7-22-74 PP-843
7H1513

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 001513

SUBJECT: Counter 15G Soil Insecticide; AC-92100; S[(tert-butylthio)methyl] O,O-diethyl phosphorodithioate and its cholinesterase inhibiting metabolites in or on corn fodder, forage and corn grain at 0.05 ppm (negligible residues).

DATE: July 22, 1974

FROM:

TO: Mr. Lee TerBush, Acting Chief
Coordination Branch
Registration Division (HM-567)

Pesticide Petition No. 4F1496
Related Petition: 3G1340

American Cyanamid
Princeton, N. J.

Toxicological Review

Data submitted in support of the temporary tolerance in PP #3G1340 were reviewed by W. E. Parkin, 2/6/73, and by D. L. Ritter, 4/2/73.

New toxicity data submitted in support of the permanent tolerance are here reviewed.

1) Acute Toxicity of Some of the Metabolites of CL-92100

Species	Study	Metabolite	LD50	Signs of Toxicity
Mouse	Acute Oral	CL 202,474[1]	2500 mg/kg	None
"	" "	CL 202,133[2]	5000 mg/kg	Diuresis; dyspnea prostration
"	" "	CL 202,134[3]	3970 mg/kg	Diuresis; convulsions
"	" "	CL 202,135[4]	3670 mg/kg	Diuresis, motor ataxia convulsions

1 CL 202,474 - (tert-butylsulfinyl) (methylsulfinyl)methane

2 CL 202,133 - Bis(tert-butylsulfinyl) methane(mixed isomers) — #100A

3 CL 202,134 - Tert-butyl(terbutylsulfinyl) methyl sulfoxide — #221H

4 CL 202,135 - Bis(tert-butylsulfinyl)methane — #99B

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EPA Form 1320-6 (Rev. 6-72)

2) Thirty-Day Rabbit Dermal Toxicity (Summary)

Sixty New Zealand white rabbits were randomly assigned to seven groups: one control (12 rabbits), and six test groups each consisting of eight animals. AC-92100 (Technical Grade) was applied daily, 5 days each week for 3 consecutive weeks at dose levels ranging from 0.004 to 0.10 mg/kg to the shaved trunks (intact and abraded) of the rabbits in 3 test groups. Three other test groups received the AC-92100 (Final Formulation) in doses ranging from 0.2 to 5.0 mg/kg in the same regimen. Control rabbits received the corn oil vehicle in a like manner.

Results of food and water intake, elimination, and general behavior revealed no adverse and/or pharmacologic effects.

Urine analyses results for all rabbits were within normal limits.

Hemagrams for all groups were comparable and within normal limits. Slight deviations including P/L shifts, and increased eosinophils and basophils were noted with equal frequency among all groups.

The edema and erythema scores for each control or test animal were recorded daily. The results indicated that application of AC-92100 (Technical Grade and Final Formulation) to the intact and abraded shaved trunks of New Zealand white rabbits produced very slight edema and erythema, which generally abated by termination of the study.

No unusual pathological findings attributable to treatment with test materials were found. However, deaths occurred in three males and three females given Final Formulation of AC-92100 at the highest dosage level (5.0 mg/kg/day) within six to twenty days of study.

We are unable to estimate a no-effect ChE inhibition level, since no blood or brain ChE determinations were made.

3) 18-Month Carcinogenicity Study of AC-92100 in Mice - (Final Report)

Methods

AC-92100 was administered to groups of 75 male and 75 female Charles River CD-1 mice each at levels of 0, 0.5, 2.0 and 8.0 ppm in the diet for 18 months. Observations were made daily for signs of toxicity and body weights and food consumption values were obtained at suitable intervals. Mice were housed 5 per cage.

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Five males and five females from each control group were killed for histopathological examination at nine months. Remaining mice were killed at 18 months and the following organs were examined:

Tissues Fixed for Histological Examination

Adrenals (2)	Nerve
Aorta	Pancreas
Brain	Pituitary
Eye	Prostate
Gonad	Salivary gland
Heart (with coronary vessels)	Skin
Intestine	Skeletal muscle
colon	Spinal cord
duodenum	Spleen
ileum	Stomach
Kidney	Thyroid
Liver	Urinary bladder (including neck)
Lung	Uterus
Lymph node	Gross lesions (including a section of normal-appearing portion of same organ)
Mammary gland (inguinal)	Tissue masses
Bone Marrow	

Number of Animals Examined Histologically

Heart, kidney, liver and lung examined from 15 males and 15 females of all dose levels. Complete histopathologic examination performed on 15 males and 15 females of control and high-dose groups.

Results

Mortality, body weight gains and signs of systemic toxicity were comparable between treated and control groups. The appearance of alopecia and signs of disturbed balance (otitis media?) were similar and were attributed to an epizootic in the colony.

Of particular interest was the appearance of severe eye effects including exophthalmos, corneal cloudiness and opacity and rupture of the eye in some animals; this was noted in both control and treated animals. A similar picture was noted in the two year rat study interim report reviewed by D. L. Ritter, 4/2/73, PP #3G1340.

Incidence of neoplasms was similar between treated and control groups.

