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MEMORANDUM

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Attached is the Toxicology Chapter for the Reregistration Eligibility Decision (RED) Document for oxyfluorfen. It contains a hazard characterization summary and executive summaries of toxicity reviews. The older studies used approximately 71% active ingredient technical material while the newer studies used the currently registered technical material of 97.4% and 99% oxyfluorfen. This document also reports conclusions of the Hazard Identification Assessment Review Committee and the Cancer Assessment Review Committee.

OXYFLUORFEN: TOXICOLOGY CHAPTER FOR RED

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1.0 HAZARD CHARACTERIZATION

Oxyfluorfen is a diphenyl ether herbicide structurally related to lactofen and acifluorfen. The diphenyl ether herbicides act by inhibiting protoporphyrinogen oxidase, which is the second-to-last enzyme in chlorophyll biosynthesis. This enzyme is the second-to-last enzyme in heme synthesis, as well (Birchfield and Casida, *Pesticide Biochemistry and Physiology*, 1997).

The older toxicity studies with oxyfluorfen used technical material of approximately 71% or 85% purity. The newer toxicity studies used a technical material of approximately 98% purity, which is the basis for the current registrations of oxyfluorfen (97.4% or 99% on labels for the 2 registrations). The newer technical material has similar impurities to the older technical material, but in reduced concentrations.

New studies with the current 98% product were submitted: subchronic toxicity in rats, developmental toxicity in rats and rabbits, a battery of mutagenicity studies, and a battery of acute studies. Toxicity was less severe for studies with the 98% product than for the 71% product.

When there were studies with both the new and old technical material, consideration for an endpoint for risk assessment purposes was given to the newer, 98% technical material which is the basis of the current registrations. The studies described in this document had doses adjusted for per cent a.i. and/or for analytical concentrations determined in the diet.

Oxyfluorfen is of low acute toxicity and is in toxicity category IV for acute oral and inhalation toxicity and is category III for acute dermal toxicity. Oxyfluorfen is a slight eye and dermal irritant and is not a dermal sensitizer.

Both subchronic and chronic studies showed that toxicity at lower doses was generally not severe. Although oxyfluorfen inhibits heme synthesis, the observed anemia was generally mild. A microcytic anemia with a decreased hematocrit, small erythrocytes, and normal RBC count was described in the 1997 subchronic rat study. In other words, the red blood cell count was normal in this study, but the red blood cell mass was decreased because of the small size of the red blood cells, presumably because of inhibition of the protoporphyrinogen oxidase enzyme. The anemia was generally mild in other studies, with varying hematologic abnormalities described in the different studies.

Mild liver toxicity also occurred. Liver weights were increased and were accompanied in several studies by slightly elevated serum alkaline phosphatase enzyme, which can be elevated by increased pressure in biliary canals in the liver, as well as by other causes in other locations in the body. Other liver enzymes also had slight elevations in the various studies. There were typically few histopathological lesions seen in the liver, although hepatocyte necrosis was occasionally noted in the different studies.

Renal toxicity was most severe in the 2-generation reproduction study in rats, in which pelvic mineralization occurred. Other studies had indications of renal toxicity: increases in organ weight and occasional histopathological observations.

Other toxicological changes included weight loss, clinical signs, lacrimation, increased urine volume, and mortality.

Developmental studies with the current 98% technical material found no developmental toxicity in rats whereas an increase in late resorptions occurred in the rabbit study (principally in 1 litter). A developmental study in rats with the older 71% technical material found increased

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early resorptions, decreased fetal weight, and increased incidence of fetal visceral and skeletal variations and malformations. A developmental study in rabbits with formulation manufactured from the older technical material found increased early resorptions and decreased litter size. A reproduction study with 71% technical material reported decreased live pups per litter and decreased pup body weights.

The current technical material was tested in 12 genetic toxicology studies, all of which were negative, except for one Ames assay which was positive. A second Ames assay with 96% material was negative. The older 71% technical material and a polar fraction were tested in 8 genetic toxicology studies, of which 3 Ames assays were positive, as was a mouse lymphoma study.

Oxyfluorfen is classified as a category C, possible human carcinogen based upon combined hepatocellular adenomas/carcinomas in the mouse carcinogenicity study. The Cancer Peer Review Committee recommended a linear, low dose extrapolation for human risk assessments, with a Q_1^* of 7.32×10^{-2} .

There is no evidence of increased sensitivity of fetuses or offspring due to pre- or postnatal exposure to oxyfluorfen.

Oxyfluorfen and other herbicidal inhibitors of protoporphyrinogen oxidase are being evaluated by EFED and ORD for possible phototoxicity based on reports of porphyrin accumulation in test animals. Since the biosynthesis of heme is inhibited by oxyfluorfen, there is the possibility that porphyrin precursors of heme could accumulate in the skin and be activated by light and cause toxicity. There have so far been no indications that oxyfluorfen does cause phototoxicity.

2.0 DATA GAPS

There are datagaps for subchronic dermal and inhalation exposure studies. The HIARC determined that the dermal and inhalation studies were both classified unacceptable.

3.0 HAZARD ASSESSMENT

Phase 3 summaries were provided for the older toxicology studies. Summaries of toxicology studies follow.

3.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity is considered complete. No additional studies are required at this time.

Oxyfluorfen is of low acute toxicity and is in toxicity category IV for acute oral and inhalation toxicity and is category III for acute dermal toxicity. Oxyfluorfen is a slight eye and dermal irritant and is not a dermal sensitizer. Acute toxicity data for oxyfluorfen technical is summarized in Table 1.

Table 1. Acute Toxicity of Technical Oxyfluorfen

Guideline No.	Study Type	MRID	Test Material	Registrant	Results	Toxicity Category
81-1	Acute Oral	44712010	96%	Agan	LD ₅₀ > 5000 mg/kg	IV
		44828903	97.1%	Rohm & Haas	LD ₅₀ > 5000 mg/kg	IV
81-2	Acute Dermal	44712011	96%	Agan	LD ₅₀ > 2000 mg/kg	III
		44828904	97.1%	Rohm & Haas	LD ₅₀ > 5000 mg/kg	IV
81-3	Acute Inhalation	44712012	96%	Agan	LC ₅₀ > 3.71 mg/L	IV
		---	---	---	---	---
81-4	Primary Eye Irritation	44712013	96%	Agan	slight irritant	IV
		44828906	96%	Rohm & Haas	negative	IV
81-5	Primary Skin Irritation	44712014	96%	Agan	slight irritant	IV
		44828905	96%	Rohm & Haas	negative	IV
81-6	Dermal Sensitization	44712015	96%	Agan	Negative	---
		44814901	23%	Rohm & Haas	Negative	
81-8	Acute Neurotox	---	---	---	---	NA

3.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The database was adequate for evaluating subchronic toxicity feeding studies in rats and mice. A subchronic non-rodent study was not available, however, an acceptable chronic feeding study in dogs was available. The subchronic dermal and inhalation exposure studies were classified unacceptable and are datagaps.

Subchronic oral toxicity in rats was well characterized in the 1997 feeding study which used the current 98% technical material. Toxicity in this study included decreased body weights, increased urine production and water consumption, slight anemia, minor changes in other hematological parameters and clinical chemistries, slight increases in liver and kidney weights, and minor histopathological observations. Toxicity in the two 1982 feeding studies in rats with the older, 72% technical material was similar, but occurred at lower doses. Similar toxicity occurred in the 1982 mouse feeding study with 72% technical, but also included mortality, clinical signs, and more severe liver toxicity.

870.3100 90-Day Oral Toxicity - Rat: 3 studies

Executive summaries for the 3 subchronic oral toxicity studies in rats follow. One study used 98% active ingredient and two studies used 72% active ingredient.

(1) In a subchronic oral toxicity study (MRID 44933101), oxyfluorfen technical (**98.0% a.i.**) was administered for 13 weeks to 10 CD rats/sex/dose at dietary concentrations of 0, 500, 1500, 6000, or 10000 ppm (equivalent to [M/F] 0/0, 46.7/50.4, 143.5/150.5, 585.0/643.8, or 1012.1/1058.6 mg/kg, respectively).

There was no treatment-related mortality and food consumption, clinical observations, and gross pathological findings were unaffected by treatment. Principal toxicity included decreased body weights, diuresis, slight anemia, minor changes in other hematological parameters and clinical chemistries, slight organ weight changes, and minor histopathological observations as detailed below. No treatment-related findings were observed in the 500 ppm group.

At 1500 ppm, mean cell hemoglobin concentration and mean cell volume were decreased in males (↓ 10%, each), but were not considered toxicologically significant because other hematological parameters were unaffected. In females, urine volume was increased (↑ 80%) and urine potassium concentration was decreased in males (↓ 43%). These changes were not considered toxicologically significant in the absence of increased water consumption, clinical chemistry changes, or organ weight changes.

At 6000 ppm, terminal body weights were decreased only in females (↓ 11%). Treatment caused a microcytic anemia in the 6000 ppm and 10000 ppm groups: there was a decreased hematocrit with small erythrocytes and normal RBC count. At 6000 ppm, hematocrits and hemoglobin were decreased (↓ 12% to 13%) in males and females. Mean cell hemoglobin and mean cell volumes were decreased (↓ 16% to 19%) in males and females. Platelet counts were increased (↑ 13%) in the 6000 and 10000 ppm male groups only. Prothrombin time was increased (↑ 46% and 62%) in 6000 and 10000 ppm males only.

Possible renal effects at 6000 ppm included increased urine volume in both sexes (↑ 48-

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160%), increased urine chloride concentration (\uparrow 76-103%), decreased urine potassium concentration (\downarrow 63-64%), and increased water consumption. Plasma urea (\uparrow 18%) and creatinine (\uparrow 13%) were increased in males only. Relative kidney weights were increased in females (\uparrow 10%, $p \leq 0.01$) only. There was an increased incidence of pigment in cortical tubular epithelium of the kidneys. Possible liver effects at 6000 ppm included increased prothrombin time in males (\uparrow 46%), and cholesterol (\uparrow 53%). Relative liver weights were increased in both sexes (\uparrow 13-28%) at 10000 ppm.

