UNITED STAES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: APRIL 16, 2007

SUBJECT: **Diflubenzuron. Human Health Risk Assessment for the Proposed Establishment of an Emergency Exemption Tolerance for Use in/on Lemons.**

Petition #	07CA04	PC Code:	108201
DP #:	336813	Class:	Insecticide
Decision #:	374651	40 CFR:	§180.377

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Under provisions in Section 18 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, the State of California has requested the quarantine use of diflubenzuron to eradicate *Diaprepes* weevils over a 42 acre outbreak site on commercial and residential plantings (including containerized nursery stock) of citrus fruits including grapefruit (pummelos and related cultivars or hybrids), avocados (including black sapote, canistel, mamey sapote, mango, papaya, sapodilla and star apple), guavas (including feijoa, jaboticaba, wax jambu, starfruit, passion fruit and acerola), lychee (including longan, Spanish lime, rambutan, and pulasan) that have been quarantined. Although diflubenzuron will be used at the above mentioned crop sites, for purposes of this risk assessment, only lemon residues will be addressed. According to the applicant, lemons are the only proposed commodity undergoing treatment that has the potential to enter into inter-state commerce. The remaining sites will be confined to residential areas and none of these food items will enter commerce. The California Department of Food and Agriculture (CDFA) is leading this eradication program and will be stripping the fruit off the tropical and sub-tropical plants post-application. However, due to the nature of the plant, residential plantings of avocados are too prolific for stripping. A residue value of 0.8 ppm will be applied in this assessment for avocados for those potential residues. The EPA strongly urges stripping of all fruit but lemons and avocados from the treated areas. Homeowner consumption, and therefore residues, of treated avocados is not regulated by the Federal Food, Drug and Cosmetic Act.

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1.0 EXECUTIVE SUMMARY

A petition has been submitted by the State of California, with support from Chemtura USA Corporation, for the establishment of a Section 18 Emergency Exemption tolerance for the insecticide/acaricide diflubenzuron (*N*-[((4-chlorophenyl)amino) carbonyl]-2,6-difluorobenzimide) in/on lemons (PP# 07CA04). Diflubenzuron acts as a chitin inhibitor to suppress the growth of many leaf-eating larvae, mosquito larvae, aquatic midges, rust mite, boll weevil, and flies. The proposed end-use product for this risk assessment is Dimilin® 2L, EPA Reg. No. 400-461. The product is to be tank mixed with spray oils which are exempt from tolerances but not specifically labeled for the proposed use. These proposed spray oils are: Superior 415 Spray Oil, EPA Reg. No. 2935-542; Britz 415 Supreme Spray Oil, EPA Reg. No. 10951-15; and Spray Oil 415, EPA Reg. No. 34704-727. According to California's request, efficacy data indicates that the addition of the spray oil can enhance the efficacy of the diflubenzuron. Eggs laid on oil treated leaves can fall off, further enhancing the efficacy of the treatment.

Tolerances for residues of diflubenzuron are established under 40CFR §180.377. Tolerances listed in 40 CFR §180.377(a)(1) are expressed in terms of diflubenzuron *per se*. Under this section, current tolerances range from 0.05 ppm in/on eggs; milk; fat and meat of cattle, goat, hog, horse, poultry, and sheep; poultry meat byproducts to 6.0 ppm in globe artichoke.

Tolerances listed in 40 CFR §180.377(a)(2) are expressed in terms of the combined residues of diflubenzuron and its metabolites 4-chlorophenylurea (CPU) and 4-chloroaniline (PCA). Under this section, current tolerances range from 0.02 ppm in/on rice grain to 55 ppm in peanut hay.

Time-limited tolerances listed in 40 CFR §180.377(b) are expressed in terms of the combined residues of diflubenzuron and its metabolites CPU and PCA, expressed as the parent diflubenzuron, in connection with use of the pesticide under Section 18 Emergency Exemptions granted by EPA. Under this section, current tolerances range from 0.10 ppm in/on wheat milled byproducts to 30 ppm in wheat aspirated grain fractions

The most recent human health risk assessment for diflubenzuron was conducted in conjunction with an Interregional Research Project No. 4 (IR-4) request for the establishment of permanent tolerances for residues of diflubenzuron in/on barley, oats, wheat, *Brassica* leafy greens (Crop Subgroup 5B), turnip greens, eggplant, okra, peanut, and pummelo (G. Kramer, DP #s: 321152, 321155, & 321158, 09/14/2006).

Under PP#07CA4, the State of California requests the establishment of tolerances for the combined residues of diflubenzuron and its metabolites CPU and PCA in/on the following raw agricultural commodities (RACs):

Lemons……..0.8 ppm

Also, due to the nature of the plant, residential plantings of avocados are too prolific for stripping. A residue value of 0.8 ppm will be applied in this assessment for avocados for those potential residues.

Human Health Risk Assessment

Toxicology/Hazard

The acute oral, dermal and inhalation toxicity of diflubenzuron is low. It is a mild eye irritant and not a skin irritant in laboratory animals. It is negative for sensitization in the guinea pig. In subchronic and chronic feeding studies, the primary endpoint of concern, produced most likely by PCA, was methemoglobinemia and/or sulfhemoglobinemia. These effects were evident in both sexes of mice, rats, and dogs and were produced by more than one route of administration in rats [i.e., oral, dermal and inhalation]. The general consequence of methemoglobinemia and/or sulfhemoglobinemia is the impairment of the oxygen transportation capacity of the blood, which is generally known to be caused by aromatic amines in both humans and animals.

The overall toxicology database is sufficient for a determination of potential hazard to infants and children. The data provide no indication of an increased susceptibility to rats or to rabbits from *in utero* or post-natal exposure to diflubenzuron.

Dose Response Assessment

On April 21, 1998 HED's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database, selected doses and endpoints for chronic dietary exposures as well as occupational and residential exposure scenarios [short-, intermediate-, and long-term exposure (dermal and inhalation)], assessed the carcinogenic potential and addressed the sensitivity of infants and children from exposure to diflubenzuron as required by the Food Quality Protection Act (FQPA) of 1996. On August 14, 2001, the HIARC revisited diflubenzuron and selected the 21-day dermal toxicity study in rats for short-term dermal exposure to be consistent with the current policy for 1- to 30-day duration. On February 12, 2002, the HIARC revisited diflubenzuron and selected the 28-day inhalation toxicity study in rats for short-, and intermediate-term inhalation exposure and reduced the uncertainty factor (UF) from 3x to 1x, since the selected study has a no-observed-adverse-effect level (NOAEL).

FQPA Assessment

The FQPA Safety Factor Committee (SFC) recommended that the FQPA safety factor used in human health risk assessments (as required by FQPA of August 3, 1996) be reduced to 1x in assessing the risk posed by this chemical (B. Tarplee, HED Document Number 012630, 06/14/1998). Consequently, the current chronic reference dose

(cRfD) and chronic population adjusted dose (cPAD) values are equivalent (0.02 mg/kg/day). This decision was based on the following: 1) there is no indication of increased susceptibility of rats or rabbits to *in utero* or postnatal exposure; 2) a developmental neurotoxicity study (DNT) with diflubenzuron is not required; 3) food and drinking water exposure assessments will not underestimate the potential exposure for infants and children; and 4) there are currently no registered or proposed residential (non-occupational) uses of diflubenzuron.

Dietary Exposure (Food/Water)

Residue Chemistry and Risk

Treatment will be limited to an area of 42 acres in Los Angeles, Orange and San Diego counties in California. The product will be applied as a foliar spray at the rate of 0.275 lb ai. per acre (in 50-1000 gallons per acre with 0.5% oil added) by ground or air and not expected to exceed a total of 158 lbs. of product (34.7 lbs. ai.) for the first year of treatment.

A residue study (MRID 45333601) was submitted but not formally reviewed for this action. The results from the field trials show that residues of diflubenzuron in lime samples were 0.151-0.172 ppm while residues in lemons were 0.245-0.551 ppm in samples harvested 21 days following the last application of a total rate of 15 oz. ai./A.

Below are the summarized findings from the previous 2006 risk assessment.

The qualitative nature of the residue in plants and fungi is adequately understood based on data from citrus, mushroom, rice, and soybean metabolism studies. The metabolism of diflubenzuron in crops tested is similar, and the radioactive components are also similar to those found in soil. The nature of the residue in livestock is also adequately understood based on acceptable poultry and ruminant metabolism studies reflecting oral dosing. The HED Metabolism Assessment Review Committee (MARC) has concluded that the residues of concern in plants, livestock, and fungi, for the purpose of tolerance expression, are diflubenzuron and its metabolites PCA and CPU.

There are adequate enforcement methods, published in the Pesticide Analytical Manual (PAM, Vol. II), for determining diflubenzuron residues of concern. In addition, a new analytical methodology for plant commodities was successfully validated by an independent laboratory as well as by Agency chemists at the Analytical Chemistry Branch (ACB)/Biological and Economics Analysis Division (BEAD) in conjunction with the approved rice petition. These methods can separately determine residues of diflubenzuron by gas chromatography/electron-capture detection (GC/ECD), CPU by GC/ECD, and PCA by GC/mass spectrometry (MS).

Water Exposure and Risk

The Environmental Fate and Effects Division (EFED) previously provided a drinking water assessment (A. Al-Mudallal, DP #: 321156, 08/25/2006). Because monitoring data were unavailable, estimates of diflubenzuron and the major degradate CPU concentrations were made only with mathematical models. The Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) models with IR scenarios and percent crop area adjustment factors were used to conduct surface water exposure assessments. Screening Concentration in Ground Water (SCIGROW) was used for groundwater. Estimated Drinking Water Concentrations (EDWCs) were generated for the total toxic residue which includes parent diflubenzuron and the major degradate CPU. The highest estimated surface water concentrations occurred with the PA pear scenario. For chronic assessments the EDWC is 2.76 ppb; this was the value used in this assessment. The groundwater estimate from SCIGROW is 0.208 ppb. This scenario presents the most conservative surface water concentration due to use of diflubenzuron, including the proposed lemon use.

Acute and Chronic Dietary Exposure Results and Characterization

No toxic effects attributable to a single (i.e., acute) exposure to diflubenzuron have been identified; therefore, an acute reference dose (aRfD) has not been established for diflubenzuron and an acute dietary exposure assessment has not been conducted.

