2-15-89

007751

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: California Department of Food and Agriculture - EPA Toxicology Review for Pendimethalin

TOX Chem No. 454BB

FROM: William B. Greear, M.P.H. William B Greear 2/15/89
Review Section II
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (TS-769C)

TO: William Burman, Acting Director
Health Effects Division (TS-769C)

THRU: Marion P. Copley, D.V.M., Section Head Copley 2/15/89
Review Section II
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (TS-769C)

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture (CDFA).

STUDY TYPE

83-5 - Combined Chronic/Oncogenicity Rat - No. 009 976069 "A Three and Twenty-four Month Oral Toxicity and Carcinogenicity Study of AC 92,553 in Rats," Bio/dynamics, Inc. August 21, 1974.

Deficiency No. 1

"Not complete nor acceptable."

EPA Response

The study is invalid. The laboratory utilized a "high purity" grade of pendimethalin for the first 5 to 6 months of testing. They then switched to a commercial grade. Nitrosamines are present in the commercial grade but are not detectable in the "high purity" grade. Thus, the animals were not exposed to the potential carcinogens during the critical periods of growth and development. (Therefore, the study is invalid.)

CONCLUSION

Concur with CDFA. However, it would still be invalid if the report was completed. (CDFA has indicated that the report is incomplete.) This study is a data gap.

CORE-GRADE

Remains unchanged: Invalid

STUDY TYPE

83-1 - Chronic Rat (see "combined" study above).

STUDY TYPE

83-1 - Chronic Dog - 060 039908 "Two-Year Toxicity Study in Dogs [AC 92,553]," Litton Bionetics, December, 1977.

Deficiency No. 1

"Not complete nor acceptable."

EPA Response

The study appears to be complete and acceptable. It is unclear why CDFA considers the study to be incomplete. No specific deficiencies were noted.

CONCLUSION

Nonconcurrence with CDFA. (It should be noted that CDFA has data pending review.) This study is not a data gap.

CORE-GRADE

Remains unchanged: Minimum

STUDY TYPE

83-2 - Oncogenicity Rat (See "combined" study above).

STUDY TYPE

83-2 - Oncogenicity Mouse - 009 19993, 976065 "18-Month Carcinogenic Study of Herbicide AC 92,553 (Prowl) in Mice," Bio/dynamics, Inc. 72R-747, April 2, 1974.

Deficiency No. 1

"Insufficient information to assess possible adverse effects."

EPA Response

The study is invalid because only a very limited number of mice were scheduled for a complete histopathological examination. In addition, animals that died on study were not examined. Also, numerous masses and lesions that were grossly observed were not followed up by a histological examination. The study cannot be upgraded.

CONCLUSION

Concur with CDFA. This study is a data gap.

CORE-GRADE

Remains unchanged: Invalid

STUDY TYPE

83-4 - Reproduction Rat - 004 976073 "Three-Generation Reproduction Study of AC 92,553 (Prowl) in Rats" Bio/Dynamics, Inc., 72R-74B, March 6, 1974.

Deficiency No. 1

". . . only two dose levels [were used]."

EPA Response

A study utilizing 2 dose levels would be acceptable if there was 1) a dose level that produced a toxic effect and 2) a dose level in which no observable effects are present. This study meets these minimum criteria.

3

Deficiency No. 2

"Insufficient numbers of animals . . . 10 males/group and less that 20 pregnant animals/treatment [were] used."

EPA Response

In general, at least 20 pregnant females/group should result from mating with 10 males/group. However, this is not considered to be a major deficiency since data are available from 3 generations instead of 2 generations which is the minimal requirement of the Guidelines. The deficiency is not expected to alter the conclusions of the study.

Deficiency No. 3

". . . no adults of any generation were systematically examined microscopically . . . ."

EPA Response

This deficiency is correct. Histopathological examination should have been conducted on all abnormal parental lesions with emphasis on reproductive organs. This deficiency is considered to be very important because there was an indication in one study, titled "A Three and Twenty-four Month Oral Toxicity and Carcinogenicity Study of AC 92,553 in Rats," Bio/dynamics, Inc., August 21, 1974, that the test material may have produced a compound-related increase in the occurrence of endometrial carcinoma. Therefore, a second reproduction study should be conducted in which histopathological examination is included.

CONCLUSION

Concur with CDFA. The study is a data gap.

CORE-GRADE

Changed from Minimum to Supplementary.

