



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

1-21-93

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Report of OPP RfD/Peer Review on Atrazine.
Caswell No. 063
CAS. No. 1912-24-9
EPA Chem Code: 080803
Reg. Group: List A (5 SRR)

FROM: George Z. Ghali, Ph.D. *G. Ghali*
Science Analysis Branch *1.21.93*
Health Effects Division (H7509C) *KLD*

TO: Robert Taylor, PM Team 25
Herbicide-Fungicide Branch
Registration Division (H7505C)
and
Jack Housenger, Chief
Special Review Branch
Special Review and Re-registration Division
(H7508W)

Thru: William L. Burnam, Chief *WLB*
Science Analysis Branch
Health Effects Division (H7509C)

On December 16, 1992 the Agency RfD Work Group held a conference call to discuss the atrazine file. OPP/HED representative in this conference included H. Spencer, H. Pettigrew, J. Rowe, M. Beringer, R. Whiting and G. Ghali. The Agency Work Group agreed with OPP/OW's evaluation and the RfD for atrazine was verified as 0.035 mg/kg/day.

The RfD was established based upon a no-observable effect level (NOEL) of 70 ppm (3.5 mg/kg/day) for body weight decrease in both sexes observed at 500 ppm (25 mg/kg/day) in a chronic feeding study in rats using an Uncertainty Factor (UF) of 100 to account for inter-species extrapolation and intra-species variability.

A. Individuals in Attendance

1. Peer Review Committee and Associates Present in One or More of the Atrazine Meetings (signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Karl Baetcke

Reto Engler

Marcia Van Gemert

Henry Spencer

Gary Burin

Roger Gardner

James Rowe

Stephen Dapson

George Ghali

Rick Whiting

William L Burnam
Karl A Baetcke
Reto Engler
Marcia Van Gemert
Henry Spencer
Gary Burin
Roger Gardner
James N. Rowe
Stephen C. Dapson
George Ghali
Rick Whiting

2. Scientific Reviewers (committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Henry Spencer

Hugh Pettigrew

Henry Spencer
Hugh Pettigrew

3. Others

Michael Beringer, Chemical Manager, CCB/HED/OPP

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield

Ruth Allen
James Karyia
Henry Spencer

Attachments

B. Background Information

The Reference Dose (RfD) for atrazine was first determined by the Health Effects Division RfD Committee on July 9, 1986 and verified by the Agency RfD Work Group on May 20, 1987. The RfD was reassessed by the HED RfD Committee on June 3, 1988 and subsequently verified by the Agency RfD Work Group on June 22, 1988 and once again on February 21, 1990. At that time the RfD value was calculated to be 0.005 mg/kg/day and was based upon a no-observable effect level (NOEL) of 0.5 mg/kg/day for decreased body weight in pups of the second generation on postnatal day 21 in a multi-generation reproduction study in rats (MRID No. 40431301), using an uncertainty factor (UF) of 100.

At the request of the registrant, Ciba-Geigy Corporation, and based on additional information submitted to the Agency by the registrant, the Health Effects Division of the Office of Pesticide Programs has reconsidered the NOEL/LEL previously established in the November 1987 review of the aforementioned rat reproduction study. In a recent evaluation of the same study, in light of the additional information provided (see memo's by H. Spencer, HED/OPP 12/23/1991 and H. Pettigrew, HED/OPP 12/10/1991), the NOEL was revised to 2.5 mg/kg/day. This NOEL was considered to be the most sensitive NOEL and was used as the basis for the RfD. The uncertainty factor remained unaffected, and the RfD was calculated to be 0.025 mg/kg/day.

On January 15, 1992 the HED RfD Committee met to consider these changes to the atrazine file before submission to the Agency RfD Work Group for verification and agreed that the NOEL/LEL should be changed as indicated and the RfD should be revised accordingly to reflect these changes.

On May 15, 1992 representatives from the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) and the Office of Water (OW) met to discuss the NOEL/LEL changes in the rat reproduction study and assess the impact of these changes on the RfD and on the Agency's overall position on this chemical.

