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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Diflubenzuron**, Toxicology Branch Chapter for the Reregistration Eligibility Decision Document (RED), Reregistration Case No. 0144

DP Barcode: D209025 Tox Chem No.: 346A
Submission No.: S476349 PC Code No.: 108201
Case: 819419

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Please find attached the Toxicology Branch Chapter for the Phase V RED for diflubenzuron.

DIFLUBENZURON

TOXICOLOGY BRANCH CHAPTER FOR RED

Reregis Case No.: 0144	Tox Chem No.: 346A
DP Barcode: D209025	PC Code No.: 108201
Submission No.: S476349	CAS Reg. No.: 35367-38-5

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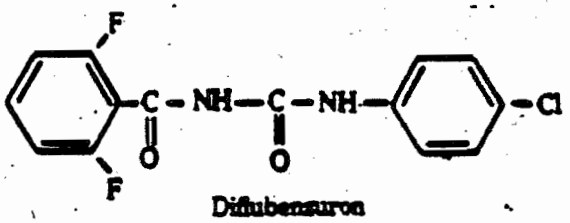
INTRODUCTION

Diflubenzuron is N-[[(4-chlorophenyl)amino] carbonyl]-2,6-difluorobenzamide. It is also known as 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea and as Du 112307 (discontinued research code name). Its trade names are Dimilin and Vigilante.

Diflubenzuron is an insect growth regulator primarily used on cotton, mushrooms, and in forests to control gypsy moths. It is also used on soybeans and woody ornamentals, in various locations to control larvae of flies, mosquitos and midges/gnats, and as a feed-through treatment for dairy and beef cattle. In addition, regional registrations for diflubenzuron include uses on cherries, citrus, walnuts, pastures and rangeland. Its mechanism of action is to interfere with the deposition of insect chitin.

Diflubenzuron is a white crystalline solid that is nearly insoluble in water and nonpolar solvents, but is soluble in most polar to very polar solvents including acetonitrile, acetone, dimethylsulfoxide, dimethylformamide and N-methylpyrolidone. Its structural formula is shown below.



Diflubenzuron

Two manufacturing-use products are presently registered--a 95% technical (EPA Reg No. 37100-10) and a 90% formulation intermediate (EPA Reg No. 37100-9). Both products are registered to Solvay Duphar B.V.

End-use products containing diflubenzuron include several 25% wettable powders (Dimilin W-25), a 2 lb/gal flowable concentrate (Dimilin 2F), and a 9.7% pellet/tablet formulation (Vigilante). The wettable powders and the flowable concentrate are generally applied as broadcast foliar sprays or as low volume or ultra low volume foliar sprays using ground or aerial equipment. The pellet/tablet formulation is administered to livestock as a controlled-release bolus.

Tolerances are established for residues of diflubenzuron *per se* in/on various raw agricultural commodities and animal feeds [40 CFR 180.377 (a) and (b) and 40 CFR 186.2000].

TOXICOLOGICAL ISSUES

1. A summary of the toxicology studies required to support the reregistration of diflubenzuron is presented in Table 1. The presently available toxicology data base is sufficient for the purposes of the Reregistration Eligibility Decision Document (RED). To support reregistration, however, the following additional studies should be submitted to the Agency for evaluation (confirmatory data).

   a. A repeat 21-day dermal study on technical diflubenzuron (Guideline 82-2) which demonstrates a NOEL for methemoglobinemia and/or sulfhemoglobinemia. The presently available study (MRID 00038716) did not demonstrate a NOEL for these effects.

   b. A new 21-day inhalation study on technical diflubenzuron which demonstrates a NOEL for methemoglobinemia and/or sulfhemoglobinemia. The presently available study (MRID 00044325) used a 25% Wettable Powder formulation, rather than the technical product, as the test material and also did not demonstrate a NOEL for methemoglobinemia and/or sulfhemoglobinemia.

