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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Fenbuconazole

CASRN. 114369-43-6
EPA Chem. Code: 129011
Caswell No. 723Q

FROM: George Z. Ghali, Ph.D. G. Ghali 5.10.93
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Cynthia Giles-Parker, PM 22
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on April 15, and again on April 29, 1993 to discuss and evaluate the toxicology data submitted in support of Fenbuconazole registration and to assess the Reference Dose (RfD) for this chemical.

The Committee considered the long-term feeding study in dogs and chronic toxicity study in rats (83-1a and -1b), the reproductive toxicity study in rats (83-4) and the developmental toxicity study in rabbits (83-3a) to be acceptable. The Committee agreed that the classification of the developmental toxicity study in rats (83-3b) should remain as Core-supplementary until discrepancies listed in the data evaluation record of this study are clarified. The Committee recommended some revisions to the data evaluation records of the chronic toxicity phase of the rat study, long-term toxicity study in dogs and the reproductive toxicity study in rats. The Committee considered the data evaluation record for the developmental toxicity study in rats to be adequate.

The Committee recommended that a Reference Dose should be established on the basis of a NOEL of 40 ppm (3.03 and 4.02 mg/kg/day for males and females respectively) established in the chronic toxicity study in rats for body weight decrease, hepatocellular enlargement and vacuolization in females, and thyroid weight and histopathological changes in both sexes observed at 800 ppm (30.62 and 43.07 mg/kg/day for males and females respectively). An uncertainty factor of 100 was used to account

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for the inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.03 mg/kg/day. It should be mentioned that although the long-term feeding study in mice demonstrated a lower NOEL (1.43 mg/kg/day) for hepatotoxicity in males, the Committee felt that the study was compromised by hepatitis infection which might have potentiated liver toxicity. Therefore, The Committee decided to use the NOEL from the rat study since it was supported by the NOEL's demonstrated in other studies and other species

The Committee referred the carcinogenicity issue to the Health Effects Division Carcinogenicity Peer Review Committee for a weight of the evidence evaluation.

Data available for review did not warrant acute toxicity concern with respect to developmental toxicity. There was no evidence to suggest that Fenbuconazole is a developmental toxicant.

There was no data available for review to address or characterize the hazard of a one-time or one-day exposure for other toxicological end-points. However, the available data did not indicate that specific effects following one-day exposure need to be investigated further.

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A. **Individual in Attendance**

1. **Peer Review Committee Members and Associates present in at least one of the two meetings** (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

James Rowe

Kerry Dearfield

John Tice

George Ghali

Rick Whiting

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

Elizabeth Doyle

San Yvette Williams

3. Others:

Stephanei Willet of CCB/HED as an observer

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Elizabeth Doyle
San Yvette Williams
James Kariya

B. Material Reviewed

Material available for review included data evaluation records for a long-term toxicity study in dogs (83-1a), a chronic toxicity/carcinogenicity study in rats (83-5 or 83-1b and -2a), a carcinogenicity study in mice (83-2b), developmental toxicity studies in rats and rabbits (83-3a and -3b) and a reproductive toxicity study in rats (83-4), and a tox. one-liner.

1. Morgan, C. (1990). RH-7592: 52 Week oral (dietary administration) toxicity in the Beagle dogs. MRID No. 41875049, HED Doc. No. 010109.

Core Classification: Core-Guideline (according to the DER)

Committee's Conclusion and Recommendations:

The chemical was tested at 0.38, 3.75 and 30 mg/kg/day. The Committee generally agreed with the reviewer evaluation and interpretation of data and the classification of the study. However, the Committee recommended that the data evaluation record for this study should be altered to reflect the Committee's recommendations regarding the NOEL/LOEL. The Committee considered the NOEL in this study should be established at 3.75 mg/kg/day and not at 0.38 mg/kg/day based on increased liver weight and decreased body weight observed at 30 mg/kg/day, the highest dose level tested. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in a non-rodent species.

2. Wolf, G. W. (1991). RH-7592 Technical: 24-Month dietary chronic toxicity/oncogenicity study in rats. MRID No. 41635301, 41635302, 41875016, HED Doc. No. 008296, 008897.

Core Classification: Core Minimum (according to the DER).

Committee's Conclusions and Recommendations:

The chemical was tested at 4, 40 and 400 ppm for weeks 1 and 2, and at 6, 60, 600 for weeks 3 and 4 and then at 8, 80 and 800 ppm from week 5 to the end of the study. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. However, the Committee recommended some editorial changes including terminology, redefining of data tables, etc... (i. e. to use "adequate dosing" instead of "MTD", to use "thyroid" instead of "thyroid/parathyroid", to clarify data tables by redefining tables headings to distinguish "terminal sacrifice" from "interim sacrifice", and "total alterations" from "terminal alterations"). After a brief discussion of the carcinogenic potential of this

chemical, the Committee decided to refer the carcinogenicity issue to the Health Effects Division Carcinogenicity Peer Review Committee for a weight of the evidence evaluation. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in the rat.