Conclusions

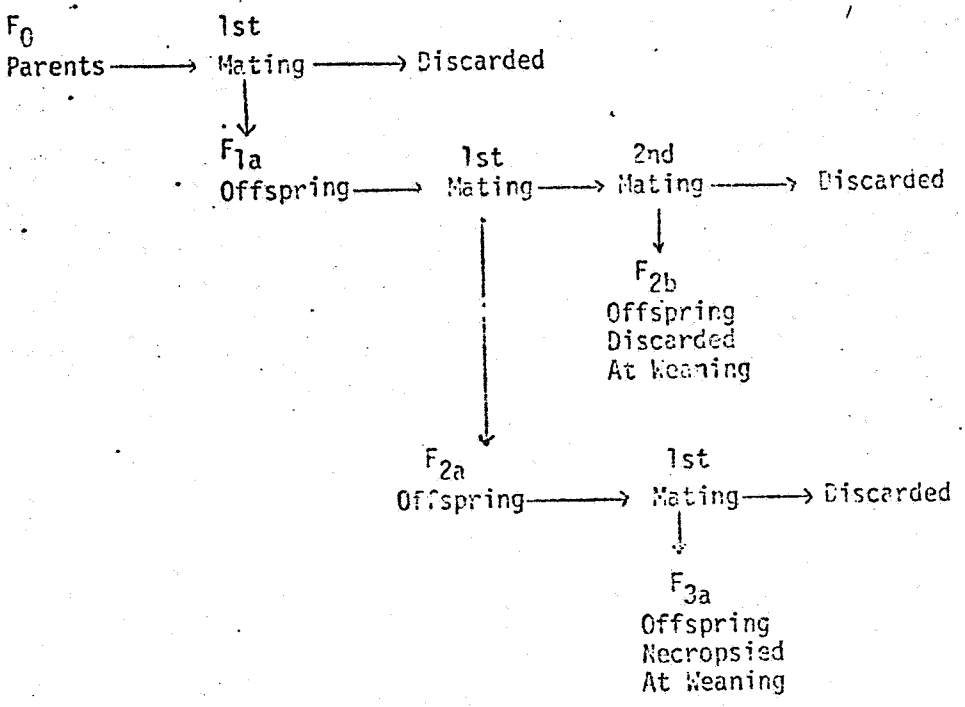
AC-92100 does not induce neoplasia in laboratory mice when fed in the diet at levels up to 8.0 ppm for 18 months.

4) Twenty-four-Month Rat Feeding Study - 18-Month Status Report

No raw data are submitted; petitioner concludes that the demonstrated NEL is 0.25 ppm AC-92100 in the diet based on ChE inhibition. A full review of this study awaits final data.

5) Three-Generation Rat Reproduction Study

AC-92100 was administered to three successive generations of Long-Evans rats at dose levels of 0, 0.25 and 1.0 ppm in the diet. The three generations were mated once, twice and once respectively, according to the following design:



Observations were made daily for signs of toxicity and mortality, and body weights and food consumption were determined at suitable intervals. Gross necropsy was performed on all animals dying spontaneously (older than 14 days) and on moribund animals and F_{3a} offspring at weaning.

Litters were culled to ten pups each, where possible, on day 4 following parturition.

Indices of Reproduction were determined (See Table I).

Results

Mortality was not affected by treatment. Body weight-gain values were increased in the treated groups when compared to controls; this was repeated in the food consumption values.

No untoward effects were noted in gross pathological findings.

Indices of reproduction were not appreciably altered by treatment.

Conclusions

AC-92100 failed to have any adverse effect in rats or their offspring when administered in the diet over a three-generation breeding cycle at levels of 0.25 or 1.0 ppm.

Discussion

AC-92100 is a potent ChE inhibitor as shown by acute and subacute data (e.g., see review of 3/7/73, Temporary Permit ST-100; 241-EXP-X, R. P. Schmidt). Principle danger appears to be both from ingestion and dermal and eye contact.

The chronic NEL for ChE inhibition appears at this time to be 0.25 ppm AC-92100 in the diet in rats, however, we await final results of the ongoing two-year rat feeding study mentioned above before making any final judgment as to this.

CB has previously concluded that this use of AC-92100 results in an essentially "no-residue" situation in connection with the temporary tolerance (memo of W. S. Cox, 2/6/73, PP No. 3G1340).

Recommendation

We recommend that the proposed tolerance for combined negligible residue of the insecticide S[(Tert-butylthio)methyl]O,O-dimethyl phosphorodithioate and its cholinesterase-inhibiting metabolites in or on corn forage, fodder and grain at 0.05 ppm be established.

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TABLE I

INDICES OF REPRODUCTION IN THREE GENERATIONS OF RATS FED AC 92100 IN THE DIET

LITTER	DIET LEVEL	FERTILITY (a)	GESTATION (b)	VIABILITY (c)	LACTATION (d)	BIRTH WT (gm)
F_{1a}	0.0 ppm	94.4%	97.9%	97.7%	92.9%	--
	0.25	100	100	92.0	100.0	--
	1.0	95	99.0	95.3	100.0	--
F_{2a}	0.0	100	97.7	64.8	64.3	5.24
	0.25	100	96.3	79.2	78.6	4.39
	1.00	100	91.8	60.6	57.9	4.83
F_{2b}	0.0	100	97.6	63.4	75.0	5.28
	0.25	100	98.3	79.5	94.4	5.37
	1.00	100	97.9	74.9	88.2	5.67
F_{3a}	0.0	94.7	92.6	87.7	93.8	5.77
	0.25	94.1	99.4	91.1	93.8	5.97
	1.00	100	96.1	92.5	100.0	6.01

(a) #pregnant/#mated
(b) #alive/#born
(c) #alive @ 4 days/#born alive
(d) % weaned

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We must have the final results of the rat two-year feeding study before any non-negligible residues tolerances could be established.

We defer to CB the question of secondary residues in meat, milk and eggs, and in corn byproducts such as oil, syrup and molasses.

We also defer to CB as to whether this use of AC-92100 still constitutes a "no-residues" or "trace residue" situation.

David L. Ritter 7/23/74

David L. Ritter, Pharmacologist
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cc:
CB
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Div. File
Br. File
PP No. 4F1496

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