STUDY TYPE

83-3 - Teratogenicity Rat - No. 042 2911 "Oral Teratology Study in Rats - AC 92,553." Hazelton Laboratories, Vienna, VA (Project No. 362-155), August 17, 1979.

Deficiency No. 1

". . . needs justification of dose levels."

4

EPA Response

There was no justification of the dose levels selected for testing as indicated by CDFA. Higher dose levels should have been tested because there were no maternal toxic effects observed. This is a major deficiency.

Deficiency No. 2

"Needs . . . individual fetal data."

EPA Response

The Toxicology Branch evaluation indicated that mean data were used in the evaluation. This apparent lack of individual animal data appears to be a deficiency. Although it is clear that a teratogenic effect does not occur, there may be a delay in development. The number of litters with anomalies was not provided.

CONCLUSION

Concur with CDFA. (It is noted that CDFA is requesting that additional clarifying information be submitted.) This study is a data gap. The study may be upgraded.

CORE-GRADE

Changed from Guideline to Supplementary

STUDY TYPE

83-3 - Teratogenicity Rat - 003 976070 "Teratogenic Study with AC 92,553 (Prowl) Technical in Albino Rats" Industrial Bio-Test Laboratories, Inc., Northbrook, IL, B2324, December 12, 1972.

Deficiency No. 1

Invalid IBT Study.

EPA Response

This study, as well as No. B1374(A), is invalid according to a data audit.

CONCLUSION

Concur with CDFA.

5

CORE-GRADE

Remains unchanged: Invalid

STUDY TYPE

83-3 - Teratology Rabbit - 066 039915 "Teratology Study is Rabbits" AC 92,553 Technical, Hazelton Laboratories, May 1, 1982.

Deficiency No. 1

"Insufficient information for assessment."

EPA Response

The statement regarding insufficient information requires clarification: What data are needed for evaluation?

CONCLUSION

Nonconcurrence with CDFA. (It should be noted that CDFA is requesting that additional information be submitted.) This study is not a data gap.

CORE-GRADE

Remains unchanged: Minimum

007751

R:53329:Greear:HED-1:KENCO:1/24/89:4/19/89:AS:VO:AS
R:50662:Greear:HED-1:KENCO:02/03/89:02/14/89:CL:VO:JH:AS

7

R:53329:Greear:HED-1:KENCO:1/24/89:4/19/89:AS:VO:AS
R:50662:Greear:HED-1:KENCO:02/03/89:02/14/89:CL:VO:JH:AS
R:50182:Greear:HED-1:KENCO:02/14/89:06/23/89:CL:jh:rw

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

### COMBINED

#### RAT

NOTE: Volume 361-073 indicates that a replacement rat chronic (combined?) study has been completed. The study has not arrived at CDFA Medical Toxicology Branch.

009 976069 "A three and twenty-four month oral toxicity and carcinogenicity study of AC 92,553 in rats". Bio/dynamics, Inc., 8/21/74 (original report). [Note that supplementary information in Vols. 61-63 (below) was dated 6/15/81]. Pendimethalin, (grade and purity not characterized) given 0, 100, 500, and 5000 ppm in diet. **Possible adverse effect: no NOEL observed** (periportal hepatocyte hypertrophy in males at all dosages; hepatocellular cytoplasmic change in both sexes at all dosages). At 500 ppm and above were observed: cytoplasmic laminated bodies in livers of females, increased secretory granules in thyroid in males, amber to brown urine in both sexes. Increased incidence of uterine endometrial adenocarcinoma in 5000 ppm females. **Not complete nor acceptable.** Study apparently not accepted by EPA. Other concerns noted. Reviews by J. Wong, 3/14/85; and by C. Aldous after receipt of Vol. 61-63, below, 7/24/86.

361-061, 062, and 063 039909-039911 Addendum to study 009:976069, includes microscopic examinations of some tissues which had been preserved in formalin for some years before blocking and staining. Upgrade of study unlikely (see 1-liner, above).

### CHRONIC

Note: 2,4-Dinitrophenol causes cataracts in humans and in some experimental animals. Test article is an analogous dinitro compound, and a rigorous long-term study in a sensitive species with careful ophthalmoscopic evaluation is required.

