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

8/21/92

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Linuron
CAS No. 330-55-2
EPA Chem. Code: 035506
Caswell No. 528
Reg. Group: List A (6A)

FROM: George Z. Ghali, Ph.D. G. Ghali 6.12.92
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)
and
Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on February 21, 1992 to evaluate data submitted in support of Linuron registration with particular emphasis on long term toxicity in rodent and non-rodent species, and developmental and reproductive toxicity.

Since the carcinogenicity issue of Linuron was evaluated and the chemical has been classified by the HED Cancer Peer Review Committee as a group C, possible human carcinogen, therefore, issues relating to the carcinogenic potential of this chemical were not discussed by the RfD Committee. However, the Committee deliberated on the chronic toxicity phase of the long term feeding studies in rats and mice because of possible impact on the RfD determination.

Linuron was first discussed by the HED RfD Committee on February 21, 1986. An RfD for this chemical was verified by the Agency RfD Work Group on May 14, 1986. At that time the RfD was based upon a LEL of 0.625 mg/kg/day (LDT) for hematological changes in a two-year feeding study in dogs (E. I. Du Pont de Nemours and Co., 1962), using an uncertainty factor (UF) of 100 to account for the inter- and intraspecies differences. An additional UF of 3 was applied to compensate for the lack of NOEL in this study.

In a more recent one-year feeding study in dogs (1988), a "no observable effect level" was established at 0.79 and 0.77 mg/kg/day (LDT) for hematological changes for males and females respectively. The LEL in this study was considered to be 4.17 and 3.49 mg/kg/day for males and females respectively. The HED RfD Committee concluded that the RfD for Linuron should be established based upon the no effect level generated in this study using an uncertainty factor of 100 to account for the inter- and intraspecies differences. On this basis, the RfD was calculated to be 0.008 mg/kg/day.

2

A. Individuals in Attendance

1. Peer Review Committee Members and Associates (signature indicates concurrence with the peer review unless otherwise stated).

Karl Baetcke

Henry Spencer

Roger Gardner 8/6/96

James Rowe

Gary Burin

George Ghali

Rick Whiting

Mike Ioannou Stephen C. Dapson for

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).

William L. Burnam

Reto Engler

Marcia Van Gemert

Stephen Dapson Stephen C. Dapson

Laurence Chitlik Laurence D. Chitlik

Esther Rinde —

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

Susan Makris

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. Malley, L. A. (1988). Chronic toxicity study with INZ326-118: one-year feeding study in dogs. Unpublished report prepared by Haskell Laboratories, submitted to the Agency by E. I. du Pont de Nemours & Company Inc. Lab Proj. No. 181-88, report dated October 28, 1988. MRID No. 49052601, HED Doc. No. 007284.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

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

2. Hodge, H. C., Downs, W. L. and Maynard, E. A. (1963). Chronic feeding studies of linuron (herbicide 326) [in dogs]. Unpublished report prepared by University of Rochester, Dept. of Pharmacology, submitted to the Agency by E. I. du Pont de Nemours and Co. (1962). MRID No. 00018374, 00018376, HED Doc. No. 000680, 000681.

Core Classification: No Core grade was designated to the study.

Committee's Conclusions and Recommendations:

Although the data evaluation records were inadequate, the Committee did not recommend for an update since a more recent study was available. The findings in this study were more or less in agreement with the recent long-term feeding study in dogs described above.

3. Kaplan, A. M., McAlack, J. W., Hall, C. L. et al. (1980). Long-term feeding study in rats with 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea (Lorox (R): Linuron; INZ-326). Unpublished report No. 100-80 prepared by Haskell Laboratories, submitted to the Agency by E. I. du Pont de Nemours and Co. MRID No. 00029680, HED Doc. No. 005926, 005670, 000675, 000674.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer evaluation and interpretation of data. The study is acceptable and the data evaluation records are adequate. The study satisfies data requirement 83-1 of subpart F of the Pesticide Assessment Guideline for long term toxicity testing in rodent species.

