211, 347.9 ,  0.003000 , 1.00 , 1.00 ,  0.

 14571 ,49378    , 1  ,F   ,4Y   , 16.20 , 3  ,   1 ,  0.0003727 ,  4445 ,7000145000 ,213,  64.7 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3400290000 ,211,  86.1 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3400290000 ,250,  61.3 ,  0.012000 , 1.00 , 1.00 ,  0.

 15285 ,50328    , 1  ,F   ,4Y   , 17.40 , 2  ,   1 ,  0.0003717 ,  2186 ,3100044000 ,210, 246.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3100047000 ,210,  58.4 ,  0.012000 , 1.00 , 1.00 ,  0.

  9050 ,42278    , 2  ,M   ,4Y   , 15.50 , 3  ,   1 ,  0.0003708 , 76528 ,3100044000 ,210, 189.6 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3100044000 ,212,  79.1 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                            ,3100047000 ,210,  54.1 ,  0.012000 , 1.00 , 1.00 ,  0.

  5029 ,37314    , 2  ,M   ,3Y   , 15.30 , 1  ,   1 ,  0.0003690 ,  5287 ,7000145000 ,213,  93.8 ,  0.040000 , 1.00 , 1.00 ,  0.

 11151 ,44974    , 2  ,M   ,4Y   , 14.00 , 1  ,   1 ,  0.0003685 ,  9713 ,7000145000 ,213,  87.8 ,  0.040000 , 1.00 , 1.00 ,  0.

 12936 ,47260    , 1  ,M   ,4Y   , 12.80 , 1  ,   1 ,  0.0003679 ,  2082 ,7000145000 ,213,  86.6 ,  0.040000 , 1.00 , 1.00 ,  0.
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  284 ,31473    , 2  ,F   ,5Y   , 18.00 , 1  ,   1 ,  0.0003644 ,  5541 ,7000145000 ,213, 143.2 ,  0.040000 , 1.00 , 1.00 ,  0.
 23114 ,60188    , 2  ,F   ,4Y   , 16.20 , 1  ,   1 ,  0.0003613 ,  5968 ,7000145000 ,212, 130.0 ,  0.040000 , 1.00 , 1.00 ,  0.
 21483 ,58178    , 1  ,F   ,3Y   , 19.10 , 2  ,   1 ,  0.0003609 ,  2455 ,7000145000 ,213, 101.6 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,5000385000 ,210,  19.4 ,  0.050000 , 1.00 , 1.00 ,  0.
 23777 ,61038    , 2  ,M   ,3Y   , 12.50 , 4  ,   1 ,  0.0003605 ,  4122 ,3100044000 ,210,  61.6 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,4000096000 ,213,  11.1 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,4000097000 ,213,  11.1 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,7000145000 ,213,  40.5 ,  0.040000 , 1.00 , 1.00 ,  0.
   509 ,31738    , 1  ,F   ,4Y   , 13.80 , 2  ,   1 ,  0.0003594 ,  5747 ,3100044000 ,212,  46.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,7000145000 ,213,  87.8 ,  0.040000 , 1.00 , 1.00 ,  0.
 13601 ,48124    , 1  ,F   ,4Y   , 16.00 , 1  ,   1 ,  0.0003586 ,  6572 ,7000145000 ,213, 128.7 ,  0.040000 , 1.00 , 1.00 ,  0.
 16931 ,52474    , 1  ,F   ,3Y   , 15.80 , 3  ,   1 ,  0.0003584 ,  3179 ,3100044000 ,213,  57.3 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,4000096000 ,213,  29.2 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,4000097000 ,213,  29.2 ,  0.050000 , 1.00 , 1.00 ,  0.
 10721 ,44428    , 1  ,M   ,4Y   , 14.70 , 2  ,   1 ,  0.0003552 ,  2207 ,7000145000 ,110,  87.3 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,3600222000 ,110,  31.4 ,  0.020000 , 1.00 , 1.00 ,  0.
  3421 ,35346    , 2  ,M   ,5Y   , 23.70 , 1  ,   1 ,  0.0003546 , 12247 ,7000145000 ,213, 143.2 ,  0.040000 , 1.00 , 1.00 ,  0.
 20334 ,56719    , 1  ,F   ,3Y   , 16.60 , 1  ,   1 ,  0.0003524 ,  2134 ,7000145000 ,213,  86.6 ,  0.040000 , 1.00 , 1.00 ,  0.
  1659 ,33147    , 1  ,M   ,4Y   , 15.20 , 3  ,   1 ,  0.0003522 ,  4123 ,4000096000 ,211,  11.1 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,4000097000 ,211,  13.2 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,7000145000 ,212,  84.6 ,  0.040000 , 1.00 , 1.00 ,  0.
 24573 ,62043    , 2  ,M   ,5Y   , 25.30 , 1  ,   1 ,  0.0003513 ,  6210 ,7000145000 ,213, 185.8 ,  0.040000 , 1.00 , 1.00 ,  0.
 21746 ,58508    , 2  ,F   ,4Y   , 15.40 , 2  ,   1 ,  0.0003512 ,  3340 ,7000145000 ,213,  92.2 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,7000145000 ,232,  24.2 ,  0.040000 , 1.00 , 1.00 ,  0.
  2695 ,34429    , 1  ,M   ,3Y   , 16.60 , 3  ,   1 ,  0.0003488 ,  1855 ,3100044000 ,210,  53.6 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,7000145000 ,212,  25.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,7000145000 ,213,  52.6 ,  0.040000 , 1.00 , 1.00 ,  0.
  7299 ,40087    , 1  ,F   ,5Y   , 17.40 , 3  ,   1 ,  0.0003465 ,  6906 ,3100044000 ,214,  51.7 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,7000145000 ,213,  87.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                             ,3600222000 ,110,  33.5 ,  0.020000 , 1.00 , 1.00 ,  0.
  2786 ,34539    , 1  ,F   ,4Y   , 13.80 , 1  ,   1 ,  0.0003420 ,  4398 ,7000145000 ,213,  91.7 ,  0.040000 , 1.00 , 1.00 ,  0.


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Children 6-12
Low percentile for CEC records: 95     Exposure (mg/day) =    0.000177
High percentile for CEC records: 99    Exposure (mg/day) =    0.000259
Number of actual records in this interval: 258


Critical foods with foodforms for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food,         FF,      N  ,  Percent,  Food Name
----------,  ---,    -----,  -------,  -------------
7000145000,  213,     191,   48.19%,  Egg, whole-Cooked; Fresh or N/S; Fried
7000145000,  212,      25,    5.28%,  Egg, whole-Cooked; Fresh or N/S; Boiled
3100044000,  210,      35,    3.22%,  Beef, meat-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,  211,      16,    1.59%,  Beef, meat-Cooked; Fresh or N/S; Baked
3100044000,  213,      21,    1.58%,  Beef, meat-Cooked; Fresh or N/S; Fried
4000096000,  210,      18,    1.57%,  Chicken, fat-Cooked; Fresh or N/S; Cook Meth N/S
7000146000,  213,       5,    1.27%,  Egg, white-Cooked; Fresh or N/S; Fried
3600222000,  110,      22,    1.18%,  Milk, fat-Uncooked; Fresh or N/S; Cook Meth N/S
3400290000,  250,      15,    0.97%,  Pork, meat-Cooked; Cured, etc; Cook Meth N/S
7000145000,  110,       6,    0.74%,  Egg, whole-Uncooked; Fresh or N/S; Cook Meth N/S
7000145000,  211,      11,    0.74%,  Egg, whole-Cooked; Fresh or N/S; Baked
4000097000,  210,       8,    0.70%,  Chicken, skin-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,  212,       5,    0.67%,  Beef, meat-Cooked; Fresh or N/S; Boiled
7000145000,  210,       8,    0.63%,  Egg, whole-Cooked; Fresh or N/S; Cook Meth N/S
4000096000,  213,       9,    0.61%,  Chicken, fat-Cooked; Fresh or N/S; Fried
3400290000,  213,       8,    0.47%,  Pork, meat-Cooked; Fresh or N/S; Fried
3100045000,  230,       3,    0.44%,  Beef, meat, dried-Cooked; Dried; Cook Meth N/S
3400290000,  211,       5,    0.37%,  Pork, meat-Cooked; Fresh or N/S; Baked
3600222000,  210,       5,    0.33%,  Milk, fat-Cooked; Fresh or N/S; Cook Meth N/S
4000097000,  213,       5,    0.30%,  Chicken, skin-Cooked; Fresh or N/S; Fried
3400290000,  210,       5,    0.30%,  Pork, meat-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,  230,       2,    0.28%,  Egg, whole-Cooked; Dried; Cook Meth N/S
3100044000,  214,       3,    0.28%,  Beef, meat-Cooked; Fresh or N/S; Fried/baked
8601000000,  110,       4,    0.27%,  Water, direct, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
4000096000,  211,       5,    0.26%,  Chicken, fat-Cooked; Fresh or N/S; Baked
3100047000,  210,       5,    0.23%,  Beef, fat-Cooked; Fresh or N/S; Cook Meth N/S
4000097000,  211,       5,    0.22%,  Chicken, skin-Cooked; Fresh or N/S; Baked
7000145000,  232,       2,    0.20%,  Egg, whole-Cooked; Dried; Boiled
5000385000,  210,       3,    0.20%,  Turkey, fat-Cooked; Fresh or N/S; Cook Meth N/S
7000146000,  223,       1,    0.18%,  Egg, white-Cooked; Frozen; Fried
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0103300000,  212,       3,    0.15%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Boiled
7000145000,  252,       1,    0.15%,  Egg, whole-Cooked; Cured, etc; Boiled
5000386000,  210,       1,    0.15%,  Turkey, skin-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,  214,       2,    0.15%,  Egg, whole-Cooked; Fresh or N/S; Fried/baked
0103299000,  211,       2,    0.13%,  Potato, tuber, w/peel-Cooked; Fresh or N/S; Baked
3600222000,  120,       2,    0.10%,  Milk, fat-Uncooked; Frozen; Cook Meth N/S
3100047000,  213,       2,    0.10%,  Beef, fat-Cooked; Fresh or N/S; Fried
7000145000,  233,       2,    0.10%,  Egg, whole-Cooked; Dried; Fried
3600222000,  214,       1,    0.09%,  Milk, fat-Cooked; Fresh or N/S; Fried/baked
3400292000,  210,       1,    0.08%,  Pork, meat byproducts-Cooked; Fresh or N/S; Cook Meth N/S
0103300000,  210,       1,    0.07%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Cook Meth N/S
4000096000,  214,       1,    0.07%,  Chicken, fat-Cooked; Fresh or N/S; Fried/baked
3400290000,  212,       1,    0.06%,  Pork, meat-Cooked; Fresh or N/S; Boiled
3600222000,  232,       1,    0.06%,  Milk, fat-Cooked; Dried; Boiled
3600222000,  230,       1,    0.06%,  Milk, fat-Cooked; Dried; Cook Meth N/S
3600222000,  211,       1,    0.05%,  Milk, fat-Cooked; Fresh or N/S; Baked
5000385000,  213,       1,    0.05%,  Turkey, fat-Cooked; Fresh or N/S; Fried
7000147000,  213,       1,    0.05%,  Egg, yolk-Cooked; Fresh or N/S; Fried
7000146000,  211,       1,    0.05%,  Egg, white-Cooked; Fresh or N/S; Baked
3400293000,  213,       1,    0.04%,  Pork, fat-Cooked; Fresh or N/S; Fried
3100047000,  212,       1,    0.04%,  Beef, fat-Cooked; Fresh or N/S; Boiled


Critical foods (without foodforms) for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food       ,      N ,  Percent,   Food Name
----------,  -----,  -------,  -------------
7000145000,    250,   56.46%,   Egg, whole
3100044000,     80,    7.34%,   Beef, meat
4000096000,     33,    2.51%,   Chicken, fat
3400290000,     34,    2.17%,   Pork, meat
3600222000,     33,    1.87%,   Milk, fat
7000146000,      7,    1.50%,   Egg, white
4000097000,     18,    1.22%,   Chicken, skin
3100045000,      3,    0.44%,   Beef, meat, dried
3100047000,      8,    0.37%,   Beef, fat
8601000000,      4,    0.27%,   Water, direct, all sources
5000385000,      4,    0.25%,   Turkey, fat
0103300000,      4,    0.22%,   Potato, tuber, w/o peel
5000386000,      1,    0.15%,   Turkey, skin
0103299000,      2,    0.13%,   Potato, tuber, w/peel
3400292000,      1,    0.08%,   Pork, meat byproducts
7000147000,      1,    0.05%,   Egg, yolk
3400293000,      1,    0.04%,   Pork, fat

Number of printed records = 25
Number of records represented = 25
 (nf = number of foods/ff reported for this daily exposure amount (exceeding minimum contribution)
 (nx = number of times this exposure amount was computed for the same person on the same day.)