At 10000 ppm, terminal body weights were decreased (males: \downarrow 22%; females: \downarrow 9%). Hematocrits and hemoglobin were decreased (\downarrow 15-19%) in males and females. Mean cell hemoglobin and mean cell volume were decreased (\downarrow 18-21%) in males and females.

Possible renal effects at 10000 ppm included increased urine volume (\uparrow 79-280%,) in males and females and water consumption. Urine sodium concentration was increased in females only (\uparrow 96%). Urine chloride concentration was increased in males and females (\uparrow 120-213%). Increases in blood chemistry parameters in males included: urea (\uparrow 25%); and creatinine (\uparrow 23%). In females, creatinine (\uparrow 18%) and relative kidney weights were increased (\uparrow 12%). Microscopically, an increase in pigment in the cortical tubular epithelium of the kidneys (7/10 vs. 0/10 controls, in males and females) was seen.

Possible liver effects at 10000 ppm in males included increased prothrombin time (\uparrow 62%), alkaline phosphatase (\uparrow 25%, $p \leq 0.01$), and total cholesterol (\uparrow 53%, $p \leq 0.01$); values in females were comparable to controls. Absolute liver weights were increased in females (\uparrow 18%), and relative liver weights were increased (\uparrow 21-26%, $p \leq 0.01$) in males and females.

Increased absolute spleen weights were observed in males (\uparrow 31%) and females (\uparrow 39%); relative spleen weights were only increased in the females (\uparrow 47%). This was accompanied by extramedullary haemopoiesis of the spleen (males-8/10 vs. 0/10 controls, females 5/10 vs. 0/10 controls) seen microscopically. Other microscopic lesions in the 10000 ppm group included increases in inflammatory cell in the zona reticularis in the adrenals and single cell necrosis in the zona reticularis in the adrenals.

The **NOAEL** for this study is 1500 ppm (equivalent to 143.5 mg/kg/day in males and 150.5 mg/kg/day in females). The **LOAEL** for this study is 6000 ppm (equivalent to 585.0 mg/kg/day in males and 643.8 mg/kg/day in females) based on body weight decrements, anemia, increased urine volume, and increased liver weights. This study is classified **acceptable/guideline** (§82-1[a]) and satisfies the guideline requirements for a subchronic oral toxicity study in rats.

(2) In a second subchronic dietary toxicity study (MRID 00117601), 15 Long Evans rats/group received oxyfluorfen (**72.5%**) in the diet for 13 weeks. Dietary concentrations of 0, 400, 800 or 1600 ppm in weeks 1 and 2 were increased to 0, 560, 1120, or 2240 ppm in weeks 3 and 4 and were increased to 0, 800, 1600, or 3200 ppm for weeks 5-13. Dietary concentrations were reportedly increased to maintain a constant compound intake and were adjusted for per cent active ingredient. Average compound intake calculated from food consumption over the 13 week period was 0, 51.4, 105, or 234 mg/kg/day in males and 0, 61.1, 124, or 260 mg/kg/day in females for control, low-, mid-, and high-dose groups, respectively. Blood was collected at 4 weeks and 13 weeks from 10 rats/sex. Urinalyses were performed from 10 rats/sex/group at 11 weeks. Diets were adequately tested for test material concentration and homogeneity (MRID

42142317).

The only clinical signs were sporadic yellow staining of the ano/urogenital area in high-dose males and females. Two males in the high-dose group and 1 male in the low-dose group died; deaths were associated with blood sampling or pneumonia and were not attributed to treatment. Body weights were decreased in mid-dose males (-13%) and high-dose males (-21%) in comparison to controls at termination. Food consumption was decreased in mid-dose males (-8%) and high-dose females (-14%). Body weights and food consumption in females were comparable to controls.

A slight anemia was present in mid-dose males (hematocrit depressed -12%) as well as high-dose males (hematocrit depressed -21%) in comparison to controls at week 13 but not at week 4. High-dose females were slightly anemic at week 13 (hematocrit depressed -9%) in comparison to controls. Associated changes in erythrocyte morphology in mid- and high-dose males and females at termination included polychromasia, poikilocytosis, nucleated erythrocytes, target cells, schistocytes, and Howell-Jolly bodies. Platelet counts were slightly decreased in mid- and high-dose groups at weeks 4 and 13 (-11% to -18% in comparison to controls).

Abnormalities in serum enzymes included slightly elevated SGPT in mid-dose males (+27% at week 4 and +33% at week 13) and high-dose males (+31% at week 4 and +94% at week 13) compared to controls. Serum alkaline phosphatase was slightly elevated in mid-dose males (+22% at weeks 4 and 13) and in high-dose males (+32% and 36% at weeks 4 and 13) in comparison to controls. GGT was elevated in high-dose males and females at weeks 4 and 13. Cholesterol was elevated in mid-dose males (+11% at week 4 and +36% at week 13), high-dose males (+33% at week 4 and +56% at week 13), mid-dose females (+26% at week 4 and +22% at week 13), and high-dose females (+39% at week 4 and +56% at week 13). Other clinical pathology abnormalities of less toxicological significance included slightly increased BUN values in all male treatment groups at week 4 and 13, decreased glucose values in all male treatment groups at week 13, increased creatinine in mid- and high-dose males at weeks 4 and 13, and decreased urinary specific gravity in mid- and high-dose males and all female treatment groups.

Absolute liver weights were increased in all male treatment groups (+17%, +20%, and +22% for low-, mid-, and high-dose groups) and in high-dose females (+24%) when compared to controls. Relative liver weights were increased in all male treatment groups (+24%, +39%, and +56% for low-, mid-, and high-dose groups) and in high-dose females (+36%) when compared to controls. Other organ weights were comparable to controls.

No gross lesions were attributed to treatment. Microscopic lesions of the liver included diffuse hepatocellular hypertrophy and eosinophilia in all male treatment groups and in high-dose females; hepatic necrosis was seen in 3 high-dose males. Hypertrophy of cells in the zona glomerulosa of the adrenals was seen in all male and female treatment groups. In the kidney, focal basophilia of renal cortical tubules and dilated collecting tubules were seen in high-dose males.

The **NOAEL** is < 800 ppm (51.4 mg/kg/day in males and 61.1 mg/kg/day in females), the lowest dose tested. The **LOAEL** is ≤ 800 ppm (51.4 mg/kg/day in males and 61.1 mg/kg/day in females) based upon increased liver weights in males, microscopic liver lesions in males, and microscopic adrenal lesions in males and females. Not all table entries in HED's microfiche copy of the study report were clearly readable; this did not interfere with verifying conclusions

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reported here, however. Several clinical pathology analyses were not conducted: blood clotting measurements, electrolytes, and SGOT. These deficiencies did not interfere with interpretation of toxicity observed in this study. This study is classified **acceptable/guideline** and **satisfies** requirements for a subchronic toxicity study in rats with oxyfluorfen.

(3) In a third subchronic dietary toxicity study (MRID 00117603), oxyfluorfen (**72%**) was administered to 10 CRJ-CDF rats/group at dietary concentrations of 0, 200, 1000, or 5000 ppm for 13 weeks. Doses corresponded to 0, 14, 71, or 361 mg/kg/day in males and 0, 18, 75, or 396 mg/kg/day in females. Stability in feed for 3 months was demonstrated. Dose selection was based upon a range-finding study.

No mortality or clinical signs were observed. Body weights were decreased in high-dose males (-18%) and females (-9%) at day 90 in comparison to controls. Food consumption was decreased in high-dose males and females in most weekly intervals. The test material reportedly imparted a phenol odor to the diet. Calculated food efficiency was not impaired by treatment. Water consumption was increased in high-dose males (+17 to +36%, typically) and females (somewhat variably) at different time intervals.

A mild anemia was present in high-dose males (hematocrit of 42.2% vs 47.0% in controls) and females (hematocrit of 42.0% vs 46.4% in controls) at day 90. An increased numbers of reticulocytes were seen on blood smears and enlarged erythrocytes were present as indicated by calculated red blood cell indices. Red blood cell parameters in low- and mid-dose groups were similar to control values. Triglycerides were decreased in high-dose males (-39%) in comparison to controls. Other clinical chemistry and urinalysis results were similar between treatment groups.

At necropsy, dark-brown livers and/or kidneys in mid- and high-dose males and females were noted. Absolute and relative liver weights were increased in mid-dose males (+6%/+11%), high-dose males (+11%/+34%), and high-dose females (+19%/+4%). Absolute and relative thymus weights were decreased in mid-dose males (-14%/-10%) and high-dose males (-32%/-18%). Changes in other absolute and relative organ weights were inconsistent were not attributed to treatment.

An increased incidence and/or severity of microscopic liver lesions in mid- and high-dose males included swelling of hepatocytes, fat deposition, and yellow/brown pigment deposition; fat deposition was also increased in high-dose females. Microscopic kidney lesions in high-dose males and mid- and high-dose females included calcium deposition, vacuolar degeneration of distal tubules, hypertrophy/hyperplasia of transitional epithelium, and yellow pigment in renal tubular epithelium. The microscopic liver and kidney lesions were generally classified slight in mid-dose animals and slight to moderate in high-dose animals. Fine vacuolation of adrenal glands (slight) and cortical atrophy of the thymus (slight) were increased in high-dose males.

The **NOAEL** is 200 ppm (males: 14 mg/kg/day; females: 18 mg/kg/day). The **LOAEL** is 1000 ppm (males: 71 mg/kg/day; females: 75 mg/kg/day) based upon brown livers and kidneys in males and females, increased relative liver weights in males, decreased absolute and relative thymus weights in males, and microscopic liver and kidney lesions in males and females (classified slight). At the high dose, decreased body weight, anemia, and increased absolute liver weight also occurred. Several clinical pathology analyses were not conducted: blood clotting measurements and electrolytes. These deficiencies did not interfere with interpretation of

toxicity observed in this study. This study is classified **acceptable/guideline**.

