10-30-95

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

OCT 30 1995

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Triadimefon [2-Butanone, 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-]

CASRN: 43121-43-3
EPA Chemical Code: 109901

FROM: Rick J. Whiting
Science Analysis Branch
Health Effects Division (7509C)

THRU: William Burnam, Chief
Chairman, RfD/Peer Review Committee
Science Analysis Branch
Health Effects Division (7509C)

TO: James Stone, PM 22
Fungicide-Herbicide Branch
Registration Division (7505C)

The Health Effects Division RfD/Peer Review Committee met on June 22, 1995 to discuss and evaluate the toxicology data submitted in support of Triadimefon (Bayleton) registration and to assess a Reference Dose (RfD) for this chemical.

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on February 21, 1986 and again reassessed on March 11, 1993. The RfD was verified by the Agency RfD Work Group on March 11, 1986. The RfD was based on a no-observable effect level (NOEL) of 2.5 mg/kg/day for decreased body weight, erythrocyte count and hemoglobin level at 25 mg/kg/day in a 2-year feeding study in rats. 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 0.03 mg/kg/day.

In the meeting of March 11, 1993 the RfD/Peer Review Committee determined that five Triadimefon studies and/or data evaluation records (DERs) need to be reevaluated or changed. These reevaluations were contained in the data package the RfD/Peer Review Committee received for the June 22, 1995 meeting.

Material available for review consisted of data evaluation records (DERS) for a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a and 83-2a)**, chronic toxicity studies in rats and mice **(83-1a)**, a carcinogenicity study in mice **(83-2b)**, a chronic (2-year) toxicity study in dogs **(83-1b)**, three developmental toxicity studies in rats and two in rabbits **(83-3a and -3b)**, two multigeneration reproduction toxicity study in rats **(83-4)** and subchronic toxicity studies in rats **(82-1)** and dogs **(82-1b)**.

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A. Chronic and Subchronic Toxicity:

The Committee considered the following studies to be acceptable:

1) 2-Year Feeding/Carcinogenicity Study in Rats (83-5, MRID No. 41412001, 42153901. HED Doc. No. 009726, 010310. Core grade minimum); NOEL for systemic toxicity in males and females is 300 ppm (16.4 and 22.5 mg/kg/day, respectively). LEL for systemic toxicity in males and females is 1800 ppm (114 and 199 mg/kg/day, respectively) based on decreased body weight and decreased body weight gain in both sexes; decreased RBC counts, HGB, HCT and MCHC, increased liver weight and cholesterol in females; increased lipopexia in hepatocytic plasma in both sexes and thyroid follicular cell hyperplasia.

2) 21-Month Feeding/Carcinogenicity Study in Mice (83-2b, MRID No. 40752101, 40865101, 92188017. HED Doc. No. 007294. Core grade guideline); NOEL for systemic toxicity in females was not established. LEL for systemic toxicity in females is 50 ppm (19.6 mg/kg/day) based on hepatocellular hypertrophy. NOEL/LEL for systemic toxicity in males is 50 and 300 ppm (13.5 and 76 mg/kg/day), respectively, based on hepatocellular hypertrophy.

3) 2-Year Feeding Study in Mice (83-1a, MRID No. 00069013, 41779701. HED Doc. No. 002009. Core grade minimum); NOEL/LEL for systemic toxicity are 50 and 300 ppm (7.5 and 45 mg/kg/day), respectively, based on increased on mortality at 12 months.

4) 2-Year Feeding Study in Dogs (83-1b, MRID No. 00032539, 00126261, 92188015, 92188016. HED Doc. No. 002008, 004695, 010310. Core grade minimum); NOEL/LEL for systemic toxicity are 330 and 1000/2000 ppm (11.4 and 33.67/60.42 mg/kg/day), respectively, based on decreased food intake in the first year for females dogs and in the second year for male dogs, depression in weight gain in both sexes after the dose was increased to 2000 ppm in the second year and significantly ($p<0.05$) increased alkaline phosphatase activity in both sexes.

5) 12-Week Feeding Study in Rats (82-1, MRID No. 00048624. HED Doc. No. 002005. Core grade minimum); NOEL for systemic toxicity is 800 ppm (40 mg/kg/day), the highest dose tested.

6) 13-Week Feeding Study in Dogs (82-1b, MRID No. 00048625. HED Doc. No. 002005. Core grade minimum); NOEL for systemic toxicity is 2400 ppm (60 mg/kg/day), the highest dose tested.

The Committee considered the following study to be supplementary:

1) 2-Year Feeding Study in Rats (83-1a, MRID No. 00032538. HED Doc. No. 002008, 007805. Core grade supplementary); NOEL/LEL for systemic toxicity are 50 and 500 ppm (2.5 and 25 mg/kg/day), respectively, based on decreased body weight gain, erythrocyte count and hemoglobin.

