Alberts

7-11-91

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: RfD/Peer Review Report of Tebuconazole (Folicur)
CAS No. 107534-96-3
EPA Chem. No. 128997
Caswell File No. 463P
Reg. Group: New Chemical

FROM: George Z. Ghali, PhD G. Ghali 7/11/91
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Susan Lewis, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on March 5, 1991 to evaluate data submitted in support of Tebuconazole registration with particular emphasis on the long term toxicity in rodent and non-rodent species, carcinogenicity in two species, and developmental and reproductive toxicity.

The Committee concluded that the chronic toxicity/carcinogenicity study in rats (83-1a and -2a), chronic toxicity study in dogs (83-1b), developmental toxicity studies (in rats, rabbits, and mice) (83-3a and -3b) and the reproductive toxicity in rats (83-4) to be acceptable. The carcinogenicity study in mice did not meet the Agency's current standards for adequate carcinogenicity testing; the chemical should have been tested at a higher dose, the MTD has not been reached in this study. This study constitutes a data gap under 83-2a of Subdivision F of the Pesticide Assessment Guidelines.

Developmental toxicity studies in rabbits, rats and mice (83-3a and -3b) and their data evaluation records are considered acceptable. The reproductive toxicity study and the data evaluation records for this study are acceptable. Developmental and reproductive toxicity effects were evident. **The Committee recommended referral of the reproductive and developmental toxicity issues to the Health Effects Division Reproductive and Developmental Toxicity Peer Review Committee for weight of the evidence determination.**

The RfD for this chemical has been calculated to be 0.01 mg/kg/day based on a NOEL of 1 mg/kg/day for lenticular and corneal opacity and hepatotoxicity in a long term toxicity study in the dog, using an uncertainty factor of 100.

A. Individuals in Attendance

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

William Burnam

Reto Engler

Marcia Van Gemert

Henry Spencer

Gary Burin

Roger Gardner

George Ghali

2. Peer Review Members and Associates in Absentia (committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the committee).

Karl Baetcke

Esther Rinde

Rick Whiting

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

Jim Rowe

Alberto Protzel

B. Material Reviewed

Material available for review by the Committee consisted of data evaluation records of the following studies:

1. **Bomhard, E. and Ramm, R. (1988). HWG 1608, Study for chronic toxicity and carcinogenicity in Wistar rats (Administration in diet for two years). Study No. 96711, Report No. 16375, prepared by Bayer AG, Toxicology Division, FRG, report dated January 25, 1988. MRID No. 407009-39. Guideline Requirement 83-1a and -2a or 83-5)**

   Core Classification: Core minimum.

   Committee's conclusion and recommendations:

   The chemical has been tested at dietary levels of 0, 100, 300 and 1000 ppm for two years. Slight but statistically significant depression in body weight in mid- and high-dose females (4-5 and 7-9% respectively) occurred throughout the study period and independent of food consumption. Alteration of hematological parameters were noted in mid-and high-dose females. Dose-related depression in female adrenal weights was noted in all dose levels in association with a dose-related decrease in adrenal cortical hemorrhagic degeneration. Also noted in females were statistically significant elevations in liver microsomal enzymes at all dose levels tested. This was based upon histological examination not enzymatic analysis. In males, there was a statistically significant elevation in the combined incidences of thyroid C-cell adenoma, carcinoma and hyperplasia but not of adenoma or carcinoma alone. However, the incidences were within the historical control range. The Committee concluded that the chemical is not carcinogenic under the test conditions. The highest dose tested was adequate for carcinogenicity testing. The data evaluation records are acceptable as presented. The Study meets the Core-minimum criteria and thus satisfies requirement 83-1a and -2a of Subdivision F of the Pesticide Assessment Guideline.

2. **Kreuz, E. V. (1987). HWG 1608, Study of chronic toxicity to dogs after oral administration (twelve-month feeding study). Study No. T6018115, unpublished report No. 16211, Lab report No. 956090, dated November 11, 1987, prepared by Bayer AG, Institute of Toxicology, Federal Republic of Germany. MRID No. 407009-40. Guideline Requirement 83-1b.**

   Core Classification: Core-minimum.

