470A

CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

JUL 9 1990

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

008023

SUBJECT: Iprodione-metabolism study in rats

TO: S. Lewis and J. Stone PM 21
Registration Division (HH7505C)

FROM: K. Clark Swentzel K. Clark Swentzel 6/29/90
Section Head, Section 2
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EPA ID No. 264-452
MRID No. 413467-01
Project No. 0-0528
Caswell No. 470A
Registrant: Rhone Poulenc

Summary

A metabolism study with Iprodione in rats, which was submitted by the registrant to satisfy a data gap, has been reviewed by Dynamac Corp. and secondarily reviewed by Toxicology Branch 2. The DER is attached.

Three groups of Charles River CD rats (5/sex/group) were used in a balance/distribution study and two groups (5/sex/group) were used in a pharmacokinetic study. In the balance distribution study, one group received a single oral dose of 50 mg [^{14}C]Iprodione/kg, o group received a single oral dose of 900 mg [^{14}C]Iprodione/kg and the third group was administered 14 single daily doses of unlabeled test material (50 mg/kg) followed by a single oral dose of [^{14}C]Iprodione on day 15. In the pharmacokinetic study, one group received a single oral dose of 50 mg/kg and the other 900 mg/kg [^{14}C] Iprodione.

[^{14}C]Iprodione was readily absorbed from the gastrointestinal tract, metabolized and excreted by animals in each group in the balance/distribution study. Absorption and elimination of [^{14}C] label from the blood fit a one-compartment model. Blood levels of radioactivity peaked at 4 and 2 hours after dosing for low-dose (50 mg/kg) males and females, respectively, and at 6 hours post dosing for high dose (900 mg/kg) rats. Elimination of radioactivity from the blood was slower in males (at the high dose, the mean half-lives of elimination were 19.8 and 12.5 hours for males and females, respectively).

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The data showed that there were dose- and sex-related differences in the absorption of Iprodione. Males absorbed a larger percentage of the low and repeated doses than females Increasing the dose from 50 to 900 mg/kg caused a significant ($0.01 < p < 0.02$) drop in the percent of Iprodione absorbed by male rats; a similar but nonsignificant trend was reported for high-dose females.

The distribution of radioactivity in tissues and organs was widespread but the levels we low. The radioactivity in all tissues combined accounted for no more than 0.5% of the total [^{14}C] dose administered and no individual tissue contained more than 0.3%.

The primary route of elimination of radioactivity in low- and repeated-dose rats was the urine while the feces was the primary route in high-dose animals.

Slight sex- and dose-related differences in the metabolism of Iprodione were observed. Primary metabolites recovered from the urine of all males and females included a dealkylated derivative of Iprodione and 2 polar but unidentified compounds. Males also produced large amounts of a hydantoin ring-opened metabolite. The urine of females typically contained a higher proportion of unchanged parent compound than the urine from males.

It was the reviewer's opinion that this study provided adequate information on the absorption, distribution and excretion of orally administered Iprodione in rats. However since the high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) methods used by the investigator failed to identify (1) at least 2 major urinary metabolites and (2) up to 22% of the urinary radioactivity and up to 88% of the fecal radioactivity, this study provided only supplementary information on the metabolism of Iprodione.

Classification: unacceptable; this study does not fulfill the guideline requirements (85-1) for a metabolism study.

Quality Assurance Statement- signed and dated

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EPA No.: 68D80056
DYNAMAC No.: 285-A
TASK No.: 2-85A
June 20, 1990

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DATA EVALUATION RECORD

IPRODIONE

Metabolism in Rats

STUDY IDENTIFICATION: Hallifax, D. Iprodione: Absorption, distribution, metabolism, and excretion study in the rat. (Unpublished study No. 89/1013 performed by Life Science Research, Ltd., Suffolk, England, for Rhone-Poulenc Agriculture Company, Essex, England; dated December 1, 1989.) MRID No. 413467-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: for Robert Weir JRW
Date: 6/20/90

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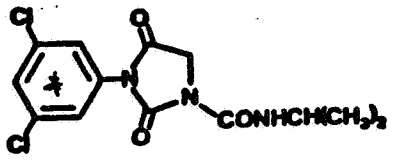
1. CHEMICAL: Iprodione; (3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazoline carboxamide.

2. TEST MATERIAL: Unlabeled iprodione (batch No. EA2002/7, purity not reported) and [^{14}C]phenyl ring-labeled iprodione (batch No. KWC 1670; specific activity 54.6 µCi/mg; radiochemical purity >99 percent) were used. The structure of [^{14}C]iprodione and radiolabel position (*) are shown below:



3. STUDY/ACTION TYPE: Metabolism in rats.

4. STUDY IDENTIFICATION: Hallifax, D. Iprodione: Absorption, distribution, metabolism, and excretion study in the rat. (Unpublished study No. 89/1013 performed by Life Science Research, Ltd., Suffolk, England, for Rhone-Poulenc Agriculture Company, Essex, England; dated December 1, 1989.) MRID No. 413467-01.

5. REVIEWED BY:

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7. CONCLUSIONS:

A. [^{14}C]Iprodione was readily absorbed from the gastrointestinal tract, metabolized, and excreted by male and female rats given a single oral dose (50 or 900 mg/kg) or repeated oral doses (50 mg/kg; 14 doses) of test material. Absorption and elimination of [^{14}C] label from the blood fit a one-compartment model. Blood levels of radioactivity peaked at 4 and 2 hours after dosing for low-dose males and females, respectively, and at 6 hours postdosing for high-dose rats. Elimination of radioactivity from the blood was slowest in males. The mean half-life of elimination from the blood was 8.9 hours for low-dose males and 6.9 hours in low-dose females; at the 900-mg/kg dose, the mean half-lives of elimination were 19.8 and 12.5 hours for males and females, respectively.

Sex- and dose-related differences in the absorption of iprodione were reported. Males absorbed a larger percent of the low and repeated doses than females. Low- and repeated-dose males absorbed approximately 69 to 76 percent of the [^{14}C] label administered, respectively, within 7 days after dosing, whereas 54 and 66 percent of the [^{14}C] dose was absorbed by females. Increasing the dose from 50 to 900 mg/kg caused a significant ($0.01 < p < 0.02$) drop in the percent of iprodione absorbed by male rats (i.e., to about 44 percent); a similar but nonsignificant trend was reported for high-dose females.

The distribution of radioactivity in tissues and organs was widespread but the levels were low. The radioactivity in all tissues combined accounted for no more than 0.5 percent of the total [^{14}C] dose administered, and no individual tissue contained more than 0.3 percent. Tissue, organ and carcass [^{14}C]-levels of low- and repeated-dose rats were ≤1 ppm; tissue [^{14}C] residue levels in high-dose animals were proportionately higher (≤10 ppm). The highest levels of radioactivity were found in the cecum, large and small intestines, liver, lymph nodes, skin, salivary glands, and fat. The data indicate that bioaccumulation of iprodione and/or its metabolites is not extensive.

The primary route of elimination of radioactivity in low- and repeated-dose rats was the urine; animals in these groups excreted approximately 53 (low-dose females) to 75 (repeated-dose males) percent of the [^{14}C] dose via this route and 20 to 39 percent in the feces. In contrast, the urine of high-dose animals accounted for only 43 to 46 percent of the [^{14}C] dose, while the feces contained 52 to 56 percent. The amount of unchanged parent compound recovered from the feces of high-dose animals was also markedly greater than that in the feces of other animals.

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These data indicate that the absorption and metabolism of the high dose are near saturation.

Slight sex- and dose-related differences in the metabolism of iprodione were observed. Primary metabolites recovered from the urine of all males and females included a dealkylated derivative of iprodione and two polar but unidentified compounds. Males also produced large amounts of a hydantoin ring-opened metabolite. Approximately 9 to 12 percent of the urinary radioactivity excreted by females was unchanged parent compound; in contrast, the urine of males contained only trace to small (<5 percent) amounts of iprodione. Several additional identified and unidentified metabolites were recovered from the urine of all animals.