870.3100 90-Day Oral Toxicity - Mouse

In a 3-month dietary toxicity study (MRID 00117602), Goal (**72.5%**) was administered to Charles River CD-1 mice (15/sex/group) at dietary concentrations of 0, 200, 800, or 3200 ppm for 13 weeks. Doses were equivalent to 0, 32.0, 134.5, or 490.5 mg/kg/day in males and 0, 44.4, 166.6, or 520.9 mg/kg/day in females. Dietary concentrations were adjusted for per cent active ingredient. Diets were adequately tested for test material concentration and homogeneity (MRID 42142316).

Treatment-related mortality was limited to the high-dose group and began after 4 days of treatment. A total of 9 male and 2 female deaths during the first 2 weeks of the study were considered treatment-related. Lethargy, passiveness, ataxia, and arched backs were seen before death and in some surviving mice in the high-dose group. Yellow- or brown-stained urogenital areas and red-staining on cage bottoms were seen in all treatment groups except for low-dose females. Other clinical signs were not noted.

Body weights were decreased during only the first 3 weeks in high-dose males and the first 2 weeks in high-dose females. Body weights were comparable to controls for other time periods and for other treatment groups. Food consumption was decreased in mid-dose males and mid- and high-dose males and females.

Anemia was most evident in high-dose males and females but there were also decreases in hematological parameters in low- and mid-dose males and mid-dose females. Hemoglobin was decreased -10%, -14%, and -30% in low-, mid-, and high-dose males, respectively, and -3%, -9%, -25% in low-, mid-, and high-dose females, respectively in comparison to controls at termination. Associated changes in erythrocyte morphology in high-dose males and females included polychromasia, poikilocytosis, anisocytosis, nucleated erythrocytes, target cells, schistocytes, and Howell-Jolly bodies. Howell-Jolly bodies were also seen in mid-dose females. Platelets were increased approximately 100% in high-dose males and females in comparison to controls. White blood cell counts were increased in high-dose males (+153%) and females (+337%).

Abnormalities in serum enzymes included elevated SGPT in low-dose females (+295%), mid-dose males (+353%) and females (+638%), and high-dose males (+1177%) and females (+1464%) in comparison to controls. Serum alkaline phosphatase was elevated in mid-dose males (+179%) and females (+109%) and to a greater extent in high-dose males (+1753%) and females (+990%) in comparison to controls. GGT was elevated in mid-dose males and females.

Cholesterol was elevated in low-dose females (+55%), mid-dose males (+76%) and females (+145%), and high-dose males (+282%) and females (+483%) in comparison to controls. Glucose was decreased in high-dose males (-43%) and females (-17%) in comparison to controls. Creatinine was elevated +23% in high-dose males and +18% in high-dose females. Ketonuria occurred in urine from all female treatment groups at week 11. At week 13, urine was darker in color in a dose-related manner in both sexes.

Mixed function oxidase liver enzyme activity in liver slices as determined by p-nitroanisole demethylation was determined at study termination. Activity was increased in mid-dose females and high-dose males and females. Increased liver microsomal protein was also

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increased in high-dose males.

Absolute and relative liver weights were increased in low-dose (+26%/+22%), mid-dose (+71%/+63%), and high-dose males (+295%/+274%) and in low-dose (+10%/+10%), mid-dose (+62%/+62%), and high-dose females (+245%/+243%).

At necropsy, enlarged livers were seen in 3/5 surviving high-dose males and 11/13 surviving high-dose females; many of these livers were darkened in females. Microscopic lesions in the liver included diffuse hypertrophy (all treatment groups), single-cell necrosis (low-dose females and mid- and high-dose males and females), focal necrosis (mid- and high-dose males), hemosiderosis (all treatment groups), and bile duct proliferation (high-dose males and females). Microscopic lesions of the spleen included atrophy (high-dose males) and red-pulp hyperplasia (all male treatment groups and high-dose females). Bone marrow hyperplasia was present in low-dose males and mid- and high-dose males and females. Vacuolation of the adrenal cortex was present in high-dose females. Thymic atrophy occurred in high-dose males and females.

The **NOAEL** is < 200 ppm (32.0 mg/kg/day in males and 44.4 mg/kg/day in females), the lowest dose tested. The **LOAEL** is ≤ 200 ppm (32.0 mg/kg/day in males and 44.4 mg/kg/day in females) based upon anemia, elevated liver enzymes (SGPT in females), increased liver weight, and microscopic liver lesions (single-cell necrosis in females and diffuse hypertrophy in males and females).

Not all entries in HED's microfiche copy of the study report were clearly readable; this did not interfere with verifying conclusions reported here, however. Several clinical pathology analyses were not performed: blood clotting measurements, electrolytes, and SGOT. These deficiencies did not interfere with interpretation of toxicity observed in this study. This study is classified **acceptable/guideline** and **satisfies** requirements for a subchronic toxicity study in mice with oxyfluorfen.

870.3150 90-Day Oral Toxicity - Dog

A subchronic oral toxicity in dogs was not available.

870.3200 21/28-Day Dermal Toxicity – Rat

In a 4-week repeated dose dermal toxicity study (MRID 00071915), groups of 4 male and 4 female New Zealand White rabbits were treated with RH 2915-technical (approximately **75% a.i.**, RH 2915-EC (emulsifiable concentrate, 31.7% a.i.), or the EC solvent-emulsifier (vehicle control). Doses of RH 2915-EC (0.1 or 0.4 mL/kg, equivalent to 24.2 or 96.8 mg/kg/day a.i. respectively) and the EC solvent/emulsifier (0.4 mL/kg) were applied as 10% solutions in water; the RH 2915-technical (1500 mg/kg/day, corrected for % a.i.) was applied as a paste in 10% solvent emulsifier in water. Animals were treated 20 times over a 4 week period. Application sites of some animals were abraded every other day. The test substance application protocol was not described (dressings, washing of the application site, duration of each exposure).

One female treated with the solvent/emulsifier died on the scheduled day of termination; cause of death was not determined. Decreased mean body weights ($p < 0.05$) were observed in males treated with 96.2 mg/kg/day RH 2915-EC and in males treated with the solvent/emulsifier

compared to untreated controls; these decreases occurred after one week of dosing and continued until the end of the study. Males and females administered RH 2915-technical exhibited transient body weight decreases (-12% in males and -16% in females compared to controls); this effect had resolved in females after the second week of treatment and in males after the third week of the study. Males in all treatment groups had decreased food consumption.

Treatment-related dermal effects included erythema, edema, skin cracking/bleeding, and desiccation in all treatment groups. Microscopic dermal abnormalities including hyperplasia and hyperkeratosis of the epidermis, focal inflammatory cell infiltration of the dermis, and sebaceous gland epithelial hyperplasia were also observed in all treatment groups.

Treatment-related increased absolute and relative liver weight was observed in males treated with RH 2915-technical. One male and one female exposed to RH 2915-technical exhibited hepatocellular hypertrophy.

Systemic NOAELs for the solvent control and RH 2915-technical were not defined. The systemic NOAEL for RH 2915-EC is 24.2 mg/kg/day. **Systemic LOAELs** of 0.4 mL/kg/day for the solvent control, 1500 mg/kg/day for the RH 2915-technical, and 96.8 mg/kg/day for the RH 2915-EC can be assigned based on decreased body weight (solvent control, RH 2915-technical and RH 2915-EC) and liver pathology (RH 2915-technical).

A **dermal NOAEL** cannot be established for any treatment group. The **dermal LOAELs** are 0.4 mL/kg for the solvent control, 1500 mg/kg/day for the RH 2915-technical, and 24.2 mg/kg/day for the RH 2915-EC based on gross and microscopic treatment-related dermal effects.

This study is classified **unacceptable** and does not satisfy the guideline requirements for a repeated-dose dermal study (82-2) in rabbits. No description of the dermal application methodology (dressings, washing of the application site, duration of each exposure) was provided. There were only 4 animals per group and only 1 dose for the technical dose group. No homogeneity, stability, or concentration data for the test material were provided.

870.3465 90-Day Inhalation – Rat

In a one-month toxicity study (MRID 00071916), Oxyfluorfen (Goal 2E) (active ingredient 2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl)benzene, **23.5% v/v**; batch TD# 77-187) was administered by inhalation to 10 CD rats/sex/dose at aerosol concentrations of 0.13 or 0.65 mg/L. Doses were equivalent to 33.2 and 166.1 mg/kg/day in males and 34.9 and 174.7 mg/kg/day in females. There were two control groups (10 rats/sex/group): filtered air only or 0.65 mg vehicle/L only. Exposure durations were 6 hours/day, 5 days/week, for 20 or 21 exposure days.

Absolute liver weights were increased in low-dose females (121% of air-only controls), but not significantly in high-dose females. Relative liver weights were increased in high-dose males (117% of air-only controls), in the female vehicle control group (117% of air-only controls), low-dose females (116% of air-only controls), and in high-dose females (113% of air-only controls). Alveolar hemorrhages were increased in the 2 male treatment groups (7/10 and 6/10 compared to 1/10 for air-only controls) and the female vehicle control group compared to the air-only control group (4/10 vs 0/10). Mortality, body weights, clinical signs, clinical chemistry, and hematology were not affected by treatment.

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The **NOAEL** is < 0.13 mg/L (males: 33.2 mg/kg/day; females: 34.9 mg/kg/day), the lowest dose tested. The **LOAEL** is ≤ 0.13 mg/L (males: 33.2 mg/kg/day; females: 34.9 mg/kg/day) based on increases in liver weight and lung pathology.

This study is classified **unacceptable**. Lung pathology may have inhibited absorption of oxyfluorfen and there were a number of deficiencies in the study.

3.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The database is adequate for prenatal developmental toxicity studies in rats and rabbits. There are acceptable developmental studies in rats and in rabbits with the current 98% technical material (1997) as well as an acceptable study in rats with 71% technical (1991) and a rabbit study with a 26.9% formulation (1981). Both maternal and developmental toxicity occurred at lower doses with the 71% technical material than with the 98% technical material.

In the developmental rat study with 98% technical material, no developmental or maternal toxicity occurred. In the developmental rat study with 71% technical material, maternal toxicity included mortality, clinical signs (red vaginal discharge, soft/scant feces, thin build), and elevated liver enzymes; developmental toxicity included increased early resorptions, decreased fetal weight, and visceral and skeletal variations and malformations.

