Micropics

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

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9/13/93

SEP 13 '93

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Picloram: review of a metabolism study in rats.

Tox.Chem No.: 39
MRID No.: 412096-02
DP Barcode: D183027
Submission No.: S426195
PC Code: 005101

From: John C. Redden, Toxicologist 9/1/93
Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

To: Venus M. Eagle
Reregistration Branch
Special Review and Reregistration Division (H7508)

Thru: Karen L. Hamernik, Ph.D. 9/1/93
Section Head Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

KH 9/3/93

ACTION:

Review the attached study.

CONCLUSIONS:

The absorption, distribution, metabolism, and excretion of picloram were studied in groups of female rats administered a single i.v. or oral gavage dose of 10 mg/kg, an oral gavage dose of 1000 mg/kg ^{14}C-picloram, or 10 mg/kg/day unlabeled picloram by gavage for 14 days followed by a single oral gavage dose of 10 mg/kg ^{14}C-picloram on day 15.

The study demonstrated that ^{14}C-picloram is rapidly absorbed, distributed, and excreted following oral and i.v. administration in rats. Total recoveries of the radioactivity were high for all groups (94-96% of administered dose); urine was the major route of excretion (76-86% of administered dose). The recovery of radioactivity in the feces was lower in the i.v. group (5% of administered dose) compared to oral groups (12-25% of administered dose). The slightly greater fecal recovery in the

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high-dose oral group compared to the single and repeated low-dose oral groups suggests that saturation may have occurred at the high-dose level. Radioactivity was not detectable in any tissues, including the carcass, 3 days after oral or i.v. dosing. The metabolism of picloram appeared to be minimal because unmetabolized picloram was the only radioactive component identified in urine and feces.

This study is classified as **Acceptable**. This study alone does not satisfy the minimum requirements set forth under Guideline 85-1 for metabolism studies because only female rats were evaluated in this study. When data from Study Report HET-K-38323-(22) (Nolan et al. 1980; MRID No. 098321; HED Doc. No. 1889 & 7069) are coordinated with the results of the present study, the toxicological requirements for adequate metabolism data in the rat are satisfied.

FINAL

DATA EVALUATION REPORT

PICLORAM

Study Type: Metabolism

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer — Karen Gan, M.S. — Date 8/27/93

Independent Reviewer — Sanju Diwan, Ph.D. — Date 8/30/93

QA/QC Manager — William McLellan, Ph.D. — Date 8/31/93

Contract Number: 68D10075
Work Assignment Number: 2-130
Clement Number: 422
Project Officer: Caroline Gordon

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GUIDELINE SERIES 85-1: Metabolism

EPA Reviewer: Paul Chin, Ph.D.
Review Section II, Toxicology Branch I
Health Effects Division

Signature: Paul Chin
Date: 8/31/93

EPA Section Head: Marion Copley, DVM
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: Marion Copley
Date: 8/31/93

DATA EVALUATION REPORT

STUDY TYPE: Metabolism in rats (Guideline Series 85-1)

EPA IDENTIFICATION NUMBER:

PC Code: 005101

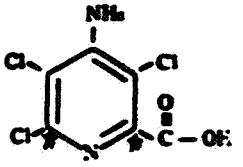
Tox Chem Number: 39

MRID Number: 412096-02

TEST MATERIAL: Picloram

SYNONYM: 4-amino-3,5,6-trichloropicolinic acid

STRUCTURE:



* denotes the position of the ^{14}C label

SPONSOR: Dow Chemical Company, Midland, MI

PERFORMING LABORATORY: Toxicology Research Laboratory, Dow Chemical Company, Midland, MI

AUTHORS: R.H. Reitz, M.D. Dryzga, D.C. Helmer, and P.E. Kasti

REPORT: Picloram: General metabolism Studies in Female Fischer 344 Rats. Study ID K-038323-044.

STUDY COMPLETION DATE: August 1989

CONCLUSIONS: The absorption, distribution, metabolism, and excretion of picloram were studied in groups of female rats administered a single i.v. or oral gavage dose of 10 mg/kg, an oral gavage dose of 1000 mg/kg ^{14}C-picloram, or 10 mg/kg/day unlabeled picloram by gavage for 14 days followed by a single oral gavage dose of 10 mg/kg ^{14}C-picloram on day 15.

The study demonstrated that ^{14}C-picloram is rapidly absorbed, distributed, and excreted following oral and i.v. administration in rats. Total recoveries of the radioactivity were high for all groups (94–96% of administered dose); urine was the major route of excretion (76–86% of administered dose). The recovery of radioactivity in the feces was lower in the i.v. group (5% of administered dose) compared to oral groups (12–25% of administered dose). The slightly greater fecal recovery in the high-dose oral group compared to the single and repeated low-dose oral groups suggests that saturation may have occurred at the high-dose level. Radioactivity was not detectable in any tissues, including the carcass, 3 days after oral or i.v. dosing. The metabolism of picloram appeared to be minimal because unmetabolized picloram was the only radioactive component identified in urine and feces.

