

US EPA ARCHIVE DOCUMENT



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

Dr. G. Ghali

010661

25 AUG 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of Metolachlor
EPA Chem Code: 108801
CAS No. 51218-45-2
Reg. Group: List A

FROM: George Z. Ghali, Ph.D. *G. Ghali 7/27/93*
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Richard Mountfort, PM 23
Herbicide-Fungicide Branch
Registration Division (H7505C)

Walter Waldrop/Connie Childress, PM 71
Special Review Branch
Special review and Re-registration Division
(H7508W)

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Re-registration Branch
Special review and Re-registration Division
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The Health Effects Division RfD/Peer Review Committee met on September 17, 1992 and again on April 1, and May 27, 1993 to evaluate data available in support of Metolachlor re-registration. Material available for review included an RfD summary document, and data evaluation records for chronic and subchronic feeding studies in rats and dogs, carcinogenicity studies in rats and mice, developmental toxicity studies in rats and rabbits and a two-generation reproduction study in rats.

A Reference Dose (RfD) for Metolachlor was assessed by the Health Effects Division RfD Committee on March 21, 1986 and verified by the Agency RfD Work Group on April 22, 1986. The RfD was then reassessed by the Health Effects Division RfD Committee on April 7, 1988 and verified by the Agency Work Group on June 22, 1988. The current RfD value on IRIS is 0.15 mg/kg/day based on a NOEL of 15 mg/kg/day for decreased body weight gain observed at 150 mg/kg/day in a long-term feeding study in rats using an uncertainty factor of 100.



Subsequently, a long-term feeding study in dogs, with a lower no-observable effect level, was submitted to the Agency. This information was considered, along with all other data, in reassessing the RfD for Metolachlor. In the meeting of May 27, 1993, the Committee recommended that an RfD should be established based upon a NOEL of 9.7 mg/kg/day for decreased body weight gain observed at 32.7 mg/kg/day in the long-term feeding study in dogs using an uncertainty factor of 100 to account for the interspecies extrapolation and the intraspecies variability.

The Committee considered the long-term toxicity study in dogs (83-1b), the chronic toxicity phase of the rat study (83-1a), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproduction study in rats (83-4) to be acceptable. In the meeting of September 17, 1992 the Committee recommended revisions and/or updates to the data evaluation records of the long-term study in dogs, the reproduction study in rats and the developmental toxicity studies in rats and rabbits. These revisions and updates were completed and the revised and updated data evaluation records were made available to the Committee in the subsequent meeting.

The RfD Committee did not discuss the carcinogenicity phase of the rat study and the mouse carcinogenicity study since the carcinogenicity issue had already been addressed by the Health Effects Division Carcinogenicity Peer Review Committee (CPRC). According to the CPRC, the chemical was classified as a "group C", possible human carcinogen. Quantification of carcinogenicity risk using a low dose extrapolation (Q^{*1}) was recommended by the same committee.

There was no evidence, based on the available data, that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions.

There were limited data available for review to address or characterize the hazard of a one-time or one-day exposure. However, data available for review did not indicate that a one-day exposure to the chemical would be of such concern as to warrant the need for acute exposure studies to be used in an acute dietary risk assessment.

A. Individual in Attendance

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

William Burnam

Ann Z. Burnam

Reto Engler

Reto Engler

Marcia Van Gemert

Marcia Van Gemert

Karl Baetcke

Karl Baetcke

Henry Spencer

Henry Spencer

William Sette

William Sette

Roger Gardner

Roger Gardner

James Rowe

James N. Rowe

Esther Rinde

Esther Rinde

John Tice

John Tice

George Ghali

G. Ghali

Rick Whiting

Rick Whiting

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

Stephen Dapson

Stephen Dapson

Mike Ioannou

J. M. Ioannou

3. Others:

Kerry Dearfield, Flora Chow, Linda Kutney and Virginia Dobozy of the Health Effects Division as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Mike Ioannou/Stephen Dapson
Rick Whiting
Flora Chow
James Kariya

B. Material Reviewed

Material available for review in one or more of the three meetings held on Metolachlor included chronic toxicity/ carcinogenicity study in rats (83-5 or 83-1a and -2a), long-term toxicity study in dogs (83-1b), carcinogenicity study in mice (83-2b), developmental toxicity study in rats (83-3a), developmental toxicity study in rabbit (83-3b), a reproduction study in rats (83-4), an RfD summary document and a tox. one-liner. The Committee focused on the following studies

1. Hazelle, J. R. and Arthur, A. T. (1989). Metolachlor technical: 52-week oral toxicity study in dogs. MRID No. 40980701, 41164501, 42218601, 42218602, MRID No. 008442, 01088.

Core Classification: This study is classified Core-Guideline according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 100, 300 and 1000 ppm (equivalent to 3.5, 9.7 and 32.7 mg/kg/day and 3.6, 9.7 and 33.0 mg/kg/day for males and females respectively). The committee generally agreed with the reviewer's evaluation and interpretation of the data. However, in the meeting of September 17, 1992 the Committee questioned the significance of body weight gain decrease since it was minimal and was accompanied by decrease in food consumption. The Committee requested food efficiency information. The Committee questioned also the increase in alkaline phosphatase in both males and females. The reviewer indicated that this increase was relative to the decrease of alkaline phosphatase in the concurrent controls and this fluctuation was within the normal biological range. The study was considered acceptable and the data evaluation record, except for minor revisions, i. e. inclusion of food efficiency data, was considered adequate. This study fulfills data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in a non-rodent species.

