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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: RfD/Peer Review Report of Acetochlor
CAS No. 34256-82-1
EPA Chem. No. 121601
Caswell File No. 003B
Reg. Group: New Chemical

FROM: George Z. Ghali, PhD G. Ghali 2.27.92
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Joanne Miller, PM 23
Herbicide-Fungicide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on February 6, 1992 to evaluate data submitted in support of Acetochlor registration with particular emphasis on long term toxicity in rodent and non-rodent species, and developmental and reproductive toxicity.

Since a weight of the evidence determination has been completed and a cancer classification has been designated by the HED Cancer Peer Review Committee (see HED Cancer Peer Review report dated January 27, 1992), the RfD/Peer Review Committee did not discuss any issue related to the carcinogenic potential of this chemical. However, the Committee deliberated on the chronic toxicity phase of the long term feeding studies in rats and mice.

Acetochlor was first discussed by the HED RfD Committee on December 12, 1990. An RfD was established based upon a NOEL of 10 mg/kg/day for body and organ weight changes occurred at 20 mg/kg/day in a two-year feeding study in rats (Monsanto Co., Study No. 83107, MRID No. 40077601) using an uncertainty factor of 100. However, the Agency RfD Work Group in their meeting of March 27, 1991 deferred the discussion of this chemical pending the completion of studies under review then by the Health Effects Division of the Office of Pesticide Programs.

Upon the completion of the toxicology data reviews, the RfD was reassessed. It was proposed that an RfD be established based upon a NOEL of 2 mg/kg/day (for increased salivation, alanine amino transferase and triglycerides and decreased blood glucose levels) generated in a chronic feeding study in dogs (ICI, Study No. 88/SUC018/0136, MRID No. 41565118) using an uncertainty factor of 100. The RfD was calculated to be 0.02 mg/kg/day.

The Committee was asked to address what appeared to be the lack of a "no-effect level" in the carcinogenicity study in CD-1 mice (ICI Americas Inc., 1989, MRID 41565119, HED Doc. 008478) because of its possible impact on the RfD determination. The effects seen at 10 ppm, the lowest dose tested, in the mouse study as stated by the reviewer were "a dose-related increase in absolute and relative kidney weight ..... accompanied by a significant increase in renal tubular basophilia at all dietary levels in males". Some similar effects were observed in an older study in CD-1 mice (Monsanto Company 1983, MRID No. 00131089, HED Doc. 004566) but were inconsistent and not dose-dependent. The Committee considered the renal tubular basophilia, observed at all dose levels in mice, to be most likely a normally occurring adaptive change of no toxicological significance. The Committee further indicated that the anatomy and physiology of the human kidney resemble that of the dog, more closely, than the rodent. The Committee recommended that no emphasis should be placed on this type of renal effects in mice and therefore should not be used for regulatory purposes.

A. Individuals in Attendance

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

William L. Burnam

Karl Baetcke

Henry Spencer

Roger Gardner

Stephen Dapson

James Rowe

George Ghali

Rick Whiting

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).

Reto Engler

Marcia Van Gemert

Laurance Chitlik —

Esther Rinde —

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

Tim McMahon

B. Material Reviewed

Please note that there are two data sets; one was submitted to the Agency by ICI and the other data set was submitted to the Agency by Monsanto. The RfD was based on comprehensive evaluation of all toxicology data available to the Agency.

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

I. ICI DATA BASE:

1. Broadmeadow, A. (1988). Toxicity study by oral (capsule) administration to Beagle dogs for 52 weeks. Unpublished report prepared by Life Science Research, Ltd, submitted to the Agency by Imperial Chemical Industries, Inc (ICI). LSR Report No. 88/SUC018/0136, dated December 2, 1988. MRID No. 41565-18, HED Doc No. 008478.

Core Classification: Guideline data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's interpretation of data and final conclusions. However, an addendum to the data evaluation records was requested to provide clinical chemistry values since they were not reported by the reviewer. These values were reported by the original reviewer in terms of increase or decrease, but the actual values were not reported. Subsequent to the meeting, an addendum (attached) was provided by the toxicology reviewer and will be incorporated with the original data evaluation records. This study satisfies data requirement 83-1 of subpart F of the Pesticide Assessment Guideline for chronic oral toxicity in non-rodents.

2. Virgo, D. M. and Broadmeadow, A. (1988). SC-5676: Combined oncogenicity and toxicity study in dietary administration to CD rats for 104 weeks. Unpublished report prepared by Life Science Research, Ltd, submitted to the Agency by ICI, Inc. Study No. 88/SUC017/0348, report dated March 18, 1988. MRID No. 415920-04, HED Doc. No. 008478.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The study is acceptable. The Committee agreed with the reviewer's

interpretation of data and final conclusion. This study satisfies data requirement 83-1 of the Pesticide Assessment Guideline for chronic toxicity testing in rodents.

3. Amyes, S. J. (1989). SC-5676: 78 Week feeding study in CD-1 mice. Unpublished report prepared by Life Science Research, Ltd., submitted to the Agency by ICI Americas Inc. Study No. 87/SUC0012/0702, report dated June 9, 1989. MRID No. 41565119, HED Doc No. 008478.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The Committee did not discuss the carcinogenicity phase of the study. The committee confined the discussion to the systemic toxicity and non-neoplastic lesions observed in the study because of its possible impact on the RfD determination. The effects seen at 10 ppm, the lowest dose tested, in the mouse study as stated by the reviewer were "a dose-related increase in absolute and relative kidney weight ..... accompanied by significant increase in renal tubular basophilia at all dietary levels in males". Some similar effects were observed in an older study in CD-1 mice (Monsanto Company 1983, MRID No. 00131089, HED Doc. 004566) but were inconsistent and not dose-dependent. The Committee considered the renal tubular basophilia, observed at all dose levels in mice, to be most likely a normally occurring adaptive change of no toxicological significance. Therefore, no emphasis was placed on the renal effects in this study since they were not accompanied by adverse histopathological changes. The Committee further indicated that the anatomy and physiology of the human kidney resembles that of the dog, more closely, than the rodent. The Committee recommended that no emphasis should be placed on this type of renal effects in mice and therefore should not be used for regulatory purposes.