The Tier 1 chronic dietary risk assessment for diflubenzuron was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03). The highest chronic drinking water concentration of 2.76 ppb was used in this analysis. The assessment was based on the assumption of recommended tolerance-level residues, 100% crop treated (%CT) and that DEEM default processing factors were used for some commodities. The results of the analysis indicate that chronic risk from the dietary (food + drinking water) exposure to diflubenzuron will not exceed HED's level of concern for the general U.S. population and all population subgroups.

Residential Exposure/Risks

Although there are no registered homeowner uses, there are registered uses for professional applications to outdoor residential and recreational areas to control mosquitoes, moths, and other insects. However, the potential for post-application residential exposure is expected to be limited. Due to the low dermal absorption rate (0.5%) of diflubenzuron and since the state is conducting a substantial homeowner outreach/education program, minimal bystander contact is expected.

Aggregate Exposure/Risks

Short-, intermediate-, and long-term aggregate-risk assessments were not performed because there are no registered or proposed uses of diflubenzuron which result in

residential exposures. Acute and cancer aggregate-risk assessments were not performed because no appropriate endpoint was available to determine the aRfD for the general population or any population subgroup and diflubenzuron is not carcinogenic.

Chronic aggregate risk estimates do not exceed HED's level of concern. Since the chronic aggregate risk exposure includes only food and water, and the chronic dietary analysis included both, no further calculations are necessary. Since the chronic dietary risk does not exceed HED's level of concern, the chronic aggregate risk does not exceed HED's level of concern.

Occupational Exposure/Risks

Based upon the proposed new use patterns, RD believes the most highly exposed occupational pesticide handlers will be mixer/loaders using open pour loading of liquids, applicators using open-cab ground-boom sprayer, applicators using open-cab airblast sprayer, applicators using fixed-wing aircraft, applicators using high-pressure hand-wand and mixer/loader/applicators using backpack sprayer with open pour loading of liquids. The toxicological endpoints for short-term dermal and short-term inhalation effects were derived from two different studies; however, both studies indicate similar toxicological effects (i.e., methemoglobinemia). The level of concern is for Margins of Exposure (MOEs) < 100.

No chemical-specific data were 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 the Pesticide Handler Exposure Database (PHED) (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" and the use of protective gloves or other PPE as might be necessary.

Environmental Justice Consideration

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all

registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment does not rely on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical.

Additional Data Needs

None are required for this petition.

Recommendations for Tolerances/Registration

ARIA concludes that there are no residue chemistry or toxicology data requirements that would precluded the establishment of the ARIA recommended time-limited tolerance of 0.80 ppm for diflubenzuron in/on lemons. ARIA also recommends for exempting the tank mixing spray oils from the requirement of a tolerance for this use.

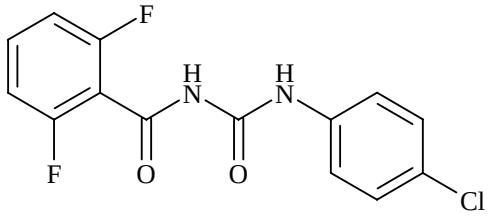
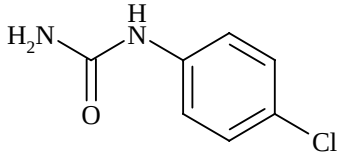
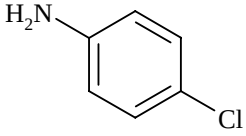
2.0 INGREDIENT PROFILE

2.1 Proposed Use

The product suggested for use is Dimilin® 2L (Reg. No. 400 - 461). The request is for use in the Counties of Los Angeles, Orange and San Diego. The rate of application is 0.275 lb ai/A in 50 - 1000 gallons of spray/A depending upon tree size. Spray should be mixed with 0.5 % Superior 415 Spray Oil. Applications may be made by ground or aerially. There is a maximum of 3 applications/yr/site. The reapplication interval is 90 days. There is a 21 day preharvest interval (PHI).

Table 2.1 Summary of Proposed Use Pattern for Diflubenzuron	
Crop/Site	Citrus, avocados, guavas and other tropical fruit
Pest	*Diaprepes* root weevil
Method of Applic.	air, ground (backpack, highpressure handwand, airblast)
Max. Applic. Rate	0.275 lb ai/A
Max. No. Applications	3/site/yr
Applic. Interval	90 days
Max. Amount Applied	35 lb ai for first year
Acres treated	estimated 42 acres
Preharvest Interval	21 days
Restricted Entry Interval	12 hours
Manufacturer	Crompton Crop Protection

2.2 Identification of Active Ingredient

TABLE 2.2 Diflubenzuron Nomenclature.	
Compound	
Common Name	Diflubenzuron
Trade and other Names	Dimilin, Vigilante, Micromite, Adept
IUPAC Name	1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea
CAS Name	*N*-[[(4-chlorophenyl)amino]carbonyl]-2,6-difluorobenzamide
CAS Registry Number	35367-38-5
End-Use Products (EP)	2 lb/gal FlC formulation; DIMILIN® 2L (EPA Reg. No. 400-461); 25% WP formulation; DIMILIN® 25W (EPA Reg. No. 400-465); 80% G formulation; Micromite® 80WGS (EPA Reg. No. 400-487);
Regulated Metabolite	
Common name	4-chlorophenylurea (CPU)
Regulated Metabolite	
Common Name	4-chloroaniline (PCA)

2.3 Physical and Chemical Properties

TABLE 2.3 Physicochemical Properties of Diflubenzuron.		
Parameter	Value	Reference
Melting range	230-232 °C	http://www.arsusda.gov/acsl/services/ppdb/textfiles/DIFLUBENZURON
pH	Not available	
Density	Not available	
Water solubility (25 °C)	0.08 ppm	
Solvent solubility (25 °C) (ppm)	6.5×10^3 Acetone 2×10^3 Acetonitrile 2.4×10^4 Dioxane 1.04×10^5 Dimethylformamide 1.2×10^5 Dimethylsulfoxide 1×10^3 Methanol 6×10^2 Dichloromethane	
Vapor pressure (25 °C)	1.2×10^{-4} mPa	
Dissociation constant, pK_a	Not available	
Octanol/water partition coefficient, $Log(K_{OW})$	3.89	

3.0 HAZARD CHARACTERIZATION

A complete hazard characterization is presented in the Section 3 risk assessment for the use of diflubenzuron on rice (Memo, G. Kramer *et al.*, DP #: 254693, 03/30/1999). For purposes of clarity, the dose-response assessment is summarized below.

3.1 Hazard and Dose-Response Characterization

In subchronic and chronic feeding studies, the primary endpoint of concern, produced most likely by PCA, was methemoglobinemia and/or sulfhemoglobinemia, which was evident in both sexes of mice, rats, and dogs and which was produced by more than one route of administration in rats [i.e., oral and inhalation]. The general consequence of methemoglobinemia and/or sulfhemoglobinemia is the impairment of the oxygen transportation capacity of the blood, which is generally known to be caused by aromatic amines in both man and animals. Additionally, the aromatic amine most likely responsible for the methemoglobinemia and/or sulfhemoglobinemia, PCA, is also the agent suspected in the production of tumors in carcinogenic studies in rodents. The overall toxicology database is sufficient for a determination of potential hazard to infants and children. The data provide no indication of an increased susceptibility to rats or to rabbits from *in utero* or post-natal exposure to diflubenzuron. Developmental and reproduction studies in rats and rabbits indicate a very low or possibly non-existent hazard potential for adverse effects. Developmental studies were tested at the limit dose of 1000 mg/kg/day without apparent effects in both dams and the fetuses. The reproduction study indicated that effects in offspring occurred at doses that were higher than the doses producing effects in parents. There was no indication of abnormalities in the development of the fetal nervous system in the prenatal developmental toxicity studies in either rats or rabbits at the maternal limit doses of 1000 mg/kg/day nor was

there evidence of effects on the nervous system following pre- and/or post-natal exposure in a two generation reproduction study in rats. There were no reports of treatment-related clinical observations indicative of central nervous system involvement or histopathological changes in the central nervous system [non-perfused tissues] in the subchronic or the chronic studies.

3.1.1 Database Summary

3.1.1.1 Studies Available and Considered

The overall toxicology database is sufficient for a determination of potential hazard to infants and children. The data provide no indication of an increased susceptibility to rats or to rabbits from *in utero* or post-natal exposure to diflubenzuron. Developmental and reproduction studies in rats and rabbits indicate a very low hazard potential for adverse effects. Developmental studies were tested at the limit dose of 1000 mg/kg/day without apparent effects in both dams and the fetuses. The reproduction study indicated that effects in offspring occurred at doses that were higher than the doses producing effects in parents. There was no indication of abnormalities in the development of the fetal nervous system in the prenatal developmental toxicity studies in either rats or rabbits at the maternal limit doses of 1000 mg/kg/day. In addition, there was no evidence of effects on the nervous system following pre- and/or post-natal exposure in a two-generation reproduction study in rats. There were no reports of treatment-related clinical observations indicative of central nervous system toxicity or histopathological changes in the central nervous system [non-perfused tissues] in the subchronic or the chronic studies.

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Diflubenzuron belongs to the benzoylphenylurea class of pesticides. It is a chitin synthesis inhibitor, a compound which disrupts the normal development of insects by blocking production of chitin, an important componet of the exoskeleton of insects, preventing insects from molting.

