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

JUL 11 1988

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MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of two metabolism studies on Iprodione®

TO: Lois Rossi/Mario Fiol
PM 21
Registration Division (TS-767)

FROM: Margaret L. Jones M. L. Jones 7/5/88
Review Section III
Toxicology Branch
Hazard Evaluation Divison (TS-769)

THROUGH: Marcia van Gemert, Ph.D., Head
Review Section III M. van Gemert 7/8/88
Toxicology Branch
Hazard Evaluation Divison (TS-769)

and Theodore M. Farber, Ph.D., Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Chemical: Iprodione®; RP 26 019;
1-isopropyl carbamoyl-3-(3,5-dichlorophenyl)- hydantoin
Record No.: 220875
Accession No: 0071925, 0071926
CAS: 36734-19-7
Registrant: Rhone-Poulenc

Action Requested: Review two metabolism studies located in EPA files after these were listed as missing data in previous communications.

Conclusions: Both studies were single oral dose studies (one used ^{14}C labelled compound) done to measure recovery and to identify metabolites.

1. Study No. 2513 used 10 (5/sex) Charles River (France) rats administered 200 mg/kg 26 019 RP in single oral doses in 10% gum arabic solution. Feces and urine were collected at 6, 12, 24, 48, 72, and 96 hours. The study reports 87% recovery of ingested dose of which 53% in feces and 3% in urine was unmodified compound.

Classification: Unacceptable; test substance analysis was not reported; tables were missing; individual animal data in table form missing; tables were not fully legible.

2. Study No. 18548 used 4 (2/sex) Charles River (France) rats administered 100 mg/kg 26 109 RP and ^{14}C-26 019 RP in a mixture (proportions unspecified) in single oral doses in 10% gum arabic solution. Feces and urine were collected at 6, 12, 24, 48, 72, and 96 hours. The report identified over 13 metabolites and reported 74-98% recovery of radioactivity. However, terms were not well defined and no conclusions can be made from the reported information.

Classification: Unacceptable; insufficient number of animals (2/sex rather than 5/sex as recommended); no test substance analysis; data not reported in table form to enable verification of curves in figures; quantities reported as "total radioactivity" were contradictory.

There are currently no acceptable metabolism studies for Iprodione® in Toxicology Branch files. As stated in the Pesticide Assessment Guidelines, Subpart F (1982), data on absorption, distribution, excretion and metabolism are desirable to aid in evaluation of test results from other toxicology studies and in the extrapolation of data from animal studies to predictions in man [§85-1,(b)(1), p. 152].

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Reviewed by: Margaret L. Jones M.L. Jones 7/8/88
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section III, Tox. Branch (TS-769C) M. van Gemert 7/8/88

DATA EVALUATION REPORT

STUDY TYPE: Metabolism/ Single oral dose

TOX. CHEM. NO.:470A
MRID:
CAS:36734-19-7

ACCESSION NUMBER: 0071925

TEST MATERIAL: Iprodione

SYNONYMS: RP 26019; 1-isopropyl carbamoyl-3-(3,5-dichlorophenyl)-hydantoin

STUDY NUMBERS: SUCRP OS An. Nord no. 2513

SPONSOR: Rhone-Poulenc Ag Company

TESTING FACILITY: Societe Des Usines Chimiques Rhone-Poulenc
Direction Scientifique
Laboratoires de Recherches Analytiques
21, rue Jean Coujon, 75008 Paris, France

TITLE OF REPORT: 26 019 RP Metabolism in the Rat

AUTHORS: ~~Laurent,~~ Buys, Julou, Pasquet

REPORT ISSUED: August 27, 1974

CONCLUSIONS: Charles River France COBS (Caesarian Originated, Barrier Sustained) rats (10 males and females, number of each not specified) were administered 26019 RP orally at 200 mg/kg in a single oral dose in suspension in a 10% aqueous gum arabic solution. Control rats received gum arabic solution alone. Urine and feces were collected at 6, 24, 48, 72, and 96 hours after administration of test substance. The report concludes 87% of ingested dose was recovered in urine and feces (53% and 3% unmodified in feces and urine respectively). Conclusions cannot be verified from reported data.

Classification: Unacceptable. Test substance analysis not reported; Table A1 missing, with weights and volumes of samples of urine and feces and organs; fully legible tables should be provided (Table A2 is not legible); individual animal data and results at each sampling of urine and feces were not reported.

