7-23-87

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

006359

JUL 23 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of Developmental Toxicity Study in Rats on Iprodione

TO: Lois Rossi, PM 21
Registration Division (TS-767

FROM: Margaret L. Jones M. L. Jones 7/1/87
Review Section III
Toxicology Branch (TS-769)

THROUGH: Marcia van Gemert, Ph.D., Head
Review Section III M. van Gemert 7/1/87

and Theodore M. Farber, Ph.D., Chief
Toxicology Branch (TS-769) 7/23/87

Compound: Iprodione (Rovral®) Tox. Chem. No.: 470A

Record No.: 186202 Registrant: Rhone Poulenc

Accession No.: 264519 Tox. Project No.:7-0382

Action Requested: Review the Developmental Toxicity study in rats which was received under the Data Call-In Program (Agency: 8/29/86, Reviewer: 2/10/87.)

Conclusions: The developmental toxicity study in rats has been core graded Supplementary pending receipt of additional information which is discussed in the attached Data Evaluation Report. The report can be upgraded once the registrant response to the points raised in the discussion is considered.

Attachment: Data Evaluation Report for unpublished report no. 85/RHA064/765, Teratogenicity Study in Rats.

006359

10 of 35

EPA: 68-02-4225
DYNAMAC No. 264-A
June 30, 1987

DATA EVALUATION RECORD

IPRODIONE

Teratogenicity Study in Rats

STUDY IDENTIFICATION: Tesh, J. M., McAnulty, P. A., Deans, C. F., Wilby, O. K., and Tesh, S. A. Iprodione (technical grade): Teratology study in the rat. (Unpublished report No. 85/RHA064/765 by Life Science Research, Suffolk, England, for Rhône-Poulenc Agrochimie, Lyon, France; dated May 28, 1986.) Accession No. 264519

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 6-30-87

006359

1. CHEMICAL: Iprodione, 3-(3,5-dichlorophenyl)-N-(1-methylethyl) 2,4-dioxo-1-imadazolidine carboxamide.

2. TEST MATERIAL: Iprodione, technical grade, lot No. DA 237, was described as an odorless, nonhydroscopic, grey-white micronized powder with a purity of 94.2%. The stability of iprodione in water was reported to be pH dependent.

3. STUDY/ACTION TYPE: Teratogenicity study in rats.

4. STUDY IDENTIFICATION: Tesh, J. M., McAnulty, P. A., Deans, C. F., Wilby, O. K., and Tesh, S. A. Iprodione (technical grade): Teratology study in the rat. (Unpublished report No. 85/RHA064/765 by Life Science Research, Suffolk, England, for Rhône-Poulenc Agrochimie, Lyon, France; dated May 28, 1986.) Accession No. 264519.

5. REVIEWED BY:

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Date: 7/1/87

7. CONCLUSIONS:

A. We tentatively assess that the NOEL for maternal toxicity in this study was higher than 200 mg/kg/day, the highest dose level tested. However, a definitive assessment of maternal effect levels cannot be conducted until the registrant responds to the following points:

1. The study authors should make some attempt to identify the reason(s) why the clinical signs observed in the range-finding study at 120 mg/kg/day and 240 mg/kg/day (flaccid muscles) did not appear in the main study at 200 mg/kg/day.

2. Were there any changes in personnel between the two studies? Were the same individuals making clinical observations in both studies.

3. Tables and Appendices with letters rather than word descriptions are difficult to read (Appendices 4, 5, 6) and do not facilitate data interpretation.

The NOEL and LOEL for developmental toxicity were 90 and 200 mg/kg/day, respectively, based on delayed fetal development, as demonstrated by slightly reduced fetal weights and an increased incidence of space between the body wall and organs in fetuses at 200 mg/kg/day.

B. This study is classified Core Supplementary pending submission of the information requested above.

Item 8--see footnote 1.

9. BACKGROUND:

The authors conducted a range-finding study (LSR report No. 85/RHA063/752) on pregnant rats dosed on gestation days 6-15 with 0, 40, 120, 240, 400, or 800 mg/kg/day. It was concluded that the dosages for the teratogenicity study should not exceed 240 mg/kg/day based on marked maternal toxic effects (e.g., weight loss, piloerection, pallor, ataxia) noted at dosages of 400 and 800 mg/kg/day. One female died and 7/14 females were killed in extremis at 800 mg/kg/day; the remaining females were killed prior to day 21 for humane reasons. At 400 mg/kg/day, 1/6 females was euthanized and the remaining females had fully resorbed litters. All females receiving 240 mg/kg/day showed flaccid muscles; 3/6 had transient ataxia or a lack of spatial awareness. At 120 mg/kg/day, 4/6 females occasionally showed flaccid muscles. One of these females also showed poor righting reflexes. Animals receiving 40 mg/kg/day were unaffected.