In the developmental rabbit study with 98% technical material, maternal toxicity included abortions and decreased food consumption; developmental toxicity included increased late resorptions and decreased number of live fetuses per doe. In the developmental rabbit study with 26.9% formulation, maternal toxicity included mortality, abortions, clinical signs (anorexia and blood in the urine); developmental toxicity included increased early resorptions and decreased litter size.

870.3700a Prenatal Developmental Toxicity Study - Rat

Executive summaries for 2 developmental toxicity studies in rats follow. One study used 98% active ingredient and the other study used 71% active ingredient.

(1) In a developmental toxicity study (MRID 44933103), oxyfluorfen (**98.0% a.i.**) in 1% (w/v) methylcellulose was administered to pregnant CD Sprague-Dawley rats (22/dose) at dose levels of 0, 375, 750, or 1000 mg/kg/day (limit dose) by gavage on gestation days (GDs) 6 through 15. Dams were sacrificed on GD 20.

No premature deaths or clinical signs of toxicity were observed at any dose level tested. When compared to concurrent controls, no treatment-related changes in body weight, food consumption, gross pathology, or reproductive parameters were noted at any dose level tested. The **maternal LOAEL** was not observed. The maternal **NOAEL** is ≥ 1000 mg/kg/day (limit dose).

No developmental toxicity was noted at any dose level tested. The **developmental LOAEL** was not observed. The **developmental NOAEL** is ≥ 1000 mg/kg/day.

This developmental toxicity study is classified **acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study in the rat.

(2) In a developmental toxicity study (MRID 41806501), oxyfluorfen (**71.4%**), was administered by gavage to pregnant CrI:CD BR rats from gestation days 6-15. There were 27 rats/group. Doses were 0, 18, 183, or 848 mg/kg/day (adjusted for analytical results).

Maternal mortality occurred in the high-dose group: 15 rats died or were sacrificed. Maternal clinical signs in the mid-dose group included red vaginal discharge, soft feces, scant

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feces. Clinical signs in the high-dose group also included alopecia, mucoid feces, and agonal signs (hunched posture, ataxia, lethargy, and pale extremities). Overall body weights and weight gains for low- and mid-dose groups were generally comparable to controls, and were not compared for the high-dose group due to the high mortality in this group. Altered clinical pathology parameters in the high-dose group included elevated alkaline phosphatase and SGOT, and increases in leukocyte count, mean cell volume, and platelets.

Mean corpora lutea, implantations, and pregnancy rates were similar in all treatment groups. There were no live pups in the high-dose group due to a 100% early resorption incidence. Mean early resorptions were also increased in the mid-dose group (0.9, 0.5, and 2.7 in control, low-, and mid-dose groups respectively) resulting in decreased live fetuses and increased postimplantation loss. Mean fetal weight was decreased in the mid-dose group (84% of control value) and was comparable to controls in the low-dose group.

There were 4 litters in the mid-dose group with vessel variations compared to 1 litter in the control group. There were 12 litters in the mid-dose group with skeletal malformations which included bent scapula, fused sternbrae, and bent bones in hindlimbs and forelimbs compared to 0 litters in the control group with skeletal malformations.

The **NOAEL for maternal toxicity** is 18 mg/kg/day; the **maternal LOAEL** is 183 mg/kg/day based on clinical signs (red vaginal discharge, soft feces, scant feces).

The **NOAEL for developmental toxicity** is 18 mg/kg/day. The **LOAEL for developmental toxicity** is 183 mg/kg/day based on increased early resorptions, decreased fetal weight, and increased incidence of fetal visceral and skeletal variations and malformations.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

Two developmental toxicity studies in rabbits were available. One study used 98% active ingredient and the second study used a formulation of 26.9% active ingredient.

(1) In a developmental toxicity study (MRID 44933102), oxyfluorfen (**98.0% a.i.**) in 1% (w/v) methylcellulose was administered to pregnant New Zealand White rabbits (15/dose) at dose levels of 0, 10, 30, or 90 mg/kg/day by gavage on gestation days (GDs) 6 through 19. Does were sacrificed on GD 29. Two premature deaths occurred in the control group; one female was sacrificed *in extremis* on GD 20 due to an ulceration on the ventral neck area and a second female aborted on GD 21. At 90 mg/kg, one female was found dead on GD 28, and two other females aborted on GD 27 or GD 29; all three females displayed reduced food consumption and fecal output from mid-gestation resulting in decreased body weight and general thin appearance prior to death. No treatment-related changes in body weight were noted at any dose level tested.

At 90 mg/kg, clinical signs were observed as follows (% incidence in total animal days): little food eaten (26.4% vs 5.0% in controls); few/loose feces in undertray (28.0% vs 11.2% in controls); and thin build (6.6% vs 0% controls). Decreases (not statistically significant) were noted in food consumption during GDs 13-28 (↓8-38%). At necropsy, the three females that died or aborted during the study appeared thin and exhibited accentuated lobular pattern of the liver. A decrease (not statistically significant) was observed in gravid uterine weight (↓20%) when compared to concurrent controls.

The **maternal NOAEL** is 30 mg/kg/day. The **maternal LOAEL** is 90 mg/kg/day, based

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on abortions, clinical signs of toxicity, decreased food consumption, and gravid uterine weight.

There was an increase in the number of late resorptions/doe (not statistically significant, 2.5/doe vs 0.9/doe in controls) and a decrease in the number of live fetuses/doe at 90 mg/kg/day (7.1/litter vs 9.6/litter in controls). Pregnancy rates and mean fetal weights were comparable among treatment groups, as were external, visceral, and skeletal observations at necropsy.

The **developmental NOAEL** is 30 mg/kg/day. The **developmental LOAEL** is 90 mg/kg/day based on increased late resorptions and decreased number of live fetuses/doe (not statistically significant and occurring principally in 1 litter).

This developmental toxicity study is classified **acceptable/non-guideline** and satisfies the guideline requirement for a developmental toxicity study in the rabbit. The study is classified non-guideline because there were 15 animals per group rather than 20.

(2) In a developmental toxicity study (MRID 00094052), 19 presumed pregnant New Zealand White rabbits per group were administered oxyfluorfen (**26.9% ai**; Lot No. CDP 0482-1) by gavage at dose levels of 0 (negative control), 0 (vehicle control), 10, 30, or 90 mg/kg/day, on gestation days (GD) 6-18, inclusive. Doses were adjusted for per cent active ingredient. The vehicle control consisted of all ingredients of the 25 WP formulation without the active ingredient administered at the equivalent of a 90 mg/kg/day dose of 25 WP.

Five premature deaths and 4 abortions occurred in the 90 mg/kg/day treatment group. Treatment related clinical signs of toxicity consisted of anorexia and red exudate in the cage pan at 30 and 90 mg/kg/day and hematuria and decreased motor activity at 90 mg/kg/day of oxyfluorfen. Ulceration, erosions, and/or petechial hemorrhages were observed at necropsy in the stomach mucosa of 3 high-dose does which died. Body weight gain was decreased during GD 13-18 at 30 mg/kg/day and throughout the dosing at 90 mg/kg/day; terminal body weights were not significantly affected at any dose level.

The **maternal NOAEL** is 10 mg/kg/day. The **maternal LOAEL** is 30 mg/kg/day based on clinical signs of toxicity and decreased body weight gain during treatment.

Decreased litter size and an increase in early resorptions occurred at 90 mg/kg/day. The small number of litters (5/11 pregnant does) evaluated precluded adequate statistical evaluation of cesarean section data. There were no treatment-related external, visceral, or skeletal malformations or variations observed at any treatment level. There was no evidence for delayed fetal growth at any treatment level compared to controls.

The **developmental NOAEL** is 30 mg/kg/day. The **developmental LOAEL** is 90 mg/kg/day based on decreased litter size and increased early resorptions.

This study is classified **acceptable/guideline** and satisfies the guideline requirements for a developmental toxicity study in rabbits.

3.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: There is an acceptable reproductive study with 71% technical material. The data base for reproductive toxicity is complete and no additional studies are required at this time. Parental toxicity included mortality, body weight decrements, and microscopic liver and kidney lesions. The kidney lesion was microscopic mineralization, which was not observed in other rat feeding studies. Reproductive/offspring effects included smaller litter size and body weight decrements on day 0 of lactation.

870.3800 Reproduction and Fertility Effects - Rat

Goal Herbicide (71.4% a.i.) was administered to groups of 25 male and 25 female Crl:CD[®]BR rats in the diet at concentrations of 0, 100, 400, or 1600 ppm of active ingredient for two generations (MRID 42014901). One litter was produced in each generation. Premating doses for the adult F₀ males were 0, 7.8, 30.9, and 120.0 mg/kg/day and for the F₀ females were 0, 8.5, 32.8, and 131.2 mg/kg/day, respectively. Premating doses for the adult F₁ males were 0, 8.9, 36.4, and 146.3 mg/kg/day and for the F₁ females were 0, 8.9, 35.7, and 151.3 mg/kg/day, respectively. F₁ pups chosen to produce the F₂ litters were weaned onto the same diets as their parents. Animals were given test or control diet for 10 (F₀) or 14 (F₁) weeks then mated within the same dose group.

One high-dose F₁ male was sacrificed moribund during week 9 of treatment; treatment-related chronic pyelonephritis secondary to pelvic mineralization was described at necropsy; this death was attributed to treatment. No treatment-related clinical signs of toxicity were observed in parental animals of either generation. Several intercurrent deaths of F₀ females and F₁ males and females were considered incidental to treatment.

