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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: NALED - Company response to evaluation of previously submitted toxicology study, submitted under Accession No. 262551.

EPA ID #239-1633 Caswell 586

To: Wm. Miller/G. Otakie, PM 16
Registration Division (TS-767)

From: Irving Mauer, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

Thru: Jane E. Harris, Ph.D., Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769)

Registrant: Chevron Chemical Company, Richmond CA

Action Requested (660): Appraise company response of April 25, 1986, to TB review and evaluation of the following rabbit teratology study:

"Teratology Study in Rabbits with Chevron Naled Technical (SX-1397). SOCAL 2206. February 28, 1985, S-2193". (Submitted under EPA Accession No. 257458), and CORE-graded SUPPLEMENTARY because the highest dose tested did not elicit any maternal or fetal toxicity, and methods for fetal visceral/skeletal examination were not cited by reference nor adequately described (TB DATA REVIEW, under cover memo: Mauer to Miller, 03/20/86, TB Document No. 005000).

Company Submission: With its response of April 25, 1986, the registrant has submitted the following (Accession No. 262551):

(1) Cover Letter - Dated April 25, 1986 ——— (REF. -1 of submission)

(2) Chevron Environmental Health Center's Response to the U.S. Environmental Protection Agency's Data Review of "Teratology Study in Rabbits with Chevron Naled Technical (SX-1397)" (EPA Accession No.: 257458) March 20, 1985 ——— (REF. -2)

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(3) Pilot Teratology Study in Rabbits with Chevron Naled Technical (SX-1397) ---------- (REF.- 3)

(4) The Acute Dermal Toxicity of Chevron Naled Technical (SX-1397) in Adult Male and Female Rabbits ---------- (REF.- 4)

Items 1 through 3 (above):

TB Conclusions: The Agency's first concern was that the HDT elicited neither maternal nor fetal effects. In REF-2, the registrant asserts that the HDT in the main study was based upon data generated in a pilot study (provided as REF-3 of this submission --- see below for TB appraisal), specifically "excessive maternal toxicity observed at dose levels of 10, 20 and 40 mg/kg/day," namely: Of 4 animals dosed at 40 mg/kg/day, one died and 3 manifested marked cholinergic signs (hence this dose level was terminated); of 4 does dosed at 20 mg/kg/day, 2 died and 2 showed marked cholinergic effects (this level also terminated); while no deaths and marked cholinergic signs were observed in all 8 does dosed at 10 mg/kg/day (including one abortion on gestation day 21). At the next lowest dose level (2 mg/kg/day), 3 animals displayed transitory, mild cholinergic effects (rapid breathing on gestation days 11 thru 13; "loose stool" in one or two early in pregnancy and/or constipation toward the end of gestation).

The registrant claims these clinical effects are consistent with those observed in an acute dermal toxicity study conducted in rabbits (and likewise submitted here as REF-4), but at doses ranging from 125 to 615 mg/kg (LD_{50} calculated as 390 mg/kg for males and 360 mg/kg for females). Thus it is the registrant's opinion that ".... test animals in the full teratology study were challenged with a maximum or near maximum dose level at 8 mg/kg."

The Agency's second concern was the lack of citation or adequate description for fetal visceral/skeletal examination. The registrant has responded in REF.-2 as follows:

"Visceral examinations were performed using the technique described by Staples (Detection of visceral alterations in mammalian fetuses. Teratology 9: A37-A38, 1974). This includes a detailed examination under a dissecting microscope of the organs in the thoracic cavity, with particular concern for the heart and major vessels, as well as the organs within the abdominal cavity. A transverse cut through the parietal bones allows examination of the fetal brain.

"Skeletons are stained with Alizarin red S following the method of Staples and Schnell (Refinements in rapid clearing technic in the KOH-Alizarin red S method for fetal bone. Stain Technology 39: 61-63, 1964). The skeletal system is evaluated for number of bones, conformation, symmetry, alignment and degree of ossification".

The Agency is satisfied with these responses and citations, hence the deficiencies regarding the two issues (the MTD, and lack of visceral/skeletal descriptions) are removed.