2. The requirement for the following studies is reserved at this time. One or more of these studies may be required to be submitted in the future.

   a. Guideline 81-8 — Acute neurotoxicity (rat)
   b. Guideline 82-7 — 90-Day neurotoxicity (rat)
   c. Guideline 85-3 — Dermal penetration
   d. Guideline 85-7 — Immunotoxicity

3. Diflubenzuron per se has been classified by the HED RfD Peer Review Committee as a Group E carcinogen (evidence of non-carcinogenicity for humans). A metabolite of diflubenzuron, p-chloroaniline (PCA), however, has been classified by the same committee as a Group B2 carcinogen (probable human carcinogen), based on the results of a National Toxicology Program (NTP) report issued in July, 1989. Another closely related metabolite of diflubenzuron, p-chlorophenylurea (CPU), is also considered by the committee to be potentially carcinogenic. The committee has concluded that estimations of the carcinogenic risk to humans resulting from chronic dietary exposure to food commodities that contain PCA and/or CPU should performed. The Q_1^* (estimated unit risk) for PCA is 6.38×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents.

4. Regarding carcinogenic risk assessments for occupational or residential exposure to diflubenzuron, it is anticipated that such risk assessments will not be necessary unless

direct exposure to the metabolites PCA and/or CPU is demonstrated under conditions of use.

5. Where no exposure to PCA and/or CPU is anticipated, toxicological endpoints for diflubenzuron per se should be used for risk assessments. The appropriate endpoints to be used are presented below.

Chronic dietary exposure--The RfD of 0.02 mg/kg/day, derived from a 52-week oral study in dogs with a NOEL of 2 mg/kg/day, should be used. The endpoint in this study was methemoglobinemia/sulfhemoglobinemia.

Intermediate term occupational or residential exposure--A NOEL of 2 mg/kg/day, derived from a 13-week feeding study in dogs, should be used. The endpoint in this study was methemoglobinemia.

Short term occupational or residential exposure--A NOEL of 40 mg/kg/day, derived from a 14-day oral study in mice, should be used. The endpoint in this study was sulfhemoglobinemia.

Acute dietary exposure (1 day)--An endpoint for acute dietary exposure was not identified.

Table 1. Diflubenzuron: Toxicology Studies Required to Support Reregistration

Guideline	Study Identification	Required	Satisfied	Comment
81-1	Acute oral toxicity	Yes	Yes	1
81-2	Acute dermal toxicity	Yes	Yes	1
81-3	Acute inhalation toxicity	Yes	Yes	1
81-4	Primary eye irritation	Yes	Yes	1
81-5	Primary dermal irritation	Yes	Yes	1
81-6	Dermal sensitization	Yes	Yes	
81-7	Delayed neurotoxicity (hen)	No	---	
81-8	Acute neurotoxicity (rat)	Reserved	---	2
82-1(a)	90-Day oral, rodent	Yes	Yes	
82-1(b)	90-day oral, nonrodent	Yes	Yes	
82-2	21-Day dermal	Yes	No	3
82-3	90-Day dermal	No	---	
82-4	Subchronic inhalation	Yes	No	4
82-6	28-Day delayed neurotox (hen)	No	---	
82-7	90-Day neurotoxicity (rat)	Reserved	---	2
83-1(a)	Chronic feeding, rodent	Yes	Yes	
83-1(b)	Chronic feeding, nonrodent	Yes	Yes	
83-2(a)	Carcinogenicity (rat)	Yes	Yes	
83-2(b)	Carcinogenicity (mouse)	Yes	Yes	
83-3(a)	Develop. toxicity (rat)	Yes	Yes	
83-3(b)	Develop. toxicity (rabbit)	Yes	Yes	
83-4	Reproduction	Yes	Yes	
83-6	Postnatal develop. tox.	No	---	
84-2	Muta./gene mutation assay	Yes	Yes	
84-2	Muta./struc. chrom. aberr.	Yes	Yes	
84-2	Muta./other genotoxicity	Yes	Yes	
85-1	General metabolism	Yes	Yes	
85-2	Domestic animal safety	No	---	
85-3	Dermal penetration	Reserved	---	2
85-4	Visual system studies	No	---	
85-7	Immunotoxicity	Reserved	---	2

1. Test material was diflubenzuron VC-90 (90% formulation intermediate).
2. Not required at this time, but may be required later.
3. Available study did not demonstrate a NOEL. A repeat study is required to be submitted (confirmatory data).
4. Available 21-day study (on 25% WP) did not demonstrate a NOEL. A new 21-day study (on technical diflubenzuron) is required to be submitted (confirmatory data).

B. Human Health Assessment

1. Toxicology Assessment

The toxicology data base in support of the food and non-food uses of diflubenzuron is adequate and will support reregistration eligibility. However, two new studies are required to be submitted as confirmatory data (see Table 1 of this document).

a. Acute Toxicity

Acute toxicity data for diflubenzuron are presented in the table below.

