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

JUN 24 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Iprodione- One-Year Feeding Study in Dogs

TO: Robert Rose/Susan Lewis PM 21

FROM: K. Clark Swentzel K. Clark Swentzel 6/15/92
Toxicology Branch II
(H7509C)

THROUGH: Marcia van Gemert, Ph.D. Marcia van Gemert 6/17/92
Branch Chief
Toxicology Branch II
(H7509C)

Submission: S-412290
Barcode: D174909
MRID NO.: 422111-01
PROJECT NO.: 2-1520
CASWELL NO.: 470A
REGISTRANT: Rhone-Poulenc

Action Requested

Review a new 1-year dog study for the basis of the ADI.

Background

A 1-year feeding study in dogs (84RH002/179) was previously reviewed by the Agency (EPA Memorandum, van Gemert to Forrest, May 18, 1987). The dietary levels of iprodione in that study were 0, 100, 600 or 3600 ppm. An LEL of 600 ppm was established based on an increased number of erythrocytes with Heinz bodies in males and decreased prostate weights; the NOEL was 100 ppm (4.2 mg/kg/day, measured dose). Since the RfD was based on this NOEL, the registrant decided to repeat the study in order to establish a higher NOEL/RfD. The test protocol for this study was previously reviewed by TB II (EPA Memorandum, Swentzel to Lewis/Stone, April 9, 1990).

Current Study (see attached DER from Clement International Corp.)

Iprodione was fed to groups of 6 beagle dogs/sex for 52 weeks at dietary levels of 0, 200, 300, 400, or 600 ppm (for males: 0, 7.8, 12.4, 17.5 or 24.6 mg/kg/day, respectively; for females: 0, 13.1, 18.4 or 26.4 mg/kg/day, respectively). This is considered a bridging study to establish a higher NOEL since the minimum requirements set forth under the Subdivision F Guidelines were not satisfied. Only a limited number of parameters were investigated based on findings in the first dog study. Compound-related systemic toxicity was observed at 600 ppm and manifested as depressed red blood cell parameters (RBC, HGB and HCT values). The NOEL and LOEL for systemic toxicity were 400 ppm (17.5 mg/kg/day for males; 18.4 mg/kg/day for females) and 600 ppm (24.6 mg/kg/day for males; 26.4 mg/kg/day for females), respectively. The combined NOEL and LOEL for the two 1-year feeding studies in dogs is considered to be 400 ppm (approximately 18 mg/kg/day) and 600 ppm, respectively.

This study will be submitted to the RfD Peer Review Committee in order for them to reconsider the current RfD.

Classification

Core Supplementary Data. Based on the proposed objectives, this study is acceptable. This study, in combination with the previous 1-year dog study (84RH002/179), satisfies Guidelines Series No. 83-1b for a chronic toxicity study in a non-rodent.

DATA EVALUATION REPORT

IPRODIONE

Study Type: Chronic Feeding Study in Dogs

Prepared for:

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

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer Pia Lindström Date 6-11-92
Pia Lindström, D.P.H.

Independent Reviewer William L. McLellan Date 6-11-92
William McLellan, Ph.D.

QA/QC Manager Sharon A. Segal Date 6-11-92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-98
Clement Number: 93-29
Project Officer: James Scott

Approved by: Clark Swentzel
EPA Reviewer/Section Head
Toxicology Branch II/HED

Signature: K. Clark Swentzel

Date: 6/15/92

DATA EVALUATION REPORT

STUDY TYPE: Chronic feeding study in dogs

EPA IDENTIFICATION NUMBERS

TOX CHEM NUMBER: 470 A

MRID NUMBER: 422111-01

TEST MATERIAL: 3-(3,5-Dichlorophenyl)-N-isopropyl-2,4-dioxoimidazolodine-1-carboxamide

SYNONYMS: Iprodione; 26019RP; Glycophene; Kidan

SPONSOR: Rhone-Poulenc Canada, Inc., Ontario, Canada

STUDY NUMBER: 84296

TESTING FACILITY: Bio-Research Laboratories, Ltd., Quebec, Canada

TITLE OF REPORT: A 52-Week Dietary Toxicity Study of Iprodione in the Beagle Dog

AUTHOR: L. Kangas

REPORT ISSUED: December 20, 1991

CONCLUSIONS: Iprodione was fed to groups of six beagle dogs/sex for 52 weeks at dosage levels of 0, 200, 300, 400, or 600 ppm (for males: 0, 7.8, 12.4, 17.5, or 24.6 mg/kg/day, respectively; for females: 0, 9.1, 13.1, 18.4, or 26.4 mg/kg/day, respectively). The study was only designed to complement a previously conducted study and to establish a NOEL. Compound-related systemic toxicity was observed at 600 ppm and manifested as depressed red blood cell (RBC, HGB, and HCT) values. The NOEL and LOEL for systemic toxicity were 400 ppm (for males 17.5 mg/kg/day; for females 18.4 mg/kg/day) and 600 ppm (for males 24.6 mg/kg/day; for females 26.4 mg/kg/day), respectively.

CLASSIFICATION: Core Supplementary Data. This study alone does not meet the minimum requirements set forth under Guideline Series 83-1 for a chronic toxicity study in dogs owing to a limited number of endpoints being evaluated. However, the objectives were met insofar that a NOEL/LOEL were established at 400/600 ppm. The initial study was classified as Core Minimum Data. When considered together, it is recommended that the two studies be classified as Core Minimum Data with a NOEL = 400 ppm (approximately 18 mg/kg/day).

A. MATERIALS

Test Compound

Description: Granular off-white powder
Lot no.: 8906201
Purity: 96.1% and 96.2%
Received: January 12, 1990 and January 7, 1991
Contaminants: Not reported

Test Animals

Species: Canis familiaris
Strain: Beagle
Age: 23-24 weeks at start of study
Weight: Males--5.7-8.7 kg; females--5.0-7.1 kg at start of study
Source: Marshall Farms, North Rose, NY

B. STUDY DESIGN

Animal Assignment: Animals were acclimated to laboratory conditions for 4 weeks and were assigned by sex to the following test groups using a computer-generated randomization procedure:

Test group	Dosage in Diet (ppm)	Males	Females
Control	0	6	6
Group 2	200	6	6
Group 3	300	6	6
Group 4	400	6	6
Group 5	600	6	6

Environmental Conditions: Animals were housed individually. Temperature and relative humidity were controlled at 20±2°C and 50±20%, respectively. A 12-hour dark/light cycle was maintained.

Dosage Rationale: Dosage levels were selected based on the results of a previously conducted 52-week chronic feeding study performed at Life Science Research, Suffolk, England (Report Number 84/RH0022/179). In that study, 100 ppm was a clear NOEL, while 600 ppm showed effects on hematology parameters and prostate weight. The purpose of the present study was to determine a NOEL between 100 and 600 ppm.

