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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 12 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Oxyfluorfen; Goal 1.6E; PP #3F4229/3H5674; Rohm and Haas Company Requests Permanent Tolerances for Residues of Oxyfluorfen and its Metabolites in/on Peanuts (Raw Agricultural and Processed Commodities)

Tox.Chem No.: 188AAA
MRID No.: 427933-00
DP Barcode No.: D192407
Submission No.: S442843

TO: Joanne Miller, PM #23
Fungicide-Herbicide Branch
Registration Division (H7505C)

FROM: William Dykstra, Ph.D., Toxicologist
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THRU: Roger Gardner, Section Head, Toxicologist
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Pamela M. Hurley 9/28/93 KB 10/5/93

ACTION REQUESTED: Rohm and Haas Company requests permanent tolerances for oxyfluorfen in/on peanuts (raw agricultural and processed commodities). Specifically, Rohm and Haas Company requests the establishment of tolerances for oxyfluorfen and its metabolites containing the diphenyl ether linkage in or on the raw agricultural commodities peanut meat, vine, hay and hulls at 0.05, 0.05, 0.05 and 0.10 ppm, respectively, and the processed peanut commodities meal, crude oil, soap stock, and refined oil, all at 0.05 ppm.

Toxicology Branch-I (TB-I) has been requested to review the Rohm and Haas Company application for these permanent tolerances.

(1)

CONCLUSIONS:

1. The toxicology studies which the Registrant, Rohm and Haas Company, references to support the registration of Goal 1.6E have been performed by the former Cannon Laboratories. These toxicology studies are invalid due to the status of **all** Cannon toxicology studies and have to be replaced as soon as possible. Additionally, the test material of these invalid studies was not Goal 1.6E but a 1974 surrogate called RH-2915 EC 24.3%. Goal 1.6E does not appear to have been ever tested toxicologically. However, there are sufficient toxicology data and studies with technical oxyfluorfen to support the requested tolerances.

2. On the basis of the exposure estimates for this peanut petition from OREB (memo of 9/1/93 from A.O. Schlosser to J. Miller), there are two average daily exposure estimates for a "Typical 90 Acre Farm" and a "Large 450 Acre Farm". The calculated carcinogenic risks and developmental margins of exposure (MOE) for the two different farm worker scenarios are presented below:

   1. Carcinogenic Risks

   (A) "Typical 90 Acre Farm"

   Mixer/Loader/Applicator
   Risk = 1.23×10^{-7}

   (B) "Large 450 Acre Farm"

   Mixer/Loader
   Risk (Mixer/Loader) = 1.99×10^{-7}

   Applicator
   Risk (Applicator) = 4.22×10^{-7}

   2. Developmental Risks

   (A) "Typical 90 Acre Farm"

   Mixer/Loader/Applicator

   MOE(Rat) = 42,857

   MOE(Rabbit) = 23,809

(B) "Large 450 Acre Farm"

Mixer/Loader MOE(Rat) = 82,911

Mixer/Loader MOE(Rabbit) = 45,662

Applicator MOE(Rat) = 40,000

Applicator MOE(Rabbit) = 22,222

3. A newly prepared Toxicology Profile for oxyfluorfen is included to address any toxicological issues which may arise in the consideration of the proposed tolerances. The existing toxicological data base is summarized in the Profile.

REVIEW:

1. Carcinogenic Risks

On the basis of the exposure estimates for this peanut petition from OREB (memo of 9/1/93 from A.O. Schlosser to J. Miller), there are two average daily exposure estimates for a "Typical 90 Acre Farm" and a "Large 450 Acre Farm".

