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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: HWG 1608 (Tebuconazole) technical. Upgrade of carcinogenicity study.
Tox Chem No. 463P
MRID Nos. 424693-01, 424693-03
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Thru: James N. Rowe, Ph.D., Head
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ACTION: Review of the following studies on the chemical HWG 1608 (Tebuconazole) Technical submitted by Miles Inc.:

1. Oncogenicity Study in NMRI-Mice in a Toxic Dose Range (Additional Study to Study No. T 6018953 with Application to the Feed Over 21 Months): The Frequency of Histiocytic Sarcomas in NMRI-Mice. A Compilation of Historical Data. [Miles Report 96709-4; EPA MRID 424693-01]. This study is a Supplemental submission to EPA MRIDs 407009-41 and 421750-01].
2. Discussion of the Toxicological Basis for Classification of Tebuconazole as an EPA Group E Non-Carcinogen. [Miles Report 103268; EPA MRID 424693-03].



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CONCLUSIONS:

1. It is recommended that the following tebuconazole carcinogenicity study in mice:

HWG 1608. Study for Carcinogenicity in NMRI Mice (Administration in Diet for up to Twenty-one Months [Report No. 96709, EPA MRID 407009-41],

taken together with the supplemental submission:

HWG 1608. Toxic Dose Range Carcinogenicity Study in NMRI Mice (Supplement to Study T 6018953 - Carcinogenicity in NMRI Mice with Administration in Diet Over a 21-Month Period) [Miles Report No. 96709-3, EPA MRID 421750-01].

be upgraded from Supplementary to Minimum

2. The Registrant has presented the view that tebuconazole should be classified as a Group E chemical (Evidence of non-carcinogenicity to humans). Their main points are summarized below and their discussion is included as Attachment 2.

DETAILED CONSIDERATIONS:

1. Review of the Registrant's compilation of historical data on histiocytic sarcomas [Miles Report 96709-4; EPA MRID 424693-01] and upgrading of carcinogenesis studies in mice [EPA MRIDs 407009-41 and 421750-01].

The Registrant initially tested HWG 1608 for carcinogenicity in NMRI mice administered the compound in the diet at levels 0, 20, 60, or 180 ppm for 21 months (MRID 407009-41, 1/25/88). In the review of this 1988 initial study (J.N Rowe, DER dated 12/24/88), the reviewer concluded that based on the findings reported in the study it appeared that the high-dose treatment (180 ppm) was not high enough to adequately test the carcinogenicity of the chemical and the study was classified as Supplementary. This conclusion was ratified by the HED RFD/Peer Review Committee following a meeting held on 3/5/91 (Memorandum from G.Z. Ghali, SACB, to S. Lewis, FHB, dated 7/11/91), and it was concluded that the chemical should have been tested at a higher dose.

In response to the requirement for testing at higher doses, the Registrant tested HWG 1608 for carcinogenicity in NMRI mice at dietary levels of 0, 500 (MDT) and 1500 (HDT) ppm for 91 months (MRID 421750-01, 12/12/88). This second study was reviewed in a DER dated 2/20/92 (Microfiche 009307). Evidence presented in this study indicating that the dose was adequate for assessing the carcinogenic potential of the chemical included:

- o Body weights: Males: statistically significant decreased body weights at 500 ppm (up to 5-6.3%) during the initial half of the study and at 1500 ppm (up to 9-11%) throughout the study up to week 84. As estimated by the reviewer, the body weight gain for weeks 0-48 was 26.5% at 500 ppm, 19.5%

at 1500 ppm and 32.9% in controls. Females: sporadic statistically significant decreased body weights at 500 ppm during the initial third of the study. At 1500 ppm there were statistically significant decreases (up to 7.6-8.5%) in body weight in 39 of the first 59 weeks. As estimated by the reviewer, the body weight gain for weeks 0-24 was 17.0% at 500 ppm, 19.4 % at 1500 ppm vs. 27.4% in controls.