Item 10—see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Technical-grade iprodione was freshly suspended each dosing day in 0.5% w/v aqueous methylcellulose. Dosage levels selected for this study were 0 (vehicle control), 40, 90, and 200 mg/kg/day. Dosing suspension samples obtained on the first and last weeks of treatment were submitted for analyses.

2. Animals and Experimental Procedures: Adult virgin female Sprague-Dawley derived CD rats were obtained from Charles River U.K., Ltd. These animals were housed five/cage, acclimated for 12 days, and then paired with males of the same source and strain. Paired animals were allowed a maximum mating period of 4 days; the day in which a copulatory plug or a sperm-positive vaginal smear was found was designated gestation day (GD) 1. Females were assigned sequentially to study groups to allow for a homogeneous distribution of animals mated on any given day. A total of 20 mated females were assigned to each group; these females were housed one per cage.

   The animal room was ventilated with 15 air changes per hour; room temperature and relative humidity ranged from 19-25°C and 40-70%, respectively. Animals were provided with a 12-hour light/12-hour dark cycle and water and certified food ad libitum.

   Animals were dosed daily by gavage on GD 6-15 with a volume of 10 mL/kg body weight. Doses were adjusted daily for changes in body weight. On GD 21, females were killed by carbon dioxide inhalation.

3. Parameters Measured: Animals were examined daily for overt signs of ill health or reaction to treatment. Body weights were recorded on GD 1, 3, 6-16, 18, and 21. Food consumption was recorded on GD 1, 3, 6, 9, 12, 16, 18, and 21.

   Females were necropsied on GD 21 and specimens of abnormal tissues were retained.

   The numbers of corpora lutea, implantation sites, early and late resorption sites, and the number and distribution of live and dead fetuses in each uterine horn were recorded. Uteri of apparently nonpregnant females were stained in ammonium sulfide to detect early resorption sites.

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[1]Only items appropriate to this DER have been indicated.

006359

Each fetus was externally examined, weighed, and sexed. Placentae were weighed and examined for abnormalities. Approximately two-thirds of the fetuses had their neck and thoracic and abdominal cavities dissected and examined. These fetuses were eviscerated, fixed, stained with alizarin red S, and examined for skeletal abnormalities. The remaining fetuses were fixed in Bouin's fluid, sectioned, and examined by methods described by Wilson.

According to the study protocol, body weights, weight changes, and litter sizes were analyzed by one-way analysis of variance and/or Student's t-test. Fetal and placental weights were analyzed by a nested analysis of variance and weighted t-test. Corpora lutea, implantations, and resorptions were analyzed by the Mann-Whitney U test. Chi-square, Fisher's exact, or Mann-Whitney U tests were used to analyze pre- and postimplantation losses. The study report, however, indicated statistical analyses only for body weight changes and for fetal and placental weights. Differences from control values with a probability of $p < 0.05$ were considered statistically significant.

B. Protocols and Amendments: See Appendix B for details.

12. REPORTED RESULTS:

A. Test Material: Chemical analysis of dosing formulations yielded the following results:

	Dosage Level (mg/kg/day)			
	0	40	90	200
Target concentration (mg/mL)	0	4	9	20
Mean actual concentration (mg/g)				
First week of treatment	0	3.93	9.29	19.5
Last week of treatment	0	3.86	9.49	20.5

B. Maternal Effects: No mortality occurred in this study. The general condition of females and necropsy findings were comparable for all groups. Maternal body weight and food consumption data were also comparable at all dose levels (Table 1).

C. Developmental Effects:

All females were pregnant, except for one high-dose animal. The numbers of corpora lutea, implantations, viable fetuses, and resorptions and the percent pre- and postimplantation losses were comparable for all groups (Table 2).

