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

APR 1 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Picloram [4-amino-3,5,6-trichloropicolinic acid].

CASRN. 1918-02-1
EPA Chem. Code: 005101
Caswell No. 039

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Robert Taylor, PM 15
Fungicide-Herbicide Branch
Registration Division (H7505C)

Lois Rossi, Chief
Re-registration Branch
Special Review and Re-registration Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on September 30, 1993 to evaluate the existing toxicology data in support of Picloram re-registration and to reassess the Reference Dose (RfD) for this chemical. The data base for this chemical was generated using the free form of picloram (picloram acid), the triisopropanolamine (CASRN 6753-47-5, Chem. Code 005102) and potassium (CASRN 2545-60-0, Chem. Code 005104) salts of picloram, and the ethylhexyl ester (also known as the isooctyl ester, CASRN 26952-20-5, Chem. Code 005103) of picloram. For toxicity testing requirement purposes, Picloram K^- salt and Picloram acid were considered to be equivalent as per the 1988 Registration Standard.

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on March 31, 1986 and was re-assessed on March 20, 1987. The RfD was verified by the Agency RfD Work Group on May 30, 1986 and again on April 15, 1987. The RfD was based on a no-observable effect level (NOEL) of 7.0 mg/kg/day for liver effects including increased absolute and relative liver weights observed at 35.0 mg/kg/day in males in a six-month feeding study in dogs. An Uncertainty Factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species

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variability. On this basis, the RfD was calculated to be 0.07 mg/kg/day.

In the meeting of September 30, 1993 the RfD Peer Review Committee recommended that the RfD for this chemical be based on a NOEL of 20 mg/kg/day for a dose-related increase in size and altered tinctorial properties of centrilobular hepatocytes in males and females at 60 and 200 mg/kg/day in a chronic toxicity study in rats. An Uncertainty Factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.20 mg/kg/day. It should be noted that no regulatory value has been established for this chemical by the World Health Organization (WHO) up to this date.

The Committee considered the chronic toxicity/carcinogenicity study in rats (83-1a and 83-2a), the chronic toxicity study in dogs (83-1b) the carcinogenicity study in mice (83-2b), the two-generation reproductive toxicity study in rats (83-4) and the developmental toxicity studies in rats and rabbits (83-3a and -3b) to be acceptable, and the data evaluation records for these studies, except for some revisions, to be adequate.

There was no evidence, based on the available data, to suggest that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions.

The dose levels tested in the carcinogenicity studies in rats and mice were considered adequate for carcinogenicity testing. The treatment did not alter the spontaneous tumor profile in these strains of rats and mice under the testing conditions. The chemical was therefore classified as a "Group E" carcinogen. This classification applies to the picloram acid and potassium salt forms for which acceptable carcinogenicity studies were available for review to the HED carcinogenicity Peer Review Committee. Carcinogenicity studies had not been required for other forms of picloram. However, subsequent to the carcinogenicity peer review meeting, it was reported that 2-ethylhexanol was detected as a metabolite of the picloram ethylhexyl ester in Fisher 344 rats. This metabolite is also a primary hydrolytic cleavage product of DEHP (di-2-ethylhexyl) phthalate, a known rodent liver carcinogen. This metabolite is thought to play a role in the ability of DEHP to act as a peroxisome proliferator and it has been suggested that peroxisome proliferation might be the underlining mechanism in DEHP carcinogenicity.

It was brought to the Committee's attention that a surrogate Q_1^* for di-(2-ethylhexyl) phthalate would be used to perform an initial assessment of possible risk to workers from potential exposure to the picloram ethylhexyl ester.

