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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: March 10, 1982

SUBJECT: Goal 2E; EPA Reg.#707-115; Additional Toxicology Studies CASWELL#188AAA Acc.#246694

FROM: William Dykstra, Toxicologist
Toxicology Branch/HED (TS-769)

TO: Richard Mountfort (23)
Registration Division (TS-767)

Recommendations:

1) The studies submitted are either acceptable or Supplementary Data.

2) Goal 25WP was not teratogenic at dosages up to 30 mg/kg/day. This study is only acceptable as Supplementary Data. A rationale, other than the one given in the range finding study protocol Appendix(I), for using Goal 25WP rather than the technical must be provided before the study can be considered acceptable as Core-Minimum Data. It is noted in Appendix (I) that PEG-400 was satisfactory in suspending the technical. Additionally, individual data and calculations are required to substantiate Table 18 (Fetal ossification sites). We also request an explanation of how the 90 mg/kg/day dose level decreased pregnancy, corpora lutea, and implantations.

3) The 90-day mouse protocol is acceptable. Toxicology Branch does not concur with the rat protocol since dosage levels are changed.

Review:

1. Goal 25 WP: Oral range finding toxicity study in female rabbits (Rohm and Haas, Report No. 81R-127; 12/18/81)

   Goal 25 WP was administered orally by gastric intubation at dosages of 1.10 gm A.I./kg (low-dose) once daily to four female NZW rabbits and 1.10 gm A.I/kg (high-dose) twice daily with a four hour interval between dosing to four female NZW rabbits.

Results:

The four high-dose rabbits died on day 6. Three low-dose rabbits died on day 9 and one on day 6. No deaths occurred in the vehicle control group of rabbits.

Necropsy:

Three rabbits in the high-dose group had pale spleens and one rabbit in the low-dose group had reddened lungs. No gross findings were observed in the control group.

Classification: Supplementary Data

2. Goal Herbicide: Oral range-finding study in pregnant rabbits (Argus Project#018-006P; 1/22/82)

Groups of 4 pregnant NZW rabbits were gavaged with 0 (Goal 25 WP blank), 31, 62, 125, 250 and 500 mg/kg/day, calculated as A.I., during days 6-18 of gestation. On day 25, the rabbits were killed and examined.

Results:

Deaths occurred in one of four at 125, four of four at 250 and four of four at 500 mg/kg/day before day 25. There was reduced weight gain at 62, 125, 250 and 500 mg/kg/day.

Decreases in litter size and live fetuses occurred in the 250 and 500 mg/kg/day groups and increased resorptions also occurred in these groups.

Conclusion:

A dosage level of 31 mg/kg/day did not produce maternal toxicity.

Classification: Supplementary Data

3. Goal Herbicide: Teratogenicity Study in Rabbits (Argus Project#018-006; 1/15/82)

Groups of 19 inseminated NZW rabbits were orally intubated with 0 (water), 0 (Goal 25WP blank), 10, 30, 90 mg/kg/day (calculated as the active ingredient) of Goal 25WP once daily on days 6 through 18 of gestation. All dosages were given at 10 ml/kg/day and reflected changes in maternal body weight. On day 29 of presumed gestation,

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surviving rabbits were sacrificed and the uterus examined for pregnancy and number and placement of implantations, early and late resorptions, and live and dead fetuses. Corpora lutea were counted. Each fetus or pup was weighed and examined for gross external, visceral, and skeletal a anomalies.

Results;

Of the 19 rabbits inseminated in each group, pregnancy occurred in 16, 13, 14, 16 and 11 rabbits of 0 (water), 0 (Goal 25WP blank), 10, 30, and 90 mg/kg/day groups, respectively.

One control (Goal 25WP blank) and five 90 mg/kg/day group rabbits died. One 10, two 30, and four 90 mg/kg/day group rabbits aborted. One control (water) rabbit delivered a litter prior to day 29.

Anorexia was observed in the 30 and 90 mg/kg/day groups.