4. Willoughby, C. R. (1989). SC-5676: Effects upon reproductive performance of rats treated continuously through two successive generations. Unpublished report prepared by Life Science Research Ltd., submitted to the Agency by ICI America Inc. Study No. 89/0414, report dated August 16, 1989. MRID No. 41565120, HED Doc. No. 008478.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's interpretation of data and final conclusion. The study is acceptable and the data evaluation records are adequate. This study satisfies data requirement 83-4 of the Pesticide Assessment Guideline.

5. Brooker, A., Stubbs, A. and John, D. M. (1989). Acetochlor: Teratogenicity study in the rat. Unpublished report No. ISN 204/89369 prepared by Huntingdon Research Centre Ltd., submitted to the Agency by ICI Americas Inc. Study No. RR 0431, report dated August 14, 1989. MRID NO. 41592005, HED Doc. No. 008478

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

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

6. Brooker, A., Stubbs, A. and John, D. M. (1989). Acetochlor: Teratogenicity study in the rabbit. Unpublished report No. ISN 205/89432 prepared by Huntingdon Research Centre Ltd., submitted to the Agency by ICI Americas Inc. Study No. RB 0432, report dated August 9, 1989. MRID NO. 41592002, HED Doc. No. 008478

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's interpretation of data and final conclusion. The study is acceptable and the data evaluation records are adequate. This study satisfies data requirement 83-3 of the Pesticide Assessment Guideline for a second species.

II. MONSANTO DATA BASE:

1. Ahmed, F. E. (1981). A one-year feeding study in dogs with MON 097. Unpublished report prepared by Pharmacopathics Research Laboratories, submitted to the Agency by Monsanto Agricultural products Co. Study No. PR-80-008, PRL No. 8006, report dated October 14, 1981. MRID No. 00116631, 00164944. HED Doc. No. 005943, 004586.

Core-classification: Core minimum data.

Committee's Conclusions and Recommendations:

The study is acceptable. The Committee agreed with the reviewer's interpretation of data and final conclusion. This study satisfies data requirement 83-1 of the Pesticide Assessment Guideline for chronic toxicity testing in non-rodent species.

2. Naylor, M. W. and Ribelin, W. E. (1986). Chronic feeding study of MON 097 in Albino rats. Unpublished report prepared by Monsanto Environmental Health Laboratory, submitted to the Agency by Monsanto Company. Study No. EHL-83107, report No. MSL-6119, dated September 25, 1986. MRID No. 40077601, HED Doc. No. 007002, 006571.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The study is acceptable. The Committee agreed with the reviewer's interpretation of data and final conclusion. This study satisfies data requirement 83-1 of the Pesticide Assessment Guideline for chronic toxicity testing in rodent species.

3. Ahmed, F. E., Tegeris, A. S. and Seely, J. C. (1983). 24-Month oncogenicity study in the mouse. Unpublished report No. PR-80-007 prepared by Pharmacopathics Research Laboratories, Inc., submitted to the Agency by Monsanto Agricultural Products Company. Report dated May 4, 1983. MRID No. 00131089, HED Doc. 004586.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's interpretation of data and final conclusion with respect to the systemic toxicity and non-neoplastic lesions.

4. Ahmed, F. E., and Seely, J. C. (1986). Chronic toxicity and oncogenicity study in the rat. Unpublished report prepared by Pharmacopathics Research Laboratories, Inc., submitted to the Agency by Monsanto Company. Project No. ML-86-44/EHL 86027, report dated November 4, 1987. MRID No. 00131088, 40484801, HED Doc. No. 004586, 006764.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's interpretation of data and final conclusion with respect to the systemic toxicity and non-neoplastic lesions.

5. Monsanto Company (1982). Two-generation reproduction study in rats. Unpublished report prepared by International Research and Development Corporation, submitted to the Agency by Monsanto Company. Study No. IR-80-053. MRID No. 00131391, HED Doc No. 004586, 005353.

Core Classification: Core-minimum data.

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Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's interpretation of data and final conclusion. The study is acceptable and the data evaluation records are adequate. This study satisfies data requirement 83-4 of the Pesticide Assessment Guideline.

6. Monsanto Company (1980). Developmental toxicity study in rats. Submitted by Monsanto Company. MRID No. 00050929, HED Doc. No. 0005865.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's interpretation of data and final conclusion. The study is acceptable. The data evaluation records though extremely short and brief, the Committee felt that there was no need to update them since there was nothing in the data to warrant that. This study satisfies data requirement 83-3 of the Pesticide Assessment Guideline for one species.

7. Adam, G. (1986). A teratology study in rabbit with MON 097 (Acetochlor). Unpublished report prepared by WIL Research Laboratories, Inc. (a subsidiary of Great lakes Chemical Corporation), submitted to the Agency by Monsanto Agricultural Company. Study No. Monsanto - RD 713, WIL Res. Lab. No. WI-80-4. MRID No. 40134101, HED Doc. No. 005968.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's interpretation of data and final conclusion. The study is acceptable and the data evaluation records are adequate. This study satisfies data requirement 83-3 of the the Pesticide Assessment Guideline for a second species.

Attachment

CC: P. Fenner/Crisp
E. Saito
K. Dearfield