Demographic data for each record:                                   Exposure contribution data by food/ff consumed (NF lines):
  PID,  SEQN,     Day,Sex,  Age,   BW-kg,  Nf,  Nx,   Tot Expos,  Samplwt,  Food,    FF, Amt(g),   Residue , Adj#1, Adj#2,  Contr
 -----, --------, ---,---,  ---,  ------,  --, ----, -----------, -------,--------, --, ------, ----------, -----, -----,  -----

 11669 ,45618    , 1  ,M   ,8Y   , 34.10 , 2  ,   1 ,  0.0002579 ,  1042 ,3100044000 ,213,  91.5 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,7000145000 ,213, 172.1 ,  0.040000 , 1.00 , 1.00 ,  0.

  8251 ,41254    , 2  ,M   ,8Y   , 30.30 , 1  ,   1 ,  0.0002578 , 33439 ,7000145000 ,213, 154.2 ,  0.040000 , 1.00 , 1.00 ,  0.

 21116 ,57721    , 1  ,M   ,6Y   , 22.00 , 1  ,   1 ,  0.0002570 ,  2170 ,7000145000 ,213,  99.3 ,  0.040000 , 1.00 , 1.00 ,  0.

 19887 ,56168    , 1  ,M   ,9Y   , 30.30 , 1  ,   1 ,  0.0002555 ,  6562 ,7000145000 ,213, 174.4 ,  0.040000 , 1.00 , 1.00 ,  0.

 10489 ,44137    , 2  ,M   ,9Y   , 47.90 , 1  ,   1 ,  0.0002552 ,  7052 ,7000146000 ,213, 244.5 ,  0.040000 , 1.00 , 1.00 ,  0.

 18385 ,54264    , 1  ,M   ,7Y   , 20.80 , 2  ,   1 ,  0.0002549 ,  7481 ,3100044000 ,210,  53.6 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,7000145000 ,213,  87.0 ,  0.040000 , 1.00 , 1.00 ,  0.

  5219 ,37538    , 1  ,M   ,10Y  , 53.00 , 1  ,   1 ,  0.0002539 ,  3582 ,7000145000 ,213, 279.3 ,  0.040000 , 1.00 , 1.00 ,  0.

  8568 ,41657    , 2  ,M   ,8Y   , 26.00 , 1  ,   1 ,  0.0002539 , 25029 ,7000145000 ,212, 100.0 ,  0.040000 , 1.00 , 1.00 ,  0.

  3986 ,36042    , 1  ,F   ,9Y   , 20.00 , 1  ,   1 ,  0.0002538 ,  1512 ,7000145000 ,213, 102.9 ,  0.040000 , 1.00 , 1.00 ,  0.

  6803 ,39483    , 1  ,F   ,9Y   , 30.20 , 3  ,   1 ,  0.0002536 ,  7500 ,3100044000 ,210, 105.2 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,7000145000 ,210,  80.1 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,7000145000 ,213,  21.3 ,  0.040000 , 1.00 , 1.00 ,  0.

  6196 ,38748    , 2  ,F   ,7Y   , 26.80 , 1  ,   1 ,  0.0002525 ,  8573 ,7000145000 ,213, 121.3 ,  0.040000 , 1.00 , 1.00 ,  0.

 24638 ,62121    , 2  ,M   ,11Y  , 35.10 , 2  ,   1 ,  0.0002509 ,  1988 ,3100044000 ,213, 173.8 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                ,7000145000 ,213, 117.1 ,  0.040000 , 1.00 , 1.00 ,  0.

 21928 ,58733    , 2  ,M   ,6Y   , 20.90 , 1  ,   1 ,  0.0002505 ,  3575 ,7000145000 ,213,  86.6 ,  0.040000 , 1.00 , 1.00 ,  0.

  7667 ,40527    , 2  ,M   ,10Y  , 38.10 , 1  ,   1 ,  0.0002505 , 68126 ,7000145000 ,213, 173.0 ,  0.040000 , 1.00 , 1.00 ,  0.

 13117 ,47509    , 1  ,F   ,11Y  , 33.50 , 1  ,   1 ,  0.0002486 , 17200 ,7000145000 ,213, 163.3 ,  0.040000 , 1.00 , 1.00 ,  0.

 11309 ,45173    , 1  ,M   ,9Y   , 32.70 , 2  ,   1 ,  0.0002485 ,  3311 ,4000096000 ,210,  27.3 ,  0.050000 , 1.00 , 1.00 ,  0.
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,,,,,,,,,                                                                  ,7000145000 ,213, 125.3 ,  0.040000 , 1.00 , 1.00 ,  0.
 16744 ,52236    , 1  ,M   ,8Y   , 22.40 , 1  ,   1 ,  0.0002483 ,  3863 ,7000145000 ,213, 116.8 ,  0.040000 , 1.00 , 1.00 ,  0.
  6346 ,38926    , 2  ,F   ,9Y   , 22.10 , 1  ,   1 ,  0.0002472 ,  7452 ,7000145000 ,213,  94.5 ,  0.040000 , 1.00 , 1.00 ,  0.
   514 ,31743    , 1  ,M   ,8Y   , 37.20 , 1  ,   1 ,  0.0002472 ,  1616 ,7000145000 ,213, 194.6 ,  0.040000 , 1.00 , 1.00 ,  0.
 18358 ,54231    , 1  ,M   ,11Y  , 42.70 , 2  ,   1 ,  0.0002469 ,  6083 ,3100044000 ,211, 103.5 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                  ,7000145000 ,213, 177.1 ,  0.040000 , 1.00 , 1.00 ,  0.
 24569 ,62039    , 2  ,F   ,12Y  , 42.70 , 1  ,   1 ,  0.0002465 ,  7203 ,7000145000 ,213, 255.3 ,  0.040000 , 1.00 , 1.00 ,  0.
  6276 ,38848    , 2  ,M   ,8Y   , 24.80 , 2  ,   1 ,  0.0002457 ,   912 ,7000145000 ,212,  45.4 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                  ,3600222000 ,110,  42.1 ,  0.020000 , 1.00 , 1.00 ,  0.
 20795 ,57298    , 2  ,F   ,9Y   , 33.20 , 3  ,   1 ,  0.0002456 , 11287 ,4000096000 ,210,  39.1 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                  ,4000097000 ,210,  33.9 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                                  ,7000145000 ,213,  66.3 ,  0.040000 , 1.00 , 1.00 ,  0.
  7748 ,40625    , 1  ,M   ,7Y   , 26.20 , 1  ,   1 ,  0.0002439 , 31482 ,7000145000 ,212, 120.1 ,  0.040000 , 1.00 , 1.00 ,  0.
 17270 ,52889    , 2  ,F   ,7Y   , 25.10 , 1  ,   1 ,  0.0002431 ,  1427 ,7000145000 ,213, 113.8 ,  0.040000 , 1.00 , 1.00 ,  0.


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Female 13-49
Low percentile for CEC records: 95     Exposure (mg/day) =    0.000097
High percentile for CEC records: 99    Exposure (mg/day) =    0.000151
Number of actual records in this interval: 494


Critical foods with foodforms for this population (as derived from these records):
  N=number of appearances in all records (including duplicates)
  %=percent of total exposure for all records (including duplicates)

Food,        FF,      N  ,  Percent,  Food Name
----------,  ---,   -----,  -------,  -------------
7000145000,  213,     347,   41.30%,  Egg, whole-Cooked; Fresh or N/S; Fried
7000145000,  212,      42,    4.52%,  Egg, whole-Cooked; Fresh or N/S; Boiled
3100044000,  213,      60,    2.61%,  Beef, meat-Cooked; Fresh or N/S; Fried
3100044000,  210,      56,    2.50%,  Beef, meat-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,  211,      36,    2.15%,  Beef, meat-Cooked; Fresh or N/S; Baked
3400290000,  210,      36,    1.62%,  Pork, meat-Cooked; Fresh or N/S; Cook Meth N/S
7000146000,  213,      15,    1.53%,  Egg, white-Cooked; Fresh or N/S; Fried
4000096000,  210,      30,    1.44%,  Chicken, fat-Cooked; Fresh or N/S; Cook Meth N/S
3600222000,  110,      42,    1.40%,  Milk, fat-Uncooked; Fresh or N/S; Cook Meth N/S
8601000000,  110,      47,    1.27%,  Water, direct, all sources-Uncooked; Fresh or N/S; Cook Meth N/S
7000145000,  211,      23,    1.08%,  Egg, whole-Cooked; Fresh or N/S; Baked
4000097000,  210,      23,    1.00%,  Chicken, skin-Cooked; Fresh or N/S; Cook Meth N/S
7000145000,  110,      10,    0.95%,  Egg, whole-Uncooked; Fresh or N/S; Cook Meth N/S
4000096000,  213,      27,    0.92%,  Chicken, fat-Cooked; Fresh or N/S; Fried
3400290000,  250,      26,    0.91%,  Pork, meat-Cooked; Cured, etc; Cook Meth N/S
7000145000,  210,      13,    0.83%,  Egg, whole-Cooked; Fresh or N/S; Cook Meth N/S
3100044000,  212,      17,    0.79%,  Beef, meat-Cooked; Fresh or N/S; Boiled
3100049000,  214,       4,    0.68%,  Beef, liver-Cooked; Fresh or N/S; Fried/baked
4000097000,  213,      17,    0.59%,  Chicken, skin-Cooked; Fresh or N/S; Fried
7000146000,  223,       5,    0.59%,  Egg, white-Cooked; Frozen; Fried
4000096000,  211,      11,    0.47%,  Chicken, fat-Cooked; Fresh or N/S; Baked
4000097000,  211,      12,    0.44%,  Chicken, skin-Cooked; Fresh or N/S; Baked
7000146000,  211,       6,    0.43%,  Egg, white-Cooked; Fresh or N/S; Baked
3400290000,  213,      10,    0.40%,  Pork, meat-Cooked; Fresh or N/S; Fried
5000386000,  210,       7,    0.39%,  Turkey, skin-Cooked; Fresh or N/S; Cook Meth N/S
5000385000,  210,       9,    0.36%,  Turkey, fat-Cooked; Fresh or N/S; Cook Meth N/S
4000096000,  212,       7,    0.27%,  Chicken, fat-Cooked; Fresh or N/S; Boiled
3400290000,  211,       7,    0.23%,  Pork, meat-Cooked; Fresh or N/S; Baked
0103300000,  212,       6,    0.21%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Boiled
3600222000,  120,       7,    0.21%,  Milk, fat-Uncooked; Frozen; Cook Meth N/S
3100044000,  214,       4,    0.20%,  Beef, meat-Cooked; Fresh or N/S; Fried/baked
3400290000,  253,       3,    0.19%,  Pork, meat-Cooked; Cured, etc; Fried
4000097000,  212,       4,    0.19%,  Chicken, skin-Cooked; Fresh or N/S; Boiled
3500339000,  210,       3,    0.16%,  Sheep, meat-Cooked; Fresh or N/S; Cook Meth N/S
3600222000,  210,       5,    0.13%,  Milk, fat-Cooked; Fresh or N/S; Cook Meth N/S
8602000000,  232,       5,    0.13%,  Water, indirect, all sources-Cooked; Dried; Boiled
3100044000,  250,       1,    0.10%,  Beef, meat-Cooked; Cured, etc; Cook Meth N/S
3100047000,  211,       4,    0.09%,  Beef, fat-Cooked; Fresh or N/S; Baked
3100047000,  213,       4,    0.09%,  Beef, fat-Cooked; Fresh or N/S; Fried
0103299000,  211,       3,    0.09%,  Potato, tuber, w/peel-Cooked; Fresh or N/S; Baked
3100047000,  210,       4,    0.09%,  Beef, fat-Cooked; Fresh or N/S; Cook Meth N/S
3600222000,  212,       2,    0.06%,  Milk, fat-Cooked; Fresh or N/S; Boiled
7000145000,  233,       1,    0.06%,  Egg, whole-Cooked; Dried; Fried
3100045000,  230,       2,    0.06%,  Beef, meat, dried-Cooked; Dried; Cook Meth N/S
7000145000,  232,       2,    0.06%,  Egg, whole-Cooked; Dried; Boiled
3400290000,  251,       1,    0.06%,  Pork, meat-Cooked; Cured, etc; Baked
7000145000,  214,       2,    0.05%,  Egg, whole-Cooked; Fresh or N/S; Fried/baked
3400293000,  210,       2,    0.05%,  Pork, fat-Cooked; Fresh or N/S; Cook Meth N/S
0103300000,  213,       2,    0.05%,  Potato, tuber, w/o peel-Cooked; Fresh or N/S; Fried
4000097000,  240,       1,    0.05%,  Chicken, skin-Cooked; Canned; Cook Meth N/S
3400290000,  212,       1,    0.04%,  Pork, meat-Cooked; Fresh or N/S; Boiled
3400290000,  252,       2,    0.04%,  Pork, meat-Cooked; Cured, etc; Boiled
3100046000,  210,       1,    0.03%,  Beef, meat byproducts-Cooked; Fresh or N/S; Cook Meth N/S
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7000147000,	212,	1,	0.03%,	Egg, yolk-Cooked; Fresh or N/S; Boiled
3400290000,	242,	1,	0.03%,	Pork, meat-Cooked; Canned; Boiled
3400293000,	250,	1,	0.03%,	Pork, fat-Cooked; Cured, etc; Cook Meth N/S
0103299000,	213,	1,	0.03%,	Potato, tuber, w/peel-Cooked; Fresh or N/S; Fried
3600222000,	215,	1,	0.03%,	Milk, fat-Cooked; Fresh or N/S; Boiled/baked
3600222000,	213,	1,	0.03%,	Milk, fat-Cooked; Fresh or N/S; Fried
0103300000,	223,	1,	0.03%,	Potato, tuber, w/o peel-Cooked; Frozen; Fried
3600222000,	211,	1,	0.03%,	Milk, fat-Cooked; Fresh or N/S; Baked
5000385000,	211,	1,	0.03%,	Turkey, fat-Cooked; Fresh or N/S; Baked
3100047000,	212,	1,	0.02%,	Beef, fat-Cooked; Fresh or N/S; Boiled
3100047000,	250,	1,	0.02%,	Beef, fat-Cooked; Cured, etc; Cook Meth N/S
3600222000,	214,	1,	0.02%,	Milk, fat-Cooked; Fresh or N/S; Fried/baked
0103296000,	213,	1,	0.02%,	Potato, chips-Cooked; Fresh or N/S; Fried
7000147000,	213,	1,	0.02%,	Egg, yolk-Cooked; Fresh or N/S; Fried
4000096000,	240,	1,	0.02%,	Chicken, fat-Cooked; Canned; Cook Meth N/S
5000386000,	211,	1,	0.02%,	Turkey, skin-Cooked; Fresh or N/S; Baked

