UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 01-APRIL-2008

SUBJECT: Human-Health Risk Assessment for Spirodiclofen for Use on Hops. Decision No. 378132. 40 CFR §180.608.

Ingredient: Spirodiclofen

PC Code: 124871
MRID No.: None
Petition No.: 7E7204
Assessment Type: Single Chemical Aggregate
T**XR No.:** None

DP No.: 339672
Registration No.: None
Regulatory Action: Section 3 Registration
Reregistration Case No.: None
CAS No.: 148477-71-8

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The Office of Pesticide Programs (OPP) HED assesses the risks posed to humans from exposure to pesticide chemicals. OPP's RD has asked HED to evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the registration of spirodiclofen (3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4,5]dec-3-en-4-yl 2,2-dimethylbutanoate) on hops. A summary of the findings and an assessment of human risk resulting from the registered and proposed spirodiclofen uses are provided in this document. The risk assessment was provided by Mary Clock-Rust (RAB1), the residue chemistry review and dietary risk assessment were provided by Mohsen Sahafeyan (RAB1), the occupational/residential exposure (ORE) assessment was provided by Mark Dow (RIMUERB), and the drinking water assessment was provided by Larry Lui and Faruque Khan of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Introduction
Spirodiclofen is part of a new class of chemicals called tetronic acid insecticides. Tectronic acids are primarily acaricides with insecticidal uses at higher doses. The mode of action occurs through the inhibition of lipid biosynthesis, which inhibits the ability to develop through the various mite growth stages and the ability to reproduce in adults. Spirodiclofen is structurally similar to spiromesifen, which is also a tetronic acid insecticide. Spirodiclofen is currently registered for use on grapes, citrus fruits, pome fruits, stone fruits and tree nuts. There are no registered or proposed residential uses.

The residue chemistry, toxicology and exposure data bases are sufficient to assess risk from the proposed use on hops. The available data are adequate to assess exposure and risk from all relevant sources.

Proposed Uses
IR-4 proposed Section 3 registration and permanent tolerances for spirodiclofen on hops. No residential uses are proposed. The use pattern summary is taken from proposed draft labeling for Envidor® 2 SC Miticide (EPA Reg. No. 264-831). Envidor® is formulated as a liquid soluble concentrate (SC) and contains 2.0 lb active ingredient (ai) (22.3 %) spirodiclofen per gallon. The target pest on hops is the twospotted spider mite.

The rate of application is 18.0-24.7 fl oz formulation/A (0.28-0.39 lb ai/A). It is to be applied in a minimum of 50 gallons of spray per acre using a ground airblast sprayer. Spirodiclofen is to be applied to hops once per season. The maximum application rate is 0.39 lb ai/A/crop season. The preharvest interval (PHI) is 14 days. The restricted entry interval (REI) is 12 hours for all use sites.

Hazard Characterization
The critical effect for the overall risk assessment is based on the toxic effects on the most sensitive target organ, the adrenal gland. The dog was the most sensitive species and the selected endpoints provide the more protective limits for potential effects on humans.

For dietary exposure, no appropriate single-dose endpoint was available for assessment of acute dietary risk for the general population, including infants and children. A one-year oral toxicity study in dogs was selected for the chronic reference dose (cRfD). The endpoint is based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes.

The endpoint for short-term incidental oral exposure is based on a subchronic oral toxicity study in dogs and is based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a no-observed-adverse-effect-level (NOAEL) for females was not established.

The endpoint for short-term dermal and inhalation risk assessments is based on a subchronic oral toxicity study in dogs. For intermediate- and long-term dermal and inhalation risk assessments, a

chronic oral toxicity study in dogs was selected. An oral study was selected because the endpoint of concern (i.e., adrenal, testes, etc.) was not measured in the 28-day dermal toxicity study.

A dermal-absorption factor of 2% based on a monkey dermal-absorption study is used for all dermal exposure assessments since dermal endpoints are from an oral study. Inhalation absorption is assumed to be 100% (default assumption) in the absence of a 21/28 day inhalation study.

The Cancer Assessment Review Committee (CARC) classified spirodiclofen as "likely to be carcinogenic to humans," and assigned a Q_1^* value of 1.49×10^{-2} mg ai/kg bw/day. Quantification of cancer risk used a $Q_1^*(mg/kg/day)^{-1}$ of 1.49×10^{-2} in human equivalents based on male rat testes Leydig cell adenoma.

Since there is a low concern for increased susceptibility, toxicological database is complete including two DNT studies, dietary analysis is based on DEEM default processing factors, projected average 100% crop treated (%CT), and drinking water estimates based on model estimates, HED concluded that the 10X FQPA SF is reduced to 1X for all exposure scenarios, except short-term, dietary/residential, for which a 3X FQPA SF has been retained due to the use of a LOAEL for a NOAEL.

Dietary Exposure
Chronic and cancer dietary risk assessments (for food and drinking water) were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID™, ver. 2.03).

An endpoint of concern for the assessment of acute dietary risk was not identified in the hazard database. Therefore, acute dietary risk was not assessed. The chronic and cancer analyses incorporated average field trial residues, experimental and DEEM default processing factors, and projected average %CT estimates and drinking water estimates generated using the Pesticide Root Zone/Exposure Analysis Modeling System (PRZM/EXAMS) model.

The resulting chronic (food + water) exposure estimates were not of concern to HED [<100% of the chronic population-adjusted dose (cPAD)] for general U.S. population (1.8 % of the cPAD) and all population subgroups; the most highly exposed population subgroup was all infants (<1 year old) with 3.2% of the cPAD.

The cancer risk estimate (food + water) was 3×10^{-6} for the general U.S. population, which is not of concern. Hops, water, and orange juice were major contributors to the cancer risk.

Aggregate Risk Assessment
No residential uses are proposed for spirodiclofen at this time. Therefore, aggregate risk consists of exposure from food and drinking water sources only. Only chronic and cancer aggregate risks were assessed.

Occupational Risk
For occupational exposure and risk assessment, pesticide handlers and workers exposed to post-application residues were assessed. Cancer risks were calculated for both pesticide handlers and

post-application workers.

Based upon the proposed use pattern, HED believes the most highly exposed occupational pesticide handlers (i.e., mixers, loaders, applicators) will be mixer/loaders using an open-pour technique and applicators using open-cab, air-blast equipment. No chemical-specific data are available to assess potential exposure to pesticide handlers, so estimates of exposure to handlers are based upon surrogate study data available in the Pesticide Handler's Exposure Database (PHED) (v. 1.1, 1998). All handler MOEs are above 300 for handlers wearing baseline personal protective equipment (PPE) and are not of concern to HED. Cancer risk for handlers is also not of concern to HED, with risks no greater than 10^{-5}.

Post-application activities for hops include training vines, scouting, stripping vines and harvesting. Hops are typically mechanically harvested. The highest transfer coefficient (TC) for hops is for training vines (TC=2,000 cm^2/hr). HED conducted a post-application risk assessment for the training vines exposure scenario. Post-application inhalation exposure is expected to be negligible. Post-application dermal risk resulted in an MOE of 2,200, and is not of concern. Post-application cancer risk also was not of concern to HED.

HED Recommendations
HED recommends for a permanent registration for spirodiclofen on hops and the following permanent tolerance:

Hop, dried cones[1] .....30 ppm

[1] Tolerance expression for plants includes residues of spirodiclofen (3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutanoate) *per se*, and for livestock includes combined residues of spirodiclofen and BAJ 2510 (3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4,5]dec-3-en-2-one).

2.0 Ingredient Profile

Spirodiclofen is a tetronic acid with acaricidal action. It acts by interfering with mite development, thereby controlling such pests as *Panonychus* spp., *Phyllocoptruta* spp., *Brevipalpus* spp., and *Aculus* and *Tetranychus* species. Spirodiclofen is active by contact to mite eggs, all nymphal stages, and adult females (adult males are not affected).

Permanent tolerances are established for spirodiclofen on grapes, citrus fruits, pome fruits, stone fruits and the tree nut crop groups at 0.10-2.0 ppm, and on processed commodities from these crops at 0.60-20 ppm [40 CFR §180.608(a)]. Tolerances are also established for the combined residues of spirodiclofen and its free enol metabolite, BAJ 2510 (3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4,5]dec-3-en-2-one), in/on livestock commodities at 0.01-0.10 ppm.

Spirodiclofen is currently registered to Bayer CropScience as a 2.0 lb/gal SC formulation (Envidor® 2 SC Miticide, EPA Reg. No. 264-831) for use as a single broadcast foliar application to grapes and fruit and nut trees at rates of 0.19-0.53 lb ai/A with PHIs of 14 days for grapes and 7 days for all other crops.

2.1 Summary of Proposed Uses

Interregional Research Project No. 4 (IR-4) is proposing the use of spirodiclofen (SC) on hops as

a single foliar-directed application at 0.28-0.39 lb ai/A with a PHI of 14 days. Applications are restricted to the use of ground equipment in a minimum of 50 gal/A. HED concludes that the use directions provided in the submitted Section B are adequate.

Table 2.1. Summary of Proposed Uses for Spirodiclofen (Envidor™ 2 SC Miticide).

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations [2]
Hops						
Single foliar application at the early stages of mite infestation; Ground equipment	2 lb/gal SC [264-831]	0.28-0.39	1	0.39	14	Apply in a minimum of 50 gal/A using conventional ground airblast spray

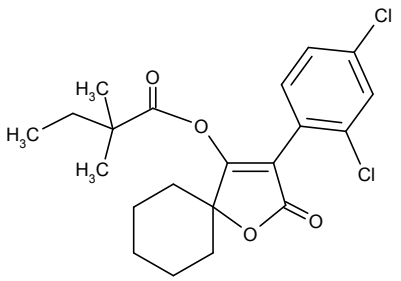
[1]Do not apply through any type of irrigation equipment or with aerial equipment.
[2]PHI = pre-harvest interval.

All proposed uses for spirodiclofen are agricultural; there are no registered or proposed residential uses.

2.2 Structure and Nomenclature

There are no isomeric forms of spirodiclofen.

Table 2.2. Spirodiclofen Nomenclature.

Compound	
Common name	Spirodiclofen
Company experimental name	BAJ2740
IUPAC name	3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4,5]dec-3-en-4-yl 2,2-dimethylbutyrate
CAS name	3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4,5]dec-3-en-4-yl 2,2-dimethylbutanoate
CAS registry number	148477-71-8
End-use product (EP)	2 lb/gal SC (ENVIDOR® 2 SC Miticide; EPA Reg. No. 264-831)

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Spirodiclofen.

Parameter	Value
Melting point	94.8ºC
pH	4.2
Density (20ºC)	1.29 g/cm^3
Water solubility (20ºC at pH 4)	50µg/L

Table 2.3. Physicochemical Properties of Spirodiclofen.		
Parameter	Value	
Solvent solubility (g/L at 20°C)	n-heptane xylene dichloromethane 2-propanol 1-octanol polyethylene glycol acetone ethyl acetate acetonitrile dimethylsulfoxide	20 >250 >250 47 44 24 >250 >250 >250 75
Vapor pressure (20ºC)	3×10^{-7} Pa	
Dissociation constant, pK_a	Not determinable due to the instability in aqueous solutions at >pH 4	
Octanol/water partition coefficient, $Log(K_{OW})$ at pH 4 and 20ºC	5.83	
UV/visible absorption spectrum	λmax = 201 nm: Not expected to absorb UV at λ >350 nm	

Reference: DP# 315459, S. Mathur, 4/20/05.

3.0 Metabolism Assessment

See Attachment 1 for metabolite structures.

3.1 Comparative Metabolic Profile

The metabolic pathway in the proposed primary crops, ruminant, and rat were similar and involved cleavage of the parent ester linkage with the formation of the free enol metabolite (BAJ 2510) followed by hydroxylation of the cyclohexane ring of BAJ 2510. In the rat and in the proposed crops, metabolism continued with cleavage of the enol ring structure leading to the formation of 2,4-dichloro-mandelic acid- cyclohexylester compounds which are further metabolized to 2,4-dichloro-mandelic acid derivatives (see Attachment 1 for structures).

3.2 Nature of the Residue in Foods

3.2.1 Description of Primary Crop Metabolism

The apple, orange, lemon, grapefruit, and grape metabolism studies indicated that metabolism of spirodiclofen in these crops was similar and involved the following steps: cleavage of the parent ester linkage with the formation of the free enol metabolite (BAJ 2510); hydroxylation of BAJ 2510 in the 3- or 4- position of the cyclohexyl ring (3-OH-enol, 4-OH-enol); cleavage of the enol ring structure leading to the formation of 2,4-dichloro-mandelic acid-cyclohexylester compounds; and hydroxylation and/or conjugation of 2,4-dichloro-mandelic acid-cyclohexylester with carbohydrates followed by further degradation to 2,4-dichloro-mandelic acid (free or conjugated).

The majority of the residues in/on fruits in each study were comprised of surface residues, with nearly all surface residues being comprised of parent compound. Overall spirodiclofen accounted for 34-99% of the total radioactive residues (TRR). Minor amounts of the following compounds were also identified: BAJ 2510 (≤2% TRR), 3-OH-enol (≤3% TRR), 4-OH-enol (<1% TRR), 2,4-dichloro-mandelic acid-cyclohexylester compounds (free and conjugated; ≤9%

TRR), and 2,4-dichloro-mandelic acid (free and conjugate; ≤12% TRR). However, grape processing study indicates that residues of spirodiclofen degrade to BAJ 2510 during processing of grapes to juice, juice concentrate, jelly and raisin (T. Bloem, D341847, 10-OCT-07).

Based on available plant metabolism studies and recently submitted and reviewed apple and grape processing studies, HED concludes the following: (1) citrus fruit, pome fruit, stone fruit, tree nut, and hop - the residue of concern for risk assessment and tolerance enforcement is spirodiclofen *per se* and (2) grape - the residue of concern for tolerance enforcement is spirodiclofen *per se* and residues of concern for risk assessment are spirodiclofen and BAJ 2510 (T. Bloem, D341847, 10-OCT-07).

As hops are a minor crop, the available metabolism data will be used to support the use on hops. However, additional plant metabolism data may be required for future crop uses. For purposes of this tolerance petition, HED concludes that the residue of concern in/on dried hops consists of spirodiclofen *per se.*

3.2.2 Description of Livestock Metabolism

Based on the results of the goat metabolism study and feeding study, HED concludes that the residues of concern in ruminants, for purposes of tolerance enforcement and risk assessment, are spirodiclofen and BAJ 2510. There are no livestock feedstuffs associated with hops.

