5/22/84

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

003815

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Naled RS - Rat Terata Study; Accession #252451.
EPA Reg. No. #239-1633 CASWELL#586

TO: William Miller/Gary Otakie, PM#16
Registration Division (TS-767)

FROM: Irving Mauer, Geneticist
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Registrant: Chevron Experimental Health Center
Richmond, California

Action Requested: Review the following submission of data to satisfy deficiency identified in the Registration Standard:

"Teratology Study in Rats with Naled Technical", performed by Science Applications, Inc.; La Jolla, California, SAI #583008, dated January 18, 1984.

Recommendation: This study has been judged adequate for assessing teratology potential of Naled technical in the rat (CORE MINIMUM DATA, Data Review attached). Under conditions of the study, Naled Technical (91.4% a.i.) was found to be non-fetotoxic and non-teratogenic by oral gavage at a dose (40 mg/kg/day = HDT) causing moderate-to-severe maternal toxicity and significant body weight loss.

1/10

003815

TOXICOLOGY BRANCH: DATA REVIEW

CHEMICAL: Naled (Dibrom)

STUDY TYPE: Teratology in rats

CITATION: Teratology Study in Rats with Naled Technical

ACCESSION NO./MRID NO.: 252451/-(NA)

SPONSOR/CONTRACTING LAB.: Chevron, Richmond, CA/Science Applications, Inc., La Jolla, CA

STUDY NO./DATE: SAI #583008/1-18-84

TEST MATERIAL: Naled technical (lot #SX-1397); a clear, colorless liquid, 91.4% a.i., suspended in CMC for testing.

PROCEDURES: A photocopy of materials and methods submitted is appended to this review. Briefly, inseminated SD rats (30/group) were intubated orally with the test substance at dose levels of 0 (CMC vehicle), 2, 10 and 40 mg/kg/day through gestation days 6 through 19, observed twice daily, and sacrificed on Day 20. Maternal body weights and food consumption were determined at regular intervals, and all standard maternal and prenatal measurements recorded (both in summary tables and for individual dams and litters in Appendices II through VI).

Although it was stated in summary (under "Experimental Design", p. 3 of report) that external, visceral and skeletal observations were made on all fetuses, as well as on head specimens preserved in Bouin's, the specifics of these procedures were not given under the Materials and Methods section (pp. 2-4), but are assumed to those proposed in Protocol 11.150, submitted as Appendix XIII (pp. 322, 323 of which are appended to this review). N.B.: A number of housekeeping and scheduling amendments to this protocol are duly noted, none of which appeared to have affected the conduct of the study. However, three deviations from the protocol which occurred during the course of the study were also submitted: (1) Room temperatures outside the recommended range (70 ± 5°F) on three days; (2) Humidity outside the recommended range (50 ± 10%) on 14 days; and (3) Single instances of improper dosages to 7 animals, as follows: two controls dosed 0.1 ml less and one 0.5 ml more; three low-dose females given 0.1 ml less (on days 16, 18 and 19); and one high-dose animal dosed on day 1 at 1.6 ml instead of 1.7 ml.

003815

Statistical analyses were performed on all data using SAI's Repro./Terata. Data System (Appendix I). All fetal malformations and variations were classified and grouped, and analyzed by Kruskal-Wallis and Gladen tests (appropriately referenced), with the litter as the experimental unit; individual fetal data were also presented for all viable fetuses by litter, as well as grouped and analyzed by total fetuses, litters, and proportions of affected. Historical control data were presented for confirmation of type and number of effects observed in this study (Appendix XI of submission).

A quality assurance statement was included in the report.

RESULTS: No dams died and no abortions occurred. The following maternal clinical toxicities were observed at the HDT only: tremors; discharges from month and eyes; dyspnea; and depressed activity. One dam at 40 mg/kg/day had a diaphragmatic hernia; another, renal hydronephrosis. The pregnancy rate and mean food consumption were comparable in all groups, but a significant decrease in mean maternal body weight was found in high-dose females; no significant differences from controls were noted for mean numbers of corpora lutea or implantations.

Although the incidence of runts (defined as fetal body weight 70% or less than mean concurrent control) was stated to be related to compound administration at the HDT (and higher than historical control), there were no statistical differences in number between concurrent controls and any test group. Both the number of litters and the mean live litter size were comparable in all groups, and no statistical differences between any test group and controls reported for mean fetal weights, sex ratios, numbers of implants/litter, or resorptions. [NB: It is noted, however, that 20 resorptions and 1 dead fetus were counted at the HDT (9% of all fetuses), compared to 9, 8, and 6 in the 0, 2 and 10 mg/kg groups, respectively.] Results of fetal examination were also comparable in all groups; a single fetus in the 40 mg/kg/day group manifested umbilical hernia, spina bifida, meningoencephalocoele and "protruding tongue", while another at the HDT had misshapened and/or ectopic kidneys and malpositioned ovaries. Hydrocephaly was observed once, but in a control fetus. A variety of skeletal variations were reported, equally distributed among all test groups and control, and all within historical control ranges. Individual litter and fetal data derived from the study's summary tables and tabulated appendices are shown on the following page.

CONCLUSION: This reviewer agrees with the report's conclusion that administration of Naled Technical to pregnant rats did not induce any major fetal malformations at doses up to 40 mg/kg/day, a dose level at which significant maternal toxicity was observed.

Previous, acceptable subchronic studies in the rat (evaluated for the Standard) had indicated that the NOEL for clinical toxicity was between 15 and 30 mg/kg/day.

TB EVALUATION: CORE MINIMUM DATA.

Negative for fetotoxicity and teratogenicity
Maternal LEL (toxicity/body wt.) = 40 mg/kg (HDT)
Maternal NOEL = 10 mg/kg/day

003815

Individual Prenatal Data	DOSE GROUP (mg/kg/day)			
Number of:	0	2	10	40
Litters	24	21	22	27*
Corpora lutea	296	243	256	310
Implants	283	251	250	307
Resorptions:**				
- litter	7	6	4	7
- sites	9	8	6	20***
Live fetuses	274	242	243	286
Dead fetuses	0	0	0	1
Fetal Data				
Number of:				
Runts	2	0	1	3
Umbilical hernia	0	0	0	1****
Spina bifida	0	0	0	1****
Meningoencephalocoele	0	0	0	1****
Protruding tongue	0	0	0	1****
Hydrocephaly	1	0	0	0
Renal ectopia	0	0	0	(1)
Renal cavitation/ hydroureter	1	0	1	(1)
Ovarian ectopia	0	0	0	(1)

*Only 26 reported in appendices.
**All early resorptions.
***Per affected litter = 2, 2, 6, 2, 4, 3, 1.
****Observed in one runt fetus.
( ) - Same fetus

Naled toxicology review

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Pages 6 through 10 are not included in this copy.

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