A. MATERIALS:

1. Test compound: Iprodione, Description: not reported, Batch # not reported, Purity: not reported, contaminants not reported; test compound was mixed to form a suspension with 10% aqueous gum arabic and administered in doses of 200 mg/kg in a single oral dose.

2. Test animals: Species: Rat, Strain: Charles River France COBS (Caesarian Originated Barrier Sustained), Age: not reported Weight: 200 g (mean), Source: Charles River France

B. STUDY DESIGN:

1. Animal assignment

Ten animals (males and females) and 10 controls were used in the study. The report does not indicate the number of animals of each sex used in the study.

2. Diet preparation

No information about diet or water was found in the test report.

3. Statistics

No information about statistical analysis was found in the test report.

4. Quality assurance was not reported, nor were GLP (good laboratory practices).

C. METHODS AND RESULTS:

1. Collection of biological material

Urine and feces were collected 6, 24, 48, 72, and 96 hours after administration. Tubes for collecting feces were rinsed with acetone each day. Weights and volumes were reported. After 96 hours, animals were sacrificed by exsanguination and organs were collected and weighed. See appended pages 1-8 for experimental methods.

2. Assay of biological materials for test substance and metabolites

Samples were prepared by hydrolysis, oxidation, distillation or various extraction methods and assayed by colorimetry or gas-liquid chromatography to measure functional groups on the test substance molecule. Results in treated animals were compared to controls and to synthetic reference products.

Reported results- The study report states none of the metabolites were found in blood and tissues, and that 87% of the ingested dose was found partly in urine and partly in feces (see Appended page 9). The report further states the breakdown in urine and feces of parent and metabolites as follows:

Feces: 53% unmodified 26019 RP (parent)
2.3% metabolites with an unhydroxylated benzene ring
3.9% metabolites with a hydroxylated benzene ring

Urine: 3% unmodified 26019 RP
11% 32490 RP + 25040 RP
0.5% 30228 RP
4% metabolites with an unhydroxylated benzene ring
7.8% metabolites with a hydroxylated benzene ring

Reported conclusions- The report concludes 87% of the 200 mg/kg was accounted for in the results, and concludes the product is rapidly metabolized. Of the dose administered, 56% (53% from urine and 3% from feces) is eliminated as unmodified product.

Toxicology Branch evaluation- The report concludes that most of the administered test substance was recovered and that the substance is rapidly metabolized. However, there is insufficient data in the report to support the conclusions. In particular, there is no individual animal data to show variation among treated and control animals. The report states urine and feces were collected at 6, 24, 48, 72, and 96 hours, however, results are pooled in a combined value for 0-96 hours. None of the statements about kinetics of elimination reported in Graph no. 1 (see Appended page 10) can be verified with the reported information. Values for each collection time should be reported so that summary tables and graphs can be validated. The report does not attempt to explain the fate of the 13% of test substance which is not accounted for in the reported results.

Other specific deficiencies are noted as follows-

Table A1 described in the report is missing with weights and volumes of samples and organ weights.

Table A2 (spectrometry) is partly illegible. The original printout or a completely legible copy should be included in the study report.

Test substance analysis at start and end of study was not reported.

Graph 1 (Elimination kinetics) showing percent elimination v. time (metabolites hydrolysable into dichloroaniline) does not account for the elimination of all metabolites and parent compound.

IPRODIONE Sh #109801

Page_____ is not included in this copy.

Pages 6 through 15 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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Reviewed by: Margaret L. Jones M.L. Jones 7/8/88
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section III, Tox. Branch (TS-769C) M. van Gemert 7/8/88

DATA EVALUATION REPORT

STUDY TYPE: Metabolism/ Single oral dose (for identification of metabolites)

TOX. CHEM. NO.:470A
MRID:
CAS:36734-19-7

ACCESSION NUMBER: 0071926

TEST MATERIAL: Iprodione

SYNONYMS: RP 26019; 1-isopropyl carbamoyl-3-(3,5-dichlorophenyl)-hydantoin

STUDY NUMBERS: R.P./R.D./C.N.G. and C.N.G. An no. 18548

SPONSOR: Rhone-Poulenc Ag Company

TESTING FACILITY: Rhone Poulenc Research and Development Directorate
Nicolas Grillet Research Centre
Analytical Research Laboratories
13, quai Jules Guesde, 94400 Vitry-sur-Seine