Critical foods (without foodforms) for this population (as derived from these records):
N=number of appearances in all records (including duplicates)
%=percent of total exposure for all records (including duplicates)

Food ,	N ,	Percent,	Food Name
7000145000,	440,	48.85%,	Egg, whole
3100044000,	174,	8.35%,	Beef, meat
3400290000,	87,	3.52%,	Pork, meat
4000096000,	76,	3.12%,	Chicken, fat
7000146000,	26,	2.55%,	Egg, white
4000097000,	57,	2.27%,	Chicken, skin
3600222000,	60,	1.91%,	Milk, fat
8601000000,	47,	1.27%,	Water, direct, all sources
3100049000,	4,	0.68%,	Beef, liver
5000386000,	8,	0.41%,	Turkey, skin
5000385000,	10,	0.39%,	Turkey, fat
3100047000,	14,	0.31%,	Beef, fat
0103300000,	9,	0.29%,	Potato, tuber, w/o peel
3500339000,	3,	0.16%,	Sheep, meat
8602000000,	5,	0.13%,	Water, indirect, all sources
0103299000,	4,	0.12%,	Potato, tuber, w/peel
3400293000,	3,	0.08%,	Pork, fat
3100045000,	2,	0.06%,	Beef, meat, dried
7000147000,	2,	0.05%,	Egg, yolk
3100046000,	1,	0.03%,	Beef, meat byproducts
0103296000,	1,	0.02%,	Potato, chips

Number of printed records = 25
Number of records represented = 25
(nf = number of foods/ff reported for this daily exposure amount (exceeding minimum contribution)
(nx = number of times this exposure amount was computed for the same person on the same day.)

Demographic data for each record: Exposure contribution data by food/ff consumed (NF lines):

PID,	SEQN,	Day,	Sex,	Age,	BW-kg,	Nf,	Nx,	Tot Expos,	Samplwt,	Food,	FF,	Amt(g),	Residue ,	Adj#1,	Adj#2,	Contr
18222 ,	54057 ,	2 ,	F ,	21Y ,	45.00 ,	2 ,	1 ,	0.0001505 ,	6613 ,	3100044000 ,	210,	151.1 ,	0.012000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										7000145000 ,	213,	96.0 ,	0.040000 ,	1.00 ,	1.00 ,	0.
11386 ,	45272 ,	1 ,	F ,	13Y ,	49.70 ,	3 ,	1 ,	0.0001489 ,	3270 ,	4000096000 ,	212,	21.1 ,	0.050000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										4000097000 ,	212,	18.9 ,	0.050000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										7000145000 ,	212,	100.0 ,	0.040000 ,	1.00 ,	1.00 ,	0.
584 ,	31824 ,	1 ,	F ,	22Y ,	54.50 ,	2 ,	1 ,	0.0001485 ,	2449 ,	7000145000 ,	213,	104.5 ,	0.040000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										8601000000 ,	110,	4665.9 ,	0.000275 ,	1.00 ,	1.00 ,	0.
6541 ,	39172 ,	2 ,	F ,	17Y ,	49.50 ,	1 ,	1 ,	0.0001477 ,	892 ,	7000145000 ,	213,	151.2 ,	0.040000 ,	1.00 ,	1.00 ,	0.
9191 ,	42466 ,	2 ,	F ,	13Y ,	41.80 ,	1 ,	1 ,	0.0001474 ,	18198 ,	7000145000 ,	213,	121.5 ,	0.040000 ,	1.00 ,	1.00 ,	0.
460 ,	31680 ,	1 ,	F ,	24Y ,	59.80 ,	3 ,	1 ,	0.0001470 ,	801 ,	4000096000 ,	210,	52.0 ,	0.050000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										4000097000 ,	210,	24.1 ,	0.050000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										7000145000 ,	213,	93.9 ,	0.040000 ,	1.00 ,	1.00 ,	0.
1145 ,	32513 ,	2 ,	F ,	22Y ,	82.50 ,	1 ,	1 ,	0.0001454 ,	2616 ,	7000145000 ,	213,	230.8 ,	0.040000 ,	1.00 ,	1.00 ,	0.
11602 ,	45540 ,	2 ,	F ,	19Y ,	55.00 ,	1 ,	1 ,	0.0001454 ,	1973 ,	7000145000 ,	213,	138.3 ,	0.040000 ,	1.00 ,	1.00 ,	0.
17299 ,	52927 ,	1 ,	F ,	35Y ,	85.60 ,	1 ,	1 ,	0.0001444 ,	20712 ,	7000145000 ,	213,	242.7 ,	0.040000 ,	1.00 ,	1.00 ,	0.
2805 ,	34564 ,	1 ,	F ,	38Y ,	60.80 ,	2 ,	1 ,	0.0001444 ,	24357 ,	3100044000 ,	211,	87.5 ,	0.012000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										7000145000 ,	213,	149.8 ,	0.040000 ,	1.00 ,	1.00 ,	0.
14565 ,	49372 ,	1 ,	F ,	14Y ,	65.10 ,	3 ,	1 ,	0.0001443 ,	7340 ,	3100044000 ,	211,	408.6 ,	0.012000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										3100047000 ,	211,	87.7 ,	0.012000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										7000145000 ,	211,	44.4 ,	0.040000 ,	1.00 ,	1.00 ,	0.
2374 ,	34032 ,	1 ,	F ,	15Y ,	66.00 ,	1 ,	1 ,	0.0001438 ,	1065 ,	7000145000 ,	213,	215.2 ,	0.040000 ,	1.00 ,	1.00 ,	0.
19074 ,	55146 ,	1 ,	F ,	43Y ,	58.70 ,	3 ,	1 ,	0.0001438 ,	5580 ,	4000096000 ,	210,	27.1 ,	0.050000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										7000145000 ,	213,	122.3 ,	0.040000 ,	1.00 ,	1.00 ,	0.
,,,,,,,,,										3400290000 ,	210,	80.3 ,	0.012000 ,	1.00 ,	1.00 ,	0.