3.1.2 Toxicological Effects

The hemopoietic system is the target site with effects including increased sulfhemoglobin and/or methemoglobin levels in rat and dog studies. No appropriate acute endpoint was identified in the hazard database to quantitate the risk to the general population or to females 13-50 years old from single dose administration of diflubenzuron. Therefore, there is no aRfD or acute population-adjusted dose (aPAD). The short-term dermal endpoint was selected from a 21-day rat dermal study with a NOAEL of 500 mg/kg/day based on a significant increase in methemoglobinemia observed at the lowest-observed-adverse-effect level (LOAEL) of 1000 mg/kg/day. The intermediate-term dermal endpoint was selected from a 13-week oral (capsule) study in the dog with a NOAEL of 2 mg/kg/day based on increased methemoglobinemia observed at the LOAEL 6.24 mg/kg/day. The short-, and

intermediate-term inhalation endpoints were selected from a 28-day rat inhalation toxicity study with a NOAEL of 0.109 mg/L (highest dose tested, HDT), based on a statistically significant increase in methemoglobin levels observed at 0.12 mg/L (LOAEL) in a 21-day rat inhalation toxicity study. The chronic dietary, long-term dermal and long-term inhalation endpoints were selected from a chronic dog study with a NOAEL of 2 mg/kg/day based on increased methemoglobin levels observed at 10 mg/kg/day (LOAEL). The cRfD is 0.02 mg/kg/day and the cPAD is 0.02 mg/kg/day. The HED RfD/Peer Review Committee classified diflubenzuron as "Group E," evidence of non-carcinogenicity for humans, based on lack of evidence of carcinogenicity in rats and mice (04/27/1995). PCA, a metabolite of diflubenzuron, tested positive for splenic tumors in male rats and hepatocellular adenomas/carcinomas in male mice in a National Toxicology Program (NTP) study. Therefore, the RfD/Peer Review Committee classified PCA as a "Group B2" probable human carcinogen. However, recently submitted acceptable rat metabolism studies show that diflubenzuron was not metabolized to either PCA or CPU. On May 8, 2001, the MARC reviewed the recently submitted metabolism studies, accepted the study findings, and concluded that cancer risks for CPU and PCA should be assessed individually. The non-carcinogenic risk assessment should include diflubenzuron, CPU and CPA.

3.1.3 FQPA

The FQPA SFC recommended that the FQPA safety factor used in human health risk assessments be reduced to 1x in assessing the risk posed by this chemical (B. Tarplee, HED Document Number 012630, 06/14/1998). Consequently, the current cRfD and cPAD values are equivalent (0.02 mg/kg/day). This decision was based on the following: 1) there is no indication of increased susceptibility of rats or rabbits to *in utero* or postnatal exposure; 2) a DNT with diflubenzuron is not required; 3) food and drinking water exposure assessments will not underestimate the potential exposure for infants and children; and 4) there are currently no registered or proposed residential (non-occupational) uses of diflubenzuron.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Recently submitted rat metabolism data (MRID#s 44875501 and 44875502) indicate that diflubenzuron does not metabolize to PCA or CPU nor is CPU converted to PCA. The HED MARC met several times (02/20/2001 and 05/8/2001), concurred with the study findings, and concluded that a 2% *in vivo* conversion factor for diflubenzuron to PCA or CPU should be dropped (MARC memo, 05/31/2001). In conclusion, the MARC recommended that non-carcinogenic risk assessment should include parent, CPU and PCA.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

Acceptable neurotoxicity, developmental and reproductive toxicity studies conducted with diflubenzuron are available in rats and rabbits. The toxicology database is considered complete for the purposes of FQPA assessment.

3.3.2 Evidence of Neurotoxicity

The data provide no indication of an increased susceptibility to rats or to rabbits from *in utero* or post-natal exposure to diflubenzuron. In addition, there was no evidence of effects on the nervous system following pre- and/or post-natal exposure in a two-generation reproduction study in rats. There were no reports of treatment-related clinical observations indicative of central nervous system toxicity or histopathological changes in the central nervous system [non-perfused tissues] in the subchronic or the chronic studies.

3.3.3 Developmental/Reproductive Toxicity Studies

Developmental and reproduction studies in rats and rabbits indicate a very low hazard potential for adverse effects. Developmental studies were tested at the limit dose of 1000 mg/kg/day without apparent effects in both dams and the fetuses. The reproduction study indicated that effects in offspring occurred at doses that were higher than the doses producing effects in parents.

3.3.4 Pre-and/or Postnatal Toxicity

3.3.4.1 Determination of Susceptibility

Based on the available developmental toxicity studies in rats and rabbits, there is no increased susceptibility to fetuses exposed *in utero*.

3.3.4.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

Based on the available reproduction toxicity studies, there is no evidence of increased susceptibility in rat fetuses following pre-/post-natal exposure.

3.3.5 Recommendation for a Developmental Neurotoxicity Study

A DNT study with diflubenzuron is not required. The HIARC recommended a dermal-absorption factor of 0.5% based on a 1- to 10-hour exposure from a rat study.

3.4 FQPA Safety Factor for Infants and Children

The FQPA safety factor for diflubenzuron has been reduced to 1X, see section 3.1.3 above.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD)

No appropriate toxicological endpoint attributable to a single exposure was identified in the hazard database, including oral developmental toxicity studies in rats and rabbits.

3.5.2 Chronic Reference Dose (cRfD)

The chronic dog study was used to select the endpoint for establishing the cRfD of 0.02 mg/kg/day. The standard 100x UF was applied to account for interspecies extrapolation and intraspecies variation. The NOAEL of 2.0 mg/kg/day was based on methemoglobinemia and sulfhemoglobinemia seen at 10 mg/kg/day (LOAEL). The FQPA SFC determined that a FQPA safety factor of 1x is applicable for chronic dietary risk assessment. Thus, the cPAD is 0.02 mg/kg/day.

3.5.3 Incidental Oral Exposure (Short- and Intermediate-Term)

These endpoints were not evaluated. There are no registered or proposed uses of diflubenzuron which result in significant residential exposure.

3.5.4 Dermal Absorption

The HIARC recommended a dermal-absorption factor of 0.5% based on a 1- to 10-hour exposure from a rat study.

3.5.5 Short-Term Dermal Exposure

A short-term dermal endpoint was selected from a 21-day rat dermal toxicity study. The NOAEL of 500 mg/kg/day was based on the significant increase in methemoglobinemia observed at 1000 mg/kg/day (limit dose). This study is route-specific, is of appropriate duration and measures the effects of concern; i.e., methemoglobin and/or sulfhemoglobin.

3.5.6 Intermediate-Term Dermal Exposure

An intermediate-term dermal endpoint was selected from a subchronic oral toxicity dog study. The NOAEL of 2.0 mg/kg/day was based on increased methemoglobinemia at 6.24 mg/kg/day. This endpoint (methemoglobinemia/ sulfhemoglobinemia) was seen consistently in the 90-day dog study and chronic toxicity studies in rats, mice and dogs at about similar ranges and it is appropriate for this exposure period of concern. Since

an oral NOAEL was selected for a dermal-exposure scenario, a dermal-absorption factor of 0.5% should be used for this risk assessment when converting dermal exposure to oral equivalents.

3.5.7 Long-Term Dermal Exposure

A long-term dermal endpoint was selected from a chronic oral toxicity study in the dog, see section 3.5.2, above. An oral study was selected since no appropriate long-term dermal study is available in the database. A 0.5% dermal-absorption factor should be used to convert to oral equivalents.

3.5.8 Short-/Intermediate-Term Inhalation Exposure

Inhalation endpoints were selected from a 28-day rat inhalation toxicity study. The NOAEL of 0.109 mg/L (HDT) in the study was based on significant increase in methemoglobinemia seen in a 21-day inhalation toxicity study at 0.12 mg/L (LOAEL at LDT).

3.5.9 Long-Term Inhalation Exposure

A long-term inhalation endpoint was selected from a chronic oral toxicity dog study, see section 3.5.2, above. An oral study was selected since no appropriate long-term inhalation study is available in the database. A 100% inhalation-absorption factor should be used to convert to oral equivalents.

3.5.10 Level of Concern for Margin of Exposure

A MOE of 100 is adequate for occupational exposure.

3.5.11 Recommendation for Aggregate Exposure Risk Assessments

Aggregate exposure risk assessments were assessed by incorporating the drinking water directly into the dietary-exposure assessment for the following scenario: chronic aggregate exposure (food + drinking water). Short-, intermediate-, and long-term aggregate-risk assessments were not performed because there are no registered or proposed uses of diflubenzuron which result in residential exposures. Acute and cancer aggregate-risk assessments were not performed because no appropriate endpoint was available to determine the aRfD for the general population or any population subgroup and diflubenzuron is not carcinogenic.

3.5.12 Classification of Carcinogenic Potential

Based on the available evidence, which included adequate carcinogenicity studies in rats and mice, and battery of negative mutagenicity studies, diflubenzuron was classified as "Group E**,"** evidence of non-carcinogenicity for humans, by the RfD Peer Review Committee (04/27/1995). Rat metabolism data generated at this time also

indicated that diflubenzuron was metabolized to PCA and CPU and estimated to be about 2% of *in vivo* conversion.

3.5.13 Summary of Toxicological Doses and Endpoints for Diflubenzuron for Use in Human Risk Assessments

Table 3.5.13. Summary of Toxicological Dose and Endpoints for Diflubenzuron for Use in Human Risk Assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations	Not Applicable	Not Applicable	No appropriate endpoint attributable to single exposure was available in oral studies. Therefore, a risk assessment is not required.
Chronic Dietary all populations	NOAEL= 2 mg/kg/day UF = 100 **Chronic RfD** = 0.02 mg/kg/day	FQPA SF = 1x **cPAD** = chronic RfD / FQPA SF = 0.02 mg/kg/day	Chronic Toxicity Study - Dog LOAEL = 10 mg/kg/day based on methemoglobinemia and sulfhemoglobinemia
Short- and Intermediate-Term Incidental Oral (1 day - 6 months) (Residential)	Not applicable	Not applicable	These endpoints were not evaluated. There are no registered uses of diflubenzuron which result in significant residential exposure.
Short-Term Dermal (1 - 30 days) (Occupational)	NOAEL = 500 mg/kg/day	**LOC for MOE** = 100	21-Day dermal rat LOAEL = 1000 mg/kg/day based on methemoglobinemia
Intermediate-Term Dermal (1 - 6 months) (Occupational)	NOAEL = 2 mg/kg/day	**LOC for MOE** = 100	13 - week oral dog LOAEL = 6.4 mg/kg/day based on methemoglobinemia
Long-Term Dermal (Longer than 6 months) (Occupational)	NOAEL = 2 mg/kg/day	**LOC for MOE** = 100	Chronic Toxicity Study - Dog LOAEL = 10 mg/kg/day based on methemoglobinemia and sulfhemoglobinemia
Short-Term Inhalation (1 - 30 days) (Occupational)	NOAEL = 20.30[2] mg/kg/day	**LOC for MOE** = 100	28-day Inhalation Toxicity Study - Rat/ 21-day Inhalation Toxicity Study - Rat LOAEL = 0.12 mg/L based on methemoglobinemia (21-day study)
Intermediate-Term Inhalation (1 - 6 months) (Occupational)	NOAEL = 20.30[2] mg/kg/day	**LOC for MOE** = 100	28-day Inhalation Toxicity Study - Rat/ 21-day Inhalation Toxicity Study - Rat LOAEL = 0.12 mg/L based on methemoglobinemia (21-day study)

Table 3.5.13. Summary of Toxicological Dose and Endpoints for Diflubenzuron for Use in Human Risk Assessment[1].			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and LOC for Risk Assessment**	**Study and Toxicological Effects**
Long -Term Inhalation (Longer than 6 months) (Occupational)	NOAEL = 2 mg/kg/day	**LOC for MOE** = 100 (Occupational)	Chronic Toxicity Study - Dog LOAEL = 10 mg/kg/day based on methemoglobinemia and sulfhemoglobinemia
Cancer (oral, dermal, inhalation)	Diflubenzuron Not Required	Not Applicable	Acceptable oral rat and mouse carcinogenicity studies; no evidence of carcinogenic or mutagenic potential. "Group E" evidence of non-carcinogenicity for humans.

1. UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no-observed-adverse-effect level, LOAEL = lowest-observed-adverse-effect level, cPAD = chronic population-adjusted dose, RfD = reference dose, MOE = margin of exposure, LOC = level of concern.
2. Conversion from mg/L to oral dose (mg/kg/day)

3.6 Endocrine disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was 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 has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

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

4.0 PUBLIC HEALTH AND PESTICIDE EPIDEMIOLOGY DATA

No public health/epidemiology data were used in developing this risk assessment.

5.0 DIETARY EXPOSURE/RISK CHARACTERIZATION

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The qualitative nature of the residue in plants and fungi is adequately understood based on data from citrus, mushroom, rice, and soybean metabolism studies. The metabolism of diflubenzuron in crops tested is similar, and the radioactive components are also similar to those found in soil. The nature of the residue in livestock is also adequately understood based on acceptable poultry and ruminant metabolism studies reflecting oral dosing.

5.1.2 Metabolism in Rotational Crops

The nature of the residue in rotational crops is adequately understood for purposes of reregistration (Residue Chemistry Chapters for the Reregistration Eligibility Decision (RED) document, 03/15/1995). Lemons though are not a rotational crop.

5.1.3 Metabolism in Livestock

There are ruminant and/or poultry feed items associated with the uses of diflubenzuron on barley, oats, wheat, and peanuts. The calculated maximum theoretical dietary burdens resulting from the registered uses are supported by previously submitted livestock feeding studies.

5.1.4 Analytical Methodology

There are adequate enforcement methods, published in the Pesticide Analytical Manual (PAM, Vol. II), for determining diflubenzuron residues of concern. In addition, a new analytical methodology for plant commodities was successfully validated by an independent laboratory as well as by Agency chemists at the Analytical Chemistry Branch (ACB)/Biological and Economics Analysis Division (BEAD) in conjunction with the approved rice petition. The new methods were forwarded to the Food and Drug Administration (FDA) for publication in PAM Vol. II as Roman Numeral Methods. These methods can separately determine residues of diflubenzuron by gas chromatography/electron-capture detection (GC/ECD), CPU by GC/ECD, and PCA by GC/mass spectrometry (MS).

5.1.5 Environmental Degradation

Diflubenzuron appears to be relatively non-persistent and immobile under normal use conditions. The major route of dissipation appears to be biotic processes (half-life of approximately 2 days for aerobic soil metabolism). Diflubenzuron is stable to

hydrolysis and photolysis. Available data indicate that it is unlikely that diflubenzuron will contaminate ground water or surface water.

5.1.6 Drinking Water Residue Profile

The drinking water residues used in the dietary risk assessment were previously provided by the Environmental Fate and Effects Division and summarized in the following memorandum: "IR-4/Section 3-Local and New Uses Registration for Diflubenzuron Use on Peanuts, Okra, Small grains (Winter, Spring, Durum, Barley, and Oats), Pummelo, Mustard Greens, Broccoli, Raab, Cabbafe (bok choy), Collards, Kale, Mizuna, Mustard spinach, Rape, Greens and Turnip greens," (A. Al-Mudallal, DP #: 321156, 08/25/2006) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Because monitoring data are unavailable, estimates of diflubenzuron and the major degradate CPU concentrations were made only with mathematical models. The PRZM/EXAMS models with IR scenarios and percent crop area adjustment factors were used to conduct surface water exposure assessments. SCIGROW was used for groundwater. EDWCs were generated for the total toxic residue which includes parent diflubenzuron and the major degradate CPU. The highest estimated surface water concentrations occurred with the PA pear scenario. For chronic assessments the EDWC is 2.76 ppb; this was the value used in this assessment. The groundwater estimate from SCIGROW is 0.208 ppb. This scenario presents the most conservative surface water concentration due to use of diflubenzuron.

5.1.7 Food Residue Profile

No new residue chemistry data was reviewed with this petition. Treatment will be limited to an area of 42 acres in Los Angeles, Orange and San Diego counties in California. The product will be applied as a foliar spray at the rate of 0.275 lb ai. per acre (in 50-1000 gallons per acre with 0.5% oil added) by ground or air and not expected to exceed a total of 158 lbs. of product (34.7 lbs. ai.) for the first year of treatment.

A residue study (*Micromite®4L and Micromite® 25W in Lemons and Limes: Magnitude of the Residue Study*, Gaydosh, K., Entocon, Inc., Study No.: RP-96028, 10/08/1999, MRID 45333601) was submitted but not formally reviewed for this action. The results from the field trials show that residues of diflubenzuron in lime samples were 0.151-0.172 ppm while residues in lemons were 0.245-0.551 ppm in samples harvested 21 days following the last application of a total rate of 15 oz. ai./A. The mean validation recovery for diflubenzuron was 82%, with a standard deviation of 11%. The proposed tolerance of 0.8 ppm is adequate to support the proposed use.

5.1.8 International Residue Limits

The Codex Alimentarius has established maximum residue limits (MRL), expressed in terms of diflubenzuron *per se*, for many commodities including: apple (5 ppm), citrus fruits (0.5 ppm), edible offal (mammalian) (0.1 ppm), eggs (0.05 ppm), meat (from mammals other than marine mammals) (0.1 ppm), milks (0.02 ppm), mushrooms (0.3 ppm), pear (5 ppm), pome fruits (5 ppm), poultry meat (0.05 ppm), rice (0.01 ppm), and rice straw and fodder (dry) 0.7 ppm). As the U.S. residue definition includes CPU and PCA, compatibility is not possible with the proposed tolerances.

5.2 Dietary Exposure and Risk

A diflubenzuron chronic dietary-exposure assessment was conducted using DEEM-FCID™ Version 2.03, which incorporates consumption data from USDA's CSFII, 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary-exposure assessments, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

The dietary exposure analysis was performed by ARIA (B. Hanson, DP #: 337826, 04/16/2007).

5.2.1 Acute Dietary Exposure/Risk

An acute dietary-exposure assessment was not performed because there were no toxic effects attributable to a single dose. Thus, an endpoint of concern was not identified to quantitate acute dietary risk to the general population or to any population subgroup.

5.2.2 Chronic Dietary Exposure/Risk

A chronic dietary assessment assuming tolerance level residues, including a 0.8 ppm avocado residue value, and 100% crop treated was conducted. The highest estimate of chronic surface water exposure (2.76 ppb) was used for drinking water in this analysis. The chronic dietary risk assessment shows that for all included commodities, the chronic dietary risk estimates are below HED's level of concern (i.e. <100% chronic population adjusted doses (cPAD). For the U.S. population the exposure for food and water utilized 12% of the cPAD. The chronic dietary risk estimate for the highest reported exposed population subgroup, children 1-2 years old, is 38% of the cPAD.

Table 5.2.2 Summary of Chronic Dietary (Food and Drinking Water) Exposure Risk for Diflubenzuron

Population Subgroup	Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD*
General U.S. Population	0.002363	12
All Infants (< 1 year old)	0.002317	12
Children 1-2 years old	**0.007533**	**38**
Children 3-5 years old	0.005880	29
Children 6-12 years old	0.003530	18
Youth 13-19 years old	0.002340	12
Adults 20-49 years old	0.001671	8
Adults 50+ years old	0.001833	9
Females 13-49 years old	0.001747	9

5.2.3 Cancer Dietary Risk

Based on the previously submitted metabolism studies, there are two possible sources for dietary exposure to PCA and CPU- residues in fungi (mushrooms) and residues in livestock commodities (milk and liver). As human exposure to PCA and CPU is not affected by these uses, the cancer dietary risk from PCA and CPU will not be addressed in this document.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

No anticipated residue or %CT information was considered in the chronic dietary analysis.

6.0 RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE/RISK CHARACTERIZATION

Although there are no registered homeowner uses, there are registered uses for professional applications to outdoor residential and recreational areas to control mosquitoes, moths, and other insects. However, the potential for post-application residential exposure is expected to be limited. Due to the low dermal absorption rate (0.5%) of diflubenzuron and since the state is conducting a substantial homeowner outreach/education program informing residents on how to avoid pesticide exposure, minimal bystander contact is expected.

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 groundboom application methods. 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. 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 and risks associated with aerial as well as other application types where appropriate.

7.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

In accordance with the FQPA, ARIA must consider and aggregate pesticide exposures and risks from non-occupational sources, including; food, drinking water, and residential pathways. 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, ARIA considers both the route and duration of exposure.

7.1 Acute Aggregate Risk

An acute aggregate-risk assessment was not performed because no appropriate endpoint was available to determine the aRfD for the general population or any population subgroup.

7.2 Short/Intermediate-Term Aggregate Risk

There are no residential uses associated with diflubenzuron; therefore, short and intermediate-term aggregate risk assessments were not performed.

7.3 Chronic Aggregate Risk

Since the chronic aggregate risk exposure includes only food and water and the chronic dietary analysis included both, no further calculations are necessary. Since the chronic dietary risk does not exceed HED's level of concern, the chronic aggregate risk does not exceed HED's level of concern.

7.4 Cancer Aggregate Risk

A cancer aggregate-risk assessment was not performed because diflubenzuron is not carcinogenic.

8.0 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 diflubenzuron and any other substances and diflubenzuron 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 diflubenzuron 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 Office of Pesticide Programs 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/.