(A) "Typical 90 Acre Farm"

Mixer/Loader/App. = 3.2×10^{-5} mg/kg/day

Dermal Penetration = 3% (Review of 1/21/93 from R. Zendzian)

$Q_1^* = .128 \times (mg/kg/day)^{-1}$

Risk = Mixer/Loader/App. x 3% x Q_1^*

Risk = 3.2×10^{-5} mg/kg/day x .03 x .128 x $(mg/kg/day)^{-1}$

Risk = 1.23×10^{-7}

(B) "Large 450 Acre Farm"

Mixer/Loader = 5.2×10^{-5} mg/kg/day

Applicator = 1.1×10^{-4} mg/kg/day

Dermal Penetration = 3%

$Q_1^* = .128 \times (mg/kg/day)^{-1}$

Risk (Mixer/Loader) = 5.2×10^{-5} mg/kg/day x .03 x .128

Risk (Mixer/Loader) = 1.99×10^{-7}

Risk (Applicator) = 1.1×10^{-4} mg/kg/day x .03 x .128

Risk (Applicator) = 4.22×10^{-7}

2. Developmental Risks

Based on the OREB memo, there are two average daily exposure estimates for a "Typical 90 Acre Farm" and a "Large 450 Acre Farm".

(A) "Typical 90 Acre Farm"

Daily exposure for Mixer/Loader/App. = 1.4×10^{-2} mg/kg/day

Dermal Penetration = 3%

Rat Developmental NOEL = 18 mg/kg/day

Rabbit Developmental NOEL = 10 mg/kg/day

$$\text{MOE(Rat)} = \frac{18 \text{ mg/kg/day}}{1.4 \times 10^{-2} \times .03}$$

MOE(Rat) = 42,857

$$\text{MOE(Rabbit)} = \frac{10 \text{ mg/kg/day}}{1.4 \times 10^{-2} \times .03}$$

MOE(Rabbit) = 23,809

(B) "Large 450 Acre Farm"

Daily exposure for Mixer/Loader = 7.3×10^{-3} mg/kg/day

Daily exposure for Applicator = 1.5×10^{-2} mg/kg/day

Dermal Penetration = 3%

Rat Developmental NOEL = 18 mg/kg/day

Rabbit Developmental NOEL = 10 mg/kg/day

$$\text{Mixer/loader MOE(Rat)} = \frac{18 \text{ mg/kg/day}}{7.3 \times 10^{-3} \times 0.03}$$

Mixer/Loader MOE(Rat) = 82,911

$$\text{Mixer/Loader MOE(Rabbit)} = \frac{10 \text{ mg/kg/day}}{7.3 \times 10^{-3} \times 0.03}$$

Mixer/Loader MOE(Rabbit) = 45,662

Applicator MOE(Rat) = $\frac{18 \text{ mg/kg/day}}{1.5 \times 10^{-2} \times 0.03}$

Applicator MOE(Rat) = 40,000

Applicator MOE(Rabbit) = $\frac{10 \text{ mg/kg/day}}{1.5 \times 10^{-2} \times 0.03}$

Applicator MOE(Rabbit) = 22,222

3. A Toxicology Profile has recently been completed for Oxyfluorfen and the Profile is intended to address toxicology issues relating to the registration of Oxyfluorfen. The existing toxicological data base is summarized in the Profile.

4. Section F:

The petitioner, Rohm and Haas Company, requests the establishment of tolerances for the residues of the herbicide oxyfluorfen [2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl)benzene] and its metabolites containing the diphenyl ether linkage in or on the following raw agricultural commodities:

	Raw Agricultural Commodity	Proposed Tolerance	Processed Commodity	Proposed Tolerance
Peanut	Meat	0.05 ppm	Meal	0.05 ppm
	Vine	0.05 ppm	Crude oil	0.05 ppm
	Hay	0.05 ppm	Soap stock	0.05 ppm
	Hulls	0.10 ppm	Refined oil	0.05 ppm

Requirements (CFR §158.35):

Technical: Registration No. 707-165 (72.5% a.i.)