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 24025 ,61359    , 2  ,F   ,42Y  , 85.30 , 1  ,   1 ,  0.0001438 ,  4960 ,7000146000 ,211, 257.6 ,  0.040000 , 1.00 , 1.00 ,  0.
 18051 ,53848    , 2  ,F   ,38Y  , 79.40 , 4  ,   1 ,  0.0001434 ,  7205 ,4000096000 ,213,  26.0 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,4000097000 ,213,  26.0 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,212, 116.0 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  76.0 ,  0.040000 , 1.00 , 1.00 ,  0.
 22353 ,59269    , 2  ,F   ,13Y  , 44.60 , 2  ,   1 ,  0.0001433 ,  8407 ,7000145000 ,213,  83.8 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3600222000 ,120,  32.8 ,  0.020000 , 1.00 , 1.00 ,  0.
  4258 ,36370    , 2  ,F   ,24Y  , 58.50 , 3  ,   1 ,  0.0001427 ,   862 ,3100044000 ,212, 154.0 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  98.1 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3600222000 ,110,  46.9 ,  0.020000 , 1.00 , 1.00 ,  0.
 11876 ,45887    , 2  ,F   ,49Y  , 47.10 , 2  ,   1 ,  0.0001423 , 21806 ,7000145000 ,213,  99.8 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3400290000 ,210, 100.8 ,  0.012000 , 1.00 , 1.00 ,  0.
  1827 ,33351    , 2  ,F   ,16Y  , 47.90 , 1  ,   1 ,  0.0001422 ,   745 ,7000145000 ,212, 132.0 ,  0.040000 , 1.00 , 1.00 ,  0.
  1282 ,32689    , 2  ,F   ,31Y  , 60.80 , 2  ,   1 ,  0.0001412 , 11819 ,3100044000 ,210, 152.2 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  98.1 ,  0.040000 , 1.00 , 1.00 ,  0.
  1690 ,33181    , 2  ,F   ,40Y  , 81.90 , 2  ,   1 ,  0.0001412 , 46683 ,3100044000 ,211, 345.4 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213, 140.6 ,  0.040000 , 1.00 , 1.00 ,  0.
  1436 ,32884    , 2  ,F   ,16Y  , 57.20 , 2  ,   1 ,  0.0001410 ,  3759 ,4000096000 ,210,  69.2 ,  0.050000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,4000097000 ,210,  42.0 ,  0.050000 , 1.00 , 1.00 ,  0.
 22205 ,59090    , 2  ,F   ,38Y  , 68.00 , 3  ,   1 ,  0.0001409 ,  8636 ,7000145000 ,213, 104.5 ,  0.040000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,3400290000 ,210, 209.9 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,8601000000 ,110,4991.8 ,  0.000275 , 1.00 , 1.00 ,  0.
  3103 ,34947    , 2  ,F   ,29Y  , 70.50 , 1  ,   1 ,  0.0001408 , 24058 ,7000146000 ,213, 198.0 ,  0.040000 , 1.00 , 1.00 ,  0.
  1845 ,33371    , 2  ,F   ,21Y  , 58.70 , 2  ,   1 ,  0.0001405 ,  2357 ,3100044000 ,213, 159.1 ,  0.012000 , 1.00 , 1.00 ,  0.
,,,,,,,,,                                                              ,7000145000 ,213,  93.7 ,  0.040000 , 1.00 , 1.00 ,  0.
```

Evaluation Copy Ver. 4.02, 05-10-c
DEEM-FCID Chronic analysis for FIPRONIL NHANES 2005-2010 2-day
Residue file name: C:\Users\lscanlan\Documents\Fipronil\Dietary\new POD\fipronil chronic tier 2 28Aug19.R10
Adjustment factor #2 NOT used.
Analysis Date 08-28-2019/10:43:18 Residue file dated: 08-28-2019/10:42:38
NOEL (Chronic) = .02 mg/kg bw/day

Chronic Tier 2 Results

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Percent of NOEL	Margin of Exposure
Total US Population	0.000016	0.08%	1,231
Hispanic	0.000018	0.09%	1,098
Non-Hisp-White	0.000015	0.08%	1,293
Non-Hisp-Black	0.000018	0.09%	1,136
Non-Hisp-Other	0.000017	0.09%	1,143
Nursing Infants	0.000005	0.03%	3,751
Non-Nursing Infants	0.000016	0.08%	1,230
Female 13+ PREG	0.000014	0.07%	1,432
Children 1-6	0.000034	0.17%	591
Children 7-12	0.000022	0.11%	921
Male 13-19	0.000018	0.09%	1,127
Female 13-19/NP	0.000013	0.07%	1,507
Male 20+	0.000016	0.08%	1,262
Female 20+/NP	0.000012	0.06%	1,669
Seniors 55+	0.000013	0.06%	1,595
All Infants	0.000013	0.06%	1,559
Female 13-50	0.000013	0.06%	1,575
Children 1-2	0.000038	0.19%	523
Children 3-5	0.000033	0.16%	615
Children 6-12	0.000023	0.11%	882
Youth 13-19	0.000015	0.08%	1,294
Adults 20-49	0.000015	0.07%	1,366
Adults 50-99	0.000013	0.06%	1,570
Female 13-49	0.000013	0.06%	1,571

Evaluation Copy Ver. 4.02, 05-10-c
DEEM-FCID Chronic analysis for FIPRONIL NHANES 2005-2010 2-day
Residue file name: C:\Users\lscanlan\Documents\Fipronil\Dietary\new POD\fipronil chronic tier 2 28Aug19.R10
Adjustment factor #2 NOT used.
Analysis Date 08-28-2019/10:43:20 Residue file dated: 08-28-2019/10:42:38
NOEL (Chronic) = .02 mg/kg bw/day

Complete commodity contribution analysis for
Total US Population

Crop Group = (1) Root and Tuber Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000002	0.0%	125,395
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	298,441
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	43,798
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000018	0.0%	10,886
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Crop group subtotal					0.0000025	0.0%	7,868

Crop Group = (1C) Tuberous and Corm Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000002	0.0%	125,395
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	298,441
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	43,798
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000018	0.0%	10,886
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Crop group subtotal					0.0000025	0.0%	7,868

Crop Group = (31) Beef

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, meat (3100044000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000035	0.0%	5,765
Beef, meat-babyfood (3100044001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000000	0.0%	>1000000
Beef, meat, dried (3100045000):							
FoodForm N/S	0.006000	1.920	1.000		0.0000000	0.0%	653,656
Beef, meat byproducts (3100046000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000001	0.0%	173,620
Beef, meat byproducts-babyfood (3100046001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000000	0.0%	>1000000
Beef, fat (3100047000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000008	0.0%	26,044

Crop Group = (31) Beef (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, fat-babyfood (3100047001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Beef, kidney (3100048000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, liver (3100049000):						
FoodForm N/S	0.050000	1.000	1.000	0.0000001	0.0%	289,226
Beef, liver-babyfood (3100049001):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000045	0.0%	4,473

Crop Group = (32) Goat

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Goat, meat (3200169000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Goat, meat byproducts (3200170000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Goat, fat (3200171000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Goat, kidney (3200172000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, liver (3200173000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (33) Horse

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Horse, meat (3300189000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (34) Pork

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Pork, meat (3400290000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000014	0.0%	14,162
Pork, meat-babyfood (3400290001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, skin (3400291000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, meat byproducts (3400292000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000001	0.0%	248,633
Pork, meat byproducts-babyfood (3400292001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, fat (3400293000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000005	0.0%	42,311
Pork, fat-babyfood (3400293001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, kidney (3400294000):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, liver (3400295000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000020	0.0%	10,036

Crop Group = (35) Sheep

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Sheep, meat (3500339000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	638,081
Sheep, meat-babyfood (3500339001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, meat byproducts (3500340000):						
FoodForm N/S	0.020000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat (3500341000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat-babyfood (3500341001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, kidney (3500342000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, liver (3500343000):						
FoodForm N/S	0.050000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000000	0.0%	483,512

Crop Group = (36) Milk

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Milk, fat (3600222000):						
FoodForm N/S	0.003230	1.000	1.000	0.0000011	0.0%	18,675
Milk, fat-baby food/infant formula (3600222001):						
FoodForm N/S	0.003230	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000011	0.0%	18,660

Crop Group = (40) Chicken

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Chicken, meat (4000093000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000002	0.0%	118,949
Chicken, meat-babyfood (4000093001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, liver (4000094000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts (4000095000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts-babyfood (4000095001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, fat (4000096000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000014	0.0%	14,153
Chicken, fat-babyfood (4000096001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, skin (4000097000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000007	0.0%	29,259
Chicken, skin-babyfood (4000097001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000023	0.0%	8,704

Crop Group = (50) Turkey

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, meat (5000382000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	567,135
Turkey, meat-babyfood (5000382001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver (5000383000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver-babyfood (5000383001):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, meat byproducts (5000384000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat byproducts-babyfood (5000384001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, fat (5000385000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000003	0.0%	61,924

Crop Group = (50) Turkey (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, fat-babyfood (5000385001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, skin (5000386000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	141,970
Turkey, skin-babyfood (5000386001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000005	0.0%	39,375

Crop Group = (60) Poultry (other)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Poultry, other, meat (6000301000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, liver (6000302000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, meat byproducts (6000303000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, fat (6000304000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, skin (6000305000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (70) Egg

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Egg, whole (7000145000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000024	0.0%	8,236
Egg, whole-babyfood (7000145001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	>1000000
Egg, white (7000146000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	136,952
Egg, white (solids)-babyfood (7000146001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, yolk (7000147000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	342,658
Egg, yolk-babyfood (7000147001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000026	0.0%	7,592

Crop Group = (86) Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000004	0.0%	48,702
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000003	0.0%	78,101
Crop group subtotal				0.0000007	0.0%	29,997

Crop Group = (86A) Direct Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000004	0.0%	48,702
Crop group subtotal				0.0000004	0.0%	48,702

Crop Group = (86B) Indirect Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000003	0.0%	78,101
Crop group subtotal				0.0000003	0.0%	78,101
Population subgroup total				0.0000162	0.1%	1,231

1. Margin of Exposure = NOEL / Dietary Exposure

Evaluation Copy Ver. 4.02, 05-10-c
DEEM-FCID Chronic analysis for FIPRONIL NHANES 2005-2010 2-day
Residue file name: C:\Users\lscanlan\Documents\Fipronil\Dietary\new POD\fipronil chronic tier 2 28Aug19.R10
Adjustment factor #2 NOT used.
Analysis Date 08-28-2019/10:43:20 Residue file dated: 08-28-2019/10:42:38
NOEL (Chronic) = .02 mg/kg bw/day

Critical Commodity Contribution Analysis for
Total US Population

Total Exposure =.0000162 mg/kg bw/day

Crop groups with total exposure contribution > 10%
Foods/Foodforms with exposure contribution > 5%

Crop group / Food / Foodform	Exposure Analysis: mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (1) Root and Tuber Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000018	11.31%	0.0%	10,886
Total for crop group	0.0000025	15.64%	0.0%	7,868
Crop Group = (1C) Tuberous and Corm Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000018	11.31%	0.0%	10,886
Total for crop group	0.0000025	15.64%	0.0%	7,868
Crop Group = (31) Beef				
Beef, meat (3100044000):				
FoodForm N/S	0.0000035	21.35%	0.0%	5,765
Total for crop group	0.0000045	27.52%	0.0%	4,473
Crop Group = (34) Pork				
Pork, meat (3400290000):				
FoodForm N/S	0.0000014	8.69%	0.0%	14,162
Total for crop group	0.0000020	12.26%	0.0%	10,036
Crop Group = (36) Milk				
Milk, fat (3600222000):				
FoodForm N/S	0.0000011	6.59%	0.0%	18,675
Total for crop group	0.0000011	6.60%	0.0%	18,660
Crop Group = (40) Chicken				
Chicken, fat (4000096000):				
FoodForm N/S	0.0000014	8.70%	0.0%	14,153
Total for crop group	0.0000023	14.14%	0.0%	8,704
Crop Group = (70) Egg				
Egg, whole (7000145000):				
FoodForm N/S	0.0000024	14.95%	0.0%	8,236
Total for crop group	0.0000026	16.21%	0.0%	7,592
Total for crop groups listed above:	0.0000150	92.38%	0.1%	1,332

1. Margin of Exposure = NOEL / Dietary Exposure

Complete commodity contribution analysis for
Nursing Infants

Crop Group = (1) Root and Tuber Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	890,369
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	38,631
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000003	0.0%	74,895
Crop group subtotal					0.0000009	0.0%	23,112

Crop Group = (1C) Tuberous and Corm Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	890,369
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	38,631
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000003	0.0%	74,895
Crop group subtotal					0.0000009	0.0%	23,112

Crop Group = (31) Beef

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, meat (3100044000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000003	0.0%	74,299
Beef, meat-babyfood (3100044001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000002	0.0%	97,941
Beef, meat, dried (3100045000):							
FoodForm N/S	0.006000	1.920	1.000		0.0000000	0.0%	>1000000
Beef, meat byproducts (3100046000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000000	0.0%	867,604
Beef, meat byproducts-babyfood (3100046001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000000	0.0%	>1000000
Beef, fat (3100047000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000001	0.0%	254,007

Crop Group = (31) Beef (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, fat-babyfood (3100047001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Beef, kidney (3100048000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, liver (3100049000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Beef, liver-babyfood (3100049001):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000006	0.0%	33,615

Crop Group = (32) Goat

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Goat, meat (3200169000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, meat byproducts (3200170000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, fat (3200171000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, kidney (3200172000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, liver (3200173000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (33) Horse

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Horse, meat (3300189000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (34) Pork

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Pork, meat (3400290000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000001	0.0%	176,983
Pork, meat-babyfood (3400290001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	555,787
Pork, skin (3400291000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, meat byproducts (3400292000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, meat byproducts-babyfood (3400292001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, fat (3400293000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000001	0.0%	348,529
Pork, fat-babyfood (3400293001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, kidney (3400294000):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, liver (3400295000):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Crop group subtotal				0.0000002	0.0%	86,589

Crop Group = (35) Sheep

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Sheep, meat (3500339000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, meat-babyfood (3500339001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, meat byproducts (3500340000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, fat (3500341000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat-babyfood (3500341001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, kidney (3500342000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, liver (3500343000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (36) Milk