3.2.3 Description of Rotational Crop Metabolism

Because neither hops nor any of the registered crops are rotated, data pertaining to rotational crops are not required to support the proposed use.

3.3 Environmental Degradation and Drinking Water Estimates

The major routes of degradation for spirodiclofen in the laboratory studies were hydrolysis, photolysis in water, and metabolism. Spirodiclofen is expected to be moderately persistent in the soil (half-life of 10-64 days), but dissipate rapidly from aquatic environments (half-life of <1 hour-4 days). The major residue identified in the aerobic soil and anaerobic/aerobic aquatic degradation studies was BAJ 2510 (52-95% the applied dose at intervals of ≤56 days; EFED refers to this compound as BAJ 2740-enol). The aerobic soil degradation study also resulted in significant residues of BAJ 2740-dihydroxy (17% of the applied dose at an interval of 120 days), BAJ 2740-ketohydroxy (44% of the applied dose at an interval of 30 days), and DCB-acid (40% of the applied dose at an interval of 120 days). The aquatic photolysis study resulted in significant residues of BAJ 2740-dioxoketone (26% of the applied dose after an interval of 1 day). Under terrestrial field conditions, the major transformation products of spirodiclofen were BAJ 2510, BAJ 2740-ketohydroxy, BAJ 2740-dihydroxy, and DCB-acid. Spirodiclofen is expected to be immobile in soil (K_{oc} range 31,037 to 238,000) while the identified degradation products are expected to be mobile.

HED determined that aquatic photolysis is not expected to be an important degradation route and, therefore, concluded that BAJ 2740-dioxoketone is not of concern in drinking water. In addition, HED concluded that DCB-acid is likely to be significantly less toxic than spirodiclofen and,

therefore, this compound was excluded from the risk assessment (see Section 3.5). Based on the currently available data, HED concludes that the residues of concern in drinking water for purposes of risk assessment are spirodiclofen, BAJ 2510, BAJ 2740-dihydroxy, and BAJ 2740-ketohydroxy.

The estimated drinking-water concentrations (EDWCs) for spirodiclofen and its three metabolites (spirodiclofen-enol, spirodiclofen-ketohydroxy and spirodiclofen-dihydroxy) were computed using PRZM/EXAMS model. Application rates ranged from 0.53 to 0.28 lbs. ai/Acre, depending on crop. Tier II surface water modeling of Florida citrus scenario using the index reservoir with the default percent cropped area (PCA=0.87) predicts the 1-in-10-year annual average concentration (non-cancer chronic) and 30 year annual average concentration (cancer) of spirodiclofen residues is not likely to exceed 4.99 and 1.67 μg/L, respectively.

3.4 Tabular Summary of Metabolites and Degradates

See Attachment 1, Chemical Names and Structures of Spirodiclofen and its Metabolites.

3.5 Toxicity Profile of Major Metabolites and Degradates

The endpoints chosen for spirodiclofen risk assessment were based on steroidogenesis effects. Based on the structure of BAJ 2510, BAJ 2740-dihydroxy, and BAJ 2740-ketohydroxy (significant residues in ruminant metabolism and/or environmental fate studies), HED concluded that these compounds are likely to be toxicologically similar to parent. The petitioner submitted a study which indicated that 2,4-dichlormandelic acid did not cause steroidogenesis effects. On the basis of this study, along with the general conclusion that the structure of 2,4-dichlormandelic acid lends itself to being less toxic than spirodiclofen and the low overall potential dietary exposure to 2,4-dichlormandelic acid as compared to spirodiclofen, HED concluded that 2,4-dichlormandelic acid should not be included in the dietary risk assessment. Furthermore, HED concluded that 2,4-dichloro-mandelic acid cyclohexylester-glucosyl pentoside; 2,4-dichloro-mandelic acid-hydroxyl-cyclohexylester; and DCB-acid (significant residues identified in washed fruit or the aerobic soil metabolism study) are substituted versions or structurally similar to 2,4-dichloro-mandelic acid and may be excluded from the risk assessment using the same reasons as those established for 2,4-dichloro-mandelic acid.

Enol Metabolite of Spirodiclofen (BAJ-2510)

The acute LD_{50} toxicity study for spirodiclofen showed no deaths and no clinical signs of toxicity up to 2,000 mg/kg. In the acute LD_{50} study for the enol metabolite of spirodiclofen, no deaths were observed in either sex at 200 mg/kg; however clinical observations revealed decreased motility in females only. Deaths (1/3 males and 2/3 females) occurred at 500 mg/kg with clinical signs of toxicity in both sexes exposed to the enol metabolite, indicating that the LD_{50} had been achieved. These differences in acute toxicity between spirodiclofen and the enol metabolite could be partially explained based on the rat metabolism study with spirodiclofen. In the spirodiclofen rat metabolism study at 2 mg/kg, approximately 62 and 33% of the radioactivity from a single bolus gavage dose was excreted in the urine and feces respectively, by 48 hours. At 100 mg/kg approximately 35 and 61% of the radioactivity from a single bolus gavage dose was excreted in the urine and feces respectively, at 48 hours. The metabolic profile of the feces

revealed that approximately 1.8% and 16% of the unchanged parent compound was present after exposure to 2 mg/kg and 100 mg/kg, respectively; indicating absorption is a limiting factor at high doses. Negligible amounts of parent compound and intact enol metabolite were detected in the bile cannulation study suggesting that the excretion of the parent and unchanged enol in the feces is due to unabsorbed dose indicating that saturation of absorption has occurred. In the rat metabolism study both the parent and enol metabolites were excreted in the feces which provides indirect evidence of conversion of parent to the enol metabolite in the gastrointestinal tract. This also could indicate absorption is the limiting factor for both parent and enol metabolite. Therefore, these differences support and provide the explanation of the differences in acute toxicity of the parent and enol metabolites.

In summary, in the rat metabolism study, intact parent and enol metabolite were detected in the feces. In the bile cannulated rats, very limited intact parent and enol metabolite were excreted. Indicating that the absorption may be a limiting factor since parent and unchanged enol metabolite were detected in the feces. In the rat metabolism study both parent and enol metabolite was excreted in the feces which provides indirect evidence of conversion of parent to enol in the gastrointestinal tract. This also could indicate saturation of absorption as the limiting factor for both parent and enol metabolite.

Acute dietary exposure is likely to occur at very low doses. As such, the results of the acute LD_{50} enol metabolite study may not be relevant for acute dietary exposure to spirodiclofen.

For the purposes of this risk assessment, EPA considers the enol metabolite and the parent spirodiclofen to be of similar toxicity for short-, intermediate and chronic exposure assessment.

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

Based on metabolism and environmental fate studies, HED made the following conclusions concerning the residues of concern in plants, livestock, rotational crops, and drinking water (the toxicity of all metabolites/degradates indicated below are considered to be identical to parent).

Table 3.6. Proposed Residues for Tolerance Expression and Risk Assessment.

Matrix	Residues included in Risk Assessment	Residues included in Tolerance Expression
Citrus fruit, Pome Fruit, Stone Fruit, Tree Nut [1]	spirodiclofen	Spirodiclofen
Grape[1]	spirodiclofen	spirodiclofen, BAJ 2510
Livestock - Ruminants	spirodiclofen, BAJ 2510	spirodiclofen, BAJ 2510
Livestock - Poultry	no data submitted	
Rotational Crops	no data submitted	
Drinking Water	spirodiclofen, BAJ 2510, BAJ 2740-dihydroxy, BAJ 2740-ketohydroxy	not applicable

[1]See reference: T. Bloem, D341847, 25-Oct-2007.

International Harmonization

Although adequate U.S. field trial data are available supporting a minimum PHI of either 21 or 28 days, IR-4 is requesting a 14-day PHI for hops in order to harmonize the U.S. and German use patterns. In addition, IR-4 is requesting a 30-ppm tolerance on dried hop cones to harmonize with the established German maximum residue limit (MRL). Considering similarity in climatic

conditions between the hops growing regions in the U.S. and Germany and the German MRL of 30 ppm being higher than the maximum residue values from the other two submitted field trial data sets having similar application rates, but longer PHIs (21 and 28 day), HED recommends establishing a permanent tolerance for spirodiclofen on hops at 30 ppm to promote free trade between NAFTA and non-NAFTA countries.

4.0 Hazard Characterization/Assessment

4.1 Hazard and Dose-Response Characterization

4.1.1 Database Summary

The toxicological database for spirodiclofen is complete. The HED HIARC requested a 28-day inhalation toxicity study as a condition of registration. However, based on the low volatility and low inhalation toxicity (Category IV) of spirodiclofen and inhalation MOEs of at least 1000 for the proposed handler uses, spirodiclofen qualifies for a waiver of the 28-day inhalation toxicity study for the proposed uses (HED Standard Operating Procedure (SOP) 2002.01: *Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*, 08/15/02). **The requirement for the 28-day inhalation toxicity study is waived for this action only.** If in the future, requests for new uses or formulations are submitted that may result in a significant change in either the toxicity profile or exposure scenarios, HED will reconsider this data requirement.

4.1.1.1 Studies Available and Considered

Acute - Acute neurotoxicity study in rats
Subchronic neurotoxicity study in rats
Developmental neurotoxicity in rats (2 studies)
Subchronic - 90-day oral studies in rats, mice and dogs
Chronic - One-year dog, 2-year rat and mouse cancer studies
Repro/developmental - Rat and rabbit developmental; 2-generation rat reproductive studies
Other - mutagenicity screens

4.1.1.2 Mode of Action, Metabolism, Toxicokinetic Data

Spirodiclofen is a foliar-applied acaricide belonging to a new chemical class of tetronic acids. Its mode of action in animal models is described as inhibitory to lipid biosynthesis which interferes with steroid biosynthesis, resulting in direct and indirect endogenously-mediated toxicological response. Following oral administration, spirodiclofen is rapidly absorbed, metabolized, and excreted *via* urine and feces. A rat whole body autoradiography study showed no accumulation in any specific organs or tissues following oral administration. A dermal-absorption study in monkeys suggested a dermal-absorption factor of 2%.

4.1.1.3 Sufficiency of Studies/Data

Data are adequate for each exposure scenario, FQPA evaluation, and for selection of endpoints and the dose-response evaluation.

4.1.2 Toxicological Effects

Spirodiclofen has a low acute toxicity *via* oral, dermal, or inhalation route. It is not an eye or dermal irritant. However, it is a potential skin sensitizer. Following oral administration, spirodiclofen is rapidly absorbed, metabolized, and excreted *via* urine and feces. A rat whole body autoradiography study showed no accumulation in any specific organs or tissues following oral administration. Evidence of developmental toxicity was not observed in the rat and rabbit developmental studies. In the two-generation reproductive toxicity study, effects were observed in males [i.e., delayed sexual maturation, decreased testicular spermatid and epididymal sperm counts (oligospermia); and atrophy of the testes, epididymides, prostate, and seminal vesicles] and females (i.e., increased severity of ovarian luteal cell vacuolation/degeneration). Spirodiclofen did not show any evidence of neurotoxicity in the acute and subchronic neurotoxicity studies. In a developmental neurotoxicity study (DNT), a decrease in retention was observed in the memory phase of the water maze for PND 60 females at all doses. In this DNT study, the morphometric measurements were not performed at the low- and mid-dose; therefore, the registrant conducted a new study using identical experimental condition as the previous study. The results of the new study demonstrated no treatment related maternal or offspring toxicity at the highest dose tested. Therefore, it can be concluded that spirodiclofen is unlikely to be a neurotoxic or developmentally-neurotoxic compound. Mutagenicity studies conducted on technical spirodiclofen formulation and its major metabolites did not demonstrate any mutagenic potential. Spirodiclofen has been shown to have endocrine disruptive effects resulting in direct and indirect endogenously-mediated toxicological responses. Testicular effects were observed in dogs, rats and mice, manifest as Leydig cell vacuolation in dogs, hypertrophy in dogs and mice and hyperplasia, progressing to adenomas in rats following chronic exposure. In female rats, increased incidence of uterine nodules and uterine adenocarcinoma were observed at terminal sacrifice in the chronic study. Cytoplasmic vacuolation in the adrenal cortex, accompanied by increased adrenal weight, was consistently observed in rats, dogs, and mice of both sexes.

Chronic toxicity and carcinogenicity studies showed increased incidence of uterine adenocarcinoma in female rats, Leydig cell adenoma in male rats, and liver tumors in mice. The CARC classified spirodiclofen as “likely to be carcinogenic to humans” by the oral route based on evidence of testes Leydig cell adenomas in male rats, uterine adenomas and/or adenocarcinoma in female rats, and liver tumors in mice.

4.1.3 Dose-Response

The critical effect for the overall risk assessment is based on the toxic effects on the most sensitive target organ, the adrenal gland, observed in rats, dogs, and mice with dogs as the most sensitive species.

For oral exposure, no appropriate single-dose endpoint was available for the acute oral exposure of the general population, including infants and children. A subchronic (90-day) oral toxicity study in dogs was chosen for the short-term incidental oral exposure scenario. A one-year oral toxicity study in dogs was selected for the intermediate-term oral exposure chronic RfD. The dog was the most sensitive species and the selected endpoints provide the more protective limits for human effects potential.

A dermal-absorption factor of 2% based on a monkey dermal-absorption study is used for all dermal exposure assessments. The dermal exposure limits for short-term exposure were based on a subchronic oral toxicity study in dog. For intermediate and chronic exposure, chronic oral toxicity in dogs was selected. An oral study was selected because the endpoint of concern (i.e., adrenal, testes, etc.) was not measured in the 28-day dermal toxicity study.

The inhalation exposure limits parallel the determinations made for the dermal exposure assessments above and use a 100% default assumption in the absence of a 21/28 day inhalation study.

Quantification of cancer risk was performed using a $Q_1^*(mg/kg/day)^{-1}$ of 1.49×10^{-2} in human equivalents based on male rat testes Leydig cell adenoma.

The uncertainty factors used in determining RfD exposure limits were 100 (10x for intraspecies variation and 10x for interspecies extrapolation).

Table 4.1. Acute Toxicity of Spirodiclofen.