	Required	Satisfied	
81-1	Y	Y	Acute Oral Toxicity
81-2	Y	Y	Acute Dermal Toxicity
81-3	Y	Y	Acute Inhalation Toxicity
81-4	Y	Y	Primary Eye Irritation
81-5	Y	Y	Primary Dermal Irritation
81-6	Y	Y	Dermal sensitization
81-7	N	N	Acute Delayed Neurotoxicity (hen)
82-1a	Y*	Y	Subchronic Oral (rodent)
82-1b	Y*	Y	Subchronic Oral (nonrodent)
82-2	Y	Y	21-Day Dermal
82-3	N	-	90-Day Dermal
82-4	N	-	90-Day Inhalation
82-5a	N	-	90-Day Neurotoxicity (hen)
82-5b	N	-	90-Day Neurotoxicity (mammal)
83-1a	Y	Y	Chronic Toxicity (rodent)
83-1b	Y	Y	Chronic Toxicity (nonrodent)
83-2	Y	Y	Carcinogenicity (two species)
83-3a	Y	Y	Developmental Toxicity (first species)
83-3b	Y	Y	Developmental Toxicity (second species)
83-4	Y	Y	Reproduction
83-5	**	-	Chronic/Carcinogenicity (see 83-1 & 83-2)
84-2a	Y	Y	Mutagenicity - Gene Mutation
84-2b	Y	Y	Mutagenicity - Structural Chrom. Aberr.
84-2c	Y	Y	Mutagenicity - Other Genotoxic Effects
85-1	Y	Y	General Metabolism

85-2	Y	Y	Dermal Penetration
86-1	N	-	Domestic Animal Safety

Formulation: Goal 1.6E (20.9% Technical in Formulation)

Registration No. 707-174

	Required	Satisfied	
81-1	Y	N	Acute Oral Toxicity
81-2	Y	N	Acute Dermal Toxicity
81-3	Y	N	Acute Inhalation Toxicity
81-4	Y	N	Primary Eye Irritation
81-5	Y	N	Primary Dermal Irritation
81-6	Y	N	Dermal sensitization

Y - Yes
N - No
W - Waived
P - Partially

† Study awaiting review in HED.

* The requirement is satisfied if an acceptable chronic study is available.

** Not required if acceptable chronic and oncogenicity studies are available.

Toxicology Profile:

Technical: Registration No. 707-165 (72.5%)

	STUDY	RESULTS
81-1	Acute Oral, Rat Acceptable / IV Document No. None MRID No. 41601001	LD_{50} > 5.0 gm/kg (both sexes) No Deaths, toxic signs consisted of bright-yellow stained anal-genital region, salivation, soft feces, yellow-stained muzzle. No effect on body weight and no necropsy findings.
81-2	Acute Dermal, Rabbit Acceptable/ IV Document No. None MRID No. 41601002	LD_{50} > 5.0 gm/kg No Deaths, no toxic signs, no effect on body weight, and no necropsy findings.
81-3	Acute Inhalation, Rat Acceptable/ IV Document No. None MRID No. 42000001	4-Hour LC_{50} > 5.4 mg/L (analytical), MMAD = 1.6 - 2.9 μm, no deaths, no toxic signs, no necropsy findings
81-4	Primary Eye Irritation, Rabbit Acceptable/ III Document No. None MRID No. 41601004	In the washed and unwashed eye, conjunctival effects (redness, discharge and chemosis) were observed at 1 - 72 hrs, but disappeared by day 7. Washing eyes did not reduce the duration or severity of conjunctival effects. No iritis or corneal opacity.
81-5	Primary Dermal Irritation, Rabbit Acceptable/ IV Document No. None MRID No. 41601003	Erythema and edema at 1, 24, and 48 hours, but clearing at 72 hours. P.I.I. at 72 hours = 0.0
81-6	Dermal Sensitization, Guinea Pig Acceptable Document No. None MRID No. 41891802	Delayed contact hypersensitivity study in guinea pigs (Buehler Method) produced equivocal results at challenge in both naive and Goal treated guinea pigs. These data do not support an interpretation of positive dermal sensitization for Goal.
82-1a	90-Day Feeding, Rat Supplementary Document No. 2621 Accession No. 248728	NOEL < 200 ppm Increase in relative weights of liver, adrenal, and thyroid Doses were 0, 200, 1000, and 5000 ppm in Sprague-Dawley rats.