In summary, the CORE classification on S-2193 is upgraded to MINIMUM, based upon the closeness of the HDT to a minimally toxic dose, as demonstrated in the pilot study.

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TOXICOLOGY BRANCH: DATA REVIEW

CHEMICAL: NALED

Caswell: 586
EPA Chem.#: 034401

STUDY TYPE: Range-finding teratology study.

CITATION: Pilot Teratology Study in Rabbits with Chevron Naled Technical (SX-1397), Socal 2194

ACCESSION NO: 262551

SPONSOR/TESTING LAB.: Chevron/Chevron Environmental Health Center, Inc., Richmond CA

STUDY NO./DATE: S-2224/January 24, 1985

TEST MATERIAL: SX-1397, Chevron Naled Technical (DIBROM®), 92.5% ai, a clear colorless liquid, suspended in CMC-Na for oral intubation.

PROCEDURES:

Five groups of young adult (6 months old) NZ White SPF female rabbits (8 per group) were artifically inseminated (2 animals per group daily for 4 days) following HCG stimulation, and administered test material from day-7 through day-19 of presumed gestation at daily oral dose levels of 0 (CMC vehicle, 5 ml/kg), 0.2, 2.0, 10 and 40/20 mg/kg (Groups I through V, respectively). The investigators report that on days-11 through -14, Group III animals (2 mg/kg/day) may have been dosed at the Group IV level (10 mg/kg/day). Animals were observed twice daily throughout gestation, weighed daily during treatment and on days-24 and 29, and sacrificed on day-29 of presumed gestation. Reproductive values of does and fetal evaluations were recorded by stated, "standard operating procedures", but no statistical analysis were performed (due to the small numbers per group).

Results: Of 4 Group V females dosed at 40 mg/kg/day, one died and 3 manifested "marked cholinergic signs" (muscle tremors, loss of coordination, etc); hence this dose level was terminated. Necropsy was negative among these high-dose animals, and "pregnancy status could not be determined". The remaining 4 Group IV animals dosed at 20 mg/kg/day also manifested severe toxicity (2 deaths plus 2 with marked cholinergic effects), and this dose level was also terminated (pregnancy status likewise was undeterminable).

All Group IV does (10 mg/kg/day) were reported to show one or more signs of moderate to severe OP toxicity (hypersensitivity to touch or sound, wobbling or loss of coordination, dyspnea, muscle tremors, salivation, and constricted pupils) throughout the dosing period, but none died. A few (3/8) animals in Group III (2 mg/kg/day) showed less severe cholinergic effects only during the mid-part of the dosing period (days-11 through 14) but, as the authors noted this may have been the consequence of mis-dosing these animals at the Group IV level (10 mg/kg/day). No clinical signs were observed among animals of either Group I (vehicle only) or Group II (0.2 mg/kg/day Naled). One abortion (1 fetus plus 1 resorption) was recorded, from a Group IV doe on day-21 of gestation; necropsy revealed 12 corpora lutea plus 2 empty implantation sites. Resorptions were reported in only one animal, a Group II (0.2 mg/kg) doe involving 12.5% of the litter, but no premature deliveries or dead fetuses in any group. No changes from control values were recorded in surviving test groups for mean body weights or food consumption, and no compound-related gross observations or histological alterations found. Pregnancy rates were comparable, and low, in all groups (not more more than 2/8), attributed by the authors to poor sperm survival ~~survival~~ (from the single bank of pooled sperm collected from bucks) due to the length of time between collection and insemination.

A decrease in mean fetal weight was recorded among Group IV litters [representing, however only 2 successful pregnancies], but no compound-related external gross malformations or skeletal variations [none would have been significant in any event due to the small sample sizes].

Conclusions: The authors conclude that ".... Chevron Naled Technical at 10 mg/kg/day (Group IV) produced maternal toxic effects (cholinergic signs) and fetal toxic effects (decreased fetal weight)".

TB Evaluations: CORE-SUPPLEMENTARY DATA (range - finding).