7-12-85

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

004556

JUL 12 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of toxicology studies with Technical Bolero®
EPA Reg. 239-2431
Accessions No. 256011 thru 256022
Caswell No. 207 DA

TO: Richard Mountfort, PM #23
Registration Division (TS-767C)

FROM: Quang Q. Bui, Ph.D. Quang Bui 7/11/85
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Laurence D. Chitlik, D.A.B.T. Winnie Testers for L DC., 7-11-85
Section Head, Section V
Toxicology Branch/HED (TS-769C)

and

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant:
Chevron Chemical Company
940 Hensley Street
Richmond, CA. 94804

Action Requested:

Review of a 2 generation reproduction study in rats, a spermhead morphology and sperm count study in rats, and an addendum to the rat chronic/oncogenic study with Technical Bolero®.

Recommendation:

A. It is recommended that the 2-generation reproduction study in rats (Bio/dynamics #82-2615) be classified as Core Supplementary Data. The control F2b pregnancy index (53.6%) and male fertility index (60%) were unacceptable low and, hence, questions must be raised as to the scientific integrity of the study. Certainly, these control data could not be used as valid reference data to make meaningful comparisons with the treatment groups.

Further, the litter information (mean values - Table 13 which is attached as page 11 of this memo) for the F1 ->F2a control was erroneously reported (see page 13 of this memo). The registrant is requested to submit an addendum to Table 13 and to provide clarification for the "missing pups" discussed on page 13 of this memo.

An increase in the incidence of cortical adenomas of the adrenal glands was found in F1 females dosed with 40 mg/kg/day Technical Bolero (5/30 animals). This finding is of concern since this neoplasm was also found in 1/5 F2a adult females (#4580) of the 40 mg/kg group after only 90 days of exposure. These adrenal gland cortical adenomas are unlikely to be of spontaneous origin due to their early appearance and their rare historical occurrence in Charles River rats (personal communication with Dr. L. Kasza, Toxicology Branch pathologist).

The reproductive NOEL and LEL cannot be determined at the present time. The registrant is requested to provide additional data and/or clarification relative to:

1. Corrected Table 13.
2. Unacceptable low F1 ->F2b control male fertility index and female pregnancy index.
3. Historical control incidence for cortical adenomas of the adrenal glands.
4. In light of several findings in the kidneys (chronic nephritis, tubular degeneration,...) and adrenal glands (cortical adenomas) of the F2a adults, it is suggested that histopathologic examinations of the F2a adults should be extended to all animals (30 instead of 5 as performed in this study).
5. High incidence of "missing pups" in the F1 and F2a generations of the 40 mg/kg group.

B. The "spermhead morphology and sperm count" study (Litton Bionetics #22204) is classified as Core Supplementary Data. The small number of animals investigated precluded a meaningful statistical analysis. However, a positive trend increase in spermhead abnormalities was still suggested from the data submitted.

C. The chronic/oncogenic study in rats (Life Science Research #84/KC1045/579) remains classified as Core Supplementary Data although the following two issues previously raised by the EPA reviewer (memo of 2/15/85) were rectified by the registrant:

1. Results were provided for the test chemical analyses performed at different intervals throughout the study.
2. Submission of final histopathologic reports rather than a draft report.

However, the registrant is still requested to provide clarification and/or submission of additional data relative to:

1. Identical cholinesterase activity values noted for different animals.
2. Significant differences in cholinesterase activity values noted between males and females of the same group.
3. Sensitivity of the test methods used to determine urinary protein.
4. Historical control data for testicular interstitial cell adenomas and pancreatic islet cell adenomas.

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STUDY REVIEW

Chemical: Bolero - Thiobencarb
Test Material: Technical Bolero - 95.3%
Study/Action Type: Chronic/Oncogenic in rats

STUDY IDENTIFICATION:
"Technical Bolero: Combined Oncogenicity and Toxicity Study in Dietary Administration to the Rats" - Amended Report

Testing Facility: Life Science Research Ltd.,
Amended Report No.: 84/KCI045/579
Amended Date: October 18, 1984
Study Director: H.A.Cummins
Accession No.: 256011 thru 256016

Reviewed by: Quang Q. Bui, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Approved by: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)

Background Information

This study was previously submitted by the registrant under Report No. 83/KCI045/248, dated 9/7/84, Accession Nos: 255042 thru 255046 and was reviewed by the Agency (Dr. Bui's memo of 2/15/85).

In his review of 2/15/85, the EPA reviewer classified this study as Core Supplementary Data pending the submission of the following information:

1. Clarification concerning:
   a. Identical cholinesterase activity values noted for different animals.
   b. Significant differences in cholinesterase activity values noted between males and females of the same group.
   c. Sensitivity of the test methods used to determine urinary protein.

2. Additional data for:
   a. Results of the test chemical analyses performed at different intervals throughout the study.
   b. "Final" histopathologic reports (only draft histopathologic reports were submitted)
   c. Historical control data for testicular interstitial cell adenomas and pancreatic islet cell adenomas.

In this action, an amended final report and a signed Quality Assurance Statement were submitted for review.

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RESULTS

The purity of Technical Bolero used was analyzed by the sponsor at different intervals throughout the study: weeks 25, 51, 78, and 104. Respective results of 95.3, 95.7, 95.6, and 95.3% were reported. However, confirming data for these analyses were not included in the study submitted on 9/7/84.

In this action, these data are now available (Accession No. 256011). Examination of the analytical data reveals that the results previously reported are correct. These data adequately answer Issue #2a mentioned above.

"Final" histopathologic reports approved and signed by the staff pathologists are included in this amended final report. Examination of the "final" histopathologic reports reveals no differences from the previously submitted "draft" reports. All findings noted in the draft report are confirmed.

The amended final report satisfactorily rectifies Issue #2b mentioned above.

CONCLUSION/RECOMMENDATION

It is recommended that this study remain classified as Core Supplementary Data pending the submission of additional data relating to Issues # 1a, 1b, 1c, and 2c. Issues #2a and 2b have been adequately addressed by the registrant by this submission.