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

SEP 7 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Metribuzin (Sencor) [4-amino-6-(1,1-dimethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one]

CASRN. 21087-64-9
EPA Chem. Code: 101101
Caswell No. 033D

FROM: George Z. Ghali, Ph.D. G. Ghali 9.1.94
Manager, RfD/Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam, Chief
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Health Effects Division (7509C)

Reto Engler, PhD
Co-Chair, RfD/Peer Review Committee
Health Effects Division (7509C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

Esther Saito, Chief
Re-registration Branch
Special Review and Re-registration Division (7508W)

The Health Effects Division RfD/Peer Review Committee met on December 02, 1993 to discuss and evaluate the existing and recently submitted toxicology data in support of Metribuzin re-registration and to re-assess the Reference Dose (RfD) for this chemical.

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

There were two chronic toxicity/carcinogenicity studies in rats dated 1974 and 1993. The chronic toxicity phase of the more recent study was originally classified by the scientific reviewer as Core-supplementary data because of the lack of a no-observable effect level (NOEL). Statistically significant increases in blood levels of thyroxine (T4) and statistically significant decreases in blood levels of triiodothyronine (T3) were observed at all dose levels in male and female rats. The relative weights for thyroid glands was significantly increased at all dose levels in males assigned to the one-year portion of the study. Although the Committee agreed with the scientific reviewer concerning effects observed at the lowest dose level, these effects were considered to be of marginal biological significance or threshold effects (It should be noted that this was a point of contention when the chemical was later presented to the Agency RfD Work Group. The Agency RfD Work Group considered the lowest dose level to be a NOEL and not a LOEL, see RfD discussion below). The Committee considered the chronic toxicity study in rats (83-1a, MRID No. 42672501; 00061261, 00065136, 00147942) and dogs (83-1b, MRID No. 00061260, 00139397) to be acceptable and the data evaluation records (HED Doc. 010175; 001147, 001148, 004767; 001147, 001148, 4262) to be adequate. The Committee recommended upgrading of the chronic toxicity phase of the recent rat study to a Core-minimum status.

The Committee considered the carcinogenicity phase of the more recent chronic toxicity/carcinogenicity study in rats (MRID No. 42672501) to be acceptable. The dose levels tested in the rat study were considered to be adequate for carcinogenicity testing based on body weight and body weight gain reduction in addition to histopathological and organ weight changes. It should be noted that the dose selection for the carcinogenicity study in rats was based on the results of a subchronic (range finding) study. The dose levels tested in the older carcinogenicity study in rats (MRID No. 00061261, 00065136, 00147942) were considered inadequate for carcinogenicity testing. The incidences of pituitary adenomas were increased in females. This increase attained a statistically significant level in the pairwise comparison with the concurrent control and was also statistically significant positive for trend for the incidences of adenomas, but not for the incidences of carcinomas or combined adenomas and carcinomas.

The Committee considered the carcinogenicity study in mice (MRID No. 00087795) to be acceptable. The dose levels tested in the mouse carcinogenicity study were considered to be adequate, or at least approaching an adequate dose level, for carcinogenicity testing based on combination of body weight gain reduction, hematological effects and increased mortality. The Committee requested summary tables for the most ferquently observed tumors in this study before a final decision could be made concerning the carcinogenic potential of this chemical in this strain of mouse.

Structural similarity of this chemical to other carcinogens i.e. Tycor was brought to the Committee's attention. The Committee also debated the question of whether the available carcinogenicity data at that time would warrant referral of the chemical to the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC) for weight of the evidence evaluation. The Committee recommended that an Ad Hoc group should examine the carcinogenicity data before a decision can be made with respect to referral to the HED-CPRC for weight of the evidence evaluation.

There were two reproductive toxicity studies in rats. The Committee considered the more recent study (MRID No. 40838401, 41590001) and the developmental toxicity studies in rats (MRID No. 00163802, 41551801) and rabbits (MRID No. 41249201) to be acceptable and the data evaluation records (HED Doc. No. 007369; 007369, 008473; 008251, 008375) to be adequate. The Committee generally agreed with the reviewer's evaluation and interpretation of data. The Committee recommended combining the NOEL for reproductive toxicity/systemic effects in the rat reproduction study (MRID No. 40838401, 41590001). There were other studies available including a reproductive toxicity study in rats (MRID No. 00061262, 00065135, HED Doc. No. 001147), a developmental toxicity study in rats (MRID No. 00061257, HED Doc. No. 001148), and a developmental toxicity study in rabbits (MRID No. 0087796, HED Doc. No. 001761) all of which were considered unacceptable. The Committee down-graded the developmental toxicity study in rabbits (MRID No. 0087796) from Guideline data to a Core-supplementary status and recommended reevaluation of the study (Note: subsequent to the meeting, the rabbit developmental toxicity study [MRID No. 0087796] was reevaluated and the data evaluation record was updated, the study is currently classified as Guideline data).