Acute Toxicity

Test	Result	Category
Acute Oral LD_{50} (rat)[1,a]	> 5,000 mg/kg	IV
Acute Dermal LD_{50} (rat)[2,a]	> 2,000 mg/kg	III
Acute Inhalation LC_{50} (rat)[3,a]	> 2.49 mg/L	IV
Eye Irritation (rabbit)[4,a]	Mild Irritant	III
Dermal Irritation (rabbit)[5,a]	No Irritation	IV
Skin Sensitization (guinea pig)[6,b]	Negative	N/A

[1-6] MRIDs 00157103, 00157104, 00163311, 00157105, 00157106 and 42251101.
[a] Test material was diflubenzuron VC-90 (90% diflubenzuron).
[b] Test material was technical grade diflubenzuron (95% purity).
N/A = not applicable.

b. Subchronic Toxicity

Technical grade diflubenzuron was administered by gavage each day for 14 days to 10 Swiss strain male mice at dose levels of 8, 40, 200, 1000 or 5000 mg/kg/day. Twenty male mice, treated similarly with vehicle only, served as a control group. At 15 days, significantly increased ($p < 0.05$) levels of methemoglobin were observed at 1000 and 5000 mg/kg/day and significantly increased ($p < 0.05$) levels of sulfhemoglobin 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. The NOEL is 40 mg/kg/day. The LEL is 200 mg/kg/day, based on increased sulfhemoglobin. (MRID 00099713)

In a 28-day feeding study, technical grade diflubenzuron was administered in the diet to CFY strain rats at dose levels of 0 (control), 800, 4000, 20000 or 100000 ppm (equivalent to 0, 40, 200, 1000 or 5000 mg/kg/day). Groups of 5 male and 5 female rats were used for each treated and control group. Methemoglobin was increased in males at all dose levels and in females at dose levels of 200 mg/kg/day and higher. Sulfhemoglobin was increased in all treated males and females. Decreased erythrocyte counts, packed cell volumes and hemoglobin were observed in males and females at 5000 mg/kg/day. A dose-related increase in spleen weights at all dose levels and in liver weights at dose levels of 200 mg/kg/day and higher was also observed. No NOEL was established in this study since treatment-related effects were observed at 40 mg/kg/day, the lowest dose level tested. The LEL is 40 mg/kg/day, based on increased methemoglobin in males, increased sulfhemoglobin in males and females and increased spleen weights in males and females. (MRID 00070018)

In a 13-week feeding study, technical grade diflubenzuron was administered in the diet to Sprague-Dawley strain rats at dose levels of 0 (control), 160, 400, 2000, 10000 or 50000 ppm (equivalent to 0, 8, 20, 100, 500 or 2500 mg/kg/day). Groups of 40 male and 40 female rats were used for each treated group and 90 male and 90 female rats were used for the control group. Mortality, clinical signs, body weights and food consumption were not affected by treatment with diflubenzuron. Methemoglobinemia was observed in male and female rats at all dose levels. Sulfhemoglobinemia was also observed in male and female rats at dose levels of 100 mg/kg/day and higher and Heinz bodies at dose levels of 500 and 2500 mg/kg/day. In addition, decreased erythrocyte counts and decreased hemoglobin were noted in male and female rats at all dose levels and increased reticulocytes at dose levels of 20 mg/kg/day and higher. At the terminal sacrifice, spleen and liver weights were increased at dose levels of 20 mg/kg/day and higher. At all dose levels, histopathological examinations indicated dose related increases of hemosiderosis and congestion of the spleen, hemosiderosis and chronic hepatitis of the liver, and mild erythroid hyperplasia of the bone marrow. No NOEL was established in this study since treatment-related effects were observed at the lowest dose level tested. The LEL is 8 mg/kg/day, based on increased methemoglobin and signs of hemolytic anemia, erythrocyte destruction in the spleen and liver and regeneration of erythrocytes in the bone marrow. In a later submission by the registrant, NOELs of 2.1 and 1.5 mg/kg/day for males and females respectively for methemoglobinemia and NOELs of 3.1 and 9.1 mg/kg/day for males

and females respectively for sulfhemoglobinemia were calculated by regression analysis (based on 7 week data). (MRID 00064550, 00074534)

