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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 351

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Second RfD/Peer Report of Pendimethalin [N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine]

CASN: 40487-42-1
EPA Chem. Code: 108501
Caswell No. : 454BB

FROM: Henry W. Spencer Ph.D. *H. Spencer 8/1/96*
Member, RfD/QA Peer Review Committee
Science Analysis Branch
Health Effects Division (7509C)

THRU: William Burnam *W. Burnam*
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Science Analysis Branch
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TO: Robert Taylor, PM 25
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The Health Effects Division-RfD/Peer Review Committee met on July 25, 1996 to discuss and evaluate supplemental toxicology information which was supplied by the Toxicology Branch 1 in support of the Pendimethalin reregistration.

The RfD/Peer Review Committee had met on January 5, 1996 (see report dated February 6, 1996) and had recommended additional changes to several DERs and questioned the significance of changes reported in the chronic rat study. This report evaluates those changes and recommends an RfD value based on the newly submitted data.

A. Chronic and Subchronic Toxicity

The Committee agrees that the previously reviewed and evaluated studies are acceptable and agrees with the DERs as evaluated by the Toxicology Branch 1 reviewer with regard to the following:

1. Chronic toxicity study in the rat (MRID No. 40174401).
Note: The NOEL is changed to 500 ppm (25 mg/kg/day) with an

LOEL of 5000 ppm (250 mg/kg/day) based on decreased survival, body weight gain and numerous other changes. The thyroid changes included diffusely dark thyroids and follicular cell hyperplasia. The study and DER were considered to be acceptable.

2. Chronic toxicity study in the male rat (MRID No. 42027802). **NOTE:** There is no NOEL for this study at a LDT of 1250 ppm (51 mg/kg/day) based on decreased colloid and increased liver weight. The LOEL was the LDT. Thyroid tumors, increased GGT enzyme and total cholesterol were increased at the 5000 ppm (213 mg/kg/day), the HDT. The DER was considered acceptable and the study was supplementary.

3. The chronic mouse study (MRID No. 40909901). **Note:** The NOEL was established at 500 ppm (62.8 and 78.3 mg/kg/day) for males and females with an LOEL established at 5000 ppm (622.1 and 806.9 mg/kg/day) for males and females based on mortality, decreased body weight, and thyroid and liver/gall bladder weight increases in males. The study and DER were considered to be acceptable.

4. The chronic oral toxicity study in dogs (MRID Nos. 1) 00058657, 2) not yet assigned for new data). **Note:** New data was evaluated for this study by the Toxicology Branch 1 and it established a NOEL of 200 mg/kg/day, the high dose tested. There was no LOEL in the study. The RfD Committee found the study acceptable and agreed with the reviewer on the results provided in the supplemental DER.

5. The subchronic oral 92-day thyroid function study in male rats (MRID No. 42054601) was evaluated following 15, 29, 57 and 92 days with 100 ppm or 5000 ppm of Pendimethalin in the diets. Changes in T_3 and T_4 were considered of minimal significant for risk characterization at 100 ppm since an increase in TSH was not seen and there was no change in the amount of hypertrophy of the thyroid gland. A NOEL was established at 100 ppm (4.98 mg/kg/day) and the LOEL was determined to be 5000 ppm in the study. The study was considered to be supplemental and was adequately presented in the DER.

6. The subchronic oral 56-day thyroid function study (28 days treatment, 28 days recovery) in male rats (MRID No. 43135001) studied male SD rats given 0, 500 or 5000 ppm of pendimethalin in the diets. A NOEL was not established. At the LDT of 500 ppm (31 mg/kg/day) there was decreased T_4 , rT_3 and free T_4 as well as increased % free T_3 and T_4 , and histologic changes of the thyroid follicular cells throughout the 28 day treatment period. The LOEL was the LDT of 500 ppm. The study was supplemental data and the DER was acceptable.

7. A 14-day intrathyroidal metabolism study in male rats with AC 92,553 (MRID No. 43135003) used 10 male SD rats per group given diets of 0, 100, or 5000 ppm Pendimethalin for 14 days. The 100 ppm dose was found to cause no effects on the thyroidal parameters while significant changes occurred at the HDT (5000 ppm). The NOEL was 100 ppm (10 mg/kg/day) and the LOEL was 5000 ppm (500 mg/kg/day). The study was supplemental data and the DER was acceptable.

8. A Biliary excretion and hepatic metabolism study in male rats (MRID No. 43135004) used 10 male SD rats per group given diets of 0, 100 or 5000 ppm Pendimethalin for 14 days. Only at 5000 ppm was a significant increase in TSH, or reduction in T3 and T4 noted. The NOEL was 100 ppm (10 mg/kg/day) with the LOEL of 5000 ppm (500 mg/kg/day). The study was supplemental and the DER was acceptable.

B. Choice of NOEL

Subchronic exposure to Pendimethalin for 28 days results in an LOEL at the lowest dose tested of 500 ppm (31 mg/kg/day) based on several hormonal and histologic thyroid changes observed throughout the 28 day treatment period. TSH and organ weights showed no overt changes at this dose. The NOEL in the 92-day study is 100 ppm (4.98 mg/kg/day) while the 5000 ppm group exhibited thyroid hormonal, histologic and organ weight changes. The NOEL in the 14-day intrathyroidal study was 100 ppm (10 mg/kg/day) with thyroid hormonal, histologic and organ weight changes also observed at 5000 ppm. The difference in the NOELs of 4.98 mg/kg/day and 10 mg/kg/day (both based on dietary concentrations of 100 ppm) is due to the time weighted average of compound intake. For the 14 day study, the rats received a higher dose of the compound than older rats due to increased body weight. It is felt that the 14-day NOEL of 10 mg/kg/day, accurately reflects a true NOEL for thyroid effects since these effects have been demonstrated to have an early onset (before 14 days). Therefore, it was the decision of the Committee to consider all three studies together and establish the LOEL at 31 mg/kg/day and the NOEL at 10 mg/kg/day.

C. Reference Dose (RfD)

The Committee recommended that a RfD for this chemical be established based on the combined rat studies noted above with a NOEL of 10 mg/kg/day. The LOEL of 31 mg/kg/day was based on hormonal and histologic thyroid changes. An Uncertainty Factor (UF) of 100 was applied to account for both the interspecies extrapolation and intraspecies variability. On this basis, the RfD was calculated to be 0.10 mg/kg/day. It should be noted that there is controversy as to whether the rat is more sensitive to thyroidal changes than the human.

The Committee discussed this issue and concluded that without data to confirm whether the human is less sensitive, the full UF should be utilized.

D. Individuals in Attendance:

Peer Review Committee members and associates present at the July 25, 1996 meeting were William Burnam, Chief SAB, Henry Spencer, Marion Copley, Mike Ioannou, Acting Chief, TB 2, Kit Farwell, Karl Baetcke, Chief, TB1, Clark Swentzel, John Leahy, G. Reddy, Jim Rowe, Ed Budd, Albin Kocialski, Roger Gardner, Bill Sette, Pam Hurley, Rick Whiting.

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

William Greear

William B. Greear

Marion Copley

Marion Copley

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated).

Karl Baetcke

Karl D. Baetcke

- CC: Stephanie Irene
- Debra Edwards
- Albin Kocialski
- Karl Baetcke
- Beth Doyle
- Jess Rowland
- William Greear
- Marion Copley
- RfD files

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