2. Estes, F. L. (1980). 6-Month chronic oral toxicity study in Beagle dogs. MRID No. 00032174, HED Doc. No. 000000

Core Classification: This study is classified Core-supplementary according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 100, 300 and 1000 ppm. This study provided useful supplemental information. The committee generally agreed with the reviewer's evaluation and interpretation of the data. When the long-term toxicity study in dogs (above) is viewed in light of the results of this six-month feeding study in dogs, they both provided a some what reasonable basis to establish a no-

observable effect level for what appeared to be marginal effects seen in the long-term study. The results of this study support a no-observable effect level of 9.7 mg/kg/day in the long-term study.

3. Tisdell, M. (1983). Two-year chronic oral toxicity and oncogenicity study with metolachlor in Albino rats. MRID No. 00129377, HED Doc. No. 000000.

Core Classification: This study is classified Core-minimum according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 30, 300 and 3000 ppm (equivalent to 1.5, 15 and 150 mg/kg/day). This study was not evaluated by the Committee in the Meeting of September 17, 1992. In the April 1, 1993 meeting the Committee requested the respective branch to update the chronic toxicity phase of the rat study because of possible impact on the reference dose assessment. In the meeting of May 27, 1993 the committee examined the updated data evaluation record of the chronic toxicity phase of the rat study and generally agreed with the reviewer's evaluation and interpretation of the data. The effects observed in this study were limited to increase relative (7%) and absolute (13%) liver weights in males. This liver changes were also observed after the four weeks recovery period. This study fulfills data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.

4. Lochry, E. A. (1985). Embryo-fetal toxicity and teratogenic potential study of CGA-24705 (FL-841697) administered orally via gavage to rats. MRID No. 00151941, HED Doc. No. 009509.

Core Classification: This study is classified as Core-minimum according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 30, 100, 300 and 1000 mg/kg/day. In the meeting of September 17, 1992 the Committee recommended to the respective branch to reevaluate the study and update the data evaluation record. The updated data evaluation records were submitted to the Committee for consideration in the meeting of April 27, 1993. The committee generally agreed with the reviewer's evaluation and interpretation of the data. However, the Committee recommended to revise the NOEL/LOEL for maternal toxicity to be 100 and 300 mg/kg/day based on increased salivation in a significant number of animals. The NOEL/LOEL for developmental toxicity were considered to be 300 and 1000 mg/kg/day respectively. This study fulfills data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Lightkep, G. E. (1980). Teratogenic potential of CGA-24705 in New Zealand white rabbits. MRID No. 00041283, HED Doc. No. 010088.

Core Classification: This study is classified as Core-minimum according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 36, 120 and 360 mg/kg/day. In the meeting of September 17, 1992 the Committee recommended to the respective branch to reevaluate the study and update the data evaluation record. The updated data evaluation records were submitted to the Committee for consideration in the meeting of April 27, 1993. The committee generally agreed with the reviewer's evaluation and interpretation of the data. The NOEL/LOEL for maternal toxicity were considered to be 120 and 360 mg/kg/day, respectively. The developmental toxicity NOEL/LOEL were considered to be > 360 mg/kg/day. This study fulfills data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

6. Page, J. G. (1981). Two-generation reproduction study in Albino rats with metolachlor technical. MRID No. 00080897, HED Doc. No. 010088.

Core Classification: This study is classified as Core-Guideline according to the data evaluation record.

Committee's Conclusions and Recommendations:

The chemical was tested at 30, 100 and 1000 ppm. In the meeting of September 17, 1992 the Committee recommended to the respective branch to reevaluate the study and update the data evaluation record. The updated data evaluation records were submitted to the Committee for consideration in the meeting of April 27, 1993. The committee generally agreed with the reviewer's evaluation and interpretation of the data. The NOEL for maternal/systemic toxicity was considered to be > 1000 ppm. Based on the reduction of body weight of the progeny in both F1a and F2a, the reproductive toxicity NOEL/LOEL were considered to be 300 and 1000 ppm respectively. This study fulfills data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

C. Conclusions and Recommendations

1. Reference Dose

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Subsequently, a long-term feeding study in dogs, with a lower no-observable effect level, was submitted to the Agency. This information was considered, along with all other data, in reassessing the RfD for Metolachlor. In the meeting of May 27, 1993, the Committee recommended that an RfD should be established based upon a NOEL of 9.7 mg/kg/day for decreased body weight gain observed at 32.7 mg/kg/day in the long-term feeding study in dogs using an uncertainty factor of 100 to account for the interspecies extrapolation and the intraspecies variability.

2. Data Base

The Committee considered the long-term toxicity study in dogs (83-1b), the chronic toxicity phase of the rat study (83-1a), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproduction study in rats (83-4) to be acceptable. In the meeting of September 17, 1992 the Committee recommended revisions and/or updates to the data evaluation records of the long-term study in dogs, the reproduction study in rats and the developmental toxicity studies in rats and rabbits. These revisions and updates were completed and the revised and updated data evaluation records were made available to the Committee in the subsequent meeting.

3. Carcinogenicity

The RfD Committee did not discuss the carcinogenicity phase of the rat study and the mouse carcinogenicity study since the carcinogenicity issue had already been addressed by the Health Effects Division Carcinogenicity Peer Review Committee (CPRC). According to the CPRC, the chemical was classified as a "group C", possible human carcinogen. Quantification of carcinogenicity risk using a low dose extrapolation (Q^1) was recommended by the same committee.

4. Acute and Subchronic Toxicity Concern

There was no evidence, based on the available data, that the

chemical was associated with significant reproductive or developmental toxicity under the testing conditions.

There were no data available for review to address or characterize the hazard of a one-time or one-day exposure. However, other data available for review did not indicate that a one-day exposure to the chemical would be of such concern as to warrant the need for acute exposure studies to be used in an acute dietary risk assessment.