Diet Preparation: Diets were prepared weekly and stored at room temperature in an air-tight plastic container. A premix was first prepared consisting of the required amount of test material and a small amount of basal diet mixed in a coffee grinder. The premix was then

blended in a Hobart mixer with the remaining amount of the diet to achieve the final concentration of test material in the diet. Stability was analyzed for the low- and high-dosage samples after storage for 7 days at room temperature followed by 8 days at -15°C. Homogeneity was determined for the low- and high-dosage levels prior to study initiation. Concentrations of the test material at all dosage levels were analyzed weekly for the first 4 weeks as well as during weeks 8, 12, 26, 39, and 52. Additional samples were analyzed for concentration during weeks 9, 14, 40, and 53.

Results: Purity of the test material was confirmed at 96.1% and 96.2% for the two batches used in this study. Stability analyses of three samples revealed mean concentrations of 99.1% (low-dosage group) and 97.5% (high-dosage group) of target.

Homogeneity analyses revealed mean concentrations (of three samples) between 91.5% and 100.7% of target.

Analyzed concentrations of the test material in the diet ranged from 69.9% to 148.8% of target (mean of two samples), including the repeat samples. These results showed unacceptable variability on several occasions, which was particularly noticeable on week 1 at 300 ppm (repeat sample was acceptable); week 2 at 200 and 300 ppm (repeat sample was not acceptable); and week 8 at 300 and 400 ppm (repeat samples were acceptable). Variability between duplicate samples that were analyzed was often large but the average of the two values gave a reasonable mean (week 1 at 400 ppm; week 1 repeat at 300 ppm; week 3 at 200 ppm). However, after week 9 and for the rest of the study period, the concentration analyses were generally acceptable and the reviewers concluded that the overall findings did not affect the interpretation of study results.

Food and Water Consumption: Animals received food (Purina® Dog Chow #5007 and/or PMI® Certified Dog Chow #5007) and tap water (treated by reverse osmosis and ultraviolet sterilization) ad libitum. Approximately 400 g of food was provided daily for a period of 4 hours. Food and water were routinely analyzed for contaminants.

Statistical Analyses: The following analyses were conducted.

- Homogeneous data--Bartlett's test for homogeneity of variance followed by ANOVA and Dunnett's t-test for inter-group differences

- Heterogeneous data--Bartlett's test for homogeneity of variance followed by Kruskal-Wallis test and Dunn's test for inter-group differences

Compliance:

- A signed statement of No Data Confidentiality Claim, dated December 17, 1991, was provided.

- A signed statement of Compliance with EPA GLP's, dated December 17 and 20, 1991, was provided.

- A signed Quality Assurance Statement, dated December 20, 1991, was provided.

C. METHODS AND RESULTS

Observations: Animals were observed twice daily for mortality, moribundity, and clinical signs of toxicity.

Results: No compound-related mortalities or clinical signs were observed. One male was found dead during week 8; the animal died of asphyxiation after trying to escape and becoming trapped in the bars of the cage. The most frequently observed clinical signs included scabs and redness of the inguinal and ventral abdominal regions and the hindlimbs. Scabs were observed in 4, 1, 3, 3, and 3 males and in 0, 3, 2, 4, and 4 females in the 0, 200, 300, 400, and 600 ppm groups, respectively. Redness was observed in 2, 1, 2, 1, and 2 males and in 2, 2, 2, 3, and 1 females in the 0, 200, 300, 400, and 600 ppm groups, respectively. These signs were more pronounced in treated animals than in controls. No dosage-response was apparent and these signs were mostly transient, therefore they were not believed to be treatment related. Incidences of soft feces and/or vomiting were similar in all groups.

Body Weight: Body weights were recorded weekly throughout the study; fasted body weights were recorded before sacrifice.

Results: No significant compound-related effects were observed in body weight or body weight change. Table 1 summarizes data on mean body weight. Body weight did not differ significantly in treated animals when compared to control animals. Incidental (but significant) changes were observed in body weight change (data not shown) in males during weeks 5-6 at 200 ppm and weeks 10-11 at 600 ppm and in females during weeks 0-1 at 200 ppm and weeks 22-24 at all dosage levels.

Net weight gain (data not shown) for control males was 141, 111, 93, and 126% between weeks 0-26, and 96, 96, 87, and 95% between weeks 26-52 at 200, 300, 400, and 600 ppm, respectively. Net weight gain for control females was 94, 104, 104, and 103% between weeks 0-26, and 30, 55, 58, and 62% between weeks 26-52 at 200, 300, 400, and 600 ppm, respectively.

Food Consumption and Compound Intake: Food consumption data was recorded daily. Water consumption data was not recorded.

Results: No compound-related effects were observed in food consumption or food efficiency. Table 2 summarizes data on mean food consumption. Incidental (but significant) changes in food consumption (g/day) were observed in males during week 26 at 600 ppm and week 49 at 200 ppm. Incidental (but significant) changes in food efficiency (body weight gain/food consumed; data not shown) were observed in males during weeks 5-6 and in females during weeks 0-1 at 200 ppm, and during weeks 22-24 at all dosage levels.

Average compound intake was 7.8, 12.4, 17.5, and 24.6 mg/kg/day for males and 9.1, 13.1, 18.4, and 26.4 mg/kg/day for females at nominal dietary levels of 200, 300, 400, and 600 ppm, respectively.

Ophthalmological Examinations: Ophthalmologic examinations were performed on all animals before initiation of the study and during weeks 4, 8, 12, 20, 28, 36, and 52 using an indirect ophthalmoscope.

Results: No compound-related lesions were observed in any animal.

Hematology : Animals were fasted overnight and blood was collected from the jugular vein the following morning from all animals prior to study initiation and during weeks 4, 8, 12, 20, 28, 36, and 52. The parameters checked (X) below were determined.

X	Hematocrit (HCT)[a]		Leukocyte differential count
X	Hemoglobin (HGB)[a]	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)[a]	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)[a]		Segmented neutrophil count (N-SEG)
X	Red cell distribution width (RDW)	X	Mean corpuscular volume (MCV)
X	Platelet count[a]		Prothrombin time (PT)
	Reticulocyte count (RETIC)		Basophil count (BASO)
	Red cell morphology		Monocyte count (MONO)
	Lymphocyte count (LYMP)		Band leucocyte (BAND)
	Eosinophil count (EOSN)		
	Atypical lymphocyte count (ATYP)		
X	Mean platelet volume (MVP)	X	Heinz bodies

[a]Recommended by Subdivision F (1984) Guidelines

Results: Compound-related effects were observed for selected hematology parameters at 600 ppm. Table 3 summarizes results for hematologic endpoints that differed significantly from controls at any point in time. In males significant changes were observed during weeks 8 (HGB at 400 ppm); week 20 (RDW at 400 ppm and MCH at 600 ppm); week 36 (MCHC at 400 ppm); and week 52 (MCHC at 300, 400, and 600 ppm). In females significant changes were observed during week 4 (RBC and HCT at 600 ppm); week 8 (MCHC at 300, 400, and 600 ppm); and week 36 (RBC, HGB, and HCT at 400 and 600 ppm). Red blood cell parameters (RBC, HGB, and HCT) were consistently depressed through week 38 at 600 ppm. Although the differences were not always statistically significant, they may have been related to treatment.