#### RAT

(See combined rat study, above)

#### DOG

060 039908 "Two-year toxicity study in dogs [AC 92,553], Litton Bionetics, Dec. 1979. Pendimethalin, 91.4%. 0, 12.5, 50, and 200 mg/kg/day by capsule. **No adverse effect indicated**: NOEL = 12.5 mg/kg/day (Increased levels of alkaline phosphatase in males at 50 and 200 mg/kg/day and SGPT in 200 mg/kg/day males; various liver lesions in 50 and 200 mg/kg/day males and females; increased liver and kidney relative weights in 50 and 200 mg/kg/day males; yellow coloration in hair coats of both sexes at 50 and 200 mg/kg/day). **Not complete, not acceptable.** Possibly upgradeable on receipt of additional data. C. Aldous, 7/17/86.

CMA 9/22/87

**ONCOGENICITY**

**RAT**

(See combined rat, above)

**MOUSE**

**Note:** A final report for a mouse oncogenicity study is due in October, 1988. (073)

009 19993, 976065 "18-Month Carcinogenicity Study of Herbicide AC 92,553 (Prowl) In Mice"; Bio/Dynamics, Inc., 72R-747, (4/2/74); Pendimethalin (AC 92,553) Purity and grade not identified. 0, 100, 500, 2500 ppm (high dose raised to 5000 ppm at 8th week), 75 males and 75 females at each dose level and for each of the controls (vehicle control and positive control). Tissues of a maximum of 15/sex/group evaluated microscopically. **No adverse effect indicated:** Thyroid weights of 5000 ppm males and of 500 and 5000 ppm females were significantly elevated. No microscopic changes in any tissues attributed by investigators to test article. 5000 ppm females had reduced body weight and increased food consumption compared to other groups. **Unacceptable; Not Upgradeable.** Insufficient information to assess possible adverse effects. (J. Wong, 3-13-85). "One-liner" by HGM/CNA, 6/9/87.

**REPRODUCTION**

**RAT**

004 976073 "Three Generation Reproduction Study of AC 92,553 (Prowl) in Rats"; Bio/Dynamics, Inc., 72R-745, 3/6/74; Pendimethalin (AC92,553); Purity and grade not given. Administration in diets of Long-Evans rats to 10 males and 20 females per dose level at 500 and 5000 ppm. Insufficient information to establish NOELs. **No adverse effect indicated.** Findings included slight but consistent reductions in body weight gains of 5000 ppm males and females during growth periods, however food consumption of 5000 ppm animals was at least as high as controls. Fewer pups born in 5000 ppm groups (reason not known). Decreased pup survival and weight gain in 5000 ppm groups, unless dams were taken off treatment during lactation periods. **Unacceptable; Not upgradeable** (only two dose levels, insufficient number of animals--10 males/group and <20 pregnant animals/treatment used, no adults of any generation were systematically examined microscopically, despite an apparent reproductive toxic effect). Insufficient information to evaluate possible adverse effects. (J. Wong, 3/8/85). "One-liner" by HGM/CNA, 6/9/87.

**TERATOGENICITY**

**RAT**

042 2911 "Oral Teratology Study In Rats--AC 92,553". Hazleton Laboratories, Vienna, VA. (Project No. 362-155), (8/17/79). Pendimethalin (Prowl, 94.2%); administered by gavage on days 6 through 15 of gestation to 33-34 females/group at 125, 250, 500 mg/kg and vehicle (corn oil) control group. **Unacceptable; Possibly upgradeable** (needs justification of dose levels, also individual fetal data to allow independent evaluation by CDFA).



Cdd 9/22/87

**Insufficient information for assessment.)** (J. Wong, 3/8/85; re-reviewed by HGM/C. Aldous 9/21/87). Note that the 3/8/85 review indicated possible fetotoxicity. This judgement was reversed in the 9/21/87 review: a marginal possibility of an increase in "delayed ossification of extremities" does not appear to warrant flagging as a "possible adverse effect", however additional clarifying information is required.

003 976070 "Teratogenic Study With AC 92.553 (Prowl) Technical in Albino Rats"; Industrial Bio-Test Labs., Inc (IBT) (Northbrook, IL.), B2324, 12/12/72; **Unacceptable; Not upgradeable; invalid IBT study.** (J. Wong, 3/12/85) "One-liner" by HGM/CNA, 6/9/87.

