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

FEB 3 1996

MEMORANDUM

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

CASRN: 40487-42-1
EPA Chem. Code: 108501
Caswell No.: 454B

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Health Effects Division (7509C)

THRU: William Burnam
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TO: Robert Taylor, PM 25
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The Health Effects Division-RfD/Peer Review Committee met on November 20, 1995 and subsequently on January 5, 1996 to discuss and evaluate the toxicology data submitted in support of Pendimethalin reregistration and to reassess 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 chronic toxicity study in dogs **(83-1b)**, two multi-generation reproductive toxicity studies in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and subchronic toxicity studies in rats **(82-1a)** including special studies designed to address the effects of Pendimethalin on thyroid hormone levels.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, MRID No. 40174401) to be acceptable as Core-minimum data, and the data evaluation record for this study (HED Doc. No. 008606) to be adequate.

The no-observable effect level (NOEL) was reported to be 100 ppm (5 mg/kg/day), and the lowest-observable effect level (LOEL) was reported to be 500 ppm (25 mg/kg/day) based on pigmentation of thyroid follicular cells in males and females. The Committee questioned the biological significance of this effect, i. e. the pigmentation of thyroid follicular cells, and recommended raising the NOEL to 25 mg/kg/day and the LOEL to 5000 ppm (250 mg/kg/day), the highest dose level tested. At the highest dose level, survival in males was slightly decreased and body weight gain was decreased. In addition, there was also decreased food consumption, increased gamma glutamyl transferase and cholesterol, increase in the absolute or relative liver and thyroid weights, generalized icterus, dark adipose tissue in females, diffusely dark thyroids, and thyroid follicular cell hyperplasia.

A second chronic toxicity study in rats (83-1a, MRID No. 42027802) was available for review by the Committee. The study was reviewed jointly with the previous study and was considered to be of supplementary nature. In this study the chemical was tested at, relatively, higher dose levels. A NOEL was not established, and a LOEL was considered to be 1250 ppm (51 mg/kg/day, lowest dose tested) based on thyroid changes. The results of this study were considered to be consistent and supportive to the findings of the other study described above particularly with regards to thyroid changes.

The Committee examined the chronic toxicity phase of the chronic toxicity/carcinogenicity study in mouse (83-5, MRID No. 40909901) and agreed with the reviewer's evaluation and interpretation of the data. The NOEL was established at 500 ppm (62.8 and 78.3 mg/kg/day for males and females, respectively). The LOEL was 5000 ppm (622.1 and 806.9 mg/kg/day for males and females, respectively) based on mortality (f); decreased body weight (f); increased thyroid, liver and gall bladder weight; amyloidosis (m).

The Committee considered the two-year chronic toxicity study in dogs (83-1b, MRID No. 00058657) to be acceptable as Core-minimum data and the data evaluation record (HED Doc. No. 001035, 004026) to be adequate. The NOEL/LOEL were considered to be 12.5 and 50 mg/kg/day based on increase in serum alkaline phosphatase and increased liver weight and other hepatic lesions.

The Committee examined several subchronic toxicity studies of different durations in rats (82-1a, MRID Nos. 00156081; 42054601; 43135001; 43135003) and considered them to be acceptable and

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appropriate for the purposes they were intended. These were primarily thyroid hormone special studies. In a study conducted on male rats (MRID No. 42054601), a LOEL was considered to be 4.98 mg/kg/day, the lowest dose level tested. At this level, changes in the thyroid hormones T3 and T4 values were observed. However, in the absence of other effects, these changes were considered to be of minimal significance for risk characterization. Effects of this type were only marginally increased at 31 mg/kg/day in another study.

B. Carcinogenicity:

The carcinogenicity issue has already been addressed by the Health Effects Division-Carcinogenicity Peer review Committee. The chemical was classified as a "Group C", possible human carcinogen, "based on statistically significant increased trend and pairwise comparison between the high dose group and controls for thyroid follicular cell adenomas in male and female rats" (HED report dated July 24, 1992) and recommended that for the purpose of risk characterization the RfD) approach should be used for quantification of human risk.

The RfD Committee was requested to consider whether the thyroid neoplasms could be attributed to a disruption of the thyroid-pituitary hormonal balance. Following evaluation of the new mechanistic studies submitted to the Agency, the Committee concluded that the hypothesis that thyroid tumors are due to a thyroid-pituitary imbalance can be supported (see Appendix for details).

C. Reproductive and Developmental Toxicity:

The Committee considered the 2-generation reproductive toxicity study in rats (83-4, 1990, MRID No. 41725203) to be acceptable and the data evaluation record (HED Doc. No. 008558, 010431) to be marginally adequate based on current standards.