9.0 OCCUPATIONAL EXPOSURE/RISK PATHWAY

ARIA provided an assessment for the use of diflubenzuron on citrus, avocados, guavas and other tropical fruit (M. Dow, DP #: 337825, 03/08/2007).

Occupational Pesticide Handler Exposure

Based upon the proposed new use patterns, RD believes the most highly exposed occupational pesticide handlers will be mixer/loaders using open pour loading of liquids, applicators using open-cab ground-boom sprayer, applicators using open-cab airblast sprayer, applicators using fixed-wing aircraft, applicators using high-pressure hand-wand and mixer/loader/applicators using backpack sprayer with open-pour loading of liquids

The total area expected to be treated the first year is about 45 acres. Most treatment blocks are expected to be rather small. Information on the size of a "typical" treatment block is not available to RD. For purposes of a screening level, conservative estimate of exposure and risk, RD will assume each method of application could be used to treat

all estimated acres treated (*i.e.*, 45 A) except for backpack in which RD assumes 5 acres are treated.

Particularly for ground applications, private (*i.e.*, grower) applicators may perform all functions, that is, mix, load and apply the material. The HED ExpoSAC SOP Number 12 (03/29/2000) directs that although the same individual may perform all those tasks, they shall be assessed separately. The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand-held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (*e.g.*, chemical-resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical-specific data were 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 the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" and the use of protective gloves or other PPE as might be necessary.

The Dimilin® 2L label instructs applicators and other handlers to wear long-sleeved shirt, long pants, chemical resistant gloves and shoes plus socks. Mixers and loaders supporting fixed wing aircraft must wear long-sleeved shirt, long pants, chemical resistant gloves, shoes plus socks and dust/mist filtering respirator with MSHA/NIOSH approval number prefix TC21C or a NIOSH approved respirator with R,P or HE filter.

HED's HIARC met to discuss the adequacy of the toxicological database relative to diflubenzuron (Memo, G. Reddy, HED DOC. NO. 0050503, "DIFLUBENZURON – 3rd Report of the Hazard Identification Assessment Review Committee, 03/06/2002). Diflubenzuron was classified in Acute Toxicity Category III for acute dermal toxicity and primary eye irritation. It was classified in Toxicity Category IV for acute inhalation and primary skin irritation and it is not a dermal sensitizer. Relative to this assessment of handler exposure and risk, the HIARC identified a short-term (1 – 30 days) dermal toxicological endpoint (methemoglobinemia) with a NOAEL of 500

mg/kg bw/day. The dermal endpoint was identified from a 21 day dermal study in the rat. The HIARC also identified a short-term inhalation endpoint (methemoglobinemia) with a NOAEL of 20.3 mg/kg bw/day. The endpoint was identified from a 28-day inhalation study in the rat. See Table 9.0 for a summary of exposure and risk to occupational pesticide handlers. The level of concern is for MOEs < 100.

Table 9.0 Estimated Handler Exposure and Risk from the Use of Diflubenzuron on the California Section 18 Use Sites

Unit Exposure[1] mg a.i./lb handled	Applic. Rate[2]	Units Treated[3] Per Day	Average Daily Dose[4] mg a.i./kg bw/day	MOE[5]	COMBINED MOE[6]
Mixer/Loader - Liquid - Open Pour					
Dermal: SLNG 2.9 HC SLWG 0.023 HC Inhal 0.0012 HC	0.275 lb a.i./A	45 A	Dermal: No Gloves 0.51 With Gloves 0.0041 Inhal 0.00021	No Glove 980 With Glove 121,950 Inhal 96,666	NG 970 WG 54,054
Applicator - Aerial (Pilots not required to wear gloves)					
Dermal: SLNG 0.0050 HC Inhal 0.000068 MC	0.275 lb a.i./A	45 A	Dermal: No Gloves 0.00088 Inhal 0.000012	No Glove 7,812 Inhal 1,691,666	NG 425,326
Applicator - Air-blast - Open-cab					
Dermal: SLNG 0.36 HC SLWG 0.24 HC Inhal 0.0045 HC	0.275 lb a.i./A	45 A	Dermal: No Gloves 0.064 With Gloves 0.042 Inhal 0.00079	No Glove 7,812 With Glove 11,904 Inhal 25,696	NG 5,991 WG 8,135
Applicator - Ground-boom - Open-cab					
Dermal: SLNG 0.014 HC SLWG 0.014 MC Inhal 0.00074 HC	0.275 lb a.i./A	45 A	Dermal: No Gloves 0.0025 With Gloves 0.0025 Inhal 0.00079	No Gloves 200,000 With Gloves 200,000 Inhal 156,154	NG 87,689 WG 87,689
Applicator - High-Pressure Hand-wand					
Dermal SLNG 1.8 LC SLWG 0.64 LC Inhal 0.079 LC	0.275 lb a.i./A	45 A	Dermal: No Gloves 0.318 With Gloves 0.113 Inhal 0.00155	No Gloves 1,572 With Gloves 4,424 Inhal 13,096	NG 1,403 WG 3,306
Mixer/Loader/Applicator - Backpack - Open Pour Liquid					
Dermal SLWG 2.5 LC Inhal 0.03 LC	0.275 lb a.i./A	5 A	Dermal: With Gloves 0.113 Inhal 0.00059	With Gloves 10,204 Inhal 34,406	WG 7,870

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. SLNG = Dermal Single Layer Work Clothing No Gloves; SLWG = Dermal Single Layer Work Clothing With Gloves; Inhal. = Inhalation. Units = mg a.i./lb ai handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from California Section 18 Quarantine request
3. Units Treated are assumed as most conservative from California Section 18 Quarantine request
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated ÷ Body Weight (70 kg).
5. MOE = Margin of Exposure = NOAEL ÷ ADD. Dermal NOAEL = 500 mg a.i./kg bw/day; Inhalation NOAEL = 20.3 mg a.i./kg bw/day
6. The toxicological endpoints for short-term dermal effects and short-term inhalation effects were derived from two different studies however both studies indicate similar toxicological effects (*i.e*., methemoglobinemia). Since the results of the two studies indicate similar toxicological effects, the Margins of Exposure (MOEs) are shown as Combined MOEs. Combined MOEs are expressed as:

$$\frac{1}{1/MOE_{Dermal} + 1/MOE_{Inhalation}}$$ (HED SOP 97.2; 26 NOV 97).

Post-Application Agricultural Worker Exposure

Typically there is the possibility for agricultural workers to experience post-application exposures to dislodgeable pesticide residues; in this case through the stripping of fruits from treated trees. There were no chemical-specific data with which to estimate post-application exposure of agricultural workers to dislodgeable residues of diflubenzuron. Therefore, theoretical estimates of exposure, based on surrogate studies, have been conducted. The ExpoSAC (SOP 003.1, Rev. 7 Aug. 2000, Regarding Agricultural Transfer Coefficients; Amended ExpoSAC Meeting notes - 13 Sept 01) lists a number of possible post-application agricultural activities relative to the subject crops that might result in pesticide exposure to agricultural workers. Transfer Coefficients (TC) expressed as cm^2/hr are identified for each of the post-application, agricultural activities. The TCs are derived from data in surrogate exposure studies conducted during the various activities listed.

The highest (*i.e*., most conservative) TCs relative to the subject crops are for hand harvesting with a TC of 3,000 cm^2/hr. For risk assessment purposes, a TC of 3,000 cm^2/hr is used in conjunction with the maximum rate of application (0.275 lb a.i./A).

The TCs used in this assessment are from an interim TC SOP developed by HED's ExpoSAC using proprietary data from the Agricultural Re-Entry Task Force (ARTF) database (SOP # 3.1). It is the intention of HED's ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 20 % of the application rate is available as DFR on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (05/07/1998 - Revised 08/07/2000).

The following convention is used to estimate post-application exposure.

Average Daily Dose (ADD) (mg a.i./kg bw/day) = DFR µg/cm^2 * TC cm^2/hr * hr/day * 0.001 mg/µg * 1/70 kg bw

and where:

Surrogate DFR = application rate * 20% available as dislodgeable residue * $(1\text{-}D)^t$ * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 .

0.275 lb a.i./A * 0.20 * $(1\text{-}0)^0$ * 4.54 x 10^8 µg/lb * 2.47 x10^{-8} A/cm^2 = 0.617 µg/cm^2 , therefore,

0.617 µg/cm^2 * 3,000 cm^2/hr * 8 hr/day * 0.001 mg/µg ÷ 70 kg bw = 0.212 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 500.0 mg/kg bw/day ÷ 0.212 mg/kg bw/day = **2,358.**

A MOE of 100 is adequate to protect agricultural workers from post-application exposures. Since the estimated MOEs are > 100, the proposed uses do not exceed RD's level of concern.

The interim worker protection standard REI of 12 hours is adequate to protect agricultural workers from post-application exposures.

10.0 DATA NEEDS AND LABEL RECOMMENDATIONS

None.

REFERENCES:

Dietary Exposure Memorandum

AMENDED Diflubenzuron Chronic Dietary Exposure Assessment for the Section 18 Use on Lemons. PP# 07CA04., B. Hanson, DP#: 337826, 04/16/2007.

Drinking Water Memorandum

IR-4/Section 3-Local and New Uses Registration for Diflubenzuron Use on Peanuts, Okra, Small grains (Winter, Spring, Durum, Barley, and Oats), Pummelo, Mustard Greens, Broccoli, Raab, Cabbafe (bok choy), Collards, Kale, Mizuna, Mustard spinach, Rape, Greens and Turnip greens.; A. Al-mudallal; DP #: 321156; 08/25/2006.

Residue Chemistry Data Review Memorandum

*Diflubenzuron. IR-4's Request To Register New Food/Feed Uses on Barley, Oats, Wheat, Brassica Leafy Greens (Crop Subgroup 5B), Turnip Greens, Eggplant, Okra, Peanut, and Pummelo. Summary of Analytical Chemistry and Residue Data***.** G. Kramer; DP #s: 321623, 321625, and 321627; 09/14/2006.

Occupational and Residential Exposure Memorandum

Diflubenzuron - Human, Non-Dietary Exposure/Risk Assessment for the California Section 18 Quarantine Use Request on Commercial and Residential Plantings of Citrus, Avocados, Guavas and Lychee.; M. Dow; DP #: 337825; 03/08/2007.