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Milk, fat (3600222000):						
FoodForm N/S	0.003230	1.000	1.000	0.0000004	0.0%	48,829
Milk, fat-baby food/infant formula (3600222001):						
FoodForm N/S	0.003230	1.000	1.000	0.0000000	0.0%	854,652
Crop group subtotal				0.0000004	0.0%	46,190

Crop Group = (40) Chicken

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Chicken, meat (4000093000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	575,526
Chicken, meat-babyfood (4000093001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	515,035
Chicken, liver (4000094000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts (4000095000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts-babyfood (4000095001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, fat (4000096000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000002	0.0%	83,143
Chicken, fat-babyfood (4000096001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000003	0.0%	61,953
Chicken, skin (4000097000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	576,369
Chicken, skin-babyfood (4000097001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000002	0.0%	124,514
Crop group subtotal				0.0000008	0.0%	23,787

Crop Group = (50) Turkey

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, meat (5000382000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat-babyfood (5000382001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	845,712
Turkey, liver (5000383000):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, liver-babyfood (5000383001):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, meat byproducts (5000384000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat byproducts-babyfood (5000384001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, fat (5000385000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	347,373

Crop Group = (50) Turkey (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, fat-babyfood (5000385001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	139,689
Turkey, skin (5000386000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, skin-babyfood (5000386001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	306,396
Crop group subtotal				0.0000003	0.0%	64,051

Crop Group = (60) Poultry (other)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Poultry, other, meat (6000301000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, liver (6000302000):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Poultry, other, meat byproducts (6000303000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, fat (6000304000):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Poultry, other, skin (6000305000):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (70) Egg

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Egg, whole (7000145000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000012	0.0%	16,420
Egg, whole-babyfood (7000145001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	>1000000
Egg, white (7000146000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	>1000000
Egg, white (solids)-babyfood (7000146001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, yolk (7000147000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	>1000000
Egg, yolk-babyfood (7000147001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	586,145
Crop group subtotal				0.0000013	0.0%	15,436

Crop Group = (86) Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000001	0.0%	189,880
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000007	0.0%	30,622
Crop group subtotal				0.0000008	0.0%	26,369

Crop Group = (86A) Direct Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000001	0.0%	189,880
Crop group subtotal				0.0000001	0.0%	189,880

Crop Group = (86B) Indirect Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000007	0.0%	30,622
Crop group subtotal				0.0000007	0.0%	30,622
Population subgroup total				0.0000053	0.0%	3,751

1. Margin of Exposure = NOEL / Dietary Exposure

Critical Commodity Contribution Analysis for
Nursing Infants

Total Exposure =.0000053 mg/kg bw/day

Crop groups with total exposure contribution > 10%
Foods/Foodforms with exposure contribution > 5%

Crop group / Food / Foodform	Exposure Analysis: mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (1) Root and Tuber Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000005	9.71%	0.0%	38,631
Potato, tuber, w/o peel-babyfood (0103300001):				
FoodForm N/S	0.0000003	5.01%	0.0%	74,895
Total for crop group	0.0000009	16.23%	0.0%	23,112
Crop Group = (1C) Tuberous and Corm Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000005	9.71%	0.0%	38,631
Potato, tuber, w/o peel-babyfood (0103300001):				
FoodForm N/S	0.0000003	5.01%	0.0%	74,895
Total for crop group	0.0000009	16.23%	0.0%	23,112
Crop Group = (31) Beef				
Beef, meat (3100044000):				
FoodForm N/S	0.0000003	5.05%	0.0%	74,299
Total for crop group	0.0000006	11.16%	0.0%	33,615
Crop Group = (36) Milk				
Milk, fat (3600222000):				
FoodForm N/S	0.0000004	7.68%	0.0%	48,829
Total for crop group	0.0000004	8.12%	0.0%	46,190
Crop Group = (40) Chicken				
Chicken, fat-babyfood (4000096001):				
FoodForm N/S	0.0000003	6.05%	0.0%	61,953
Total for crop group	0.0000008	15.77%	0.0%	23,787
Crop Group = (70) Egg				
Egg, whole (7000145000):				
FoodForm N/S	0.0000012	22.84%	0.0%	16,420
Total for crop group	0.0000013	24.30%	0.0%	15,436
Crop Group = (86) Water				
Water, indirect, all sources (8602000000):				
FoodForm N/S	0.0000007	12.25%	0.0%	30,622
Total for crop group	0.0000008	14.23%	0.0%	26,369

Crop group Food Foodform	Exposure Analysis mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (86B) Indirect Water				
Water, indirect, all sources (8602000000):				
FoodForm N/S	0.0000007	12.25%	0.0%	30,622
Total for crop group	0.0000007	12.25%	0.0%	30,622
Total for crop groups listed above:	0.0000048	89.81%	0.0%	4,177

1. Margin of Exposure = NOEL / Dietary Exposure

Complete commodity contribution analysis for
Non-Nursing Infants

Crop Group = (1) Root and Tuber Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	186,960
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	228,704
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	356,267
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	191,000
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000018	0.0%	10,884
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	36,952
Crop group subtotal					0.0000027	0.0%	7,283

Crop Group = (1C) Tuberous and Corm Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	186,960
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	228,704
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	356,267
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	191,000
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000018	0.0%	10,884
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	36,952
Crop group subtotal					0.0000027	0.0%	7,283

Crop Group = (31) Beef

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, meat (3100044000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000015	0.0%	13,350
Beef, meat-babyfood (3100044001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000010	0.0%	19,302
Beef, meat, dried (3100045000):							
FoodForm N/S	0.006000	1.920	1.000		0.0000000	0.0%	>1000000
Beef, meat byproducts (3100046000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000001	0.0%	182,159
Beef, meat byproducts-babyfood (3100046001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000000	0.0%	>1000000
Beef, fat (3100047000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000004	0.0%	52,253

Crop Group = (31) Beef (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, fat-babyfood (3100047001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000001	0.0%	234,280
Beef, kidney (3100048000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, liver (3100049000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Beef, liver-babyfood (3100049001):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000031	0.0%	6,415

Crop Group = (32) Goat

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Goat, meat (3200169000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, meat byproducts (3200170000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, fat (3200171000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, kidney (3200172000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, liver (3200173000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (33) Horse

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Horse, meat (3300189000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (34) Pork

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Pork, meat (3400290000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000005	0.0%	39,610
Pork, meat-babyfood (3400290001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000003	0.0%	59,890
Pork, skin (3400291000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, meat byproducts (3400292000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	451,977
Pork, meat byproducts-babyfood (3400292001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, fat (3400293000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000002	0.0%	113,060
Pork, fat-babyfood (3400293001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	638,937
Pork, kidney (3400294000):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, liver (3400295000):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Crop group subtotal				0.0000011	0.0%	18,214

Crop Group = (35) Sheep

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Sheep, meat (3500339000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, meat-babyfood (3500339001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, meat byproducts (3500340000):						
FoodForm N/S	0.020000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat (3500341000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat-babyfood (3500341001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, kidney (3500342000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, liver (3500343000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (36) Milk

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Milk, fat (3600222000):						
FoodForm N/S	0.003230	1.000	1.000	0.0000011	0.0%	17,617
Milk, fat-baby food/infant formula (3600222001):						
FoodForm N/S	0.003230	1.000	1.000	0.0000000	0.0%	496,190
Crop group subtotal				0.0000012	0.0%	17,013

Crop Group = (40) Chicken

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Chicken, meat (4000093000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000001	0.0%	213,202
Chicken, meat-babyfood (4000093001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000001	0.0%	256,438
Chicken, liver (4000094000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts (4000095000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts-babyfood (4000095001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, fat (4000096000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000006	0.0%	36,012
Chicken, fat-babyfood (4000096001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000007	0.0%	29,954
Chicken, skin (4000097000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	154,410
Chicken, skin-babyfood (4000097001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000003	0.0%	79,075
Crop group subtotal				0.0000018	0.0%	11,112

Crop Group = (50) Turkey

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, meat (5000382000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat-babyfood (5000382001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	584,145
Turkey, liver (5000383000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver-babyfood (5000383001):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, meat byproducts (5000384000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat byproducts-babyfood (5000384001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, fat (5000385000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	144,144

Crop Group = (50) Turkey (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, fat-babyfood (5000385001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000002	0.0%	87,365
Turkey, skin (5000386000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	526,316
Turkey, skin-babyfood (5000386001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	173,048
Crop group subtotal				0.0000006	0.0%	34,860

Crop Group = (60) Poultry (other)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Poultry, other, meat (6000301000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, liver (6000302000):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Poultry, other, meat byproducts (6000303000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, fat (6000304000):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Poultry, other, skin (6000305000):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (70) Egg

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Egg, whole (7000145000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000023	0.0%	8,834
Egg, whole-babyfood (7000145001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	598,578
Egg, white (7000146000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	761,687
Egg, white (solids)-babyfood (7000146001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, yolk (7000147000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	212,095
Egg, yolk-babyfood (7000147001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	424,554
Crop group subtotal				0.0000025	0.0%	8,114

Crop Group = (86) Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000002	0.0%	111,826
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000031	0.0%	6,438
Crop group subtotal				0.0000033	0.0%	6,087

Crop Group = (86A) Direct Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000002	0.0%	111,826
Crop group subtotal				0.0000002	0.0%	111,826

Crop Group = (86B) Indirect Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000031	0.0%	6,438
Crop group subtotal				0.0000031	0.0%	6,438
Population subgroup total				0.0000163	0.1%	1,230

1. Margin of Exposure = NOEL / Dietary Exposure

Evaluation Copy Ver. 4.02, 05-10-c
DEEM-FCID Chronic analysis for FIPRONIL
Residue file: C:\Users\lscanlan\Documents\Fipronil\Dietary\new POD\August 2019 - final input and analysis\fipronil chronic tier
Adjust. #2 NOT used
Analysis Date 09-28-2020 Residue file dated: 08-28-2019/10:42:38
Reference dose (NOEL) = 0.02 mg/kg bw/day

Chronic Tier 2 Residue File

Food EPA Code	Crop Grp	Food Name	Residue (ppm)	Adj.Factors #1	#2
3100044000	31	Beef, meat	0.006000	1.000	1.000
3100044001	31	Beef, meat-babyfood	0.006000	1.000	1.000
3100045000	31	Beef, meat, dried	0.006000	1.920	1.000
3100046000	31	Beef, meat byproducts	0.006000	1.000	1.000
3100046001	31	Beef, meat byproducts-babyfood	0.006000	1.000	1.000
3100047000	31	Beef, fat	0.006000	1.000	1.000
3100047001	31	Beef, fat-babyfood	0.006000	1.000	1.000
3100048000	31	Beef, kidney	0.006000	1.000	1.000
3100049000	31	Beef, liver	0.050000	1.000	1.000
3100049001	31	Beef, liver-babyfood	0.050000	1.000	1.000
4000093000	40	Chicken, meat	0.000300	1.000	1.000
4000093001	40	Chicken, meat-babyfood	0.000300	1.000	1.000
4000094000	40	Chicken, liver	0.010000	1.000	1.000
4000095000	40	Chicken, meat byproducts	0.000300	1.000	1.000
4000095001	40	Chicken, meat byproducts-babyfoo	0.000300	1.000	1.000
4000096000	40	Chicken, fat	0.025000	1.000	1.000
4000096001	40	Chicken, fat-babyfood	0.025000	1.000	1.000
4000097000	40	Chicken, skin	0.025000	1.000	1.000
4000097001	40	Chicken, skin-babyfood	0.025000	1.000	1.000
7000145000	70	Egg, whole	0.006750	1.000	1.000
7000145001	70	Egg, whole-babyfood	0.006750	1.000	1.000
7000146000	70	Egg, white	0.006750	1.000	1.000
7000146001	70	Egg, white (solids)-babyfood	0.006750	1.000	1.000
7000147000	70	Egg, yolk	0.006750	1.000	1.000
7000147001	70	Egg, yolk-babyfood	0.006750	1.000	1.000
3200169000	32	Goat, meat	0.006000	1.000	1.000
3200170000	32	Goat, meat byproducts	0.006000	1.000	1.000
3200171000	32	Goat, fat	0.006000	1.000	1.000
3200172000	32	Goat, kidney	0.006000	1.000	1.000
3200173000	32	Goat, liver	0.050000	1.000	1.000
3300189000	33	Horse, meat	0.006000	1.000	1.000
3600222000	36	Milk, fat	0.003230	1.000	1.000
3600222001	36	Milk, fat-baby food/infant formu	0.003230	1.000	1.000
3400290000	34	Pork, meat	0.005000	1.000	1.000
3400290001	34	Pork, meat-babyfood	0.005000	1.000	1.000
3400291000	34	Pork, skin	0.006000	1.000	1.000
3400292000	34	Pork, meat byproducts	0.005000	1.000	1.000
3400292001	34	Pork, meat byproducts-babyfood	0.005000	1.000	1.000
3400293000	34	Pork, fat	0.006000	1.000	1.000
3400293001	34	Pork, fat-babyfood	0.006000	1.000	1.000
3400294000	34	Pork, kidney	0.005000	1.000	1.000
3400295000	34	Pork, liver	0.010000	1.000	1.000
0103296000	1C	Potato, chips	0.004190	1.000	1.000
0103297000	1C	Potato, dry (granules/ flakes)	0.004190	1.000	1.000
0103297001	1C	Potato, dry (granules/ flakes)-b	0.004190	1.000	1.000
0103298000	1C	Potato, flour	0.004190	1.000	1.000
0103298001	1C	Potato, flour-babyfood	0.004190	1.000	1.000
0103299000	1C	Potato, tuber, w/peel	0.004190	1.000	1.000
0103299001	1C	Potato, tuber, w/peel-babyfood	0.004190	1.000	1.000
0103300000	1C	Potato, tuber, w/o peel	0.004190	1.000	1.000
0103300001	1C	Potato, tuber, w/o peel-babyfood	0.004190	1.000	1.000
6000301000	60	Poultry, other, meat	0.000300	1.000	1.000