OPPTS Guideline	Study Type	Results	Toxicity Category
870.1100	Acute oral toxicity / rat	LD_{50} => 2000 mg/kg (males and females)	III
870.1200	Acute dermal toxicity / rat	LD_{50} => 2000 mg/kg (males and females)	III
870.1300	Acute inhalation toxicity / rat	LC_{50} => 5.03 mg/L (males and females)	IV
870.2400	Primary eye irritation / rabbit	Non-irritating	IV
870.2500	Primary dermal irritation / rabbit	Non-irritating	IV
870.2600	Dermal sensitization / guinea pig	Sensitizer	–

4.2 Food Quality Protection Act (FQPA) Considerations

4.2.1 FQPA Hazard Considerations

The database is adequate in terms of endpoint studies and dose response information to characterize any potential for prenatal or postnatal risk for infants and children.

4.2.2 Adequacy of the Toxicity Database

HED determined that the toxicology database for spirodiclofen is adequate for FQPA consideration. The following studies are available:

- Developmental toxicity studies in rats and rabbits
- Two-generation reproduction study in rats
- Acute and subchronic neurotoxicity studies in rats
- Developmental neurotoxicity study in rats (2 studies)

4.2.3 Evidence of Neurotoxicity

In a subchronic neurotoxicity study, functional-observational-battery (FOB) effects and decreased motor and locomotor activities were observed in females at the high dose only (above the limit dose). The effects were considered to be due to the large decrease of body weight in these animals. In a developmental neurotoxicity study in rats, a decrease in retention (memory) was observed in the PND 60 females in the water maze test.

4.2.3.1 Acute Neurotoxicity

In an acute neurotoxicity study (MRID 45696725), groups of fasted, nine weeks old Wistar (Crl:WI(HAN)BR) rats (12/sex/group) were given a single oral dose of Technical Grade Spirodiclofen (97.7 to 97.9%, Mixed batch number 06480/0002) in 0.5% methylcellulose/0.4% Tween 80 in deionized water at doses of 0, 200, 500 or 2000 mg/kg bw and observed for 14 days. A neurobehavioral assessment (functional observational battery and motor activity testing) was performed one week prior to treatment, approximately 4 hours after administration of the dose, and 7, and 14 days following treatment. At study termination, 6 animals/sex/group were euthanized and perfused [*in situ*] for neuropathological examination. Of the perfused animals, 6/sex from the control and high dose group were subjected to histologic evaluation of brain and peripheral nervous system tissues.

There were no treatment-related effects on mortality, clinical signs, body weight, brain weight or gross and histologic pathology or neuropathology. FOB and motor activity testing revealed no effects that were considered treatment related.

Based on the absence of effects in this study, the NOAEL for spirodiclofen in rats is the limit dose of 2000 mg/kg bw. The LOAEL was not identified.

4.2.3.2 Subchronic Neurotoxicity

In a subchronic neurotoxicity study (MRID 45696726), groups of young adult Wistar rats (12/sex/dose) were fed spirodiclofen in the diet at doses of 0, 100, 1000 or 12,500 ppm (0, 7.2, 70.3 or 1088.8 mg/kg bw/day for males and 0, 9.1, 87.3, or 1306.5 mg/kg bw/day for females, respectively) for 13 weeks. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in all animals (12/sex/group) with 6/sex/dose used for micropathology. Cholinesterase activity was not determined. Of the perfused animals, 6/sex/dose were subjected to histopathological evaluation of brain and peripheral nervous system tissues. The following observations and measurements were included in the study: clinical observations, mortality, body weight, food consumption, automated measurements of activity (figure-eight maze), functional observational battery, ophthalmic exams, brain weight, and a gross necropsy. Skeletal muscle, peripheral nerves, eyes, (with optic nerves) and tissues from the central nervous system were also examined microscopically for lesions.

There was no mortality at any dose level prior to scheduled terminal sacrifice. At 12,500 ppm clinical signs were limited to urine stain observed in both sexes. High-dose females also showed oral stain and red-tinged stains at locations such as paws, snout, forelimbs and ears. Body weights were reduced ($p<0.05$) 25% for males and 15% for females at the high dose, but not at

lower doses. Food consumption was reduced ($p<0.05$) at the high dose for both sexes.

For the FOB there were compound-related effects in both sexes at the high dose, but not at any lower doses. Clinical observations associated with treatment were limited to various stains (oral, urine, nasal) and red-tinged stains in the high-dose females and males (urine stain only). The high dose animals of both sexes tended to have slightly lower landing foot splay and grip strength measurements on some test occasions.

No compound-related effects were noted on motor and locomotor activity in the figure-eight maze at any dose level for males. High-dose females showed a consistent slight decrease in motor and locomotor activity during week 4. Habituation was not affected by treatment. No changes were noted in ophthalmic findings.

Under conditions of this study, the LOAEL for spirodiclofen in rats was 12500 ppm (1088.8 and 1306.5 mg/kg bw/day for males and females, respectively) based on decreased body weights, food consumption, and increased urine staining in both sexes and decreased motor and locomotor activity (week 4) in females. The NOAEL was 1000 ppm (70.3 and 87.3 mg/kg bw /day for males and females).

4.2.4 Developmental Toxicity Studies

4.2.4.1 Developmental Toxicity Study in Rats

In a developmental toxicity study (MRID 45696906), spirodiclofen was administered to 28 female Wistar (Hsd Cpb:WU) rats/dose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day from days 6 through 19 of gestation. On gestation day (GD) 20, all surviving dams were sacrificed and examined grossly. Each fetus was weighed and examined externally for abnormalities, including the palate, and for sex determination. Approximately one-half of the fetuses in each litter were examined viscerally by sectioning according to a modified Wilson technique. The remaining one-half of the fetuses in each litter were eviscerated and processed for skeletal (bone and cartilage) examination.

No treatment-related deaths or clinical signs of toxicity were observed in any animal and gross necropsy was unremarkable. No treatment-related effects on maternal absolute body weights, body-weight gains, or food consumption were found between the treated and control groups at any time during the study. Maternal necropsy observations were unremarkable.

The maternal toxicity LOAEL is not identified and the maternal toxicity NOAEL is 1000 mg/kg bw/day.

No treatment-related differences were noted between the treated and control groups for numbers of corpora lutea and implantations, placental and gravid uterine weights, live fetuses per dam, resorptions, fetal sex ratios, and pre- or post-implantation losses. Fetal body weights were similar between the treated and control groups. An increased fetal and litter incidence of slight dilatation of the renal pelvis was observed at 1000 mg/kg bw/day. No other dose- or treatment-related external, visceral, or skeletal malformations or variations were observed.

The developmental toxicity LOAEL is 1000 mg/kg bw/day, based on an increased incidence of slight dilatation of the renal pelvis, and the developmental toxicity NOAEL is 300 mg/kg bw/day.

4.2.4.2 Developmental Toxicity Study in Rabbits

In a developmental toxicity study (MRID 45696714), spirodiclofen was administered to 22 female Himalayan CHBB:HM rabbits/dose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day from days 6 through 28 of gestation. On GD 29, all surviving does were sacrificed and examined grossly. Each fetus was weighed and examined for external abnormalities and for sex determination. Fetuses were examined viscerally by a modified Staples technique including a transverse section through the brain in about 50% of the fetuses. The eviscerated carcasses were processed for skeletal examination including cartilage staining. For approximately half of the fetuses, the head was examined via a transverse section through the brain and left intact for skeletal processing and examination; for the remainder of the fetuses, the heads were sectioned by a modified Wilson technique for an evaluation of internal cranial structures.

There were no treatment-related mortalities in maternal animals. Reduced feces were observed in 8, 14, and 17 does in the control, low-, mid-, and high-dose groups, respectively. In addition, light colored feces were seen in 14 high-dose animals compared with none of the control, low-, or mid-dose animals. Increased incidences of alopecia and discolored urination were also noted in high-dose does. No statistical differences in absolute body weights were found between the treated and control groups at any time during the study. However, marked body-weight loss occurred in the mid- and high-dose groups after the initiation of treatment. Weight loss during GD 6-9 was significantly ($p \leq 0.05$ or 0.01) greater in the mid- (-55.8 g) and high-dose (-72.7 g) groups compared with the control group (-23.7 g) with the most pronounced effects on GD 6-7. Body-weight loss and reduced feces correlated with decreased food consumption values at the mid- and high-dose (which were 72% and 58%, respectively, of the control levels for GD 6-9). Weight changes and food consumption by the low-dose group were similar to the control group throughout the study. Maternal necropsy was unremarkable.

The maternal toxicity LOAEL for spirodiclofen in rabbits is 300 mg/kg/day based on body-weight loss and decreased food consumption; the maternal toxicity NOAEL is 100 mg/kg/day.

No statistically significant differences were noted between the treated and control groups for numbers of corpora lutea, implantations, live fetuses, or resorptions, fetal sex ratios, placental weight and appearance, and pre- or post-implantation losses. Fetal body weights were similar between the treated and control groups. No treatment-related external, visceral, or skeletal malformations or deviations were observed in fetuses.

The developmental toxicity LOAEL for spirodiclofen in rabbits was not determined; the developmental toxicity NOAEL is 1000 mg/kg/day.

4.2.5 Reproductive Toxicity Study

In a two-generation reproduction study (MRID 45696802), spirodiclofen was administered to groups of 25 F_0 male and 25 F_0 female Wistar [Crl:WI(WU)BR] rats for 12 weeks before mating and during mating, gestation and lactation of one litter. Groups of 25 F_1 male and 25 F_1 females selected to parent the F_2 generation received the same diets as their F_0 parents for 13 weeks before mating, during mating, gestation and lactation of one litter. Weight-normalized doses during the premating period were as follows for the 0-, 70-, 350-, and 1750-ppm groups, respectively: 0, 5.2, 26.2, and 134.8 mg/kg bw/day for F_0 males; 0, 5.5, 27.6, and 139.2 mg/kg bw/day for F_0 females; 0, 6.4, 30.2, 177.6 mg/kg bw/day for F_1 males; 0, 7.0, 34.4, 192.7 mg/kg bw/day for F_1 females. Dose selection was based on a one-generation study conducted in Wistar rats administered dietary concentrations of 0, 250, 2500, or 10,000 ppm (MRID 45696709).

No treatment-related clinical signs or deaths occurred in parental male or female rats of either generation receiving any dose of the test material. Mean body weights were significantly ($p<0.01$ or <0.05) decreased by 6-8% throughout the study in high-dose F_0 males and by 5% at various time points in mid-dose group F_0 males compared with control weights. High-dose F_1 males weighed 17-23% ($p<0.01$) less than controls throughout the study, and low- and mid-dose F_1 males had weights similar to those of controls. High-dose F_0 and F_1 males gained 9% and 16% less weight, respectively, than controls over the entire study. High-dose F_0 females weighed 5-7% ($p<0.01$ or <0.05) less than controls during a few premating weeks and gained 19% less weight, whereas high-dose F_1 females showed no toxicologically significant effect on body weights or weight gain. No treatment-related effect was observed on premating food consumption in either sex or generation and food efficiency was only slightly decreased. Mean body weights and weight gain for females were only slightly decreased (up to 10% less than controls) or showed no toxicologically significant effect during gestation or lactation for either generation.

Clinical chemistry parameters were evaluated in a subset of F_1 males and females at the end of the premating period. Statistically significant decreases in plasma triglyceride, cholesterol, and/or unesterified fatty acid levels were observed at all doses in males and at the mid and high dose in females, and were considered to be indicative of alterations in lipid metabolism. Alkaline phosphatase activity was elevated slightly more than two-fold in high-dose group F_1 male and female rats, and was attributed to significantly increased incidences of vacuolation in the epithelium of the small intestine in high-dose animals. Absolute liver weights were decreased by 12-15% ($p<0.01$) and relative liver weights were decreased by 8-9% ($p<0.01$) at all dose levels in F_0 males, and absolute and relative liver weights were decreased by 26% and 13% ($p<0.01$), respectively, in high-dose F_1 males. The severity, but not the incidence, of adrenal cortical vacuolation was increased in high-dose F_0 males, mid- and high-dose F_0 females, and mid- and high-dose F_1 males and females.

The LOAEL for spirodiclofen systemic parental toxicity in rats was 350 ppm for both sexes (26.2-30.2 mg/kg bw/day for males and 27.6-34.4 mg/kg bw/day for females) based on the following findings:

- **in parental <u>males</u>: decreased body weight in F_0 males; decreased absolute and relative liver weight in F_0 males; decreased cholesterol and triglycerides in F_1 males; and increased severity of adrenal cortical vacuolation in F_1 males;**
- **in parental <u>females</u>: decreased unesterified fatty acids in F_1 females, and**

increased severity of adrenal cortical vacuolation in F_0 and F_1 females.

The parental systemic NOAEL is 70 ppm (5.2-6.4 mg/kg bw/day for males and 5.5-7.0 mg/kg bw/day for females).

Evaluation of reproductive performance and function showed no treatment-related effects on the fertility index, gestation index, total number of pups born, number of stillbirths, post implantation loss or number of live litters produced in either generation, mean gestation interval, estrous cycle length, the number of females with prolonged or abnormal cycles, day of vaginal patency in F_1 females, percent motile sperm or percent abnormal sperm in both generations, or testicular spermatid and epididymal sperm count in high-dose F_0 males. The insemination (mating) index, testicular spermatid count, and epididymal sperm count were reduced in high-dose F_1 males. Sexual maturation as measured by day of preputial separation was delayed by 2 days in high-dose F_1 males. Postmortem examination of reproductive organs showed decreases (12%, N.S.) in testes and epididymis (13%, $p<0.05$) weights related to atrophy in the testis (4/25) and atrophy and oligospermia in the epididymis (4/25) in high-dose F_1 males compared with none of the controls. For two of these males, atrophy of the prostate and seminal vesicles was also observed. A small increase in the severity of vacuolation/ degeneration in the luteal cells of the ovaries was noted in high-dose F_1 females. All observed adverse treatment-related effects on the reproductive system in this study were observed at the highest dose tested (1750 ppm) in second generation (F_1) males and females, but not in first generation (F_0) parental animals. This would suggest that early life stage (developmental) exposure to spirodiclofen was a critical factor in eliciting this response, even though a number of the adverse outcomes were not observed until the animals were mature.

The LOAEL for spirodiclofen for reproductive effects in rats is 1750 ppm (134.8-177.6 mg/kg bw/day for males and 139.2-192.7 mg/kg bw/day for females) based on the following findings:

- **in F_1 <u>males</u>: delayed sexual maturation; decreased testicular spermatid and epididymal sperm counts (oligospermia); and atrophy of the testes, epididymides, prostate and seminal vesicles;**
- **in F_1 <u>females</u>: increased severity of ovarian luteal cell vacuolation/degeneration.**

The reproductive NOAEL is 350 ppm (26.2-30.2 mg/kg bw/day for males and 27.6 and 34.4 mg/kg bw/day for females).