Decreased body weight gain was observed in the 30 and 90 mg/kg/day groups. The number of rabbits pregnant and delivered by cesarean section on day 29 were 15, 12, 13, 14 and 5 for the 0 (water), 0 (Goal 25WP blank), 10, 30 and 90 mg/kg/day groups, respectively. Corpora lutea, implantations and litter size were reduced in the 90 mg/kg/day group as shown in Table 8. These decreases were not statistically significant. Resorptions were increased in the 90 mg/kg/day group. This increase was not statistically significant. Fetal body weight was decreased at 90 mg/kg/day group.

The number of fetuses or pups evaluated was 109, 85, 84, 98 and 22 for the control (water), control (Goal 25WP blank), 10, 30 and 90 mg/kg/day groups, respectively.

Examination of gross external variations showed 1 fetus with umbilical hernia and, 1 fetus with limb muscle separated and nerve exposed at 0 (water control) and 1 fetus with hematomas on the limbs, 1 fetus with exencephaly and 1 fetus with hematomas on the body at 30 mg/kg/day group.

Examination of soft tissue variations showed 1 fetus with umbilical hernia in the control (water) and 1 fetus with median lobe of the lung absent in the other control (Goal 25WP blank).

Examination of skeletal variations showed the following:

1 fetus with incompletely ossified occipitals in the control (Goal 25WP blank), 1 fetus at 30 mg/kg/day with frontals not ossified and 1 fetus with incompletely ossified parietals in the 30 mg/kg/day group.

In addition, 1 fetus in the control (Goal 25WP blank) had the hyoid not ossified. One fetus each at both 30 and 90 mg/kg/day groups had hemivertebrae.

With respect to the sternebrae, two or more fused sternebrae appeared in 1 fetus control (Goal 25WP blank), 1 fetus from 10 mg/kg/day, 7 fetuses in 3 litters from 30 mg/kg/day, and 1 fetus from 90 mg/kg/day. With respect to one or more asymmetric sternebrae, there appeared 1 fetus in the blank control, 1 fetus at 10 mg/kg/day and one fetus at 30 mg/kg/day.

With respect to one or more split vertebrae, there appeared one fetus at 0 (water) and one fetus at 10 mg/kg/day.

Conclusion:

Goal 25WP was not teratogenic at dosages up to 30 mg/kg/day given during days 6-18 of gestation. The fetotoxic NOEL is considered to be 10 mg/kg/day.

The maternal toxic NOEL is also 10 mg/kg/day. Since only five litters (22 fetuses) were available at 90 mg/kg/day, this dose level could not be properly evaluated, although no teratogenic effects were observed.

Classification: Supplementary Data (See Recommendations)

5. Protocols for 90-day mouse feeding study and 90-day rat feeding study; we note that these studies have been initiated.

a. 90-day mouse study with Charles River COBS-CD-1 mice.

Test material: RH-2915 technical (Goal)

Group	Dose (ppm in diet)	No. of Mice M	No. of Mice F	Lab. Studies[d]	Post Mortem Ex.
1	0	15	15	10M, 10F	ALL
2	200	15	15	10M, 10F	ALL
3	800	15	15	10M, 10F	ALL
4	3200	15	15	10M, 10F	ALL

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Lab studies after 13th week

Hematology: packed cell volume, red cell count, hemoglobin, total and differential white cell count, platelets, bone marrow differential.

Clinical Chemistry: glucose, BUN, SGPT, SAP, total protein, cholesterol, albumin, globulin, A/G ratio, gamma glutamyl transpeptidase, creatine.

Urinalysis: sp. gr., pH, protein, glucose, ketones, bilirubin, occ. blood, color, clarity.

Organ Weights: adrenals, brain, gonads, kidney, liver, spleen, thymus, heart.

Histopathology: 38 tissues

Classification: Acceptable

b. 90-day rat feeding study with Long-Evans rats.

Test Material: RH-2915 technical (Goal)

Group	Dose (ppm in diet)			No. of Rats	
				M	F
1	0(wk 1-2)	0 (wk 3-4)	0 (wk 5-13)	15	15
2	400	560	800	15	15
3	800	1120	1600	15	15
4	1600	2240	3200	15	15

Lab studies, organ weights, and histopathology are the same as in mouse protocol.

Classification: Not acceptable.

(a) Dosage levels are changed during the study.

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