6000302000	60	Poultry, other, liver	0.010000	1.000	1.000
6000303000	60	Poultry, other, meat byproducts	0.000300	1.000	1.000
6000304000	60	Poultry, other, fat	0.025000	1.000	1.000
6000305000	60	Poultry, other, skin	0.025000	1.000	1.000
3500339000	35	Sheep, meat	0.006000	1.000	1.000
3500339001	35	Sheep, meat-babyfood	0.006000	1.000	1.000
3500340000	35	Sheep, meat byproducts	0.020000	1.000	1.000
3500341000	35	Sheep, fat	0.006000	1.000	1.000
3500341001	35	Sheep, fat-babyfood	0.006000	1.000	1.000
3500342000	35	Sheep, kidney	0.020000	1.000	1.000
3500343000	35	Sheep, liver	0.050000	1.000	1.000
5000382000	50	Turkey, meat	0.000300	1.000	1.000
5000382001	50	Turkey, meat-babyfood	0.000300	1.000	1.000
5000383000	50	Turkey, liver	0.010000	1.000	1.000
5000383001	50	Turkey, liver-babyfood	0.010000	1.000	1.000
5000384000	50	Turkey, meat byproducts	0.000300	1.000	1.000
5000384001	50	Turkey, meat byproducts-babyfood	0.000300	1.000	1.000
5000385000	50	Turkey, fat	0.025000	1.000	1.000
5000385001	50	Turkey, fat-babyfood	0.025000	1.000	1.000
5000386000	50	Turkey, skin	0.025000	1.000	1.000
5000386001	50	Turkey, skin-babyfood	0.025000	1.000	1.000
8601000000	86A	Water, direct, all sources	0.000033	1.000	1.000
8602000000	86B	Water, indirect, all sources	0.000033	1.000	1.000

Chronic Tier 2 CEC

Critical Commodity Contribution Analysis for
Non-Nursing Infants

Total Exposure =.0000163 mg/kg bw/day

Crop groups with total exposure contribution > 10%
Foods/Foodforms with exposure contribution > 5%

Crop group / Food / Foodform	Exposure Analysis: mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (1) Root and Tuber Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000018	11.30%	0.0%	10,884
Total for crop group	0.0000027	16.89%	0.0%	7,283
Crop Group = (1C) Tuberous and Corm Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000018	11.30%	0.0%	10,884
Total for crop group	0.0000027	16.89%	0.0%	7,283
Crop Group = (31) Beef				
Beef, meat (3100044000):				
FoodForm N/S	0.0000015	9.21%	0.0%	13,350
Beef, meat-babyfood (3100044001):				
FoodForm N/S	0.0000010	6.37%	0.0%	19,302
Total for crop group	0.0000031	19.17%	0.0%	6,415
Crop Group = (36) Milk				
Milk, fat (3600222000):				
FoodForm N/S	0.0000011	6.98%	0.0%	17,617
Total for crop group	0.0000012	7.23%	0.0%	17,013
Crop Group = (40) Chicken				
Total for crop group	0.0000018	11.07%	0.0%	11,112
Crop Group = (70) Egg				
Egg, whole (7000145000):				
FoodForm N/S	0.0000023	13.92%	0.0%	8,834
Total for crop group	0.0000025	15.16%	0.0%	8,114
Crop Group = (86) Water				
Water, indirect, all sources (8602000000):				
FoodForm N/S	0.0000031	19.10%	0.0%	6,438
Total for crop group	0.0000033	20.20%	0.0%	6,087

Crop group Food Foodform	Exposure Analysis mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (86B) Indirect Water				
Water, indirect, all sources (8602000000):				
FoodForm N/S	0.0000031	19.10%	0.0%	6,438
Total for crop group	0.0000031	19.10%	0.0%	6,438
Total for crop groups listed above:	0.0000146	89.71%	0.1%	1,371

1. Margin of Exposure = NOEL / Dietary Exposure

Complete commodity contribution analysis for
All Infants

Crop Group = (1) Root and Tuber Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	248,789
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	302,048
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	446,894
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	266,247
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000014	0.0%	14,060
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	43,957
Crop group subtotal					0.0000022	0.0%	9,283

Crop Group = (1C) Tuberous and Corm Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	248,789
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	302,048
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	446,894
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	266,247
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000014	0.0%	14,060
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	43,957
Crop group subtotal					0.0000022	0.0%	9,283

Crop Group = (31) Beef

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, meat (3100044000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000011	0.0%	17,993
Beef, meat-babyfood (3100044001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000008	0.0%	25,824
Beef, meat, dried (3100045000):							
FoodForm N/S	0.006000	1.920	1.000		0.0000000	0.0%	>1000000
Beef, meat byproducts (3100046000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000001	0.0%	242,424
Beef, meat byproducts-babyfood (3100046001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000000	0.0%	>1000000
Beef, fat (3100047000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000003	0.0%	69,656

Crop Group = (31) Beef (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, fat-babyfood (3100047001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000001	0.0%	312,901
Beef, kidney (3100048000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, liver (3100049000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Beef, liver-babyfood (3100049001):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000023	0.0%	8,605

Crop Group = (32) Goat

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Goat, meat (3200169000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, meat byproducts (3200170000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, fat (3200171000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, kidney (3200172000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, liver (3200173000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (33) Horse

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Horse, meat (3300189000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (34) Pork

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Pork, meat (3400290000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000004	0.0%	52,405
Pork, meat-babyfood (3400290001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000002	0.0%	83,257
Pork, skin (3400291000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, meat byproducts (3400292000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	575,954
Pork, meat byproducts-babyfood (3400292001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, fat (3400293000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000001	0.0%	143,567
Pork, fat-babyfood (3400293001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	898,957
Pork, kidney (3400294000):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, liver (3400295000):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Crop group subtotal				0.0000008	0.0%	24,233

Crop Group = (35) Sheep

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Sheep, meat (3500339000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, meat-babyfood (3500339001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, meat byproducts (3500340000):						
FoodForm N/S	0.020000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat (3500341000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat-babyfood (3500341001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, kidney (3500342000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, liver (3500343000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (36) Milk

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Milk, fat (3600222000):						
FoodForm N/S	0.003230	1.000	1.000	0.0000009	0.0%	22,051
Milk, fat-baby food/infant formula (3600222001):						
FoodForm N/S	0.003230	1.000	1.000	0.0000000	0.0%	571,635
Crop group subtotal				0.0000009	0.0%	21,232

Crop Group = (40) Chicken

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Chicken, meat (4000093000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000001	0.0%	265,846
Chicken, meat-babyfood (4000093001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000001	0.0%	304,535
Chicken, liver (4000094000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts (4000095000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts-babyfood (4000095001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, fat (4000096000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000005	0.0%	43,821
Chicken, fat-babyfood (4000096001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000006	0.0%	35,764
Chicken, skin (4000097000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	200,552
Chicken, skin-babyfood (4000097001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000002	0.0%	89,326
Crop group subtotal				0.0000015	0.0%	13,349

Crop Group = (50) Turkey

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, meat (5000382000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat-babyfood (5000382001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	647,098
Turkey, liver (5000383000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver-babyfood (5000383001):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, meat byproducts (5000384000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat byproducts-babyfood (5000384001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, fat (5000385000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	176,678

Crop Group = (50) Turkey (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, fat-babyfood (5000385001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000002	0.0%	99,034
Turkey, skin (5000386000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	664,452
Turkey, skin-babyfood (5000386001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	200,501
Crop group subtotal				0.0000005	0.0%	40,695

Crop Group = (60) Poultry (other)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Poultry, other, meat (6000301000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, liver (6000302000):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Poultry, other, meat byproducts (6000303000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, fat (6000304000):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Poultry, other, skin (6000305000):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (70) Egg

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Egg, whole (7000145000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000019	0.0%	10,336
Egg, whole-babyfood (7000145001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	742,783
Egg, white (7000146000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	827,643
Egg, white (solids)-babyfood (7000146001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, yolk (7000147000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	293,508
Egg, yolk-babyfood (7000147001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	464,851
Crop group subtotal				0.0000021	0.0%	9,537

Crop Group = (86) Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000002	0.0%	128,433
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000023	0.0%	8,566
Crop group subtotal				0.0000025	0.0%	8,030

Crop Group = (86A) Direct Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000002	0.0%	128,433
Crop group subtotal				0.0000002	0.0%	128,433

Crop Group = (86B) Indirect Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000023	0.0%	8,566
Crop group subtotal				0.0000023	0.0%	8,566
Population subgroup total				0.0000128	0.1%	1,559

1. Margin of Exposure = NOEL / Dietary Exposure

Critical Commodity Contribution Analysis for
All Infants

Total Exposure =.0000128 mg/kg bw/day

Crop groups with total exposure contribution > 10%
Foods/Foodforms with exposure contribution > 5%

Crop group / Food / Foodform	Exposure Analysis: mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (1) Root and Tuber Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000014	11.09%	0.0%	14,060
Total for crop group	0.0000022	16.80%	0.0%	9,283
Crop Group = (1C) Tuberous and Corm Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000014	11.09%	0.0%	14,060
Total for crop group	0.0000022	16.80%	0.0%	9,283
Crop Group = (31) Beef				
Beef, meat (3100044000):				
FoodForm N/S	0.0000011	8.67%	0.0%	17,993
Beef, meat-babyfood (3100044001):				
FoodForm N/S	0.0000008	6.04%	0.0%	25,824
Total for crop group	0.0000023	18.12%	0.0%	8,605
Crop Group = (36) Milk				
Milk, fat (3600222000):				
FoodForm N/S	0.0000009	7.07%	0.0%	22,051
Total for crop group	0.0000009	7.34%	0.0%	21,232
Crop Group = (40) Chicken				
Total for crop group	0.0000015	11.68%	0.0%	13,349
Crop Group = (70) Egg				
Egg, whole (7000145000):				
FoodForm N/S	0.0000019	15.09%	0.0%	10,336
Total for crop group	0.0000021	16.35%	0.0%	9,537
Crop Group = (86) Water				
Water, indirect, all sources (8602000000):				
FoodForm N/S	0.0000023	18.21%	0.0%	8,566
Total for crop group	0.0000025	19.42%	0.0%	8,030

Crop group Food Foodform	Exposure Analysis mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (86B) Indirect Water				
Water, indirect, all sources (8602000000):				
FoodForm N/S	0.0000023	18.21%	0.0%	8,566
Total for crop group	0.0000023	18.21%	0.0%	8,566
Total for crop groups listed above:	0.0000115	89.72%	0.1%	1,738

1. Margin of Exposure = NOEL / Dietary Exposure

Complete commodity contribution analysis for
Children 1-2

Crop Group = (1) Root and Tuber Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000003	0.0%	62,082
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000002	0.0%	81,776
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	500,605
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000006	0.0%	33,875
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000047	0.0%	4,233
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	256,269
Crop group subtotal					0.0000060	0.0%	3,326

Crop Group = (1C) Tuberous and Corm Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000003	0.0%	62,082
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000002	0.0%	81,776
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	500,605
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000006	0.0%	33,875
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000047	0.0%	4,233
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	256,269
Crop group subtotal					0.0000060	0.0%	3,326

Crop Group = (31) Beef

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, meat (3100044000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000061	0.0%	3,301
Beef, meat-babyfood (3100044001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000002	0.0%	115,121
Beef, meat, dried (3100045000):							
FoodForm N/S	0.006000	1.920	1.000		0.0000000	0.0%	>1000000
Beef, meat byproducts (3100046000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000004	0.0%	52,775
Beef, meat byproducts-babyfood (3100046001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000000	0.0%	>1000000
Beef, fat (3100047000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000016	0.0%	12,802

Crop Group = (31) Beef (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, fat-babyfood (3100047001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Beef, kidney (3100048000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, liver (3100049000):						
FoodForm N/S	0.050000	1.000	1.000	0.0000002	0.0%	127,146
Beef, liver-babyfood (3100049001):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000083	0.0%	2,395

Crop Group = (32) Goat

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Goat, meat (3200169000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, meat byproducts (3200170000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, fat (3200171000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, kidney (3200172000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, liver (3200173000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (33) Horse

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Horse, meat (3300189000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (34) Pork

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Pork, meat (3400290000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000025	0.0%	8,152
Pork, meat-babyfood (3400290001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	645,369
Pork, skin (3400291000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	535,131
Pork, meat byproducts (3400292000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000002	0.0%	128,995
Pork, meat byproducts-babyfood (3400292001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, fat (3400293000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000009	0.0%	22,590
Pork, fat-babyfood (3400293001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, kidney (3400294000):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, liver (3400295000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000036	0.0%	5,608

Crop Group = (35) Sheep

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Sheep, meat (3500339000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	804,570
Sheep, meat-babyfood (3500339001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, meat byproducts (3500340000):						
FoodForm N/S	0.020000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat (3500341000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat-babyfood (3500341001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, kidney (3500342000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, liver (3500343000):						
FoodForm N/S	0.050000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000000	0.0%	530,673

Crop Group = (36) Milk

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Milk, fat (3600222000):						
FoodForm N/S	0.003230	1.000	1.000	0.0000051	0.0%	3,888
Milk, fat-baby food/infant formula (3600222001):						