In a 14-week feeding study, technical grade diflubenzuron was administered in the diet to HC/CFLP strain mice at dose levels of 0 (control), 80, 400, 2000, 10000 or 50000 ppm (equivalent to 0, 12, 60, 300, 1500 or 7500 mg/kg/day). Groups of 40 male and 40 female mice were used for each treated group and 96 male and 96 female mice were used for the control group. Mortality, body weights and food consumption were not affected by treatment. Methemoglobinemia and sulfhemoglobinemia (accompanied by Heinz bodies) were observed in male and female mice at all dose levels. Decreased erythrocyte counts, decreased packed cell volume and increased reticulocytes were noted at dose levels of 60 mg/kg/day and higher. At the terminal sacrifice, spleen weights were increased at $\geq$ 60/mg/kg, liver weights were increased at $\geq$ 300 mg/kg/day, seminal vesicle weights were decreased at $\geq$ 300 mg/kg/day and kidney weights were decreased at $\geq$ 1500 mg/kg/day. At dose levels of $\geq$ 60 mg/kg/day, histopathological examinations indicated hemosiderosis of the spleen and in the liver, hepatocytic enlargement, hepatocytic cytoplasmic vacuolation, inflammatory foci and necrosis in varying degrees. No NOEL was established in this study. The LEL is 12 mg/kg/day, based on increased methemoglobinemia and sulfhemoglobinemia. In a later submission by the registrant, NOELs of 3.3 and 1.9 mg/kg/day for males and females respectively for methemoglobinemia and a NOEL of 2.6 mg/kg/day for males for sulfhemoglobinemia were calculated by regression analysis (based on 7 week data). (MRID 00114330, 00074534)

In a 13-week feeding study, technical grade diflubenzuron was administered in the diet to beagle dogs at dose levels of 0 (control), 10, 20, 40 or 160 ppm (equal to 0, 0.42, 0.84, 1.64 or 6.24 mg/kg/day). Groups of 3 male and 3 female dogs were used for each treated and control group. 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 6.24 mg/kg/day (after 6 weeks). No gross necropsy, organ weight or histopathological changes were reported at any level that could be related to treatment with diflubenzuron. The NOEL is 1.64 mg/kg/day. The LEL is 6.24 mg/kg/day, based on increased methemoglobinemia. (MRID 00038706)

In a 21-day dermal study, 21.5%, 10% or 4.64% suspensions of technical grade diflubenzuron suspended in aqueous 0.5% gum tragacanth were applied 5 days/week to the shaved dorsal skin of 10 male and 10 female New Zealand white rabbits. Each application was at the rate of 1.5 ml/kg/day. One-half of the animals in each group were abraded and one-half were nonabraded. Ten male and 10 female control animals received vehicle only.

Slight erythema was occasionally observed in some animals, but was sporadic and could not be related to the test material. Mortality, clinical signs, body weights, food consumption and hematology were negative. Increased methemoglobin was observed in all groups treated with test material. Gross necropsies, organ weight measurements and histopathological examination of tissues were negative. No NOEL was established in this study since treatment-related effects were observed at the lowest dose level tested. The LEL is calculated to be 69 mg/kg/day (based on a 4.64% suspension being applied at the rate of 1.5 ml/kg/day). (MRID 00038716). A repeat 21-day dermal study on technical grade diflubenzuron which demonstrates a NOEL for methemoglobinemia and sulfhemoglobinemia is required to be submitted (confirmatory data).

In a 21-day inhalation study designed to study methemoglobinemia, Sprague-Dawley strain rats were exposed to dust concentrations of 0 (control), 0.121, 0.866 or 1.85 mg/liter of Diflubenzuron 25% Wettable Powder. Exposures were for 1 hour/day, 5 days/week for 3 weeks. Five male and five female rats were used for each treated and control group. Particle sizes were in the respirable range. An increase in methemoglobin was observed in all treated groups of both sexes. Reticulocyte counts were unaffected by treatment. No NOEL was established in this study since treatment-related effects were observed at the lowest dose level tested. The LEL is 0.121 mg/liter (of 25% wettable powder). (MRID 00044325). A new 21-day inhalation study on technical grade diflubenzuron which demonstrates a NOEL for methemoglobinemia and sulfhemoglobinemia is required to be submitted (confirmatory data).