TITLE OF REPORT: 26 019 RP Metabolism Study in the Rat Using ^{14}C Labelled Material

AUTHORS: Laurent, Brunie, Buys, Heusse, and Chabassol

REPORT ISSUED: February 26, 1976

CONCLUSIONS: Charles River France COBS (Caesarian Originated, Barrier Sustained) 4 rats (2 males and 2 females) were administered 26 019 RP orally at 100 mg/kg in a single oral dose in suspension in a 10% aqueous gum arabic solution. The suspension administered was a mixture of unlabeled 26 019 RP and labeled 26 019 RP uniformly labeled on the benzene ring (sp. activ. 0.44 mCi/mM). The report identifies over 13 metabolites and reports 74-98% recovery of radioactivity.

Classification: unacceptable. Insufficient number of animals (2/sex rather than 5/sex). No test substance analysis. Deficiencies are discussed on page 3.

A. MATERIALS:

1. Test compound: Iprodione, fungicide 26 109 RP labelled with ^{14}C in the benzene ring ("uniformly labeled on the benzene ring"); Description: not reported, Batch # not reported, Purity: 92.4% radiochemical purity, not verified with analysis sheet, and no description of contaminants/impurities in the remaining 7.6%; Specific activity of dosing mixture: 0.44 mCi/mM, a mixture of labeled and unlabeled compound in unspecified proportions

2. Test animals: Species: Rat, Strain: Charles River France COBS (Caesarian Originated Barrier Sustained), Age: not reported Weight: 220 g (mean), Source: Charles River France

B. STUDY DESIGN:

1. Animal assignment and test substance administration:

Rats (2 males and 2 females) were administered 100 mg/kg 26 019 RP and ^{14}C-26 019 RP (mixture of unspecified proportions) in a single oral dose in suspension in 10% aqueous gum arabic solution.

2. Diet preparation

No information about diet or water was found in the test report.

3. Statistics

No information about statistical analysis was found in the test report.

4. Quality assurance was not reported, nor were GLP (good laboratory practices).

C. METHODS AND RESULTS:

1. Collection of biological material

Appended pages 1-6 show the methods of collection of biological materials analysed in the study.

Urine and feces were collected 6, 24, 48, 72, and 96 hours after administration. Exhaled CO_2 was trapped with potassium hydroxide. Tubes for collecting feces were rinsed with acetone each day. Weights and volumes were reported. After 96 hours, animals were sacrificed by decapitation, blood was collected in heparin and liver, heart & lungs, kidneys, digestive system, skin, and carcass were removed. Each cage was rinsed with 250 ml of methanol.

2. Identification of metabolites, kinetics of elimination, and degree of retention in animals

Appended pages 1-6 show the methods and procedures for determination of metabolites and counting procedures.

Biological samples were burned and CO_2 trapped in absorbent material. Solutions from exhaled CO_2 and from digestion of skins were counted in scintillation medium. Counting yields were determined using an external standard.

Metabolites were idenitified using methods of methylation, acetylation, gas-liquid chromatography, I.R. spectrophotometry, mass spectrometry, and comparison with synthetic reference material.

Reported results are shown in appended pages 7-11. See comments under 3., below.

Toxicology Branch evaluation - The report makes several confusing statements and the terms are not well-defined, making interpretation difficult. No conclusions can be made without additional information. Deficiencies are discussed below.

1. Insufficient number of animals. Two animals/sex/group is not an adequate number to account for individual variation within a group. The recommended number is 5/sex/group.

2. Figures 2 and 3 (not appended) do not have data to enable verification of the curves. Data points should be presented in table form.

3. Definition of terms is the most serious deficiency, preventing interpretation of the results. The term, "total radioactivity", is used repeatedly in Tables 1-5, however, the numbers differ in each table. It is not clear which quantity the term "total radioactivity" represents. Appended pages 7-11 show these tables. The numbers in each table which refer to "total radioactivity" range from 26-36 for feces and 48-62 for urine. (Again, it is unclear whether the term refers to total radioactivity in collected specimens, total radioactivity originally administered, or another quantity.) The numbers reported are percentages, which indicates a measured value was compared to a total amount. The total radioactivity originally administered in the study is not reported, therefore it is unclear how the percentages were derived.