Committee's conclusion and recommendations:

The chemical was tested at dietary concentrations of 0, 40, 200 and 1000/2000 ppm (1-39, 40-52 weeks respectively). The treatment caused lenticular and corneal opacity in mid- and high-dose animals. There was elevation in liver enzymes such as alkaline phosphatase, N-demethylase activity and elevation of triglycerides in males and females of the high dose. Gross changes in appearance of the liver were also observed along with an increase in the presence of iron-containing pigments and lipids in mid- and high dose groups. Other effects such as moderate anisocytosis of the blood, increased cytoplasmic vacuoles of z. fasciculata of the adrenals and elevated weights of kidneys and spleen in both sexes of the mid- and high- dose groups were observed. The systemic LEL and NOEL, based upon ocular lesions and hepatic toxicity in either sex are set at 200 and 40 ppm respectively. The Committee considered the study and the data evaluation records to be acceptable. The study meets the Core-minimum classification criteria. The study satisfies data requirement 83-1b of Subdivision F of the Pesticide Assessment Guideline.

3. **Bomhard, E. and Ramm, R. (1988). HWG 1608, Study for carcinogenicity in NMRI mice (administration in diet for up to twenty-one months). Study No. 96709, Report No. 16376, dated January 25, 1988, prepared by Bayer AG, Toxicology Division, Federal Republic of Germany. MRID No. 407009-41. Guideline Requirement No. 83-2b.**

Core Classification: Core-supplementary.

Committee's conclusion and recommendations:

The chemical was tested at 0, 20, 60 and 180 ppm for 21 months. The treatment produced slight depression of body weight in males but not females at the high dose tested during the first third of the study. The major target organ is the liver in both sexes with elevation in bilirubin and liver weights in the mid- and high-dose groups associated with slight centrilobular and periportal vacuolation and lipid deposition. Mid- and high-dose females also had increased minimal medullary hemopoiesis and sinusoidal cellularity. In males, there was an increase in adrenal cortical cell size and hyperplasia in the mid- and high-dose groups. Both sexes had an elevation in stomach gastritis in the high-dose group. Females were reported with an increase in pancreatic interstitial edema in the mid- and high-dose groups. A slight apparent elevation in benign but not malignant liver tumors was reported in males; the

combined incidences of these tumors are within the historical control range. The Committee concluded that the highest dose tested was not adequate for carcinogenicity testing. The data evaluation records were acceptable as presented. The Committee agreed that the classification of the study should remain as Core-supplementary, and therefore, constitute a data gap for data requirement 83-2b under Subdivision F of the Pesticide Assessment Guideline.

4. **Becker, H. (1987). Embryotoxicity (including teratogenicity) study with HWG 1608 technical in the rabbit. Study No. 074070, Report No. 0023302, 96764, dated February 26, 1987, prepared by Research & Consulting Company. MRID No. 407009-45. Guideline Requirement No. 83-3a.**

Core Classification: Minimum data.

Committee's conclusion and recommendations:

Oral administration of tebuconazole at 0, 10, 30 and 100 mg/kg/day during days 6-18 of gestation in the Chinchilla rabbit produced a minimal depression in mean body weight gain at the highest dose tested associated with a decrease in food consumption. There was an increase in postimplantation losses (both early and late resorptions), a small decrease in the rate of ossification in the right and left digits or toes of the fore- and hindlimb, and frank malformations in 8 fetuses of 5 litters (peromelia, and palatoschisis, malrotation of right hindlimb, agenesis of claws) at the highest dose tested as compared to concurrent controls or historical data. These effects are considered to be compound-related. Maternal toxicity NOEL is set at 30 mg/kg/day. The developmental toxicity NOEL is set at 30 mg/kg/day, and the LOEL at 100 mg/kg/day. The study was classified as Core-minimum data. However the registrant is requested to explain the meaning of the skeletal findings stated as "various bones". The data evaluation records are acceptable. The study satisfies data requirement 83-3a of Subdivision F of the Pesticide Assessment Guideline.

5. **Becker, H. (1988). Embryotoxicity (including teratogenicity) study with HWG 1608 technical in the rat. Study No. 074057, Report No. 96756, Bayer: T 9023301, dated April 28, 1988, prepared by Research & Consulting Company. MRID No. 407009-43. Guideline Requirement No. 83-3b.**

Core Classification: Minimum data.

Committee's conclusion and recommendations:

Oral administration of tebuconazole at 0, 30, 60 and 120 mg/kg/day during days 6-15 of gestation in Wistar rats produced slight maternal toxicity as evidenced by a small depression in mean maternal body weight associated with depressed food consumption. Mean liver weights and liver to body weight ratios were statistically significantly increased in the mid- and high-dose groups. The maternal NOEL was set at 30 mg/kg/day.

