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

006607

FEB 23 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Oftanol 5% Granular, EPA Reg. #3125-330, and 1.5% Granular, 3125-331; Caswell # 447AB; Project # 8-0376; Record Nos. 208706, 208707

TO: William H. Miller
Product Manager (16)
Registration Division (TS-767C)

FROM: James N. Rowe. Ph.D.
Section V, Toxicology Branch
Hazard Evalution Division/HED (TS-769C)
James N. Rowe 2/22/88

THRU: Quang Q. Bui, Ph.D, D.A.B.T.
Section Head, Section V
Quang Q Bui 2/22/88

and
Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)
[illegible] 2/23/88

ACTION: Request expansion of Oftanol's present use on turf grass (Granular formulations 5% and 1.5%) to cover uses on other non-crop areas such as fence rows and roadsides, ornamentals and nurseries and soil mix for ornamentals including potting soil mix.

RECOMMENDATIONS:

The expansion of Oftanol use to cover other non-food uses cannot be toxicologically supported at the present time. Additional data requested from the test laboratory which performed the previously reviewed subchronic delayed neurotoxicity study in hens must be submitted (see conclusions below). The 21-day dermal study has been reviewed and is acceptable.

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Review

1) Subchronic delayed neurotoxicity study in hens

This study has been previously reviewed (D.E.R. dated 9/2/86; Mobay repor . # 90231). Findings from the study are as follows:

Based on the significant depressions in body weight and cholinesterase activity at the high dose, without any evidence of neuronal degeneration--as determined by no change in gait at any dose level during the course of the study and no apparent histopathological changes at the high dose level--isofenphos does not appear to produce delayed neurotoxicity. The tentative delayed neurotoxicity NOEL is set at >2 mg/kg (HDT). The slight, consistent nerve degeneration observed in the spinal cord of the vehicle control and high dose groups is stated in the report to be the result "of the conventional husbandry of these chickens, which had been commercially used before the study". The reviewer is concerned that these findings could mask any subtle effect of isofenphos. Therefore, it is requested that additional data be submitted to substantiate that this is a normal background neuropathological change in chickens.

The study is designated as Core Supplementary data. It may be upgraded upon submission and approval of the requested additional data.

2) The submitted 21-day dermal rabbit study has been reviewed and the D.E.R. is attached (report # 339-113). The findings of the study are noted below:

Based on the absence of dermal [illegible] at any dose [illegible] in either sex, a dermal irritation NOEL is set at the HDT of 253.0 mg/kg/day. Based upon statistically significant depressions in plasma ChE in both male and female rabbits at the mid and high dose level, a plasma ChE inhibition NOEL of 50 mg/kg/day (LDT) is determined. A RBC and brain ChE inhibition NOEL is set at 253 mg/kg/day (HDT).

This study is designated Core Minimum data.

Conclusions:

The registrant's request to expand Oftanol registered use on turf grass to cover ornamentals and nurseries, and certain other non-crop areas cannot be toxicologically suppported at the present time until the following additional data for the subchronic delayed neurotoxicity hen study is submitted:

- **evidence that the slight, consistent nerve degeneration observed in the spinal cord of the vehicle control and high dose groups (as stated in the report) is the result "of the conventional husbandry of these chickens, which had been commercially used before the study".**

Reviewed by: James N. Rowe, Ph.D. James N. Rowe 2/22/88
Section V, Tox. Branch (TS-769C)
Secondary reviewer: Quang Q. Bui, Ph.D.
Section V, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: 21-Day dermal (§82-2) TOX. CHEM. NO.: 447AB

ACCESSION NUMBER: 40217401 MRID NO.: N/A

TEST MATERIAL: Oftanol 5G

SYNONYMS:

STUDY NUMBER(S): 339-113

SPONSOR: Mobay Corporation, Health, Environment and Safety, Corporate Toxicology Department, 17745 S. Metcalf Avenue, Stilwell, Kansas 66085

TESTING FACILITY: Hazleton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia 22180

TITLE OF REPORT: 21-day dermal toxicity study with Oftanol 5G in rabbits

AUTHOR(S): D.E. Bailey, Ph.D

[illegible] September [illegible], 1987

CONCLUSIONS:

Based on [illegible] absence of dermal irritation at any dose level, [illegible] a dermal [illegible] NOEL [illegible] mg/kg/day. Based upon statistically significant depressions [illegible] plasma ChE in both male and female rabbits at the mid and high dose level, a plasma ChE inhibition NOEL of 50 mg/kg/day (LDT) is determined. A RBC and brain ChE inhibition NOEL is set at 253 mg/kg/day (HDT).

This study is designated Core Minimum data.

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METHODS:

A photocopy of the experimental methods is attached. The following comments are noted:

1) The powder applied topically was not moistened as recommended by the EPA guidelines.