82-1b	90-Day Gavage, Dog Ungraded Document No.4288	NOEL = 400 ppm
82-2	21-Day Dermal, Rabbit Minimum Document No. 7358 Accession No. None	NOEL < 2000 mg/kg/day, increased liver weight at 2000 mg/kg/day in NZW Rabbits
83-1a	Chronic Feeding, Rat	See 83-5
83-1b	Chronic Feeding, Dog (2 years) Minimum Document No. 426, 707 Accession No. 245398	NOEL = 100 ppm and LEL = 600 ppm . Effects were increased liver weight, alkaline phosphatase increases, renal tubule vacuolization, and thyroid C-cell hyperplasia. Doses were 100, 600, and 2000 ppm in 6/sex/dose in Beagle Dogs
83-2a	Carcinogenicity, Rat	See 83-5
83-2b	Carcinogenicity, Mouse (20-Month) Minimum Document No. 4288, 4289, 4290 Accession No. None	Oncogenic Potential: Positive; Hepatocellular adenomas and carcinomas in male CD-1 mice; NOEL = 2.0 ppm and LEL = 20 ppm; increased absolute liver weight and increased non-neoplastic liver lesions. Doses were 0, 2, 20, and 200 ppm for 20-months.
83-3a	Developmental Toxicity, Rat Minimum Document: 8538 MRID No. 418065-01	Maternal NOEL = 18 mg/kg/day, Maternal LEL = 183 mg/kg/day, (decreased weight gain and food consumption, increased incidences of soft or scant feces, increased alkaline phosphatase and SGOT and mortality at high-dose) Developmental NOEL = 18 mg/kg/day Developmental LEL = 183 mg/kg/day (decreased fetal body weight, increased resorptions, and an increase in the incidences of left carotid artery arising from the innominate, bent bones of the forelimbs, and other ossification irregularities; these effects were confined to the mid-dose level, since there was 100% litter loss in the high-dose groups as the result of maternal mortality and resorptions) Doses were 0, 18, 183, and 848 mg/kg/day (Days 6-15 of gestation) in Sprague-Dawley rats.

83-3b	Developmental Toxicity, Rabbit (25W) Minimum Document No. 1572, 4288, 1883 MRID No. None	Maternal NOEL = 10 mg/kg/day Maternal LEL = 30 mg/kg/day (anorexia, decreased body weight gain) Developmental NOEL = 10 mg/kg/day Developmental LEL = 30 mg/kg/day (fused sternebrae) Doses were 0, 10, 30 and 90 mg/kg/day in NZW strain.
83-4	2-Generation Reproduction, Rat Guideline Document No. 10421 MRID No. 420149-01, -02	Reproductive NOEL = 400 ppm Reproductive LEL = 1600 ppm (decreased pup body weight during lactation in both the F_1a and F_2a litters and also a decreased litter size at birth in F_1a and F_2a litters. Systemic NOEL = 400 ppm and LEL = 1600 ppm (Pelvic mineralization of P_1 males, P_2 males and females, and pelvic papillary hyperplasia in P_1 and P_2 males and P_2 females. Also at 1600 ppm, there were additional kidney effects, consisting of dilatation of collecting ductules in both P_2 sexes. Other high-dose histological findings consisted of hepatocellular hypertrophy in both sexes of P_1 and P_2 animals. Additional high-dose effects were alopecia in both sexes of P_1 and P_2 animals during growth, and decreased weight gain during growth and gestation of P_1 and P_2 parental animals). Doses were 0, 100, 400, and 1600 ppm in Sprague-Dawley rats.
83-5	Chronic Feeding/Carcinogenicity, Rat Minimum Document No. 3307, 4288 Accession No. None	Oncogenic Potential: Negative; Systemic NOEL = 40 ppm and LEL = 800/1600 ppm (Minimal hypertrophy of centrilobular hepatocytes) Doses were 0, 2, 40, 800/1600 ppm in Long-Evans rats.
84-2a	Gene Mutation: Ames Assay Acceptable Document No. 1854 Accession No. 247206	A negative response was seen in <u>Salmonella</u> strains TA1535, TA1537, TA100 and TA98 both with and without metabolic activation.
	Gene Mutation: Ames Assay Acceptable Document No. 1854 Accession No. 247206	Positive in TA98, TA100, and TA1537 at 2500 ug/plate with activation and at 6000 ug/plate without activation.

