REVIEWER

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

OCT 9 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Terbutryn - Registrant's Minutes of Meeting Held on July 23, 1987.
EPA ID No: 100-540
Tox. Br. Proj. No.: 7-1075 Tox. Chem. No.: 125D

To: Robert Taylor
James Yowell
Product Manager # 25
Registration Division (TS-767C)

From: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 10/7/87
Section Head, Section VI
Toxicology Branch/HED (TS769C)

Thru: Theodore M. Farber, Ph.D., Chief
Toxicology Branch/HED (TS-769C) 10/8/87

Action Requested: Comment on registrant's minutes of meeting held on July 23, 1987 regarding the registration standard on terbutryn.

Comments:

1. Special Field Dissipation Study with Bromide Tracer

This section should be commented on by Residue Chemistry Branch.

2. Mutagenicity Requirement for Rat Sister Chromatid Exchange Study

The registrant has asked that the requirement for a sister chromatid exchange study in the rat be waived. They argue that they have already submitted an acceptable chromosomal aberration study in the Chinese hamster, that they are conducting a micronucleus test in the rat which also falls into the same category for mutagenicity testing and that the sister chromatid assay is unreliable for reasons outlined in their submission.

Tox. Branch Comments:

The assay for sister chromatid exchange in the rat was requested in the registatration standard on terbutryn to obtain a better understanding of the mechanism of oncogenesis of terbutryn in the rat. Since the registrant is conducting a micronucleus test in the rat, Toxicology Branch upon reconsideration can waive the requirement for a sister chromatid

exchange assay in the rat. We would like to note, however, that this assay could also fit into the category of other as listed in the Part 158 requirements for mutagenicity assays.

3. Special Rat Chronic Feeding Study

The registrant is requesting that "the agency re-review the chronic portion of the rat chronic feeding study based on information provided during the meeting". They also state that they are "reanalysing the data pursuant to the comments of C. J. Nelson (the EPA statistician present ar the meeting).

Tox. Branch Comments:

The Tox. Branch will rereview the chronic portion of the rat chronic feeding study, especially with regards to hematological parameters, when the registrant submits their reanalysis of the data. The historical control data presented in this submission on clinical laboratory values on Charles River CD rats will also be considered during the rereview. When this review is completed we will be able to determine whether or not a repeat of the chronic portion of the study will be necessary in order to determine a NOEL for hematological effects due to terbutryn in the CD rat.

4. Terbutryn Risk Assessment

a. The registrant is arguing that that the MTD was exceeded in the chronic rat feeding study at 3000 ppm. This was the dose at which a statistically significant increase in tumors was seen in male and female CD rat at several different sites. At 3000 ppm, according to their argument, body weight gain was reduced in both sexes from 23 to 46%. The agency's draft paper on the MTD states that one of the parameters that would indicate an MTD has been attained in an oncogenicity study is a significant decrease in cumulative body weight gain approaching 10% in the first 90 days.

Tox. Branch Comments:

As we stated in the meeting, we agree that according to the draft paper on the MTD, the MTD had been exceeded at 3000 ppm in female rats and was slightly exceeded in male rats. However, no increases in mortality were seen at this dosage level by the end of the study indicating that survival was not affected by this dosage level. Furthermore, 3000 ppm was well tolerated by other measurements such as the fact that there were no clinical signs toxicity. The mid dose (300 ppm) in this study did not approach an MTD by the body weight gain criteria nor any other criteria oulined in the MTD paper, so that this dose cannot be considered an adequate dose for testing the oncogenicity of terbutryn. Overall, we do not feel that the body weight gain reduction seen at the 3000 ppm dosage level compromised the results obtained regarding the oncogenicity of terbutryn.

We also noted during the meeting, that dosage selection for this study was poor. For example, the doses chosen were too far apart and were not based on the results of a 90 day feeding study.

b. The registrant also feels strongly that a quantitative risk assessment on terbutryn tumor data is not warranted. They feel that a qualitative risk assessment should be performed using a safety factor. They argue that tumors were seen only at a dose that exceeded the MTD, that terbutryn was negative for mutagenicity in a battery of mutagenicity assays, that it was negative for oncogenicity in the mouse and that other thiomethyl triazines have not been shown to be oncogenic in the rat or mouse. They also cite the SAP's classification of oxadiazon as a category C oncogen because of the lack of genotoxicity and because an oncogenic response in the rat occurred only when the MTD was exceeded.

The registrant does agree with the category C classification for terbutryn.

Tox. Branch Comments:

At the present time, Toxicology Branch feels that the category C classification with a risk assessment is warranted based upon the results obtained in the chronic rat study and as concluded by the Toxicology Peer Review Committee on June 11, 1987.

5. Special Packaging Requirement (Water Soluble Packaging)

Toxicology Branch cannot comment on this item.

6. Other points:

a. Toxicology Branch does not understand the registrant's comment on page 6 of the submission that "an erroneous tumor count number was utilized by the Agency in the terbutryn risk assessment which was 2 1/2 times lower than the correct tumor incidence".

b. There are several numbers in C-8 Table 4 that disagree with our numbers. Primarily the denominators for control (we show 6 less) and 3000 ppm (we show 8 less).