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

APR 20 1994

MEMORANDUM

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of **Metalaxyl** [N-(2,6-Dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester.

CASRN. 57837-19-1  
EPA Chem. Code: 113501  
Caswell No. 375AA

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

TO: Sidney Jackson, PM 21  
Fungicide-Herbicide Branch  
Registration Division (H7505C)

Lois Rossi, Chief  
Reregistration Branch  
Special Review and Re-registration Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on March 3, 1994 to discuss and evaluate the existing toxicology data in support of Metalaxyl re-registration and re-assess the Reference Dose (RfD) for this chemical in light of recently submitted data.

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on May 23, 1986 and verified by the Agency RfD Work Group on July 8, 1986. At that time the RfD was based on a six-month feeding study in dogs with a no-observable effect level (NOEL) of 6.25 mg/kg/day. Increased alkaline phosphatase activity and increased relative liver weights were observed at the next dose level of 25 mg/kg/day. The increase in liver weights was also observed in other species treated with metalaxyl. An uncertainty factor (UF) of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.06 mg/kg/day.

In the meeting of March 3, 1994 the Committee recommended that the RfD remain unchanged. It should be noted that this chemical had been reviewed and an acceptable daily intake (ADI) of 0.03 mg/kg/day has been established for this chemical by the World Health Organization (WHO) in 1982.

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00071598  
00071600  
00144372  
00034110



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Health Organization (WHO) in 1982.

The Committee considered the chronic toxicity study in rats (83-1a, MRID No. 00071565, 00080302, 00098481, 00137471, 00144310), the 6-month feeding study in dogs (83-1b, MRID 00071598) to be acceptable and the data evaluation records to be adequate as presented.

The developmental toxicity studies in rats (83-3a, MRID No. 00144422, 00145224) and rabbits (83-3b, MRID No. 00144371, 00144372) were considered to be acceptable and the data evaluation records for these studies (HED Doc. No. 005780, 005780, 004416, 004416) were considered to be adequate as presented. The reproductive toxicity study in rats (83-4, MRID No. 00071600) was considered to be, tentatively, acceptable. The Committee recommended reevaluation of the study to confirm the findings and conclusions reported in the data evaluation record of this study. Furthermore, the Committee recommended that summary data tables be included in the data evaluation record of this study. There were two other developmental toxicity studies in rats (MRID No. 00161405) and rabbits (MRID No. 00161404) classified as supplementary data. The classification of these two studies should remain unchanged. There was no evidence, based on the available data, to suggest that metalaxyl was associated with significant developmental or reproductive effects under the testing conditions.

Two subchronic studies in mice (82-1, MRID 00148087, 00149817) and dogs (82-1, MRID No. 00084111) were available for evaluation and were considered to be of supplementary nature. The data evaluation records for these two studies (HED Doc. 005442 and 003309) were very limited.

The need for acute and subchronic neurotoxicity testing was discussed because of centrally-mediated convulsions and some ataxia observed in some studies with metalaxyl, but the need for these studies was ruled out since these effects were observed only at relatively high dose levels.

The carcinogenicity studies in rats (83-2a, MRID No. 00071598) and mice (83-2b, MRID No. 00071598) were not discussed by the RfD Peer Review Committee. The carcinogenicity issue has already been addressed by the Health Effects Division Carcinogenicity Peer Review Committee (HED-CPRC) and the chemical was classified as a "Group E" (HED report dated December 31, 1985).

\* In the RfD meeting of 1986, the NOEL (6.25 mg/kg/day) in the six month dog study was calculated based on a standard conversion food factor. In the meeting of 1994, the Committee decided to use the actual food intake to calculate the NOEL in this study. On the basis of actual food intake the NOEL was calculated to be 7.8 mg/kg/day.

Individuals in Attendance

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

Marcia Van Gemert

Marcia van Gemert

Karl Baetcke

Karl Baetcke

Henry Spencer

Henry Spencer

Roger Gardner

Roger Gardner

James Rowe

James N. Rowe

William Sette

William Sette

Stephen Dapson

Stephen C. Dapson

George Ghali

G. Ghali

2. Peer Review Committee Members and associates in absentia (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

W. Burnam

Reto Engler

Reto Engler

Rick Whiting

Rick Whiting

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

Roger Gardner

Roger Gardner

4. Others:

T. McMahon and K. Locke of HED as observers

CC: Penny Fenner-Crisp  
Richard Schmitt  
Kerry Dearfield  
Karl Baetcke  
Roger Gardner  
James Kariya  
Rick Whiting/RfD File  
George Witmor/Caswell File  
John Tice

B. Material Reviewed

1. Whitney, A. R. et al. (1980). CGA 489881: Toxicity and oncogenicity in dietary administration to rats for two years. MRID No. 00071565, 00080302, 00098481, 00137471, 00144310, HED Doc. No. 005780. Classification: Core-minimum data. This study satisfies data requirement 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Beck, L. S. et al. (1981). Six-month chronic oral toxicity study with CGA-48988 technical in beagle dogs. MRID No. 00071598, HED Doc. No. 005780. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for a long-term feeding testing in a non-rodent species.

3. MaShehy, T. et al. (1981). CGA-48988: Oncogenicity on dietary administration to mice for two years. MRID No. 00103354, 00127880, 00130951, HED Doc. No. 005778, 005780. Classification: Core-minimum data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

4. Traster, P. E. (1985). Range-finding and definitive teratology study in rats. MRID No. 00144422, 00145224, HED Doc. No. 004416. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Spoede, S. J. and Campbell, W. R. (1984). Expanded report on the segment II reproduction study with CGA-48988 technical in the rat (test for teratogenic or embryotoxic effects). MRID No. 00161405, HED Doc. No. 004408. Classification: Core-supplementary data. This study does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Kend. M. F. (1984). Range-finding and definitive teratology studies conducted in rabbits. MRID No. 00144371, 00144372, HED Doc. No. 004416. Classification: Core-minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

7. Buttler, B. and Campbell, W. R. (1984). Expanded report on a Segment II reproduction study in the rabbit with CGA-48988 technical (test for teratogenic and embryotoxic effects). MRID No. 00161404, HED Doc. No. 003310, 004408. Classification: Core-supplementary data. This study does not satisfy data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

8. Cozens, D. D. et al. (1980). Effects of CGA48988 on reproductive function of multiple generations in the rat. MRID Doc. No. 00071600, HED Doc. No. 0003310, 005780. Classification: Core-minimum data. This study does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rabbits.

C. Outstanding Issues

The reproductive toxicity study in rats (83-4, MRID No. 00071600) was considered to be, tentatively, acceptable. The Committee recommended reevaluation of the study to confirm the findings and conclusions reported in the data evaluation record of this study. Furthermore, the Committee recommended that summary data tables be included in the data evaluation record of this study.