B. This study provides adequate information on the absorption, distribution, and excretion of orally administered iprodione in rats. However, because the high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) methods used by the study author failed to identify (1) at least two major urinary metabolites and (2) up to 22 percent of the urinary radioactivity and up to 88 percent of the fecal radioactivity, this study provides only supplementary information on the metabolism of iprodione.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

1. The radiochemical purity of [^{14}C]iprodione was determined by TLC using three solvent systems (toluene:ethyl acetate 90:10, v/v; toluene:ethyl acetate 95:5, v/v; dichloromethane:ethyl acetate 95:5, v/v).

2. Male and female CD rats (180 to 200 g) purchased from Charles River (UK) Ltd. (Margate, Kent) were used. Animals were allowed at least 5 days to acclimate before dosing.

Items 8 through 10--see footnote 1.

[1]Only the items appropriate to this DER are included.

3. Dosing solutions were prepared by suspending the test material in 0.5 percent (w/v) carboxymethylcellulose in distilled water. The radiochemical purity of the [^{14}C]-labeled suspensions were determined by TLC as described above. The concentration of unlabeled iprodione in the repeated-dose solutions was determined by HPLC. Formulations were prepared to deliver 50 or 900 mg iprodione/kg and 11 μCi [^{14}C]/animal in a dose volume of 2 mL.

4. Animals were assigned to a preliminary study, a balance/distribution study, or a pharmacokinetic study (Table 1). Each of the two rats (one/sex) in the preliminary study received a single oral dose of 50 mg [^{14}C]iprodione/kg. Animals in this study were placed in metabolism cages immediately after dosing, and urine, feces, and expired air (i.e., CO_2) were collected between 0 to 6 and 6 to 24 hours after compound administration. Excreta were collected separately on ice, and expired air was drawn through two traps, each of which contained 2M NaOH.

   Three groups of five male and five female rats were assigned to the balance/distribution study. One group received a single oral dose of 50 mg [^{14}C]iprodione/kg (low-dose group), while a second group was given a single oral dose of 900 mg [^{14}C]iprodione/kg (high-dose group). The third group of rats received 14 single daily doses of unlabeled iprodione (50 mg/kg) followed by a single oral dose of [^{14}C]-labeled iprodione (50 mg/kg) on day 15. All animals in the balance/distribution study were placed in individual metabolism cages immediately after administration of the radiolabeled test material. Urine and feces were collected separately on ice at 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdosing. Cages were washed with a small volume of acetonitrile at the end of the 7-day collection period. Animals were sacrificed 7 days after administration of the radiolabeled test material. The following tissues were removed, weighed, homogenized, solubilized, and radioassayed: adrenals, blood, bone (femur), brain, cecum (plus contents), carcass, eyes, fat (abdominal), heart, large intestine (plus contents), small intestine (plus contents), kidneys, liver, lungs, lymph nodes (mesenteric), muscle (skeletal), ovaries (females), pancreas, salivary glands, skin, spleen, stomach (plus contents), testes (males), thymus, thyroid, and uterus (females). Because of low total recoveries of radioactivity, all three experiments in the balance/distribution study were repeated; however, in the repeated experiments, no organs or

TABLE 1. Treatment Groups for Animals Administered Oral Doses of Iprodione[a]

Group	Number of Animals (number/sex)	Target Dose[b] (mg/kg)	Actual Dose[b] (mg/kg)	Actual Dose as Percent of Target Dose
Preliminary study				
Single low dose	1	50	55.1 (M)[c]; 51.4 (F)[c]	110 (M); 103 (F)
Balance/distribution study				
Single low dose	5	50	48.4 (M); 48.5 (M)	97 (M); 97 (F)
Single low dose (repeated)[d]	5	50	51.1 (M); 53.5 (F)	102 (M); 107 (F)
Single high dose	5	900	1,000 (M); 1,120 (F)	111 (M); 124 (F)
Single high dose (repeated)[d]	5	900	948 (M); 853 (F)	105 (M); 95 (F)
Repeated low dose[e]	5	50	51.4 (M); 48.7 (F)	103 (M); 97 (F)
Repeated low dose (repeated)[d]	5	50	49.4 (M); 52.4 (F)	99 (M); 105 (F)
Pharmacokinetic study				
Single low dose	5	50	56.8 (M); 49.9 (F)	114 (M); 100 (F)
Single high dose	5	900	911 (M); 960 (F)	101 (M); 107 (F)

[a]Compiled by the reviewer.

[b]Radiolabeled doses only. Values may vary slightly from those in Appendix 1 (CBI pp. 84-86) because of rounding.

[c]M = male(s), F = female(s).

[d]Because of low total recoveries of radioactivity, the balance/distribution studies were repeated, with the exception that no organs or tissues were removed from the carcass and the carcass was analyzed whole (except for the skin, which was analyzed separately).

[e]Animals were given a single daily oral dose of 50 mg unlabeled iprodione/kg (actual dose 46 mg/kg) for 14 days followed by a single oral dose of 50 mg [^{14}C]iprodione/kg on day 15.

Source: CBI pp. 27-30, 36-37.

tissues were removed, and the carcass was analyzed whole (except for the skin, which was analyzed separately).

The two groups of rats (five/sex/dose level) in the pharmacokinetic study were given a single oral dose of either 50 or 900 mg [^{14}C]iprodione/kg. Following compound administration, animals were housed individually in cages, and blood was withdrawn at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 96, 120, and 168 hours postdosing.

For all studies, the test material was administered by gavage, and the doses administered were calculated by weighing the dosing syringe before and after dosing, washing the syringe with acetonitrile, and radioassaying the residual material.

5. Aliquots of residual dosing material, trapping fluid (expired air), urine, and plasma were analyzed directly for their [^{14}C] content by liquid scintillation assay (LSC). Whole blood and skin samples were solubilized, and tissues, organs, and carcasses were homogenized in distilled water prior to counting. Feces were homogenized in distilled water (for the first series of balance/distribution experiments) or acetonitrile (for the repeated balance/distribution experiments), combusted, and radioassayed. Background radioactivity and counting efficiencies were corrected for by using external standard quench parametric analysis.

6. The urine and feces of one male and one female from each of the experiments in the balance study were analyzed for iprodione metabolites by HPLC and TLC. Samples collected during the first 24 hours after dosing were pooled; the 24- to 48-hour samples were analyzed separately. Prior to chromatographic analyses, fecal samples were extracted twice with acetonitrile; these extracts were pooled. Additional extractions with water and hexane were performed; the residual aliquots were combusted and counted. Urine samples and fecal extracts were filtered before injection/HPLC analysis; aliquots applied to silica gel plates were developed in toluene:acetonitrile (50:1, v/v). Reference compounds were analyzed using the same HPLC and TLC methods.

7. Group means ± standard deviations were analyzed statistically using the Student's t-test. Data from the pharmacokinetic study were analyzed using the statistical package, Statistics Analysis Systems (SAS).

B. Protocol: A protocol was included in this report (see Appendix A).

12. REPORTED RESULTS:

A. Animals in the preliminary study excreted approximately 42 to 44 percent of the [^{14}C] dose in the urine, 41 to 44 percent in the feces, and 0.1 to 0.2 percent in the exhaled air as [^{14}C]CO_2 within 24 hours after compound administration. Cage washes contained about 2 to 3 percent of the radiolabeled dose, and total [^{14}C] recoveries (at 24 hours) were between 87 and 88 percent. (Data are not presented in tabular form in this DER.)

B. Total mean percent recoveries of radioactivity from the first balance/distribution study ranged from unacceptable (80.1 percent) to acceptable (≥90.0 percent). Recoveries of radioactivity from individual animals in this study were low: total recoveries for 3/10 rats in the low-dose group were between 76.0 and 83.5 percent; 6/10 animals in the high-dose group had total recoveries between 55.3 and 88.9 percent; and only 2/10 rats in the first repeated-dose experiment had total recoveries ≥90 percent. Total mean and individual recoveries of radioactivity were higher in the repeated balance/distribution experiments than in the previously conducted experiments (i.e., total mean recoveries were 91.5 to 90.4 percent versus 80.1 to 92.6 percent, respectively). Recoveries for certain rats from these two studies (i.e., those with the highest [^{14}C] recoveries) were collated by the study authors to represent the behavior of [^{14}C]iprodione (Table 2); these composite data were discussed and evaluated in detail by the study authors and are presented below.