FoodForm N/S	0.003230	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000052	0.0%	3,880

Crop Group = (40) Chicken

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Chicken, meat (4000093000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000004	0.0%	47,122
Chicken, meat-babyfood (4000093001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, liver (4000094000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts (4000095000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts-babyfood (4000095001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, fat (4000096000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000032	0.0%	6,331
Chicken, fat-babyfood (4000096001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	235,988
Chicken, skin (4000097000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000010	0.0%	19,538
Chicken, skin-babyfood (4000097001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	342,906
Crop group subtotal				0.0000048	0.0%	4,183

Crop Group = (50) Turkey

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, meat (5000382000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000001	0.0%	259,505
Turkey, meat-babyfood (5000382001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver (5000383000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver-babyfood (5000383001):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, meat byproducts (5000384000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat byproducts-babyfood (5000384001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, fat (5000385000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000008	0.0%	24,140

Crop Group = (50) Turkey (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, fat-babyfood (5000385001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	915,332
Turkey, skin (5000386000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000003	0.0%	67,969
Turkey, skin-babyfood (5000386001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000012	0.0%	16,154

Crop Group = (60) Poultry (other)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Poultry, other, meat (6000301000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, liver (6000302000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, meat byproducts (6000303000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, fat (6000304000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, skin (6000305000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (70) Egg

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Egg, whole (7000145000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000078	0.0%	2,558
Egg, whole-babyfood (7000145001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	>1000000
Egg, white (7000146000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000003	0.0%	77,938
Egg, white (solids)-babyfood (7000146001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, yolk (7000147000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	213,747
Egg, yolk-babyfood (7000147001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000082	0.0%	2,443

Crop Group = (86) Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000006	0.0%	35,118
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000003	0.0%	57,563
Crop group subtotal				0.0000009	0.0%	21,811

Crop Group = (86A) Direct Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000006	0.0%	35,118
Crop group subtotal				0.0000006	0.0%	35,118

Crop Group = (86B) Indirect Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000003	0.0%	57,563
Crop group subtotal				0.0000003	0.0%	57,563
Population subgroup total				0.0000383	0.2%	523

1. Margin of Exposure = NOEL / Dietary Exposure

Critical Commodity Contribution Analysis for
Children 1-2

Total Exposure =.0000383 mg/kg bw/day

Crop groups with total exposure contribution > 10%
Foods/Foodforms with exposure contribution > 5%

Crop group / Food / Foodform	Exposure Analysis mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (1) Root and Tuber Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000047	12.35%	0.0%	4,233
Total for crop group	0.0000060	15.72%	0.0%	3,326
Crop Group = (1C) Tuberous and Corm Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000047	12.35%	0.0%	4,233
Total for crop group	0.0000060	15.72%	0.0%	3,326
Crop Group = (31) Beef				
Beef, meat (3100044000):				
FoodForm N/S	0.0000061	15.84%	0.0%	3,301
Total for crop group	0.0000083	21.83%	0.0%	2,395
Crop Group = (34) Pork				
Pork, meat (3400290000):				
FoodForm N/S	0.0000025	6.41%	0.0%	8,152
Total for crop group	0.0000036	9.32%	0.0%	5,608
Crop Group = (36) Milk				
Milk, fat (3600222000):				
FoodForm N/S	0.0000051	13.45%	0.0%	3,888
Total for crop group	0.0000052	13.47%	0.0%	3,880
Crop Group = (40) Chicken				
Chicken, fat (4000096000):				
FoodForm N/S	0.0000032	8.26%	0.0%	6,331
Total for crop group	0.0000048	12.50%	0.0%	4,183
Crop Group = (70) Egg				
Egg, whole (7000145000):				
FoodForm N/S	0.0000078	20.44%	0.0%	2,558
Total for crop group	0.0000082	21.40%	0.0%	2,443
Total for crop groups listed above:	0.0000361	94.23%	0.2%	555

1. Margin of Exposure = NOEL / Dietary Exposure

Complete commodity contribution analysis for
Children 3-5

Crop Group = (1) Root and Tuber Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	42,428
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000002	0.0%	106,099
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	719,516
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000004	0.0%	48,044
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000039	0.0%	5,092
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Crop group subtotal					0.0000050	0.0%	3,975

Crop Group = (1C) Tuberous and Corm Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000005	0.0%	42,428
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000002	0.0%	106,099
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	719,516
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000004	0.0%	48,044
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000039	0.0%	5,092
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Crop group subtotal					0.0000050	0.0%	3,975

Crop Group = (31) Beef

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, meat (3100044000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000062	0.0%	3,248
Beef, meat-babyfood (3100044001):							
FoodForm N/S	0.006000	1.000	1.000		0.0000000	0.0%	>1000000
Beef, meat, dried (3100045000):							
FoodForm N/S	0.006000	1.920	1.000		0.0000000	0.0%	435,116
Beef, meat byproducts (3100046000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000003	0.0%	62,427
Beef, meat byproducts-babyfood (3100046001):							
FoodForm N/S	0.006000	1.000	1.000		no exposure		
Beef, fat (3100047000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000016	0.0%	12,884

Crop Group = (31) Beef (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, fat-babyfood (3100047001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Beef, kidney (3100048000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, liver (3100049000):						
FoodForm N/S	0.050000	1.000	1.000	0.0000001	0.0%	278,552
Beef, liver-babyfood (3100049001):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000082	0.0%	2,450

Crop Group = (32) Goat

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Goat, meat (3200169000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	407,747
Goat, meat byproducts (3200170000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, fat (3200171000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Goat, kidney (3200172000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, liver (3200173000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000001	0.0%	395,413

Crop Group = (33) Horse

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Horse, meat (3300189000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (34) Pork

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Pork, meat (3400290000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000027	0.0%	7,442
Pork, meat-babyfood (3400290001):						
FoodForm N/S	0.005000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, skin (3400291000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	493,243
Pork, meat byproducts (3400292000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000002	0.0%	108,181
Pork, meat byproducts-babyfood (3400292001):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, fat (3400293000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000010	0.0%	20,385
Pork, fat-babyfood (3400293001):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, kidney (3400294000):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, liver (3400295000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000039	0.0%	5,108

Crop Group = (35) Sheep

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Sheep, meat (3500339000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, meat-babyfood (3500339001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, meat byproducts (3500340000):						
FoodForm N/S	0.020000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat (3500341000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat-babyfood (3500341001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, kidney (3500342000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, liver (3500343000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (36) Milk

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Milk, fat (3600222000):						
FoodForm N/S	0.003230	1.000	1.000	0.0000031	0.0%	6,445
Milk, fat-baby food/infant formula (3600222001):						
FoodForm N/S	0.003230	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000031	0.0%	6,444

Crop Group = (40) Chicken

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Chicken, meat (4000093000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000004	0.0%	49,273
Chicken, meat-babyfood (4000093001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, liver (4000094000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts (4000095000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts-babyfood (4000095001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, fat (4000096000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000030	0.0%	6,729
Chicken, fat-babyfood (4000096001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, skin (4000097000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000011	0.0%	18,114
Chicken, skin-babyfood (4000097001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000045	0.0%	4,432

Crop Group = (50) Turkey

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, meat (5000382000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000001	0.0%	290,123
Turkey, meat-babyfood (5000382001):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver (5000383000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver-babyfood (5000383001):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, meat byproducts (5000384000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat byproducts-babyfood (5000384001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Turkey, fat (5000385000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000008	0.0%	24,789

Crop Group = (50) Turkey (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, fat-babyfood (5000385001):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, skin (5000386000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000003	0.0%	57,845
Turkey, skin-babyfood (5000386001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal				0.0000012	0.0%	16,303

Crop Group = (60) Poultry (other)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Poultry, other, meat (6000301000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, liver (6000302000):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Poultry, other, meat byproducts (6000303000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, fat (6000304000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, skin (6000305000):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (70) Egg

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Egg, whole (7000145000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000053	0.0%	3,752
Egg, whole-babyfood (7000145001):						
FoodForm N/S	0.006750	1.000	1.000	0.0000000	0.0%	>1000000
Egg, white (7000146000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000003	0.0%	64,939
Egg, white (solids)-babyfood (7000146001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, yolk (7000147000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	184,115
Egg, yolk-babyfood (7000147001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Crop group subtotal				0.0000057	0.0%	3,479

Crop Group = (86) Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000005	0.0%	37,661
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000002	0.0%	92,993
Crop group subtotal				0.0000007	0.0%	26,805

Crop Group = (86A) Direct Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000005	0.0%	37,661
Crop group subtotal				0.0000005	0.0%	37,661

Crop Group = (86B) Indirect Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000002	0.0%	92,993
Crop group subtotal				0.0000002	0.0%	92,993
Population subgroup total				0.0000325	0.2%	615

1. Margin of Exposure = NOEL / Dietary Exposure

Critical Commodity Contribution Analysis for
Children 3-5

Total Exposure =.0000325 mg/kg bw/day

Crop groups with total exposure contribution > 10%
Foods/Foodforms with exposure contribution > 5%

Crop group / Food / Foodform	Exposure Analysis: mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (1) Root and Tuber Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000039	12.08%	0.0%	5,092
Total for crop group	0.0000050	15.47%	0.0%	3,975
Crop Group = (1C) Tuberous and Corm Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000039	12.08%	0.0%	5,092
Total for crop group	0.0000050	15.47%	0.0%	3,975
Crop Group = (31) Beef				
Beef, meat (3100044000):				
FoodForm N/S	0.0000062	18.94%	0.0%	3,248
Total for crop group	0.0000082	25.10%	0.0%	2,450
Crop Group = (34) Pork				
Pork, meat (3400290000):				
FoodForm N/S	0.0000027	8.27%	0.0%	7,442
Total for crop group	0.0000039	12.04%	0.0%	5,108
Crop Group = (36) Milk				
Milk, fat (3600222000):				
FoodForm N/S	0.0000031	9.54%	0.0%	6,445
Total for crop group	0.0000031	9.54%	0.0%	6,444
Crop Group = (40) Chicken				
Chicken, fat (4000096000):				
FoodForm N/S	0.0000030	9.14%	0.0%	6,729
Total for crop group	0.0000045	13.88%	0.0%	4,432
Crop Group = (70) Egg				
Egg, whole (7000145000):				
FoodForm N/S	0.0000053	16.40%	0.0%	3,752
Total for crop group	0.0000057	17.68%	0.0%	3,479
Total for crop groups listed above:	0.0000305	93.72%	0.2%	656

1. Margin of Exposure = NOEL / Dietary Exposure

Complete commodity contribution analysis for
Children 6-12

Crop Group = (1) Root and Tuber Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000003	0.0%	67,209
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	147,692
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000003	0.0%	67,409
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000028	0.0%	7,256
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Crop group subtotal					0.0000035	0.0%	5,709

Crop Group = (1C) Tuberous and Corm Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000003	0.0%	67,209
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	147,692
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000003	0.0%	67,409
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000028	0.0%	7,256
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Crop group subtotal					0.0000035	0.0%	5,709

Crop Group = (31) Beef

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, meat (3100044000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000051	0.0%	3,950
Beef, meat-babyfood (3100044001):							
FoodForm N/S	0.006000	1.000	1.000		no exposure		
Beef, meat, dried (3100045000):							
FoodForm N/S	0.006000	1.920	1.000		0.0000001	0.0%	252,049
Beef, meat byproducts (3100046000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000002	0.0%	88,570
Beef, meat byproducts-babyfood (3100046001):							
FoodForm N/S	0.006000	1.000	1.000		no exposure		
Beef, fat (3100047000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000012	0.0%	16,440

Crop Group = (31) Beef (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, fat-babyfood (3100047001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, kidney (3100048000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, liver (3100049000):						
FoodForm N/S	0.050000	1.000	1.000	0.0000000	0.0%	995,025
Beef, liver-babyfood (3100049001):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000066	0.0%	3,028

Crop Group = (32) Goat

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Goat, meat (3200169000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Goat, meat byproducts (3200170000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, fat (3200171000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Goat, kidney (3200172000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, liver (3200173000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (33) Horse

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Horse, meat (3300189000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (34) Pork

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Pork, meat (3400290000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000019	0.0%	10,561
Pork, meat-babyfood (3400290001):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, skin (3400291000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	876,271