2) The assumption is made (p. 2) that the material, Oftanol 5G, is 100% pure for the purpose of dosage calculations. Since the material is known to contain 5% of the active ingredient, the actual dosages applied are (stated dosage) x (0.05) = 50 (1000), 112.5 (2250) and 253 (5060) mg/kg/day.

RESULTS:

Body weights/gains

Oftanol 5G had no effect upon mean body weights or body weight gains during the test period in either the male or female rabbits.

Food consumption

No statistically significant depression in mean food consumption or total food consumption occurred during the treatment period as a result of Oftanol 5G dermal exposure.

Neither male or female skin in the controls or treated groups gave evidence of dermal irritation (erythema and eschar formation, edema [illegible] of exposure to the test compound.

Hematology/clinical chemistries

Minor effects upon blood or clinical biochemistry parameters were reported (see table T-1 of selected values below).

Segmented neutrophils and basophils were statistically significantly lower ($p \leq 0.05$) in females and males, respectively.

Globulin values were lower in the mid and high dose groups (statistically significant negative trend, $p \leq 0.05$) of treated males as compared to the controls. Both phosphorus and blood urea nitrogen levels were elevated (statistically significant, $p \leq 0.05$) in females of the high dose group as compared to the controls. This elevation in P and BUN, in conjunction with the suggestion of increased histopathological findings in the kidneys, would seem to confirm that some impairment of kidney function may be occurring in the females in the HDT.

T-1 Selected hematology/clinical parameters

	Hematology		Clinical chemistry		
mg/kg	SEG (TH/UL)	BASO (TH/UL)	Globulin (G/DL)	Phosphorus (MG/DL)	BUN (MG/DL)
MALES			†		
0	2.4(2.09)[a]	0.4(0.17)	1.4(0.11)	7.0(0.47)	18(2.8)
50	2.6(1.43)	0.2(0.11)	1.4(0.29)	7.4(0.33)	19(1.9)
112.5	1.5(0.57)	0.3(0.08)	1.1(0.10)	6.6(0.67)	17(3.6)
253.0	1.8(0.81)	0.1*(.11)	1.2(0.09)	7.4(0.48)	19(4.2)
FEMALES	§			¶	
0	2.0(0.74)	0.3(0.08)	1.2(0.24)	6.5(0.66)	21(3.1)
50	2.2(0.89)	0.3(0.15)	1.4(0.30)	6.6(0.22)	20(1.5)
112.5	1.0(0.39)	0.3(0.11)	1.3(0.16)	6.9(0.62)	20(1.1)
253.0	0.9*(.61)	0.2(0.08)	1.3(0.29)	7.7*(.43)	24*(1.2)

[a] mean (S.D.)

¶ significantly positive trend for females ($p<0.05$)
† significantly negative trend for males ($p<0.05$)
* significantly different from control value ($p<0.05$)

Organ weights(g)/ratios (%)

No changes in organ weights or organ weight ratios were observed among any dose group of either male or female rabbits.

Gross/histopathology (Table T-2)

No gross necropsy findings of a compound-related nature were reported for any dose group of male or female rabbits.

There is a suggestion in females that the kidney may be slightly affected by dermal exposure to Oftanol 5G in the high dose group as compared to the control group. In the control females, only 2/5 animals are reported with some kidney findings as opposed to 3/5 in the high dose group. There are twice the total number of changes (5 vs 10) in the treated as control animals. In addition to focal mononuclear infiltration, regenerative tubular epithelium and cortical fibrosis/scars, which are observed in the controls (slight or minimal vs. slight to moderate or minimal in treated), chronic interstitial nephritis (slight) is observed in 3/5 of HDT as opposed to 0/5 in control females.

T-2 Histopathology for the kidneys (females)

Controls

Animal #	Finding
E 40411	- focal mononuclear infiltration--slight - regenerative tubular epithelium--slight - cortical fibrosis/scars--minimal
E 40412	- tubular cell vacuolation--minimal - regenerative tubular epithelium--minimal
E 40413	----------
E 40414	----------
E 40415	----------

High dose

E 40441	----------
E 40442	----------
E 40443	- focal mononuclear infiltration--moderate - regenerative tubular epithelium--moderate - cortical fibrosis/scars--moderate - chronic interstitial nephritis--moderate
E 40444	- focal mononuclear infiltration--slight - regenerative tubular epithelium--slight - chronic interstitial nephritis--slight
[illegible]	- focal mononuclear infiltration--slight - regenerative tubular epithelium--minimal - chronic interstitial nephritis--slight

Cholinesterase activity (table T-3)

RBC and plasma cholinesterase activities were affected by dermal application of Oftanol 5G.

RBC ChE activity appears to be depressed somewhat in the HDT group males as compared to the control values in Week 2 and 3 (81 and 76% of concurrent control values, not statistically significant).