Orally administered [^{14}C]iprodione was readily absorbed and excreted by all rats. At least 79 percent of the [^{14}C] dose was recovered from the urine and feces within 48 hours after dosing (data not tabulated in this DER); 90.5 to 98.4 percent of the [^{14}C] administered was found in the urine and feces within 7 days (Table 2). The urine was the primary route of elimination of radioactivity in low- and repeated-dose rats; these animals excreted approximately 52.6 to 74.7 percent of the [^{14}C] dose in the urine and 25.0 to 38.8 percent in the feces. In contrast, relatively similar amounts of radioactivity were recovered from the urine and feces of high-dose rats (43.0 to 46.1 and 51.6 to 55.6 percent, respectively). Excretion of radioactivity in the urine was significantly ($p < 0.02$) lower in high-dose males when compared with low-dose males and repeated-dose

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TABLE 2. Composite of Mean Percent Recoveries of Radioactivity in Rats 7 Days After Oral Dosing with [^{14}C]Iprodione[a]

	Percent of [^{14}C] Administered to Rats Dosed at:					
	50 mg/kg[b]		900 mg/kg[b]		Repeated Dose[c]	
Fraction	Males	Females	Males	Females	Males	Females
Urine	67.4 ± 6.9[d]	52.6 ± 11.2	43.0 ± 11.3	46.1 ± 8.0	74.7 ± 6.2	65.1 ± 11.8
Feces	25.0 ± 6.4	38.8 ± 11.4	55.6 ± 9.9	51.6 ± 17.6	20.4 ± 5.7	28.0 ± 11.6
Cagewash	1.1 ± 0.7	0.9 ± 0.4	0.4 ± 0.3	0.8 ± 0.5	1.1 ± 0.2	0.6 ± 0.2
Tissues[e]	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.4 ± 0.1	0.3 ± 0.0
Total	93.8 ± 2.0	92.5 ± 2.0	99.3 ± 6.0	98.5 ± 10.2	96.6 ± 1.5	94.0 ± 3.5

[a]Compiled by the study authors; includes data from the first and second set of balance experiments.

[b]Animals were given a single oral dose of either 50 or 900 mg [^{14}C]iprodione/kg.

[c]Animals were given a single oral dose of 50 mg unlabeled iprodione/kg/day for 14 days followed by a single oral dose of 50 mg of [^{14}C]iprodione/kg on day 15.

[d]Each value represents the mean ± standard deviation of the five animals/sex with highest recoveries, as selected from the first and second studies.

[e]Does not include blood or plasma.

Source: CBI Tables XII-XIV, CBI pp. 63-65.

males ($p < 0.01$); urinary [^{14}C] levels of high-dose females were significantly ($p < 0.05$) lower than those of repeated-dose females but were not statistically different from levels in low-dose females. All tissues combined (excluding blood and plasma) contained no more than 0.5 percent of any dose, and cage washes accounted for 0.4 to 1.1 percent of the [^{14}C] administered. Total recoveries of radioactivity ranged from 92.5 to 99.3 percent.

C. Individual organs and tissues contained <0.05 percent of the radiolabeled dose, except (1) the carcass and skin of low-dose rats (both sexes), each of which accounted for 0.1 percent; (2) the skin of repeated-dose males, which contained 0.1 percent; and (3) the carcass and skin of repeated-dose females, which accounted for 0.1 and 0.3 percent of the dose, respectively. Individual tissue and carcass levels of [^{14}C] were very low (≤1 ppm) for low- and repeated-dose rats; tissue [^{14}C] residue levels in high-dose rats were proportionately higher (<10 ppm) than concentrations in the other two groups of rats (Table 3). The highest levels of radioactivity were found in the cecum (and contents), large and small intestines (and contents), liver, lymph nodes, skin, salivary glands, and fat. [^{14}C] concentrations in the blood of low- and repeated-dose rats were ≤0.14 ppm; the blood of high-dose animals had [^{14}C] residue levels between 0.75 and 1.6 ppm. Similarly, plasma radioactivity levels were ≤0.12 ppm for low- and repeated-dose animals and about 1.5 to 2.0 ppm for rats in the high-dose group.

D. Pharmacokinetic data from rats given a single low or single high dose of [^{14}C]iprodione were fitted to a one-compartment model (Table 4, Figures 1 and 2). [^{14}C]Iprodione was readily absorbed by all animals, with relatively high levels of radioactivity (6.64 to 25.1 ppm) appearing in the blood within 15 minutes after oral dosing (Table 4).

Absorption of radioactive material occurred somewhat more rapidly in low-dose animals than in high-dose animals, but no sex-related differences in absorption were observed. Removal of radioactivity from the blood generally was slower in males than in females and after administration of the high dose. Blood [^{14}C] levels peaked between 2 and 4 hours after dosing in low-dose rats (28.2 ppm for males, 24.1 ppm for females) and at 6 hours after administration of the high dose (81.7 and 71.6 ppm for males and females, respectively). The area under the blood concentration:time curve (AUC) was significantly ($p < 0.05$) greater for males when compared with similarly dosed females. Mean AUC values (± standard deviation) for low-dose males and females were 471 ± 110 and 306 ± 70 μg eq g^{-1} hr^{-1}, respectively; for high-dose animals, the values corresponded to

TABLE 3. Distribution of Radioactivity in Tissues of Rats 7 Days After Oral Dosing with [^{14}C]Iprodione[a]

Organ/ Tissue	[^{14}C]Iprodione Equivalents (ppm) for rats dosed at:					
	50 mg/kg[b]		900 mg/kg[b]		Repeated dose[c]	
	Males	Females	Males	Females	Males	Females
Liver	0.375[d](0)[e]	0.502(0)	3.99(0)	5.00(0)	0.400(0)	0.411(0)
Stomach (plus contents)	0.00960(0)	0.154(0)	0.402(0)	1.30(0)	0.0433(0)	0.0803(0)
Small intestine (plus contents)	0.177(0)	0.280(0)	2.16(0)	5.34(0)	0.226(0)	0.366(0)
Large intestine (plus contents)	0.452(0)	0.666(0)	5.33(0)	6.68(0)	0.250(0)	1.04(0)
Cecum (plus contents)	0.429(0)	0.694(0)	6.72(0)	9.90(0)	0.418(0)	1.00(0)
Pancreas	0.0568(0)	0.145(0)	1.57(0)	1.54(0)	0.184(0)	0.161(0)
Spleen	ND[f](ND)	0.0278(0)	0.764(0)	1.68(0)	ND(ND)	0.0177(0)
Kidneys	0.207(0)	0.209(0)	2.44(0)	2.11(0)	0.301(0)	0.199(0)
Testis/uterus	ND(ND)	0.136(0)	0.656(0)	1.20(0)	ND(ND)	0.128(0)
Lungs	0.0538(0)	0.0764(0)	1.57(0)	0.694(0)	0.0351(0)	0.0752(0)
Heart	0.00850(0)	0.0513(0)	0.823(0)	0.638(0)	ND(ND)	0.0491(0)
Thymus	ND(ND)	0.0397(0)	0.526(0)	1.46(0)	ND(ND)	ND(ND)
Salivary glands	0.166(0)	0.117(0)	1.78(0)	2.38(0)	0.0953(0)	0.152(0)
Brain	0.0122(0)	0.0101(0)	0.157(0)	0.319(0)	ND(ND)	ND(ND)
Muscle (skeletal)	0.0251(0)	0.0118(0)	0.146(0)	0.138(0)	ND(ND)	0.0152(0)
Carcass	0.0484(0.1)	0.0474(0.1)	0.568(0)	0.536(0)	0.0145(0)	0.0553(0.1)
Skin	0.0163(0.1)	0.226(0.1)	2.44(0)	2.54(0)	0.296(0.1)	0.877(0.3)
Fat (abdominal)	0.135(0)	0.308(0)	2.63(0)	1.92(0)	0.208(0)	0.262(0)
Bone (femur)	0.0169(0)	0.0152(0)	0.105(0)	0.0496(0)	0.00430(0)	ND(ND)
Eyes	0.0304(0)	0.0347(0)	0.236(0)	0.513(0)	0.0418(0)	0.0355(0)
Adrenals	0.0459(0)	0.106(0)	0.610(0)	2.66(0)	0.110(0)	0.113(0)