B. Carcinogenicity:

The Committee did not discuss the carcinogenicity phase (83-2a, MRID No. 41412001, 42153901) of the chronic toxicity/carcinogenicity study in rats or the carcinogenicity study in mice (83-2b, MRID No. 40752101, 40865101, 92188017). The carcinogenic potential of Triadimefon has been addressed by the Health Effects Division Carcinogenicity Peer Committee (HCPRC). The chemical has been classified as a "Group C", possible human carcinogen, based on a statistically significant increase in hepatocellular adenomas, with a positive dose-related

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trend, in both males and female mice.

C. **Mutagenicity:**

The Committee recommended that the Tox 1-Liners for the mutagenicity studies be corrected as per the recommendations of the Health Effects Division Carcinogenicity Peer Review Committee.

D. **Reproductive and Developmental Toxicity:**

The Committee considered the following studies to be acceptable:

1) Developmental Toxicity Study in Rats (83-3a, MRID No. 00149336, 92188018. HED Doc. No. 006841, 010310. Core grade minimum); NOEL/LEL for maternal toxicity are 30 and 90 mg/kg/day, respectively, based on statistically significant body weight gain decrement during gestational days 6-15. NOEL/LEL for developmental toxicity are 30 and 90 mg/kg/day, respectively, based on the increased incidence of skeletal variations, hyoid unossified and incompletely ossified and full and rudimentary extra ribs.

2) Developmental Toxicity Study in Rabbits (83-3b, MRID No. 41446201, 42089601. HED Doc. No. 008467, 008878. Core grade minimum); NOEL/LEL for maternal toxicity are 50 and 120 mg/kg/day, respectively, based on increased clinical signs such as hyperactivity in 2 dams and reddish discharge in 1 dam and statistically significant decreased body weight gain during gestational days 6-10. NOEL/LEL for developmental toxicity are 20 and 50 mg/kg/day, respectively, based on irregular spinous process and incomplete ossification of the anterior and posterior phalanges and vertebral, skull, sternebrae and appendage anomalies and fetal weight decrement and miscellaneous malformations at 120 mg/kg/day.

The Committee also considered a 2-Generation Reproduction Study (1984, MRID No. 00155075, 92188019, 92188020. HED Doc. No. 006563, 010310), a 3-Generation Reproduction Study (1979, MRID No. 00032541, 92188019, 9218820. HED Doc. No. 004695, 010310), two older rat developmental toxicity studies (1981, MRID No. 00089023. HED Doc. No. 001533; 1976, MRID No. 00048629, 00060228. HED Doc. No. 002005) and a older rabbit developmental toxicity study (1982, MRID No. 00149335. HED Doc. No. 006841). The Committee concluded that all of these studies were unacceptable. The Committee also questioned whether another 2-generation study on reproduction would adequately answer the questions about the potential reproductive toxicity of Triadimefon. Thus the Committee recommended that the registrant should confer with EPA prior to conducting a new reproduction study. Since a 90-day neurotoxicity study is required, it may be possible to collect the necessary data from added elements to this study.

E. **Acute and Subchronic Neurotoxicity:**

The scientific reviewer informed the Committee that acute and subchronic neurotoxicity studies have been requested.

F. **Reference Dose:**

The Committee recommended that an RfD for this be established based upon the 2-Year Feeding Study in Dogs. In this study, Triadimefon was administered to dogs at doses of 0, 100, 330 and 1000 ppm (0, 5.7, 11.4 and 33.67 mg/kg/day) for 2-years. After 54 weeks the highest dose tested was increased to 2000 ppm (60.42 mg/kg/day). The NOEL for

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systemic toxicity in dogs of either sex was 330 ppm and the LEL was 1000/2000 ppm based on the following: decreased food intake of approximately 11% the first year in 4/4 females dogs [this decrease in food consumption was more pronounced (approximately 15%) in 4/4 males when the high-dose group was increased to 2000 ppm the second year]; depression in weight gain in both sexes (5/8 animals) after the dose was increased to 2000 ppm in the second year (Male = 20% less than controls; Female: 11% less than controls); and significantly ($p<0.05$) increased alkaline phosphatase activity in both sexes.