- o Food Consumption: Statistically significantly increased food consumption at 500 ppm in males and at 1500 ppm in both sexes was reported. Increased food consumption values coupled to the observed decreases in body weights are consistent with decreased food efficiency at 500 and 1500 ppm in males and at 1500 ppm in females.
- o Hematology: Statistically significant changes in hematology at 1500 ppm. In males these changes included leucocytosis, and changes consistent with anemia (decreased erythrocytes, hemoglobin, MCHC, and hematocrit values). In addition, statistically significantly increased platelet counts and decreased thromboplastin times were observed 1500 ppm. In females
- o Clinical Chemistry: Dose-dependent and statistically significant increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported for both sexes in the interim and final sacrifices. Alkaline phosphatase (AP) increased with dose in both sexes and reached statistical significance at 1500 ppm. These changes correlated with dose-dependent and statistically significant histopathological findings (See below).
- o Organ weight changes: Dose-dependent and statistically significant increases in absolute and relative liver weights were seen in males at interim and final sacrifice. Dose dependent increases in absolute and relative liver weights (statistically significant at the high dose) were seen in females at interim and final sacrifice. These changes correlated with dose-dependent and statistically significant histopathological findings (See below).
- o Histopathology: Males: dose-dependant and statistically significant increases in hepatic panacinar fine fatty vacuolation at 500 (14/48) and 1500 (25/48) ppm vs 0/47 in controls and statistically significant increases in focal hyperplasia of hepatocytes (23/48) and oval cell proliferation (23/48) at 1500 ppm vs 0/47 in controls. Females: dose-dependant increase in hepatic panacinar fine fatty vacuolation (19/46) which was statistically significant at 1500 ppm. In addition, at 1500 ppm there were increases in periacinar hepatocyte hypertrophy (13/46), oval cell proliferation (17/46), and eosinophilic foci of hepatocyte alteration (7/46) which were statistically significant vs controls (0/47). Additionally, neoplastic findings included a statistically significant increase in the incidence of hepatocellular adenomas (17/48) in males at 1500 ppm vs 3/47 in controls plus a statistically significant increase in the incidence of hepatocellular carcinomas in males (10/48) and females (12/46) at 1500 ppm vs 0/47 and 1/47 in male and female controls, respectively.

Although the second mouse carcinogenesis study fulfilled its initial requirement of achieving adequate dosing for assessing the carcinogenicity of the chemical, the study was classified as core supplementary. It was noted that the study could be upgraded to minimum, allowing it to fulfill (in conjunction with the initial mouse study, MRID 407009-41) the requirements of Guideline 83-2a (Subdivision F) if the following information was submitted and deemed acceptable:

- a. A signed and dated Quality Assurance Statement. Although a dated Quality Assurance statement was included, the corresponding signatures were not included; only the signature of the translator was included.
- b. Historical control data on the incidence of histiocytic sarcomas in male and female mice of the same strain under comparable experimental conditions. The data should encompass the 2-4 year period around the period in which the study was conducted.

The Registrant has now responded with additional information (MRID 424693-00: transmittal letter and MRID 424693-01: historical data), which is presented below:

Item a.

A signed and dated Quality Assurance Statement is required. Although a dated Quality Assurance statement was included, the corresponding signatures were not included; only the signature of the translator was included.

Registrant's Response:

The original German quality assurance statement with signatures is included on pages 1222 and 1223 of the report.

Agency's Response:

The original German quality assurance statement has been examined and it contains the required dates and signatures.

Item b.

Historical control data on the incidence of histiocytic sarcomas in male and female mice of the same strain under comparable experimental conditions. The data should encompass the 2-4 year period around the period in which the study was conducted.

Registrant's Response (In transmittal letter):

The data are contained in the enclosed Miles Rpt. No. 96709-4.

Agency's Response:

The data have been reviewed below. The data is considered to be acceptable. It is noted, however, that because only animals suspected of having histiocytic sarcomas were re-examined there is a potential for missing whatever animals were

misdiagnosed in the initial evaluation as not offering a suggestion of histiocytic sarcoma. Comparison of observed incidences after treatment with historical controls indicates that the incidence of histiocytic sarcoma in 1500 ppm males (3/48) exceeds the historical control range of 0/50-2/50 for control male NMRI mice. Females are within the historical control range.

The following is a review of the historical data submitted on histiocytic sarcomas submitted in Miles Report 96709-4 [EPA MRID 424693-01].

i. Materials and Methods:

Historical data were obtained from 9 studies with NMRI mice started at Bayer Fachbereich Toxicology between 3/82 and 10/85. All studies were 21-months in duration; the mice in all the studies came from the same supplier and were kept under the same conditions as those of the second mouse study. One of these 9 studies (T6018953) is the initial mouse carcinogenicity study on tebuconazole (MRID 407009-41), which was started on 2/85.

The submitted historical data do not encompass the period (8/22/88-5/25/90) in which the second, high-dose, carcinogenicity study of tebuconazole in mice was performed. The registrant indicated that no data are available for studies started after 10/85 because chronic/carcinogenicity studies at Bayer Fachbereich Toxicology after 1985-86 were performed with B6C3F1 mice, except for the second mouse tebuconazole study, which used NMRI mice.