A. Individual in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

Reto Engler

Marcia Van Gemert

Karl Baetcke

Kerry Dearfield

Henry Spencer

William Sette

James Rowe

John Tice

David Anderson

Stephen Dapson

George Ghali

2. Peer Review Committee Members and Associates in Absentia (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

3. Scientific Reviewer(s) (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Brian Dementi

Karen Hamernik

4. Others

S. Makris, J. Doherty and J. Smith as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Karen Hamernik/Brian Dementi
James Kariya
Jane Smith
RfD File/Caswell File

B. Material Reviewed:

Material available for review by the Committee included data evaluation records for chronic toxicity/carcinogenicity studies in rats (83-1a), long-term toxicity studies in dogs (83-1b), a carcinogenicity study in mice (83-2b), developmental toxicity studies in rats and rabbits (83-3a and -3b) and a reproductive toxicity study in rats (83-4) and the tox-one liner. The Committee focused the discussion on the following studies:

1. Cassia, P. F. et al. (1992) Picloram: Two-year dietary chronic toxicity/oncogenicity study in Fischer 344 rats. MRID 42619302, HED Doc. No. 010571.

Core Classification: Core-minimum for the carcinogenicity phase of the study. Core minimum for the chronic toxicity phase when considered together with study evaluated under MRID No. 00132705 and 00155940.

Committee's Conclusions and Recommendations:

The chemical was tested in Fischer 344 rats at 250 and 500 mg/kg/day of picloram. A NOEL was not established. The LOEL was considered to be < 250 mg/kg/day, the lowest dose tested, for increase in the incidence and the severity of glomerulonephritis, the presence of blood in urine, decreased urine specific gravity and increased size of hepatocytes accompanied by altered staining properties. The Committee agreed with the reviewer's evaluation and interpretation of data. The high dose tested was considered adequate for carcinogenicity testing. The treatment did not alter the spontaneous tumor profile in this strain of rats under the testing conditions. This study, in conjunction with another rat study reviewed under MRID No. 00132705 and 00155940 below, satisfies data requirement 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Landry, T. D. et al. (1986). Picloram: a two-year dietary chronic toxicity oncogenicity study in Fischer 344 rats. MRID No. 00132705, 00155940, HED Doc. No. 005721, 007064.

Core Classification: Core-Guideline (according to the DER).

Committee's Conclusions and Recommendations:

The chemical was tested in Fischer 344 rats at 20, 60 and 200 mg/kg/day of picloram. The NOEL/LOEL were considered to be 20 and 60 mg/kg/day, respectively, based on a dose-related increase in size and altered tinctorial properties of centrilobular hepatocytes in males and females and increased absolute and/or relative liver weights. The Committee agreed with the reviewer's evaluation and interpretation of data, however, the Committee felt that the LOEL

might have been higher. The RfD Committee reiterated the Carcinogenicity Peer Review Committee's conclusion that the high dose tested was inadequate for carcinogenicity testing. However, when this study is considered together with the chronic toxicity/carcinogenicity study discussed above under MRID No. 42619302, the two studies are considered adequate. The study (MRID 00132705) should be downgraded from Core-Guideline to a Core-minimum status. The treatment did not alter the spontaneous tumor profile in this strain of rats under the testing conditions. This study, in conjunction with another rat study reviewed under MRID No. 42619302, satisfies data requirement 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

3. Scott, W. T. et al. (1992). Picloram: two-year dietary oncogenicity study in B6C3F1 mice. MRID No. 42619301, HED Doc. No. 010571.

Core Classification: Core-Guideline.

Committee's Conclusions and Recommendations:

The chemical was tested in B6C3F1 mice at 100, 500 and 1000 mg/kg/day of picloram. The NOEL was considered to be 1000 mg/kg/day, the highest dose tested. The data evaluation record stated that although there was a significant increase in absolute and relative kidney weight in males, no histopathological changes were found to corroborate these changes. The Committee disagreed with the NOEL/LOEL as reported in the data evaluation record. The Committee felt that the kidney effects observed in mice were seen in other species, therefore, these effects were considered to be treatment-related effects and the NOEL should have been set at 500 mg/kg/day and not at 1000 mg/kg/day. Since the results of the mouse study, with or without revisions, will not impact the RfD for this chemical, the Committee felt that revision of the data evaluation records would not be necessary (the respective Toxicology Branch has decided later to revise the DER to reflect the Committee's position). Otherwise, the Committee agreed with the reviewer's evaluation and interpretation of data. The Committee concluded that the high dose tested was adequate for carcinogenicity testing. The treatment did not alter the spontaneous tumor profile in this strain of mice under the testing conditions. This conclusion is also supported by the findings of another bioassay in mice (MRID No. 00081275) sponsored by the NIH in the same strain of mice. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

4. Barna-Lloyde, T. et al. (1988). Picloram: 12-month dog chronic dietary toxicity study. MRID No. 40834301, HED Doc. No. 010558.

