8-3-92

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cyanazine: Report of the RfD/Peer Review
Caswell No. 420
EPA Chem Code: 079401
CAS No. 115-29-7
Reg. Group: List A (6A)

FROM: George Z. [redacted] Ph.D. G. Z. [redacted] 8.3.92
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Robert Taylor, PM 25
Herbicide-Fungicide Branch
Registration Division (H7505C)

and

Lois Rossi, Chief
Reregistration Branch
Reregistration and Special Review Division (H7508)

The Health Effects Division RfD/Peer Review Committee met on March 12, 1992 to evaluate the existing data base for Cyanazine and determine whether the available data are adequate for the purpose of risk assessment in accordance with the current Agency's Guidelines and Standards.

This chemical has been classified by the HED Carcinogenicity Peer Review Committee as a Group C, possible human carcinogen. Quantification of human risk, using a low-dose extrapolation model (Q^1), was also recommended. Therefore, there was no need to discuss material relating to the carcinogenic potential of this chemical at this meeting. However, the chronic toxicity phase of the rat and mouse carcinogenicity studies was examined by the Committee.

Cyanazine was first evaluated by the HED RfD Committee on May 29, 1986 and an RfD had been verified by the Agency RfD Work Group on July 8, 1986. The RfD was reassessed by the HED RfD Committee on May 5, 1988 and an RfD was verified by the Agency RfD Work Group on May 25, 1988. At that time the RfD was based on a "no-observable effect level" of 0.625 mg/kg/day for reduced body

weight, body weight gain, hematological effects and reduced total protein, albumin and calcium in males and females observed at 2.5 mg/kg/day in a one-year feeding study in dogs, using an Uncertainty Factor of 100 to account for the intra- and inter-species differences, and an additional 3 to compensate for the lack of an adequate chronic toxicity study in rats.

Subsequently, a chronic toxicity study in rats was submitted to the Agency with a "no-observable effect level" of 0.20 and 0.26 mg/kg/day for males and females for body weight gain decrease in males and hyperactivity in females observed at 0.99 and 1.37 mg/kg/day in males and females respectively. The RfD was reassessed accordingly. **The HED RfD/Peer Review Committee recommended that an RfD be established on the basis of the "no-observable effect level" of 0.2 mg/kg/day demonstrated in the rat chronic toxicity study using an Uncertainty Factor of 100. On this basis, the RfD was calculated to be 0.002 mg/kg/day.**

The Committee was requested to evaluate a new multi-generation reproduction study in the rat which ~~has~~ had been submitted recently to the agency as a substitute for an older Core-supplementary study.

The Committee was also requested to address what appeared to be lack of a "no-observable effect level" for body weight changes in the mouse carcinogenicity study because of possible impact on the RfD determination. The one-liner indicated that the "no-observable effect level" in this study is equal to or less than 10 ppm (1.4 mg/kg/day). However, it was stated in the data evaluation records for this study that" The NOEL for systemic toxicity may be 10 ppm (LDT), although 3 to 7 percent body weight gain decreases were observed in females during most of the study".

There were several developmental toxicity studies available to the Committee. However, the Committee did not discuss any of them and made reference to the SAP report on the developmental toxicity issue indicating that the developmental toxicity issue has been adequately addressed in the SAP report as well as in several memos and reports by S. Dapson and Q. Bui.

A. Individuals in Attendance

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

- William Burnam
- Reto Engler
- Karl Baetcke
- Marcia Van Gemert
- Henry Spencer
- George Ghali
- Rick Whiting
- Gary Burin
- James Rowe
- Lawrence Chitlik
- Stephen Dapson
- Roger Gardner 8/14/92

2. Peer Review Members and Associates in Absentia (committee members and associates who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the committee).

Esther Rinde —

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

William Dykstra

B. Material Reviewed

The material available for review consisted of an RfD summary document and data evaluation records (DER's) of the following studies:

1. Bogdanffy, M. S. (1990). Combined chronic toxicity/oncogenicity study with cyanazine (INR-1957) 2-year feeding study in rats. Unpublished report prepared by Haskell Laboratory, submitted to the Agency by E. I. du Pont de Nemours and Company. Project No. 23-90, report dated May 11, 1990. MRID No. 41509902, HED Doc. No. 008280, 009353.

Core Classification: The study was originally classified as Core supplementary data (HED Doc No. 008280 and was then elevated by the respective toxicology branch to Core Guideline data (HED Doc No. 009353).

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer conclusions and interpretation of data. The data evaluation records are adequate. The study satisfies data requirement 83-1 of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rodents.