TABLE 3. (continued)

Organ/ Tissue	[^{14}C]Iprodione Equivalents (ppm) for rats dosed at:					
	50 mg/kg[b]		900 mg/kg[b]		Repeated dose[c]	
	Males	Females	Males	Females	Males	Females
Thyroid	ND(ND)	ND(ND)	ND(ND)	1.75(0)	ND(ND)	ND(ND)
Lymph nodes	0.130(0)	0.239(0)	1.95(0)	5.58(0)	0.128(0)	0.222(0)
Ovaries	NA[g]	0.147(--)	NA	1.86(0)	NA	0.139(0)
Blood	0.103(--)[h]	0.109(--)	1.62(--)	0.754(--)	0.135(--)	0.0715(--)
Plasma	0.0507(--)	0.0605(--)	1.91(--)	1.47(--)	0.121(--)	0.0641(--)

[a]Data are from the first set of balance/distribution experiments (see Materials and Methods, 11.A.4).

[b]Animals were given a single oral dose of either 50 or 900 mg [^{14}C]iprodione/kg.

[c]Animals were given a single oral dose of 50 mg unlabeled iprodione/kg/day for 14 days followed by a single oral dose of 50 mg of [^{14}C]iprodione/kg on day 15.

[d]Each value represents the mean of five animals.

[e]Values in parentheses represent the percent of the radiolabeled dose administered. Values of zero represent <0.05 percent of the [^{14}C]dose.

[f]ND = results were within background range (limits of detection not given).

[g]NA = not applicable.

[h]Value not given.

Source: CBI Tables III, VI, and IX; CBI pp. 54, 57, and 60.

TABLE 4. Mean Concentrations of Radioactivity in the Blood of Male and Female Rats Administered a Single Oral Dose of [^{14}C]Iprodione

Time after Dosing (hr)	[^{14}C]Iprodione equivalents (ppm) in the blood of rats dosed at:			
	50 mg/kg		900 mg/kg	
	Males	Females	Males	Females
0.25	6.64 ± 2.82	9.40 ± 1.67	11.3 ± 1.19	25.1 ± 7.25
0.5	16.5 ± 3.12	16.5 ± 1.36	18.4 ± 3.05	30.4 ± 11.8
1	21.3 ± 4.65	23.9 ± 2.97	33.1 ± 6.03	48.0 ± 16.8
2	26.6 ± 7.77*	24.1 ± 3.12	47.7 ± 5.86	54.5 ± 20.2
3	27.9 ± 7.00*	22.6 ± 3.33	57.4 ± 9.63	61.7 ± 25.6
4	28.2 ± 6.81*	21.8 ± 3.83	70.7 ± 17.3	67.6 ± 28.8
6	25.6 ± 7.09*	20.5 ± 5.29	81.7 ± 11.8	71.6 ± 23.8
8	22.9 ± 5.55*	15.2 ± 3.04	72.0 ± 8.83	62.0 ± 20.4
12	15.7 ± 7.54*	8.07 ± 3.02	63.8 ± 10.0	43.3 ± 5.90
24	5.32 ± 2.84*	2.07 ± 1.49	68.5 ± 11.8	25.2 ± 18.0
48	0.743 ± 0.729*	0.893 ± 1.49	5.86 ± 1.99	1.74 ± 0.0943
96	0.0990 ± 0.0314*	0.206 ± 0.300	3.20 ± 5.84	0.480 ± 1.08
120	0.124 ± 0.146*	0.150 ± 0.0955	ND	ND
168	0.161 ± 0.190*	0.0351 ± 0.0333	ND	ND

[a]Each value represents the mean ± standard deviation of five animals, except for values marked with an asterisk (*), which represent the mean ± standard deviation of four rats.

[b]ND = results were within background range. For the low dose, the limit of detection was approximately 0.0392 ppm for males and 0.0318 ppm for females; the high-dose limit of detection was 0.680 ppm for males and 0.570 ppm for females.

Source: CBI Table XI, CBI p. 62.

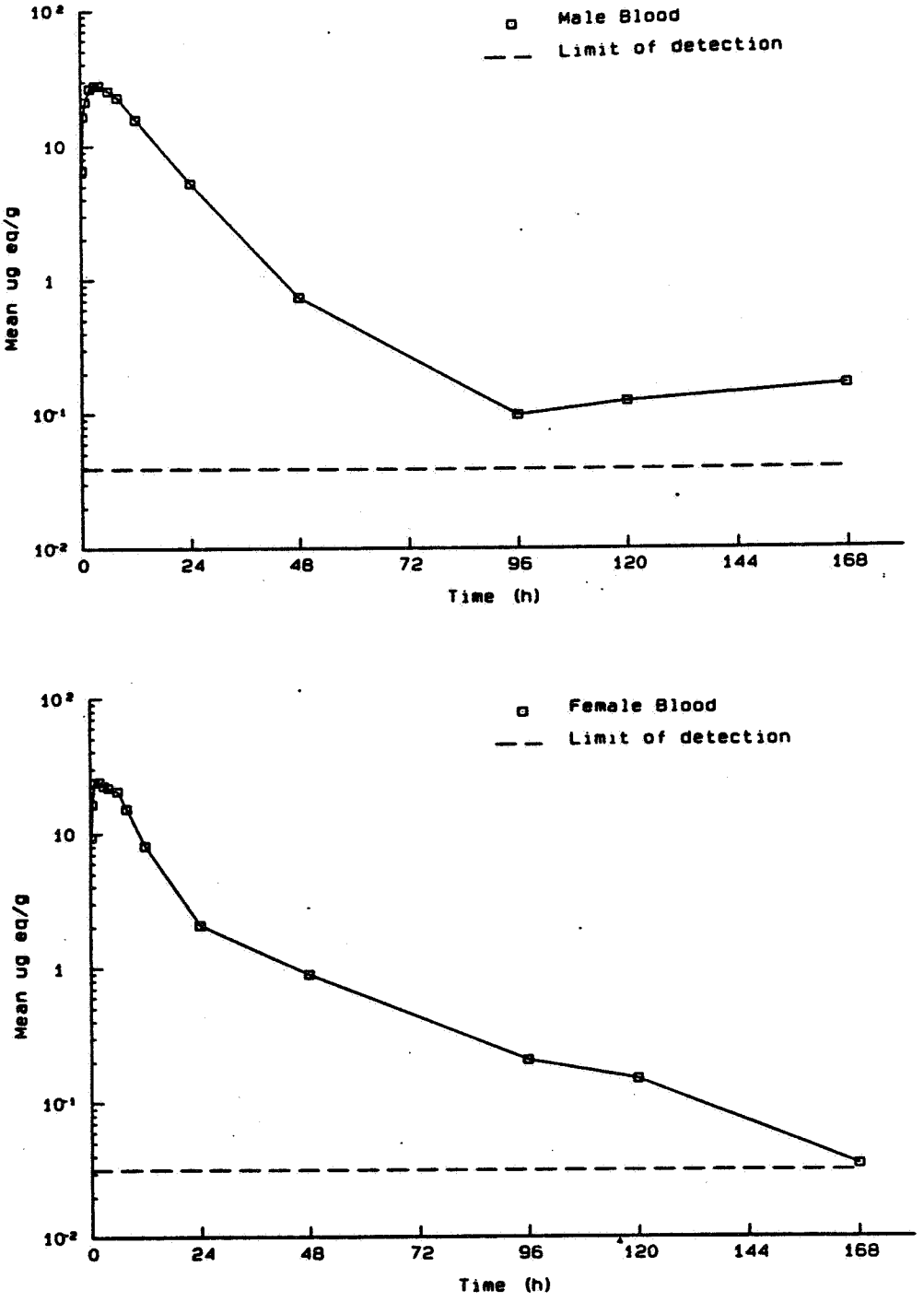

Figure 1. Whole-blood [^{14}C]-elimination curves for male (top) and female (bottom) rats given a single oral dose of 50 mg [^{14}C]iprodione/kg (each square represents the mean of four or five animals).