84-2b	Structural Chromosome Aberration: In Vivo Cytogenetic Assay/Rat Acceptable Document No. 1854 Accession No. 247206	Negative for cytogenetic chromosomal aberrations both with and without metabolic activation.
84-2c	Other Genotoxic Effects: Mouse Lymphoma Forward Mutation Assay Acceptable Document No. 1854, 2166, 2414 Accession No. 247909	Positive mutagen in the presence of an activation system at the thymidine kinase locus of mouse lymphoma L51787Y (TK +/-) cells.
85-1	Metabolism Acceptable Document No. 010337, 010306 MRID No. 42652401, 42374201	C^{14}-oxyfluorfen is rapidly absorbed, distributed, metabolized and excreted following oral administration to groups of 5/sex/dose Sprague-Dawley rats at 3 different doses: 4 mg/kg, 320 mg/kg and, following pretreatment for 2 weeks with 40 ppm Goal technical, were "pulse" dosed with 4 mg/kg C^{14}-oxyfluorfen. The total radioactivity was 97-99, 84-91, and 85-56% for the low, high, and pulse-doses, respectively. Most radioactivity was excreted in 2 days and found primarily in the feces. Highest concentrations were found in fat, liver, adrenal, thyroid, kidney, lung, and ovaries. The parent compound and about 19 metabolites were found in the excreta. Three major pathways include O-deethylation, reduction of the nitro group, and diphenyl ether cleavage.
85-2	Dermal Penetration Acceptable MRID No. 92136101	At dermal doses of 0.02, 0.10, and 1.44 mg C^{14}-oxyfluorfen/cm^2 in male Sprague-Dawley rats for durations of 1, 2, 4, 10, and 24 hours, maximum absorption was 8.06, 2.49, and 1.09%, respectively. Significant absorption continued after skin wash. Blood concentrations with time followed after a single dermal dose of 4.8 mg C^{14}-oxfluorfen/kg.

V. Action Taken to Obtain Additional Information or Clarification:

Data gaps for the technical have been requested in a FIFRA '88 DCI.

VI. Reference Dose (RfD):

The RfD is 0.003 mg/kg/day. This value was calculated by using the 20-Month Mouse Feeding study NOEL of 0.30 mg/kg/day and an uncertainty factor of 100. It was verified by both HED and the Agency.

VII. Pending Regulatory Actions:

There are at this writing no pending regulatory actions against the Registration of this pesticide.

VIII. Toxicologic Issues Pertinent to Granting this Request:

The pesticide is a Group C carcinogen, with quantification, due to a statistically significant trend increase in hepatocellular adenomas and carcinomas in male CD-1 mice across doses. The mutagenic potential is positive in two categories of genotoxic studies.

In order to quantify human risk, the HED Peer Review Committee recommended the use of the Q_1*. The Q_1* is 0.128 $(mg/kg/day)^{-1}$ in human equivalents.

William Dykstra, Ph.D., D.A.B.T.
Updated: September 14, 1993