Evaluation of offspring parameters showed no treatment-related or adverse effects on survival indices, (live birth, viability, and lactation), sex ratios, live litter size, clinical signs, relative organ weights (brain, thymus, and spleen), or gross findings. During the 28-day lactation period, high-dose F_1 and F_2 male pups weighed 9-23% and 6-17% less, respectively, than controls and gained 24% and 17% less weight, respectively, than controls. Mid-dose F_1 male pups weighed 2-6% ($p<0.01$ or <0.05) less than controls during lactation, and mid-dose F_2 male pups weighed significantly less (5%, $p<0.05$) than controls only on the day of birth. High-dose F_1 and F_2 female pups weighed 5-21% ($p<0.01$) and 12-21% ($p<0.01$) less than controls, respectively, and gained 22% and 19% less weight, respectively, than controls during lactation. Mid-dose F_1 female pups weighed 3-9% ($p<0.01$) less than controls, and mid-dose F_2 female pups weighed

significantly less (7%, $p<0.01$) than controls only on the day of birth.

The LOAEL for spirodiclofen for offspring effects in rats is 350 ppm (26.2-30.2 mg/kg bw/day for males and 27.6-34.4 mg/kg bw/day for females) based on decreased body weight and weight gain in F_1 male and female pups. The offspring NOAEL is 70 ppm (5.2-6.4 mg/kg bw/day for males and 5.5-7.0 mg/kg bw/day for females).

4.2.6 Developmental Neurotoxicity Study

In a DNT study (MRID 46324901) spirodiclofen (96.8-97.1% ai; Batch #: 06480/0002) was administered in the diet to pregnant Wistar Hannover rats (30/dose) continuously from gestation day 0 to lactation day 21 at nominal doses of 0, 70, 350, or 1500 ppm (equivalent to 0/0, 6.5/14.0, 32.1/69.7, and 135.9/273.8 mg/kg/day [gestation/lactation]).

For maternal toxicity, no treatment-related effects were observed in mortality, clinical signs, FOB, serum cholesterol level, reproductive performance and postmortem examinations. The number of animals with vocalizations during removal from the home-cage was increased ($p\leq0.05$) at 1500 ppm on GD 20 (10/30 treated vs 2/30 controls); however, this was the only statistically significant FOB finding, and it was considered not to be biologically important. No treatment-related differences were noted in body weights, body-weight gains, or food consumption during gestation period. During lactation, statistically significant body-weight decrease ($\downarrow$5%, $p\leq0.05$) was observed in the 1500 ppm dams on LD 21. Food consumption was decreased ($p\leq0.05$) by 8% in the 1500 ppm dams during LD 7-14. However, body-weight changes within each group did not show significant difference while compared with the control group. The body-weight decrease may be treatment-related but was not considered biologically significant.

The maternal NOAEL was 1500 ppm (equivalent to 135.9 mg/kg/day). The maternal LOAEL was not established.

For offspring, no significant differences were noted between the treated and control groups in live litter size, sex ratio, or number of deaths during PND 0 to PND 4 (pre-cull) or PND 4 (post-cull) to PND 21, and the litter indices (live birth, viability, and lactation). No treatment-related clinical signs were observed at any dose in either sex.

During pre-weaning, body weights were decreased ($p\leq0.05$) by 5-8% in the 1500 ppm animals on PNDs 17 and 21. Body-weight gains were decreased ($p\leq0.05$) by 6-18% at 1500 ppm in both sexes at most intervals, and overall (PNDs 0-21) body-weight gain was decreased by 9% in each sex at 1500 ppm. During post-weaning, body weights were recovered in the 1500 ppm group. Post-weaning food consumption was similar between the treated and control males.

No treatment-related effects were observed on sexual maturation (mean time to preputial separation or mean time to vaginal patency). For behavioral assessment, no treatment-related FOB, motor activity, or locomotor activity were observed in the treated pups compared to controls during the pre-weaning and post-weaning periods. No treatment-related differences in the passive avoidance tests were observed at any dose. The trials to criterion for the retention phase of the water maze test for PND 60 females showed a treatment-related effect at all doses

(number of animals with $\leq$ 6 consecutive errorless trials: 14/16, 8/16, 7/16, and 8/16 for the control, low, mid, and high-dose groups, respectively). Four of the high dose females failed to complete five consecutive errorless trials (criterion for success).

For postmortem examination, no significant differences in absolute brain weight or cerebrum and cerebellum lengths were observed at any dose in either sex at any time-point. The following morphometric measurement differences ($p \leq 0.05$) were noted in the 1500 ppm group: (i) caudate putamen (↓3%) and (ii) hippocampal gyrus (↑7%) in the PND 21 females; (iii) parietal cortex (↓6%) in the terminal males; (iv) caudate putamen (↑3%) and (v) hippocampal gyrus (↑6%) in the terminal females. Due to these findings, along with the effects on memory observed at all doses in the PND 60 females in the water maze test, morphometric analyses of the caudate putamen, parietal cortex, hippocampal gyrus, and dentate gyrus at the mid and low doses are requested for both sexes.

The offspring LOAEL was 70 ppm (equivalent to 6.5 mg/kg/day) based on effects in memory phase of the water maze test in PND 60 females. There was no offspring NOAEL in this study.

The study classification is **reserved** for the guideline requirement (OPPTS 870.6300; OECD 426) for a developmental neurotoxicity study in rats pending receipt of additional morphometric measurements for the low and mid dose groups.

In a second DNT study, an abbreviated developmental neurotoxicity study (MRID 47166501), technical spirodiclofen (97.5-98.3 % ai, batch 06480/0002) was administered in the diet to 30 female Wistar Han Crl:WI (Han) rats per dose at dose levels of 0, 70, 350 or 1500 ppm (average daily intake of 0, 5.4, 28.6 and 119.2 mg/kg/day, respectively, during gestation and 0, 13.0, 65.7 and 262.1 mg/kg/day, respectively, during lactation) from GD 0 through lactation day (LD) 21. Because of increased food consumption during lactation, dietary levels were adjusted to achieve a more consistent mg/kg/day dosage throughout the exposure period. On PND 4, litters were culled to yield four males and four females (as closely as possible). Offspring were allocated for clinical observations, body-weight measurements, ophthalmic examinations and assessment of learning and memory (water maze testing using M-Maze and Cincinnati Water Maze). Whole-brain tissue was collected from 10/sex/dose level on PND 21 and at study termination (PND 75 ±5) for morphometry. The study was conducted to address questions about brain measurements and M-Maze results in the original developmental neurotoxicity study.

No deaths or clinical signs of toxicity were observed in parental females. The slight decrease in food consumption (4-5% as compared to controls) during lactation produced a minimal decrease in body-weight gain (4% as compared to controls) for LDs 0-20. The findings are not considered adverse due to the low magnitude of the changes and the lack of statistical significance. No treatment-related effects on reproduction were reported.

No clinical signs of toxicity were observed in offspring during lactation or postweaning. Litter size and viability were not affected by treatment. Beginning on PND 17, a decrease in body weight was observed in the high-dose group, with statistically significant decreases of 8% and 7% in males and females as compared to controls, respectively, on PND 21. Statistically significant decreases in body-weight gain were observed in high dose males and females for the

periods PND 4-21 (9-10%), PND 11-21 (13%) and PND 17-21 (21%). During postweaning, body weight was decreased (5-6% as compared to controls) in high-dose males on PND 29 through PND 50, which was statistically significant on PNDs 35 and 42. No treatment-related effects on learning and memory were observed in either the M-Maze or the Cincinnati Water Maze testing. In the previous study, there was a significant increase in the trials to criterion observed in females in all dose groups during session 2 (memory). A request was made for the submission of positive control data which has not been received as yet. Despite the lack of positive control data, it was observed that the trials to criterion for both male and female rats ranged from 5.4-7.9 seconds in the previous and current studies; thus indicating no treatment related changes in this study. Therefore, the results of the previous study were not replicated in this new study. No treatment-related effects on ophthalmic examinations, brain weight or postmortem macroscopic and morphometric findings were observed.

The maternal LOAEL for spirodiclofen in rats was not established. The maternal NOAEL is 1500 ppm (119.2 and 262.1 mg/kg/day during gestation and lactation, respectively).

The offspring LOAEL for spirodiclofen in rats is 1500 ppm (119.2 and 262.1 mg/kg/day during gestation and lactation, respectively) based on decreased preweaning body weight and body-weight gain in males and females and decreased post-weaning body weight in males. The offspring NOAEL is 350 ppm (28.6 and 65.7 mg/kg/day during gestation and lactation, respectively).

4.2.7 Additional Information from Literature Sources

No additional hazard information from published literature was identified.

4.2.8 Pre- and/or Postnatal Toxicity

4.2.9 Determination of Susceptibility

The database is adequate to evaluate the potential increased susceptibility of infants and children. The HIARC determined that there is no evidence (qualitative or quantitative) of increased susceptibility in the rabbit developmental toxicity study and the rat reproduction toxicity study following *in utero* and/or pre-/post-natal exposure of spirodiclofen. However, evidence for quantitative susceptibility was observed in a rat developmental toxicity study where an increased incidence of slight dilatation of the renal pelvis was observed at a dose (1000 mg/kg/day) which did not cause any maternal toxicity. Previously, the HIARC concluded that there is evidence of increased susceptibility of rat offspring in the first DNT study (second DNT study was not available) because the toxicity in the offspring was observed in the absence of maternal toxicity, indicating increased susceptibility. In this study, there was no maternal toxicity was observed (135.9 mg/kg/day; HDT; highest dose tested). The offspring toxicity LOAEL was 6.5 mg/kg/day based on marginal effects in the memory phase of the water maze test in female offspring on post natal day 60 and differences in morphometric measurements at the HDT (135.9 mg/kg/day). Additionally, treatment-related changes were seen at the HDT (135.9 mg/kg/day) in several brain morphometric parameters (caudate putamen, parietal cortex, hippocampal gyrus, and dentate gyrus). Consequently, evaluations were requested for these parameters at the mid- and low-dose groups. However, the registrant has informed that the brain tissues were not appropriately

preserved; therefore, additional brain morphometric analyses at the mid and low doses are not possible. Therefore, the registrant conducted the second study. In a second DNT study, there is evidence for increased susceptibility of rat offspring due to exposure to spirodiclofen. In this study, the offspring toxicity such as decreased pre-weaning body weight and body-weight gain in males and females and decreased post-weaning body weights in males at the LOAEL of 119.2 mg/kg/day and NOAEL was 28.6 mg/kg/day. There was no maternal toxicity at the doses up to and including 119.2 mg/kg/day.

4.2.10 Degree-of-Concern Analysis for Pre and/or Post-natal Susceptibility

The HIARC determined that the degree of concern is low for the quantitative susceptibility seen in rats. The increased incidence of slight renal pelvic dilation in the rat developmental toxicity was observed at the limit-dose only without statistical significance and dose response. Renal pelvic dilation was considered to be a developmental delay and not a severe effect for developmental toxicity. The low background incidences in this study may be idiosyncratic to this strain (Wistar) of rats since renal pelvis dilations are commonly seen at higher incidences in other strains (Sprague-Dawley or Fisher) of rats. In addition, doses selected for risk assessment of spirodiclofen are much lower than the dose that caused these developmental delays. The two DNT studies suggest increased evidence of susceptibility of offspring due to exposure to spirodiclofen. However, there is no concern for the increased susceptibility seen the first DNT study because the results were not reproduced in the second DNT study conducted using the identical doses and experimental conditions in a second study. The concern for increased susceptibility in a second DNT study is low because there is a well established NOAEL, marginal toxicity (slight changes in body weights), and all developmental/functional parameters were comparable to controls. In addition, doses selected for risk assessment of spirodiclofen are much lower than the dose that caused these marginal changes in the body weights of offspring in the second DNT study. There is no concern for increased susceptibility in the developmental toxicity in rabbits, two-generation reproduction study in rats. The FQPA factor of 3X has been applied for use LOAEL instead of NOAEL for short-term oral, short-term dermal and inhalation exposure scenarios. HIARC determined that a 3x (as opposed to a 10x) uncertainty factor is adequate (for the use of a LOAEL) since the extrapolated NOAEL (8.4/3= 2.8 mg/kg/day) is comparable to the NOAEL (1.38 or 1.52 mg/kg/day for males or females, respectively) in the chronic study.

4.3 Hazard Identification and Toxicity Endpoint Selection

4.3.1 Acute Reference Dose (aRfD) - All Populations

An endpoint of concern attributable to a single dose was not identified in the hazard database. The increased incidence of slight dilation of the renal pelvis, observed only at the limit dose was not considered to be a single dose effect and therefore was not selected for establishing the aRfD.

In the first developmental neurotoxicity study, offspring effects (brain morphometry and learning and memory) were noted in the absence of toxicity in the dams. However, these effects were not observed in the repeat study using the same doses and identical experimental conditions.

4.3.2 Chronic Reference Dose (cRfD)

A cRfD was determined based on increased relative adrenal weights in both sexes, increased relative testis weight in male dogs and histopathology findings in the adrenal gland of both sexes of dogs seen at the LOAEL of 4.33 mg/kg/day. The NOAEL was 1.38 mg/kg/day. The chronic oral toxicity study in dogs (MRID 45696810) was selected for chronic dietary risk assessment because, while the effects were seen in rats, dogs and mice, dogs were considered the most sensitive species. These endpoints will provide the most protective limits for human effects. This study is of the appropriate duration and route of exposure.

In a chronic toxicity study (MRID 45696810), spirodiclofen was administered to beagle dogs (4/sex/dose) in the diet at dose levels of 0, 20, 50, 150, or 500/600 ppm (equivalent to 0, 0.56, 1.38, 4.33, or 16.1 mg/kg bw/day for males and 0, 0.59, 1.52, 4.74, or 17.7 mg/kg bw/day for females, respectively) for 52 weeks. The highest dose was increased from 500 ppm to 600 ppm in study week 4.

There were no compound related effects on mortality, clinical signs, food consumption, body-weight gains, urinalysis, hematology, clinical chemistry, and ophthalmoscopic examinations. Liver enzyme activities showed dose-dependent increases of N-DEM, and O-DEM activities which indicated an induction of hepatic metabolic activity in response to spirodiclofen administration.