An uncertainty factor (UF) of 300 was applied to account for inter-species extrapolation (10), intra-species variability (10) and the lack of an adequate reproduction study in rats (3). **On this basis, the RfD was calculated to be 0.04 mg/kg/day.**

It should be noted that this chemical has been reviewed and an Acceptable Daily Intake (ADI) of 0.03 mg/kg/day has been established by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR) in 1985. In establishing the ADI, the WHO/FAO Joint Committee considered three studies on Triadimefon: 1) a chronic rat feeding study with a NOEL of 2.5 mg/kg/day, 2) a chronic dog feeding study with a NOEL of 8.25 mg/kg/day, and 3) a chronic mouse study with a NOEL of 40 mg/kg/day. In these three studies, triadimefon produced a dose-related increase in liver weights accompanied by elevation of serum hepatic alkaline phosphatase and transaminase activities. The rat was most sensitive, but enzymatic induction was readily reversible on cessation of exposure. Triadimefon also increased the liver weights of dogs, rats and mice which, in dogs and mice, correlated with biochemical evidence of hepatotoxicity at higher doses. Therefore, the ADI was based on the rat study to which a safety factor of 100 was applied yielding an ADI of 0.03 mg/kg/day.

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G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam, Karl Baetcke, Kerry Dearfield, David Anderson, William Sette, Barbara Madden and Joseph Tavano.

Scientific reviewer (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Paul Chin Paul Chin

Joycelyn Stewart Joycelyn Stewart

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Marion Copley Marion Copley

H. Material Reviewed:

1. Bomhard, E.; Schilde, B. (1991). MEB 6447: Chronic Toxicity an Cancerogenicity Studies on Wistar Rats with Administration in Di over a Period of 105 Weeks. MRID No. 41412001, 42153901. HED Do No. 009726, 010310. Classification: Core-minimum data. **This study satisfies data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.**

2. Bomhard, E.; Loser, E. (1978). Meb 6447 Chronic Toxicity Study on Rats (Two-Year Feeding Experiment). MRID No. 00032538. HED Doc. No. 002008, 007805. Classification: Core-supplementary data. **This study does not satisfy data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.**

3. Bombard, E.; Hahnemann, S. (1986). MEB 6447: Common Name: Triadimefon, the Active Ingredient of Bayleton: Carcinogenicity Study on NMRI Mice. MRID No. 40752101, 40865101, 92188017. HED Doc. No. 007294. Classification: Core-guideline data. **This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.**

4. Bomhard, E.; Loser, E. (1980). MEB 6447: Chronic Toxicity Study on Mice: (Two-year Feeding Experiment). MRID No. 00069013, 41779701. HED Doc. No. 002009. Classification: Core-minimum data. **This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.**

5. Hoffmann, K.; Groning, P.; Lorke, D. (1978). MEB 6447: Long-term Toxicity Study on Dogs (Two-year Feeding Study). MRID No. 00032539, 00126261, 92188015, 92188016. HED Doc. No. 002008, 004695, 010310. Classification: Core-minimum data. **This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic testing in dogs.**

6. Eiben, R. (1984). MEB 6447 (Triadimefon): Two-generation Study with Rats. MRID No. 00155075, 92188019, 92188020. HED Doc. No. 006563, 010310. Classification: Core-supplementary data. **This study does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in the rat.**

7. Loser, E.; Lorke, D. (1979). Meb 6447 Multigeneration Reproduction Study on Rats. MRID No. 00032541, 92188019, 9218820. HED Doc. No. 004695, 010310. Classification: Core-supplementary data. **This study does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in the rat.**

8. Unger, T.; Van Goethem, D.; Shellenberger, T. (1982). A Teratological Evaluation of Bayleton in Mated Female Rats. MRID No. 00149336, 92188018. HED Doc. No. 006841, 010310. 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.**

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9. Nagumo, K.; Teraki, Y.; Chiba, T.; et al. (1981). Teratogenicity Test of MEB 6447 in Pregnant Rats. MRID No. 00089023. HED Doc. No. 001533. Classification: No classification was assigned. **This study does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.**

10. Machemer, L. (1976). Meb 6447 (Triadimefon): Evaluation for Embryotoxic and Teratogenic Effects on Rats following Oral Administration. MRID No. 00048629, 00060228. HED Doc. No. 002005. Classification: No classification was assigned. **This study does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.**

11. Clemens, G.; Hartnagel, R. (1990). Teratology Study in the Rabbit with MEB 6447 (Triadimefon). MRID No. 41446201, 42089601. HED Doc. No. 008467, 008878. 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.**

12. Roetz, R. (1982). MEB 6447: Study of Embryotoxic and Teratogenic Effects on Rabbits after Oral Administration. MRID No. 00149335. HED Doc. No. 006841. 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.**

13. Mohr, U. (1976). Meb 6447: Subchronic Toxicity Study on Rats (Twelve-Week Feeding Experiment). MRID No. 00048624. HED Doc. No. 002005. Classification: Core-minimum data. **This study satisfies data requirement 82-1 of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.**

14. Hoffman, K.; Luckhaus, G. (1974). Meb 6447: Subchronic Toxicity Study on Dogs (Thirteen-Week Feeding Experiment). MRID No. 00048625. HED Doc. No. 002005. Classification: Core-minimum data. **This study satisfies data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.**

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