In females, there is a statistically significant negative trend of depressed activities in the compound-treated groups as compared to controls at Week 2. Week 3 values are similar (as % of concurrent control; not statistically significant). The biological significance of these findings is questionable since the concurrent control values for Weeks 2 and 3 vary so much from either the initial ChE activities in pretreatment or week 1 values.

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T-3 Cholinesterase (RBC, Plasma) values (from table 5 of report)

Dose group[c]	Pretreatment (umol/ml)	Week 1	Week 2	Week 3
RBC ChE:				
Males				
1	9.3(1.13)[a]	9.4(0.72)/100	10.1(1.11)/100	10.1(1.18)/100
2	9.4(2.10)	9.5(1.53)/101[b]	9.8(1.36)/ 97	9.1(2.08)/ 90
3	10.5(1.40)	9.6(0.62)/102	9.4(1.11)/ 93	9.2(0.58)/ 91
4	9.0(1.40)	8.6(1.16)/ 92	8.2(1.49)/ 81	7.6(1.92)/ 76
Females			(XX)	
1	8.3(1.38)	8.5(1.52)/100	9.9(0.88)/100	8.9(0.82)/100
2	7.5(1.06)	7.9(1.86)/ 92	8.8(1.08)/ 89	7.9(1.75)/ 89
3	7.5(1.88)	7.4(1.43)/ 87	7.9(1.60)/ 80	7.0(1.70)/ 79
4	8.3(1.17)	8.7(1.36)/102	8.3(1.01)/ 84	7.6(1.19)/ 85
PLASMA ChE				
Males				
1	2.8(0.38)	2.6(0.32)/100	2.0(0.34)/100	2.8(0.34)/100
3	2.6(0.28)	*2.0(0.20)/ 79	2.4(0.31)/119	*2.3(0.33)/ 81
4	2.8(0.41)	2.2(0.40)/ 83	2.5(0.31)/124	*2.3(0.25)/ 81
Females		(XX)	(XX)	(XXX)
1	3.2(0.15)	2.8(0.22)/100	3.0(0.12)/100	2.9(0.14)/100
2	3.3(0.86)	2.6(0.22)/ 91	2.8(0.69)/ 94	*2.7(0.73)/ 93
3	3.3(0.74)	2.3(0.42)/ 81	2.4(0.69)/ 81	*2.4(0.46)/ 84
4	3.1(0.45)	2.2(0.29)/ 80	2.4(0.41)/ 81	*2.4(0.29)/ 82

[a] mean (standard deviation)
[b] average percent activity (treated) mean concurrent control enzyme activity; [c] respective doses of 0, 50, 112.5, 253 mg/kg/day
_____ : values are indicative of a significant difference from control value ($p \leq 0.05$) when statistically analyzed utilizing pretreatment values as the covariate
* significantly different from concurrent control value ($p \leq 0.05$)
(XX) significantly negative trend in females ($p \leq 0.05$)
(XXX) significantly negative trend in males and females ($p \leq 0.05$)

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Plasma ChE activities in males were consistently lower (statistically significant, $p \leq 0.05$) than pretreatment values in the mid or high dose groups, or concurrent control values, at Week 1 or Week 3. Week 2 values were somewhat lower than the preinitiation values but much higher than the concurrent control values which were significantly depressed as compared to other time periods (e.g. Week 2 control = 2.0 vs Week 1 control = 2.6 or Week 3 = 2.8).

Female plasma ChE values were similarly depressed (around 80% of concurrent control values) at the mid and high dose levels for all three weeks on test. Generally, these values were statistically significantly lower than pretreatment actiivities and for Week 3 they were also significantly lower than the concurrent controls.

No effects of Oftanol 5G upon brain ChE were noted at any dose level as compared to control treatment.

SUMMARY/CONCLUSIONS:

Dermal application of Oftanol 5G powder at actual calculated active ingredient concentrations of 50, 112.5 and 253 mg/kg/day to male and female rabbits for three weeks produced no evidence of any dermal irritation, depression in body weights/body weight gains, decrease in food consumption, changes in organ weights (kidneys, testes, liver) or gross pathology. A small impairment of kidney function in the high dose females is suggested based on statistically significant elevation in serum phosphorus and blood urea nitrogen.

[illegible] high dose levels, depression of approximately [illegible] control values; generally statistically significant for either trends in activity, comparison against pretreatment values or concurrent control values) in both male and female rabbits. No consistent effects upon RBC or brain ChE were apparent.

Based on the absence of dermal irritation at any dose level, in either sex, a dermal irritation NOEL is set at the HDT of 253.0 mg/kg/day. Based upon statistically significant depressions in plasma ChE in both male and female rabbits at the mid and high dose level, a plasma ChE inhibition NOEL of 50 mg/kg/day (LDT) is determined. A RBC and brain ChE inhibition NOEL is set at 253 mg/kg/day (HDT).

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