According to the data evaluation record, the systemic toxicity NOEL was considered to be 500 ppm (34 and 43 mg/kg/day, in males and females, respectively), and the LOEL was considered to be 2500 ppm (172 and 216 mg/kg/day, in males and females, respectively) based on decreased body weight gain and food consumption in males and females. However, the Committee determined that in the absence of significant clinical signs (e. g. emaciation, decreased feces, reduced activity) and organ weight data, a systemic NOEL can not be established. There were no weight gain or food efficiency data from premating periods. There were decreases in food consumption and body weight, but food efficiency data were lacking. The Committee determined that food efficiency data would be required to support conclusion regarding palatability/parental systemic toxicity.

According to the data evaluation record, the reproductive toxicity NOEL was considered to be 500 ppm and the LOEL was considered to be 2500 ppm, based on decreased number of pups born and pup body weight. However, the Committee noted that pup survival data during the lactation period were not included in the data evaluation record. The Committee noted also that decreases in mean litter size of live pups were not consistent with the gestation index which was reported to be unaffected. Therefore, the Committee recommended raising the reproductive toxicity NOEL/LOEL to 2500 and 5000 ppm (346 and 436 mg/kg/day in males and female, respectively).

The adequacy of the three-generation reproductive toxicity study in rats (83-4, 1972, MRID No. 000266671, 00040304, 00059470) could not be determined because of the inadequacy of the data evaluation record.

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 00025752, 41725202) to be unacceptable because no maternal toxicity was observed at the highest dose level. The data evaluation record of this study (HED Doc. No. 00544, 007751, 008558) was initially considered to be inadequate because litter data and details on the nature of delayed ossification were lacking. The Committee reevaluated the study subsequent to the RfD meeting and prepared a new data evaluation record for this study conforming to the current standard and format. **The conclusions of the new review** are that the study is supplementary and should be used in conjunction with the rabbit developmental toxicity study (discussed below) to satisfy guideline requirements. There were no maternal or developmental effects noted at any dose level tested, therefore the NOELs for developmental and maternal toxicity are equal to or greater than 500 mg/kg/day (highest dose tested).

The Committee could not determine the acceptability of the developmental toxicity study in rabbits (83-3b, 1982, MRID No. 00117444); the data evaluation record (HED Doc. No. 002406) was considered inadequate. There were no maternal or litter data included in the original data evaluation record. Based on the data presented, the maternal and/or developmental toxicity NOEL/LOEL for this study could not be established. The Committee reevaluated this study subsequent to the RfD meeting and prepared a new data evaluation record for this study conforming to the current standard and format. **The conclusions of the new review** are that the study is supplementary and does not meet the guideline requirements at this time. However, it is potentially upgradable upon submission of individual litter data (fetal alterations) and historical control data. If, however, the additional data indicates the lack of any developmental or maternal effects at any dose, an additional developmental study would be required. There were no maternal effects at any dose level tested (highest dose 60 mg/kg/day) while a developmental NOEL/LOEL could not be determined from this study.

Although there was evidence of skeletal effects at the high dose, this could not be confirmed.

D. Acute and Subchronic Neurotoxicity:

There were no acute or subchronic neurotoxicity studies in rats (81-8 and 82-7) available for review by the Committee. The Committee did not recommend that such studies be conducted for this chemical.

E. Mutagenicity:

There were no mutagenicity data (84-2) available for review by the Committee. The mutagenicity issue has already been addressed by the Health Effects Division-Carcinogenicity Peer Review Committee (HED report dated July 24, 1992).

F. Reference Dose (RfD):

The Committee recommended that a RfD for this chemical be established based on the chronic toxicity study in dogs with a NOEL of 12.5 mg/kg/day. At the next higher dose level (50 mg/kg/day), increase in serum alkaline phosphatase and liver weight and other hepatic lesions were observed. 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 0.13 mg/kg/day.

G. Individuals in Attendance:

Peer Review Committee members and associates present at one or both meetings were William Burnam (Chief, SAB; Chairman, RfD/QA Peer Review Committee), George Ghali (Manager, RfD/QA Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief, TB II), Stephen Dapson, Roger Gardner, William Sette, Henry Spencer and Rick Whiting. In attendance also was Kit Farwell and William Greear of HED as an observer.

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

John Doherty

Marion Copley

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

Karl Baetcke

CC: Stephanie Irene
Debra Edwards
Marion Copley
Karl Baetcke
John Doherty
Albin Kocialski
Karen Whitby
[redacted]
Beth Doyle
Amal Mahfouz (OW)
RfD File
Caswell File

H. Material Reviewed:

1. Weltman, R. (1987). Chronic dietary toxicity and oncogenicity study in rats fed with AC 92,553. MRID No. 40174401, HED Doc. No. 008606. Classification: Core-minimum data. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats. It should be noted that the acceptability of the carcinogenicity phase has been determined by the HED-Carcinogenicity Peer Review Committee.