Risk Assessment Document

Diflubenzuron on Barley, Oats, Wheat, Brassica Leafy Greens (Crop Subgroup 5B), Turnip Greens, Eggplant, Okra, Peanut, and Pummelo (PP#s 5E6965, 5E6966, and 5E6967).; G. Kramer, DP #s: 321152, 321155, & 321158; 09/14/2006.

Appendix A: TOXICOLOGY ASSSESSMENT

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.377) for food use of diflubenzuron are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1 Toxicology Data Requirements for Prosulfuron

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	yes	yes
870.3465 90-Day Inhalation	yes	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	no	-
870.6200b 90-Day Neuro. Screening Battery (rat)	no	-
870.6300 Develop. Neuro	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	-
Special Studies for Ocular Effects	no	-
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

A.2 Toxicity Profiles

Table A.2 Acute Toxicity of Diflubenzuron

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00157103	LD_{50} =>5,000 mg/kg	IV
81-2	Acute Dermal	00157104	LD_{50} =>2000 mg/kg	III
81-3	Acute Inhalation	00163311	LC_{50} =>2.49 mg/L	IV
81-4	Primary Eye Irritation	00157105	mild irritant	III
81-5	Primary Skin Irritation	00157106	no irritation	IV
81-6	Dermal Sensitization	42251101	negative	n/a

A.3 Executive Summaries

Non-Guideline Short-Term Inhalation Exposure (1 - 30 Days)

Study Selected: Twenty-eight day rat inhalation

MRID No.: 44950601

Executive Summary: In a subchronic inhalation toxicity study (MRID 44950601), dimilin technical (96.5% a.i., Batch FUX021000-FUN91A10A) was administered to groups of 10 male and 10 female Sprague-Dawley albino rats/concentration. Exposure was by nose-only inhalation at concentrations of 0, 12, 34, or 109 mg/m^3 (0. 0.012, 0.034, or 0.109 mg/L) for 6 hours/day, 5 days/week, for approximately 4 weeks (22-23 consecutive exposures, excluding weekends, over a 30-31 day calendar period).

There was no test material-related effect on mortality, body weight or weight gain, food consumption, clinical signs, ophthalmoscopy, urinalysis, organ weights, and gross or microscopic pathology. Slight but statistically significant decreases were seen in erythrocyte counts, hemoglobin, and hematocrit in both sexes (93-95% of controls) and in serum bilirubin in males (increased from 0.1 to 0.2 mg/dL) administered 100 mg/m^3. It is unclear whether these alterations were induced by treatment, however, they were too small to be biologically significant and lacked microscopic correlates, and were thus considered toxicologically unimportant. Under the conditions of this study, therefore, a LOAEL was not established and the NOAEL is the highest dose tested, i.e., 109 mg/m^3 (0.109 mg/L).

This subchronic inhalation toxicity study in the rat is Acceptable/Non-Guideline. The study satisfies the guideline requirement for a subchronic inhalation toxicity study in rats as requested by the HIARC.

Dose and Endpoint for Risk Assessment: NOAEL = 20.30 mg/kg/d[1] (0.109 mg/L; HDT).

Comments about Study/Endpoint**:** The study is of appropriate for route and duration of exposure. The concentration selected for risk assessment did not elicit any adverse effect following 28 days of inhalation exposure. The HIARC, however, selected this dose based on methemoglobinemia which was consistently observed across species and studies even though it was not seen in the critical study.

Non-Guideline Intermediate-Term Inhalation Exposure (1 - 6 months)

Study Selected: Twenty-eight day rat inhalation

MRID No.: 44950601

Executive Summary: see Short-Term Inhalation

Dose and Endpoint for Risk Assessment: NOAEL = 20.30 mg/kg/d (0.109 mg/L; HDT).

Comments about Study/Endpoint: The study is of appropriate for route and duration of exposure. The concentration selected for risk assessment did not elicit any adverse effect following 28 days of inhalation exposure. The HIARC, however, selected this dose based on methemoglobinemia which was consistently observed across species and studies even though it was not seen in the critical study.

A.3.1 Subchronic Toxicity

870.3100 Oral Subchronic Toxicity - Rodent

Study Selected: 14 day subchronic oral toxicity study in mice.

MRID No.: 00099713

Executive Summary: In a 14-day subchronic oral toxicity study, technical grade diflubenzuron was administered each day by gavage to 10 Swiss strain male mice at a dose level of 8, 40, 200, 1000 or 5000 mg/kg/day. The mice were fasted for 16 hours prior to the first dose of test material. The test material was administered as a suspension in 1% tragacanth. Twenty control animals were treated similarly with a blank suspension. Blood was drawn from all animals at 15 days after the first dose and analyzed for methemoglobin, sulfhemoglobin and Heinz bodies in the erythrocytes. At

day 15, the animals were sacrificed and those of the control and highest dose groups were autopsied. Significantly increased ($p < 0.05$) levels of methemoglobin were observed at 1000 and 5000 mg/kg/day. Significantly increased ($p < 0.05$) levels of sulfhemoglobinemia were observed at 200, 1000 and 5000 mg/kg/day. The percentage of erythrocytes containing Heinz bodies was highly increased at 1000 and 5000 mg/kg/day. No effect on body weights or on organs and tissues examined at autopsy was observed.

Dose and Endpoint for Risk Assessment: NOEL = 40 mg/kg/day based on increased sulfhemoglobin at 200 mg/kg/day.

870.31050 Oral Subchronic Toxicity - Nonrodent

Study Selected: 13 week oral [subchronic] feeding study in dogs.

MRID No.: 00038706

Executive Summary: In a subchronic feeding study, technical grade diflubenzuron (batch # P7227) was administered in the diet to beagle dogs at dose levels of 0 (control), 10, 20, 40 and 160 ppm (equal to 0, 0.42, 0.84, 1.64 and 6.24 mg/kg/day). Groups of 3 male and 3 female dogs were used for each treated and control group. Hematology and blood chemistries were performed at 2, 4, 6 and 12 weeks: methemoglobin, sulfhemoglobin and urinalyses were performed at 6 and 12 weeks. Ophthalmoscopic examinations were conducted at 6 and 12 weeks. Gross necropsies were performed on all dogs. Organ weights were determined and histopathological examinations were performed at the terminal sacrifice at 13 weeks. Mortality, clinical signs, body weights and food consumption were not affected by treatment with diflubenzuron. Ophthalmoscopic examinations were negative. Methemoglobinemia was observed in the dogs at 160 ppm (after 6 weeks). No gross necropsy, organ weight or histopathological changes were reported at any level that could be related to treatment with diflubenzuron.

Endpoint and dose for use in risk assessment: Calculated NOEL 2.0 mg/kg/day based on increased methemoglobinemia at 6.24 mg/kg/day.

Comments about studies and/or endpoint: In this 13-week feeding study in dogs, a steady state for methemoglobinemia was observed to occur after 6 weeks.
In both the rat study and the mouse study, a NOEL of about 2 mg/kg/day was calculated by regression analysis. Considering all the available data (including data from chronic feeding studies in rats, dogs and mice in which the NOEL for methemoglobinemia/sulfhemoglobinemia to be used to calculate the RfD also was 2 mg/kg/day), it was concluded that the NOEL for intermediate term risk assessments should be 2 mg/kg/day (rather than the slightly lower NOEL of 1.64 mg/kg/day determined in the dog study above).

870.3200 21-Day Dermal Toxicity – Rat

Study Selected: 21-Day dermal toxicity study in rat

MRID No.: 43954101

Executive Summary: In a subchronic, 21-day dermal toxicity study, Dimilin (diflubenzuron tech. 96.7% a.i.) was administered to 10/sex/dose in 0.25% gum tragacanth in distilled, deionized water to the dorsal skin on the backs of the test animals at 0, 20, 500, or 1,000 mg/kg/day for 6 hour period each day.

Dermal treatment for 21 days did not affect mortality, clinical signs, body weight changes, food consumption and/or organ weight changes. At 1,000 mg/kg/day, slight dermal irritation and traces of acanthosis and hyperkeratosis were noted in males and females. Liver and kidney histopathology was remarkable. Males exhibited slight elevations in the white cell count in the mid and high dose groups. Males also had small reductions in hemoglobin and hematocrit at 1000 mg/kg dose group. In females at the top two doses there were statistically significant ($P < 0.05$) decreases in RBC count, hemoglobin levels and hematocrit values. Hematological changes in males and females were within in the historical ranges for this species and age of rat, and therefore, considered not biologically significant. Methemoglobin levels increased significantly ($P < 0.05$ & 0.01) in males and females at 1000 mg/kg dose. There was increased incidence of anisocytosis, hypochromasia and polychromasia in males and females at the top dose. On August 14, 2001, the HED HIARC re-evaluated the study and concluded that the increased methemoglobinemia in males and females at 1000 mg/kg should be considered as toxicity-induced change. Therefore, the NOAEL is 500 mg/kg and LOAEL is 1000 mg/kg based on methemoglobinemia.

Dose and Endpoint for Risk Assessment: NOAEL = 500 mg/kg/day based on increased methemoglobinemia at 1000 mg/kg/day.

Comments about Study/Endpoint: This dermal toxicity study in rats is route- specific, is of appropriate duration and measures the effects of concern, i.e., methemoglobin and/or sulfhemoglobin. Previously, the end-points for short-term exposure were based on a 14- day mouse feeding study. The HIARC re-evaluated the 21-day dermal study in rat and revised the NOAEL from 20 mg/kg/day to 500 mg/kg/day, since the methemoglobinemia seen at 500 mg/kg/day was within normal physiological parameters, but occurred at adverse levels at 1000 mg/kg/day.

870.3250 Intermediate-Term Dermal Toxicity – Dog

Study Selected: Chronic Toxicity - Dog.

MRID No.: 00146174

Executive Summary: See 870.4100b Chronic Toxicity – Nonrodent, below.

Dose and Endpoint for Risk Assessment: NOAEL = 2 mg/kg/day based on methemoglobinemia and sulfhemoglobinemia at 10 mg/kg/day (LOAEL). Corrected for 0.5% dermal absorption.