In this meeting, Dr. H. Spencer presented OPP's position and answered questions relating to the reevaluation of the reproduction study, the subject of this meeting. Dr. Spencer indicated that, generally, effects on pups body weight in the first 14 days of the rat reproduction study might be regarded as reproductive effects since pups rely completely on nursing during the first two weeks. But effects seen on pups body weights in the third week should not be considered as such since they can not be attributed to nursing alone but also to feeding of pups on the treated diet since pups start feeding normally on about day 14 or 15. Therefore, OPP concluded that effects seen in pups in the third week in this study most probably are systemic effects resulting from the atrazine in the diet and not from the testing material in mother's milk.

According to Dr. Spencer's analysis of data, the decrease in body weight of pups of the second generation was statistically significant ($p = 0.05$) at the high-dose level (500 ppm or 25 mg/kg/day). Therefore, the "no-observable-effect level" in the study should be the middle-dose level (50 ppm or 2.5 mg/kg/day). Dr. Spencer indicated that in the analysis of body weight data, the changes in food intake of pups were taken into consideration along with the body weight changes in OPP's reevaluation. The biological significance of body weight decrease of pups and the actual magnitude of this decrease was not addressed.

Dr. H. Kahn, OW's lead statistician, presented the Office of Water's position on this issue. According to Dr. Kahn's analysis of data, the decrease in body weight of pups of the second generation was statistically significant at the middle dose level (50 ppm or 2.5 mg/kg/day). Therefore, the "no-observable effect level in this study, according to OW's analysis of data, should be 10 ppm or 0.5 mg/kg/day. Dr. Kahn, in his presentation, made a reference to an article by V. Chew published in Hort. Science, Vol.11 (4), August 1976.

In the meeting of May 15, representatives of both programs agreed that the biological significance of the issue at hand should be taken into consideration along with the statistical significance, and also agreed to exchange information needed to complete the evaluation before another meeting between the two programs could be scheduled to resolve outstanding issues.

Several meetings took place within HED/OPP to discuss, reassess and better define the nature of effects seen in the reproduction study with atrazine. A Work Group consisted of HED scientists with expertise in the area of developmental/reproductive toxicity and statistics met to address these issues. On September 23, 1992, the Work Group issued a report defining OPP/HED's position. The Work Group concluded that "HED does not believe that the difference in pup weight between the control group and 50 ppm F2 males at day 21 is biologically significant and HED also questions the statistical significance of the body weight changes". A copy of the Work Group memorandum is attached to this RfD report. Copies of this memorandum was also sent to OW a few days before the meeting of September 28, 1992.

On September 28, 1992 representatives from OPP/HED and OW met to discuss and finalize their position on the reproduction study and together decide on an appropriate end-point to establish an RfD for atrazine. Representatives of HED/OPP reiterated their position as stated in the HED Work Group memo of September 23, 1992 mentioned above. Representatives of the two programs agreed that the reproduction study in rats was not the most appropriate study to use to establish the RfD for atrazine, especially with an end-point (body weight decrease in the pups of F2 generation) that appears, most likely, to be a systemic effect rather than a

reproductive effect. Body weight decrease was observed and was better documented in the same species in both males and females in a long-term study in rats. Since the RfD by definition reflects a chronic exposure measure, the two programs felt that the use of the long-term study in rats would be most appropriate to establish an RfD for atrazine. Furthermore, the NOEL established in the long-term study in rats was also within the same range of NOEL's established in long-term feeding studies in other species. The RfD for atrazine was therefore established based upon a NOEL of 70 ppm (3.5 mg/kg/day) for body weight decrease in both sexes observed at 500 ppm (25 mg/kg/day) in the long term study in rats using an uncertainty factor of 100 to account for inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.035 mg/kg/day.

On December 16, 1992 the Agency RfD Work Group held a conference call to discuss the atrazine file. OPP/HED representative in this conference included H. Spencer, H. Pettigrew, J. Rowe, M. Beringer, R. Whiting and G. Ghali. The Agency Work Group agreed with OPP/OW's evaluation and the RfD for atrazine was verified as 0.035 mg/kg/day.