The Committee recommended that an RfD be established on the basis of a two-year feeding study in rats. Increased absolute and relative weight of thyroid, decreased lung weight in females and significant changes in T3 and T4 levels were observed in males and/or females at 30 ppm at the lowest dose tested (1.3 g/kg/day for males and 1.6 mg/kg/day in females). An uncertainty factor (UF) of 100 was applied to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.013 mg/kg/day. Since the effects observed at the lowest dose tested were considered to be of marginal biological significance (threshold effects), the Committee did not recommend for an additional UF to compensate for the lack of a NOEL. It was also recommended to use the reproductive toxicity study with a NOEL of 1.3 mg/kg/day as a Co-critical study. However, when the chemical was submitted to the Agency RfD Work Group for verification in their meeting of February 16, 1994, the Work Group did not concur with the Health Effects Division - RfD/Peer Review Committee's position with respect to the LOEL in the chronic rat study. The Work Group felt that the lowest dose level should be defined as a NOEL and not a threshold LOEL. In

their meeting of March 17, 1994, the Health Effects Division - RfD/Peer review Committee concurred with the Agency RfD Work Group's position. It should be emphasized that the only change to the RfD would be redefining the LOEL as an NOEL.

It should be noted that this chemical has not been reviewed by the World Health Organization (WHO) and an acceptable daily intake has not been generated.

Individuals in Attendance

Peer Review Committee members and associates present were William Burnam (Chief, SAB, Co-chair), Reto Engler (HED, Senior Science Advisor, Co-Chair), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), George Ghali (Manager, HED-RfD/QA), Rick Whiting, Henry Spencer, William Sette, Esther Rinde, James Rowe and Roger Gardner.

Other non-members present were Jane Smith (HED, CCB), Pamela Hurley (HED, TB I), Deborah McCall (HED, CCB), Arliene Aikens (HED, CCB) and William Dykstra (HED, TB I)

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

Stephen Dapson Stephen G. Dapson

Mike Ioannou M. Ioannou

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

Marcia Van Gemert Marcia Van Gemert

CC: Richard Schmitt
Stephanie Irene
Marcia Van Gemert
Mike Ioannou
Stephen Dapson
Debra Edwards
Kerry Dearfield
James Kariya
RfD File
Caswell File

Material Reviewed

Material available for review included data evaluation records for two chronic toxicity/carcinogenicity studies in rats **(83-5 or 83-1a and -2a)**, a carcinogenicity study in mice **(83-2b)**, a chronic toxicity study in dogs **(83-1b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, two multi-generation reproductive toxicity studies in rats **(83-4)**, and subchronic toxicity studies in rats, mice and dogs (82-1a and -1b).

1. Christenson, W. R., and Whale, B. S. (1993). Technical grade metribuzin (Sencor): A combined chronic toxicity/ oncogenicity feeding toxicity study in the rat. MRID No. 42672501, HED Doc. No. 010175. Classification: Core-supplementary for chronic toxicity, and Core-minimum for carcinogenicity. This study satisfies data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in rats but does not satisfy data requirement 81-1a for chronic toxicity testing in rats.

2. Loser, E. (1974). Bay 94 337 Chronic toxicity studies on rats (2-year feeding experiment). MRID No. 00061261, 00065136, 00147942, HED Doc. No. 001147, 001148, 004767. Classification: Core-supplementary for carcinogenicity, and Core-minimum for chronic toxicity. This study satisfies data requirement 82-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats but does not satisfy data requirement 81-2a for carcinogenicity testing in rats.

3. Loser, E. and Mirea, D. (1974). Bay 94 337 chronic studies on dogs (two-year feeding experiment). MRID No. 00061260, 00139397, HED Doc. No. 001147, 001148, 004262. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Porter, M. C. et al. (1988). A two-generation reproduction study in rats with Sencor technical (Metribuzin). MRID No. 40838401, 41590001, HED Doc. No. 007369. Classification: Guideline data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Loser, E. and Siegmund, F. (1974). Bay 94 337, Multigeneration study in rats. MRID No. 00061262, 00065135, HED Doc. No. 001147, 001148. 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 rats.

6. Kowaski, R. L. et al. (1986). A teratology study with Sencor technical (Metribuzin) in the rat. MRID No. 00163802,

41551801, HED Doc. No. 007369, 008473. 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.

7. Machemer, L. (1972). Sencor (Bay 94 337), Studies for possible embryotoxicity and teratogenic effects on rats after oral administration. MRID No. 00061257, HED Doc. No. 001148. 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.

8. Clemens, G. R. and Hartnagel, R. E. (1989). Teratology study in the rabbit with Sencor technical (Metribuzin). MRID No. 41249201, HED Doc. No. 008251, 008375. 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.

9. Unger, T. M. and Shellenberger, T. E. (1981). A teratology evaluation of Sencor. MRID No. 0087796, HED Doc. No. 001761. Classification: Guideline data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

10. Hayes, R. H. (1981). Metribuzin (Sencor) oncogenicity study in mice. MRID No. 00087795, HED Doc. No. 001761, 003911. Classification: Guideline data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

11. Loser, E. and Spicer, J. (1970). Bay 94 337 Subchronic toxicological studies on rats (three-month feeding experiment). MRID No. 00084141, HED Doc. No. 001146, 004262. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

12. Loser, E. et al. (1969). Bay 94 337 Subchronic toxicological studies on rats (three-month feeding experiment). MRID No. 00106161, HED Doc. No. 001146. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

13. Lindberg, D. and Richter, W. (1970). Ninety-day Subacute oral toxicity study of Bay 94337 in beagle dogs. MRID No. 00106162, HED Doc. No. 001146, 001151. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.