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

MEMORANDUM

5/17/82

001883

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

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Goal 2E; Goal 25 WP; EPA Reg.#707-145; Rohm and Haas Responses to Toxicology Branch Questions
CASWELL#188AAA Accession#247406

Recommendation:

The registrant has satisfactorily addressed all of the Toxicology Branch questions in memo of 3/25/82 from W. Dykstra to R. Mountfort. The rabbit teratology study is now acceptable as Core-Minimum Data. The protocol for the rat subchronic feeding study is acceptable.

Review:

1. Toxicology Branch Question:

Provide a rationale other than the one given in Appendix I of the range finding toxicity study for using Goal 25 WP rather than the technical in the teratology studies.

Rohm and Haas Response:

The results given in the three reports submitted, the pilot toxicity study, the teratology range finder, and the fullscale teratology study clearly demonstrated that the wettable powder formulation is a suitable vehicle for assessing the toxic properties of technical grade Goal, the substance which was being tested.

"The issue is not whether another vehicle, such as PEG-400 might be equally acceptable as a vehicle for administering Goal technical to pregnant rabbits; the issue is whether the vehicle used was suitable, and it was."

According to the National Academy of Science, Principles and Procedures for Evaluating the Toxicity of Household Substance (NAS, 1979) suitable vehicles for teratology studies "are nontoxic and should not appreciably change the bioavailability and pharmacokinetics of the test agent or alter the physiology and visceral histology of the test animals."

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Similarly the FIFRA Guidelines (43 FR 37352, August, 1978) say:

"If a vehicle is used to dissolve or dilute the test substance or positive control substance, it shall be chosen to possess the following characteristics to the greatest degree known: (A) it does not alter the absorption, distribution, metabolism, or retention of the test substance; (B) it does not alter the chemical properties of the test substance or enhance, reduce, or alter the toxic characteristics of the chemical; (C) it does not effect the food and water consumption or the nutritional status of the animals; (D) at the levels used in the study it does not produce physiological effects; and (E) it closely resembles the vehicle if any, to be used under expected conditions of use".

After preliminary studies demonstrated that Goal technical was not soluble enough in corn oil to allow administration of a minimally toxic dose to the rabbits, we selected the wettable powder formulation, among other candidate vehicles, for trial because:

(a) WP s are designed to achieve a stable suspension in water, the most preferred liquid dosing medium, without altering the chemical properties of the technical.

(b) the carrier primarily consists of [redacted] by the oral route and is approved as a direct food additive for both humans and food producing animals.

(c) it would present the Goal technical in a finely divided form which is physically similar to the form of any residues which might occur in food crops and which would, if anything, facilitate absorption by the GI tract.

(d) [redacted] in the formulation would also facilitate absorption from the GI tract, and

(e) it is one of the vehicles "to be used under expected conditions of use."

INERT INGREDIENT INFORMATION IS NOT INCLUDED

The pilot study when demonstrated that Goal 25 WP produced signs of toxicity including decreased body weights, clinical signs, and deaths which were attributable to the technical material and not [redacted] These observations were confirmed in the range finding study where doses of 125 mg Goal ai/kg bw/day administered on days 6-18 of pregnancy produced both abortions and maternal deaths while the vehicle blank (formulation ingredients other than Goal technical, mixed in the proper proportions) showed no evidence of toxicity.

Finally in the fullscale study, there were no significant differences in any parameters examined, including maternal anorexia and other clinical signs, body weight gain, pregnancy, and litter data, between the sham treatment water control and the vehicle control thus proving that the 25 WP vehicle at the levels used in the study did not affect the growth or nutritional status of the dams and did not produce physiological effects. The maternal anorexia, body weight gain depression, and abortions observed in the 30 and 90 mg ai/kg bw/day dose group establish that the 25 WP vehicle was capable of delivering maximum tolerated dose of Goal technical.

The combination of these facts demonstrates that the wettable powder formulation, Goal 25 WP, is a suitable vehicle for assessing the teratogenicity of Goal technical in rabbits. Rohm and Haas agrees that the fullscale study demonstrated that Goal technical is not teratogenic or embryofetotoxic at doses up to and including those which produce maternal toxicity. It should be added that, although Goal technical was satisfactorily suspended in neat PEG 400 as Appendix I states, the addition of water precipitated it out in large clumps (observation inadvertently left out of the Appendix). Since water would be present in the GI tract, PEG 400 did not appear acceptable as a vehicle for Goal.

