Date: 

January 14, 1974

To: 

Mr. Lee TerBush, Acting Chief
Coordination Branch
Registration Division

Zocon Corp.
Palo Alto, Calif.

Subject: used for control of floodwater mosquitoes, amendment of 11/30/73.

Pesticide Petition No. 361343

Petitioner amends to request extension of previously granted temporary tolerances for negligible residues of altosid in forage grasses and legumes at 0.2 ppm in rice and rice straw at 0.01 ppm. He also proposes new temporary tolerances for negligible residues of 0.1 ppm in feed, fat and meat by-products of cattle, horses, sheep, goats, hogs, poultry, eggs, fish and shellfish. An additional new negligible residue tolerance is proposed in milk at 0.01 ppm.

Initial toxicity data are reviewed in TB memo of 2/14/73, D.L. Ritter.

New data of concern to TB are submitted in support of the petition.

Altosid - New Toxicity Data

1. Acute Toxicity

<table>
<thead>
<tr>
<th>Species</th>
<th>Acute</th>
<th>Material</th>
<th>Results</th>
<th>Toxic signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>28-day feeding</td>
<td>815 Tech</td>
<td>NEL=6600 ppm</td>
<td>yellow liver</td>
</tr>
<tr>
<td>Rat</td>
<td>Acute Inhal.</td>
<td>Altosid SS</td>
<td>LD₅₀=203.8mg/L</td>
<td>Preening</td>
</tr>
<tr>
<td>Rat</td>
<td>Acute Oral</td>
<td>ZR-669</td>
<td>LD₅₀ = 8.3mg/L</td>
<td>CNS, Depression</td>
</tr>
<tr>
<td>Rat</td>
<td>Acute Oral</td>
<td>ZR-1945</td>
<td>LD₅₀ = 5.3mg/L</td>
<td>&quot;Ab&quot;</td>
</tr>
</tbody>
</table>

* Metabolites of Altosid
1. Acute Toxicity (continued)

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>Material</th>
<th>Results</th>
<th>Toxic sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Acute Oral</td>
<td>ZR 1602</td>
<td>LD$_{50}$ &gt; 5 g/kg</td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Acute Oral</td>
<td>ZR 1566</td>
<td>LD$_{50}$ &gt; 5 g/kg</td>
<td></td>
</tr>
</tbody>
</table>

2. Subacute Toxicity

A. Final Report on Dry Dog Feeding Study (Histopathology)

This report consists of final histological data requested in our review of 2/14/73. The test levels were 0, 250, 500, and 5000 ppm in the diet; the control and 500 ppm groups were subjected to histopathological survey and reported at the time of initial submission, but we failed to see all group results. We concluded that the no-effect feeding level for this study was 500 ppm based on increased liver weights and increased alkaline phosphatase values in the 5000 ppm group animals.

At that time, no histological lesions were noted that could be attributed to altosid ingestion.

These new data include the final histopathological examination results of all animals.

Methylates of Altosid

\[
\begin{align*}
\text{ZR-669} & : \text{MeO} & \text{CO}_2\text{Pr} \\
\text{ZR-724} & : \text{MeO} & \text{CO}_2\text{H} \\
\text{ZR-725} & : \text{MeO} & \text{CO}_2\text{H} \\
\text{ZR-1945} & : \text{MeO} & \text{CO}_2\text{Pr} \\
\text{AL10510}^{1}{0} & : \text{formerly ZR-515}
\end{align*}
\]
Results

Pathological examination of representative tissues from animals in all test and control groups again fail to demonstrate lesions associated with alizarid ingestion.

Conclusions

These data confirm our previous finding that the demonstrated IEL for this study is 560 ppm based on increased liver/body weight ratios and increased alkaline phosphatase values in the 5600 ppm animals.

Rabbit Teratology Study - (IBI 401883)

Methods

New Zealand albino does were first paired with pituitary III and then artificially inseminated with pooled buck semen on day 6 of gestation. They were then randomized into one of four groups containing at least 10 animals each and received 0, 250 or 500 mg/kg alizarid technical, or 37.5 mg/kg thalidomide as a positive control by gelatin capsule on days 6 through 10 inclusive. Abnormalities, if any, were noted. On gestation day 29 the embryos were obtained by caesarian section, examined carefully, weighed, and placed in an incubator for 24 hours and observed for signs of viability. Numbers of implantation sites, corpora lutea, resorption sites, live young, and numbers of fetuses aborted were determined.

The young were killed and dissected to detect anomalies of soft tissues and viscera, and skeletal development was evaluated following alizarin staining.

Results

Body weights of does and embryos were not materially affected by alizarid treatment. Numbers of implantation sites and corpora lutea were unaffected by treatment. There was a modest increase in the number of resorption sites in the 500 mg/kg group when compared to controls. The number of live young per kg implantation sites was materially reduced for this group, and one high dose doe suffered complete abortion.

The positive control animals showed increased early resorptions, reduced number of live young and increased number of total resorption sites.
Of the fetuses examined, only 2 of 46 in the positive control group, and 1 of 55 in the 250 mg/kg group showed deviations from normal; there were no abnormal fetuses in the control or 500 mg/kg group. Petitioner has classified as chemical such findings as incompletely ossified or non-ossified sternebrae and supernumerary and thickened ribs; these were common to all groups.