Neither a 90-day dermal study nor a 90-day inhalation study is required to support the reregistration of diflubenzuron.

c. Chronic Toxicity

In a 104-week chronic feeding study, technical grade diflubenzuron was administered in the diet to Sprague-Dawley strain rats at dose levels of 0 (control), 10, 20, 40 or 160 ppm (equivalent to 0, 0.35, 0.70, 1.43 or 5.83 mg/kg/day in males and to 0, 0.43, 0.88, 1.73 or 7.05 mg/kg/day in females). Sixty male and 60 female rats comprised each dose level. Information in this study was used to establish a NOEL for methemoglobinemia and sulfhemoglobinemia in chronic rat studies in which the test material was administered by the oral route. Other experimental parameters determined in this study were judged to be of no usefulness. Examinations of blood were conducted at weeks 13, 26, 52, 78 and 102. Sulfhemoglobin and methemoglobin formation were assayed for the control, 40 and 160 ppm groups only. Sulfhemoglobin formation was not detected in this study (below the level of detectibility). The NOEL for methemoglobinemia in this study was determined to be 1.43 mg/kg/day in males and 1.73

mg/kg/day in females. The LEL is 5.83 mg/kg/day in males and 7.05 mg/kg/day in females. (MRID 00044329, 00099712)

In a 104-week chronic feeding study, technical grade diflubenzuron was administered in the diet to Sprague-Dawley strain rats at dose levels of 0 (control), 156, 625, 2500 or 10000 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. Statistically significant increases in methemoglobin and sulfhemoglobin were consistently observed in male and female rats at 52 weeks and 104 weeks at all treatment levels tested. The increases tended to be dose-related. At higher dose levels (particularly $\geq$ 125 mg/kg/day), signs of hemolytic anemia were observed in males and females at 52 weeks, but not at 104 weeks. At similar dose levels, increased reticulocytes were also noted in males and females at 52 weeks, but only in females at 104 weeks. Increased spleen and liver weights were observed in males and females at $\geq$ 125 mg/kg/day. Histopathological signs of erythrocyte destruction and compensatory regeneration were observed in both males and females at dose levels of $\geq$ 7.8 mg/kg/day. No NOEL was established in this study. The LEL is 7.8 mg/kg/day, the lowest dose level tested. (MRID 00145467)

In a 91-week chronic feeding study, technical grade diflubenzuron was administered in the diet to HC/CFLP strain mice at dose levels of 0 (control), 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. Additional mice (36/sex/treated group and 72/sex/control group) were used for hematology, blood chemistry and urinalyses at 26, 52, 78 and about 90 weeks and for interim sacrifices at 26 and 52 weeks. Mortality, body weights, food consumption, blood chemistries and urinalyses were not affected by treatment with diflubenzuron. Dose-related, statistically significant 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 $\geq$ 300 mg/kg/day), signs of hemolytic anemia, erythrocyte destruction and compensatory regeneration were observed in both males and females. At similar dose levels, histopathological effects in the liver were also observed. These effects included hepatocyte enlargement, hepatocyte vacuolation and congested/dilated centrilobular sinusoids. Increased platelet counts were also reported at $\geq$ 60 mg/kg/day in both males and females. The NOEL in this study is 2.4 mg/kg/day and the LEL is 12 mg/kg/day.

Effects observed at the LEL were methemoglobinemia and sulfhemoglobinemia. (MRID 00142490)

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 $\geq$ 10 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 $\geq$ 50 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 $\geq$ 50 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 NOEL in this study is 2 mg/kg/day and the LEL is 10 mg/kg/day, based on methemoglobinemia and sulfhemoglobinemia. (MRID 00146174)

d. Carcinogenicity

In a 104-week carcinogenicity study, technical grade diflubenzuron was administered in the diet to Sprague-Dawley strain rats at dose levels of 0 (control), 156, 625, 2500 or 10000 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 dose levels of $\geq$ 7.8 mg/kg/day. Signs of hemolytic anemia, increased reticulocytes and increased spleen and liver weights were noted at $\geq$ 125 mg/kg/day. Treatment with diflubenzuron was not associated with an increased incidence of neoplastic lesions in either males or females. Dosing was adequate since the highest dose level tested, 500 mg/kg/day, approached the limit dose of 1000 mg/kg/day for carcinogenicity studies and significant toxicity (particularly methemoglobinemia, sulfhemoglobinemia, erythrocyte destruction, compensatory regeneration of erythrocytes and hemolytic anemia) was observed at this dose level. (MRID 00145467)