2. Dickie, B. C. (1987). One-year oral dosing study in dogs with the triazine herbicide, cyanazine. An unpublished report prepared by Hazleton Laboratories America, Inc., submitted to the Agency by E. I. du Pont de Nemours and Company. Study No. 6160-104, Project No. 80276 (T 84-567), report dated February 18, 1987. MRID No. 40081901, 40229001, HED Doc. No. 006350.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer conclusions and interpretation of data. The data evaluation records are adequate. The study satisfies data requirement 83-1 of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in non-rodent species.

3. Nemec, M. (1987). Two generation reproduction study of technical Bladex herbicide (SD 15418) in rats. Unpublished report prepared by WILL Research Laboratories, Inc. for Shell Company (sponsorship was transferred from Shell to Du Pont on October 31, 1986). Study No. SRO 15-87 and WILL 93001. MRID No. 40360001, 41111001, HED Doc. No. 006597, 007804.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

Generally, the Committee agreed with the reviewer conclusions and interpretation of data. However, it was noted by some members of the Committee that "there was no NOEL for systemic toxicity based upon decreases in body weights. At the same time, it was pointed out that the NOEL for reproductive effects for this same study was based upon essentially the same effects, decreased body weights of pups. In addition, it was apparent that such decreases in body weights were observed (as noted by the reviewer) at various time intervals throughout the study but apparently not assessed by the reviewer as a continuous event. Hence, it was the suggestion of another Committee member that there may not be a NOEL for either reproductive or systemic effects. However, the Committee concluded that although a trend may have been apparent at the lower dose levels, findings were not statistically significant for pup weights at that dose level. On this basis, the NOEL for this potentially continuous effect was not changed by the Committee. It was the suggestion of another member of the Committee that the effect might be assessed by the bench-mark approach".

"In reference to the amendment to the review dated May 9, 1990, which upgrades the study to Core-minimum status, it was pointed out that the discussion relating to mating performance provided on page No. 3 of this review was incorrect. Reference to the F1 generation should have been to the F0 generation and those to the F2 generation should have been to the F1, if the table and discussion are to make sense".

Other than that, the data evaluation records are adequate. The study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for the reproductive toxicity testing.

C. Other Studies Available

There were several developmental toxicity studies available to the Committee. However, the Committee did not discuss any of them and made reference to the SAP report on the developmental toxicity issue indicating that the developmental toxicity issue has been adequately addressed in the SAP report as well as in several memos and reports by S. Dapson and Q. Bui. Therefore, it is assumed that data available on developmental toxicity satisfies data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in two species. The developmental toxicity studies and reports available to the Committee include the following:

1. Lu, C. C., Tang, B. S., Chai, E. Y. et al. (1981). Technical Bladex (SD 15418) teratology study in rats. Project No. 61230. Unpublished report submitted by Shell Oil Co. MRID No. 00091020, 00129112, 00129113, HED Doc No. 001418, 002446, 003358.

2. Shell Toxicology Laboratory (Tunstall) (1982). A teratology study in New Zealand white rabbit given Bladex orally. Unpublished report prepared by Sittingbourne Research Center. MRID No. 00125660, HED Doc. No. 002703.

3. Lochry, E. A., Hoberman, A. M. and Christian, M. S. (1985). Study of the developmental toxicity of technical Bladex herbicide (SD-15418) in Fischer 344 rats. Unpublished report No. 619-002 dated April 18, 1985 prepared by Argus Research Laboratory, Inc. MRID No. 00143400, 00145596, HED Doc. No. 004525.

4. Lochry, E. (1984). Teratology pilot study of technical cyanazine (Bladex) in Fischer 344 and Sprague Dawley rats. Un published report prepared by Argus Research Laboratories, Inc. Final report dated November 18, 1984. MRID No. 00156210, HED Doc. 004491.

5. A report by Q. Bui entitled "An overview of the developmental toxicity potential and assessment of the developmental toxicity risk for cyanazine (Bladex)", dated August 14, 1986, HED Doc. No. 005331.

6. A report by Q. Bui dated October 26, 1984, entitled "Evaluation of additional data pertaining to the teratology study with Bladex in SD-CD rats. HED Doc. 004077.

7. Shell Development Company (1983). Teratogenic evaluation of Bladex in SD CD rats. Unpublished report No. 31T-2564, dated July 6, 1983. HED Doc. No. 000811.

D. Reference Dose (RfD)

The HED RfD/Peer Review Committee recommended that an RfD be established on the basis of the "no-observable effect level" of 0.2 mg/kg/day demonstrated in the rat chronic toxicity study using an Uncertainty Factor of 100. On this basis, the RfD was calculated to be 0.002 mg/kg/day.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Roger Gardner
William Dykstra
Esther Saito