Sacrifice and Pathology: All animals (found dead or sacrificed) were subjected to gross pathological examination. Following overnight fasting, surviving animals at term were weighed, anesthetized with pentobarbital, exsanguinated by incision of the axillary or femoral arteries and necropsied. Adrenals, kidneys, and prostate were weighed and preserved in 10% formalin for histological examination. In addition, all gross lesions were preserved. Microscopic evaluations were conducted on prostate from all males and on kidneys from all females.

Results

- Organ weights: No compound-related effects were observed in absolute or relative (to body weight) organ weights.

- Gross pathology: No compound-related lesions were observed in either sex. Table 4 summarizes gross findings that were found in more than one animal. Gross lesions were noted in two or more animals for the following organs: lungs (both sexes); lymph node (females); spleen (males); and skin (females). Incidental lesions (data not shown) including lesions in the ileum, gallbladder, urinary bladder, adrenal, heart, liver, kidney, pituitary, masses, trachea, vagina, buccal cavity, and bronchi, were noted in all dosage groups, including the control group.

- Microscopic pathology: No compound-related microscopic pathology was observed in kidneys or prostate; other tissues were not examined.

D. STUDY AUTHOR'S CONCLUSIONS

Iprodione was administered in the diet to beagle dogs at nominal concentrations of 0, 200, 300, 400, or 600 ppm for 52 weeks. No compound-related effects were observed in any parameter for any sex and dosage level. One accidental death occurred. Clinical signs (scabbing and reddening of the skin) were noted in all animals. Hematology endpoints occasionally differed from controls but were still within the normal historical range and were, therefore, not considered to be treatment-related. Sporadic changes in food consumption and body weight were considered to be normal variations. Based on these results, the NOEL for systemic toxicity was 600 ppm for both sexes.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

This study was only designed to complement a previously conducted study (Life Science Research, Suffolk, England; Study Number 84/RH002/179) and to establish a NOEL for systemic toxicity. Urinalysis, clinical chemistry, and a microscopic evaluation of all organs were not conducted in this study since these parameters had not been affected at 600 ppm in the earlier study.

The data reporting was acceptable and the summary means that were validated were supported by the individual animal data. However, the reviewers disagree with the study author that none of the effects observed in this study was compound-related. Red blood cell parameters (RBC, HBG, and HCT) at 600 ppm, were consistently depressed (albeit not always significant) through week 38 and were perhaps caused by the test compound. This conclusion is further supported by the observation that iprodione has caused similar effects upon RBC parameters in other studies.

The reviewers agree with the study author that, although clinical signs appeared to be more severe in the treated animals than in the controls, no consistent pattern was observed across sexes and dosages, and recovery was

noted for several animals. Therefore, these signs were not assessed to be treatment-related.

Prostate weights which previously were reported as affected at 600 ppm, were clearly negative in this study at this same dosage level.

Based on the effects upon red blood cell parameters, the NOEL and LOEL for systemic toxicity were 400 ppm (for males 17.5 mg/kg/day; for females 18.4 mg/kg/day) and 600 ppm (for males 24.6 mg/kg/day; for females 26.4 mg/kg/day), respectively.

F. CLASSIFICATION: Core Supplementary Data.

The present study alone does not meet the minimum requirements set forth under Guideline Series 83-1 for a chronic toxicity study in dogs owing to a limited number of endpoints being evaluated. However, the objectives were met and a NOEL and LOEL could be established. The initial study was classified as Core Minimum Data and the NOEL/LOEL were 100/600 ppm (based on decreased prostate weights and the presence of Heinz bodies in male erythrocytes). The present study, indicates a NOEL/LOEL of 400/600 ppm based on changes in red blood cell parameters.

TABLE 1. Mean Body Weight at Representative Intervals in Dogs Fed Iprodione for 52 Weeks[a]

Body Weight (kg ± S.D.) during Week:	Dietary Level (ppm) 0	200	300	400	600
			Males		
0	7.0 ± 0.96	7.3 ± 0.90	7.4 ± 0.94	7.2 ± 0.91	7.1 ± 0.88
1	7.2 ± 1.01	7.6 ± 0.83	7.7 ± 0.90	7.7 ± 0.83	7.4 ± 0.97
7	8.3 ± 1.13	9.2 ± 0.89	8.9 ± 1.46	8.6 ± 0.90	8.9 ± 1.04
14	9.4 ± 1.19	10.4 ± 1.20	10.0 ± 1.72	9.4 ± 0.85	10.0 ± 1.22
20	9.7 ± 1.26	10.9 ± 1.26	10.3 ± 1.98	9.7 ± 1.13	10.3 ± 1.50
36	9.8 ± 1.56	11.7 ± 1.70	11.1 ± 1.99	10.3 ± 1.30	11.2 ± 1.59
44	10.3 ± 1.76	11.9 ± 1.88	11.4 ± 2.18	10.5 ± 1.35	11.6 ± 1.67
52	10.5 ± 1.78	12.0 ± 2.10	11.2 ± 2.09	10.5 ± 1.72	11.5 ± 1.55
			Females		
0	6.2 ± 0.54	6.2 ± 0.52	6.2 ± 0.80	6.0 ± 0.64	5.9 ± 0.58
1	6.8 ± 0.56	6.4 ± 0.59	6.5 ± 0.86	6.4 ± 0.69	6.3 ± 0.60
7	7.6 ± 0.99	7.4 ± 0.97	7.4 ± 0.71	7.2 ± 0.75	7.0 ± 0.82
14	8.4 ± 1.22	8.3 ± 1.15	8.4 ± 0.74	8.1 ± 0.78	7.9 ± 0.95
20	8.6 ± 1.56	8.5 ± 1.17	8.6 ± 0.61	8.3 ± 0.83	8.2 ± 1.13
36	9.1 ± 1.82	9.2 ± 1.23	9.5 ± 0.53	9.1 ± 0.81	9.1 ± 1.38
44	9.4 ± 1.54	9.1 ± 1.19	9.5 ± 0.55	9.2 ± 1.11	9.3 ± 1.40
52	9.8 ± 1.46	9.0 ± 1.14	9.5 ± 0.54	9.4 ± 1.30	9.3 ± 1.45

[a]Data were extracted from Study No. 84296, Appendix 2.