Mean body weights, body weight gains, and food consumption by the low- and mid-dose males and females of both generations were comparable to their respective controls. Body weights of the high-dose F₀ males were slightly (n.s.) lower than the controls throughout pre-mating with overall body weight gains 92% of the control level. Absolute body weights of the high-dose F₀ females were significantly ($p \leq 0.05$) less than the controls during weeks 4-7, with overall body weight gain 88% of controls. Food consumption by the high-dose F₀ males was significantly (89-92% of control; $p \leq 0.05$) less than the controls during weeks 0, 2, and 4-8 of the pre-mating interval. Food consumption by the high-dose F₀ females was 85-94% of the control levels during the pre-mating period with statistical significance ($p \leq 0.05$) reached during weeks 0-6 and 8. High-dose F₁ males and females had significantly ($p \leq 0.05$) lower body weights than the controls throughout the pre-mating interval (84-89% and 79-93%, respectively of the controls). Overall body weight gains were 89% and 97%, respectively, of control levels. Food consumption was significantly ($p \leq 0.05$) less than the controls by the high-dose F₁ males during treatment weeks 0-9 and 12 and by high-dose F₁ females during weeks 0-3, 5, and 8. High-dose F₀ dams had significantly ($p \leq 0.05$) lower body weights than the controls on GD 21 and on lactation day 14. Body weights of the high-dose F₁ dams were significantly ($p \leq 0.05$) less than the controls throughout gestation and on lactation days 0, 7, and 14.

Body weights of the high-dose F₁ pups were significantly (78-89% of controls; $p \leq 0.05$) less than the controls throughout lactation. High-dose F₂ pups had significantly (82-89%; $p \leq$

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0.05) lower body weights than the controls on lactation days 0, 14, and 21. Body weight gains by the high-dose pups of both generations were 81-85% of the control level for lactation days 0-14 and were 73-77% of the control level for lactation days 14-21. Because the most pronounced effect on pup body weight gain was after they started to eat the test diets, the lower pup body weights are considered a systemic effect and not a lactational effect.

No treatment-related findings were observed at necropsy of the F₀ or F₁ females. Gritty material was observed in the renal pelvis of 2/25 high-dose F₀ males and in 1/25 and 5/25 mid- and high-dose F₁ males, respectively. This was not observed in any control or low-dose males.

Dose-related increases in the incidence rates of liver and kidney lesions were observed in males and females of both generations. Hepatocellular hypertrophy was observed in 1/25, 1/25, 1/25, and 12/25 ($p \leq 0.01$) F₀ males; in 1/25, 0/25, 0/25, 14/25 ($p \leq 0.01$) F₀ females; in 2/25, 2/25, 1/25, 17/25 ($p \leq 0.01$) F₁ males; and in 0/25, 0/25, 0/25, 8/25 ($p \leq 0.01$) F₁ females in the 0, 100, 400, and 1600 ppm groups, respectively. The incidence rates of mineralization of the renal pelvis were 0/25, 1/25, 3/25, 7/25 ($p \leq 0.01$) in F₀ males; 4/25, 2/25, 3/25, 7/25 in F₀ females; 1/25, 1/25, 5/25, 11/25 ($p \leq 0.01$) in F₁ males; and 3/25, 2/25, 8/25, 13/25 ($p \leq 0.01$) in F₁ females, respectively. In the kidney of high-dose F₁ animals, there were increased incidences of dilatation of the collecting ducts (0/25, 0/25, 2/25, 11/25 [$p \leq 0.01$] males and 1/25, 0/25, 0/25, 9/25 [$p \leq 0.01$] females) and hyperplasia of the pelvic/papillary epithelium (4/25, 5/25, 6/25, 11/25 [$p \leq 0.05$] males and 1/25, 3/25, 2/25, 8/25 [$p \leq 0.05$] females).

The **NOAEL for parental toxicity** is 400 ppm (males: 30.9 mg/kg/day; females: 32.8 mg/kg/day). The **LOAEL for parental toxicity** is 1600 ppm (males: 120.0 mg/kg/day; females: 131.2 mg/kg/day) based on mortality, body weight decrements, and microscopic kidney and liver lesions.

No treatment-related effects were noted on fertility or mating indices of either generation. No dose- or treatment-related effects were observed in either generation for number of litters, per cent male pups, or pup survival indices. No clinical signs of toxicity were seen in any pups from either generation.

On lactation day 0 the high-dose group of both generations had significantly ($p \leq 0.05$) fewer live pups/litter and lower mean pup body weights as compared to controls. The **reproductive toxicity NOAEL** is 400 ppm (32.8 mg/kg/day). The **LOAEL for reproductive toxicity** is 1600 ppm (131.2 mg/kg/day) based on fewer live pups/litter and body weight decrements.

This study is classified **acceptable/guideline** and satisfies the guideline requirement for a reproduction study (83-4) in rats.

3.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete and no additional chronic studies are required at this time. The 2-year combined chronic toxicity/carcinogenicity study in rats (85.7% a.i.) was classified unacceptable because no treatment-related toxicity occurred at the highest dose and because there were a number of deficiencies in this 1977 study which would not meet current guideline requirements. A new chronic toxicity study in rats was not required by the HIARC because a NOAEL could be established and because toxicity occurred in the chronic dog study at a lower dose.

Toxicity in the chronic dog study (71% a.i.) included anemia, elevated serum alkaline phosphatase enzyme activity, increased liver weight, lacrimation, decreased food consumption and thin appearance. In the mouse carcinogenicity study, liver toxicity, shown by increased liver weights, elevated serum enzyme levels, microscopic liver lesions, and liver tumors, occurred (see Carcinogenicity section, below, for more details on the mouse study).

870.4100a (870.4300) Chronic Toxicity – Rat

In a chronic toxicity/carcinogenicity study (MRID 00083445, 00135072, 92136061), RH-2915 technical (**82.2% and 85.7% a.i.**) was administered in the diet to groups of 50 male and 50 female Long Evans rats at concentrations of 1.0, 20.0, or 400.0 ppm for weeks 1–2; 1.4, 28.3, or 565.6 ppm for week 3–4; 2.0, 40.0, or 800.0 ppm for weeks 5–56 (800 ppm was actually 686 ppm for weeks 6–48); and 2.0, 40.0, or 1600 ppm for weeks 57–104. Based on % active ingredient, doses in males were approximately equivalent to 0, 0.10, 1.94, and 56.96 mg/kg/day, and in females were 0, 0.12, 2.43, and 72.57 mg/kg/day, in the respective dose groups.

The mortality rate at study termination was 54, 48, 52, and 40% for male and 22, 40, 26, and 20% for females administered the control, low, mid, and high doses, respectively; no treatment-related effect was observed. No treatment-related clinical signs or masses were observed in either sex.

Body weights of high-dose group male rats were similar to those of controls throughout the study except for a statistically significant ($p < 0.01$) 26% decrease during week 0. No treatment-related decreases in weight gain were observed for treated male rats; male controls lost 31 and 35% more weight than mid- and high-dose rats, respectively, during the second year of treatment. Body weights for low-, mid- and high-dose group females were 9, 7, and 11% less ($p < 0.01$ or < 0.05) than control weights at most time points during the study. Body weight gain for all treated female groups was 9–12% less than that of controls for the first year of treatment and 9–10% less overall. No dose-response relationships were observed for the effects on body weights and weight gain in females suggesting that the effects were not treatment-related.

No treatment-related effects were observed on hematologic or the clinical chemistry parameters evaluated in this study. Absolute and/or relative organ weights in the high-dose groups that showed statistically significant changes relative to control weights (thyroid gland in both sexes and kidney in females at 12 months and brain, pituitary, and spleen in females sacrificed at 24 months) had no microscopic correlates and are not considered toxicologically significant. Gross lesions were not observed in animals sacrificed at 12 or 24 months.

Microscopic changes observed at 12 months included binucleate hepatocytes (6/10),

central lobular hepatocyte hypertrophy (7/10), and enlarged hepatocyte nuclei (6/10) in high dose females compared to 0/5 for controls. Similar changes were not seen at the terminal sacrifice, despite the fact that the animals received higher doses during the last 12 months of the study. Therefore the findings at 12 months may be an adaptive effect.

The changes that were statistically increased in the 24-month group were polypoid hyperplasia of the papillary epithelium in the kidney of high dose females (20/40 vs 13/45 controls, $p < 0.05$) and cortical cysts in the kidney of mid- and high-dose males (6/25 ($p < 0.01$) and 4/40 ($p < 0.05$) vs 0/45 for controls). The lack of a dose-response relationship for the changes in males and the high background for the finding in females suggest that the microscopic findings were not treatment related.

The **NOAEL** is ≥ 56.96 mg/kg/day in males and ≥ 72.57 mg/kg/day in females, the highest dose group. A **LOAEL** was not determined. No treatment-related neoplastic lesions were observed in either male or female rats receiving the test material under this study protocol. Dosing was not considered adequate for assessing carcinogenicity because no treatment-related effects were observed at any dose. In addition, dosages were varied during the course of the study. Animals received substantially lower doses at the beginning of the study than at the latter part of the study. This study is classified **unacceptable** because no treatment-related toxicity occurred in the study and because there were a number of deficiencies in this 1977 study which would not meet current guideline requirements. The study was, however, adequate to determine a NOAEL value.

870.4100b Chronic Toxicity - Dog

In a chronic oral toxicity study (MRID 00078767 and 92136062), oxyfluorfen (**71.4-73.8% a.i.**) was administered to six beagle dogs/sex/dose in the feed (400 gm/day) at concentrations of 100, 600, or 3600-2000 ppm (3600 ppm for days 1-8, 0 ppm for days 9-14, 2800 ppm for days 15-28, and 2000 ppm from day 29 to termination) for up to 104 weeks. The equivalent average daily doses were 3.1, 18.5, or 61.0 mg/kg/day (males) and 3.0, 18.8, or 60.3 mg/kg/day (females) when corrected for purity and analytical concentration. Ten dogs/sex served as untreated controls.

One mid-dose female was found dead during week 35 of unknown causes. A high-dose male was sacrificed moribund during week 83 due to inguinal herniation of the abdominal viscera.

Treatment-related clinical signs included thin appearance and heavy lacrimation primarily at the high dose. Heavy lacrimation was noted in 6/8 high-dose dogs. Corresponding to this finding was epiphora in 1/4 males and 3/4 females at the high dose during ophthalmoscopic examination.