4. Mullin, L. (1990) Reproductive and fertility effects with INZ326-118 (Linuron): Multigeneration reproduction study in rats. Unpublished report No. 20-90 prepared by Haskell Laboratory, submitted to the Agency by E. I. du Pont de Nemours and Co. Study No. MR 8511-001, Report dated March 29, 1990 MRID No. 41463401, HED Doc. 008113.

Core Classification: Guideline.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer evaluation and interpretation of data. The study is acceptable and the data evaluation records are adequate. The study satisfies data requirement 83-4 of subpart F of the Pesticide Assessment Guideline. Since the "no-observable effect level" in this study is very close to that of the critical study used as the basis for the RfD, it was suggested by one member to use this study as a "co-critical" study in support of the RfD. However, the Committee did not go along with this suggestion and recommended that the "no-observable effect level" and "least-effect level" in this study should be judged in light of the corresponding levels established in the older reproduction study which was classified as supplementary. It was suggested that the two reproduction studies should be brought up and closer to the critical study on the RfD summary document.

5. E. I. du Pont de Nemuours and Company (1978). Teratogenicity study of 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea in rats. Unpublished report No. 33-79, submitted by E. I. du Pont de Nemours and Company. MRID No. 00018167, HED Doc. No. 000676.

Core Classification: Guideline.

Committee's Conclusions and Recommendations:

The Committee considered the "data evaluation records" to be inadequate and recommended the reevaluation of the study and updating the "data evaluation records". The Committee recommended that the respective Tox Branch should request the individual animal data from the registrant. The Core-classification for this study will be reserved until the completion of data reevaluation.

6. Hoberman, A. (1985). Developmental toxicity study of INZ-326

5

administration via gavage to New Zealand white rabbits. Unpublished report prepared by Argus Research Laboratories, Inc., submitted to the Agency by E. I. de Pont de Nemours and Co., Inc. Study protocol No. 104-009, report dated September 16, 1985. MRID No. 00153867, HED Doc. 005557, 006561.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer evaluation and interpretation of data. The study is acceptable and the data evaluation records are adequate. The study satisfies data requirement 83-3 of subpart F of the Pesticide Assessment Guideline for one species.

7. Wood, C., Richard, R., Hall, C. et al. (1982). Long-term feeding study with ... Lorox, Linuron, INZ-326 in mice. Unpublished report No. 758-82 prepared by Haskell Laboratory, submitted to the Agency by E. I. de Pont du Nemours and Co., Inc. MRID No. 00124195, HED Doc. No. 007821.

The Committee did not deliberate on this study. This study was evaluated by Bernard Heberman and Chao Chen of the Cancer Assessment Group (CAG), report dated April 30, 1984. The carcinogenic potential for this chemical has been evaluated by the HED Cancer Peer Review Committee. The chemical was classified as Group C, possible human carcinogen.

8. Hodge, H. C., Downs, W. L. and Maynard, E. A. (1962). Chronic feeding of linuron (herbicide 326) in rats. Unpublished report prepared by University of Rochester submitted to the Agency by E. I. de Pont du Nemours and Co., Inc. MRID No. 00018379, 00018381, HED Doc. 000680, 000681.

The Committee did not deliberate on this study. The carcinogenic potential for this chemical has been evaluated by the HED Cancer Peer Review Committee. The chemical was classified as Group C, possible human carcinogen.

9. Pastoor, T. P. (1985). Effect of INZ-326 on methemoglobin and sulfhemoglobin concentration in rats. Unpublished report No. 521-85 prepared by Haskell Laboratory, submitted to the Agency by E. I. de Pont du Nemours and Co., Inc. Report dated September 4, 1985. MRID No. 00149883, HED Doc. 004775, 005708.

The Committee did not deliberate on this study. This study was designed to address specific effects on hematological parameters.

CC: P. Fenner-Crisp
R. Schmitt
K. Dearfield
E. Saito

7