UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Evaluation of Rat Teratology Study of Endosulfan (Thiodan)
CASWELL#420 Accession#243707

FROM: Gary J. Burin, Toxicologist Gary J Burin 4/20/81 4/20/81
Toxicology Branch, HED (TS-769)

TO: G. LaRocca (15)
Registration Division (TS-767)

THRU: Chris Chaisson, Acting Chief
Toxicology Branch, HED (TS-769)

Submitted By: FMC Corp.
Agricultural Chemical Group
2000 Market Street
Philadelphia, Pa. 19103

Review of Data:

Teratology Study of Endosulfan (Thiodan), Rats. Performed by Raltech Scientific Services and submitted by FMC Corp., November 11, 1980.

Virgin female CD Sprague Dawley rats (8 weeks old) were treated with 0, 0.66, 2.0 or 6.0 mg/kg of FMC 5462 (Endosulfan, 97.37% pure, Lot No. 3/827) in corn oil after being mated with virgin males of the same strain. Treatment, by daily oral gavage, occurred on days 6-19 of gestation with test material administered in 5 ml/kg of corn oil. Although the original protocol specified 25 animals per treatment group, ten additional animals were added to the high dose group (due to mortality among the original animals) and five additional animals were added to the control group (due to a loss of some tissues during processing).

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Dams were weighed on gestation days 0, 6, 9, 12, 18 and at sacrifice on day 20. Observation for abnormal signs occurred twice daily throughout the test period.

On day 20 dams were asphyxiated with $CO_2$. The ovaries and uterus were removed from each animal subsequent to a midline laparotomy. The ovaries were examined grossly and the number of corpora lutea were counted. The gravid uterus was also examined grossly and was weighed. Conceptuses were removed and the number and location of live and dead fetuses, resorptions, empty sites and gross abnormalities were recorded.

Fetuses were sexed, measured, weighed, examined grossly and given a visceral examination. Freehand razor sections of the heads of one-half of the fetuses was performed and all fetuses were stained and examined for skeletal abnormalities.

Dams were grossly examined for internal and external abnormalities. Apparent lesions were preserved for possible future histopathological examination.

Raw data sheets for each dam and fetus were included in the final report. Summary sheets were also submitted for a variety of parameters. Statistical comparisons of fetal gross, visceral and skeletal abnormalities were performed using the Chi Squared method. All other parameters were compared using the Kruskal-Wallis test.

Results:

Maternal toxicity was apparent in the high dose group in the form of significantly reduced body weights and body weight gain during gestation ($p < .01$). Toxic signs observed in the high dose group included face rubbing (20/35 animals), brown exudate (4/35), rough coat (5/35), flaccidity (8/35) and hyperactivity (11/35).

Seven high dose dams died during the course of the study and five of these deaths were apparently the result of the improper gavage of the animals (the gavage tube inserted into the lungs rather than the esophagus). The remaining two deaths may have been compound related as suggested by a decrease in body weight prior to death. However, these two animals were not reported to have exhibited signs of toxicity prior to death. One control animal also died on test, apparently from improper gavage.

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Maternal toxicity was not demonstrated in the low or mid-dose groups. No mortality was reported in these groups and body weights (and gains in body weight) were not significantly effected. Face rubbing was reported in 6/25 of mid dose animals and alopecia was reported in 2/25. No face rubbing was reported in low dose animals or controls.

One animal in the control, one high dose and two low dose animals were not pregnant at necropsy. Fetal and embryolethality were not apparent in any group and all pregnant animals had viable litters. Mean fetal weight and crown-rump length were significantly reduced ($p < .05$ and $p < .01$, respectively) in the 6 mg/kg group. No effect on fetal weight or length was found in the low or mid-dose groups.

A number of external and visceral abnormalities were observed in the 6 mg/kg group. Out of a total of 27 litters containing 405 fetuses, one fetus had skin of the upper forelimb webbed to the chest and 5 other animals of this litter had edema and lordosis, a fetus from another litter was observed to have edema and short limbs (although the short limbs were not confirmed on skeletal examination), one fetus from each of two high dose litters had clubbed hind left limbs and one fetus from each of two high dose litters had cardiovascular abnormalities (a hypoplastic aortic arch was present in one fetus and the heart of another was small and displaced within the thoracic cavity). There was also a significant increase in the incidence of small 4th and unossified 5th sternebrae ( $p \leq .05$ and $p \leq .01$, respectively) in fetuses from the high dose group.

The only statistically significant developmental effects noted in the low and mid-dose groups were misaligned sternebrae ( $p < .05$ in each group). A single instance of microstomia was found in the low dose group.

Conclusions:

A number of skeletal, visceral and external anomalies, as well as significant reductions in size and weight, were reported in fetuses from dams administered 6.0 mg/kg on a daily basis on days 6-19. However, at this dose level maternal toxicity was evident in the form of decreased body weight and body weight gain ($p < .01$) and clinical observations indicating CNS stimulation.

At lower dose levels, no compound-related terata were apparent although misaligned sternebrae were noted. This effect can be considered a variation, rather than a teratogenic response. The NOEL for fetal and maternal toxicity in this study is therefore considered to be 2 mg/kg.

Core-Classification

Core-Minimum Data. A positive control group was not used and maternal food consumption was not quantified.

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