The relative organ weight showed dose-related increases in adrenal glands of both sexes, in kidneys (females only), and in testes, epididmydes and prostates of males. Histopathology of the adrenal gland revealed an increased incidence of cortical vacuolation in the zona fasciculata of both sexes at 150 and 500/600 ppm. In the testes, increased incidences of Leydig cell vacuolation, slight Leydig cell hypertrophy, and tubular degeneration were observed in males at 500/600 ppm.

Under the conditions of this study, the NOAEL is 50 ppm (1.38 mg/kg bw/day for males and 1.52 mg/kg bw/day for females) and the LOAEL is 150 ppm (4.33 mg/kg bw/day for males and 4.74 mg/kg bw/day for females) based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes.

The dose and endpoint for establishing the cRfD are the NOAEL = 1.38 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes at 4.33 mg/kg/day (LOAEL). An uncertainty factor of 100X has been incorporated into the cRfD (10x for interspecies extrapolation and 10x for intraspecies variations).

Chronic RfD = 1.38 mg/kg (NOAEL) = 0.014 mg/kg/day

4.3.3 Incidental Oral Exposure: Short-Term (1-30 days)

The endpoint for short-term incidental oral risk assessment was chosen based on the results of a subchronic oral toxicity study in dogs (MRID 45696803). The endpoints are increased adrenal

gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females and the study and results are summarized below. The study and endpoint are of the appropriate duration and route of exposure for short-term incidental oral risk assessment.

In a 90-day oral toxicity study spirodiclofen was administered to beagle dogs (4/sex/dose) via diet at dose levels of 0, 200, 630, or 2000 ppm (equivalent to 0, 7.7, 26.6, or 84.7 mg/kg bw/day for males and 0, 8.4, 28.0, 81.0 mg/kg bw/day for females, respectively) for 14 weeks.

There were no compound related effects on mortality, clinical signs, food consumption, hematology, urinalysis, and ophthalmoscopic examinations. There was a dose-dependent decrease of body-weight gain in both sexes. A significant decrease of body-weight gain was observed in males at doses of 630 ppm and above compared with the controls. Increased plasma transaminase activities (ASAT, ALAT) and increased APh and GLDH levels were seen at doses of 630 ppm and above of both sexes. A trend to lower cholesterol was observed in the 630 and 2000 ppm groups of both sexes. The activities of liver enzymes showed an induction of phase I enzymes (cytochrome p-450-dependent monooxygenases (ECOD, EROD, ALD)) in response to spirodiclofen administration. There were no effects on the phase II enzyme activities (GS-T and GLU-T). The EH was induced at the high dose in females only. Dose-dependent increases of N-DEM, O-DEM, ECOD and ALD levels were seen in both sexes. The changes of liver enzyme activities suggest an induction of hepatic metabolic activity in response to administration of spirodiclofen. These changes are considered adaptive effects and not regard as adverse effects.

Based on dose-dependent relationship, increased relative organ weights were observed in the liver at 630 and 2000 ppm of both sexes, kidney at 2000 ppm of both sexes, pituitary at 630 and 2000 ppm of males, and adrenal gland at 630 and 2000 ppm of both sexes. Decreased relative prostate weight also was observed in males at 630 and 2000 ppm. Histopathological examination revealed treatment-related findings in the liver, kidney, adrenal gland, prostate, testis, and thymus. Hepatocellular cytoplasmic changes, inflammatory infiltrates, and single cell necrosis were seen in females only at the highest dose. Dilation of the proximal tubules of the renal cortex was seen in both sexes at the 2000 ppm. The dilation is considered an adaptive effect since no degenerative changes were seen. In testes, vacuolation and hypertrophy/activation of Leydig cells was observed in males at 630 and 2000 ppm. In addition, degeneration and/or immaturity of the testicular germinal epithelium, oligo- and aspermia of the epididmydes, and immature prostates were detected at doses of 630 ppm and above. A dose-dependent increase of cytoplasmic vacuolation of the adrenal cortex was observed in females at all doses and in males at the 630 ppm and above. The adrenal effects were also observed in rat and mouse studies and were considered significant.

The LOAEL for males was 630 ppm (26.6 mg/kg bw/day) based on decreased body-weight gains, decreased relative prostate weight, increased relative liver and adrenal weights and histopathology findings in the adrenal glands, testes, and prostates; the NOAEL was 200 ppm (7.7 mg/kg bw/day). The LOAEL for females was 200 ppm (8.4 mg/kg bw/day) based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands); the NOAEL for females was not established.

The dose and endpoint for risk assessment are the LOAEL of 8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a NOAEL for females was not established.

The dose/endpoint is appropriate for the population (infants and children) of concern. The HIARC selected the 90-day study for this duration (short-term) since similar target organ toxicity (adrenal glands) was also seen in the chronic study in dogs as well as in mice. The Committee determined that a 3x (as opposed to a 10x) uncertainty factor is adequate (for the use of a LOAEL) since the extrapolated NOAEL (8.4/3= 2.8 mg/kg/day) is comparable to the NOAEL (1.38 or 1.52 mg/kg/day for males or females, respectively) in the chronic study.

4.3.4 Incidental Oral Exposure: Intermediate-Term (1-6 Months)

The dose and endpoint for intermediate-term incidental oral risk assessment was chosen based on the results of the chronic oral toxicity study in dogs (MRID 45696810). The endpoints are increased relative adrenal weights in both sexes, increased relative testis weight in male dogs and histopathology findings in the adrenal gland of both sexes of dogs. The study is summarized above in Section 4.3.2. This study and endpoint are of the appropriate duration and route of exposure for intermediate-term incidental oral risk assessment.

The dose and endpoint for risk assessment are the NOAEL of 1.38 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes at 4.33 mg/kg/day (LOAEL).

4.3.5 Dermal Absorption

A dermal-absorption factor of 2% was determined based on the results of two dermal-absorption studies in monkeys. The dermal-absorption rate is appropriate for estimating dermal risk for all time durations.

4.3.6 Short-Term Dermal Exposure (1-30 days)

The dose and endpoint for short-term dermal risk assessment were chosen based on the results of a subchronic oral toxicity study in dogs (MRID 45696803). The endpoint is increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females. The study and results are summarized in Section 4.3.3. The study and endpoint are of the appropriate duration and route of exposure for short-term dermal risk assessment.

The dose and endpoint for risk assessment are the LOAEL of 8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a NOAEL for females was not established.

The HIARC did not select the 28-day dermal toxicity study because the target organs (i.e., adrenal, testes, etc.) were not evaluated in this study. The HIARC selected the 90-day study for

this duration (short-term) since similar target organ toxicity (adrenal glands) was also seen in the chronic study in dogs as well as in mice. The Committee determined that a 3x (as opposed to a 10x) uncertainty factor is adequate (for the use of a LOAEL) since the extrapolated NOAEL (8.4÷3 = 2.8 mg/kg/day) is comparable to the NOAEL (1.38 or 1.52 mg/kg/day for males or females, respectively) in the chronic study. Since an oral LOAEL was selected, 2% dermal-absorption factor should be used for route-to-route extrapolation.

4.3.7 Intermediate-Term Dermal (1-6 Months)

The dose and endpoint for intermediate-term dermal risk assessment were chosen based on the results of a chronic oral toxicity study in dogs (MRID 45696810). The endpoints are increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes. The study and results are summarized above in Section 4.3.2. The study and endpoint are of the appropriate duration and route of exposure for intermediate-term dermal risk assessment.

The dose and endpoint for use in risk assessment are the NOAEL of 1.38 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes at 4.33 mg/kg/day (LOAEL).

This dose/endpoint/study was selected for establishing the chronic RfD. Since an oral NOAEL was selected, 2% dermal-absorption factor should be used for route-to-route extrapolation.

4.3.8 Long-Term Dermal (>6 Months) Exposure

The dose and endpoint selected for long-term dermal risk assessment were chosen based on the results of a chronic oral toxicity study in dogs (MRID 45696810). The endpoints are increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes. The study and results are summarized above in Section 4.3.2. The study and endpoint are of the appropriate duration and route of exposure for long-term dermal risk assessment.

The dose and endpoint for use in risk assessment are the NOAEL of 1.38 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes at 4.33 mg/kg/day (LOAEL).

This dose/endpoint/study was selected for establishing the chronic RfD. Since an oral NOAEL was selected, 2% dermal-absorption factor should be used for route-to-route extrapolation.

4.3.9 Short-Term Inhalation (1-30 days) Exposure

The dose and endpoint for short-term inhalation risk assessment were chosen based on the results of a subchronic oral toxicity study in dogs (MRID 45696803). The endpoints are increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females. The study and results are summarized in Section 4.3.3. The study and endpoint are of the appropriate duration and route of exposure for short-term inhalation risk assessment.

The dose and endpoint for risk assessment are the LOAEL of 8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a NOAEL for females was not established.

The dose and endpoint for use in risk assessment are the LOAEL of 8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which coincided with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a NOAEL for females was not established.

The HIARC selected the 90-day study for this duration (short-term) since similar target organ toxicity (adrenal glands) was also seen in the chronic study in dogs as well as in mice. The Committee determined that a 3x (as opposed to a 10x) uncertainty factor is adequate (for the use of a LOAEL) since the extrapolated NOAEL (8.4/3 = 2.8 mg/kg/day) is comparable to the NOAEL (1.38 or 1.52 mg/kg/day for males or females, respectively) in the chronic study. In the absence of a repeated exposure inhalation study, the HIARC selected an oral study. Inhalation absorption is assumed to be equivalent to oral (i.e., 100%).

4.3.10 Intermediate-Term Inhalation (1-6 months) Exposure

The dose and endpoint for intermediate-term inhalation risk assessment were chosen based on the results of a chronic oral toxicity study in dogs (MRID 45696810). The endpoints are increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes. The study and results are summarized above in Section 4.3.2. The study and endpoint are of the appropriate duration and route of exposure for intermediate-term inhalation risk assessment.

The dose and endpoint for use in risk assessment are the NOAEL of 1.38 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes at 4.33 mg/kg/day (LOAEL).

This dose/endpoint/study was selected for establishing the chronic RfD.

The dose and endpoint for use in risk assessment are the NOAEL of 1.38 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes at 4.33 mg/kg/day (LOAEL).

In the absence of a repeated exposure inhalation study, the HIARC selected an oral study. Inhalation absorption is assumed to be equivalent to oral (i.e., 100%).

4.3.11 Long-Term Inhalation (>6 months) Exposure

The dose and endpoint for long-term inhalation risk assessment were chosen based on the results of a chronic oral toxicity study in dogs (MRID 45696810). The endpoints are increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes. The study and results are summarized above in

Section 4.3.2. The study and endpoint are of the appropriate duration and route of exposure for long-term dermal risk assessment.

The dose and endpoint for use in risk assessment are the NOAEL of 1.38 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes at 4.33 mg/kg/day (LOAEL).

This dose/endpoint/study was selected for establishing the chronic RfD.

The dose and endpoint for use in risk assessment are the NOAEL of 1.38 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes at 4.33 mg/kg/day (LOAEL).

In the absence of a repeated exposure inhalation study, the HIARC selected an oral study. Inhalation absorption is assumed to be equivalent to oral (i.e., 100%).

4.3.12 Margins of Exposure

Table 4.3.12. Summary of Target MOEs for Risk Assessment.

Route Duration	Short-Term (1-30 Days)	Intermediate-Term (1-6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	300	100	100
Inhalation	300	100	100
Residential (Non-Dietary) Exposure			
Oral	300	100	100
Dermal	300	100	100
Inhalation	300	100	100

For Occupational Exposure: For short-term dermal and inhalation exposure risk assessments, a MOE of 300 is required. For intermediate and long-term dermal and inhalation exposure risk assessments, a MOE of 100 is required. This includes the conventional 100x and an additional 3x for the use of a LOAEL for short-term dermal and inhalation risk assessment. For intermediate– and long-term dermal and inhalation risk assessments, the conventional 100x UF is used.

For Residential Exposure: Not applicable for this action. There are no residential uses proposed.

4.3.13 Recommendation for Aggregate Exposure Risk Assessments

Chronic and cancer aggregate risk estimates include exposure from drinking water and from food sources. Short- and intermediate-term aggregate risk assessments are not required since there are no residential uses proposed at this time.

4.3.14 Carcinogenicity

4.3.14.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

In a combined chronic toxicity/carcinogenicity study (MRID 45696808), spirodiclofen was administered to Wistar rats (50/sex/dose) via diet at dose levels of 0, 50, 100, 350, or 2500 ppm (0, 2.0, 4.1, 14.7, or 110.1 mg/kg bw/day for males and 0, 2.9, 5.9, 19.9, or 152.9 mg/kg bw/day for females, respectively) for two years. Additional groups of rats (10/sex/dose) were treated likewise with spirodiclofen for interim sacrifice after one year.

No significant treatment-related effects were observed in clinical signs and mortality. Significant decreases in body weights were observed in the 2500 ppm group of both sexes compared to controls (↓8-10% for males up to weeks 101; ↓6-7% for females up to weeks 53). Body-weight gains were decreased at 2500 ppm of both sexes up to week 3 and recovered thereafter. Blood analyses showed no significant effects in hematological examinations; however, significant increases of alkaline phosphatase (APh) and decreases of cholesterol and triglyceride levels (not statistically significant) were observed in both sexes at 2500 ppm at all test points. Significantly increased thyroxine (T4) levels were observed in 2500 ppm males at weeks 53 and 105. Increased thyroid stimulating hormone was observed at 2500 ppm of both sexes but the statistical significance was observed only in females at weeks 79 and 105. Gross and histopathology examinations showed an increased incidence of vacuolated enterocytes in the jejunum (both sexes), increased incidence and severity of vacuolation in Zona fasciculata cells of the adrenal cortex (males only), increased portion of ovarian stroma, and increased incidence of uterus nodules (females) at 2500 ppm. Increased incidence of Leydig cell hyperplasia was observed in males at 350 ppm and above with a positive trend.

Under conditions of this study, the LOAEL is 350 ppm for males (14.7 mg/kg bw/day) based on increased incidence of Leydig cell hyperplasia. The LOAEL is 2500 ppm (152.9 mg/kg/day) for females is based on decreased body weights, decreased body-weight gain, increased APh levels, increased thyroid stimulating hormone (TSH), uterus nodules, and increased vacuolated jejunum enterocytes. The NOAEL is 100 ppm for males (4.1 mg/kg/day) and 350 ppm for females (19.9 mg/kg/day).

