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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Ethoprop: Review of Chronic Toxicity/Oncogenicity,
Reproduction and Teratology Studies. EPA Identification
No. 359-694.

Tox Chem File No. 434C

TO: Mr. William Miller, PM Team #16
Registration Division

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K-LH 2/25/87

ABK 2/25/87

Alfa 2/26/87

Attached are three Dynamac and one Mitre DERs for studies conducted with Ethoprop technical. Each review is accompanied by a Toxicology Branch (TB) addendum. These addenda were written because the Tox Branch reviewer was not in total agreement with Dynamac's or Mitre's findings and/or the TB reviewer wanted the sponsor to clearly know what additional data/information were to be provided for those studies that were not sufficient to support the registration of Ethoprop. Since the studies were submitted to the agency some time ago, the TB reviewer was of the opinion that, in this case, writing the addenda would expedite the review process.

The studies reviewed and their current core classifications are indicated below:

1. Ethoprop Teratogenicity Study in Rabbits, Study No. 230-233, by Hazleton Laboratories America, Inc., Vienna, VA., 8/10/81. EPA Accession No. 263801. Core classification Supplementary. NOELs/LOELs for developmental and maternal toxicity in this study cannot be estimated at this time since more data are required for evaluation.

2. Ethoprop Technical Three-Generation Reproduction Study in Rats, Study No. 413-858-41, by Gulf South Research Institute, New Iberia, LA, 12/3/80. EPA Accession No. 263796. Core classification Supplementary. NOELs/LOELs for reproductive effects and maternal toxicity cannot be estimated at this time since more data are required for evaluation.
3. Ethoprop Toxicity/Oncogenicity Study in Rats, Study No. 413-858-41, by Gulf South Research Institute, New Iberia, LA, 1/20/83. EPA Accession No's. 263802-263807. The Core Classification of the chronic feeding portion of this study is Supplementary. It cannot be upgraded since no NOEL for cholinesterase inhibition was observed. The LOEL for cholinesterase inhibition (brain, serum) was the lowest dose tested. More data/information concerning the chronic toxicity portion of this study has been requested in the addenda and a satisfactory response to this request is still required. The oncogenicity portion of this study is also considered to be Core Supplementary but this portion of the study may be upgraded pending the sponsor's satisfactory response to issues indicated in the Tox Branch addenda. Until these concerns are satisfactorily addressed, a NOEL/LOEL for oncogenicity cannot be estimated.
4. Ethoprop. Chronic Oncogenic Evaluation of Ethoprop with B6C3F1 Mice (78 weeks), Study No. 5-5849, by Food and Drug Research Labs, 1/26/83. EPA Accession No's. 263797-263800. There was no direct evidence to suggest that Ethoprop was an oncogen in this study under the planned dosing regimen tested, however a Maximum Tolerated Dose could not be ascertained (see discussion in appropriate addendum). Therefore, the Core Classification is judged to be Supplementary and a new mouse oncogenicity study is requested unless the sponsor can provide a satisfactory argument that the doses tested in this study are consistent with the concept of Maximum Tolerated Dose. No NOEL could be established for cholinesterase inhibition and the LOEL for this parameter was 15 ppm (the LTD).

Two other types of studies are also requested in order to address the issue of potential ocular toxicity. The appropriate addendum details the requirements for the conduct of these studies.

The sponsor should specify the purity of the Ethoprop technical used to perform the mouse oncogenicity study.

5. The sponsor is asked if the technical material tested in the three-generation reproduction study, the rabbit teratology study, the rat chronic oncogenicity study, and the mouse oncogenicity study is the same as that technical being currently marketed. If not, the sponsor shall detail the similarities and differences.

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ETHOPROP: ADDENDUM TO DYNAMAC'S REVIEW OF A TERATOGENICITY STUDY IN RABBITS (Study conducted by Hazleton Laboratories America, Inc., Vienna, VA, report dated 8/10/81, Study No. 230-233). EPA Record No. 103099. Accession No. 263801.

Introduction

Having read the Dynamac reviewer's report on the Ethoprop Teratogenicity Study in Rabbits, this Toxicology Branch (TB) reviewer cannot concur fully with the conclusions and recommendations written therein. It is the purpose of this addendum to indicate major points of concurrence and non-concurrence between the TB reviewer and the Dynamac reviewer with regard to the findings in the study and to inform the sponsor what additional information needs to be provided to the agency in order that the study might be further evaluated. With regard to any additional data the sponsor may be asked to submit, this addendum supercedes Dynamac's report.

Synopsis of Dynamac Findings

The Dynamac report indicated the following conclusions/recommendations:

1. a complete evaluation of the possible maternal and developmental effects of the test material could not be made due to inadequate data reporting;
2. no biologically significant maternal effects resulted from administration of the test material; therefore, a maternal LOEL could not be established;
3. LOELs for embryotoxicity and teratogenicity were estimated;
4. testing at additional dose levels was recommended.

Toxicology Branch Findings

Issue of Inadequate Data Reporting

This reviewer would agree that judgements relating to possible maternal and developmental effects of the test material are hampered by inadequate data reporting by the study authors. However, the sponsor should (and will) be given the opportunity to address (and hopefully resolve) any concerns that have arisen with regard to the study. Requests for additional data and/or data tabulations will be made in the paragraphs below. Tabulated data should be in an easily readable form which would facilitate the review process.