CLASSIFICATION: Acceptable. This study alone does not satisfy the minimum requirements set forth under Guideline Series 85-1 for metabolism studies because only female rats were evaluated in this study. When data from Study Report HET-K-38323-(22) (Nolan et al. 1980; MRID No. 098321; HED Doc. No. 1889 & 7069) are coordinated with the results of the present study, the toxicological requirements for adequate metabolism data in the rat are satisfied.

A. MATERIALS

1. Test Substance

The nonradiolabeled test material (lot number AGR#221371) had a purity of 99.4%. Radiolabeled test material (lot number GHD 1265-40A, Inv. 660) was labeled with ^{14}C at the 2 and 6 carbon positions on the pyridine ring. The radiochemical purity was >99.5%, and the specific activity was 16.28 mCi/mmol.

2. Test Animals

Female Fischer 344 rats (5/group) were obtained from Charles River Breeding Laboratories, Kingston, NY. Animals weighed 125–155 g. A single oral gavage dose of 10 mg/kg (low-dose group) or 1000 mg/kg (high-dose group) of labeled picloram was administered to rats. Another group received daily doses of 10 mg/kg unlabeled picloram for 14 days followed by a single oral gavage dose of 10 mg/kg ^{14}C-labeled picloram on day 15 (repeated-dose group). An additional group received a single i.v. dose of 10 mg/kg labeled picloram (i.v. group).

The doses were selected because they span the dose range of toxicological interest as shown in previous studies (Gorzinski 1979[1]; Nolan et al. 1980[2]).

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[1]Gorzinski, S. 1979. Protocol for a 90-day toxicity study on picloram in rats. The Dow Chemical Company, Toxicology Research Laboratory, Midland, MI.

[2]Nolan, R.J., Smith, F.A., Muller, C.J., and Curl, T.C. 1980. Kinetics of ^{14}C-labeled picloram in male Fischer 344 rats. Dow Research Report HET-K-38323-(22).

B. METHODS

1. Acclimation

Rats were acclimated to the laboratory environment for at least 1 week prior to use. Animals were individually housed in glass Roth-type metabolism cages 3-4 days prior to radioactive dosing. Animals in the repeated-dose group were housed in wire mesh cages during the dietary pretreatment phase and then transferred to metabolism cages at time of radiolabeled dosing. Animals were provided Purina Certified Rodent Lab Chow (#5002) and tap water ad libitum throughout the study, except 16 hours prior to radioactive dosing and 4 hours after dosing. Animals administered picloram intravenously were fitted with an indwelling jugular vein cannula to facilitate administration and to collect plasma samples.

2. Dosing Solutions

For the repeated-dose group, the nonlabeled 10-mg/kg dosing solution (potassium salt) was prepared by adding water and mixing with a 10% KOH solution until picloram was in solution. The dosing solution was neutralized with 6N HCl and diluted to the desired volume with water. The volume of administration was 10 mL solution/kg of body weight. The concentration of the solution was found to be 96.2% of the initial concentration after 18 days, indicating good stability of the dosing solution.

Preparation of the radiolabeled solutions were similar to the nonlabeled solution. The radiolabeled dosing solutions were prepared by adding unlabeled picloram to water and then mixing in a 10% KOH solution until picloram was in solution. The dosing solutions were neutralized with 6N HCl and diluted to the desired volume with water. The solutions were spiked with ^{14}C-picloram to achieve target doses, with radioactivities of 5.781-6.824 µCi. The volume of administration was 10-12.5 mL/kg of body weight. The radioactive solutions were determined to be stable; concentrations were found to be 95.4% of initial concentration for the 10-mg/kg solution after 18 days. Stability was not reported for the 1000-mg/kg solution.

Intravenous dosing solutions were infused over a 1-minute period through the jugular cannula and then flushed into the animal with saline.

3. Sample Collection

Urine, feces, and cage rinses were collected, over dry ice, daily for 3 days for all dosing groups (except for urine from the i.v. group which was collected at 0-12 and 12-24 hours postexposure). Expired organics were trapped in charcoal, and expired $^{14}CO_2$ was trapped in a solution of 1-methoxy-2-propanol:monoethanolamine (7:3). The expired radioactivities were collected during first 24 hours after exposure. At 72 hours postdosing, animals were sacrificed and the following tissues were collected and analyzed for radioactivity: bone, brain, fat, gonads, heart, kidneys, liver, lung, blood, skeletal muscle, spleen, skin, and carcass. Tissues were homogenized and oxidized prior to

radioanalysis. The $^{14}CO_2$ released on oxidation of tissues was trapped and quantified. For the kinetic analysis, blood samples from cannulated animals were collected at 0.17, 0.33, 0.5, 1, 1.5, 2.5, 3.5, and 5 hours after i.v. administration.

Radioactivity of all collected samples was quantitated by liquid scintillation counting using a Beckman LS 3801 or Beckman LS 9000 scintillation counter (Fullerton, CA).