Core Classification: Core-minimum.

Committee's Conclusions and Recommendations:

The chemical was tested in Beagle dogs at 7, 35 and 175 mg/kg/day of picloram. The NOEL was considered to be 175 mg/kg/day, the highest dose tested. According to the data evaluation record the high dose tested is supported by the range finding study even though there are no signs of toxicity in the-long term study. The data evaluation record considered the increase in absolute and/or relative liver weights to be an adaptive response and not a toxicological effect. However, since this effect was observed in other species and was accompanied by histopathological changes (in the other species), the Committee concluded that this effect in fact is a toxicological effect and, therefore, the NOEL should be set at 35 mg/kg/day and not at 175 mg/kg/day. Furthermore, effects on body weight gain were seen in a 6-month study in Beagle dogs at the same level. This indicates that the high dose level is an effect level rather than a no-observable effect level. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs. The 6 month dog study (MRID 00110534) clarifies the toxicity in this study.

5. Barna-Lloyd, T. et al. (1982). Results of a six-month dietary toxicity study of picloram administered in the diet to male and female dogs. MRID No. 00110534, HED Doc. No. 003954.

Core Classification: Core-minimum.

Committee's Conclusions and Recommendations:

The chemical was tested in Beagle dogs at 7, 35 and 175 mg/kg/day of picloram. The NOEL was considered to be 7 mg/kg/day based on liver weight changes in males. However, since the changes in liver weight were not statistically significant and in light of the longer term toxicity study in dogs discussed above, the Committee felt that the NOEL should be established at 35 mg/kg/day. This study helps to clarify the overall toxicity seen the one year dog study and helps in defining the NOEL in that study (MRID 408343-01).

6. Breslin, W. J. et al. (1991). Two-generation dietary reproduction study in Sprague-Dawley rats. MRID No. 42078701, HED Doc. No. 010535.

Core Classification: Core-minimum.

Committee's Conclusions and Recommendations:

The chemical was tested in Sprague-Dawley rats at 20, 200 and 1000 mg/kg/day of picloram. The NOEL/LOEL for parental toxicity were

considered to be 200 and 1000 mg/kg/day based on histopathological lesions in kidney, primarily of the tubules and papilla(e), blood in the urine, decreased urine specific gravity, increased absolute and relative kidney weights and decreased body weight gain. The NOEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered acceptable and the data evaluation record was considered adequate provides that additional data tables be included to support the conclusions made by the reviewer. It should be noted that the scientific reviewer had provided the additional data tables as requested by the Committee. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

7. Schroeder, R. E. (1990). A teratogenicity study in rats with picloram triisopropanolamine salt. MRID No. 41382504, HED Doc. No. 010202.

Core Classification: Guideline data.

Committee's Conclusion and Recommendation:

The chemical (picloram triisopropanolamine salt, 61% purity) was administered to Sprague-Dawley rats at doses of 100, 500, and 1000 mg/kg/day, (or 56, 280, and 560 mg/kg/day when adjusted for picloram acid equivalency (mass % = 56) and purity. Maternal toxicity NOEL/LOEL were considered to be 280 mg/kg/day and 560 mg/kg/day based on increased incidence of clinical signs of toxicity and decreased body weight gain and food consumption during the dosing period. The Developmental toxicity NOEL was considered to be 560 mg/kg/day, the highest dose tested. The Committee agreed with the reviewer's evaluation and interpretation of the data. The study was considered acceptable and the data evaluation record was considered adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

8. Vadula, U. et al. (1991). 2-Ethylhexyl ester of picloram: oral gavage teratology study in Sprague-Dawley rats. MRID No. 42296901, HED Doc. No. 010210.

Core Classification: Guideline data.