In the first week of the study, the high dose animals had significant loss of body weight caused by lack of food consumption. As a consequence, the high dose was gradually lowered over 28 days from 3600 to 2000 ppm. At week 4, mean body weights for the high-dose males and females were 79-81% (n.s.) of controls and remained lower to study termination (70-75% of controls at week 104; n.s.). Overall weight gains at week 104 corresponded to 106%, 74%, and 11% of controls (males) and 61%, 44%, and 15% of controls (females) at the low, mid, and high doses, respectively. Food consumption was decreased in the high-dose group.

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There were decreases in hematocrit, hemoglobin, and erythrocyte values in high-dose males (values were 74-77% of controls) at week 104; decreased ($p<0.05$) hemoglobin values in high-dose males at weeks 13, 52, and 82 (84-89% of controls). Serum alkaline phosphatase activity was increased in high-dose males and females (225-884% of control values) and in mid-dose males (298% of control values) at termination, as well as during the study.

No treatment-related gross lesions were observed at the interim or terminal sacrifices. Increased liver weights, generally dose-related, were seen at the interim and terminal sacrifices.

Respective liver weights for low-, mid-, and high-dose males were 110, 147, and 147% of controls (absolute); 109, 153, and 195% of controls (relative); and for females, 106, 118, and 150% of controls (absolute) and 121, 144, and 222% of controls (relative) at termination. The only treatment-related histopathological lesion in the liver was slight to moderate bile pigmented hepatocytes in both sexes after 104 weeks (n.s.) and hepatocellular vacuolization was seen in high-dose females.

The **NOAEL** is 100 ppm (males: 3.1 mg/kg/day; females: 3.0 mg/kg/day). The **LOAEL** is 600 ppm (males: 18.5 mg/kg/day; females: 18.8 mg/kg/day) based on decreased weight gains, increased alkaline phosphatase activity, increased absolute/relative liver weights. This study is classified **acceptable/guideline** and satisfies the guideline requirement for a chronic oral toxicity study (83-1b) in the dog.

3.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time. The 2-year combined chronic toxicity/carcinogenicity study in rats was classified unacceptable because no treatment-related toxicity occurred and because there were a number of deficiencies in this 1977 study which would not meet current guideline requirements. A new carcinogenicity study in rats was not requested because a new study would not add to the understanding of the carcinogenic potential of oxyfluorfen; neoplasia did not occur in this study but did occur at lower doses in the mouse study.

In the mouse study, combined hepatocellular adenomas and carcinomas were increased in males at the high dose (8/52 vs 1/47 and 0/47 in the 2 control groups). This study was used to determine the Q1* for oxyfluorfen (see Section 4.3, below). There was no treatment-related effect on carcinogenicity in the rat study.

870.4200a Carcinogenicity Study - rat

See chronic toxicity section, above, for the executive summary for the 2-year combined chronic toxicity/carcinogenicity study in rats.

870.4200b Carcinogenicity (feeding) - Mouse

In an oncogenicity study (MRID 00037939, 92136017), oxyfluorfen (RH-2915 Technical, **87.5% a.i.**) was administered in the diet to 60 male and 60 female Charles River CD-1 mice at concentrations of 0 (negative control), 0 (ethanol control), 2, 20, and 200 ppm for up to 87 weeks. The corresponding dose levels (adjusted for % a.i.) were 0, 0, 0.3, 3.0, and 33.0 mg/kg/day for males, and 0, 0, 0.4, 4.0, and 42.0 mg/kg/day for females. One control group received only the basal diet; the second control group received the basal diet mixed with ethanol. There was an interim sacrifice of 5 mice/sex for both control groups and the high dose group.

Body weights, body weight gain, and food consumption were similar in all groups. Liver toxicity was shown by increased liver weights, elevated enzyme levels, microscopic liver lesions, and liver tumors. Treatment-related toxicity was more pronounced in males. Absolute and relative liver weights were increased 23-35%, relative to controls, in high-dose animals. Microscopic lesions increased in livers of high-dose animals included hepatocyte necrosis, hepatic regeneration and hyperplastic nodules. Alkaline phosphatase (+110%) and SGPT (+77%) were increased in high-dose males.

Combined hepatocellular adenomas and carcinomas were increased in 200 ppm males (8/52 vs 1/47 and 0/47 in the 2 control groups). Results from this study were used to determine the Q1* for oxyfluorfen (see Section 4.3, below).

The **NOAEL** is 20 ppm for males (3.0 mg/kg/day) and females (4.0 mg/kg/day). The **LOAEL** is 200 ppm in male (33.0 mg/kg/day) and female (42.0 mg/kg/day) mice, based on liver toxicity (microscopic liver lesions; increased absolute and relative liver weights; and elevated liver enzymes). This oncogenicity study in the mouse is classified **acceptable** for assessing the carcinogenic potential of oxyfluorfen.

3.7 Mutagenicity

Adequacy of data base for Mutagenicity: The acceptable studies performed with the $\geq 96\%$ test material satisfy the 1991 mutagenicity guidelines and no further testing is warranted.

Tables 2 and 3 show results for 20 genetic toxicology studies with 96-99.7% test material, approximately 72% test material, and a polar fraction. The newer technical material (96-99% a.i.) was tested in 12 genetic toxicology studies, all of which were negative, except for one Ames assay which was positive. A second Ames assay with 96% material was negative. The older 72% technical material and a polar fraction were tested in 8 genetic toxicology studies, of which 3 Ames assays were positive, as was a mouse lymphoma study. (See the HIARC report, dated 4/23/01 for more details.)

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Table 2. Genetic Toxicity Profile for Oxyfluorfen (96-99 %)

Assay	Test Material			MRID No.	Result
	ID	Lot No.	Purity (%)		
Ames	RH-2915	TTF068	99.7	00098421	Neg. to HDT (7500 $\mu\text{g}/\text{plate}$); no ppt.
Mouse Lymphoma	RH-2915	0453	99.7	00098419	Neg; ppt at $\geq 62.5 \mu\text{g}/\text{mL}$
Ames ^a	AG 510 Tech.	252/1	96	44942801	Pos. TA 100 at high insoluble doses ($\geq 1667 \mu\text{g}/\text{plate} +\text{S9}$)
Ames ^a	AG 510 Tech.	252/1	96	44933104	Neg to HDT (5000 $\mu\text{g}/\text{plate}$); insoluble at this level
Mouse Micronucleus	AG 510 Tech.	P-8	96	44933105	Neg to HDT (2000 mg/kg, ip); cytotoxic to bone marrow
In vivo Rat UDS	AG 510 Tech.	P-8	96	44933106	Neg to HDT (2000 mg/kg)
Ames	Goal Herb	NA	99.2	44947206	Neg; unacceptable but upgradable
Mouse Lymphoma	Goal Tech Herb	NA	97.1	44947202	Neg; ppt. not reported
CHO/HGPRT	Goal Tech Purified Herb	NA	99.2	44947205	Neg; ppt at $\geq 50 \mu\text{g}/\text{mL}$
CHO/Chromo Aberrations	Goal Tech Purified Herb	NA	99.2	44947204	Neg; ppt at $\geq 450 \mu\text{g}/\text{mL}$
In vivo Mouse Cytogenetics	Goal Tech Purified Herb	NA	97.1	44947203	Neg to HDT (5000 mg/kg)
Bacterial DNA Damage/Repair	Goal Tech Herb	NA	97.1	44947201	Neg; ppt. at 1000 $\mu\text{g}/\text{plate}$

^a The two Ames studies were conducted in different contract laboratories; each protocol required the performance of two independent trials.

Abbreviations:

HDT = Highest dose tested ppt = precipitation ip = intraperitoneal NA = not available

This table is from the HIARC report dated 4/23/01.

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Table 3. Genetic Toxicity Profile for Oxyfluorfen (71 %)

Assay	Test Material			MRID No.	Result
	ID	Lot No.	Purity (%)		
Ames	Goal Herb Tech	AMB18-42A	71.4	40992201	Pos strains TA98 & TA100 at insoluble ($\geq 1600 \mu\text{g}/\text{plate} +\text{S9}$) and soluble ($900 \mu\text{g}/\text{plate} +\text{S9}$) doses; weak unconfirmed response -S9
In vivo Rat Cytogenetics	Goal Herb Tech	2-0956	71.4	41873801	Neg to HDT (5 g/kg)
<i>In vivo</i> Rat Cytogenetics	Goal Herb Tech	2-3985	72.5	00098418	Neg up to lethal dose (1.19 mg/kg)
Ames	RH-2915	2-3985	72.7	00098420	Pos. strain TA1537 ($\geq 2500 \mu\text{g}/\text{plate} +\text{S9}$; $\geq 6000 \mu\text{g}/\text{mL} -\text{S9}$); TA98 ($\geq 500 \mu\text{g}/\text{plate} +\text{S9}$; $\geq 1000 \mu\text{g}/\text{mL} -\text{S9}$); TA100 ($\geq 250 \mu\text{g}/\text{plate} +\text{S9}$; $\geq 2500 \mu\text{g}/\text{mL} -\text{S9}$); no ppt reported
Mouse Lymphoma	RH-2915	2-3985	72.7	00109283	Pos. 1.95-40 $\mu\text{g}/\text{mL} +\text{S9}$; no dose response; ppt at $\geq 62 \mu\text{g}/\text{mL}$
<i>In vitro</i> UDS Rat Hepato	RH-2915	7530	73	00098423	Neg to cytotox doses (25 $\mu\text{g}/\text{mL}$)
Ames	Polar fraction RH-2915, Lot #2-3985	WJZ 1861	NA	00098422	Pos. (only tested TA98) ; 50-7500 $\mu\text{g}/\text{plate} +/-\text{S9}$ not dose related; stronger response +S9
<i>In vitro</i> UDS Rat Hepato	Polar fraction RH-2915, Lot #2-3985	WJZ 1861	NA	00098424	Neg up to cytotox dose (25 $\mu\text{g}/\text{mL}$)

This table is from the HIARC report dated 4/23/01.

3.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: Neurotoxicity is not a major component of toxicity for this chemical. Clinical signs in the developmental rat study and decreased motor activity were judged to be agonal in nature. No neurotoxicity studies were available for oxyfluorfen and none are required.

