6-23-86

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

005207

JUN 23 [redacted]

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of additional data pertaining to a 1-year dog feeding study with Thiobencarb (Bolero).
EPA No. 239-2431 Caswell No. 207 DA

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

FROM: Quang Q. Bui, PhD.,
Section V, Toxicology Branch Quang Q Bui 6/16/86
Hazard Evaluation Division (TS-769C)

THRU: Laurence D. Chitlik, DABT., W. Testers for L. Chitlik 6-16-86
Head, Section V
Toxicology Branch/HED (TS-769C)
and
Theodore M. Farber, PhD., 6/23/86
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Chevron Chemical Co.,
940 Hensley St.,
Richmond, CA. 94804

Action Requested:

Review additional data submitted by the registrant pertaining to a 1-year dog feeding study (IRDC #415-042).

Background Information:

A one-year subchronic oral toxicity study in dogs (IRDC #415-042) was previously submitted by the registrant under Accession No. 257362 and was reviewed by the Agency on 10/23/85 (memo of Q. Bui to R. Mountfort). The study was classified as Core Supplementary Data pending the submission of data relative to:

1. Purity of the test material used
2. Diet preparation
3. Correction of alanine aminotransferase level for control female #4688
4. Historical control range for cholesterol level

In this action, the registrant submitted additional data and/or provided clarification as requested by the Agency.

1. Purity of the test material

Page 11 of the final report has been revised by the registrant and now includes the purity of the test material (96.3% a.i.) used in this one-year dog study.

The registrant has adequately rectified this issue.

2. Dosage preparation data

This reviewer in his memo of 10/23/85 indicated that "in the absence of dosage preparation data, it is unclear as to whether the dose levels used in this study represent the technical material or have been corrected to 100% purity".

The revised page 11 of the final report now indicates "The doses were prepared on the basis of the test material supplied and were not corrected for purity".

The registrant has adequately rectified this issue.

3. Alanine aminotransferase level

During the evaluation of this 1-year dog study, this reviewer noted that "a value of 355 IU/L was found for animal #4688 at week 25 and apparently is a typographical error" and requested the testing facility to clarify.

The testing laboratory, IRDC, indicated that the value presented for control female #4688 at week 25 (355 IU/L) was verified and found correct.

To this reviewer, the registrant has adequately rectified this issue since this is only a minor issue and would not alter the conclusions reached during review of the study.

4. Cholesterol levels

Apparent trend increases in cholesterol values were found in the treated groups with a statistically significant difference found at the 64 mg/kg dosage level (HDT). The lack of statistical differences at the 1 and 8 mg/kg dosage levels may be attributed to the large variations found and the small number of animals per group (6 per sex/dose). In the males at final sacrifice, the cholesterol levels of the 0, 1, 8, and 64 mg/kg groups were, respectively, 157, 191, 190, and 227 mg/dl. Respective cholesterol levels of 173, 232, 243, and 281 were found in females. To fully assess the biological significance of these findings, historical control ranges for cholesterol were requested by the Agency.

In this action, the registrant submitted the cholesterol ranges found at the testing facility for both males and females:

Males: N = 146, Mean = 168, Range = 110-227 ($\pm$ 2 S.D.)

Females: N = 142, Mean = 188, Range = 104-272 ($\pm$ 2 S.D.)

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CONCLUSION AND RECOMMENDATION

The registrant has adequately rectified all four issues mentioned in the Agency review (memo of Q. Bui to R. Mountford, dated 10/23/85) of the 1-year dog study with Thiobencarb (IRDC No. 415-042, 3/20/85).

It is recommended that this study be upgraded to Core Minimum Data with the following findings:

1. Biologically significant depression in plasma cholinesterase levels (greater than 20% inhibition) was found in both males and females of the 8 and 64 mg/kg groups throughout the entire investigation. Decreases in RBC cholinesterase levels were noted in both 64 mg/kg males and females. However, no changes in brain cholinesterase activities were noted in either males or females at study termination.

   Plasma ChE NOEL = 1 mg/kg (LDT) ; Plasma ChE LEL = 8 mg/kg
   RBC ChE NOEL = 8 mg/kg ; RBC ChE LEL = 64 mg/kg (HDT)
   Brain ChE NOEL = 64 mg/kg (HDT)

2. Significant decreases in serum albumin and protein were noted in both 64 mg/kg males and females and in 8 mg/kg males. In the absence of consistent effects, the biological significance of this decrease in males at 8 mg/kg is not known with certainty. Decreased erythrocyte counts and hemoglobin levels associated with a reduction in hematocrit were noted in both males and females in the 64 mg/kg group. Significant decreases in alanine aminotransferase and cholesterol levels were found for animals in the 64 mg/kg group. Compound-related increases in both the absolute and relative kidney and liver weights were found at the 64 mg/kg dosage level. Under the conditions of this study, the systemic NOEL is established at 8 mg/kg with the systemic LEL at 64 mg/kg.