**Conclusion**

Although the evidence suggests that there may be slight adverse reproductive effect on does treated with 500 mg/kg, we consider this to be a toxicity reaction and therefore unrelated to any direct reproductive effect.

The lack of serious deformities in the young accordingly permits us to conclude that altosid is not a teratogen in the rabbit at levels given orally up to 500 mg/kg/day on days 6 through 18 of gestation.

Rat Dominant Lethal Test - (Woodard Research Corp.)

**Methods**

Various doses of altosid were given by intraperitoneal injection to adult male albino rats. There were 10 rats per dose level, and of these five received a single injection of 0.1, 0.3, or 20 mg/kg once, while five received 20 or 200 mg/kg for five consecutive days. Five also received 2000 mg/kg only twice owing to insufficient compound. Control groups of five rats each received saline once or five times and positive control rats received triethylenglycolamine (TEG) 0.4 mg/kg once or 0.03 mg/kg five times.

Following the last injection each male was mated with two untreated adult virgin females per week for eight weeks (single dose or seven weeks multiple doses).

At day 14 of gestation each female was delivered by caesarean section and examined for:

- Live and dead fetuses
- Uterine resorption sites
- Total uterine implantation sites
- Corpora lutea

*In the 250 mg group one pup showed acrania and unilateral talipes varus (twisted foot). For the positive control group, one pup had unilateral talipes varus and another had talipes varus (foot turned inward).*
Results

Three males receiving 2000 mg/kg/day Altosid died after two doses. All single-dose Altosid groups showed conception rates, numbers of live fetuses, resorption sites and implantation sites that were similar to those of the control group. Both treated groups showed deleterious reversals of values for these parameters for the first two weeks then exhibited a normalizing trend appearing in the values for the subsequent weeks.

A similar pattern emerged for the multiple (5) dose groups, however, since only two of the 2000 mg/kg males survived, any conclusion that might be drawn would be doubtful value.

Conclusion

Altosid does not induce deleterious effects on male rat reproductive capacity at levels up to 200 mg/kg given once or five times daily. A positive control agent, TCE, causes such effects, which some scientists classify as being due to alleged mutagenic properties of the test chemical.

Metabolism of Altosid in Various Animals

1. House

This study was conducted with tritium-labeled material and during the course of the experiment 0% of the label disappeared. None of this 18% was retained in the house. The whole organs as well as remaining carcasses were analyzed and found to be completely devoid of radioactivity. It was suspected that the label was lost due to poor urine and fecal collection techniques whereby both urine and feces were exposed to open air for periods of up to 10 hours prior to collection allowing for potential evaporation. For this reason, it was decided to conduct a subsequent study using 14C-labeled Altosid and to conduct this study in the rat.

2. Rat - (Study incomplete)

(a) After a single oral dose of [14C]-Altosid (25 mg/kg) to rats, 13.2% of the administered dose was excreted in the urine after 24 hours, increasing to 21.4% after 5 days. 12.9% was excreted in the feces after 48 hours increasing to 20.6% after 5 days. 24.6% was excreted in the expired air after 24 hours increasing to 36.5% after 5 days. After 5 days, 26.7% of the administered dose was still retained in the carcass. The maximum excretion half-life for 60% of the radioactivity was about 30 hours and 107 hours for a further 20%.
The rate of biliary excretion was most rapid during 24 hours after dosing, and 26.6% of the administered dose was excreted after 48 hours.

Plasma concentrations of radioactivity reached a peak at about 6 hours and declined slowly. The total amount of radioactivity in plasma at 6 hours corresponded to about 1.66% of the administered radioactivity.

Tissue distribution studies showed that, except in the liver, no specific uptake of radioactivity occurred during the first 6 hours after dosing. After 12 hours however, the data indicated localization of radioactivity in liver, kidneys, lungs, heart, brain and fat. This radioactivity may have arisen from incorporation of $^{14}C$ acetate produced from $^{14}C$-altosid by biotransformation, into pathways of intermediary metabolism. Whole-body autoradiographs showed that much of this radioactivity was located in organs that would be concerned with the absorption, biotransformation and excretion of altosid.

3. Guinea Pig

$^{14}C$-labeled altosid given orally to a guinea pig showed 24% excreted in the urine, 9% in the feces and 17.2% in the expired CO$_2$.

Recommendations:

TB considers that the toxicity of altosid has been adequately defined for negligible residues tolerances in RAC's. Accordingly, we recommend that, CB considerations permitting, the requested extensions of temporary tolerances for negligible residues of altosid [isopropyl (E,E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienolate] in forage grasses and legumes at 0.2 ppm, and in rice and rice straw at 0.01 ppm, and for establishment of new temporary negligible residues tolerances in meat, fat and meat byproducts of cattle, horses, sheep, goats, hogs, poultry, eggs, fish and shellfish at 0.1 ppm, and in milk at 0.01 ppm be granted.

David L. Ritter, Pharmacologist
Toxicology Branch
Registration Division

cc:
CB Div. File PP 43G1343
ED Dr. File DRBitter/cc: 1/16/74
R/D Init: CMWilliams
Init: CMWilliams