In a 91-week carcinogenicity study, technical grade diflubenzuron was administered in the diet to HC/CFLP strain mice at dose levels of 0 (control), 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 $\geq$ 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 males or females. Dosing was adequate since the highest dose tested, 1500 mg/kg/day, exceeded the limit dose of 1000 mg/kg/day for carcinogenicity studies. (MRID 00142490)

Carcinogenicity Studies on p-Chloroaniline (Metabolite of Diflubenzuron)

In a 24-month carcinogenicity study, p-chloroaniline (>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 (vehicle control), 2, 6 or 18 mg/kg/day of p-chloroaniline (PCA). Groups of 50 male and 50 female rats were used for each treated group and the control group. Hematology examinations and methemoglobin 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 the spleen, liver, bone marrow and adrenal gland. A treatment-related increased incidence of uncommon sarcomas of the spleen was observed in the 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, 1/50, 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 6 mg/kg/day and 1 osteosarcoma at 18 mg/kg/day. No additional uncommon sarcomas of the spleen were observed in the 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. [Reference 1; National Toxicology Program (NTP) Report No. 351; July, 1989]

In a 24-month carcinogenicity study, p-chloroaniline (>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 (vehicle control), 3, 10 or 30 mg/kg/day of p-chloroaniline. 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 incidences 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 was 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 incidences 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. [Reference 1; National Toxicology Program (NTP) Report No. 351; July, 1989]

e. Developmental Toxicity

In a developmental toxicity study, technical grade diflubenzuron was administered by gavage to groups of 24 Sprague-Dawley strain female rats on days 6 through 15 of gestation at dose levels of 0 (control) or 1000 mg/kg/day (limit-dose study). No maternal toxicity or toxicity to the developing fetus was

observed. The NOEL for maternal toxicity is 1000 mg/kg/day and the NOEL for developmental toxicity is 1000 mg/kg/day. (MRID 41703504)

In a developmental toxicity study, technical grade diflubenzuron was administered by gavage to groups of 16 New Zealand white strain female rabbits on days 7 through 19 of gestation at dose levels of 0 (control) or 1000 mg/kg/day (limit-dose study). No maternal toxicity or toxicity to the developing fetus was observed. The NOEL for maternal toxicity is 1000 mg/kg/day and the NOEL for developmental toxicity is 1000 mg/kg/day. (MRID 41703505)

f. Reproductive Toxicity

In a 2-generation reproduction study, technical grade diflubenzuron was administered in the diet to Sprague-Dawley strain rats at dose levels of 0 (control), 500, 5000 or 50000 ppm (equivalent to about 0, 25, 250 or 2500 mg/kg/day). Starting at 6 weeks of age, F0 animals (32/sex/dose level) were treated continuously for 10 weeks prior to mating at 16 weeks of age and until completion of weaning of all F1 litters at 21 days post-partum. Direct treatment of the F1 generation (28/sex/dose level) was initiated at about 4 weeks of age and continued to mating at 16 weeks of age and until all of the F2 litters were weaned. Treatment-related effects were observed in F0 and F1 adults at all dose levels. The most prominent of these effects were increased methemoglobin levels, hemolytic anemia and signs of erythrocyte destruction. Additional signs of toxicity observed at 250 and 2500 mg/kg/day in F0 and F1 animals included pathological effects in the spleen and liver. No effects on reproductive performance were observed at any dose level in F0 or F1 males or females in this study. Regarding litter parameters, litter and mean pup weights were slightly decreased from birth to 21 days post-partum in F1 offspring at 2500 mg/kg/day. No NOEL for parental adults is identified in this study. The LEL is 25 mg/kg/day, based on methemoglobinemia, hemolytic anemia, destruction of erythrocytes, and pathological changes in the spleen and liver. The NOEL for reproductive performance in parental adults is 2500 mg/kg/day. The NOEL for developmental effects in offspring is 250 mg/kg/day. The LEL is 2500 mg/kg/day, based on decreased body weights in F1 pups from birth to 21 days post-partum. (MRID 43578301)

g. Mutagenicity

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 ug/plate. The high dose was selected on the basis of slight compound precipitation at 1000 ug/plate. Preparations for

metabolic S9 activation were made from Aroclor 1254 induced rat liver. The solvent used was DMSO. Positive controls were adequate. 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. (MRID 41703503)