TABLE 2. Mean Food Consumption at Representative Intervals in Dogs Fed Iprodione for 52 Weeks[a]

Food Consumption (g/day ± S.D.) during Week:	Dietary Level (ppm) 0	200	300	400	600
			Males		
0	290 ± 31.6	292 ± 56.6	306 ± 19.9	281 ± 80.8	309 ± 33.3
1	316 ± 39.4	315 ± 48.4	341 ± 26.8	333 ± 77.8	347 ± 71.2
7	413 ± 44.3	425 ± 12.3	418 ± 36.3	387 ± 69.9	406 ± 48.8
14	444 ± 54.1	449 ± 17.0	462 ± 38.0	438 ± 47.0	443 ± 26.0
20	438 ± 53.9	464 ± 19.5	459 ± 29.1	466 ± 19.6	434 ± 36.5
36	402 ± 59.5	413 ± 36.4	416 ± 35.6	432 ± 41.0	441 ± 35.5
44	401 ± 72.0	355 ± 36.0	396 ± 58.9	405 ± 67.8	394 ± 58.9
52	419 ± 26.0	417 ± 21.4	412 ± 32.0	409 ± 32.0	429 ± 14.7
			Females		
0	251 ± 44.8	244 ± 28.7	274 ± 21.6	249 ± 53.0	263 ± 44.1
1	289 ± 47.4	293 ± 40.4	326 ± 23.1	292 ± 54.3	303 ± 51.3
7	338 ± 77.1	373 ± 59.4	382 ± 30.4	386 ± 76.1	334 ± 60.4
14	398 ± 71.1	416 ± 47.2	406 ± 38.5	420 ± 59.7	381 ± 57.8
20	420 ± 54.9	431 ± 51.0	420 ± 47.6	440 ± 44.0	407 ± 40.2
36	372 ± 66.4	375 ± 67.0	367 ± 47.3	369 ± 66.6	377 ± 48.5
44	362 ± 81.2	324 ± 49.1	351 ± 36.3	364 ± 94.1	338 ± 54.0
52	389 ± 55.2	395 ± 38.2	368 ± 48.1	377 ± 51.6	363 ± 55.3

[a]Data were extracted from Study No. 84296, Appendix 4.

TABLE 3. Selected Mean Hematology Values in Dogs Fed Iprodione for 52 Weeks[a]

Dietary Level (ppm)	RBC ($x10^6$)	HGB (g/dL)	HCT (%)	MCHC (g/dL)	RDW (%)
Males Week 8					
0	5.85	13.8	39.2	35.2	14.3
200	5.93	14.2	40.2	35.3	14.7
300	5.74	13.8	38.8	35.4	14.7
400	6.33	15.4*	43.3	35.6	14.4
600	5.67	13.5	37.7	35.7	14.7
Males Week 20					
0	6.58	15.4	43.6	35.4	15.0
200	6.64	15.8	44.6	35.5	14.9
300	6.37	15.3	42.8	35.7	14.8
400	6.47	15.6	43.8	35.7	14.2*
600	6.28	15.1	41.8	36.1*	14.5
Males Week 36					
0	6.85	16.3	45.7	35.6	14.8
200	6.90	16.7	46.8	35.6	14.7
300	6.74	16.3	45.3	36.0	14.7
400	6.73	16.4	45.3	36.1**	14.1
600	6.56	15.6	43.5	35.9	14.2
Males Week 52					
0	6.94	15.9	46.1	34.6	14.7
200	7.15	16.9	48.4	34.9	14.9
300	6.95	16.4	46.5	35.2*	14.8
400	7.10	16.7	47.4	35.3**	14.5
600	7.07	16.6	46.8	35.5**	14.4
Females Week 4					
0	6.53	15.2	44.2	34.3	14.6
200	6.07	14.2	41.4	34.3	15.1
300	5.93	14.1	40.5	34.7	14.3
400	6.04	14.2	40.7	34.8	14.4
600	5.52**	13.0	37.6**	34.6	14.3
Females Week 8					
0	6.35	14.9	42.5	35.0	14.4
200	6.17	14.8	41.7	35.4	15.2
300	5.96	14.4	40.5	35.7**	14.2
400	6.20	14.7	41.4	35.5*	14.8
600	5.76	13.8	39.0	35.5*	14.8
Females Week 36					
0	6.94	16.6	46.9	35.4	14.4
200	6.66	16.1	45.1	35.6	14.4
300	6.76	16.3	45.6	35.7	14.4
400	6.20**	14.9**	41.9**	35.6	14.5
600	6.28*	15.3*	42.8*	35.7	13.9

[a]Data were extracted from Study No. 84296, Table 7.

*Significantly different from control ($p < 0.05$).
**Significantly different from control ($p < 0.01$).

TABLE 4. Macroscopic Observations at Termination in Dogs Fed Iprodione for 52

TABLE 4. Macroscopic Observations at Termination in Dogs Fed Iprodione for 52 Weeks[a,b]

Observation	Dietary Level (ppm) 0	200	300	400	600
Total no. of animals examined	6	6	6	6	6
			Males		
Lung					
Area dark	0	0	0	0	2
Discoloration	0	2	0	0	0
Area raised	2	0	4	0	5
Area depressed	0	0	2	0	0
Prostate					
Small	0	0	0	2	0
Spleen					
Area depressed	0	0	2	1	0
Thymus					
Small	1	0	0	2	0
			Females		
Lung					
Area raised	3	3	2	3	2
Lymph node					
Discoloration	2	0	1	2	1
Skin					
Thickening	0	0	1	2	0

[a]Data were extracted from Study No. 84296, Table 10.

[b]Includes all incidences occurring in two or more animals

CASWELL FILE

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

005882

MAY 18 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Re-review of the 1-year dog study

To: Robert Forrest, PM-21
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D.
Head, Section III
Toxicology Branch, HED
M. van Gemert 5/14/87

Thru: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch, HED
Theodore M. Farber 5/14/87

Chemical: Iprodione

Company: Rhone-Poulenc

Caswell No: 470A

Project No: 7-0608

Rhone-Poulenc has submitted arguments on several points concerning their 1-year dog study on Iprodione. They stated that in fact the low dose of 100 ppm was actually measured in the feed of the dogs and as measured was 4.2 mg/kg rather than the theoretical amount of 2.5 mg/kg stated in the original Tox. Branch memo. Tox Branch agrees with Rhone-Poulenc and the ADI has been changed to reflect the larger amount.

Rhone-Poulenc has also presented arguments concerning the toxicological effects of Iprodione seen at the mid dose in the previous tox review of this study by A. Arce. This study was re-reviewed by M. van Gemert and the DER of this re-evaluation is attached. The new review supports for the most part the conclusions made in the old review and has restated that the NOEL is 100 ppm based on decreased prostate weights and Heinz bodies in male erythrocytes seen at the mid dose.

Rhone Poulenc might submit historical control data from this laboratory and strain of dog on Heinz bodies and prostate weights to support their argument that these are not toxicological effects. A new study might also be initiated looking primarily at the hematological, liver and prostate endpoints using doses between and including the 100 and 600 ppm to clarify the NOEL for this compound.

This reviewer did not feel that a re-review of the subchronic dog study was necessary.

