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

AUG 1 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Second Peer Review of Atrazine

From: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 7/7/88
Section Head, Section VI
Toxicology Branch/HED (TS-769C)

To: Robert Taylor/Clare Grubbs
Product Manager #25
Registration Division (TS-767C)

and

Jude Andreasen
Special Review Branch
Registration Division (TS-767C)

The Toxicology Branch Peer Review Committee met on June 6, 1988 to discuss and reevaluate the weight of the evidence on the oncogenic potential of atrazine in light of the results of a recently submitted oncogenicity study in the mouse.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

Theodore M. Farber	Theodore M. Farber
William Burnam	William F Burnam
Reto Engler	Reto Engler
John A. Quest	John A. Quest
Esther Rinde	Esther Rinde
Judith W. Hauswirth	Judith W. Hauswirth
Lynnard Slaughter	L. J. Slaughter
Kerry Dearfield	Kerry F Dearfield
Richard Levy	

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Robert Beliles

2. Scientific Reviewers: (Non-committee members responsible for presentation of data; signature indicates technical accuracy of panel report.)

Sanford Bigelow

3. Peer Review Committee Members in Absentia: (Committee members who were not able to attend the discussion; signatures indicated concurrence with the overall conclusions of the Committee.)

Anne Barton

Richard Hill

Diane Beal

Marion Copley

B. Material Reviewed:

The material available for review consisted of a package prepared by Dr. Hauswirth containing a data evaluation report of a mouse oncogenicity study, a Draft peer review report of the first atrazine meeting of September 10, 1987, and a review of the available mutagenicity data on atrazine (Dr. K. Dearfield, memorandum dated April 26, 1988).

C. Background Information:

Atrazine was tentatively classified as a category C oncogen by the Toxicology Branch Peer Review Committee on September 10, 1987 based upon the results of a chronic toxicity/oncogenicity study in the Sprague-Dawley rat. According to the report:

> ....administration of atrazine to Sprague-Dawley rats was associated with an increased incidence of mammary gland fibroadenomas and adenocarcinomas in female rats. The increase in testicular interstitial cell tumors seen at the high dose in male rats was not considered to be treatment-related by the Committee since the incidence was within the historical control range and was seen at a dosage level that exceeded the MTD. Atrazine has not shown any mutagenic activity in any assays available to the Committee; however, it is structurally related to propazine and terbutryn which induce mammary gland tumors in female rats and have been classified as category C oncogens.

D. Evaluation of Mouse Oncogenicity Study:

Ref.: Atrazine - technical: 91-week oral carcinogenicity study in mice. J.R. Hazelette and J. D. Green. Conducted by Divison of Toxicology

Ciba-Geigy Corp., Summit, NJ. Study No.: 842120. MRID No. 404313-02.

CD-1 [Crl: Cdl (ICR) BR] mice were placed on diets containing 0, 10, 300, 1500 and 3000 ppm atrazine. The number of mice in each group was as follows: 60 for the control, 300, 1500, and 3000 ppm female groups, 59 for the 10 ppm female group, 60 for the 10, 300 and 1500 ppm male groups, 59 for the male control group and 58 for the male 3000 ppm group.

This study has been classified as a Core guideline study with a NOEL of 300 ppm (45 mg/kg/day) and a LEL of 1500 ppm (225 mg/kg/day) based upon decreases of 23.5% and 11% in mean body weight gain found at 91 weeks in male and female mice, respectively and an increased incidence of cardiac thrombi found in female mice. Based upon the depression in body weight gain seen in male and female mice at 1500 and 3000 ppm and increased mortality of female mice at 3000 ppm, adequate dosage levels were tested to determine the oncogenic potential of atrazine in the mouse. No oncogenic effects were noted at any level that could be attributed to atrazine.

E. Additional Information:

The registrant submitted a position paper on the available mutagenicity data on atrazine, including studies conducted by the registrant and those found in the open literaure. This paper was written by Dr. D. Brusick and was reviewed by Dr. K. Dearfield in Toxicology Branch.

Dr. Dearfield concluded:

> It appears from a review of the many atrazine studies available to OPP from submissions and through the published literature that atrazine does not induce genotoxic activity in in vitro studies ± mammalian activation systems. However, there does appear to be genotoxic potential by atrazine as revealed in in vivo studies.

He noted that further mutagenicity testing on atrazine is required to satisfy the guideline requirements in this area and that atrazine is a plant activated promutagen suggesting that testing of isolated plant metabolites be conducted. Dr. Hauswirth noted that the registrant has informed her that mutagenicity testing has been conducted on one plant metabolite and that they were about to submit this data.

F. Classification of Oncogenic Potential:

The Committee concluded that the new data presented on atrazine did not alter their conclusion that atrazine was a category C oncogen and that a quantification of risk should be performed as outlined in their June 6, 1988 report of the first peer review meeting on atrazine. The oncogenicity study in the CD-1 mouse was negative for oncogenicity and the review of the mutagenicity data base on atrazine did not provide information that would change this categorization.

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