2. Baily, D. E. (1991). Effects of chronic administration of AC 92,553 on the function and structure of male rat thyroids. MRID No. 42027802, HED Doc. No. 009821. Classification: 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. However, the study is acceptable for the purpose it was intended to address and compliments reference # 1 above.

3. Johnson, D. E. (1988). Chronic dietary and oncogenicity study with AC 92,533 in mice. MRID No. 40909901, HED Doc. No. 008606. Classification: Supplementary for the chronic toxicity phase. The carcinogenicity phase of the study has been evaluated by the HED-Carcinogenicity Peer Review Committee. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

4. Cueto, C. and Manus, A. G. (1979). Two-year toxicity study in dogs: AC 92,553. MRID No. 00058657, HED 001035, 004026. 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.

5. Irvine, L. F. H. and Boughton, P. (1990). Dietary rat two-generation reproduction toxicity study with AC 92,553. MRID No. 41725203, HED Doc. No. 010431. Classification: Core-minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

6. Rapp, W. R. and Kasner, J. A. et al. (1974). A three-generation reproduction study of AC 92,553 in rats. MRID No. 00026671, 00040304, 00059470, HED Doc. No. 004026. Classification: Could not be determined, inadequate DER. This study, as presented, does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

7. Mistretta, L. H. and Miller, P. (1979). Oral teratology study in rats with AC 92,553: Final Report. MRID No. 00025752,

41725202, HED Doc. No. 00544, 007751, 008558, 000000[1]. Classification: supplementary as down-graded by the Committee. This study does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

8. Wolf, G. et al. (1982). Teratology study in rabbits: AC 92,553 technical. MRID No. 00117444, HED Doc. No. 002406, 000000. Classification: Could not be determined, inadequate DER. This study, as presented, does not satisfy data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

9. Fischer, J. E. (1986). AC 92,553: A thirteen week rat feeding study. MRID No. 00156081, HED Doc. No. 005311. Classification: Guideline. This study satisfies data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

10. Fischer, J. E. (1991). 92-Day thyroid function study in albino rats with AC 92,553. MRID No. 42054601, HED Doc. No. 009821. Classification: Supplementary. This study was intended to address a specific issue and not to satisfy a particular data requirement of Subpart F of the Pesticide Assessment Guideline.

11. Fischer, J. E. (1993). 56-Day thyroid function study in albino rats with AC 92,553. MRID No. 43135001, HED Doc. No. 000000. Classification: Supplementary. This study was intended to address a specific issue and not to satisfy a particular data requirement of Subpart F of the Pesticide Assessment Guideline.

12. DeVito, W. J. and Braverman, L. E. (1993). A 14-day intrathyroidal metabolism study in male rats with AC 92,553. MRID No. 43135003, HED Doc. No. 000000. Classification: Supplementary. This study was intended to address a specific issue and not to satisfy a particular data requirement of Subpart F of the Pesticide Assessment Guideline.

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[1] Document number 000000 means no number has been assigned yet.

APPENDIX

THYROID CARCINOGENESIS

In the Peer Review document on the potential carcinogenicity of pendimethalin, the Committee provided three factors that must be addressed in order to determine whether the thyroid tumors associated with administration of pendimethalin could be attributed to disruption of the thyroid-pituitary hormonal balance. These factors are discussed below with respect to pendimethalin.

FACTOR I.

Consideration of whether the thyroid tumors associated with administration of pendimethalin can be attributed to disruption of the thyroid-pituitary hormonal balance. (In addressing this factor, the Policy states, six indicators should be considered.)

a. Goitrogenic activity in vivo:

Thyroid follicular cell hypertrophy was observed in males (only sex tested) in a 92-day thyroid function study and in a 2-year rat Study No. 2. In 2-year rat Study No. 1 there was increased pigmentation of the follicular cells and discolored colloid of the thyroid in males and females. There was decreased colloid in the follicles in males (only sex tested) in the 2-year rat Study No. 2. Thyroid follicular cell hyperplasia was observed in rats in the 2-year chronic/carcinogenicity feeding Study No. 1 (both sexes) and Study No. 2. There was a dose-related increase in absolute and relative thyroid weight in males (only sex tested) in the 92-day hormonal mechanism study. In both 2-year rat studies (No. 1 and 2), there was also increased absolute and/or relative thyroid weight (males and females when tested). There were also significant increases in the absolute and/or relative thyroid weight in the chronic/carcinogenicity mouse Study No. 1.

In a 56-day (only males tested) thyroid function study, there were increased absolute and relative thyroid weights. There were histologic changes in the thyroid: increase in follicular cell height, the area of the follicles occupied by colloid was decreased and the diameter of the thyroid follicles was decreased. The ultrastructural changes (numerous distended rough endoplastic reticulum, prominent Golgi apparatuses associated with small granules, numerous colloid droplets and large mitochondria) in the thyroid were stated to be indicative of a mild to moderate TSH stimulation. The majority of these parameter tended to be reversible after the 28 day recovery period.