Reviewed by: Marcia van Gemert, Ph.D. Marcia van Gemert 5/14/87
Head, Section III, Tox. Branch (TS-769C)
Secondary reviewer: Theodore M. Farber, Ph.D.
Chief, Tox. Branch (TS-769C)

005882

DATA EVALUATION REPORT

STUDY TYPE: Re-evaluation of the 1-year dog study

TOX. CHEM. NO.: 470A

ACCESSION NUMBER: none

MRID NO.: .

TEST MATERIAL: Iprodione

SYNONYMS:

STUDY NUMBER(S): 84/RH002/179

SPONSOR: Rhone-Poulenc Agrochimie

TESTING FACILITY: Life Sciences Research, Suffolk, England

TITLE OF REPORT: Iprodione: 52-week toxicity study in Dietary administration to Beagle dogs

AUTHOR(S): P. Lee, R. Ashby, et al

REPORT ISSUED: Sept. 28, 1984

CONCLUSIONS: 6 dogs/sex/group were treated with 0, 100, 600 or 3600 ppm for 52 weeks. Effects were seen at the high dose in the liver, with increased absolute and relative weights, alkaline phosphatase, SGOT, SGPT, LDH enzyme levels. Heinz bodies were seen in both mid and high dose males and high dose female erythrocytes, with RBCs, PCV, Hb and MCHC down at the high dose. There was a slight increase in hyperreflection in the eyes seen at the high dose. Adrenal relative and absolute weights were increased at the high dose with microscopic changes seen. Prostate weights were decreased at the mid and high dose with statistical significance seen in absolute weights at the mid and high dose and relative weights at the high dose.
NOEL = 100 ppm (4.2 mg/kg)
LEL = 600 ppm

Classification: core-minimum

Special Review Criteria (40 CFR 154.7)

A. MATERIALS:

1. Test compound: Iprodione, Description white, slightly lumpy powder.
Batch # DA-237-OP-81-461
Purity 86,5%, contaminants: list in CBI appendix

2. Test animals: Species: Dog, Strain:Beagle, Age: 15-17 weeks Weight: 2.7-6.8 kg. Source: Balbeggie Kennels, Fife, Scotland

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 52 weeks male	female
1 Cont.	0	6	6
2 Low (LDT)	100	6	6
3 Mid (MDT)	600	6	6
4 High(HDT)	3600	6	6

2. Diet preparation

Diet was prepared twice per week and stored at 4°C before use. Samples of treated food were analyzed for stability and homogeneity before treatment and for concentration during weeks 1, 13, 26, 29, and 52. Stability and homogeneity sampling methods are on appended pages 1 and 2.

Results -
Test compound was found to be stable in bulk for for the entire experimental period.

3. Animals received food (500 gms dry food (650 gms wet) Laboratory Diet A, Special diet services Ltd. Witham England and water ad libitum were given. Formulation of diet and quality control of dosage are on appended page 1.

4. Statistics - The statistical procedures used are on appended page 3,4 and 5.

5. Quality assurance statement was given in the text and signed Oct. 3, 1984.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected for signs of toxicity and mortality before start of the experiment and after weeks 3, 8, 11, 16, 19, 24, 27, 31, 35, 39, 43, 47 and 51 weeks.
During these examinations, attention was paid to:
Teeth and gums
Mucous membrane and skin
Ears (external auditory canal)
Superficial lymph nodes
Abdomen- including palpation
External genitalia and mammary glands
Chest- including auscultation of heart and lungs
Gait and stance, including palpation of limbs
General behaviour and appearance

Toxicity - Results:
The study text claims that there were no treatment-related signs of toxicity with Iprodione.

Mortality- results:
One female in the 600 ppm group was killed in extremis with convulsions, which did not appear to be treatment-related.

2. Body weight

Animals were weighed weekly throughout the test period.

Results: No treatment-related changes in body weight were evident throughout the study.

3. Food consumption and compound intake

Each animal was given 500 gms dry or 650 gms wet food per day. Any uneaten portion of the food was removed. Food consumption was not affected by treatment.

Compound Intake, Results: The achieved doses are on appended pages 6 and 7.

4. Ophthalmological examinations

Performed before start of the study and after 3, 8, 12, 18, 35 and 50 weeks of treatment, both eyes of all dogs were examined using a Fison Binocular Indirect Ophthalmoscope after infusing Mydriacyl (tropicamide, 1%).

Results:
There was a slightly increased incidence of hyperreflection in groups 3 and 4 males and females. However, the results in the individual animal data indicate that the hyper-reflection seen was for the most part slight, and wasn't seen consistently in the same animal over the seven observation periods, and was also seen on occasion in controls. For example at week 19 hyperreflection was seen in one control male and four control females. One would assume that if this were a true toxicological phenomen it would appear in the same animals consistently, and the severity would increase. Neither of these two happened, and it is therefore difficult to call hyperreflection in this situation a toxicological consequence of Iprodione Administration. See page 8 for details. However, electron microscopy could have been done on the tissues of the animals with hyperreflection, to determine if any treatment-related effects were evident.

Two male dogs in group 4 showed finely scattered opalescent particles (asteroid bodies) in the vitreous humor. This unilateral for both animals. This may be a treatment-related phenomen since no control dogs exhibited this and it was not seen until 13 weeks after the start of the experiment. (see appended page 8 for details)

5. Blood was collected before treatment and at 4, 8, 13, 17, 21, 25, 38 and 51 weeks, after an overnight fast for hematology and clinical chemistry analyses from each animal.
The checked (X) parameters were examined. Those with an (A) preceding were examined pre-treatment.

a. Hematology

	X	Hematocrit*
A	X	Hemoglobin *
A	X	Leukocyte count *
A	X	Erythrocyte count *
A	X	Platelet count *
		Blood clotting measurements
	X	Thromboplastin time
		clotting time
A	X	Prothrombin time (PTTK)

	X	Leukocyte differential count*
A	X	Mean corpuscular HGB
A		Mean corpuscular HGB conc.
		Mean corpuscular volume
	X	Reticulocyte count
A	X	Packed cell volume
A	X	Erythrocyte sedimentation rate
A	X	Mean cell volume

* required for subchronic and chronic studies

Heinz bodies were examined after 4 weeks using the film prepared for reticulocyte count. These were graded as follows below (using the number of erythrocytes containing Heinze bodies):

0 = None seen
1 = Very occasional
2 = Up to two per field
3 = Two to five per field
4 = Six to 50 per field
5 = Over 50 per field.

Bone marrow samples were taken from the femur under local anaesthetic several days before necropsy. In addition a costal bone marrow smear was prepared at necropsy for the dog which died in extremis.

Results:

Week 4

PCV, Hb and RBC were decreased in group 4 males, Platelets and PTTK were increased in group 4 males.
Hb and MCHC were decreased in group 4 females and PTTK was increased in group 4 females.

Week 8

PCV, Hb, RBC and MCHC were decreased in group 4 males. MCV and PTTK were increased in group 4 males and platelets were increased in groups 2 and 4 in males.
MCHC was decreased in group 1 and 4 females. MCV was increased in group 3 and 4 females, and platelets and PTTK were increased in group 4 females.