Conclusion:

Rohm and Haas response is acceptable.

2. Toxicology Branch Question:

Provide individual data and calculations to substantiate Table 18 (Fetal Ossification Sites).

Rohm and Haas Response:

Copies of the raw data for the fetal skeletal examinations are attached (attachment 2, raw data pp 366-466, 81P87). Table 18 was prepared directly from the raw data. Because of the sheer volume of numbers involved, neither Rohm and Haas nor Argus's Standard Operating Procedures call for including individual litter mean fetal ossification site data in teratology reports.

Conclusion:

Rohm and Haas response is acceptable.

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3. Toxicology Branch Question:

Explain how the 90 mg/kg/day dose level decreased pregnancy, corpora lutea, and implantations.

Rohm and Haas Response:

The first thing to say here is that neither Rohm and Haas nor the contractor, Argus Laboratories, concluded that the 90 mg ai/kg bw/day dose level did in fact decrease pregnancy, corpora lutea, or implantations. The abstract says that: "In the 90 mg/kg/day group an insufficient number of litters precluded evaluation of embryo and fetal parameters", and the report currently reads: "The small number of rabbits available for evaluation in the high dosage group precludes conclusions pertaining to embryo- and fetal-toxicity. In the five litters examined, there was no evidence of agent-related gross malformations in fetuses. However, the limited data suggest a decrease in pregnancy, corpora lutea, implantations and litter size and an increase in resorptions in rabbits in this dosage group".

Rohm and Haas recognizes that the concept of a conventional teratology study experimental design calls for dosing to begin just after implantation occurs, thereby excluding compound-related effects on pregnancy, corpora lutea and implantations. However, the standard FIFRA/OECD protocol, which this study followed, specifies dosing on days 6-18 (days 6-29) of gestation in the rabbit whereas histologic implantation occurs on day 7-8 (Hoar, 1981; Leone; 1977). Thus implantation and any further events which depend on implantation can be affected. The actual data recorded in this study suggest that the 90 mg ai/kg bw/day Goal treatments may have affected the number of animals who were verifiably pregnant (i.e., they aborted, delivered naturally, or had fetuses, resorptions or implantations at Caesarean section on day 29), and the mean numbers of grossly observable corpora lutea and implantations. To clarify this point for future readers of this report, Dr. Mildred Christian of Argus has provided the attached revised pages for the final report (attachment 4; 2 sets, one with changes underlined, one without underlining for substitution in the report) and a set of references on the timing of developmental events in the rabbit (attachment 5). She further notes that, when the number of implantation sites is reduced, the decrease in normal hormonal feedback from the implantation sites can lead to regression of the corpora lutea. (Attachment 6 describes how this interaction occurs in humans.) The regression can proceed to the point where one or more corpora lutea are not distinguishable at gross examination.

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Thus one cannot exclude the possibility of compound-related effects on pregnancy, corpora lutea, or implantation on theoretical grounds; the data on the 5 surviving litters in this study suggest, but do not prove, that effects on these parameters may have occurred; and the report so states.

Conclusion:

Rohm and Haas response is acceptable.

4. Toxicology Branch Question:

Reasons for changing the dosing level in the rat subchronic study.

Rohm and Haas Response:

Rohm and Haas feels that the EPA reviewers should reconsider their reservations on this protocol. There were two basis reasons for raising the ppm concentrations of Goal in the rat diets during the test period. The first is that we agree with the EPA reviewers that it is desirable to maintain a reasonably constant dosing level on a mg/kg bw/day basis during the course of the subchronic study. Since young rats gain weight rapidly (they were 6 weeks old at the initiation of dosing) their food consumption on a g food/kg bw/day basis decreases proportionately, and thus it is necessary-and standard laboratory practice-to increase the concentration of the test chemical in the diet at intervals to compensate. The preliminary mean compound intake (mg/kg bw/day) data for this study demonstrate that a reasonably constant dosing level was achieved.

Second, one of the objectives of this study was to provide an estimate of the maximum tolerated dose of Goal in Long Evans rats for comparison with the doses used in the previous 2 year chronic/oncogenic study (Bio/dynamics, 1977). The changes in concentration in the current study thus follow the schedule of the Bio/dynamics study.

Conclusion:

Rohm and Haas response is acceptable.

William Dykstra, Ph.D WRD
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attachments

WRD for LDC
5/17/82

TS-769:th:TOX/HED:WDykstra:5-13-82:card 5

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