PP-1057
TOR-853

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000353

SUBJECT: (See Below)

DATE: August 27, 1974

FROM:

TO: Mr. Lee Terbush
Acting Chief
Coordination Branch
Registration Division (WH-567)

SUBJECT: Altosid: Methoprene; Isopropyl (E,F)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, proposal for negligible residues tolerances as a result of application to floodwaters for mosquito control:

Rice and rice straw, milk, potable water - 0.01 ppm;
Fish, shellfish, meat and meat byproducts (excluding fat) of cattle, horses, sheep, goats, hogs, eggs and poultry - 0.1 ppm;
Fat of cattle, horses, sheep, goats, hogs and poultry - 0.25 ppm;
Forage grasses and forage legumes - 0.5 ppm.

Pesticide Petition No.: 4F1514 - Zoecon Corporation
Palo Alto, California

Related Petition: 3G1343

No new toxicity data per se are submitted; summaries of chronic studies currently underway are included and are here cited.

1. Two year rat feeding/carcinogenicity study - six months

   Levels fed - 250, 1000 and 5000 ppm
   Signs of toxicity to date - none

2. Eighteen month mouse carcinogenicity study - six months

   Levels fed - 250, 1000 and ~~5000~~ ppm 2500 ppm QAB
   Signs of toxicity to date - none

3. Three generation rat reproduction study - eight months

   Levels fed - 500 and 2500 ppm
   Signs of toxicity to date - none

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Metabolic fate of altosid in mammals.

1. Mouse

Tritiated altosid was intubated into 10 mice, 2 of which were gravid. Urine and feces were collected and the activity in each was determined. An animal was killed and whole-body autoradiographs were made at suitable time intervals up to 96 hours.

68% of the administered activity appeared in the urine and 14% appeared in the feces.

Autoradiographs showed complete elimination by 48 hours, and some biliary excretion was noted.

No transplacental transfer of activity was seen in the gravid mice.

2. Rat

A single oral dose of [^{14}C]-Altosid^{TM} (ZR-515) was administered to rats at a dosage of 25 mg/kg (equivalent to a dietary intake of 750 ppm), and studies carried out on the absorption, distribution, biotransformation and excretion of the compound and its metabolites.

After a single oral dose of [^{14}C]-ZR-515, a mean (±S.E.M.) of 13.0% of the administered dose was excreted in the urine after 24 hours, increasing to 19.6 ± 2.0% after 5 days. 11.9% was excreted in the feces after 48 hours increasing to 18.0 ± 2.1% after 5 days. 25.5% was excreted in the expired air after 24 hours increasing to 38.8 ± 3.4% after 5 days. After 5 days, a mean (±S.E.M.) of 17.2 ± 2.7% of the administered dose had been retained in the carcass. The maximum excretion half-life for about 60% of the radioactivity was about 10 hours and 107 hours for a further 15%.

The rate of biliary excretion was most rapid during the first 24 hours after dosing, and 27.4% was excreted after 48 hours.

Plasma concentrations of radioactivity reached a peak at about 6 hours and declined slowly with a half-life of about 48 hours during the second to the fifth days after dosing. The total amount of radioactivity in plasma at 6 hours corresponded to about 1.63% of the administered radioactivity being equivalent to about 38µg of ZR-515.

Tissue distribution studies showed that, except in the liver and kidneys, no specific uptake of radioactivity occurred during the first 6 hours after dosing. Later significant uptake was detected in the kidneys, lungs, heart, adipose tissue and adrenal glands. Whole-body

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autoradiography showed that much of the radioactivity was located in organs that would be concerned with absorption, biotransformation and excretion. A relatively high level of radioactivity was located in the adrenal cortex, lacrimal glands, and adipose tissue after 48 hours.

The metabolites excreted in urine and feces were not the result of simple ester hydrolysis and/or O-demethylation, but probably the products of further biotransformation.