Week 13

PCV, Hb, and RCB were decreased in group 4 males, platelets were increased in groups 2 and 4 males.

Platelets and PTTK were increased in group 4 females.

Week 17

MCHC was decreased in group 4 males, platelets were increased in groups 2 and 4 males.
PTTK was increased in group 4 females.

Week 21

MCHC was decreased in group 4 males and platelets were increased in groups 2 and 4 males.
MCH was decreased, and neutrophils and PTTK were increased in group 4 females.

Week 25

PCV, Hb, RBC were decreased, total WBC, neutrophils, leukocytes and eosinophils and platelets were increased in group 4 males.
Neutrophils, platelets and PTTK were increased in group 4 females.

Week 38

PCV, Hb, and RBC were decreased and platelets were increased in group 4 males.
PCV, Hb, and RBC were decreased and platelets and PTTK were increased in group 4 females.

PCV, Hb, and RBC were decreased in groups 2 and 4 males and platelets and PTTK were increased in group 4 males.
PTTK was increased in group 4 females.

Bone Marrow Smears

No significant treatment-related effects were seen in the bone marrow smears.

TABLE I

HEMATOLOGY

Week 4:

males						females		
Groups	PCV	Hb	RBC	Plt	PTTK	Hb	MCHC	PTTK
1	42	14.1	6.23	220	12.8	14.8	35	12.8
SD	4	1.2	0.49	55	0.9	1.8	1	1.7
2	42	14.2	6.21	294[a]	12.1	15.2	34	12.2
SD	3	1.1	0.42	29	0.7	1.1	0	1.4
3	42	14.1	6.26	245	12.4	14.2	34	12.4
SD	5	1.7	0.90	38	1.3	1.0	1	0.2
4	35[b]	11.7[b]	5.06[b]	377[c]	15.9[c]	12.8[a]	33[a]	22.5[c]
SD	3	0.9	0.38	72	1.9	2.2	1	3.1

SD- Standard deviation
a- Significantly different from controls, $P < 0.05$
b- Significantly different from controls, $P < 0.01$
c- Significantly different from controls, $P < 0.001$

TABLE-1 cont.

005882

Week 8

males								females		
Groups	PCV	Hb	RBC	MCHC	MCV	Pltlt	PTTK	MCV	Pltlt	PTTK
1	46	15.4	6.80	34	67	292	11.7	66	315	11.5
SD	3	1.1	0.41	1	2	35	0.9	1	67	1.2
2	44	14.7	6.54	33	67	367[a]	11.3	67	373	11.3
SD	2	0.5	0.29	1	2	33	0.6	2	50	1.1
3	45	15.1	6.75	33	67	299	11.7	69[a]	340	11.4
SD	4	1.5	0.63	1	3	70	1.3	1	34	0.6
4	40[b]	12.9[c]	5.68[c]	33[b]	70[a]	474[c]	14.7[a]	69[b]	450[b]	15.6[c]
SD	2	0.9	0.38	1	1	53	4.4	2	96	1.5

Week 13

males					females	
groups	PCV	Hb	RBC	Pltlt	Pltlts	PTTK
1	45	16.7	6.64	261	282	12.7
SD	3	1.4	0.47	46	57	1.0
2	44	16.3	6.47	318[a]	342	11.4
SD	2	0.9	0.32	31	35	0.7
3	47	17.2	6.88	296	306	12.2
SD	5	1.8	0.64	24	28	0.7
4	41[a]	14.9[a]	5.89[b]	422[a]	390[b]	18.8[c]
SD	3	1.1	0.35	61	103	4.2

Week 17

males			females
Groups	MCHC	Pltlts	PTTK
1	35	277	13.2
SD	1	21	1.2
2	34	339[b]	12.6
SD	1	42	0.7
3	35	286	12.6
SD	1	33	0.7
4	34[a]	357[c]	16.5[b]
SD	1	33	2.6

Week 21

males			females		
	MCHC	Pltlts	MCH	Neut	PTTK
1	35	266	23	5.1	13.1
SD	1	40	1	0.6	1.8
2	35	322[a]	23	5.2	11.7
SD	0	43	1	1.5	1.1
3	35	274	23	5.7	12.2
SD	1	9	1	0.8	1.1
4	34[a]	350[b]	22[a]	7.6[a]	27.5[c]
SD	1	50	0	3.2	6.8

Week 25

males			Total						females		
groups	PCV	Hb	RBC	WBC	Neut.	Leuk.	Eosin	Pltlts	Neut	Pltlts	PTTK
1	50	17.1	7.23	11.1	4.5	5.2	0.9	240	4.6	271	12.8
SD	4	1.4	0.60	1.5	1.1	1.1	0.3	52	1.0	53	1.4
2	46	16.0	6.84	11.0	4.1	4.8	1.3	284	3.8	285	14.0
SD	4	1.1	0.51	2.0	1.1	0.9	0.6	34	1.4	45	4.2
3	49	17.1	7.16	10.8	5.5	3.5	1.1	250	4.1	264	13.0
SD	5	1.7	0.61	2.1	1.3	0.9	0.6	25	0.8	29	1.4
4	39[c]	13.6[c]	5.67[c]	14.6[a]	6.0[a]	6.1[a]	1.9[b]	358	7.0[b]	410[c]	17.6[a]
SD	3	1.2	0.39	3.2	1.0	1.9	0.6	100	0.8	95	4.6

SD = Standard Deviation
a- Significantly different from controls, $P < 0.05$
b- Significantly different from controls, $P < 0.01$
c- Significantly different from controls, $P < 0.001$

Week 38

males groups	PCV	Hb	RBC	Pltlts	females PCV	Hb	RBC	Pltlts	PTTK
1	51	17.8	7.14	227	52	17.9	7.32	260	13.6
SD	4	1.7	0.56	37	6	2.2	0.80	44	2.5
2	49	16.5	6.79	287[a]	51	17.7	7.25	279	12.3
SD	3	0.8	0.37	45	4	1.3	0.60	45	0.6
3	52	18.1	7.25	257	51	17.5	7.29	265	13.5
SD	6	2.3	0.80	36	1	0.2	0.29	30	1.0
4	45[b]	15.3[a]	6.27[a]	338[c]	45[a]	15.3[a]	6.38[a]	359[b]	19.2[c]
SD	3	0.9	0.36	48	5	1.8	0.58	67	1.9

Week 51

males groups	PCV	Hb	RBC	Pltlts	PTTK	females PTTK
1	50	17.9	7.14	208	11.1	11.5
SD	5	2.0	0.72	42	0.6	1.4
2	43[a]	15.4[a]	6.29[a]	255	11.2	11.3
SD	3	1.1	0.43	37	0.6	0.2
3	48	17.1	6.86	230	11.0	12.1
SD	6	2.3	0.93	19	1.6	0.8
4	43[a]	15.3[a]	6.19[a]	333[c]	12.8[a]	14.9[c]
SD	3	1.3	0.42	54	1.8	1.6

SD = Standard Deviation
a- Significantly different from controls $P < 0.05$
b- Significantly different from controls $P < 0.01$
c- Significantly different from controls $P < 0.001$

Appended pages 11 and 12 contain tables of the hematology data in the various weeks compared to the pre-treatment levels. The results are essentially the same as those seen comparing the treated results with concurrent control data. Group 4 platelets PTTK, PCV, Hb, and RBCs in both males and females were effected by treatment with Iprodione.