Developmental toxicity was evidenced at both the mid- and high-dose levels by delays in ossification of thoracic, cervical and sacral vertebrae, the sternum and fore- and hind limbs along with an increase in supernumerary ribs. Frank malformations were observed in two fetuses of two high dose dams as missing tail, agnatha, microstomia and anophthalmia. The developmental NOEL is set at 30 mg/kg/day. The study meets the Core minimum data classification criteria. The data evaluation records are acceptable as presented. The study satisfies data requirement 83-3b of Subdivision F of the Pesticide Assessment Guideline.

6. **Renhof, M. (1988). HWG 1608, Study of embryotoxic effects on mice after oral administration. Study No. 97411, Bayer Report No. 16527; T5021859, dated March 14, 1988, prepared by Bayer AG Institute of Toxicology. MRID No. 408215-01. Guideline Requirement No. 83-3c.**

Core Classification: Minimum data.

Committee's conclusion and recommendations:

Oral gavage of tebuconazole at 0, 10, 30 and 100 mg/kg/day to mice during days 6-15 of gestation did not produce any overt signs of maternal toxicity (However, results from an associated maternal toxicity study (MRID 408215-01, study No. 77025712) indicated significantly decreased hematocrit and MCV at doses of 20-100 mg/kg in addition to enzymatic and histopathological changes in liver at all doses). Developmental toxicity was noted at the mid- and high-dose levels in the form of runts (fetuses weighing less than 1.3 gm). In addition, the compound produced frank malformation (skull, "neural tube") at the high-dose tested associated with a reduced rate of ossification in cranium as compared to controls. The maternal toxicity NOEL is set at 10 mg/kg/day and the LOEL is set at 20 mg/kg/day (reduction in hematocrit). The developmental NOEL, based upon increase number of runts, is 10 mg/kg/day (LDT) and the LOEL is 30 mg/kg/day. The data evaluation records are considered

acceptable. The study meets the Core-minimum data classification criteria. The study satisfies data requirement 83-3b of Subdivision F of the Pesticide Assessment Guideline.

7. **Eiben, R. (1987). HWG 1608, Two generation study in rats. Lab Proj. ID No. 91064, Study No., T 5017647, Report No. 16223, dated November 12, 1987, prepared by Bayer AG Toxicology Division. MRID No. 407009-46. Guideline Requirement No. 83-4.**

Core Classification:

Committee's conclusion and recommendations:

Dietary administration of tebuconazole at dosages of 0, 100, 300 and 1000 ppm to male and female Wistar rats resulted in parental toxicity primarily at the HDT expressed as increased clinical signs of toxicity (loss of hair), depressed body weights, increased severity of spleen hemosiderosis (females only) and decreased liver and kidney weights in both F0 and F1b males and/or females. Decreased pup viability was observed in F0 but not F1b neonates while there was a significant depression in pup body weight of all littering groups (F1a, F1b, F2a, F2b) at the HDT from birth on. A systemic toxicity LOEL (based upon depressed body weights, increased clinical signs of toxicity, decreased food consumption, increased spleen hemosiderosis and decreased liver and kidney weights) is set at 1000 ppm and a NOEL is set at 300 ppm. The reproductive LOEL, based upon neonatal birth weight depression, is set at 1000 ppm and the NOEL is set at 300 ppm. The data evaluation records are acceptable. The study meets the Core minimum data classification criteria. The study satisfies data requirement 83-4 of Subdivision F of the Pesticide Assessment Guideline.

C. <u>RfD Determination</u>:

The RfD for this chemical has been calculated to be 0.01 mg/kg/day based on a NOEL of 1 mg/kg/day for lenticular and corneal opacity and hepatotoxicity in a long term toxicity study in the dog, using an uncertainty factor of 100.

D. Conclusions and Recommendations:

Except for the carcinogenicity study in mice (83-2b), all studies are considered acceptable.

The classification of carcinogenic potential of this chemical has been deferred until an acceptable carcinogenicity study in the mouse is submitted.

Developmental and reproductive toxicity effects were evident. The Committee recommended referral of the reproductive and developmental toxicity issues to the Health Effects Division Reproductive and Developmental Toxicity Peer Review Committee for weight of the evidence determination.

The RfD for this chemical has been calculated to be 0.01 mg/kg/day based on a NOEL of 1 mg/kg/day for lenticular and corneal opacity and hepatotoxicity in a long term toxicity study in the dog, using an uncertainty factor of 100.

CC: Penny Fenner-Crisp
Esther Saito