Source: CBI Figures 7 and 8, CBI pp. 79 and 80.

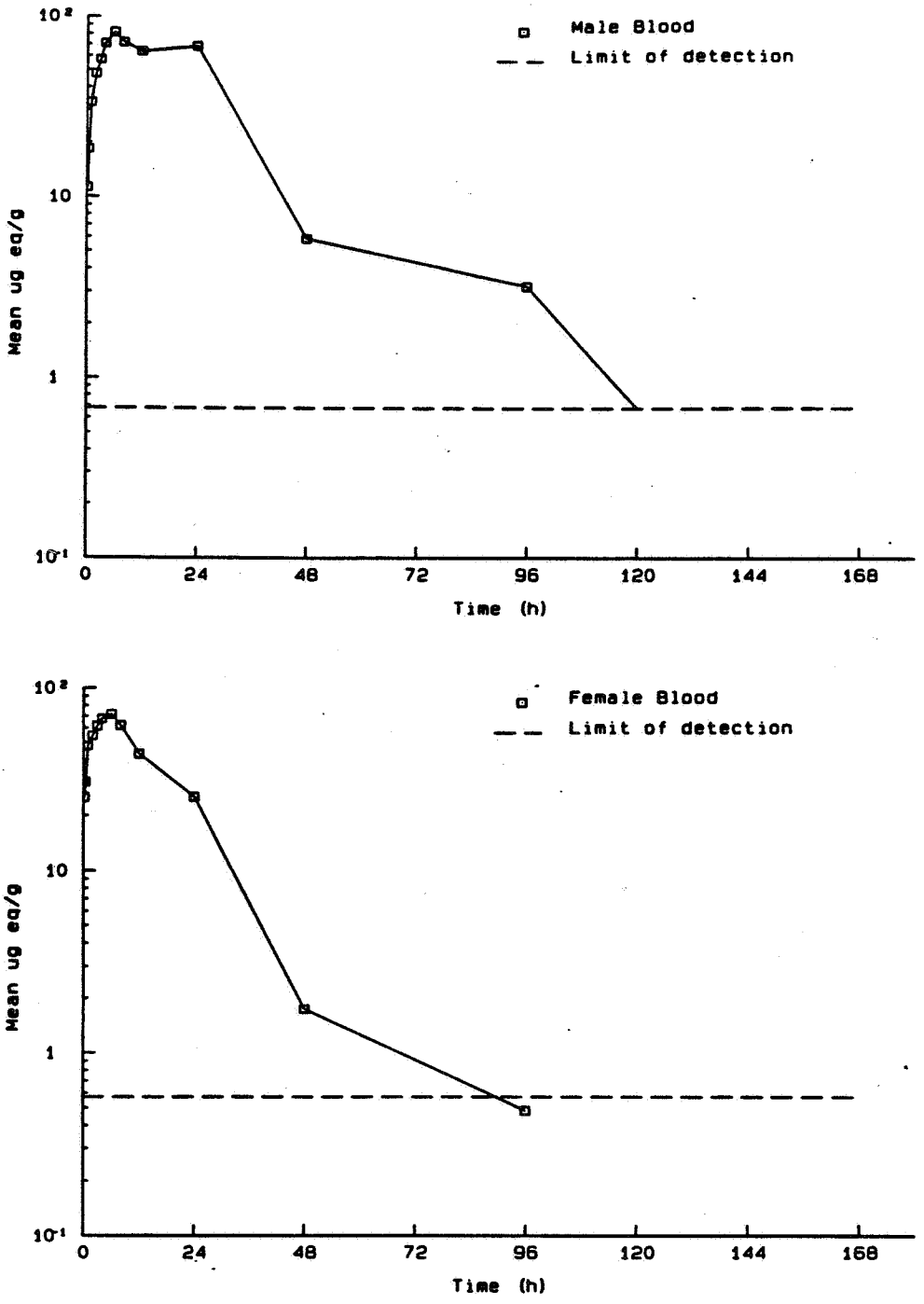

Figure 2. Whole-blood [^{14}C]-elimination curves for male (top) and female (bottom) rats administered a single oral dose of 900 mg [^{14}C]iprodione/kg (each square represents the mean of five animals).

Source: CBI Figures 9 and 10, CBI pp. 81 and 82.

2,870 ± 450 and 1,520 ± 480 μg eq g^{-1} hr^{-1}. The mean blood elimination half-lives (± standard deviation) for low-dose males (8.9 ± 1.5 hours) and females (6.9 ± 1.7 hours) were not statistically ($p < 0.05$) different. In contrast, high-dose males eliminated radioactivity at a somewhat slower rate ($p < 0.05$) than females (elimination half-lives 19.8 ± 3.8 and 12.5 ± 3.0 hours, respectively). Dose-related statistical differences in AUCs and elimination half-lives were not reported.

E. Iprodione was extensively metabolized by all animals, with at least 10 metabolites isolated in the urine and 5 in the feces within 48 hours after dosing (Tables 5, 6, and 7). About half of the radioactivity in the urine collected from males and females during the first 24 hours corresponded to four to six reference compounds; the remaining [^{14}C] was associated with five to nine relatively more polar but unidentified metabolites (33.63 to 50.80 percent), iprodione (0 to 11.61 percent), and residual radioactivity (2 to 19 percent for females; 11 to 22 percent for males). During the 24- to 48-hour collection period in females and high-dose males, the amount of urinary radioactivity that corresponded to identified metabolites dropped to a range of 14 to 22 percent. Major urinary metabolites (i.e., those accounting for >10 percent of the [^{14}C] in a sample) excreted by all females included 32490 RP -- the dealkylated derivative of iprodione (see Figure 2) -- and the unchanged parent compound. Two unidentified polar metabolites with retention times (t_rs) of approximately 10 and 8.5 minutes were also isolated from the urine of all female rats. In addition, high-dose females excreted relatively large amounts of 36114 RP, which is produced by opening of the hydantoin ring of iprodione. In contrast with females, the two major metabolites found in the urine of all male rats included 32490 RP and 36114 RP; unchanged parent compound accounted for no more than 4.5 percent of the urinary radioactivity recovered during the entire 48-hour postdosing period. Other major urinary metabolites excreted by males included the two unidentified polar compounds described above.

Table 6 summarizes HPLC data for acetonitrile extracts of feces, while Table 7 summarizes HPLC data for water extracts of feces. Acetonitrile extracted about 60 to 70 percent of the radioactivity, whereas the subsequent water extraction accounted for only 9 to 12 percent of the radioactivity. Not all of the extracted radioactivity was associated with peaks on HPLC chromatography. In acetonitrile extracts of the 0- to 24-hour samples, 9 to 38 percent was not associated with any peaks; this percentage was generally greater than that in the 24- to 48-hour fecal extracts (21 to 42 percent). Between 2 and 58 percent of the radioactivity in the water extracts of feces was not

TABLE 5. Relative Proportions of Radioactive Components in the Urine of Rats Dosed Orally With [^{14}C]Iprodione