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 ug/ml. Preparations for S9 metabolic activation were made from Aroclor 1254 induced rat liver. The solvent used was DMSO. Positive controls were adequate. The test material did not induce an increase in structural chromosome aberrations over background levels at any of the evaluated concentrations. (MRID 41703502)

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 ug/ml. At the high dose of 333 ug/ml, cytotoxicity was observed (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 genotoxic effect in this assay system. (MRID 41703501)

h. Metabolism

The absorption, distribution, metabolism and excretion of diflubenzuron were studied in male and female Sprague-Dawley rats administered oral doses of ^{14}C-diflubenzuron (by gavage) at single dose levels of 5 or 100 mg/kg or at a dose level of 5 mg/kg following 14 days of unlabeled diflubenzuron in the diet at a dose level of 5 mg/kg/day. An additional group of rats, with cannulated bile ducts, was given a single oral dose of 5 mg/kg of ^{14}C-diflubenzuron. Diflubenzuron was only partially absorbed from the gastrointestinal tract. In the bile duct cannulated rats, about 33% of the administered dose was absorbed and of the amount absorbed, about 50% (17% of the administered dose) was excreted in the bile. At low doses of 5 mg/kg, 19-21% of the administered dose was recovered in the urine and 77-80% in the feces by 7 days and at the high dose of 100 mg/kg, about 3% was recovered in the urine and 96% in the feces by 7 days. Radioactivity in expired air was negligible. The half-life of radioactivity in blood was about 14 hours. By 7 days, over 98% of the administered radioactivity was excreted. Very little bioaccumulation in tissues was observed. At 48 hours, the highest levels of radioactivity were observed in the erythrocytes

and liver. Ten urinary metabolites were identified, including p-chloroaniline (PCA) and p-chlorophenylurea (CPU), which together accounted for about 2% of the administered dose (at 5 mg/kg). In the feces, only unchanged parent compound was detected. No sex differences were observed. (MRID 41720901, 41919001)

i. Neurotoxicity

No potential for neurotoxicity has been observed in any of the animal laboratory studies with diflubenzuron. Neither an acute delayed neurotoxicity study in hens nor a 28-day delayed neurotoxicity study in hens is required. The requirements for an acute neurotoxicity study in rats and a 90-day neurotoxicity study in rats are reserved.

j. Dermal Penetration and Immunotoxicity

The requirement for a dermal penetration study is reserved. A study may be required at a later time. The requirement for immunotoxicity testing is reserved. Information may be required to be submitted at a later time.

k. Endpoints to be used for Risk Assessment

Carcinogenicity: Based on the available evidence, which included adequate carcinogenicity studies in rats and mice (MRID 00145467, 00142490) and a battery of negative mutagenicity studies, diflubenzuron per se was classified as a Group E carcinogen (evidence of non-carcinogenicity for humans) by the HED RfD Peer Review Committee on March 16, 1995. At the same meeting, however, p-chloroaniline (PCA), a metabolite of diflubenzuron, was classified as a Group B2 carcinogen (probable human carcinogen). The classification for PCA was based on the results of a National Toxicology Program (NTP) study reported in July, 1989 (Reference 1) in which p-chloroaniline hydrochloride was administered by gavage to rats and mice for 2 years. In rats, clearly increased incidences of uncommon sarcomas (fibrosarcomas, hemangiosarcomas and/or osteosarcomas) of the spleen were observed in males. In females, 2 additional sarcomas of the spleen were also found. Pheochromocytomas of the adrenal gland may also have been associated with the test material in male and female rats. In mice, increased incidences of hepatocellular neoplasms in the liver and of hemangiosarcomas in the spleen and/or liver were observed in males. In females, no evidence of carcinogenic activity was observed. The results of several mutagenicity studies on PCA were also included in the same NTP report (studies not included in this RED). PCA was mutagenic in Salmonella strains TA98 and TA100 with metabolic activation. Gene mutations were induced by PCA in cultured mouse lymphoma cells with and without metabolic activation. In cultured Chinese hamster ovary (CHO) cells, treatment with PCA produced significant increases in sister chromatid exchanges

(SCEs) with and without metabolic activation. Chromosomal aberrations were also significantly increased in CHO cells in the presence of metabolic activation.

