10/24/83

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

CASWELL#586

MEMORANDUM

TO: William Miller, PM#16
Registration Division (TS-767C)

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

SUBJECT: Naled - Receipt of 1-year interim chronic oral toxicity report in rats (2 volumes). Acc.#250501

Action Requested: Review subject report (RS chemical) submitted June 6, 1983; study performed by Bio-Research Labs, Montreal (Canada).

Registrant: Chevron Chemical, Richmond, California

Recommendation: Preliminary findings (1-year of 2-year study in rats) are reviewed, (see attached), but these data not evaluated, nor study core-graded until final report is submitted. This is an interim report, and no conclusions can be drawn before the final report is received. In their covering letter, the registrant noted that the in-life portion of the study has been completed, with the final report due to be submitted by the May, 1985 reporting deadline.

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Caswell No.: 586
Shaughnessy No.: 044301

TOXICOLOGY BRANCH: DATA REVIEW

Chemical: Nale l

Study Type: Chronic Oral Toxicity/Carcinogenicity Study in Rats

Citation: "Dibrom Chronic Oral Toxicity/Carcinogenicity Study in Rats - One-Year Interim Report"

Accession No./MRID No.: 250501/NA

Sponsor/Contracting Lab.: Chevron Chemical (Canada) Limited Burlington, Ontario/Bio-Research Laboratories Ltd. (Montreal) Senneville, Quebec, Canada

Report No./Date: 9394/December 23, 1982

Test Material: Dibrom technical, [redacted] SX-1278 (purity not stated), a yellow viscous liquid, dissolved in Na-CMC.

Procedures: Four groups of 65 male and 65 female juvenile (28-day old on receipt) CD-CR:(SD)BR albino rats each were given test compound by daily oral gavage at doses of 0 (CMC vehicle control), 0.2, 2.0 and 10.0 mg/kg for 8 weeks, following which each group was reduced to 55 animals/sex. Data presented here were obtained during the first year of treatment (2-yr study). Animals were observed daily for clinical signs; body weights and food consumption recorded weekly; and clinical laboratory values (hematology, chemistry profile, urinalysis, cholinesterase) of 20 males:20 females/group monitored before treatment as well as during weeks 25/26 and 51/52. Ophthalmoscopic examinations were performed on all animals before dosing began, and during week-52 of treatment, both by funduscope (indirect ophthalmoscopy) and by biomicroscope (slit lamp). Complete necropsies were performed on all animals which died during the study, or were sacrificed after the first 8 weeks of treatment (culling to 55 animals/sex/group). At termination (2 years), a complete set of organs will be weighed, and prepared for histopathological examination (including all gross lesions).

Results: During the pre-culling period (first 8 weeks of treatment), 4 high-dose males died (3 due to accidental perforation of the esophagus during dosing), and 2 mid-dose females and one male sacrificed in distress, as well as one control male (during week-8). A total of 10 males and 6 females died or were killed in distress during weeks 9 through 52: Two high-dose females (weeks-47, -51), both with enlarged pituitary; 2 mid-dose males (weeks-28, -51) and 1 mid-dose female (week-37), with enlarged pituitary/spleen; 4 low-dose males (weeks-27, -42, -44, -46) with

perforated esophagus, and 2 females (weeks-38, -57) with enlarged pituitary; and 4 control males (weeks-48, -50, -51, -52) with enlarged intestinal organs (1 animal), s.c. (abdominal) masses (2), or enlarged pituitary (1), plus 1 control female (week-50) with an abdominal mass.

No marked clinical signs were reported in any survivor of 52 weeks treatment, but 4 high-dose females manifested brief tremors on isolated occasions during weeks-45 to -52. Other signs observed were common to the strain, and occurred equally in all groups (patchy alopecia, ocular/nasal discharges, fur stains, swollen pinna, salivation, and occasional respiratory distress). Evidence of preputial gland abscesses were found in about 25% to 30% of males in all groups, and the incidence of palpable s.c. masses among females at week 52 was approximately the same in all groups (13 controls, 12 low-dose, 6 mid-dose and 16 high-dose).

Sialodacryoadenitis was common in a majority of rats early in treatment, but all animals recovered without residual clinical consequences.

Increases in mean body weights over controls among high-dose females were occasionally recorded, coincident with increased food consumption. No ponderal or dietary changes were recorded among any treated male group.

No treatment-related ophthalmoscopic abnormalities were found in any group at 52 weeks, but singular instances of cataract, hemorrhage and/or conjunctivitis were recorded equally in all groups.

Non dose-related lower rbc, hb and hematocrit values than concurrent controls were recorded for mid- and high-dose males and females at both the week-26 and week-52 samplings as well as higher platelet counts in both high-dose groups. Both parameters were stated to be within the normal "background" ranges for this strain of rats. No change in leucocyte values were found at either sampling time, nor in other blood chemical values, and no evidence of effect of treatment upon urinary parameters.

"Lower plasma cholinesterase activities were recorded at week-26 and -52 for males and females treated with 10 mg/kg/day. Lower plasma activity was also recorded for animals treated at 2 mg/kg/day, at both week-26 and week-52, particularly for the males on the latter occasion.

"There was no consistent effect on the red blood cell cholinesterase activity of treated males or females. At week-26, the red blood cell cholinesterase activities of [fasted] males

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treated with Dibrom at 2 or 10 mg/kg/day were 67% and 58% of the control values, respectively, whereas at week-52 the activities were 87% and 79% of the control values. For the [fasted] females, only the week-52 value for those treated at 10 mg/kg/day showed evidence of inhibition of cholinesterase activity to a level of 74% of the control value."

Conclusions: [This is an interim report, and no conclusions can be drawn before the final report is received. In their covering letter, the registrant, Chevron Chemical Co., (Richmond, CA) noted that the in-life portion of the study has been completed, with the final report due to be submitted by the May, 1985 reporting deadline.]

Irving Mauer, Geneticist
Toxicology Branch/HED (TS-769)

10/24/83

TS-769:th:TOX/HED:IMauer:10-19-83:card #2