3.9 Metabolism

Adequacy of data base for metabolism: Two metabolism studies were available and the data base for metabolism is considered complete. No additional studies are required at this time.

Oxyfluorfen was rapidly absorbed, extensively metabolized, and rapidly eliminated. Most compound was eliminated in the feces; females eliminated more in the urine than did males. Bioaccumulation did not occur.

870.7485 Metabolism - Rat

(1) In a metabolism study (MRID 42374201), groups of 5/sex/dose Sprague-Dawley rats were orally dosed once ¹⁴C-oxyfluorfen at 3 different doses: 4 mg/kg, 320 mg/kg, and, following pretreatment for 2 weeks with 40 ppm oxyfluorfen technical, were pulse dosed with 4 mg/kg ¹⁴C-oxyfluorfen. Excreta were collected up to 7 days and analyzed for radiolabel. Groups of rats were sacrificed at 6 hours and 7 days and plasma, whole blood, tissues, and carcasses analyzed for C¹⁴ residues. In addition, groups of rats were serially bled over the 7 day period and plasma and whole blood were analyzed for radiolabel.

Total recovery of radioactivity was 97-99%, 84-91%, and 85-86% for the low-, high-, and pulse-dose groups, respectively. Most (82-98%) of the radioactivity was excreted within 2 days and found predominately in the feces. In contrast to males, the urine of females contained 3-4 time more radiolabel than the urine of males. After 7 days only 0.1-1.4% of radioactivity remained in the carcasses of all dose groups. Elimination of radioactivity from plasma was biphasic in both low- and high-dose groups (rapid phase = 9-13 hours; slow phase = 26-32 hours). Highest concentrations were found in fat, liver, adrenal, thyroid, kidney, lung, and ovaries. Pretreatment with 40 ppm for 2 weeks did not affect distribution of radioactivity.

This study is classified acceptable/guideline.

(2) In a pharmacokinetic study (MRID 42652401), groups of rats were administered a single, oral gavage dose of 4 or 320 mg/kg ¹⁴C-oxyfluorfen or 40 ppm (4 mg/kg/day) unlabelled oxyfluorfen in the diet for 14 days followed by a single oral gavage dose of 4 mg/kg ¹⁴C-oxyfluorfen on day 15. This report is supplemental to a pharmacokinetic study conducted on ¹⁴C-oxyfluorfen in rats (MRID 42374201).

¹⁴C-oxyfluorfen was rapidly absorbed, distributed, metabolized, and excreted following oral administration. Recovery of radioactivity was high in most groups (84-99% of administered dose). Most radiolabel was eliminated in the feces, with a higher urinary excretion in females at all dose levels. Metabolism was extensive with only slight dose- and sex-related differences in amount and pattern of metabolites. Parent compound and approximately 19 metabolites were

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identified in excreta. In feces, parent compound represented the highest amount of radioactivity. In urine, most compounds were conjugates. A greater amount of unmetabolized compound was detected in feces of the high-dose group compared to the low-dose groups (single and repeated dosing). Three major pathways include O-deethylation, nitro reduction, and diphenyl ether cleavage.

This study is classified acceptable non-guideline.

870.7600 Dermal Absorption - Rat

In a dermal absorption study (MRID 921361-01), ¹⁴C-Oxyflourfen and unlabeled Oxyflourfen (99.6%), were applied to the backs of male Charles River Crl:CD rats for durations of 1, 2, 4, 10 & 24 hours. An additional group was carried for 168 hours after a wash at 10 hours for dermal absorption and a final group carried for 144 hours after a wash at 10 hours for serial collection of blood.

At dermal doses of 0.02, 0.10 and 1.44 mg/cm², absorption at 10 hours was 3.46%, 1.28%, and 0.66% for the respective dose groups; 14.79%, 11.42%, and 5.81%, respectively, remained on the skin and was considered potentially absorbable. At 24 hours, absorption was 8.06%, 2.49%, and 1.09% for the respective dose groups; 6.35%, 3.23%, and 3.07%, respectively, remained on the skin. Absorption at 168 hours (0.1 mg/cm²), with a wash at 10 hours, was 16.17%, of which 15.28% was excreted; 1.02% remained on the skin. This study is classified acceptable/guideline.

4.0 TOXICITY ENDPOINT SELECTION

4.1 Toxicity Endpoints

The Hazard Identification Assessment Review Committee (HIARC) selected toxicity endpoints for use in human risk assessments. The toxicity endpoints and doses for risk assessment are shown in Table 4, below. The details for these selections are contained in the HIARC report (dated 4/23/01).

For occupational exposure risk assessments, a margin-of-exposure (MOE) of 100 is adequate for short-term dermal or inhalation exposure risk assessments. A MOE of 300 is required for intermediate-term dermal or inhalation exposure risk assessments because of the use of LOAEL for these exposure scenarios. A MOE of 100 is adequate for long-term dermal or inhalation exposure risk assessments. The MOEs for residential exposure are reported by the FQPA Safety Factor Committee.

4.2 Dermal Absorption

Dermal Absorption Factor: 18%

This value is derived from the dermal absorption study in rats (MRID 92136101). A dermal absorption factor was selected because the subchronic dermal toxicity study was classified unacceptable. The dermal absorption factor of 18% is the 10-hour value from the low-dose group (0.02 mg/cm²), which had the maximal absorption of the different dose groups. The 18% value includes compound on the skin, which is considered potentially absorbable.

The dermal absorption factor is required for short-, intermediate-, and long-term dermal risk assessments because oral doses were selected for these exposure periods.

4.3 Classification of Carcinogenic Potential

In accordance with the 1986 guidance for carcinogenic risk assessment, the Cancer Peer Review Committee has classified oxyfluorfen as a category C, possible human carcinogen based upon combined hepatocellular adenomas/carcinomas in the mouse carcinogenicity study. The Cancer Peer Review Committee recommended a linear, low dose extrapolation for human risk assessments using a $Q_1^* = 7.32 \times 10^{-2}$ (Lori Brunsman memo, HED doc. 012879, 9/24/98).

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Table 4. Summary of Endpoints for Oxyfluorfen for Use in Human Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	An appropriate endpoint attributed to a single dose was not available. Therefore, an acute RfD was not established.		
Chronic Dietary	NOAEL = 3.0 UF = 100	Liver toxicity occurring in dogs and mice.	Chronic dog study and mouse carcinogenicity
		Chronic RfD = 0.03 mg/kg/day	
Cancer	$Q_1^* = 7.32 \times 10^{-2}$	Combined hepatocellular adenomas and carcinomas.	Mouse carcinogenicity study
Incidental Oral, Short-Term	An appropriate endpoint attributed to short-term, incidental oral exposure was not available.		
Incidental Oral, Intermediate-Term	LOAEL = 32	Liver toxicity and anemia.	90-day mouse
Dermal, Short-Term ^a	NOAEL = 30	Abortions and clinical signs.	Developmental rabbit study (1998)
Dermal, Intermediate-Term ^a	LOAEL = 32	Liver toxicity and anemia.	90-day mouse
Dermal, Long-Term ^a	NOAEL = 3.0	Liver toxicity occurring in dogs and mice.	Chronic dog study and mouse carcinogenicity
Inhalation, Short-Term ^b	NOAEL = 30	Abortions and clinical signs.	Developmental rabbit study (1998)
Inhalation, Intermediate-Term ^b	LOAEL = 32	Liver toxicity and anemia.	90-day mouse
Inhalation, Long-Term ^b	NOAEL = 3.0	Liver toxicity occurring in dogs and mice.	Chronic dog study and mouse carcinogenicity

This table is from the Hazard Identification Assessment Review Committee report for oxyfluorfen, dated 4/23/01.

a An oral endpoint was used for dermal exposure: dermal absorption factor of 18% of oral exposure shall be used.

b An oral endpoint was used for inhalation exposure: inhalation exposure assumed equivalent to oral exposure.

NOAEL = no observed adverse effect level

LOAEL = lowest observed adverse effect level

5.0 Food Quality Protection Act (FQPA) CONSIDERATIONS

5.1 Special Sensitivity to Infants and Children

In the developmental toxicity study in rats with 98% a.i., no developmental toxicity was seen at the limit dose. In the developmental toxicity study in rabbits with 98% a.i., there was no quantitative or qualitative evidence of susceptibility. Developmental toxicity, characterized as decreases in live fetuses per doe occurred at the same dose that caused maternal toxicity, including increased abortions, clinical signs, and decreased food consumption. Also, the decrease in live fetuses occurred primarily in one litter and were not statistically significant. In the two generation reproduction study in rats with 71% a.i., offspring toxicity was manifested as decreased live pups per litter and decreased pup body weight in the presence of maternal toxicity (mortality in one doe, decreased body weight gain, and liver and kidney lesions) at the same dose. The HIARC determined that any uncertainty with respect to the fetal deaths observed in this study were allayed since the pup deaths seen at Day 0, (i.e., prenatal death) were not seen at a much higher dose (1000 mg/kg/day) in the prenatal developmental toxicity study in rats conducted with the 98% a.i.

5.2 Recommendation for a Developmental Neurotoxicity Study

It is recommended that a developmental neurotoxicity study **not** be required. This conclusion was reached with the following considerations:

Evidence that suggest requiring a developmental neurotoxicity study: No neurotoxicity studies are available. Signs suggestive of neurotoxicity occurred in developmental studies. One rabbit had decreased motor activity at 90 mg/kg/day in a developmental toxicity study (MRID 00094052) prior to death. Clinical signs at 848 mg/kg/day in a developmental rat study included hunched posture, ataxia, lethargy, pale extremities, alopecia, and mucoid feces; 15 rats in this group died. These signs are attributed to agonal death.

Evidence that **does not** support the need for a developmental neurotoxicity study: The above mentioned signs suggestive of neurotoxicity occurred at lethal doses and were considered agonal. There were no gross or microscopic neurotoxic lesions of treatment-related damage to the nervous system. No increase in susceptibility of fetuses or offspring occurred in developmental or reproductive studies.