The Q_1^* (estimated unit risk) for PCA, based upon spleen sarcoma rates in male rats, was calculated to be 6.38×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents (Reference 2).

The HED Metabolism Committee met several times in 1993-1994 to consider diflubenzuron and recommended that estimations of the carcinogenic risk to humans resulting from chronic dietary exposure should be performed for food commodities that contain PCA, CPU and/or PCAA (see below). For the purpose of calculating dietary risk assessments, the following procedure was suggested by the committee (Reference 3):

1) p-chlorophenylurea (CPU) and p-chloroacetanilide (PCAA), additional metabolites of diflubenzuron that are closely related to PCA and for which there are no adequate carcinogenicity data available, should be considered to be potentially carcinogenic and to have the same carcinogenic potency (Q_1^*) as PCA.

   Note--It has subsequently been determined that PCAA does not occur in animal or plant tissues in significant amounts. See Chemistry Branch Chapter for the RED (April, 1995).

2) The sum of PCA, CPU and PCAA residues in ingested food should be used to estimate the dietary exposure of humans to the carcinogenic metabolites of diflubenzuron.

3) In addition to ingested residues of these three metabolites, amounts of PCA, CPU and/or PCAA formed in vivo following ingestion of diflubenzuron should also be included when estimating the total exposure of humans to the carcinogenic metabolites of diflubenzuron. The in vivo conversion of ingested diflubenzuron to PCA and/or CPU was estimated to be 2.0%, based on data in the rat metabolism study (MRID 41720901, 41919001)(Reference 4).

The HED Metabolism Committee also concluded that where no PCA, CPU and/or PCAA are present, the toxicological endpoint for diflubenzuron per se should be used for risk assessments.

Regarding potential carcinogenic risks to humans resulting from dermal and/or inhalation exposures to PCA, CPU and/or PCAA occurring during occupational or residential exposures to diflubenzuron, it has been determined that these risks are likely to be negligible since exposure to these metabolites is not

anticipated. Only in the event that direct exposure to one or more of these metabolites of diflubenzuron is demonstrated would it be necessary to perform such risk assessments.

Chronic dietary exposure--Reference Dose (RfD): The RfD for diflubenzuron is 0.02 mg/kg/day and is based on the NOEL of 2 mg/kg/day in the 52-week chronic oral study in dogs (MRID 00146174). An uncertaintly factor (UF) of 100 was used to calculate the RfD. At the LEL of 10 mg/kg/day, the effects in the dog study were methemoglobinemia and sulfhemoglobinemia. The RfD was approved by the HED RfD Peer Review Committee on March 16, 1995 (Reference 5).

The HED Less Than Lifetime (LTL) Committee met on March 16, 1995 to identify toxicology endpoints and dose levels of concern for use in risk assessments corresponding to the categories shown below. A Toxicology Endpoint Selection Document, dated April 4, 1995, (Reference 6) was prepared by Toxicology Branch I to summarize the results of this meeting.

Intermediate term occupational or residential exposure (1 week to several months): The Toxicology Endpoint Selection Document recommends that risk assessments be performed for intermediate term occupational or residential exposures. The endpoint is methemoglobinemia observed in the 13-week subchronic feeding study in dogs (MRID 00038706). For the purpose of risk assessments, the NOEL of 1.64 mg/kg/day in this study should be considered to be 2 mg/kg/day so as to be consistent with the NOEL of 2 mg/kg/day in the chronic study used to calculate the RfD. The LEL in this study was 6.24 mg/kg/day.

Short term occupational or residential exposure (1 to 7 days): The Toxicology Endpoint Selection Document recommends that risk assessments also be performed for short term occupational or residential exposures. The endpoint is sulfhemoglobinemia observed in the 14-day subchronic oral study in mice (MRID 00099713). The NOEL in this study was 40 mg/kg/day and the LEL was 200 mg/kg/day.

Acute dietary exposure (1 day): The Toxicology Endpoint Selection Document indicates that risk assessments for acute dietary exposures are not necessary. One day single dose oral studies in rats and mice indicated only marginal effects on methemoglobin levels at a dose level of 10,000 mg/kg of 25% Wettable Powder formulation (studies not included in this RED). Sulfhemoglobin levels and Heinz bodies were not affected.

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