3. Wolf, G. W. (1991). RH-7592 Technical: 104 week dietary chronic toxicity/oncogenicity study in male rats. MRID No. 4205501, HED Doc. 008877.

Core Classification: Core Supplementary (according to the DER).

Committee's Conclusions and Recommendations:

This study does not conform to the Guideline requirements 83-1 and -2 because it was conducted on males only. Therefore, this study is classified as Core-supplementary. However, when this study is considered in conjunction with the previous study they are both considered as Core-minimum. This study in conjunction with the previous two-year feeding study in rats satisfy data requirements 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity and carcinogenicity testing in the rat.

4. Wolf, G. W. (1991). RH-7592 Technical: 78-Week dietary oncogenicity in mice. MRID No. 441635303, 41893301, HED Doc. No. 008296, 010109.

Core Classification: Core Guideline (according to the DER).

Committee's Conclusions and Recommendations:

The Committee determined that the NOEL and LOEL for males should 1.43 and 28.6 mg/kg/day respectively. However, the Committee felt that the study might have been compromised by the use of animals infected with hepatitis which might have potentiated liver effects.

After a brief discussion of the carcinogenic potential of this chemical, the Committee decided to refer the carcinogenicity issue to the Health Effects Division Carcinogenicity Peer Review Committee for a weight of the evidence evaluation. The acceptability of the study will be determined by the same Committee.

5. Solomon, H. M. and Kulwich, B. A. (1990). Rh-7592: Two-generation reproduction study in rats. MRID No. 41875015, HED Doc. 010109.

Core Classification: Core Guideline (according to the DER).

Committee's Conclusions and Recommendations:

The chemical was tested at 8, 80 and 800 ppm (equivalent to 0.4,

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4.0, and 40 mg/kg/day). The Committee generally agreed with the reviewer evaluation and interpretation of data and classification of the study. However, the Committee recommended that the combined NOEL for maternal and reproductive toxicity should be 80 and not 800 ppm. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in the rat.

6. Solomon, H. M. and Lutz, M. F. (1988). RH-7592 Technical: Oral (gavage) developmental toxicity study in rats. MRID No. 41031214, HED Doc. No. 007677.

Core Classification: Core Minimum (according to the DER).

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer evaluation and interpretation of data and classification of the study. The study is acceptable and the DER is adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in the rat.

7. Solomon, H. M. and Lutz, M. F. (1989). RH-7592 Technical: Oral (gavage) developmental toxicity study in rabbits. MRID No. 41875014, HED Doc. No. 010109.

Core Classification: Core Supplementary (according to the DER).

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer interpretation of data and classification of the study. The study is unacceptable for reasons mentioned in the data evaluation record of this study. This study does not satisfy data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in a second species. However, it was mentioned in the data evaluation record of this study that the study can be upgraded upon the clarification of the discrepancies.

C. Conclusions and Recommendations

1. Data Base

The Committee considered the long-term feeding study in dogs (83-1a) and rats (83-1b), the developmental toxicity study in rats and rabbits (83-3a) and the reproductive toxicity study in rats (83-4) to be acceptable and the data evaluation records to be generally adequate. The Committee recommended some revisions to the data evaluation records of the chronic toxicity studies in rats and dogs and the reproductive toxicity study in rats. Until, discrepancies in the developmental toxicity study in rabbits are clarified, the study should remain as Core-supplementary. The carcinogenicity issue has been referred to the Cancer Peer Review Committee, therefore, the acceptability of the rat and mouse carcinogenicity studies was not determined.

2. Reference Dose (RfD)

The Committee recommended that a Reference Dose should be established on the basis of a NOEL of 40 ppm (3.03 and 4.02 mg/kg/day for males and females respectively) established in the chronic toxicity study in rats for body weight decrease, hepatocellular enlargement and vacuolization in females, and thyroid weight and histopathological changes in both sexes observed at 800 ppm (30.62 and 43.07 mg/kg/day for males and females respectively). An uncertainty factor of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.03 mg/kg/day.

It should be mentioned that although the long-term feeding study in mice demonstrated a lower NOEL (1.43 mg/kg/day) for hepatotoxicity in males, the Committee felt that the study was compromised by hepatitis infection which might have potentiated liver toxicity. Therefore, The Committee decided to use the NOEL from the rat study since it was supported by the NOEL's demonstrated in other studies and other species.

3. Carcinogenicity

After consideration of the carcinogenic potential of Fenbuconazole, the Committee decided to refer the carcinogenicity issue to the Health Effects Division Carcinogenicity Peer Review Committee for a weight of the evidence determination.

4. Acute Toxicity Concern

Data available for review did not warrant acute toxicity concern with respect to developmental toxicity. There was no evidence to suggest that Fenbuconazole is a developmental toxicant.

There was no data available for review to address or

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characterize the hazard of a one-time or one-day exposure for other toxicological end-points. However, the available data did not indicate that specific effects following one-day exposure need to be investigated further.

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