The results suggest that an oral dose of ZR-515 was slowly and incompletely absorbed and slowly eliminated. Enterohepatic circulation of ZR-515 metabolites excreted in the bile may occur. ZR-515 was extensively and in part completely metabolized. The major metabolite, which occurred in bile, may be an amino acid conjugate.

3. Guinea pig

50.86 mg of ^{14}C-labeled altosid was given PO to a guinea pig and the feces, urine and expired air were collected for 24 hours. These were analyzed for activity.

Results:

Approximately 24% of the administered label is excreted in the urine; 9% in the feces; and 17.2% in the exhaled CO_2. A calculation of the percent of administered label remaining in the blood and tissue was not made. The fact that 17.2% of the administered label was evolved as carbon dioxide was extremely important. This indicated that Altosid is extensively degraded. Although structure elucidation experiments were not conducted, chromatographic analyses show that the radioactivity found in the feces was greater than 80% Altosid; whereas, that found in the urine contained neither Altosid nor its known metabolites. The urine radioactivity was probably in the form of polar conjugates (glucuronides) of the known metabolites, ZR-724, ZR-725 and ZR-659.

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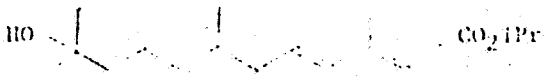
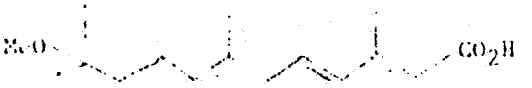
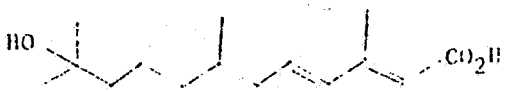
Metabolite



ZR-669



ZR-725



ZR-724

ZR-1945

Steer Metabolism Study

A young steer weighing 276 kg. was dosed orally with 2000 mg of [5-^{14}C]trans-2 Altosid (3.9mC) and the fate of the label was determined using standard laboratory techniques for feces, urine and expired CO_2. After two weeks, the steer was slaughtered and organ content of label was determined. See Table 1.

Results:

Excretion was primarily in feces (39%) with a lesser amount being lost in the urine (21%). The remainder was lost via the expired CO_2 (27% - calculated).

Petitioner claims degradation of unexcreted material is extensive and fragments incorporate into natural body constituents such as cholesterol and cholic acid by way of intermediary acetate.

Recommendations:

1. The toxicity of MP has been defined for the purpose of establishing negligible residues tolerances in rats (see reviews of 1/14/74 and 2/13/73, D. L. Ritter, PP# 3G1343).

Therefore, we recommend that the tolerances as proposed above for negligible residues of altosid be established.

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Table 1

RADIOLABEL BALANCE TABLE TWO WEEKS AFTER
TREATMENT OF A STEER WITH 5-^{14}C LABELED ALTOSID

A. Tissue	B. Tissue Weight (grams)	C. µg Equivalent/gram (as Altosid)	D. Total µg as Altosid	E. [illegible]
gall bladder contents	80	31.20	[illegible]	[illegible]
gall bladder	32	23.34	[illegible]	[illegible]
adrenal gland	58[1]	4.23[2]	[illegible]	[illegible]
brain	333	1.43	[illegible]	[illegible]
heart	1,106	2.01	[illegible]	[illegible]
kidney	480	5.07	[illegible]	[illegible]
liver	3,609	5.40	[illegible]	[illegible]
lung	2,240	3.54	[illegible]	[illegible]
spleen	556	4.65	[illegible]	[illegible]
muscle (3 sites)	101,250[1]	[illegible][2]	[illegible]	[illegible]
fat (3 sites)	30,3??[1]	[illegible][2]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

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[redacted]

David L. Ritter, Pharmacologist
Toxicology Branch
Registration Division (WH-567)

cc: CB
EEB
Division File
Branch Reading File
Inerts File

R/D Init:CHWilliams:8/22/74
DLRitter:ssi:8/22/74
Init:CHWilliams

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11. Tabular Summary of Toxicology Studies

