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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Evaluation of additional data pertaining to the teratology study with Bladex in SD-CD rats. PP#9F2232; Accession #072838; CASWELL #188C

TO: Robert Taylor, PM#25
Registration Division (TS-767C)

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LDC 10/26/84
WLB 11/04/84

Registrant: Shell Oil Company
1025 Connecticut Ave., N.W.
Washington, D.C. 20036

OCT 6 1984

Action Requested:

Review of individual animal data for the teratology study with Bladex in SD-CD rats (WRC RIR-311).

BACKGROUND:

This study (WRC RIR-311) has been previously submitted (Accession #071738) for review and was classified as Core Supplementary Data (memo of A. Mahfouz, 11/14/83). Individual animal data were then requested to confirm the findings. Dr. Mahfouz also indicates that this study may potentially be upgraded if maternal toxic effects can be demonstrated from the dosage levels selected.

In this action (Accession #072838), raw data of both the dose-range finding and main studies are submitted by the registrant as a basis for upgrading the study.

REVIEW:

I. Dose-range finding study

This study was conducted by Research Triangle Institute from 1/20/83 to 2/14/83.

Groups of 8 SD-CD females each were treated with technical Bladex at 0, 1, 3, 10, 30, and 60 mg/kg/day from gestational days 6-15 (inclusive). All animals were sacrificed by days 20 of gestation and the maternal reproductive status and fetal data were collected.

Since the maximum tolerated dose is at issue in this action, only findings at the two highest doses (30 and 60 mg/kg) are discussed by this reviewer.

1. Body Weight Data

During the dosing period (days 6-15 of gestation), the 30 and 60 mg/kg groups gained significantly less weight than the control. Body weight reductions of 50.5 and 70.9% of control values were noted in the 30 and 60 mg/kg groups, respectively.

2. Pregnancy Rate

A pregnancy rate of 100% was found for the control, 30, and 60 mg/kg groups.

3. Clinical Observations

Piloerection was observed only in the treated groups. 75% of the animals in the 30 and 60 mg/kg groups exhibited piloerection as compared to 0% of the controls. This clinical sign, then, may be regarded as compound-related.

4. Litter Size

The mean litter size of the 30 and 60 mg/kg groups were slightly reduced in comparison with the control. These means were 13.0, 11.87, and 11.37 for the control, 30, and 60 mg/kg groups, respectively.

5. Resorptions and Dead Fetuses

No statistically or biologically significant differences were noted between the control and treated groups in terms of mean resorptions and dead fetuses per litter.

6. Conclusion

Although the dosage levels of 30 and 60 mg/kg/day were not associated with reproductive effects, they did exhibit maternal systemic toxicity as evidenced by decreased body weight gain during the dosing period. Under the conditions of this study, the 30 mg/kg dosage level may be considered as a LEL.

II. Teratology Study with Bladex in SD-CD Rats (WRC RIR-311)

This study was previously classified as Core Supplementary Data (A. Mahfouz's memo of 11/14/83) with the following issues:

a) Randomization process
b) Selection of data for report
c) Lack of individual data to confirm the clinical observations, necropsy data, and body weight data.
d) Maximum tolerated dose was not tested.

To fully evaluate this study, submission of raw data was then requested.

1. Randomization Process

There are evidences in the raw data to confirm that the animals were assigned randomly (by body weight) to groups receiving 0, 1, 3, or 30 mg/kg of technical Bladex. Mating was performed on February 24-28, 1983. Mated females were then equally distributed to all test groups for each mating day.

2. Selection of Data for Report

Thirty (30) mated females were assigned to each group. However, data analysis was performed on only about twenty (20) litters in each group. Concerns were raised by Dr. Mahfouz as to the basis of litter selection.

From the raw data, there are evidences to indicate that the selection design was not based upon body weight, reproduction status, or clinical observations. In this study, once an appropriate number of litters (approximately twenty) had been reached for a group, the remaining dams would then be discarded. This approach would eventually ensure that a minimum of approximately twenty litters was obtained for each group. All the discarded females belonged to the last batch of animals mated (2/28/83). Necropsy was performed on these dams but was excluded from data analysis.

3. Clinical Observations

From the raw data, identification of the animals with clinical signs is now permissible. Dams with health-related clinical signs were not excluded from data analysis.

Piloerection was observed in 0/30, 2/30, 3/30, and 14/30 females in the groups receiving respectively 0, 1, 3, and 30 mg/kg. Since piloerection was observed only in the treated groups (similar observation in the dose-range finding study), this clinical sign may be identified as compound related.

4. Necropsy Data

It is now possible to confirm that Control dam #89 had only 1 fetus (born with malformations). Because of the single pup in this dam, the mean number of live fetuses per dam in the control was reduced and became slightly lower than that of the treated groups.

5. Body Weight Data

Body weight data were calculated from females providing the litters actually examined (19-20 in each group).

During the dosing period (days 6-15 of gestation), females in the 30 mg/kg group gained significantly less weight than those of the control (19.8% reduction of control values). The absolute maternal weight gain (weight gain during gestation minus gravid uterine weight) of the 30 mg/kg group was significantly less than that of the control although the gravid uterine weight of the 30 mg/kg group was significantly higher than that of the control.

	Control	30 mg/kg
Mean maternal weight gain (6-15)	47.5	38.1*
Mean maternal weight gain (0-20)	131.8	135.6
Mean uterine weight (gravid)	69.5	84.7*
Mean absolute matenal weight gain	62.3	50.9*

During pregnancy, two factors are known to contribute to the maternal body weight gain: maternal and fetal weight. As shown in the above table, the dosage level of 30 mg/kg did not exhibit harmful effects on the fetuses but actually did significantly increase the fetal weight. The increase in fetal weight would then negate the would be differences in maternal weight gain between the two groups throughout the entire study (days 0-20). Because of variable fetal weights, the mean absolute maternal weight gain would then be a more reliable index to assess maternal toxicity in reproduction and teratology studies. In this study, significant decrease in absolute maternal weight gain was observed at 30 mg/kg hence should be considered as an indication of maternal toxicity. However, this reviewer agrees with Dr. Mahfouz's statement that the 30 mg/kg dosage level was not associated with additional effects such as litter size, mean implantations, mean resorptions, and mean fetal weights.

CONCLUSIONS:

Based upon the newly submitted raw data for both the preliminary and primary teratology studies, maternal toxicity was demonstrated at 30 mg/kg as evidenced by:

1. Increased clinical sign incidences (piloerection) in both studies.

2. Decreased maternal weight gain during the dosing period observed in both studies.

3. Decreased absolute maternal weight gain noted in the primary study.

Furthermore, the 30 mg/kg dosage level appears to fulfill the requirements of the 1982 FIFRA Guidelines which indicate that "the highest dosage level should induce some overt maternal toxicity such as slight weight loss".

Under the conditions of this study:

Maternal NOEL = 3 mg/kg
Maternal LEL = 30 mg/kg (decreased body weight gain and increased incidences of piloerection)
Fetotoxic NOEL $\geq$ 30 mg/kg (highest dose tested)
Terata NOEL $\geq$ 30 mg/kg (highest dose tested)

CORE CLASSIFICATION: This study is now upgraded to Core MINIMUM DATA.