4. Metabolite Analysis

The 0-24-hour urinary and fecal samples were pooled for each group. For the metabolite analysis, pooled urinary and fecal samples were analyzed by high-performance liquid chromatography (HPLC). Fecal homogenates were prepared and oxidized in an OX-300 Biological Materials Oxidizer (R.J. Harvey Instrument Corporation, Hillsdale, NJ) prior to HPLC analysis. Radiolabeled urinary and fecal metabolites were separated by reverse phase HPLC with a linear gradient program of water:acetonitrile.

For identification of metabolites, pooled urinary and fecal samples were extracted with ethyl acetate (extraction efficiencies were 87-120%). Extracts were characterized by HPLC or derivatized with diazomethane and analyzed by radiogas chromatography/mass spectrometry (RGC/MS) (also GC/MS/MS for fecal extracts). Identification of extracted radioactivity was determined by MS. Standards were used to identify parent compound and metabolites.

5. Compliance

The quality assurance statement and the statement of compliance with Good Laboratory Practices for the study were signed on August 7 and August 10, 1989, respectively.

C. REPORTED RESULTS

1. Elimination and Recovery

Administered doses ranged from 102% to 110% of the target doses. No signs of toxicity were observed in the dosed animals.

After 72 hours postdosing, total mean recovery of radioactivity was 94.27-96.16% of the administered dose for all dosed groups. Most of the radioactivity was eliminated in the urine (68.90-86.04% of the administered dose), with the lowest amount found in the 1000-mg/kg group. Most of the radioactivity in the urine was recovered in the first 24 hours after oral administration while most of the recovery in the urine from i.v. administration occurred in the first 12 hours postdosing. The feces contained 5.47-24.65% of the administered radioactivity, with the lowest amount found in the i.v. group and the highest amount in the high-dose group. Most of the fecal elimination occurred within 24 hours postdosing. Radioactivity in cage washes was minimal; 0.48-2.75% of the administered radioactivity at 3 days postdosing. Radioactivity in expired $^{14}CO_2$ and organics and tissues (including carcass) was not detectable or below the detection limit.

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2. Metabolism

Only one radioactive peak was found in the urine samples and fecal extracts by HPLC analysis. This peak was identified as unmetabolized parent compound. Analysis by RGC/MS and GC/MS/MS detected one peak that was identified as picloram methyl ester. Representative HPLC radiochromatograms and mass spectra of 0-24-hour urine and fecal extracts showed no other major radioactive peaks.

3. Kinetic Analysis

A biphasic time course of radioactivity was observed in the plasma of female rats after i.v. administration. The highest recovery of radioactivity in the plasma was found at the first collection time (10 minutes postdosing). Using the two-compartment model, the terminal rate of clearance of ^{14}C from plasma was apparently first order for the 1C mg/kg dose, with a half-life of about 88 minutes. The initial rapid phase had a half-life of 5 minutes.

D. CONCLUSIONS BASED ON REVIEWERS' DISCUSSION AND INTERPRETATION OF DATA

The study demonstrated that ^{14}C-picloram is rapidly absorbed, distributed, and excreted following oral and i.v. administration in rats. Total recoveries of the radioactivity were high for all groups. The urine was the major route of excretion (≈76-86% of administered dose). The recovery of radioactivity in the feces was lower in the i.v. group (5.47% of administered dose) compared to oral groups (12.41-24.65% of administered dose) suggesting that a small amount of the administered oral dose is unabsorbed. The slightly greater fecal recovery in the high-dose group compared to the low-dose and repeated-dose groups suggests a slight dose-related difference in absorption. This finding demonstrated that saturation may have been reached at the high-dose level. The kinetic data indicate that picloram is rapidly absorbed into and eliminated from the blood. Tissue distribution and bioaccumulation of picloram appeared to be negligible since radioactivity was not detectable in any tissues, including the carcass, 3 days after oral or i.v. dosing.

The metabolism of picloram appeared to be minimal because unmetabolized picloram was the only radioactive component identified in urine and feces. However, the amount of the parent compound in the excreta was not determined. The authors did not proposed a metabolic pathway for picloram, however, the excreta data seem to indicate that most of the picloram dose is not metabolized in the rats.

E. STUDY DEFICIENCY

Sex-related differences in the absorption, distribution, metabolism, and excretion of picloram could not be determined because only one sex of rat was evaluated in the study. However, the authors noted that a previous kinetic study was conducted on male rats (Nolan et al. 1980; MRID No. 098321; HED Doc. No. 001889 & 007069).

TABLE 1. Excretion of Radioactivity 72 Hours Following Administration of ^{14}C-Picloram in Female Rats[a]

Dose Group[b]	Percent of Administered Dose				
	Urine	Feces	Cage Wash	Other[c]	Total Recovery
10 mg/kg (single oral)	76.44	18.62	1.10	NA	96.16
1000 mg/kg (single oral)	68.90	24.65	1.15	NA	94.70
10 mg/kg (repeated oral)	83.12	12.41	0.48	NA	96.01
10 mg/kg (i.v.)	86.04	5.47	2.75	NA	94.26

[a]Data were extracted from Table 3, p. 30

[b]5/group

[c]Includes expired $^{14}CO_2$, charcoal, tissues, and carcass.

NA = not detectable or below the detection limit