Neoplastic pathology showed an increased incidence of treatment related neoplastic findings in reproductive organs of males (testes) and females (uterus). In males, a significantly increased frequency of Leydig cell adenoma (4%, 2%, 0%, 8%, or 20% at dose levels of 0, 50, 100, 350, or 2500 ppm, respectively) was observed at 350 ppm and above with a positive trend. Concurrently, increased incidence of Leydig cell hyperplasia (8%, 8%, 8%, 14%, or 38%, respectively) was observed at 350 ppm and above with a positive trend. The majority of Leydig cell adenomas and focal hyperplasias were found in males at the termination of the study suggesting a late onset of these alterations. In females, increased incidence of uterine adenocarcinoma (8%, 10%, 6%, 4%, or 28%, respectively) was observed at 2500 ppm. The majority of the uterine adenocarcinoma (11 out of 14) was found in females which died or had to be sacrificed before the termination of the study. The pathology report also indicated that many of the adenocarcinomas had metastasized by invasion and intra-abdominal spread into various organs of the abdominal cavity such as ovaries, liver, spleen, pancreas, mesenteric lymph node, kidney, lung, and bone marrow. Slightly increased incidences of C-cell adenoma in thyroid

gland were observed in males (8%, 12%, 10%, 8%, or 14%, respectively) and in females (4%, 4%, 6%, 10%, or 12%, respectively) at 2500 ppm; however, the incidences were within the historical control ranges (6-24% in males and 6-22% in females).

Discussion of Tumor Data: Male rats had a significant increasing trend at $p<0.01$, and a significant difference in the pair-wise comparison of the 2500 ppm dose group with the controls at $p< 0.05$, for testicular Leydig cell adenomas. The incidence of Leydig cell adenomas of 20% for the high dose group is outside the historical control range of the performing laboratory (2-8%). The incidence of Leydig cell adenomas for the 350 ppm dose group of 8%, although not statistically significant, was just within the boundary of the historical control range (2-8%) and was considered to be biologically significant. This is supported by an increase (not statistically significant) in focal Leydig cell hyperplasia at 350 ppm.

Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for uterine adenocarcinomas and combined adenomas and/or adenocarcinomas, all at $p<0.01$. The incidence of adenocarcinomas of 28% at the high dose was outside the laboratory historical control range of 2-10% for adenocarcinomas.

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on body-weight decrease, clinical chemistry, and histopathological findings. Significant decreases in body weights were observed in the 2500 ppm group of both sexes compared to controls (↓8-10% for males up to weeks 101; ↓6-7% for females up to weeks 53). Body-weight gains were decreased at 2500 ppm of both sexes up to week 3 and recovered thereafter. Significant increases of APh and decreases of cholesterol and triglyceride levels (not statistically significant) were observed in both sexes at 2500 ppm at all test points. Significantly increased thyroxine (T4) levels were observed in 2500 ppm males at weeks 53 and 105. Increased TSH was observed at 2500 ppm of both sexes but the statistical significance was observed only in females at weeks 79 and 105. Gross and histopathology examinations showed an increased incidence of vacuolated enterocytes in the jejunum (both sexes), increased incidence and severity of vacuolation in Zona fasciculata cells of the adrenal cortex (males only), increased portion of ovarian stroma, and increased incidence of uterus nodules (females) at 2500 ppm. Increased incidence of treatment related neoplastic findings in reproductive organs of males (testes) and females (uterus) were observed at the 2500 ppm group.

4.3.14.2 Carcinogenicity Study in Mice

In a carcinogenicity study (MRID 45696724), spirodiclofen (97.6-98.6% ai, batch/lot # 06480/0002) was administered to CD-1 mice (50/sex/dose) via diet at dose levels of 0, 25, 3500, or 7000 ppm (equivalent to 0, 4.1, 610, or 1216 mg/kg bw/day for males, and 0, 5.1, 722, or 1495 mg/kg bw/day for females, respectively) for 18 months.

There were no compound-related effects on mortality, clinical signs, body weight, food consumption, and hematology examinations. Increased organ weights were observed in livers and adrenal glands at 3500 and 7000 ppm of both sexes. Increased testis weights were observed in males at 7000 ppm. Decreased absolute and relative kidney weights were observed in 3500 ppm and 7000 ppm of both sexes. Gross pathology showed enlarged adrenal glands at 3500 and

7000 ppm of both sexes. Histopathology examination revealed increases of incidence and severity of vacuolation in the adrenal cortex at 3500 and 7000 ppm of both sexes. In the liver, dose-dependent increases of incidence and severity of hepatocytomegaly were observed in males only. In the testis, increases of incidence and severity on hypertrophy and hyperplasia of the interstitial cell were noted in 3500 and 7000 ppm males. A dose-related increased incidence of amyloid was observed in various organs of both sexes. The lesion in the testis consisted of increased cell size as well as numbers of cells. Additional histopathology findings included discolored testis in mid dose males, epididymis aspermia in high dose males, lymphocytic infiltrate in high dose females and increased incidence of focal opacity in high dose males.

Under conditions of this study, the NOAEL is 25 ppm (4.1 mg/kg bw/day for males and 5.1 mg/kg bw/day for females). The LOAEL is 3500 ppm (610 mg/kg bw/day) for males based on increased absolute and relative liver and adrenal weights, decreased absolute and relative kidney weight, enlarged adrenal gland, discolored testis, adrenal gland vacuolization, interstitial cell degeneration of the testes and amyloid. **The LOAEL is 3500 ppm (722 mg/kg bw/day) for females** based on increased absolute and relative adrenal weight, decreased absolute and relative kidney weight, increased incidences of adrenal gland pigmentation, adrenal vacuolization and amyloid.

Neoplastic pathology examination showed increases of neoplastic lesions in the liver. The incidences of hepatocellular adenoma were 0/50, 0/50, 5/50, or 6/50 for males and 0/50, 0/50, 3/50, or 1/50 for females at 0, 25, 3500, or 7000 ppm, respectively. The incidences of hepatocellular carcinoma were 1/50, 1/50, 3/50 or 5/50 for males and 0/50, 0/50, 2/50, or 2/50 for females at 0, 25, 3500, or 7000 ppm, respectively. The combined frequencies of hepatocellular neoplasm (hepatocellular adenoma and carcinoma) were 1/50 (2%), 1/50 (2%), 8/50 (16%), or 10/50 (20%) for males and 0/50, 0/50, 5/50 (10%), or 3/50 (6%) for females at 0, 25, 3,500 or 7,000 ppm, respectively. Comparing with historical control, the combined frequencies of hepatocellular adenoma and carcinoma at 3500 ppm (16% in males and 10% in females) and 7000 ppm (22% in males and 6% in females) are higher than the ranges seen in either in-house control (4-14% in males and 0-2% in females) or literature historical data (0-9.6% in males and 0-2.7% in females).

Discussion of Tumor Data: Male mice had significant increasing trends in liver adenomas and adenomas and/or carcinomas combined, both at $p<0.01$. There was a significant increasing trend in liver carcinomas at $p<0.05$. There were significant differences in the pair-wise comparisons of the 3500 and 7000 ppm dose groups with the controls for liver adenomas, both at $p< 0.05$. There were significant differences in the 3500 ppm dose group at $p<0.05$ and in the 7000 ppm dose group at $p<0.01$ with the controls for liver adenomas and/or carcinomas combined. The incidences of combined liver adenomas and carcinomas of 16% and 22% for the 3500 ppm and 7000 ppm dose groups, respectively, are outside the historical control range of the performing laboratory (4-14%).

Female mice had a significant increasing trend, and a significant difference in the pair-wise comparison of the 3500 ppm dose group with the controls, for liver adenomas and/or carcinomas combined, both at $p<0.05$. The incidences of combined liver adenomas and carcinomas of 10% (statistically significant) and 6% (not statistically significant) for the 3500 ppm and 7000 ppm dose groups, respectively, are outside the historical control range of the performing laboratory (0-

2%).

Adequacy of the Dose Levels Tested: Dosing was considered adequate and not excessive based on observations of increased organ weights and histopathological findings. A limit dose of 7000 ppm was used in this study. Increased organ weights were observed in livers and adrenal glands at 3500 and 7000 ppm of both sexes. Increased testis weights were observed in males at 7000 ppm. Gross pathology showed enlarged adrenal glands at 3500 and 7000 ppm of both sexes. Histopathology examination revealed increases of incidence and severity of vacuolation in the adrenal cortex at 3500 and 7000 ppm of both sexes. In the liver, dose-dependent increases of incidence and severity of hepatocytomegaly were observed in males only. In the testis, increases of incidence and severity on hypertrophy and hyperplasia of the interstitial cell were noted in 3500 and 7000 ppm males.

4.3.14.3 Classification of Carcinogenic Potential

The CARC met on May 5, 2004 to evaluate the carcinogenic potential of spirodiclofen. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC classified spirodiclofen as **"likely to be carcinogenic to humans"** by the oral route. This classification was based on evidence of testes Leydig cell adenomas in male rats, uterine adenomas and/or adenocarcinoma in female rats, and liver tumors in mice. The CARC recommended using a linear low-dose extrapolation approach for the quantification of human cancer risk (TXR No. 0052552). The unit risk, Q_1^*(mg/kg/day)$^{-1}$ for spirodiclofen is 1.49 x 10^{-2} based on male rat testes Leydig cell adenoma (TXR No. 0052535).

4.3.15 Mutagenicity

HED concluded that there is no concern for mutagenicity. Neither technical spirodiclofen, a formulation, nor major metabolites (BAJ 2740 enol, BAJ 2740 - MA-3OH-cyclohexylester, BAJ 2740-ketohydroxy, BAJ 2740-hexylester or C6-hydroxyester) were mutagenic in *Salmonella typhimurium* when tested up to the limit dose (5000 µg/plate +/- S9) (MRID Nos. 45696702, 45696817, 45696805, 45696818, 45696819, 45696921 or 45696909), respectively. Technical spirodiclofen was also not mutagenic in mammalian cells (MRID 45696614) or clastogenic in cultured mammalian cells (MRID 45696615) and was not clastogenic or aneugenic in the mouse micronucleus assay up to an overtly toxic dose (800 mg/kg) (MRID 45696701). Similarly, the spirodiclofen formulation, spirodiclofen 240 SC was not clastogenic in cultured Chinese hamster lung (V79) cells (MRID 45696821).

Table 4.3. Summary of Toxicology Endpoint Selection for Spirodiclofen.			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary	**Acute RfD** = Not established.	An appropriate endpoint attributable to a single dose was not identified. Assessment not necessary/	
Chronic Dietary (All populations)	NOAEL= 1.38 mg/kg/day UF = **100** **Chronic RfD** = 0.014 mg/kg/day	FQPA SF = 1X **cPAD** = Chronic RfD / FQPA SF = 0.014 mg/kg/day	**Chronic Oral Toxicity Study in Dogs** LOAEL= 4.7 mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes.
Short-term Incidental Oral; Short-term Dermal; Short-term Inhalation (1-30 Days)	LOAEL = 8.4 mg/kg/day (dermal-absorption rate= 2%)	**Residential** LOC for MOE = 300 **Occupational** LOC for MOE = 300	**Subchronic Oral Toxicity Study in Dogs** LOAEL= 8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which corroborated with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands) in females; a NOAEL for females was not established.
Intermediate-term Incidental Oral; Intermediate-term Dermal; Intermediate-term Inhalation (1-6 Months)	NOAEL = 1.38 mg/kg/day (dermal-absorption rate = 2%)	**Residential** LOC for MOE = 100	**Chronic Oral Toxicity Study in Dogs** See above under Chronic Dietary.
Long-term Dermal; Long-term Inhalation (>6 Months)	Oral NOAEL= 1.38 mg/kg/day (dermal-absorption rate = 2%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Chronic Oral Toxicity Study in Dogs** See above under Chronic Dietary.
Cancer (Oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" with Q_1* $(mg/kg/day)^{-1} = 1.49 \times 10^{-2}$.		

4.4 Endocrine Disruption

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

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

5.0 Exposure Characterization/Assessment

5.1 Dietary Exposure/Risk Pathway

5.1.1 Residue Profile

Magnitude of the Residue - Plants: Adequate field trial data on hops are available from 3 trials conducted in the U.S. in Zones 11 and 12 during 2004. In each trial, spirodiclofen (2 lb/gal FlC) was applied to hops as a single foliar-directed application at 0.387-0.412 lb ai/A (1x rate) during cone development and maturation. Applications were made using ground equipment at volumes of 43-175 gal/A, and did not include the use of any spray adjuvants. The resulting residues of spirodiclofen were 1.97-13.1 ppm in/on 6 samples of dried hop cones harvested 21 days after treatment (DAT) and 2.85-5.72 ppm in/on 6 samples harvested at 28 DAT. Average spirodiclofen residues were 6.42 and 3.99 ppm at 21 and 28 DAT, respectively.

The petitioner also submitted supplemental hops field trial data from 8 trials conducted in Germany during 2003 and 2004. In each of these trials, spirodiclofen (240 g/L FlC) was applied to hops as a single foliar application at 0.34-0.43 kg ai/ha (0.30-0.38 lb ai/A, ~1x proposed U.S. rate) during cone development and maturation (BBCH 71-87), using ground equipment at volumes of 2100-3547 L/ha (225-380 gal/A). Residues of spirodiclofen were 3.9-24.0 ppm in/on 8 samples of dried hops harvested at the proposed PHI of 14 days. Residues were 3.9-10.9 ppm in/on 4 samples by 21 DAT and 3.1-10.0 ppm in/on 6 samples by 28 DAT. Average residues were 11.6, 7.23, and 7.07 ppm at 14, 21 and 28 DAT, respectively, indicating that residues declined slowly from 14-28 DAT.

As there are no regulated processed commodities associated with hops, no processing studies are required for this petition. Data pertaining to residues in rotational crops are also not required as hops are a perennial crop.

The submitted U.S. field trial data supports a minimum PHI of either 21 or 28 days; however, IR-4 is requesting a 14-day PHI for hops in order to harmonize the U.S. and German use patterns. In addition, IR-4 is requesting a 30-ppm tolerance on dried hop cones to harmonize with the established German maximum residue limit (MRL). Considering similarity in climatic conditions between the hops growing regions in the U.S. and Germany and the German MRL of 30 ppm being higher than the maximum residue values from the other two submitted field trial data sets having similar application rates, but longer PHIs (21 and 28 day), HED recommends establishing a permanent tolerance for spirodiclofen on hops at 30 ppm to promote free trade between North-American Free Trade Agreement (NAFTA) and non-NAFTA countries.