Committee's Conclusion and Recommendation:

The chemical (picloram 2-ethylhexyl ester, purity 89.7%) was tested in CD rats at 100, 500 and 1000 mg/kg/day (equivalent to 68, 340 and 680 mg/kg/day of picloram acid (mass % = 68). Maternal toxicity NOEL/LOEL were considered to be 68 and 340 mg/kg/day based on decreased body weight gain during the early dosing period. Developmental toxicity NOEL was considered to be 680 mg/kg/day, the

highest dose tested. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered acceptable and the data evaluation record was considered adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

9. Shroeder, R. E. (1990). A teratogenicity study in rats with picloram potassium salt. MRID No. 41382502, HED Doc. 009356.

Core Classification: Core-minimum data.

Committee's Conclusion and Recommendation:

The chemical (potassium salt of picloram acid, 34.7% purity) was tested in Sprague-Dawley rats at 100, 500 and 1000 mg/kg/day or, 35, 174 and 347 mg/kg/day of picloram potassium salt when adjusted for purity (equivalent to 30, 150 and 298 mg/kg/day of picloram acid (mass % = 86), adjusted for purity). Maternal toxicity NOEL/LOEL were considered to be 150 and 298 mg/kg/day based on excessive salivation in the high dose dams. Developmental toxicity NOEL was considered to be 298 mg/kg/day, the highest dose tested. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered acceptable and the data evaluation record was considered adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

10. Vadula, U. et al. (1992). Picloram triisopropanolamine salt: oral gavage teratology study in New Zealand white rabbits. MRID No. 42460901, HED 010198.

Core Classification: Guideline.

Committee's Conclusion and Recommendation:

The chemical (picloram triisopropanolamine salt, 61% purity) was tested in two phases in New Zealand white rabbits at 180, 538 and 1000 mg/kg/day in the first phase or 101, 301 and 560 mg/kg/day of picloram acid; and at 54, 180, 538 and 1000 mg/kg/day, or 30, 101, 301 and 560 mg/kg/day picloram acid in the second phase. Maternal toxicity NOEL/LOEL were considered to be 30 and 101 mg/kg/day based on increased rate of abortion and increased incidence of clinical signs of toxicity. Developmental toxicity NOEL was considered to be 560 mg/kg/day, the highest dose tested. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered acceptable and the data evaluation record was considered adequate. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

11. Zablotny, K. E. et al. (1991). 2-Ethylhexyl ester of picloram: Oral gavage teratology study in New-Zealand white rabbits. MRID No. 42121104, HED Doc. No. 010210.

Core Classification: Core-minimum data.

Committee's Conclusion and Recommendation:

The chemical (2-ethylhexyl ester of picloram, 89.7% purity) was tested in New Zealand white rabbits at 20, 100 and 500 mg/kg/day (equivalent to 14, 68 and 340 mg/kg/day of picloram acid. Maternal toxicity NOEL/LOEL were considered to be 14 and 68 mg/kg/day based on increased incidence of clinical signs of toxicity and decreased body weight gain during the dosing period. Developmental toxicity NOEL was considered to be 340 mg/kg/day, the highest dose tested. The Committee generally agreed with the reviewer's evaluation and interpretation of data, but felt that the maternal LOEL is some what equivocal and it could be higher. However, the Committee did not recommend any revision to the data evaluation record. The study was considered acceptable and the data evaluation record was considered adequate. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

12. John, T. et al. (1984). Oral teratology study in rabbits: picloram potassium salt. MRID No. 00138703, 41069501, HED Doc. No. 004169, 007777.

Core Classification: Core-minimum data (in DER).

Committee's Conclusion and Recommendation:

The chemical (picloram potassium salt, purity 34.7%) was tested in New Zealand white rabbits at 40, 200 and 400 mg/kg/day of picloram acid. Maternal toxicity NOEL/LOEL were considered to be 40 and 200 mg/kg/day based on decreased body weight gain during the dosing period. Developmental toxicity NOEL/LOEL were considered to be 40 and 200 mg/kg/day based on increased mean resorption rate. The Committee felt that the developmental NOEL should be set at 400 mg/kg/day, the highest dose tested. The Committee also recommended reevaluation of the study or, at least, updating the data evaluation record by the addition of more data tables. It should be noted that the additional data tables were provided by the scientific reviewer. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.