Comments about Study/Endpoint: Long term dermal studies are not available for diflubenzuron therefore a chronic feeding study was chosen. However, since an oral NOAEL was selected for a dermal endpoint a dermal absorption factor of 0.5% should be used for this risk assessment when converting dermal exposure to oral equivalents. Therefore the dermal equivalent dose producing a NOAEL by the oral route is 400.0 mg/kg/day [i.e. 2.0 mg/kg/day ÷ 0.005 = 400.0 mg/kg/day.]

870.3465 90-Day Inhalation – Rat

Study Selected: Chronic Toxicity - Dog

MRID No.: 00146174

Executive Summary: See 870.4100b Chronic Toxicity – Nonrodent, below

Dose and Endpoint for Risk Assessment: NOAEL = 2.0 mg/kg/d based on methemoglobinemia and sulfhemoglobinemia at 10 mg/kg/day (LOAEL).

Comments about Study/Endpoint/Uncertainty Factor: An oral study was selected since no appropriate inhalation study is available in the database. This study is of appropriate duration of exposure. Assume that inhalation absorption is equivalent to oral absorption.

A.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rodent

Study Selected: Developmental Toxicity – Rat

MRID No.: 41703504

Executive Summary: In a developmental toxicity in rats, Technical grade diflubenzuron [97.6% pure] was administered in 1.0% gum tragacanth solution by oral gavage to 2 groups of 24 Sprague Dawley rats on days 6-15 of gestation at dose levels of either 0 or 1000 mg/kg/day [the limit dose]. No maternal or developmental toxicity was observed. For maternal and developmental toxicity, the NOAEL was 1000 mg/kg/day (Limit-Dose); a LOAEL was not achieved.

870.3700b Prenatal Developmental Toxicity Study – Nonrodent

Study Selected: Developmental Toxicity – Rabbit

MRID No.: 41703505

Executive Summary: In a developmental toxicity study with rabbits, Technical grade diflubenzuron [97.6% pure] was administered in 1.0% gum tragacanth solution by oral gavage to 2 groups of New Zealand White rabbits on days 7-19 of gestation at dose levels of either 0 or 1000 mg/kg/day [the limit dose]. No maternal or developmental toxicity was observed. For maternal and developmental toxicity, the NOAEL was 1000 mg/kg/day (Limit-Dose); a LOAEL was not achieved.

A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

Study Selected: 2-Generation Reproduction Study - Rats

MRID No.: 42700002

Executive Summary: In a 2-generation reproduction study in rats (Sprague-Dawley) complete in 1992, 30 rats/sex/dose received either 0, 10, 200, 2000, or 4000 ppm (0, 0.67, 13.3, 136, and 278 mg/kg/day for P0 males and 0, 0.76, 15.3, 152, and 3l1 mg/kg/day for P_0 females during the premating growth periods, respectively) of CGA-152005 (99.1% a.i.) mixed in the feed. Note that organ weights were not obtained in this study.

The study is classified as Core Minimum Data and satisfies the guideline requirement for a reproduction study.

A.3.4 Chronic Toxicity

870.4100a

Study Selected: Carcinogenicity/Oncogenicity Study - Rat

MRID No. 00145467

Executive Summary: See 870.4300 Carcinogenicity - Rat, below.

The combined chronic oral toxicity/oncogenicity study in the rat is classified Acceptable/guideline and satisfies the guideline requirements for a chronic toxicity and oncogenicity study in rats.

Adequacy of Dose Levels Tested: Dosing was considered adequate since the highest dose level tested, 500 mg/kg/day, approached the limit dose of 1000 mg/kg/day for cacinogenicity studies and significant toxicity (particulary methemoglobinemia, sulfhemoglobinemia, erythrocyte destruction, compensatory regeneration of erythrocytes and hemolytic anemia) was observed at this dose level.

870.4100b Chronic Toxicity – Nonrodent

Study Selected: Chronic Toxicity - Dog

MRID No.: 00146174

Executive Summary: In a 52-week chronic oral study, technical grade diflubenzuron was administered in gelatin capsules to beagle dogs once each day (7 days/week) at dose levels of 0 (control), 2, 10, 50 or 250 mg/kg/day. Groups of 6 male and 6 female dogs were used for each treated group and 12 male and 12 female dogs were used for the control group. Mortality, clinical signs, food consumption and water consumption were not affected by treatment with diflubenzuron. Except for a slight decrease in mean body weight gain observed in female dogs at 250 mg/kg/day, body weights were also not affected. Ophthalmoscopic examinations, clinical chemistries and urinalyses were negative. Statistically significant increases in methemoglobin and sulfhemoglobin were observed in male and female dogs at dose levels of ³10 mg/kg/day. Heinz bodies were also observed in the erythrocytes of male dogs at 250 mg/kg/day and in those of female dogs at ³50 mg/kg/day. At dose levels of 50 mg/kg/day and higher, signs of hemolytic anemia, destruction of erythrocytes and of compensatory regeneration of erythrocytes were observed. Increased platelet counts were also noted in females at ³50 mg/kg/day. Absolute spleen and liver weights, but not relative organ body weight ratios, were increased in male dogs at 50 and 250 mg/kg/day. Organ weights were not increased in female dogs. The NOAEL in this study is 2 mg/kg/day and the LOAEL is 10 mg/kg/day, based on methemoglobinemia and sulfhemoglobinemia.

Dose and Endpoint for Establishing RFD: NOAEL = 2.0 mg/kg/day based on methemoglobinemia and sulfhemoglobinemia at 10 mg/kg/day (LOAEL).

Uncertainty Factor(s):

$$\text{Chronic RfD} = \frac{2.0 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.02 \text{ mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: The HIARC concurred with the dose, end point, and the uncertainty factor selected by the RFD Committee in 1986.

A.3.5 Carcinogenicity

870.4200a Carcinogenicity – Rat

Study Selected: Oncogenicity Study - Rat

MRID No.: NTP Report No. 351, July 1989

Executive Summary: In a carcinogenicity study, p-choloroaniline (> 99% purity) was dissolved in equimolar equivalents of hydrochloric acid and administered by gavage (5 days/week) to F344/N rats at dose levels of 0, 2, 6, or 18 mg/kg/day for 24-months. Groups of 50 male and 50 female rats were used for each treated groups and the control group. Hematology examinations and mehtemoglobin measurements were conducted on 15 rats/sex/group at 6, 12, 18, and 24 months. Increased survival was observed in male rats at 2 and 6 mg/kg/day and in female rats at 2, 6, and 18 mg/kg/day relative to control rats. The authors of the study attributed the increased survival in these treatment groups to a decreased incidence of mononuclear cell leukemia in the same groups. Mean body weights for treated male and female groups generally remained within 5% of the control male and female weights throughout the study. Results of hematology examinations and methemoglobin measurements showed mild hemolytic anemia and dose-related increases in methemoglobin at dose levels of 6 and 18 mg/kg/day. Male rats at 6 and 18 mg/kg/day and female rats at 18 mg/kg/day had blue extremities indicative of cyanosis. Histopathological examinations indicated nonneoplastic treatment-related effects in spleen, liver, bone marrow and adrenal gland. Treatment-related increased incidence of uncommon sarcomas of the spleen was observed in male rats in this study. These sarcomas included fibrosarcomas, hemangiosarcomas, and osteosarcomas, many of which metastasized to other sites. The combined incidence of these sarcomas in male rats was 0/49, 3/50, and 38/50 at dose levels of 0, 2, 6 and 18 mg/kg/day, respectively. In addition, in female rats, 1 fibrosarcoma was observed at a 6 mg/kg/day and 1 osteosarcoma at 18 mg/kg/day. No additional uncommon sarcomas of the spleen were observed in female rats in this study. A marginally increased incidence of pheochromocytomas was also observed in the adrenal gland of male and female rats at 18 mg/kg/day. For male rats, the incidence was 13/49, 14/48, 15/48 and 26/49 and for female rats was 2/50, 3/50, 1/50, and 6/50 at dose levels of 0, 2, 6 and 18 mg/kg/day, respectively. Decreased incidences of mononuclear cell leukemias and of malignant lymphomas were also noted in the treated male and female rats in this study.

Systemic toxicity NOAEL was 2 mg/kg/day based on mild hemolytic anemia, dose-related increased in methemoglobin levels in males and females, cyanosis in females observed at 6 mg/kg/day (LOAEL).

This oncogenicity study in the rat is classified Acceptable/non-guideline and does not satisfy the guideline requirements for a oncogenicity study in rats.

Discussion of Tumor Data: Treatment-related increased incidence of uncommon sarcomas of the spleen was observed in male rats in this study. These sarcomas included fibrosarcomas, hemangiosarcomas, and osteosarcomas, many of which metastasized to other sites. The combined incidence of these sarcomas in male rats was 0/49, 3/50, and 38/50 at dose levels of 0, 2, 6 and 18 mg/kg/day, respectively. In addition, in female rats, 1 fibrosarcoma was observed at a 6 mg/kg/day and 1 osteosarcoma at 18 mg/kg/day. No additional uncommon sarcomas of the spleen were observed in female rats in this study. A marginally increased incidence of pheochromocytomas was also observed in the adrenal gland of male and female rats at 18 mg/kg/day. For male rats, the incidence was 13/49, 14/48, 15/48 and 26/49 and for female rats was 2/50, 3/50, 1/50, and 6/50 at dose levels of 0, 2, 6 and 18 mg/kg/day, respectively. Decreased incidences of mononuclear cell leukemias and of malignant lymphomas were also noted in the treated male and female rats in this study. There was no increased incidence neoplastic lesions in either male or female mice.

Adequacy of Dose Levels Tested: Dosing was considered adequate to test the carcinogenic potential of p-chloroaniline. Systemic toxicity (LOAEL) was observed in males and females at 6 mg/kg/day as evidenced by mild hemolytic anemia, dose-related increased in methemoglobin levels, and cyanosis in females. The NOAEL was 2 mg/kg/day.