Magnitude of the Residue - Livestock: As there are no livestock feedstuffs associated with the proposed use on hops, data requirements pertaining to meat, milk, poultry, and eggs are not relevant to this tolerance petition.

Analytical Enforcement Method : Samples from the U.S. hops field trials were analyzed for residues of spirodiclofen using a liquid chromatography (LC)/mass spectrometry (MS)/MS method, which was derived from the proposed enforcement method. The proposed enforcement method has undergone a successful independent laboratory validation (ILV) trial, and has been reviewed by the Analytical Chemistry Branch (ACB). ACB determined that the method would be adequate for tolerance enforcement provided that a revised copy of the method was submitted incorporating the changes and clarifications recommended by ACB (D308566, E. Kolbe, 5/18/05).

The LC/MS/MS method used for determining residues of spirodiclofen in/on dried hops in the field trials was adequately validated prior to and in conjunction with the analysis of field trial samples. Given the similarity between the data collection method and the LC/MS/MS enforcement method (nutmeats), the enforcement method will be adequate for regulating residues in/on dried hops.

Hop, dried cones[1] .....30 ppm

[1] Tolerance expression includes residues of spirodiclofen (3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutanoate) *per se*.

5.1.2 Dietary Exposure and Risk

Dietary (food + water) chronic and cancer dietary risk assessments for spirodiclofen were conducted using the DEEM-FCID (ver. 2.03).

DEEM-FCID uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII; 1994-1996 and 1998). Acute dietary risk assessment was not conducted since an appropriate endpoint attributable to a single dose was not identified for U.S. general population and its population subgroups.

The chronic and cancer analyses incorporated average field trial residues, experimental and DEEM default processing factors, and projected average %CT information and EDWCs.

The EDWCs for spirodiclofen and its three metabolites (spirodiclofen-enol, spirodiclofen-ketohydroxy and spirodiclofen-dihydroxy) were computed using PRZM/EXAMS model. Application rates ranged from 0.53 to 0.28 lbs. ai/Acre, depending on crop. Tier II surface water modeling of Florida citrus scenario using the index reservoir with the default percent cropped area (PCA=0.87) predicts the 1-in-10-year annual average concentration (non-cancer chronic) and 30-year annual average concentration (cancer) of spirodiclofen residues is not likely to exceed 4.99 and 1.67 µg/L, respectively.

For chronic dietary risk assessments, HED is concerned when dietary risk exceeds 100% of cPAD.

The results are summarized in Tables 5.1.2.1 and 5.1.2.2 below for chronic and cancer dietary analyses, respectively.

The resulting chronic (food + water) exposure estimates were not of concern to HED (<100% of the cPAD) for U.S. general population (1.8 % cPAD) and all population sub-groups; the most highly exposed population subgroup was all infants (<1 year old) at 3.2% cPAD.

The cancer risk estimates for the U.S. general population with and without drinking water were 3 x 10^{-6} and 2 x 10^{-6}, respectively, and are not of concern. HED also notes that the cancer risk estimates were generated using average residues derived from crop field trial studies (maximum application rate and minimum PHI), incorporated maximum theoretical processing factors for juice, and incorporated surface drinking water estimates which assumed 87% of the basin was cropped and 100% of the cropped area was treated at the maximum rate. Based on a critical commodity analysis conducted in DEEM-FCID™, the major contributors to the cancer risk were hops (41% of the total exposure), water (19% of the total exposure), and orange juice (17% of the total exposure).

Table 5.1.2.1. Summary of Chronic Dietary Exposure and Risk for Spirodiclofen (drinking water included).

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
General U.S. Population	0.014	0.000253	1.8
All Infants (< 1 year old)		0.000452	**3.2**
Children 1-2 years old		0.000424	3.0
Children 3-5 years old		0.000345	2.5
Children 6-12 years old		0.000210	1.5
Youth 13-19 years old		0.000160	1.1
Females 13-49 years old		0.000197	1.4
Adults 20-49 years old		0.000280	2.0
Adults 50+ years old		0.000211	1.5

The bolded %cPAD is the highest.

Table 5.1.2.2. Summary of Cancer Dietary Exposure and Risk for Spirodiclofen.

Population Subgroup	Q_1*	Exposure (mg/kg/day)	Risk
With drinking water			
General U.S. Population	0.0149	0.000183	3 x 10^{-6}
without drinking water			
General U.S. Population	0.0149	0.000148	2 x 10^{-6}

5.2 Residential (Non-Occupational) Exposure/Risk Pathway

Spirodiclofen has no existing or proposed residential or recreational uses. Therefore, a residential or recreational risk assessment was not performed.

5.3 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for spirodiclofen. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift

management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT™ computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

6.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

For spirodiclofen, no residential uses are proposed. Therefore, aggregate risk consists of exposure from food and drinking water sources. Since an effect of concern attributable to a single dose was not identified in the database, acute aggregate risk was not addressed. Chronic and cancer aggregate risks were calculated and are discussed in detail below.

Drinking water quality model output concentrations were incorporated directly into dietary risk assessments.

6.1 Acute Aggregate Risk

Since an effect of concern attributable to a single dose was not identified in the hazard database, acute aggregate risk was not calculated. Therefore, an acute aggregate risk assessment was not performed.

6.2 Short-Term Aggregate Risk

Since there are no existing or proposed residential uses for spirodiclofen, short-term aggregate risk was not performed.

6.3 Intermediate-Term Aggregate Risk

Since there are no existing or proposed residential uses for spirodiclofen, intermediate-term aggregate risk was not performed.

6.4 Chronic Aggregate Risk

Since there are no residential uses, chronic aggregate risk consists of food and drinking water exposure only. Chronic dietary risk is presented in Table 5.1.2.1 and represents chronic aggregate risk. Drinking water estimates were incorporated directly into the dietary analysis. The

chronic analyses incorporated average field trial residues, experimental and DEEM default processing factors, and projected average %CT estimates and surface drinking water estimates using PRZM/EXAMS model. The DEEM-FCID™ chronic aggregate risk estimates (including drinking water) were not of concern to HED [≤3.2% cPAD; all infants (<1 year old) were the most highly exposed population].

6.5 Aggregate Cancer Risk

Since there are no residential uses, aggregate cancer risk consists of food and drinking water exposure only. Dietary cancer risk is presented in Table 5.1.2.2 and represents aggregate cancer risk. Cancer aggregate risk was calculated for the U.S. population only. Drinking water estimates were incorporated directly into the dietary analysis. The cancer analyses incorporated average field trial residues, experimental and DEEM default processing factors, and projected average %CT estimates and surface drinking water estimates using PRZM/EXAMS model. The cancer risk estimate (food + water) for the U.S. population was 3×10^{-6} for the general U.S. population, and is not of concern to HED.

7.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to spirodiclofen and any other substances and spirodiclofen does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that spirodiclofen has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Exposure/Risk Pathway

Spirodiclofen is to be applied to hops once per crop season by airblast equipment. It may not be applied aerially or through any type of irrigation equipment or in any type of enclosed structures such as green houses or plant houses.

The use pattern summary is taken from proposed draft labeling for Envidor® 2 SC Miticide (EPA Reg. No. 264-831). Envidor® is formulated as a liquid soluble concentrate and contains 2.0 lb active ingredient (ai) (22.3 %) spirodiclofen per gallon. The target pests on hops are twospotted spider mites.

The rate of application to hops is 18.0-24.7 fl oz formulation/A (0.28-0.39 lb ai/A). It is to be applied in a minimum of 50 gallons of spray per acre in conventional ground airblast sprayer. The PHI is 14 days. The REI is 12 hours.

8.1 Short- and Intermediate-term Occupational Handler Risk

Based upon the proposed use pattern, HED believes the most highly exposed occupational pesticide handlers (i.e., mixers, loaders, applicators) will be mixer/loaders using liquid, open pour technique and applicators using open-cab, air-blast equipment.

With a single application on proposed labels, commercial and private (i.e., grower operators) pesticide handlers are typically expected to be exposed over the short-term duration (i.e., 1-30 days). The acreage involved with hops using an airblast sprayer (40 acres/day) is relatively small as compared to high acreage field crops such as cotton, corn or soybeans (more than 1000 acres/day with aerial application).

No chemical-specific data are available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in PHED (v. 1.1, 1998).

For pesticide handlers, it is HED policy to present estimates of dermal exposure for "baseline;" that is, with a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks and no protective gloves as well as "baseline" **and the use of** protective gloves or other PPE as might be necessary. The proposed Envidor® label directs mixers, loaders and other handlers to wear a long-sleeved shirt and long pants, waterproof gloves and shoes plus socks.

Table 8.1. Spirodiclofen Handler Risk for Proposed Use on Hops.

Unit Exposure[1] mg ai/lb handled	Applic. Rate[2] lb ai/A	Units Treated[3] Acres Per Day	Average Daily Dose[4] mg ai/kg bw/day	Combined MOE[5]
Mixer/Loader - Liquid - Open Pour for Airblast Application				
Dermal: SLNG 2.9 SLWG 0.023 Inhal 0.0012	0.39	40	Dermal: No Gloves 0.013 With Gloves 0.000103 Inhal 0.00027	No Gloves 630 With Gloves 23,000
Applicator - Air-blast - Open Cab				
Dermal: SLNG 0.36 SLWG 0.24 Inhal 0.0045	0.39	40	Dermal: NG 0.0016 WG 0.00107 Inhal 0.001	No Gloves 3,200 With Gloves 4,100

1. Unit Exposures are taken from "PHED Surrogate Exposure Guide", from The Pesticide Handler Exposure Database Version 1.1, August 1998. Dermal: SLNG = Single layer of work clothing with no gloves; SLWG = Single layer of work clothing with gloves; Inhal. = Inhalation.
2. Application Rate. = Taken from proposed Envidor® 2 SC label.
3. Units Treated are taken from ExpoSAC SOP No. 9.1; 5/7/2000.
4. Average Daily Dose (ADD) = Unit Exposure * Applic. Rate * Units Treated * Absorption Factor (2% dermal; 100 % inhalation) ÷ Body Weight (70 kg).
5. MOE = LOAEL ÷ ADD. In this case, dermal exposure and inhalation exposures are combined (summed) since the dose and endpoint for these risk assessments are from the same study. The LOAEL is 8.4 mg ai/kg bw/day for (short-term duration exposures).

A MOE of 300 is adequate to protect occupational pesticide handlers. All MOEs are above 300; therefore, the proposed use is not of concern.

8.2 Short- and Intermediate-term Post-Application Risk

Post-application exposure is assumed to consist of dermal exposure only; inhalation exposure is assumed to be negligible.

Typically, there are possibilities for agricultural workers to experience post-application exposures to pesticides. In this case, there were no compound specific data with which to estimate post-application exposures to agricultural workers. Assumptions regarding transfer of residues were obtained in the Science Advisory Council for Exposure (ExpoSAC) SOP 003.1 (Revised 7 August 2000) and amended by "ExpoSAC meeting Notes - 9/13/01″). The SOP lists a number of possible post-application agricultural activities relative to the proposed use on hops that might result in post-application or "re-entry" exposure.

Post-application activities in hops include training vines, scouting, stripping vines and harvesting. However, hops are typically mechanically harvested. In addition, there is a 14 day PHI. Therefore, HED believes harvesting is not likely to result in the highest dermal post-application exposures. However, training vines with a TC of 2,000 cm^2/hr was used as it is the highest TC identified for any post-application activity in hops.

Post-application, re-entry exposure may be estimated using the following convention.
$PDR_t = DFR_t * CF1 * TC * ET$ where:

PDR_t = potential dose rate on day "t" (mg/day)
DFR_t = dislodgeable foliar residue on day "t" (ug/cm^2)
CF1 = weighted unit conversion factor changing µg to mg (0.001 mg/µg)
TC = transfer coefficient (cm^2/hr) (2,000 cm²/hr)
ET = Exposure Time (hr/day)

where
$DFR_t = (AR * F) * (1 - D)^t * CF2 * CF3$ where:

AR = application rate (lb ai/ft^2 or lb ai/Acre) (0.39 lb ai/A)
F = fraction of ai retained on foliage (unitless = 20%)
D = fraction of residue that dissipates daily (unitless) (10%)
t = post-application day on which exposure is being assessed
CF2= conversion factor lb ai to µg for DFR (4.54×10^8 µg/lb)
CF3 = conversion factor to convert surface area units (ft^2) in application rate to cm^2 for DFR value (1.08×10^{-3} ft^2/cm^2 or 2.47×10^{-8} acre/cm^2 if rate is per acre).

In this case, the DFR_t is calculated as:

$0.39 \text{ lb ai/A} * 0.2 * (1 - D)^0 * 4.54 \times 10^8 \text{ µg/lb} * 2.47 \times 10^{-8} \text{A/cm}^2 = 0.87 \text{ µg ai/cm}^2$ and

$PDR_t = 0.87 \text{ µg ai/cm}^2 * 0.001 \text{ mg/µg} * 2{,}000 \text{ cm}^2\text{/hr} * 8 \text{ hr/day} = 14 \text{ mg/day}.$

14 mg/day * 0.02 (% dermal absorption) ÷ 70 kg bw = 0.0039 mg ai/kg bw/day.

MOE = NOAEL ÷ Dose; therefore: $\frac{8.4 \text{ mg ai/kg bw/day}}{0.0039 \text{ mg ai/kg bw/day}}$ =

MOE = 2,200

A MOE of at least 300 is not of concern for agricultural workers. Since the calculated MOE is above 300, the proposed use is not of concern.

8.3 Occupational Handler and Post-Application Cancer Risk

There are no definitive data regarding the numbers of exposures per year or numbers of years "worked" per lifetime of pesticide handlers or of agricultural workers. Therefore, HED calculated risk for handlers and post-application workers assuming 10 and 30 days of exposure per year over a 35-year "working" lifetime and a 70-year lifespan. As can be seen below in Tables 8.3.1 and 8.3.2, risks are not of concern even for 30 days of exposure per year.