The study text states that "at each examination Heinz bodies were observed in moderate numbers of the erythrocytes of male and female dogs receiving 3600 ppm. A small number of erythrocytes were also affected up to Week 18 in dogs receiving 600 ppm. The incidence of Heinz bodies in the erythrocytes of dogs receiving 100 ppm was similar to that of the controls."
Appended pages 16 and 17 have the tabulated numbers and severity of Heinz bodies seen in all doses at all the time period tested. There was some indication of an effect in the 600 ppm male animals, especially in the earlier time periods, as well as a definite effect seen in the high dose groups, in terms of severity and increased incidence. The high dose increase in Heinz bodies definitely correlates with the other effects seen in hematological parameters, such as decreased hemoglobin, red blood cells, PCV, and MCHC.

b. Clinical Chemistry

X	Electrolytes:	X	Other:
X	Calcium*		Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
	Phosphorous*	X	Cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin*
X	Alkaline phosphatase	X	Total Serum Protein*
	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
X	Lactic acid dehydrogenase	X	Direct bilirubin
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		
X	Electrophoretic protein fractions		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies

Results:

Week 4
Alkaline phosphatase, and potassium were increased in group 4 males, glucose and alpha globulins were decreased in group 4 males.
Alkaline phosphatase, total bilirubin and ALT were increased in group 4 females, urea and albumin were increased in groups 2 and 4 females and gamma globulins were decreased in group 4 females.

Week 8
Alkaline phosphatase was in increased in group 4 males.
Alkaline phosphatase, ALT, urea, total bilirubin, alpha-2 globulins, and potassium were increased in group 4 females. LDH was decreased in group 2 and 4 females, and sodium was increased in group 2 and 4 females.

Week 13
Alkaline phosphatase, total bilirubin, and albumin were increased in group 4 males, alpha-2 globulins were decreased in group 4 males and potassium was increased in both group 3 and 4 males.
Alkaline phosphatase, ALT, AST, total bilirubin, total cholesterol total proteins, B-globulins were all increased in group 4 females, and LDH was increased in both group 3 and 4 females, while calcium was decreased in groups 3 and 4.

Week 17
Alkaline phosphatase, and ALT were increased in group 4 males, calcium was decreased in the same group.
Alkaline phosphatase, total proteins, and albumin were increased in group 4 females, while total bilirubin was increased in both groups 2 and 4 females.

Week 21
Alkaline phosphatase, LDH, total and total bilirubin were increased in group 4 males, gamma globulins were decreased slightly in group 4 males.
Alkaline phosphatase was increased in group 4 females and albumin levels were increased at all dose levels.

Week 25
Alkaline phosphatase and total bilirubin were increased in group 4 males, glucose and calcium were decreased in group 4 males and alpha 2 globulins were decreased in group 3 and 4 males.
Alkaline phosphatase, LDH and total bilirubin were increased in group 4 females, Albumin was increased in both groups 3 and 4 females, and alpha-2 globulins were decreased in group 4 females.

Week 38
Alkaline phosphatase and gamma globulins were increased in group 4 males. Glucose and albumin were decreased in group 4 males.
Alkaline phosphatase, LDH and total bilirubins were increased in group 4 females, urea was increased in both group 2 and 4 females.

Week 51
Alkaline phosphatase and total cholesterol were increased in group 4 males, and alpha-2 globulins were decreased in group 3 and 4 males.
Alkaline phosphatase and albumin were increased in group 4 females.

TABLE II

Clinical Chemistry

Week 4

males			globulins		females			Total		
Group	AP	Glu	A-1	K	AP	ALT	Urea	Bili	Alb	g-glob
1	109	121	0.3	4.4	101	42	27	0.2	2.7	0.5
SD	26	5	0.1	0.2	18	8	6	0.0	0.2	0.1
2	101	122	0.3	4.3	88	37	38[b]	0.3	3.0[a]	0.4
SD	21	7	0.0	0.3	17	7	8	0.1	0.2	0.1
3	112	128	0.4	4.5	80	38	30	0.2	2.9	0.4
SD	17	5	0.1	0.3	13	7	3	0.0	0.2	0.1
4	145[a]	113[a]	0.3[a]	4.7[a]	164[c]	103[a]	37[b]	0.5[c]	3.2[c]	0.3[a]
SD	41	7	0.1	0.4	40	82	5	0.1	0.2	0.1

SD = Standard Deviation
a- Significantly different from controls $P < 0.05$
b- Significantly different from controls $P < 0.01$
c- Significantly different from controls $P < 0.001$

Week 8

males		females				Total globulins			
Group	AP	AP	ALT	LDH	Urea	Bili	a-2	Na	K
1	99	91	46	143	31	0.3	0.7	141	4.2
SD	22	19	12	62	4	0.1	0.1	1	0.2
2	83	91	38	80[a]	32	0.3	0.7	142[a]	4.0
SD	21	18	7	27	4	0.1	0.1	1	0.1
3	97	72	43	122	33	0.4	0.6	141	4.1
SD	26	12	12	59	4	0.1	0.0	1	0.1
4	133[a]	164[c]	160[c]	86[a]	37[a]	0.5[c]	0.8[a]	143[b]	4.5[a]
SD	33	26	155	25	6	0.1	0.1	1	0.2

Week 13

Males		Total	Globulins		females				Total	Total	tot.	B-	
Gr	AP	Bili	Alb	a-2	K	AP	ALT	AST	LDH	Bili	Chol	Prot.	Glob.	Ca
1	82	0.4	3.1	0.8	4.1	87	66	32	124	0.2	127	6.0	1.4	5.9
SD	26	0.1	0.3	0.1	0.2	15	68	4	15	0.1	15	0.3	0.2	0.2
2	81	0.4	3.1	0.9	4.1	73	38	29	134	0.2	118	6.3	1.5	5.7
SD	29	0.1	0.1	0.1	0.2	20	9	3	30	0.1	9	0.2	0.2	0.3
3	103	0.3	3.1	0.7	4.4[a]	66	42	31	191[b]	0.2	127	6.1	1.4	5.5[b]
SD	33	0.1	0.3	0.1	0.1	16	8	3	46	0.1	7	0.1	0.1	0.1
4	153[b]	0.6[a]	3.4[b]	0.6[a]	4.4[a]	169[c]	285[a]	48[a]	191[b]	0.6[c]	154[a]	6.5[c]	1.6[a]	5.5[b]
SD	46	0.1	0.1	0.1	0.2	26	287	26	48	0.1	32	0.2	0.1	0.2

