MEMORANDUM

DATE: 3-24-82

SUBJECT: Methoprene; Additional Subchronic Dermal Toxicity in the Rabbit
(Acc. No. 246914, ID No. 20954-1, Caswell No. 28AAA).

FROM: George Z. Ghali, Ph.D.
Review Section IV
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TO: Franklin Gee
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THRU: Christine F. Chaisson, Ph.D.
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Registrant: Zoecon Chemical Corporation
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Palo Alto, California

Action Requested:
Review and evaluation of subchronic dermal toxicity in the rabbit.

Conclusions and Recommendations:
This study is acceptable as Core-minimum and can satisfy the requirement for subchronic dermal toxicity. The NOEL is considered to be 0.1gm (undiluted material)/kg of body weight.

Review
Subchronic Dermal Toxicity in the Rabbit

Test Chemical:
Altosid technical batch No. 060054, obtained from

Testing Laboratory:
Nomura Research Laboratory, Japan, project No. NRI-74-2465. Report dated 12/30/77.

Procedure:
Five groups of five male and five female Japanese rabbits were acclimated for 20 days and treated with undiluted altosid (methoprene) at the rate of 0, 300, 900, or 2700 mg/kg/day for thirty days. The chemical was applied topically on the back of the animal which was previously shaved. The animals were observed and weighed daily. Food and water consumption were measured every five days.
Hematology tests were performed before the application of the chemical and at necropsy. The following parameters were examined: RBC, WBC, Ht, Hb, and differential WBC. Clinical chemical tests were performed before the treatment and at necropsy. The following parameters were examined: SGOT, SGPT, ALP, LDH, total protein, albumin globulin, glucose, BUN, cholesterol, sodium and potassium. Urine analysis was performed weekly, and the following parameters were examined semiquantitatively: protein, glucose, Ketone bodies, occult blood and pH.

The animals were sacrificed and grossly examined at the end of the study. The following organs were then fixed in formalin for histopathological examination: brain, thymus, lung, heart, liver, kidney, adrenal, thyroid, pituitary, testes, epididymus, ovary, uterus, mesentery lymph nod, prostate, seminal vesicle, urinary bladder, and bone marrows. The absolute and relative weights were determined for the following organs: brain, thymus, lung, heart, liver, kidney, adrenal, thyroid, pituitary, testes, epididymus, ovary, uterus, and prostate.

Results:

General Observation:

Except for redness observed from day 4 to 29 at the application sites in the highest dose group, no treatment related effects were observed.

Body Weight:

Increase in the weight of males of the controls and the low dose groups was observed. On the other hand, males in the higher dose level groups had the tendency to lose weight. In females, loss of weight was observed in the three low dose groups until the middle of the experiment, then the weight increased. Loss of weight or depression of weight gain were observed in the high dose group.

Food and water consumption:

No treatment-related effects were observed.

Urinalysis:

In most specimens urinary protein was positive in labsticks analysis (30-100 mg/100 ml urine).

Hematology:

After treatment, the WBC count showed an increasing trend in males and females of all treated groups.

The average percentage of neutrophilia of both males and females at all dose levels were 40-60%. But after treatment, there was an increasing tendency in high, middle, and middle high dose level females and males, and in low dose females.
Clinical Chemical Testing:

Increase in SGOT values for males of the high and middle high dose groups, also in females of the low dose and control groups was observed. The values in the other animals were essentially constant or tended to decrease. This fluctuations of SGOT were not dose dependent.

Gross Pathology:

Injuries of the skin at the application sites were observed as a result of irritation and scratching especially in the high dose groups. These effects were not seen in the low dose groups.

At necropsy, gross inspection showed out of 50 cases of fibrotic, atrophied, and degenerated thymus glands; 2 cases of lung nodule; one case of local congestion of kidney, 8 cases of submucosal edema of the urinary bladder. These effects were distributed among the control and treated groups.

Organs Weight:

Liver and kidney had greater absolute and relative weights in the high dose group. Relative weight of the kidney also increased in the middle high dose males.

Histopathology:

Eosinophilic colloid inside the lumen of the thyroid follicle decreased in all groups including the control group. The thymus medulla atrophied in one male and two females at the high dose and one control. In the lung cellular infiltration was distributed around the bronchus. One male of the high dose group had degenerated adrenal medulla.

In all groups, both treated and control, there were cases in which sperm could hardly be seen in the testis and epididymis and also cases of submucosal edema of the urinary bladder.

NOEL:

0.1 g/m of the undiluted material/kg of body weight. Higher doses caused decrease body weight gain.

Classification:

Core-minimum.