Compound/Component[c]	Percent of urinary radioactivity in samples from animals dosed at: 50 mg/kg[a] Males 0-24 hr	50 mg/kg[a] Males 24-48 hr	50 mg/kg[a] Females 0-24 hr	50 mg/kg[a] Females 24-28 hr	900 mg/kg[a] Males 0-24 hr	900 mg/kg[a] Males 24-48 hr	900 mg/kg[a] Females 0-24 hr	900 mg/kg[a] Females 24-48 hr	Repeated dose[b] Males 0-24 hr	Repeated dose[b] Males 24-48 hr	Repeated dose[b] Females 0-24 hr	Repeated dose[b] Females 24-48 hr
Iprodione	1.49[d]	--[e]	11.39	3.65	4.56	--	9.02	1.44	--	--	11.61	--
30228 RP	--	--	--	--	--	--	--	--	--	--	--	--
36115 RP and 36119 RP[f]	3.03	--	0.93	--	4.04	2.76	2.37	--	1.57	0.65	--	--
32490 RP	25.06	--	29.43	14.35	22.27	1.84	7.77	1.75	15.59	4.27	26.86	6.45
36112 RP	--	--	--	--	3.53	--	4.47	1.54	2.55	--	2.44	--
25040 RP	--	--	--	--	--	--	--	--	--	--	--	--
36116 RP	1.69	--	0.50	--	1.43	1.21	--	--	1.98	3.36	0.95	--
36118 RP	2.24	8.69	0.91	--	3.33	--	--	--	4.75	2.61	1.00	--
36114 RP	15.81	35.48	3.72	--	11.68	16.45	22.44	12.60	20.50	34.39	4.67	7.21
Total, identified metabolites	49.32	44.17	46.88	18.00	50.84	22.26	46.07	17.33	46.94	42.28	47.53	13.66
Unidentified metabolites[g]	2.62	3.57	1.39	--	--	--	--	0.50	--	0.91	--	--
	2.06	--	0.77	--	2.95	2.90	3.47	4.40	2.99	3.42	2.49	4.66
	3.88	1.63	5.01	7.13	14.19	7.34	--	--	6.19	--	4.54	--
	6.44	--	1.45	--	3.15	--	9.78	6.44	15.31*	20.00*	5.7*	10.75*

(continued)

TABLE 5. (continued)

Compound/ Component	Percent of urinary radioactivity in samples from animals dosed at: 50 mg/kg[a] Males 0-24 hr	50 mg/kg[a] Males 24-48 hr	50 mg/kg[a] Females 0-24 hr	50 mg/kg[a] Females 24-28 hr	900 mg/kg[a] Males 0-24 hr	900 mg/kg[a] Males 24-48 hr	900 mg/kg[a] Females 0-24 hr	900 mg/kg[a] Females 24-48 hr	Repeated Dose[b] Males 0-24 hr	Repeated Dose[b] Males 24-48 hr	Repeated Dose[b] Females 0-24 hr	Repeated Dose[b] Females 24-48 hr
Unidentified metabolites (continued)[g]	2.1	--	2.65	--	9.18*	19.03*	12.82*	13.85*	9.14**	15.71**	17.55**	42.81**
	--	--	1.49	--	8.71**	23.52**	15.43**	34.94**	--	--	3.69	8.98
	10.47*	14.73*	6.63*	12.29*	1.26	--	--	--				
	10.57**	14.32**	26.32**	50.11**	--	2.69	--	7.13				
	1.30	--	5.09	7.75								
Total, unidentified metabolites	39.44	34.24	50.80	77.28	39.44	55.48	41.50	67.26	33.63	40.04	33.97	67.20
Radioactivity not associated with any peak	11.24	22.48	2.32	4.72	9.72	22.26	12.53	15.41	19.43	14.68[h]	18.50	19.14

[a]Animals were given a single oral dose of either 50 or 900 mg [^{14}C]iprodione/kg.

[b]Animals were given a single oral dose of 50 mg unlabeled iprodione/kg/day for 14 days followed by a single oral dose of 50 mg of [^{14}C]iprodione/kg on day 15.

[c]Standard reference compounds are numbered. Structures are provided in Figure 3.

[d]Values are for one male or one female rat.

[e]No peak was detectable for this compound or at this retention time.

[f]Compounds could not be separated by thin-layer chromatography.

[g]Respective retention times for unidentified compounds are as follows (min'sec): for the 50-mg/kg group - 27'48, 26'34, 17'00, 14'36, 13'44, 11'24, 09'51, 08'31, 6'30; for the 900-mg/kg group - 28'10, 17'28, 14'42, 13'52, 10'00, 08'33, 07'27, 06'44; for the repeated-dose group - 27'35, 17'23, 14'02, 10'03, 08'47, 06'47.

[h]Values in this column total 97 percent.

*Compounds with retention times (min'sec) between 9'51 and 10'03.

**Compounds with retention times (min'sec) between 8'31 and 8'47.

Source: CBI Tables XV-XVII, CBI pp. 66-68.

TABLE 6. Relative Proportions of Radioactive Components in Acetonitrile Extracts of Feces of Rats Dosed Orally With [^{14}C]Iprodione

Compound/ Component[c]	Percent of fecal radioactivity in samples from animals dosed at:											
	50 mg/kg[a]				900 mg/kg[a]				Repeated dose[b]			
	Males		Females		Males		Females		Males		Females	
	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr
Iprodione	34.04[d]	8.51	31.21	4.28	79.35	13.79	85.12	17.57	66.88	5.08	31.41	5.96
30228 RP	1.01	--[e]	3.67	--	1.24	2.07	1.38	--	3.48	--	2.96	--
36115 RP and 36119 RP[f]	3.62	16.98	6.81	13.13	1.91	16.34	--	19.72	1.28	6.28	6.79	19.54
32490 RP	9.81	--	13.63	8.88	2.01	4.72	--	--	2.49	--	8.75	5.88
36112 RP	2.20	--	4.35	8.83	0.79	4.44	--	12.00	1.66	--	2.95	--
25040 RP	--	--	2.05	--	--	--	--	--	0.89	--	--	--
36116 RP	5.44	13.47	4.76	--	1.02	6.74	--	--	0.97	--	4.35	8.29
36118 RP	--	--	10.14	7.19	--	--	--	--	0.91	--	0.86	--
36114 RP	5.90	13.17	11.68	36.24	1.85	13.44	1.53	8.56	1.56	--	10.22	17.73
Total, identified metabolites	62.02	52.13	88.30	78.55	88.17	61.54	88.03	57.85	80.12	11.36	68.29	57.40
Unidentified metabolites[g]		5.30	2.26			6.16		7.18			1.34 1.25	
Total, unidentified metabolites	--	5.30	2.26	--	--	6.16	--	7.18	--	--	2.59	--
Radioactivity not associated with any peak	37.99	42.57	9.44	21.45	11.83	32.30	11.97	34.97	19.88	88.64	29.39	42.60

(continued)

TABLE 6. (continued)

[a]Animals were given a single oral dose of either 50 or 900 mg [^{14}C]iprodione/kg.

[b]Animals were given a single oral dose of 50 mg unlabeled iprodione/kg/day for 14 days followed by a single oral dose of 50 mg [^{14}C]iprodione/kg on day 15.

[c]Standard reference compounds are numbered.

[d]Values are for one male or one female.

[e]No peak was detectable for this compound or at this retention time.

[f]Compounds could not be separated by thin-layer chromatography.

[g]Respective retention times for unidentified compounds are as follows (min'sec): for the 50-mg/kg group - 10'12; for the 900-mg/kg group - 10'14 (females), 45'55 (males); for the repeated-dose group - 10'42, 08'16.

Source: CBI Tables XVIII-XX, CBI pp. 69-71.