Issue of Maternal Toxicity

1. It would appear from the data presented that administration of the test material did result in effects indicative of a compound-related decrement in maternal body weight gain. However, some additional data and information are (is) required to evaluate this parameter more thoroughly before an attempt can be made to establish a maternal NOEL or LOEL.
 - a. Please describe the daily dosing regimen for the main study and the pilot study, particularly as it relates to the daily observations, feeding schedule, and anorexia.
 - b. By what criteria were animals judged to be anorexic?
 - c. Please tabulate daily incidences of anorexia for each animal. (Each animal should be designated by its unique number in the tabulations).
 - d. Food consumption data which would aid in substantiating observations of anorexia and would be helpful in evaluating the effects of the test material on maternal weight gain were not presented in the study report. If food intake was quantified, please provide this data. If not, please justify why it was not measured.
 - e. The large intra-group variation in maternal body weights (i.e. at study initiation, there was a weight range of approximately 1.2 kg or more in 3 of the test groups) may have served to effectively dilute treatment-related inter-group differences in maternal body weight gains during the study. This may account, at least in part, for the lack of statistical significance in the dose-related decreases in maternal body weight gains observed between treated and control groups over the dosing period. From a scientific standpoint, why were animals with such a wide range of body weights selected for this study?
2. Other data, not previously provided, that would be useful in evaluating potential maternal (and developmental) toxicity in this study are requested below:
 - a. Please tabulate and present daily clinical observations and necropsy findings for each dam/doe since these individual animal data will be useful in evaluating maternal health and only a summary table of these findings (in which no animal numbers were specified) was submitted in the study report.

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- b. No details were provided for the pilot study that was used as a basis for dose selection in this study. The Hazleton report indicated that a number of deaths occurred in the pilot study but did not indicate whether they were treatment-related, nor were any accompanying clinical signs delineated. Interestingly, it was reported that 2 out of 4 animals did not survive a dose of 1 mg/kg/day which is one-half the high dose used in the present study. A summary of the findings in the pilot study should be submitted, including the pregnancy status of the animals, clinical signs, times of deaths, body weights, food consumption, and litter and fetal parameters, dosing regimen, etc.
3. Note: There would not appear to be a need to "test Ethoprop at higher dose levels capable of producing more significant maternal effects", as indicated in the Dynamac report if, in fact, there was enough evidence to support that developmental toxicity had occurred (even in the absence of maternal toxicity).

Issue of Developmental Toxicity

The incidence data presented do not provide any strong evidence that the anomalies noted in this study were treatment-related. Considering that visceral and skeletal anomalies per number of fetuses examined in the low, mid, and high dose groups respectively appeared to be 4/100, 2/96, and 1/93, a zero incidence in the control group of 75 fetuses does not readily suggest a teratogenic effect. Although, there does appear to have been an increase in skeletal variations in treated groups compared to controls, it would be premature to make conclusions regarding developmental toxicity in this study or to estimate a NOEL or LOEL for developmental effects. This is because no formal tabulations of individual fetal or litter data were submitted in the study report and such data are necessary to a thoroughly evaluate potential embryotoxic, fetotoxic, and teratogenic effects of the test material. Tox Branch needs to be able to correlate a particular fetal datum or abnormality with a specific fetus in a given litter. Therefore, additional data/information is requested as indicated below.

- a. provide the criteria for designating an abnormality as a malformation, anomaly, or variation;
- b. the position of each fetus in the uterine horns of each dam should be provided along with a complete description of any abnormality found for that fetus and the fetus' body weight and crown-to-rump length. Any abnormality should be appropriately designated as a skeletal or visceral malformation, anomaly, or variation.
- c. complete individual litter data for each dam should also be submitted. The fate of each implant in the uterine horns of a particular doe/dam should be tabulated. Early and late resorptions and instances of spontaneous abortions, etc. should be differentiated.

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- d. To better evaluate the types of fetal defects noted, historical control data for all malformations, anomalies, and variations (soft tissue and skeletal) observed in this study is requested. The data should come from the same laboratory in which the present study was conducted and should pertain to the same species/strain used in the present study. In addition, the data should encompass the time two years prior to the study and, if possible, the years following completion of the study. Tabulations should include the following: the number of litters with a finding per the number of litters examined and the number of fetuses with a finding per the number of fetuses examined. Other corresponding litter and fetal data should be provided (i.e. implants, early and late resorptions, number of live births, etc.). Corresponding maternal weight gain data should also be submitted. The vehicle used in historical control studies should be specified.

- e. The method used in this study to determine the pregnancy status of uteri and verify the number of implants is requested.

Additional Data

Data are needed to indicate the purity, concentration, and stability of the solutions of the test material used in dosing.

Issue of Necessity for Additional Testing

A new study is not required at this time. However, as delineated in full in the paragraphs above, additional data/information is required of the sponsor. TB will re-evaluate the Ethoprop teratology study in rabbits after the requested data have been submitted.

Conclusion/Recommendation

Based on the data submitted and evaluated thus far, this study does not fully meet regulatory requirements and has been found by Toxicology Branch to be Core Supplementary. However, the study may be upgraded pending receipt and evaluation of data from the sponsor which can satisfactorily resolve the concerns raised in this addendum. The data and information required by TB are delineated under the section of this addendum entitled "Toxicology Branch Findings". Estimations of maternal and developmental LOELs and/or NOELs are considered by TB to be premature at this time.

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