6.0 OTHER ISSUES

Product chemistry reviews and confidential statements of formula were reviewed in order to compare impurities in the current oxyfluorfen registrations (approximately 98% purity) with those of the earlier registration (approximately 71%). It was concluded that the current oxyfluorfen registrations (approximately 98% purity) had similar profiles of impurities, but in reduced concentrations when compared to those found in the earlier registration.

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8.0 APPENDIX

Toxicity Profile for Oxyfluorfen

Table 5. Toxicity Profile for Oxyfluorfen

Guideline No. / Study Type / % a.i.	MRID (year) / Classification / Doses	Results
870.3100 90-Day oral toxicity - rats 98.0%	44933101 (1997) acceptable/guideline 0, 500,1500,6000,10000 ppm M: 0, 46.7, 143.5, 585.0, 1012.1 mg/kg/d F: 0, 50.4, 150.5, 643.8, 1058.6 mg/kg/d	NOAEL = 1500 ppm (M: 143.5 mg/kg/day; F: 150.5 mg/kg/day) LOAEL = 6000 ppm (M: 585.0 mg/kg/day; F: 643.8 mg/kg/day) based on ↓ BW, ↑ urine volume, ↓ erythrocyte volume and Hb, ↑ rel. liver wt
870.3100 90-Day oral toxicity - rats 72.5%	00117601 (1982, Rohm & Haas), 92136011, 42142317 acceptable/guideline 0, 800, 1600, 3200 ppm M: 0, 51.4, 105, 234 mg/kg/day F: 0, 61, 61.1, 124, 260 mg/kg/day	NOAEL < 800 ppm (M: 51.4 mg/kg/day; F: 61.1 mg/kg/day) LOAEL ≤ 800 ppm (M: 51.4 mg/kg/day; F: 61.1 mg/kg/day) based on ↑ liver wt and liver histo (M: hypertrophy; eosinophilia; and hepatic necrosis in 3 males) and adrenal histo (M, F)
870.3100 90-Day oral toxicity - rats 72%	00117603 (1982, Nomura Institute) acceptable/guideline 0, 200, 1000, 5000 ppm M: 14, 71, 361 mg/kg/day F: 18, 75, 396 mg/kg/day	NOAEL = 200 ppm (M: 14 mg/kg/day; F: 18 mg/kg/day) LOAEL = 1000 ppm (M: 71 mg/kg/day; F: 75 mg/kg/day) based on brown livers and kidneys, ↑ relative liver wt (M), ↓ absolute/relative thymus wt (M), liver and kidney histo (slight)
870.3100 90-Day oral toxicity - mice 72.5%	0017602 (1982), 92136012, 42142316 acceptable/guideline 0, 200, 800, 3200 ppm M: 0, 32.0,134.5, 490.5 mg/kg/day F: 0, 44.4, 166.6, 520.9 mg/kg/day	NOAEL < 200 ppm (M: 32.0 mg/kg/day; F: 44.4 mg/kg/day) LOAEL ≤ 200 ppm (M: 32.0 mg/kg/day; F: 44.4 mg/kg/day) based on anemia ↑ SGPT, ↑ liver wt, liver histopathology MFO activity determined in this study.
870.3200 28-day dermal toxicity - rabbits technical 75% EC 31.7%	00071915 (1978), 92136014. unacceptable tech: 1500 mg/kg/day EC: 24.2, 96.8 mg/kg/day solvent control: 0.4 mL/kg/day	NOAEL for technical not defined LOAEL for technical = 1500 mg/kg/day based on ↓ BW, ↑ liver wt, and microscopic hepatic hypertrophy in 1/4 animals in males and females NOAEL for EC formulation = 24.2 mg/kg/day LOAEL for EC formulation = 96.2 mg/kg/day based on ↓ BW NOAEL for solvent control not defined LOAEL for solvent control = 0.4 mL/kg based on ↓ BW dermal toxicity occurred in all treatment groups (erythema, dryness, edema)
(870.3465) non-guideline 1-month inhalation toxicity 23.5%	00071916 (1978), 000163582, 163584. unacceptable 0, 0 (vehicle control), 0.13, 0.65 mg/L M: 33.2 and 166.1 mg/kg/day F: 34.9, 174.7 mg/kg/day	NOAEL < 0.13 mg/L (M: 33.2 mg/kg/day; F: 34.9 mg/kg/day) LOAEL ≤ 0.13 mg/L (M: 33.2 mg/kg/day; F: 34.9 mg/kg/day) based on ↑ liver wt in low-dose females, but not high-dose females, lung pathology. Low-dose group sometimes showed more toxicity than high-dose group, many problems with this study.

Table 5. Toxicity Profile for Oxyfluorfen

Guideline No. / Study Type / % a.i.	MRID (year) / Classification / Doses	Results
870.3700a Developmental - rats 98.0%	44933103 (1997) acceptable/guideline 0, 375, 750, 1000 mg/kg/day	Maternal NOAEL ≥ 1000 mg/kg/day (HDT) Maternal LOAEL > 1000 mg/kg/day (HDT) Developmental NOAEL ≥ 1000 mg/kg/day (HDT) Developmental LOAEL > 1000 mg/kg/day (HDT)
870.3700a Developmental - rats 71.4%	41806501 (1991) acceptable/non-guideline 0, 18, 183, 848 mg/kg/day	Maternal NOAEL = 18 mg/kg/day Maternal LOAEL = 183 mg/kg/day based on clinical signs (red vaginal discharge, scant feces). At 848 mg/kg/day, severe maternal mortality. Developmental NOAEL = 18 mg/kg/day Developmental LOAEL = 183 mg/kg/day based on ↑ early resorptions, ↓ fetal BW, vessel variations, bent scapula, fused sternbrae, bent bones in fore- and hindlimbs
870.3700b Developmental - rabbits 98.0%	44933102 (1997) acceptable/non-guideline 0, 10, 30, 90 mg/kg/day	Maternal NOAEL = 30 mg/kg/day Maternal LOAEL = 90 mg/kg/day based on abortions, clinical signs (loose feces, thin build), ↓ FC, ↓ gravid uterine wt Developmental NOAEL = 30 mg/kg/day Developmental LOAEL = 90 mg/kg/day based on ↑ late resorptions, ↓ live fetuses/doe
870.3700b Developmental - rabbits 26.9% WP formulation	00094052 (1981), 00094051, 92136018, 92136019 acceptable/guideline 0, 0 (vehicle), 10, 30, 90 mg/kg/day	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = 30 mg/kg/day based on ↓ BW gain and clinical signs (anorexia, red exudate). At 90 mg/kg/day, also severe maternal mortality, abortions, hematuria, ↓ motor activity Developmental NOAEL = 30 mg/kg/day Developmental LOAEL = 90 mg/kg/day based on ↓ litter size and ↑ early resorptions
870.3800 Reproduction - rats 71.4%	42014901 (1991) acceptable/guideline 0, 100, 400, 1600 ppm M: 0, 7.8, 30.9, 120 mg/kg/day F: 0, 8.5, 32.8, 131.2 mg/kg/day	Parental NOAEL = 400 ppm (M: 31; F: 33 mg/kg/day) Parental LOAEL = 1600 ppm (M: 120; F: 131 mg/kg/day) based on mortality, ↓ BW, and liver and kidney histopathology (hepatocellular hypertrophy, renal pelvic mineralization, etc) Offspring NOAEL = 400 ppm (M: 31; F: 33 mg/kg/day) Offspring LOAEL = 1600 ppm (M: 120; F: 131 mg/kg/day) based on ↓ BW/smaller litter size

Table 5. Toxicity Profile for Oxyfluorfen

Guideline No. / Study Type / % a.i.	MRID (year) / Classification / Doses	Results
870.4100b Chronic toxicity dogs 71.4-73.8%	00078767 (1981), 92136062, 92136016 acceptable/guideline 0, 100, 600, 2000 ppm M: 0, 3.1, 18.5, 61.0 mg/kg/day F: 0, 3.0, 18.8, 60.3 mg/kg/day	NOAEL = 100 ppm (M: 3.1 mg/kg/day; F: 3.0 mg/kg/day) LOAEL = 600 ppm (M: 18.5 mg/kg/day; F: 18.8 mg/kg/day) based on ↓ BW gains, ↑ SAP, ↑ liver wt
870.4300 combined chronic toxicity/ carcinogenicity - rats 85.7%	00083445 (1978), 00135072, 92136061 unacceptable 0, 2, 40, 800/1600 ppm M: 0, 0.1, 1.94, 56.96 mg/kg/day F: 0, 0.12, 2.43, 72.57 mg/kg/day	NOAEL ≥ 800/1600 ppm (M: 56.96 mg/kg/day; F: 72.57 mg/kg/day) LOAEL > 800/1600 ppm (M: 56.96 mg/kg/day; F: 72.57 mg/kg/day). No toxicity, no neoplasia
870.4200 Carcinogenicity mice 87.5%	00037939 (1977), 92136017 acceptable 0, 0 (ethanol), 2, 20, 200 ppm M: 0, 0 (ethanol), 0.3, 3.0, 33 mg/kg/day F: 0, 0 (ethanol), 0.4, 4.0, 42.0 mg/kg/day	NOAEL = 20 ppm (M: 3.0; F: 4.0 mg/kg/day) LOAEL = 200 ppm (M: 33; F: 42 mg/kg/day) based on ↑ liver wt, ↑ SAP and SGPT, liver histopathology (including hepatocyte necrosis) Combined adenomas/carcinomas increased: used to set Q₁*
870.7485 Metabolism and pharmacokinetics	42374201 (1992) 42652401 (1993)	Rapidly absorbed, extensively metabolized, and rapidly eliminated. Most compound eliminated in the feces; females eliminated more in the urine than did males.
870.7600 Dermal penetration	42142306 (1989), 92136095 acceptable	Maximal absorption = 18% at LDT when compound remaining on skin is considered potentially absorbable.

ABBREVIATIONS:

M = Male, F = Female, BW = body weight

SAP = serum alkaline phosphatase enzyme

SGPT = serum glutamate pyruvate transaminase enzyme or ALT

Hb = hemoglobin, PT = prothrombin time

MFO = mixed function oxidase

EC = emulsifiable concentrate formulation, WP = wettable powder formulation

LDT = lowest dose tested in study.