## RABBIT

**066 039915** "Teratology study in rabbits", AC 92,553 Technical. Hazleton Labs., 5/11/82. Pendimethalin, 92.2%. Dosed 0, 15, 30, and 60 mg/kg/day by gavage in corn oil. **"Insufficient information for assessment"** of possible adverse effects. Maternal NOEL = 15 mg/kg/day (anorexia, adipsia). **Possible adverse effect:** no developmental NOEL could be established (slight dilatation of the lateral ventricle in all treatment groups) **Not complete, not acceptable.** Possible upgrade: more information requested in 7/25/86 review. C. Aldous, 7/25/86 and 9/22/87.

066 039914 Pilot study for 066:039915, above. Data support choice of dosage groups employed in the primary study.

## GENE MUTATION

073 51176 "CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay." (Pharmakon International, Inc., Study No. PH 314-AC-002-85, 10/26/85) AC 92,553, 90.9%, lot AC5042-37D; tested at 0, 10, 25, 50, 75, 100, 125, 150, 175 ug/ml with S-9 and 0, 1, 5, 7.5, 10, 20, 30, 40, 50 ug/ml without S-9 (Aroclor induced Rat Liver S-9 activation) uncorrected for purity; 5 hour exposure period (activated and nonactivated); **NO ADVERSE EFFECT.** Test article cytotoxic to CHO cells at 30, 40, 50 ug/ml without S-9, and at 125, 150, 175 ug/ml with S-9. For all other dose levels mutation frequencies per $10^6$ survivors were not statistically significantly greater than the negative controls. **UNACCEPTABLE** (No repeat trial). HGM/J. Gee, 6/15/87.

** 067 39916 **"Mutagenicity Tests of Typical Prowl Herbicide and of Minor Component CL 94,269"** (American Cyanamid, Report submitted to EPA in 1977); Pendimethalin, **several lots up to 99% purity;** Salmonella strains TA 1535, TA 1537, TA 98, **TA 100, E. coli** uvrA; Tested at 0, 10, 100 and 1000 ug/plate ± S-9 plate incorp or 1000 ug/disk; mouse host-mediated at 6.4 and 10.0 mg/mouse; ***NO ADVERSE EFFECT. Acceptable.*** *JR Gee (7/24/86). NOTE: Previous review of a less complete version of this study (volume 361-052 record number 16859)* by J. Wong (3/8/85) resulted in the determination that the study was unacceptable due to insufficient data.



CNA 9/22/87

007751

**CHROMOSOME**

**073 51178 "In Vitro Chromosome Aberration Analysis in Chinese Hamster Ovary (CHO) Cells." (Pharmakon Research International, Inc., Study No. PH320-AC-002-85, 10/29/85); Pendimethalin, AC 92,553, 90.9%, lot # AC 5042-37D, tested at 0, 10, 50, 100 ug/ml with Aroclor 1254 induced rat liver and at 0, 7.5, 37.5, 75.0 ug/ml without activation. NO ADVERSE EFFECT. There were no statistically significant increases in aberrations/cell and proportion of aberrant metaphases at any dose level tested. ACCEPTABLE. HGM/J. Gee, 6/15/87.

003 967074 "Dominant Lethal Study In Rats With AC 92,553." (Food and Drug Research Laboratories, Inc., Waverly Division, Lab. Project No. 2006, 10/5/73): Pendimethalin, AC 92,553, Lot No. 1984-79-3; 0, 500 and 2500 ppm administered in feed to 15 male rats/group for 60 days, rats then mated 1:1 with virgin female rats. **Insufficient information to assess possible adverse effects. Unacceptable.** (Major variances from guidelines, including, omission of positive control group, use of only two dose levels, sacrificed females early). (J. Wong, 3/12/85). "One-liner" by HGM/CNA, 6/19/87.

**DNA DAMAGE**

**073 51177 "Rat Hepatocyte Primary Culture/DNA Repair Test." (Pharmakon International, Inc., Study No. PH 311-AC-003-85, 10/25/85); Pendimethalin, AC 92,553, 90.9%, lot #C 5042-37D; treated at 0, 0.003, 0.005, 0.15, 0.3, 0.5, 1.5, 3.0, 5.0, [illegible] 30, 50, 150, 300, 500, 1500, 3000, 5000 ug/ml, uncorrected for pur[illegible] 18-20 hour exposure; NO ADVERSE EFFECT. No significant increase i[illegible]an net nuclear counts. ACCEPTABLE. Worksheet and HGM. J. Gee, 6/15/87.

NEUROTOXICITY

Not required at this time.

CNA 9/22/87