Chemical Being Tested

STANDARD TOXICOLOGY STUDIES

WITH ALTOSID TECHNICAL

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TEST	RESULT
Hormone Bioassay - Mouse & Rat	No hormone (juvenilian endocrine) activity. No estrogenic, androgenic, anabolic, or glucocorticoid activity.
Acute Oral - Rat	LD_{50} > 34,600 mg/kg (HDT*)
Acute Oral - Dog	5,000 mg/kg > LD_{50} < 10,000 mg/kg.
14-Day Subacute Oral - Rat	No effect at 20,000 ppm.
14-Day Subacute Oral - Dog	Hypertrophic livers at 5,000 ppm and above. No other effects observed.
28-Day Subacute Oral - Rat	No effect at 10,000 ppm.
28-Day Subacute Oral - Mouse	No effect at 8,000 ppm.
90-Day Subacute Oral - Rat	No effect at 1,000 ppm.
90-Day Subacute Oral - Dog	No effect at 500 ppm. Increased liver weight at 5,000 ppm.
18-Month Chronic Oral/Carcinogenicity - Mouse	No effect on body weight, food consumption, or survival at any dose level including 2,500 ppm (HDT*). Neither compound-related tumorigenic effects nor gross pathological lesions were observed at any level. An unidentified brown pigment was observed upon microscopic examination in the livers of most mice treated at 2,500 ppm and a minority of mice treated at 1,000 ppm. This pigment was not found in the 250 ppm group.
2-Year Chronic Oral - Rat	No changes related to compound were seen in general behavior or appearance, opthalmoscopy, body weights, food consumption, hematological, biochemical, or urinalysis studies. No compound related gross or microscopic pathologic lesions, organ weight variations or tumorigenic effects were observed in rats fed Altosid at doses up to and including 5,000 ppm (HDT).
3-Generation Reproduction - Rat	No effects at any level including 2,500 ppm (HDT*) on adult mortality, mating, pregnancy and fertility rates, food consumption values, gestation lengths, offspring viability at parturition, offspring survival, litter survival, and sex ratios. No abnormal tissues were noted upon necropsy.
Acute Intraperitoneal - Rat	LD_{50} = 4,800 mg/kg.
Repeated Intraperitoneal - Rat	No cumulative effect at 3,000 mg/kg (HDT*).
Eye Irritation - Rabbit	Nonirritating.
Primary Skin Irritation - Rabbit	Primary irritation score: 0.0 (Nonirritating).
Acute Dermal - Rabbit	3,038 mg/kg > LD_{50} < 10,250 mg/kg.
21-Day Subacute Dermal - Rabbit	No abnormal effects at 400 mg/kg (HDT*).
Acute Aerosol Inhalation - Rat	LC_{50} > 210 mg/liter (HDT*). Classification: nontoxic.
Acute Aerosol Inhalation - Guinea Pig	LC_{50} > 210 mg/liter (HDT*). Classification: nontoxic.
21-Day Subacute Inhalation - Rat	No abnormal effects at 20 mg/liter or 2,000 ppm (HDT*).
Teratology - Rat	No teratogenic effects at 1,000 mg/kg (HDT*).
Teratology - Rabbit	No teratogenic effects at 500 mg/kg (HDT*).
Dominant Lethal Mutagenicity - Rat	No mutagenic effects at 2,500 mg/kg (HDT*).
8-Day Subacute Oral - Chicken	LC_{50} > 4,640 ppm (HDT*).
Oral Feeding Studies - Bovine	No adverse effects.

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STANDARD TOXICOLOGY STUDIES
WITH ALTOSID® IMPURITIES

IMPURITY	TEST	RESULT
cis-isomer	Acute Oral - Rat	LD_{50} > 5,000 mg/kg (HDT*).