TABLE 7. Relative Proportions of Radioactive Components in Water Extracts of Feces of Rats Dosed Orally With [^{14}C]Iprodione

Compound/ Component[c]	Percent of fecal radioactivity in samples from animals dosed at:											
	50 mg/kg[a]				900 mg/kg[a]				Repeated dose[b]			
	Males		Females		Males		Females		Males		Females	
	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr
Iprodione	--[d,e]	--	2.28	--	12.27	1.84	5.40	4.00	3.03	--	2.85	--
30228 RP	--	--	--	--	2.12	--	--	--	--	--	--	--
36115 RP and 36119 RP[f]	--	--	--	4.54	--	--	12.45	3.51	--	--	3.11	9.13
32490 RP	17.09	--	11.91	9.49	3.28	3.98	10.59	9.15	19.12	11.11	25.58	8.24
36112 RP	--	--	1.91	3.76	--	--	4.11	2.32	1.78	--	--	--
25040 RP	--	--	--	--	3.87	--	--	--	--	--	--	--
36116 RP	--	--	3.45	--	6.06	5.17	5.30	2.07	--	--	5.55	4.32
36118 RP	16.77	--	7.78	10.74	--	--	5.29	3.67	5.55	8.68	--	--
36114 RP	33.60	17.95	21.95	36.48	16.79	29.91	34.57	7.72	13.56	42.33	28.31	25.91
Total, identified metabolites	67.46	17.95	49.28	65.01	44.39	40.9	77.71	32.44	43.04	62.12	65.40	47.65
Unidentified metabolites[g]	--	--	1.44	--	2.45	--	--	--	1.41	5.16	--	--
	17.64	6.66	17.09	15.56	9.53	17.02	--	--	--	--	0.89	--
	--	5.36	--	--	8.93	10.49	8.35	5.01	3.64	--	4.40	--
	--	--	--	1.74					3.46	10.75	--	--
	12.70	--	12.70	14.05					--	12.38	13.88	10.61
	--	12.35	--	--					3.43	--	8.50	19.85
Total, unidentified metabolites	30.34	24.37	31.23	31.35	20.91	27.51	8.35	5.01	11.94	28.29	27.67	30.46
Radioactivity not associated with any peak	2.20	57.68	19.49	3.64	34.70	31.59	13.94	62.55	45.02	9.59	6.93	21.89

(continued)

TABLE 7. (continued)

[a]Animals were given a single oral dose of either 50 or 900 mg [^{14}C]iprodione/kg.

[b]Animals were given a single oral dose of 50 mg unlabeled iprodione/kg/day for 14 days followed by a single oral dose of 50 mg [^{14}C]iprodione/kg on day 15.

[c]Standard reference compounds are numbered.

[d]Values are for one male or one female.

[e]No peak was detectable for this compound or at this retention time.

[f]Compounds could not be separated by thin-layer chromatography.

[g]Respective retention times for unidentified compounds are as follows (min'sec): for the 50-mg/kg group - 17.64, 10'26, 08'04, 05'00, 03'07, 02'32; for the 900-mg/kg group - 41'26, 11'10, 02'32; for the repeated-dose group - 43'54, 34'50, 14'02, 11'06, 09'24, 02'35.

Source: CBI Appendices 63-65, CBI pp. 302-304. Compiled by the reviewers.

accounted for; however, no time- or dose-related patterns were observed. In the 0- to 24-hour acetonitrile-extracted samples, unmetabolized iprodione accounted for 55 and 89 percent of the identified radiolabel in male feces at doses of 50 and 900 mg/kg, respectively; corresponding values for females were 35 and 96 percent.

In the 24- to 48-hour fecal acetonitrile extracts, metabolites accounted for most of the identified radioactivity, although at the 900-mg/kg dose, 23 and 30 percent of the identified radioactivity in males and females, respectively, was parent compound. Unchanged parent compound accounted for much smaller amounts of the identified radiolabeled material (i.e., between 0 and 28 percent) recovered from all water extracts of feces. Several metabolites were seen in the feces at 24 hours. The major metabolites in the 24- to 48-hour acetonitrile-extracted fecal samples from both sexes were 36115 RP/36119 RP and 36114 RP (see Figure 3 for structures). Major identified metabolites recovered from water extracts of feces included 32490 RP, 36118 RP, and 36114 RP; several unidentified metabolites (i.e., those with t_rs of approximately 2.5 to 3.0, 9.5, and 10.5 to 11.0 minutes) also were isolated (Table 7). In the repeated-dose study, parent compound accounted for 84 and 45 percent of the identified radioactivity in the 0- to 24-hour acetonitrile-extracted samples from males and females, respectively, but ≤7 percent of that in the water-extracted fecal samples (of both sexes). Figure 3 presents the proposed metabolic pathway for iprodione in rats.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study author concluded that a single oral dose of 50 or 900 mg iprodione/kg and repeated oral doses of 50 mg iprodione/kg were readily absorbed, metabolized, and excreted by rats. Distribution of radioactive material in the body was widespread but at low levels in all groups of animals.

Problems associated with the recovery of radioactivity were attributed to difficulty in calculating the net [^{14}C] dose given to individual rats, which, in turn, was believed to be due to the inhomogeneity of the [^{14}C]iprodione dosing suspensions. Variations in the repeated mass balance study were also thought to have resulted from radioactive "hot spots" in the [^{14}C]iprodione suspensions. Because of this problem, and to give a realistic profile of the absorption and excretion of orally administered [^{14}C]iprodione, the study author collated individual rat data from the first and second mass balance studies (Table 4, this DER). This approach was considered acceptable because the residual radioactivity in the carcass, tissues, and organs was low in all animals. The study author also concluded that, because tissue/organ [^{14}C] levels were low, any inaccuracy caused by inhomogeneity of the dosing solutions would not markedly affect tissue radioactivity levels.

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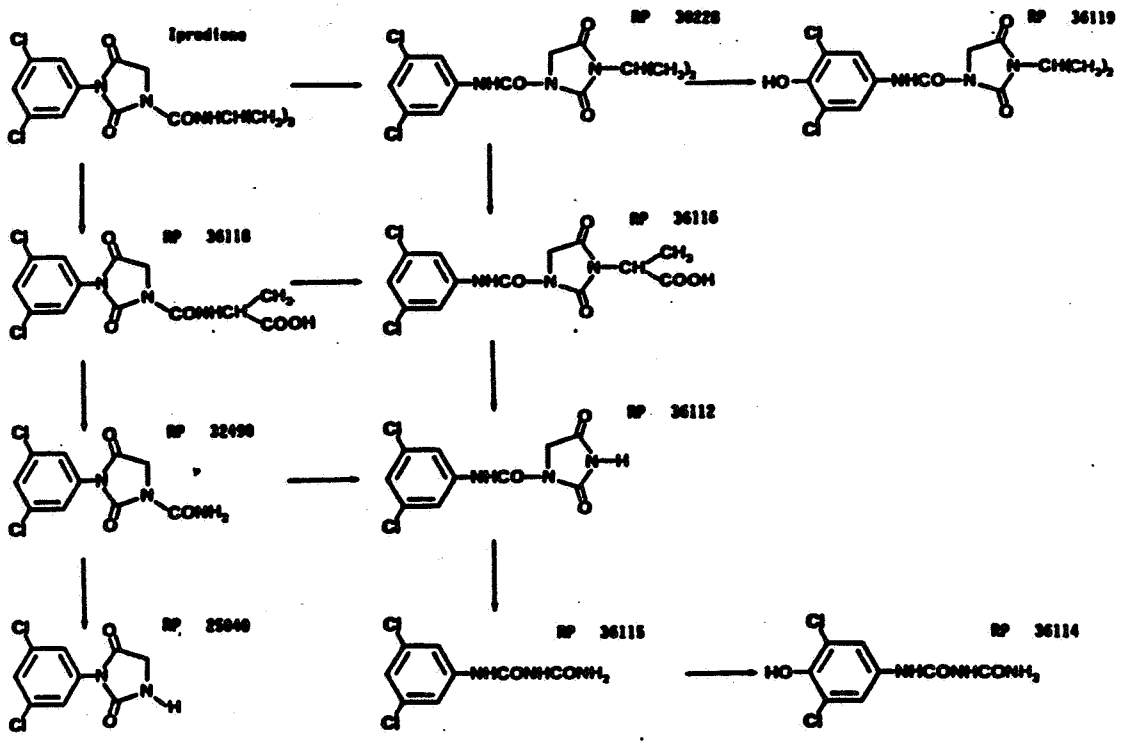

Figure 3. Proposed metabolic pathway for iprodione in orally dosed rats.

Source: CBI Figure 11, CBI p. 83.