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b. Clinical chemistry changes (e.g., reduced thyroid hormone and increased TSH serum concentrations):

In the 92-day hormonal mechanism study, T_3 and T_4 were significantly elevated in males (only sex tested) and TSH was significantly decreased. In the 2-year rat study No. 2, there was an increase in TSH in males (only sex tested), but T_3 and T_4 levels were quite variable.

In the 56-day thyroid function study, T_3 and T_4 were decreased during the 28-day treatment period. In a 14-day intra thyroidal metabolism study, TSH was increased and T_3 and T_4 were decreased.

c. Specific evidence of reduced hormone synthesis (e.g., inhibited iodine uptake) or increased thyroid hormone clearance (e.g., enhanced biliary excretion):

In the 14-day intra thyroidal metabolism study, there were decreases in T_3 and T_4, and increases in TSH and ^{131}I uptake by the thyroid. Pendimethalin did not affect the organofication of ^{131}I or the percentage of ^{131}I incorporated into T_4, monoiodotyrosine (MIT) or diiodotyrosine (DIT). Pendimethalin, therefore, does not appear to affect the synthesis of thyroid hormones or iodine metabolism. Pendimethalin is not considered to be a primary goitrogen and the increase in ^{131}I uptake is attributed to a secondary effect resulting from an increase in serum TSH.

In a 14-day biliary excretion study, pendimethalin caused decreases in serum T_3 and T_4 and an increase in TSH. There was increased liver weight, bile flow and cumulative biliary excretion of ^{125}I-T_4 glucuronide which was attributed to T_4-glucuronytransferase activity. There was also a decrease in T_4 binding to its specific transport protein (transthyretin) in the 56-day thyroid function study. The increased metabolic clearance of T_4 and enhanced biliary excretion of T_4 and T_4-glucuronide all contribute to the decrease in thyroid hormones.

d. Evidence of progression (e.g.., hypertrophy/hyperplasia, nodular hyperplasia - neoplasia):

There is possible evidence of progression in both 2-year rat studies based on increases in hypertrophy and/or hyperplasia and adenomas of the thyroid follicular cells. There is no evidence of progression to malignancy. Only hypertrophy was apparent in the 92-day rat study and the 56-day thyroid function study.

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e. Reversibility of lesions after exposure is terminated:

In the 56-day thyroid function study, pendimethalin was administered to male rats for 28 days, followed by a 28-day recovery period. After the end of 28 days, T_3 and T_4 were decreased, TSH increased and hypertrophy of follicular cells was observed. After the 28 day recovery period, hypertrophy of the follicular cells reversed, and T_3, T_4 and TSH returned to levels comparable to controls.

f. SAR to other thyroid tumorigens:

Pendimethalin is structurally related to trifluralin and oryzalin with reservations noted in the SAR section of the Peer Review document.

Based on the overall judgment of the six indicators in Factor I, it may be concluded that there is sufficient evidence that the thyroid tumors in the rat associated with administration of pendimethalin may be due to a disruption in the thyroid-pituitary status.

FACTOR II

Consideration of the extent to which genotoxicity may account for the observed tumor effects.

The mutagenicity data on pendimethalin considered by the Cancer Peer Review Committee were equivocal. There were some possible indications of mutagenic activity in the point mutation tests (frame shift). Although one host mediated assay was negative, a second test was questioned. A second Ames test, HGPRT (CHO), dominant lethal, in vitro cytogenetics (CHO) and DNA repair were negative.

A new microbial study submitted subsequent to the Cancer Peer Review using Salmonella and E.coli produced negative effects when tested with the same batch of technical pendimethalin used in the 1991 carcinogenicity study that produced positive thyroid tumors. Two additional microbial tests were conducted using a purified sample of technical pendimethalin (99.5%) and a 1991 batch of technical pendimethalin. Negative results were obtained in these assays. A new CHO/HGPRT study was conducted that also produced negative results. In addition, a new alkaline elution assay was conducted that produced negative results. Therefore the total mutagenicity evidence submitted to date indicates that pendimethalin is not genotoxic to mammalian somatic and germ cells.

FACTOR III

Evaluation of neoplasms in addition to thyroid follicular tumors, including pituitary tumors.

No other treatment-related neoplastic lesions were observed in any study.

CONCLUSIONS

The evidence, when taken collectively, indicates that:

- pendimethalin is not genotoxic to mammalian cells and
- that the production of thyroid tumors (the only tumor type produced) may be attributed to **the disruption of the thyroid-pituitary hormonal balance.**

As a result of this determination, threshold considerations should be considered in the carcinogenic risk assessment of pendimethalin.