870.4200b Carcinogenicity – Mouse

1) Study Selected: Oncogenicity Study - Mouse

MRID No. 00142490

Executive Summary: In a 91-week carcinogenicity study, technical grade diflubenzuron was administered in the diet to HC/CFLP strain mice at dose levels of 0, 16, 80, 400, 2000, or 10000 ppm (equivalent to 0, 2.4, 12, 60, 300, or 1500 mg/kg/day). Groups of 52 male and 52 female mice were used for each treated group and 104 male and 104 female mice were used for the control group. Mortality, body weights and food consumption were not affected by treatment with diflubenzuron. Increases in methemoglobin and sulfhemoglobin were consistently observed in male and female mice throughout the study at dose levels of 12 mg/kg/day and higher. A blue/gray discoloration of the skin and extremities and dark eyes accompanied the increased methemoglobin and sulfhemoglobin. At higher dose levels (particularly > 300 mg/kg/day), signs of hemolytic anemia, erythrocyte destruction and compensatory regeneration were observed as were histopathological effects in the liver. Treatment with diflubenzuron was not associated with an increased incidence of neoplastic lesions in either male or female mice. Dosing was considered adequate since the highest dose tested, 1500 mg/kg/day, exceeded the limit dose of 1000 mg/kg/day for carcinogenicity studies.

The systemic toxicity NOAEL is determined to be 2.4 mg/kg/day. The systemic toxicity LOAEL is 12 mg/kg/day based on increased methemoglobin and

sulfhemoglobin levels consistently observed in male and female mice throughout the study.

The study is classified Acceptable/guideline and it satisfies the guideline requirements for a carcinogenicity study in mice.

Discussion of Tumor Data: There was no increased incidence of neoplastic lesions in either male or female mice.

Adequacy of Dose Levels Tested: Dosing was considered adequate since the highest dose level tested, 1500 mg/kg/day, exceeded the limit dose of 1000 mg/kg/day.

2) Study Selected: Oncogenicity Study - Mouse

MRID No.: NTP Study, Report No. 351, July 1989.

Executive Summary: In a carcinogenicity study, p-choloroaniline (> 99% purity) was dissolved in equimolar equivalents of hydrochloric acid and administered by gavage (5 days/week) to B6C3F1 mice at dose levels of 0, 3, 10, or 30 mg/kg/day for 24-months. Groups of 50 male and 50 female mice were used for each treated group and the control group. Increased mortality was observed in male mice at 10 mg/kg/day after 99 weeks, but not at 30 mg/kg/day. Treatment did not affect mortality in female mice. Mean body weights for treated male and female groups were not affected by treatment with the test material. At 24 months, hemosiderin was observed in the kupffer cells of the livers of male and female mice and in the renal tubules of female mice at 30 mg/kg/day. Proliferation of hematopoietic cells was noted in the livers of female mice at all treatment levels. Increased incidence of combined hepatocellular adenomas/carcinomas were observed in the male mice in this study. Incidences were 11/50, 21/49, 20/50 and 21/50 at dose levels of 0, 3, 10, and 30 mg/kg/day, respectively. The increase in combined tumors were primarily due to a dose-related increase in hepatocellular carcinomas as follows: 3/50, 7/49, 11/50, and 17/50 at 0, 3, 10, and 30 mg/kg/day, respectively. Many of these carcinomas metastasized to the lungs (1/50, 1/49, 2/50, and 9/50 at 0, 3, 10, and 30 mg/kg/day, respectively). Increased incidence of hemangiosarcomas in the spleen and/or liver were also observed in the male mice in this study at 30 mg/kg/day. Incidences were 4/50, 4/49, 1/50, and 10/50 at dose levels of 0, 3, 10, and 30 mg/kg/day, respectively. Incidences of malignant lymphomas were decreased in the treated male and female mice. No evidence of carcinogenicity was observed in the female mice in this study.

Systemic toxicity NOAEL was 10 mg/kg/day based on hemosiderin accumulation in kupffer cells of the liver in male and female mice at 30 mg/kg/day (LOAEL).

This oncogenicity study in mice is classified Acceptable/non-guideline and does not satisfy the guideline requirements for a oncogenicity study in mice.

Discussion of Tumor Data: Increased incidence of combined hepatocellular adenomas/carcinomas were observed in the male mice in this study. Incidences were 11/50, 21/49, 20/50 and 21/50 at dose levels of 0, 3, 10, and 30 mg/kg/day, respectively. The increase in combined tumors were primarily due to a dose-related increase in hepatocellular carcinomas as follows: 3/50, 7/49, 11/50, and 17/50 at 0, 3, 10, and 30 mg/kg/day, respectively. Many of these carcinomas metastasized to the lungs (1/50, 1/49, 2/50, and 9/50 at 0, 3, 10, and 30 mg/kg/day, respectively). Increased incidence of hemangiosarcomas in the spleen and/or liver were also observed in the male mice in this study at 30 mg/kg/day. Incidences were 4/50, 4/49, 1/50, and 10/50 at dose levels of 0, 3, 10, and 30 mg/kg/day, respectively.

Adequacy of Dose Levels Tested: Dosing was considered adequate to test the carcinogenic potential of p-chloroaniline. Systemic toxicity (LOAEL) was observed in male and female mice at 30 mg/kg/day as evidenced by hemosiderin accumulation in kupffer cells of the liver. The NOAEL was 10 mg/kg/day.

870.4300 Chronic/Oncogenicity

Study Selected: Carcinogenicity Study - Rat

MRID No. 00145467

Executive Summary: In a 104-week carcinogenicity study, technical grade diflubenzuron was administered in the diet to Sprague-Dawley strain rats at dose levels of 0, 156, 625, 2500 or 10,000 ppm (equivalent to 0, 7.8, 31, 125 or 500 mg/kg/day). Groups of 50 male and 50 female rats were used for each treated group and 100 male and 100 female rats were used for the control group. Mortality, clinical signs, body weights and food consumption were not affected by treatment with diflubenzuron. Increases in methemoglobin and sulfhemoglobin were observed at all treatment levels. Histopathological signs of erythrocyte destruction and compensatory regeneration were observed at levels of >7.8 mg/kg/day. Signs of hemolytic anemia, increased resticulocytes and increased spleen and liver weights were noted at >125 mg/kg/day. Treatment with diflubenzuron was not associated with increased incidence of neoplastic lesions in either males or females. Dosing was considered adequate since the highest dose level tested, 500 mg/kg/day, approached the limit dose of 1000 mg/kg/day for cacinogenicity studies and significant toxicity (particulary methemoglobinemia, sulfhemoglobinemia, erythrocyte destruction, compensatory regeneration of erythrocytes and hemolytic anemia) was observed at this dose level. Systemic Toxicity NOAEL was not establised. The LOAEL is the lowest dose tested 7.8 mg/kg/day based on signs of erythrocyte destruction and compensatory regeneration.

This combined chronic oral toxicity/oncogenicity study in the rat is classified Acceptable/guideline and satisfies the guideline requirements for a chronic toxicity and oncogenicity study in rats.

Discussion of Tumor Data: There was no increased incidence of neoplastic lesions in either male or female rats.

Adequacy of Dose Levels Tested: Dosing was considered adequate since the highest dose level tested, 500 mg/kg/day, approached the limit dose of 1000 mg/kg/day for cacinogenicity studies and significant toxicity (particulary methemoglobinemia, sulfhemoglobinemia, erythrocyte destruction, compensatory regeneration of erythrocytes and hemolytic anemia) was observed at this dose level.

A.3.6 Mutagenicity

870.5100 Mutagenicty – Bacterial

MRID No.: 41703503

Executive Summary: In a Salmonella/mammalian microsome plate incorporation assay, strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to technical grade diflubenzuron with and without S9 metabolic activation at concentrations of 0, 8, 40, 200, or 1000 ·g/plate. The high dose was selected on the basis of slight compound precipitation at 1000 ·g/plaste. Preparations for metabolic S9 activation were made from Aroclor induced rat liver. The solvent used was DMSO. Diflubenzuron was not cytotoxic with or without S9 activation in any of the Salmonella strains in this assay. There was no evidence of induced mutant colonies over background levels at any of the evaluated concentrations.

870.5xxx Mutagenicty – Structural Chromosomal Aberrations

MRID No.: 41703502

Executive Summary: In an *in vitro* chromosome damage assay, cultures of Chinese hamster ovary (CHO) cells were exposed to technical grade diflubenzuron with and without S9 metabolic activation. The test material was tested at concentrations up to cytotoxic/precipitating levels of 200 - 250 ·g/ml. Preparations for S9 metabolic activation were made from Aroclor 1254 induced rat liver. The solvent used was DMSO. The test material did not induce an increase in structural chromosome aberrations over background levels at any of the evaluated concentrations.

870.5xxx Mutagenicty – Other

MRID No.: 41703501

Executive Summary: In an unscheduled DNA synthesis (UDS) assay, cultures of primary rat hepatocytes were exposed to technical grade diflubenzuron at concentrations ranging from 0.1 to 333 ·g/ml. At the high dose of 333 ·g/ml, cytotoxicity was oserved (36% cell survival in an initial assay and 8% cell survival in a confirmatory assay). The solvent used was DMSO. Positive controls were adequate.

The test material did not cause an appreciable increase in net nuclear grain counts compared to the solvent control at any of the evaluated concentrations. Diflubenzuron did not induce a gentoxic effect in this assay system.

A.3.7 Neurotoxicity

Acute and subchronic neurotoxicity studies are not required. There is no evidence in the available studies that dimilin targets the nervous system [RFD Committee Report of 03/16/1995].

A.3.8 Metabolism

870.7485 Metabolism – Rat

Study Selected: Metabolism Study - Rat

MRID No.: 44875501, 44875502

Recently submitted rat metabolism data indicate that diflubenzuron does not metabolize to PCA or CPU nor is CPU converted to PCA. The HEDMARC met several times (2/20/01 and 5/8/01), concurred with the findings and concluded that a 2% *in vivo* conversion factor for diflubenzuron to PCA or CPU should be dropped (MARC memo dated May 31, 2001). In conclusion, the MARC recommended that non-carcinogenic risk assessment should include parent, CPU and PCA; and cancer risk for CPU and PCA should be assessed individually.

870.7600 Dermal Absorption – Rat

Dermal Absorption Factor: 0.5 percent.

Twenty four male Sprague-Dawley rats were divided into two groups of 12 males each and given either 0.005 or 0.05 mg/cm.sq. of C-14 diflubenzuron technical in gum tragacanth [0.25%]. Four 4 animals per dose group were sacrificed after either 1, 4, or 10 hours of exposure. The control group consisted of 3 males with 1 animal sacrificed at the end of 1, 4, or 10 hours of exposure. Systemic absorption was less than 0.5% at each time interval regardless of the dose. Approximately 4.7 - 6.2% diflubenzuron was bound to the skin at the application site.

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