TABLE 1. Effects of Iprodione on Mean (± S.D.) Maternal Body Weight and Food Consumption in Rats

Gestation Day	Dosage (mg/kg/day) 0	40	90	200
	Body Weight (g)			
1	225±13	224±11	225±10	226± 9
6	243±14	246±13	244±12	247±12
8	251±14	253±12	254±13	256±13
16	298±15	300±15	301±17	299±18
21	364±15	366±21	372±23	367±21
	Food Consumption (g/rat/day)			
1-2	20±2	20±2	20±2	20±2
3-5	22±2	21±3	21±2	22±2
6-8	22±2	23±2	23±1	22±2
9-11	23±2	23±2	24±2	22±3
12-15	25±2	26±2	26±2	25±3
16-17	27±3	28±3	29±2	27±3
18-20	27±2	27±3	28±2	27±2

006359

TABLE 2. Effects of Iprodione on Developmental Parameters in Rats

	Dosage (mg/kg/day)			
	0	40	90	200
No. pregnant	20	20	20	19
Mean (± S.D.) No. per litter				
Corpora lutea	15.4±1.4	15.9±2.0	16.6±1.2	16.3±1.8
Implantations	14.7±1.5	15.1±1.5	14.8±2.2	14.9±1.6
Viable fetuses	13.8±1.3	13.7±2.4	14.3±2.7	13.9±2.4
Resorptions				
early	0.7±0.8	1.2±1.1	0.3±0.5	0.9±0.9
late	0.2±0.4	0.2±0.4	0.3±0.5	0.1±0.3
total	0.9±0.9	1.4±1.2	0.5±0.7	1.0±1.0
Percent per group				
Preimplantation loss	5.2	6.5	10.8	8.4
Postimplantation loss	6.1	9.0	3.4	6.7
Mean (± S.D.) per litter				
Fetal weight (g)	3.27±0.06	3.18±0.06	3.16±0.09	3.15±0.07
Placental weight (g)	0.51±0.02	0.52±0.02	0.51±0.05	0.52±0.03

Fetal body weights decreased slightly with increasing dose; none of the differences were statistically significant (Table 2). Placental weights were comparable for all groups.

No compound-related effects were reported for findings from external or skeletal examinations; however, the incidence of space between the body wall and organs was 4.3, 5.3, 5.8, and 11.2% for fetuses in the 0-, 40-, 90-, and 200-mg/kg/day groups, respectively. The authors indicated that most of the affected fetuses in this study were noted as being small (i.e., weighing less than 2.7 g) at the time of necropsy and that the findings were consistent with delayed fetal development in the high-dose group.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that the oral administration of iprodione at dosage levels of 0, 40, 90, and 200 mg/kg/day did not produce adverse maternal effects. Fetal weights were slightly, but not statistically, reduced in the dosage groups. Fetuses from the 200 mg/kg/day group had an increased incidence of space between body wall and organs, an indication of delayed fetal development.

B. A quality assurance statement was signed and dated May 30, 1986.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Test Material Analyses: Based on the results of the chemical analyses, we assess that the dosing preparations in this study were acceptable.

B. Maternal Effects: We assess that the test material did not elicit signs of toxicity even at the highest dosage level (200 mg/kg/day) tested in this study.

C. Developmental Effects: Possible adverse effects were suggested by a dose-related decrease in fetal body weights and by an increase in the incidence of space between the body wall and organs among fetuses from the group dosed with 200 mg/kg/day. Although fetal body weights decreased with increasing dosage levels, none of the values were significantly different from control values, nor were they outside of the historical control range. The incidence of fetuses with space between body wall and organs was slightly (but not significantly) increased in the high-dose group. Although these values were within the historical control range, the authors stated that most fetuses with a space between the body wall and organs were considered to be small in size at necropsy; the incidences of small fetuses (i.e., weighing less than 2.7 g) were 2.9, 5.1, 4.9, and 8.0% for the 0-, 40-, 90-, and 200-mg/kg/day groups, respectively. All of these values are within the range (0.4-18.4%) for historical controls in 98 previous studies involving 23,937 fetuses.

Based on the slight decreases in fetal weight and on the increased incidence of space between body wall and organs, we assess that an adverse effect on fetuses at 200 mg/kg/day cannot be ruled out.

Item 15—see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 2-10; Appendix B, Protocols and Amendments, CBI pp. 61-74.

APPENDIX A

Materials and Methods

IPRODIONE Sh #109801

Page_____ is not included in this copy.

Pages 12 through 35 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.

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____ The product confidential statement of formula.

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