STANDARD TOXICOLOGY STUDIES
WITH ALTOSID® METABOLITES

COMPOUND	TEST	RESULT
ZR-669	Acute Oral - Rat	LD_{50} > 6,300 mg/kg (male = 8,900 mg/kg; female = 8,260 mg/kg).
ZR-724	Acute Oral - Rat	LD_{50} > 6,810 mg/kg (HDT*).
ZR-725	Acute Oral - Rat	LD_{50} > 6,810 mg/kg (male). LD_{50} = 4,870 mg/kg (female).
ZR-731	7-Day Subacute Oral - Rat	No effect at 10,000 ppm (HDT*).
ZR-1564	Acute Oral - Rat	LD_{50} > 5,000 mg/kg (HDT*).
ZR-1564	Eye Irritation - Rabbit	Nonirritating.
ZR-1564	Primary Skin Irritation - Rabbit	Nonirritating.
ZR-1602	Acute Oral - Rat	LD_{50} > 5,000 mg/kg (HDT*).
ZR-1945	Acute Oral - Rat	LD_{50} > 10,000 mg/kg (male). LD_{50} = 4,763 mg/kg (female).

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Table 1: References to Standard Toxicology Studies with Altosid Technical

Study	Document*	Page
Hormone Bioassay - Mouse & Rat	1	12
Acute Oral - Rat	1	30
Acute Oral - Dog	1	51
14-Day Subacute Oral - Rat	1	72
14-Day Subacute Oral - Dog	1	83
28-Day Subacute Oral - Rat	1	98
28-Day Subacute Oral - Mouse	1a	11
90-Day Subacute Oral - Rat	1	111
90-Day Subacute Oral - Dog	1, 1a	111, 27
18-Month Chronic Oral Carcinogenicity - Mouse	2	162
2-Year Chronic Oral - Rat	2	32
3-Generation Reproduction - Rat	3	35
Acute Intraperitoneal - Rat	1	159
Repeated Intraperitoneal - Rat	1	166
Eye Irritation - Rabbit	1	171
Primary Skin Irritation - Rabbit	1	183
Acute Dermal - Rabbit	1	191
21-Day Subacute Dermal - Rabbit	1	214
Acute Aerosol Inhalation - Rat	1	279
Acute Aerosol Inhalation - Guinea Pig	1	284
21-Day Subacute Inhalation - Rat	1	289
Teratology - Rat	1	324
Teratology - Rabbit	1a	45
Dominant Lethal Mutagenicity Rat	1a	88
8-Day Subacute Oral - Chicken	1	291
Oral Feeding Studies - Bovine	5	176

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Table 1: (continued) References to Standard Toxicology Studies with Altosid Impurities

Study	Impurity	Document*	Page
Acute Oral - Rat	[redacted]	1	591

Table 1: (continued) Standard Toxicology Studies with Altosid Metabolites

Study	Compound	Document*	Page
Acute Oral - Rat	ZR-669	1	333
Acute Oral - Rat	ZR-724	1	602
Acute Oral - Rat	ZR-725	1	607
Acute Oral - Rat	ZR-1564	4	62
Acute Oral - Rat	ZR-1602	1	347
Acute Oral - Rat	ZR-1945	1	339
Eye Irritation - Rabbit	ZR-1564	4	64
Primary Skin Irritation - Rabbit	ZR-1564	4	74

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Table 1: (continued) References to Standard Toxicology Studies with Altosid SR-10

Study	Document*	Page
Acute Oral - Rat	1	39
Eye Irritation - Rabbit	1	175
Primary Skin Irritation - Rabbit	1	187
Acute Dermal - Rabbit	1	207
Acute Aerosol Inhalation - Rat	1	41

* See Section C of:

Document 1 - Pesticide Petition #3G1343 submitted in December, 1972.

Document 1a- Pesticide Petition #3G1343 submitted in December, 1973.

Document 2 - Altosid Briquet Application #20954-EUP-5 submitted on January 22, 1976.

Document 3 - Pesticide Petition #5G1596 submitted on December 18, 1974.

Document 4 - Pesticide Petition #4F1514 submitted in June, 1974.

Document 5 - Altosid CP-10 Application #20954-2 submitted in October, 1974.

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