Pork, meat byproducts (3400292000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000001	0.0%	177,659
Pork, meat byproducts-babyfood (3400292001):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, fat (3400293000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000007	0.0%	28,681
Pork, fat-babyfood (3400293001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Pork, kidney (3400294000):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, liver (3400295000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000027	0.0%	7,335

Crop Group = (35) Sheep

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Sheep, meat (3500339000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, meat-babyfood (3500339001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, meat byproducts (3500340000):						
FoodForm N/S	0.020000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat (3500341000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat-babyfood (3500341001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, kidney (3500342000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, liver (3500343000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (36) Milk

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Milk, fat (3600222000):						
FoodForm N/S	0.003230	1.000	1.000	0.0000019	0.0%	10,744
Milk, fat-baby food/infant formula (3600222001):						
FoodForm N/S	0.003230	1.000	1.000	no exposure		
Crop group subtotal				0.0000019	0.0%	10,744

Crop Group = (40) Chicken

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Chicken, meat (4000093000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000003	0.0%	79,648
Chicken, meat-babyfood (4000093001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Chicken, liver (4000094000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts (4000095000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts-babyfood (4000095001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Chicken, fat (4000096000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000019	0.0%	10,291
Chicken, fat-babyfood (4000096001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Chicken, skin (4000097000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000008	0.0%	24,890
Chicken, skin-babyfood (4000097001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal				0.0000030	0.0%	6,648

Crop Group = (50) Turkey

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, meat (5000382000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	407,588
Turkey, meat-babyfood (5000382001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Turkey, liver (5000383000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver-babyfood (5000383001):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, meat byproducts (5000384000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat byproducts-babyfood (5000384001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Turkey, fat (5000385000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000005	0.0%	39,675

Crop Group = (50) Turkey (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, fat-babyfood (5000385001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Turkey, skin (5000386000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000002	0.0%	91,303
Turkey, skin-babyfood (5000386001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal				0.0000008	0.0%	25,798

Crop Group = (60) Poultry (other)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Poultry, other, meat (6000301000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, liver (6000302000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, meat byproducts (6000303000):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Poultry, other, fat (6000304000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, skin (6000305000):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (70) Egg

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Egg, whole (7000145000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000034	0.0%	5,909
Egg, whole-babyfood (7000145001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, white (7000146000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000002	0.0%	118,046
Egg, white (solids)-babyfood (7000146001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, yolk (7000147000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	242,786
Egg, yolk-babyfood (7000147001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Crop group subtotal				0.0000036	0.0%	5,500

Crop Group = (86) Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000004	0.0%	48,374
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000001	0.0%	141,511
Crop group subtotal				0.0000006	0.0%	36,051

Crop Group = (86A) Direct Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000004	0.0%	48,374
Crop group subtotal				0.0000004	0.0%	48,374

Crop Group = (86B) Indirect Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000001	0.0%	141,511
Crop group subtotal				0.0000001	0.0%	141,511
Population subgroup total				0.0000227	0.1%	882

1. Margin of Exposure = NOEL / Dietary Exposure

Critical Commodity Contribution Analysis for
Children 6-12

Total Exposure =.0000227 mg/kg bw/day

Crop groups with total exposure contribution > 10%
Foods/Foodforms with exposure contribution > 5%

Crop group / Food / Foodform	Exposure Analysis: mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (1) Root and Tuber Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000028	12.15%	0.0%	7,256
Total for crop group	0.0000035	15.44%	0.0%	5,709
Crop Group = (1C) Tuberous and Corm Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000028	12.15%	0.0%	7,256
Total for crop group	0.0000035	15.44%	0.0%	5,709
Crop Group = (31) Beef				
Beef, meat (3100044000):				
FoodForm N/S	0.0000051	22.32%	0.0%	3,950
Beef, fat (3100047000):				
FoodForm N/S	0.0000012	5.36%	0.0%	16,440
Total for crop group	0.0000066	29.11%	0.0%	3,028
Crop Group = (34) Pork				
Pork, meat (3400290000):				
FoodForm N/S	0.0000019	8.35%	0.0%	10,561
Total for crop group	0.0000027	12.02%	0.0%	7,335
Crop Group = (36) Milk				
Milk, fat (3600222000):				
FoodForm N/S	0.0000019	8.21%	0.0%	10,744
Total for crop group	0.0000019	8.21%	0.0%	10,744
Crop Group = (40) Chicken				
Chicken, fat (4000096000):				
FoodForm N/S	0.0000019	8.57%	0.0%	10,291
Total for crop group	0.0000030	13.26%	0.0%	6,648
Crop Group = (70) Egg				
Egg, whole (7000145000):				
FoodForm N/S	0.0000034	14.92%	0.0%	5,909
Total for crop group	0.0000036	16.03%	0.0%	5,500
Total for crop groups listed above:	0.0000213	94.07%	0.1%	937

1. Margin of Exposure = NOEL / Dietary Exposure

Complete commodity contribution analysis for
Female 13-49

Crop Group = (1) Root and Tuber Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	154,630
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	462,706
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000004	0.0%	57,038
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000015	0.0%	13,351
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Crop group subtotal					0.0000020	0.0%	9,858

Crop Group = (1C) Tuberous and Corm Vegetables

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Potato, chips (0103296000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000001	0.0%	154,630
Potato, dry (granules/ flakes) (0103297000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	462,706
Potato, dry (granules/ flakes)-babyfood (0103297001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, flour (0103298000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000000	0.0%	>1000000
Potato, flour-babyfood (0103298001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/peel (0103299000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000004	0.0%	57,038
Potato, tuber, w/peel-babyfood (0103299001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Potato, tuber, w/o peel (0103300000):							
FoodForm N/S	0.004190	1.000	1.000		0.0000015	0.0%	13,351
Potato, tuber, w/o peel-babyfood (0103300001):							
FoodForm N/S	0.004190	1.000	1.000		no exposure		
Crop group subtotal					0.0000020	0.0%	9,858

Crop Group = (31) Beef

Food name	residue (ppm)	Adjustment Factors			Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, meat (3100044000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000026	0.0%	7,578
Beef, meat-babyfood (3100044001):							
FoodForm N/S	0.006000	1.000	1.000		no exposure		
Beef, meat, dried (3100045000):							
FoodForm N/S	0.006000	1.920	1.000		0.0000000	0.0%	766,834
Beef, meat byproducts (3100046000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000001	0.0%	285,120
Beef, meat byproducts-babyfood (3100046001):							
FoodForm N/S	0.006000	1.000	1.000		no exposure		
Beef, fat (3100047000):							
FoodForm N/S	0.006000	1.000	1.000		0.0000006	0.0%	36,169

Crop Group = (31) Beef (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Beef, fat-babyfood (3100047001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, kidney (3100048000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Beef, liver (3100049000):						
FoodForm N/S	0.050000	1.000	1.000	0.0000001	0.0%	290,276
Beef, liver-babyfood (3100049001):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000034	0.0%	5,957

Crop Group = (32) Goat

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Goat, meat (3200169000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Goat, meat byproducts (3200170000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, fat (3200171000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Goat, kidney (3200172000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Goat, liver (3200173000):						
FoodForm N/S	0.050000	1.000	1.000	no exposure		
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (33) Horse

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Horse, meat (3300189000):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Crop group subtotal						

Crop Group = (34) Pork

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Pork, meat (3400290000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000010	0.0%	20,469
Pork, meat-babyfood (3400290001):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, skin (3400291000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Pork, meat byproducts (3400292000):						
FoodForm N/S	0.005000	1.000	1.000	0.0000001	0.0%	342,085
Pork, meat byproducts-babyfood (3400292001):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, fat (3400293000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000003	0.0%	59,592
Pork, fat-babyfood (3400293001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Pork, kidney (3400294000):						
FoodForm N/S	0.005000	1.000	1.000	no exposure		
Pork, liver (3400295000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000014	0.0%	14,442

Crop Group = (35) Sheep

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Sheep, meat (3500339000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	717,617
Sheep, meat-babyfood (3500339001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, meat byproducts (3500340000):						
FoodForm N/S	0.020000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat (3500341000):						
FoodForm N/S	0.006000	1.000	1.000	0.0000000	0.0%	>1000000
Sheep, fat-babyfood (3500341001):						
FoodForm N/S	0.006000	1.000	1.000	no exposure		
Sheep, kidney (3500342000):						
FoodForm N/S	0.020000	1.000	1.000	no exposure		
Sheep, liver (3500343000):						
FoodForm N/S	0.050000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000000	0.0%	559,096

Crop Group = (36) Milk

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Milk, fat (3600222000):						
FoodForm N/S	0.003230	1.000	1.000	0.0000008	0.0%	26,257
Milk, fat-baby food/infant formula (3600222001):						
FoodForm N/S	0.003230	1.000	1.000	no exposure		
Crop group subtotal				0.0000008	0.0%	26,257

Crop Group = (40) Chicken

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Chicken, meat (4000093000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000001	0.0%	138,313
Chicken, meat-babyfood (4000093001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Chicken, liver (4000094000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts (4000095000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Chicken, meat byproducts-babyfood (4000095001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Chicken, fat (4000096000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000012	0.0%	16,344
Chicken, fat-babyfood (4000096001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Chicken, skin (4000097000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000006	0.0%	30,886
Chicken, skin-babyfood (4000097001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal				0.0000020	0.0%	9,833

Crop Group = (50) Turkey

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, meat (5000382000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	617,496
Turkey, meat-babyfood (5000382001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Turkey, liver (5000383000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, liver-babyfood (5000383001):						
FoodForm N/S	0.010000	1.000	1.000	no exposure		
Turkey, meat byproducts (5000384000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Turkey, meat byproducts-babyfood (5000384001):						
FoodForm N/S	0.000300	1.000	1.000	no exposure		
Turkey, fat (5000385000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000003	0.0%	71,955

Crop Group = (50) Turkey (continued)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Turkey, fat-babyfood (5000385001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Turkey, skin (5000386000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000001	0.0%	146,681
Turkey, skin-babyfood (5000386001):						
FoodForm N/S	0.025000	1.000	1.000	no exposure		
Crop group subtotal				0.0000004	0.0%	44,538

Crop Group = (60) Poultry (other)

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Poultry, other, meat (6000301000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, liver (6000302000):						
FoodForm N/S	0.010000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, meat byproducts (6000303000):						
FoodForm N/S	0.000300	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, fat (6000304000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Poultry, other, skin (6000305000):						
FoodForm N/S	0.025000	1.000	1.000	0.0000000	0.0%	>1000000
Crop group subtotal				0.0000000	0.0%	>1000000

Crop Group = (70) Egg

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Egg, whole (7000145000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000018	0.0%	11,017
Egg, whole-babyfood (7000145001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, white (7000146000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	138,359
Egg, white (solids)-babyfood (7000146001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Egg, yolk (7000147000):						
FoodForm N/S	0.006750	1.000	1.000	0.0000001	0.0%	378,653
Egg, yolk-babyfood (7000147001):						
FoodForm N/S	0.006750	1.000	1.000	no exposure		
Crop group subtotal				0.0000020	0.0%	9,937

Crop Group = (86) Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000005	0.0%	43,783
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000002	0.0%	102,877
Crop group subtotal				0.0000007	0.0%	30,712

Crop Group = (86A) Direct Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, direct, all sources (8601000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000005	0.0%	43,783
Crop group subtotal				0.0000005	0.0%	43,783

Crop Group = (86B) Indirect Water

Food name	residue (ppm)	Adjustment Factors		Exposure Analysis mg/kg body wt/day	Percent of NOEL	Margin of Expsr
Water, indirect, all sources (8602000000):						
FoodForm N/S	0.000033	1.000	1.000	0.0000002	0.0%	102,877
Crop group subtotal				0.0000002	0.0%	102,877
Population subgroup total				0.0000127	0.1%	1,571

1. Margin of Exposure = NOEL / Dietary Exposure

Critical Commodity Contribution Analysis for
Female 13-49

Total Exposure =.0000127 mg/kg bw/day

Crop groups with total exposure contribution > 10%
Foods/Foodforms with exposure contribution > 5%

Crop group / Food / Foodform	Exposure Analysis mg/kg body wt/day	% of Total Exposure	Percent of NOEL	Margin of Exposr
Crop Group = (1) Root and Tuber Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000015	11.77%	0.0%	13,351
Total for crop group	0.0000020	15.93%	0.0%	9,858
Crop Group = (1C) Tuberous and Corm Vegetables				
Potato, tuber, w/o peel (0103300000):				
FoodForm N/S	0.0000015	11.77%	0.0%	13,351
Total for crop group	0.0000020	15.93%	0.0%	9,858
Crop Group = (31) Beef				
Beef, meat (3100044000):				
FoodForm N/S	0.0000026	20.73%	0.0%	7,578
Total for crop group	0.0000034	26.37%	0.0%	5,957
Crop Group = (34) Pork				
Pork, meat (3400290000):				
FoodForm N/S	0.0000010	7.67%	0.0%	20,469
Total for crop group	0.0000014	10.88%	0.0%	14,442
Crop Group = (36) Milk				
Milk, fat (3600222000):				
FoodForm N/S	0.0000008	5.98%	0.0%	26,257
Total for crop group	0.0000008	5.98%	0.0%	26,257
Crop Group = (40) Chicken				
Chicken, fat (4000096000):				
FoodForm N/S	0.0000012	9.61%	0.0%	16,344
Chicken, skin (4000097000):				
FoodForm N/S	0.0000006	5.09%	0.0%	30,886
Total for crop group	0.0000020	15.97%	0.0%	9,833
Crop Group = (70) Egg				
Egg, whole (7000145000):				
FoodForm N/S	0.0000018	14.26%	0.0%	11,017
Total for crop group	0.0000020	15.81%	0.0%	9,937
Total for crop groups listed above:	0.0000116	90.94%	0.1%	1,727

1. Margin of Exposure = NOEL / Dietary Exposure