FR-4290

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

JAN 11 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: EPA Reg. #: 707-174, Goal 1.6E, PP# 4F3119;
Oxyfluorfen in/on tree nuts crop group
Caswell #: 188AAA
Accession #: 072717, 072718

TO: Richard Mountfort
Product Manager (23)
Registration Division (TS-767)

and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Christine F. Chaisson, Ph.D. C.F. Chaisson 1/10/85
Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D. William Dykstra 12/12/84
Toxicology Branch
Hazard Evaluation Division (TS-769)

Action Requested:

Review petition for establishment of permanent tolerances for oxyfluorfen in/on tree nuts crop group.

Background:

Oxyfluorfen was an RPAR pesticide due to the presence of small amounts of perchlorethylene. During the RPAR process, the issues which most concerned the SAP were teratogenicity, oncogenicity, and mutagenicity of oxyfluorfen. With respect to teratology, two teratology studies were submitted, a rat and rabbit. The teratogenic potential of both studies were negative; and NOEL's for fetotoxicity were established.

Additionally, a mouse teratology was performed by Dr. Neal Chernoff of EPA/RTP. The mouse study was also negative with oxyfluorfen.

The oncogenicity studies with oxyfluorfen were in the mouse and in the rat and also have been focuses of attention by SAP, CAG, and Toxicology Branch.

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In the mouse study, the dosages were 2, 20, and 200 ppm. The NOEL was 2 ppm and the LEL was 20 ppm. The effects at the LEL were increased absolute liver weight and non-neoplastic histological lesions. These effects set the basis for the ADI.

Also, the occurrence of adenomas and carcinomas in the liver of male mice was observed (slides evaluated by Dr. Squire).

Statistically, the occurrence of mouse liver tumors showed a significant trend across the doses (trend analysis significance = 0.008), although the significance of P = 0.068 was observed at the high dose. CAG considered the mouse study as marginal for oncogenicity.

In the rat study, dosages employed were 2, 40 and 1600 ppm. There was no evidence of tumorigenicity according to CAG. Non-neoplastic liver lesions were observed at 1600 ppm.

CAG stated that both the rat and mouse chronic studies did not use the MTD and there were no subchronic studies from which to determine the MTD.

To address this concern, 90 day rat and mouse studies were performed which could be used as an estimate to determine the MTD.

In these studies, a NOEL for toxicity based on several criteria was not established. Toxicology Branch concluded that the 90 day studies were adequate to assess the MTD for both the rat study and the mouse study and no additional chronic studies were needed.

Additionally, Toxicology Branch recommended that, based on all of the data, CAG should evaluate the oncogenic potential of oxyfluorfen.

Following this recommendation, oxyfluorfen received unconditional registration by the Agency.

Oxyfluorfen was positive for mutagenicity in several assays, except UDS. An impurity in the technical oxyfluorfen was considered to be the mutagenic agent.

Both technical and purified oxyfluorfen were negative for mutagenicy in the UDS assay. Additional mutagenicity studies have not been requested.

Recommendations:

1. The tolerance in/on tree nuts crop group can be toxicologically supported. The increase in the TMRC for these tolerance are 0.20%. This incremental risk is acceptable.

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Review:

1. No new toxicity data were submitted. Toxicology Branch's "one-liners" are attached. The formulation to be used is Goal 1.6E (EPA Reg.# 707-174). . Inerts are cleared under 180.1001.

2. No RPAR criteria have been exceeded and no regulatory actions are pending against the pesticide.

3. Tolerances are established in 40 CFR 180.381.

4. Section F

The petitioner requests that the following permanent tolerance be established for residues of oxyfluorfen (GOAL herbicide), 2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluromethyl) benzene and its metabolites containing the diphenylether linkage:

Tree Nuts Crop Group (except Almond Hulls) . . . . 0.05 ppm

Almond Hulls . . . . . 0.10 ppm

5. Calculation of the ADI

The ADI is based on the NOEL of 2.0 ppm in the chronic/oncogenic mouse feeding study. This LEL is 20 ppm and the effects are increased liver weigh' and increased histological effects in the liver.

A 100-fold safety factor was used to calculate the ADI.

$$ADI = 0.30 \text{ mg/kg/day} \times \frac{1}{100}$$

ADI = 0.003 mg/kg/day

The MPI for a 60 kg person is 0.18 mg/day

6. Published tolerances utilze 21.87% of the ADI. The current action increases the TMRC by 0.00008 mg/day. This increase in TMRC is 0.20%. The incremental increase is acceptable.

Conclusions:

The tolerances in/on tree nuts crop group can be toxicolgically supported. The increase in TMRC is 0.20%. This incremental risk is acceptable.

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File last updated 10/29/84

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ACCEPTABLE DAILY INTAKE DATA

House mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	ADI mg/day(60kg)
0.300	2.00	100	0.0030	0.1800

Published tolerances

Cum-action not needed

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Eggs(54)	0.050	4.77	0.00286
Milk&Dairy Products(33)	0.050	28.62	0.02146
Cattle(20)	0.050	7.18	0.00539
Goats(62)	0.050	0.03	0.00002
Hogs(69)	0.050	3.43	0.00258
Horses(205)	0.050	0.03	0.00002
Poultry(120)	0.050	2.94	0.00221
Sheep(145)	0.050	0.19	0.00015
Almonds(1)	0.050	0.03	0.00002
Stone Fruits(151)	0.050	1.25	0.00094
Grapes, inc raisins(50)	0.050	0.49	0.00037
Cottonseed (Oil)(41)	0.050	0.15	0.00011
Peppermint(119)	0.050	0.03	0.00005
Pistachio nuts(210)	0.050	0.03	0.00002
Spearmint(149)	0.050	0.03	0.00005
Walnuts(167)	0.050	0.03	0.00002
Cherries(30)	0.050	0.10	0.00006
Figs(57)	0.050	0.03	0.00002
Pears(110)	0.050	0.01	0.00001
Soybeans (Oil)(146)	0.050	0.02	0.00005
Corn,grain(65)	0.050	1.00	0.00075
Peanuts(37)	0.050	1.42	0.00107
Coffee(35)	0.050	0.75	0.00056
Onion(dry bulb)(106)	0.050	0.72	0.00054

TMRC	TMRC	% ADI
1.1000 mg/day(60kg)	0.324 mg/day(1.5kg)	21.97

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Current Action 4F3115,4F3116,4F3117,4F3118,4F3119

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Stone Fruits(191)	0.050	1.25	0.00094
Pome Fruits(120)	0.050	2.79	0.00209
Kiwi (214)	0.050	0.03	0.00002
Pomegranate (214)	0.050	0.03	0.00002
Figs(51)	0.050	0.03	0.00002
Olives(104)	0.050	0.05	0.00003
Avocados(40)	0.050	0.03	0.00002
Artichokes(4)	0.050	0.03	0.00002
Filberts(56)	0.050	0.03	0.00002
Macadamia nuts(57)	0.050	0.03	0.00002
Walnuts(167)	0.050	0.03	0.00002
Pecans(210)	0.050	0.03	0.00002

TMRC	TMRC	% ADI

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