Orally administered [^{14}C]iprodione was rapidly absorbed from the gastrointestinal tract. Blood levels of radioactivity in low-dose males and females peaked at 4 and 2 hours after compound administration, respectively; absorption of the high dose was somewhat slower, with blood [^{14}C] levels peaking at 6 hours postdosing. No sex-related differences in mean peak blood [^{14}C] concentrations were reported. However, peak blood concentrations of [^{14}C] were about three times greater in high-dose rats that in low-dose animals, and the area under the blood concentration:time curve (AUC) values were five to six times larger for high-dose rats than for low-dose animals. AUCs also were significantly ($0.02 < p < 0.05$) higher for low- and high-dose males than for the corresponding females. In addition, elimination half-lives of high-dose males were significantly ($p < 0.05$) longer when compared with values for high- dose females; elimination half-lives were similar for low-dose males and females. The study author stated that these differences reflected relatively slow declines in mean blood [^{14}C] concentrations (of males in particular) that resulted from some high individual animal data. Elimination of radioactivity following a single low oral dose of [^{14}C]iprodione was primarily via the urine, while elimination in high-dose animals was more equally divided between the urine and feces. The higher amounts of [^{14}C] in the feces of high-dose animals represented a reduction in the amount of iprodione absorbed from the gastrointestinal tract when compared with other groups of animals.

[^{14}C]Iprodione was extensively metabolized by animals in all groups. In both sexes, a large proportion of the radioactive dose -- about half -- corresponded to reference compounds. Dealkylation and cleavage of the hydantoin ring were two primary steps in the metabolism of the test material. Hydroxylation of the phenyl ring and oxidation of the alkyl chain also occurred. Sex-related differences in urinary metabolite profiles were reported with females excreting much larger amounts of the unchanged parent compound than males, and males producing more of the hydantoin ring-opened metabolite of iprodione (36114 RP) than females. The other major urinary metabolites recovered from both males and females were the dealkylated compound 32490 RP and two unidentified polar metabolites. Several urinary metabolites were not identified; most of these compounds had short retention times (when compared with the reference compounds), indicating their relatively polar nature. The study author suggested that many of these compounds were conjugated. The feces contained much larger amounts of unchanged parent compound than the urine; it was suggested that the [^{14}C] radioactivity in the feces represented unabsorbed iprodione and metabolites or, possibly, hydrolyzed conjugates of absorbed material.

B. A quality assurance statement was signed and dated December 14, 1989. A statement declaring compliance with EPA's Good Laboratory Practice Standards was signed and dated January 1, 1990.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

This study was conducted adequately, and the data presented support the conclusions made by the study author. The doses chosen were appropriate per EPA guidelines (Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, 1984, pp. 152-154); the low dose corresponded to a no-effect level, and the high dose was described in the CBI Protocol Amendments (CBI p. 405; see Appendix A of this DER) as being able to produce signs of toxicity but not mortality. Providing toxicity data would have supported this statement. The study author met the EPA requirement that five animals/sex/dose level be used in metabolism studies; thus, sufficient numbers of animals were used to evaluate the pharmacokinetics/metabolism of orally administered iprodione. An intravenous dosing study was not conducted because of the poor aqueous solubility of the test material.

The study author stated that difficulty in producing a consistently homogeneous dosing suspension most likely caused the considerable variation in recovery of radioactivity, even in the series of repeated mass balance studies. However, it is not known whether dosing suspensions were vortexed or continually stirred before dosing (these procedures generally assist in achieving or maintaining homogeneity). In addition, tests for homogeneity were not conducted, and the study author did not provide results for recovery of radioactivity in samples spiked with a [^{14}C]iprodione-labeled suspension. On the basis of results presented by the study author, high-dose rats in the first mass balance/distribution study received between 111 and 124 percent of the target [^{14}C] dose (see Table 1 of this DER); however, individual total [^{14}C] recovery data ranged from 55.3 to 103 percent of the administered dose. For other animals in the first mass balance study (i.e., those given a single low or repeated low doses of iprodione), individual total [^{14}C] recovery values were between 74 and 102 percent. The study author more closely approached the target doses in the second series of studies and reported a smaller -- albeit still relatively large -- variation in total individual recoveries (88.5 to 95.8 percent for low-dose animals; 67.9 to 114 percent, high-dose animals; 79.0 to 99.1 percent, repeated-dose rats). The collation of results from the first and second mass balance studies is acceptable since tissue and organ [^{14}C] levels were low; however, data presented should be considered as only rough estimates of percent of dose absorbed, excreted, etc.

The reviewers agree with the study author that single low, single high, and single repeated oral doses of [^{14}C]iprodione are readily absorbed, metabolized, and excreted by male and female rats. Examination of blood concentration:time curves (Figures 1 and 2, this DER) indicate that the elimination of radioactivity from the blood of orally dosed animals may follow a two-compartment (rather than a one-compartment) model; however, the study author reported that the high mean [^{14}C] blood levels recorded several days after dosing resulted from individual outliers and that all data fit a one-component model.

Using the composite data presented in Table 2 of this DER, the reviewers estimate that within 7 days after compound administration, low-dose males and females absorbed approximately 69 and 54 percent of the [^{14}C] dose, respectively; corresponding values for repeated-dose animals were 76 and 66 percent. High-dose males and females absorbed about 44 and 47 percent, respectively. Thus, males absorbed a larger percent of both the low and repeated doses than females, and increasing the oral dose from 50 to 900 mg/kg caused a lower percent of parent compound to be absorbed by males.

As noted by the study author, retention of radioactivity in the body was low, with all tissues accounting for no more than 0.5 percent of the dose and no individual tissue accounting for more than 0.3 percent. Tissues/organ and carcass [^{14}C] levels of low- and repeated-dose rats were ≤1 ppm; tissue [^{14}C] residue levels in high-dose animals were proportionately higher (≤10 ppm). Plasma and blood levels followed a similar pattern; values for low- and repeated-dose rats were ≤0.14 ppm, and values for high-dose animals were <2.0 ppm. The highest levels of radioactivity were found in the cecum, large and small intestines, liver, lymph nodes, skin, salivary glands, and fat. The data indicate that the radioactivity associated with orally administered [^{14}C]iprodione did not accumulate in the body to an appreciable extent.

Iprodione was rapidly and extensively metabolized by both male and female rats, although the recovery of about 10 percent of the urinary [^{14}C] as unchanged parent compound in females (versus less than 5 percent in males) indicates that metabolism in females was somewhat less complete than in males. Males and females of all groups eliminated in the urine relatively large amounts of a dealkylated metabolite of iprodione, which corresponded to the reference compound 32490 RP, and two unidentified polar metabolites. The urine of all males and high-dose females also contained large quantities of 36114 RP, a hydantoin ring-opened metabolite of iprodione. The recovery of increased amounts of this and several other unidentified metabolites in the urine of repeated- and high-dose females (when compared with low-dose females) indicates a possible induction of liver enzymes. High recoveries of fecal [^{14}C] label as unchanged parent compound

in high-dose animals also indicate that, at the 900-mg/kg dose, the metabolism of iprodione was near saturation. In the metabolic pathway proposed by the study author (Figure 3, this DER), iprodione undergoes dealkylation or oxidation of its alkyl chain and is subject to oxidation and hydrolysis of the hydantoin ring to produce a carbamyl urea (biuret) derivative of the compound. The addition of a hydroxyl group on the fourth carbon of the dichlorophenyl ring also occurred. Despite the recovery and identification of many metabolites, the TLC and HPLC methods used by the study author failed to identify several major urinary metabolites. In addition, large fractions of radioactivity (up to 22 and 88 percent in the urine and feces, respectively) were not associated with any compound, indicating that the analytical scheme used by the study was inadequate. The study author failed to address the distribution of radioactivity in water extracts of feces (presented by the reviewers in Table 7 of this DER). It was suggested that the unassigned radioactivity in the feces may have been hydrolyzed conjugates of metabolites of absorbed material, thus implying enterohepatic cycling of iprodione and/or its metabolites. Since biliary material was not examined, no conclusions regarding this supposition can be made. However, this suggestion may be considered in light of the fairly large amounts of polar but unidentified material recovered from the urine and the extensive array of reference compounds found in the feces.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Study Protocol and Study Protocol Amendments, CBI pp. 377-409.