An estimate of cancer risk is calculated by multiplying the Q_1^* value by a Lifetime Average Daily Dose (LADD). The LADD is calculated using the following convention:

$$\frac{(\text{Average Daily Dose (mg ai/kg bw/day } [\textit{dermal} + \textit{inhalation}]) * 10 \text{ day/yr} * 35 \text{ year}}{70 \text{ year} * 365 \text{ day/yr}}$$

The ADD is taken from Table 8.1 for occupational handlers and from the post-application discussion in Section 8.2 for agricultural workers. A sample calculation for a mixer/loader using protective gloves is as follows:

$$\frac{(0.000103 \text{ mg ai/kg bw/day}_{\text{dermal}} + 0.00027 \text{ mg ai/kg bw/day}_{\text{inhalation}}) * 10 \text{ day/yr} * 35 \text{ yr}}{70 \text{ year} * 365 \text{ day/yr}}$$

5.1×10^{-6} mg ai/kg bw/day.

Cancer risk is calculated by Q_1^* * LADD and in the example

1.49×10^{-2} mg ai/kg bw/day * $5.1 \times 10^{-6} = 7.6 \times 10^{-8}$.

See Table 8.3.1 and 8.3.2 below for a summary of cancer risks assuming 10 and 30 work days per year.

Table 8.3.1. Handler and Post-Application Cancer Risks From Exposure to Spirodiclofen Assuming 10 work days per year.		
Lifetime Average Daily Dose (mg ai/kg bw/day)	**Q_1^*** (mg ai/kg bw/day)	
Mixer/loader Using Gloves 5.1×10^{-6}	1.49×10^{-2}	7.6×10^{-8}
Airblast Applicator Using Gloves 2.8×10^{-5}		4.2×10^{-7}
Airblast Applicator Not Using Gloves 3.6×10^{-5}		5.4×10^{-7}
Hops Training vines 5.3×10^{-5}		8.0×10^{-7}

Table 8.3.2. Handler and Post-Application Cancer Risks From Exposure to Spirodiclofen Assuming 30 work days per year.		
Lifetime Average Daily Dose (mg ai/kg bw/day)	**Q_1^*** (mg ai/kg bw/day)	
Mixer/loader Using Gloves 1.5×10^{-5}	1.49×10^{-2}	2.0×10^{-7}
Airblast Applicator Using Gloves 8.5×10^{-5}		1.2×10^{-6}
Airblast Applicator Not Using Gloves 1.2×10^{-4}		1.5×10^{-6}
Hops Training vines 8.4×10^{-4}		1.2×10^{-5}

Since the estimated cancer risks are below 10^{-5} for all scenarios, HED does not have a concern for the proposed use on hops.

REI

Spirodiclofen is classified in Acute Toxicity Category III for acute oral and acute dermal toxicity and Acute Toxicity Category IV for acute inhalation, primary eye irritation and primary skin irritation. It is a dermal sensitizer. The interim Worker Protection Standard (WPS) REI of 12 hours is adequate to protect workers training hops vines after treatment. The proposed labels are in compliance with the WPS REI.

9.0 Data Needs and Label Requirements

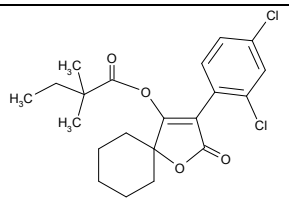
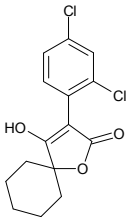
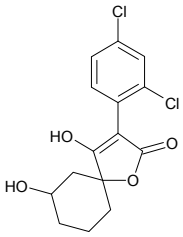
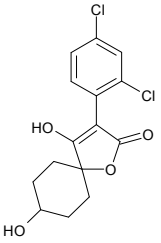
Toxicology

The toxicological database for spirodiclofen is complete. The HED HIARC requested a 28-day inhalation toxicity study as a condition of registration. However, based on the low volatility and low inhalation toxicity (Category IV) of spirodiclofen and inhalation MOEs of at least 1000 for the proposed handler uses, spirodiclofen qualifies for a waiver of the 28-day inhalation toxicity

study for the proposed uses (HED SOP 2002.01: *Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*, 08/15/02). **The requirement for the 28-day inhalation toxicity study is waived for this action only.** If in the future, requests for new uses or formulations are submitted that may result in a significant change in either the toxicity profile or exposure scenarios, HED will reconsider this data requirement.

Attachments follow (2)
Attachment 1: Chemical Names and Structures of Spirodiclofen and its Metabolites
Attachment 2: Toxicity Profile for Spirodiclofen

Attachment 1: Chemical Names and Structures of Spirodiclofen and its Metabolites

Chemical Name	Structure
Spirodiclofen; BAJ2740 3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4,5]dec-3-en-4-yl 2,2-dimethylbutanoate	
BAJ 2510 3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one	
3-OH-enol 3-OH-enol spirodiclofen	
4-OH-enol 4-OH-enol spirodiclofen	

Attachment 2: Toxicity Profile for Spirodiclofen

Subchronic, Chronic and Other Toxicity Profile for Spirodiclofen

Guideline No./ Study Type/	MRID Nos. Doses/Classification	Results
870.3100 Subchronic Oral - Rat	45696715, 45696716 (1998,2003) (0,100,500,2500,12500 ppm) M:0,6.6,32.1,166.9,851.4 mg/kg/day F:0,8.1,47.1 215.3995.8 mg/kg/day Acceptable/guideline	For males, NOAEL = 32.1 mg/kg/day, LOAEL = 166.9 mg/kg/day based on increased incidence and severity of small cytoplasmic vacuolation in the cortex of adrenal glands, decreased cholesterol (week 5 and 13), and decreased triglycerides (week 5). For females, NOAEL= 8.1 mg/kg/day, LOAEL= 47.1 mg/kg/day based on increased incidence of small cytoplasmic vacuolation in the cortex of adrenal glands.
870.3100 Subchronic Oral - Mouse	45696711,45696712,45696713(1997) (0,100,1000,10,000 ppm) M:0,15,164,1640 mg/kg/day F: 0,30,234,2685 mg/kg/day Acceptable/guideline	For males, NOAEL= 15 mg/kg/day, LOAEL= 164 mg/kg/day based on an increased incidence of hypertrophic Leydig cells in the testes. For females, NOAEL = 30 mg/kg/day, LOAEL= 234mg/kg/day based on an increased incidence of cytoplasmic vacuolation of the adrenal cortex.
870.3150 Subchronic Oral - Dog	45696803,45696804 (2000) (0,200,630,2000 ppm) 0,7.7,26.6,84.7 mg/kg/day (M) 0,8.4,28.0,81.0 mg/kg/day(F) Acceptable/guideline	For males, NOAEL= 7.7 mg/kg/day, LOAEL = 26.6 mg/kg/day based on decreased body-weight gains, increased liver and adrenal weights, decreased prostate weights, and histopathology findings in the adrenal glands, testes, epididymis, thymus, and prostates. For females, NOAEL ≤8.4 mg/kg/day. LOAEL=8.4 mg/kg/day based on increased adrenal gland weight (two out of four animals) which coincided with histopathology findings (cytoplasmic vacuoles in the Zona fasciculata of the adrenal glands).
870.3200 28-Day dermal toxicity - Rat	45696806 (1999) 0, 1000 mg/kg/day Unacceptable/Guideline	The NOAEL=1000 mg/kg/day (HDT; highest dose tested); however, the histopathology was not appropriately conducted as required by the guideline. The study did not examine all of the tissues, especially the possible target organs (i.e., uterus, prostate, etc).
870.3700a Prenatal developmental - Rat	45696906 (2000) 0,100,300,1000 mg/kg/day Acceptable/Guideline	Maternal: NOAEL =1000 mg/kg/day (HDT) Developmental:NOAEL= 300 mg/kg/day, LOAEL =1000 mg/kg/day based on an increased incidence of slight dilatation of the renal pelvis.
870.3700b Prenatal developmental - Rabbit	45696714 (1998) 0,100,300,1000 mg/kg/day Acceptable/guideline	Maternal: NOAEL = 100 mg/kg/day, LOAEL =300 mg/kg/day based on body-weight loss and decreased food consumption. Developmental: NOAEL =1000 mg/kg/day (HDT)
870.3800	45696802,45696709 (2000)	**Parental/system:**

Guideline No./ Study Type/	MRID Nos. Doses/Classification	Results
Reproduction and fertility effects - Rat	(0,70,350,1750 ppm) M: 0,5.2,26.2,134.8 mg/kg/day F: 0,5.5,27.6,139.2 mg/kg/day Acceptable/guideline	For males: NOAEL= 5.2-6.4 mg/kg/day, LOAEL =26.2-30.2 mg/kg/day based on decreased body weight in F_0 males; decreased absolute and relative liver weight in F_0 males; decreased cholesterol and triglycerides in F_1 males; and increased severity of adrenal cortical vacuolation in F_1 males. For females, NOAEL= 5.5-7.0 mg/kg/day, LOAEL= 27.6-34.4 mg/kg/day based on decreased unesterified fatty acids in F_1 females, and increased severity of adrenal cortical vacuolation in F_0 and F_1 females. **Reproductive**: For males: NOAEL= 26.2-30.2 mg/kg/day, LOAEL=134.8-177.6 mg/kg/day based on delayed sexual maturation; decreased testicular spermatid and epididymal sperm counts (oligospermia); and atrophy of the testes, epididymides, prostate and seminal vesicles. For females: NOAEL= 27.6-34.4 mg/kg/day, LOAEL= 139.2-192.7 mg/kg/day based on increased severity of ovarian luteal cell vacuolation/ degeneration. **Offspring**: NOAEL= 5.2-6.4 (M)/5.5-7.0 (F) mg/kg/day, LOAEL= 26.2-30.2 (M)/ 27.6-34.4(F) mg/kg/day based on decreased body weight and weight gain in F_1 male and female pups.
870.4300 Chronic toxicity -Rat	45696808,45696809 (2000) (0,50,100,350,2500 ppm) M: 0,2.0,4.1,14.7,110.1 mg/kg/day F: 0,2.9,5.9,19.9,152.9 mg/kg/day Acceptable/guideline	For males: NOAEL= 14.7 mg/kg/day, LOAEL= 110.1 mg/kg/day based on decreased body weights, decreased body-weight gain, increased APh levels, decreased cholesterol and triglyceride levels, increased vacuolated jejunum enterocytes, and increased incidences of Leydig cell hyperplasia. For females: NOAEL= 19.9 mg/kg/day, LOAEL= 152.9 mg/kg/day based on decreased body weights, decreased body-weight gain, increased APh levels, increased TSH, uterus nodules, and increased vacuolated jejunum enterocytes. **↑testes Leydig cell adenoma in males, ↑uterine adenoma and/or adenocarcinoma in females.**
870.4100b Chronic toxicity - dog	45696810,45696811 (2001) (0,20,50,150,500/600 ppm) M: 0,0.56,1.38,4.33,16.1 mg/kg/day F: 0,0.59,1.52,4.74,17.7 mg/kg/day Acceptable/guideline	NOAEL= 1.38 (M)/1.52(F) mg/kg/day, LOAEL= 4.33(M)/4.74 (F) mg/kg/day based on increased relative adrenal weights in both sexes, increased relative testis weight in males and histopathology findings in the adrenal gland of both sexes.
870.4200b Carcinogenicity - mouse	45696724 (2000) (0,25,3500,7000 ppm) M: 0,4.1,610,1216 mg/kg/day F: 0,5.1,722,1495 mg/kg/day Acceptable/guideline	NOAEL= 4.1(M)/5.1(F) mg/kg/day, LOAEL= 610 (M) mg/kg/day based on increased absolute and relative liver and adrenal weights, decreased absolute and relative kidney weight, enlarged adrenal gland, discolored testis, adrenal gland vacuolization, interstitial cell degeneration of the testes. For females, LOAEL= 722 mg/kg/day based on increased absolute and relative adrenal weight, decreased absolute and relative kidney weight, increased incidences of adrenal gland pigmentation, and adrenal vacuolization.

Guideline No./ Study Type/	MRID Nos. Doses/Classification	Results
		↑Hepatocellular adenoma and carcinoma.
870.5100 Gene mutation Salmonella typhimurium	45696702 Acceptable/guideline	There was no evidence of increased revertant colonies above control in 5 Salmonella strains (TA1535, TA1537, TA1538, TA100, TA98) ± S9 at concentrations up to 5000 µg/plate.
870.5300 In vitro Mammalian Cell Gene Mutation	45696614 Acceptable/guideline	Negative, tested in Chinese Hamster lung fibroblast V79 cells at concentrations up to 300 ug/mL -S9 and +S9. Cytotoxicity was observed at ≥15 ug/mL -S9 and 80 ug/mL +S9.
870.5375 In vitro Mammalian Chromosome Aberration	45696615 (1996) Acceptable/guideline	Negative, tested in Chinese hamster lung (V79) cells at concentrations 5-80 ug/mL or 0.75-12 ug/mL -S9 or 10-160 ug/mL +S9.
870.5395 In vivo Mouse Bone Morrow Micronucleus	45696701 (1996) Acceptable/guideline	Negative, tested at a dose 800 mg/kg (MTD). Clinical signs and cytotoxicity were seen at 800 mg/kg.
870.6200 Acute Neurotoxicity - Rat	45696725 (2000) 0,200,500,2000 mg/kg Acceptable/guideline	NOAEL = 2000 mg/kg/day, no neurotoxicity observed.
870.6200 Subchronic neurotoxicity - Rat	45696726 (2001) (0,100,1000,12500 ppm) M: 0,7.2,70.3,1088.8 mg/kg/day F: 0,9.1,87.3,1306.5 mg/kg/day Acceptable/guideline	NOAEL= 70.3(M)/87.3(F) mg/kg/day. LOAEL= 1088.8(M)/ 1306.5(F) mg/kg/day based on decreased body weights, food consumption, and increased urine staining in both sexes and decreased motor and locomotor activity (week 4) in females only.
870.6300 Developmental neurotoxicity	46324901 (2004) (0, 70, 350 or 1500 ppm) 0/0, 6.5/14.0, 32.1/69.7 or 135.9/273.8 mg/kg/day (gestation/lactation) The study classification is reserved for the guideline requirement pending receipt of additional morphometric measurements for the low and mid dose groups.	Maternal NOAEL = 135.9/273.8 mg/kg/day LOAEL = Not established. Offspring NOAEL = Not established LOAEL = 6.5/14.0 mg/kg/day based on effects in memory phase of the water maze test in PND 60 females.
870.6300 Developmental neurotoxicity	47166501 (2007) (0, 70, 350 or 1500 ppm) 0/0, 5.4/13.0, 28.6/65.7 and 119.2/262.1 mg/kg/day (gestation/lactation)	Maternal NOAEL=119.2/262.1 mg/kg/day LOAEL= Not established Offspring NOAEL = 119.2/262.1 mg/kg/day LOAEL= Not established