Because the data from the nine available studies was the work of 8 different pathologists, selected slides from control animals from the 9 studies were re-evaluated by one pathologist [R. Burnett, Life Sciences Research]. Animals were re-examined in which the original diagnosis suggested the possible presence of histiocytic sarcomas, including lymphomas, sarcomas or mesenchymal uterine tumors. It is noted that this procedure might have missed slides in which there was no suggestion of histiocytic sarcoma due to misdiagnosis in the original examination. Out of a total of 900 control animals (450/sex) a total of 231 animals were re-examined and the breakdown is as follows:

| Study Number | No. Males examined | No. Females examined |
|-----------------------|--------------------|----------------------|
| T6011121 | 5 | 31 |
| T5016332 | 4 | 9 |
| T5016954 | 6 | 22 |
| T4016962 | 3 | 15 |
| T9017407 | 8 | 29 |
| T2018454 | 7 | 13 |
| T6018953 ^a | 5 | 16 |
| T9019388 | 6 | 35 |
| T4021010 | 3 | 14 |
| Total: ^b | 47 | 184 |

^a The initial mouse tebuconazole oncogenicity study.

^b Grand total (males + females): 231 animals.

ii. Results

The incidence of histiocytic sarcoma in male historical controls was 0/50-2/50 and in female historical controls was 1/50-5/50 (Table 1 and Attachment 1).

Table 1. Incidence of histiocytic sarcoma in NMRI mice historical controls (from p. 21 of MRID 424693-01)

| Study Number | Males (n=50/study) | Females (n=50/study) |
|--------------|--------------------|----------------------|
| T6011121 | 2 | 5 |
| T5016332 | 1 | 1 |
| T5016954 | 1 | 2 |
| T4016962 | 0 | 3 |
| T9017407 | 1 | 3 |
| T2018454 | 1 | 1 |
| T6018953 | 0 | 2 |
| T9019388 | 1 | 3 |
| T4021010 | 0 | 2 |

The incidences of histiocytic sarcoma in the second tebuconazole carcinogenicity study in NMRI mice are summarized below in Table 2. Comparison of Tables 1 and 2 indicates that the incidence of histiocytic sarcoma in 1500 ppm males (3/48) exceeds the historical control range of 0/50-2/50 for control male NMRI mice. Females are within the historical control range.

Table 2. Incidences of histiocytic sarcoma in NMRI mice dosed for 21 months with tebuconazole. From p. 21 of MRID 424693-01.

| | <u>Males</u> | | | <u>Females</u> | | |
|----------------------|--------------|-----|------|----------------|-----|------|
| | 0 | 500 | 1500 | 0 | 500 | 1500 |
| Dose (HWG 1608 ppm): | 0 | 500 | 1500 | 0 | 500 | 1500 |
| No. per Group: | 50 | 50 | 50 | 50 | 50 | 50 |
| No. examined: | 48 | 49 | 48 | 47 | 45 | 46 |
| Histiocytic Sarcoma: | 1 | 2 | 3 | 1 | 3 | 5 |

2. Review of Miles, Inc.'s document: Discussion of the Toxicological Basis for Classification of Tebuconazole as an EPA Group E Non-Carcinogen. [Miles Report 103268; EPA MRID 424693-03].

Miles, Inc. has presented the following arguments in support of the point of view that tebuconazole should be classified as a Class E chemical (the complete discussion is included as Attachment 2):

- a. Neoplastic changes were observed only at the highest dose.

Neoplastic changes in the liver were observed in the second mouse oncogenicity study, only at the highest dose tested (1500 ppm). This dose was 3-fold higher than the MTD (of 500 ppm). Tumor response at this dose level is due to factors which do not operate at or below the MTD.

b. No evidence of mutagenicity.

Mutagenicity tests present no evidence that tebuconazole is capable of interacting with or damaging genetic material. The liver tumor seen in the treated animals result from an epigenetic mechanism. Liver cell death followed by increased cell division may result in the development of tumors. The data are consistent with a threshold effect.

c. Metabolic saturation.

Metabolism data for tebuconazole provide evidence that the metabolic pathways were saturated at 1500 ppm (\approx 225 mg/kg/day). In metabolism studies conducted with rats, at single dose levels of 2 and 20 mg/kg dose-dependent changes in metabolism ratios were observed. At the higher dose level (20 mg/kg) oxidative biotransformation is saturated.

d. Human exposure levels.

The dose levels at which liver tumors were observed in mice have no biological relevance to human exposure levels. In a chronic dietary exposure analysis submitted by Miles, Inc (MRID 424693-03), exposure to tebuconazole residues from its use in peanuts were estimated to range from 0.00008 to 0.000021 mg/kg/day. The high-dose in the mice study is 10,714,285 times greater than the highest dietary exposure to tebuconazole residue.

Agency's Response:

The carcinogenic status of tebuconazole awaits evaluation by the HED/Peer Review Committee on May 26, 1993. The text of the Registrant's comments is included as Attachment 2.

Page _____ is not included in this copy.

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