Week 17

males				females	total		
Gr.	AP	ALT	Ca	AP	Bili	prot	Alb.
1	86	29	5.4	80	0.3	5.8	2.7
SD	30	4	0.2	14	0.1	0.2	0.2
2	83	27	5.1[a]	79	0.5[a]	5.9	3.0
SD	19	6	0.2	30	0.1	0.3	0.2
3	90	34	5.4	68	0.4	5.8	3.0
SD	25	8	0.2	10	0.1	0.3	0.3
4	140[b]	47[a]	5.1[b]	127[c]	0.7[c]	6.2[b]	3.2[b]
SD	32	28	0.1	13	0.1	0.2	0.3

Week 21

males			Total		females	
Gr	AP	LDH	Bili	G-glob.	AP	Alb.
1	77	100	0.1	0.5	94	3.0
SD	25	28	0.0	0.1	58	0.2
2	89	102	0.1	0.5	64	3.4[b]
SD	28	32	0.0	0.1	25	0.1
3	95	128	0.1	0.5	60	3.3[a]
SD	31	67	0.0	0.1	11	0.2
4	177[c]	180[a]	0.2[a]	0.4[a]	149[a]	3.4[b]
SD	41	60	0.1	0.0	29	0.3

SD = standard deviation
a- Significantly different from controls $P < 0.05$
b- Significantly different from controls $P < 0.01$
c- Significantly different from controls $P < 0.001$

Week 25

males						females				
Gr	AP	Gluc.	Tot. Bili	Glob. A-2	Ca	AP	LDH	Tot. Bili.	Alb.	Glob. A-2
1	64	103	0.1	0.7	5.8	64	137	0.1	3.0	0.9
SD	29	7	0.0	0.1	0.3	22	35	0.1	0.4	0.2
2	69	103	0.1	0.7	5.6	50	127	0.2	3.1	0.7
SD	26	4	0.0	0.1	0.2	25	33	0.1	0.2	0.1
3	79	105	0.1	0.5[c]	5.6	52	152	0.2	3.5[a]	0.9
SD	21	4	0.0	0.1	0.1	16	53	0.0	0.6	0.1
4	147[c]	94[a]	0.2[c]	0.5[b]	5.5[b]	111[b]	235[b]	0.3[c]	3.7[b]	0.4[c]
SD	44	7	0.0	0.1	0.2	22	81	0.1	0.2	0.1

Week 38

males					females			
Gr	AP	Gluc.	Alb.	Glob. Gamma	AP	LDH	Urea	Total Bilir.
1	62	107	3.1	0.5	63	140	31	0.2
SD	22	6	0.2	0.1	11	28	4	0.1
2	60	101	3.1	0.5	46	148	38[a]	0.3
SD	22	6	0.2	0.1	12	65	7	0.1
3	92	108	3.3	0.6	51	150	31	0.2
SD	58	8	0.4	0.1	17	45	4	0.0
4	149[b]	97[a]	2.7[a]	0.8[c]	129[c]	231[b]	37[a]	0.4[c]
SD	46	10	0.2	0.1	31	59	4	0.1

Week 51

males				females	
Gr	AP	Total Chol.	Glob A-2	AP	Alb
1	77	114	0.8	66	3.0
SD	41	10	0.1	17	0.2
2	72	129	0.7	53	3.1
SD	36	9	0.1	24	0.2
3	93	118	0.6[c]	63	3.2
SD	31	9	0.1	30	0.3
4	207[c]	143[b]	0.6[b]	138[c]	3.3[a]
SD	89	21	0.1	19	0.2

SD = Standard Deviation
a- Significantly different from controls $P < 0.05$
b- Significantly different from controls $P < 0.01$
c- Significantly different from controls $P < 0.001$

6. Urinalysis°

Urine was collected from fasted animals at 3, 7, 12, 16, 20, 24 37 and 50 weeks. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*	X	Nitrate
X	Protein*	X	Urobilinogen
X	Total reducing substances		

* Required for chronic studies
° Not required for subchronic studies

Results: No treatment-related changes in urinalysis were evident.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination and examined. . The (XX) organs in addition were weighed.

X	Digestive system
X	Tongue
X	.Salivary glands*
X	.Esophagus*
X	.Stomach*[c]
X	.Duodenum*
X	.Jejunum*
X	.Ileum*
X	.Cecum*
X	.Colon*
	.Rectum*
XX	.Liver*†
X	Gall bladder*#
X	.Pancreas*
	Respiratory
X	.Trachea*
XX	.Lung*
	Nose°
X	Bronchi
	Larynx°

X	Cardiovasc./Hemat.
X	.Aorta*
XX	.Heart*
	.Bone marrow*
X	.Lymph nodes*[a]
XX	.Spleen*
X	.Thymus*
	Urogenital
XX	.Kidneys*†
X	.Urinary bladder*
XX	.Testes*†
X	Epididymides
XX	Prostate
	Seminal vesicle
XX	Ovaries*†
XX	.Uterus*
X	Cervix

X	Neurologic
XX	.Brain*†[d]
X	Periph. nerve*#
X	Spinal cord (3 levels)*#
XX	.Pituitary*
X	Eyes (optic n.)*#
	Glandular
XX	.Adrenals*
	Lacrimal gland#
X	Mammary gland*#[b]
	.Parathyroids*††
XX	.Thyroids*††
	Other
X	Bone*# (sternum)
X	Skeletal muscle*#
X	Skin*#
X	All gross lesions and masses*

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies
a- cervical, mesenteric and peribronchial
b- caudal, cranial
c- fundus, pylorus
d- sectioned to include cerebellum, cerebral cortex, thalamic nuclei, mid-brain and medulla, and the spinal cord was prepared in transverse section at the cervical and thoraco-lumbar levels.

a. Organ weight

Absolute weights:
Liver and adrenal weights were increased in the high dose males and prostate weights ere decreased in mid and high dose males. Adrenal weights were increased in high dose females.

Relative weights:
Relative liver and adrenal weights were increased in high dose males and relative prostate weights were decreased in this group. In females, relative heart, liver and adrenal weights were increased in the high dose.

b. Gross pathology
Very little pathology was seen on gross examination. One high dose male had a swollen and pale liver. 2/6 high dose females had enlarged adrenals. One high dose female had crystalline bile.

c. Microscopic pathology

1) Non-neoplastic
Treatment-related effects were seen in the adrenals, gall bladder, kidneys, urinary bladder and liver. The study text states that "the changes seen in the adrenal glands, kidneys, and gall bladder were exacerbations of physiological changes. The changes seen in the urinary bladder and the more serious lesion in the liver were of a distinctly pathological nature."

Table III
Histopathological Changes

Group/Sex	1m	2m	3m	4m	1f	2f	3f	4f
N	6	6	6	6	6	6	5	6
Adrenals								
Deep pallid Zona fasiculata	0	0	0	6	0	0	0	5
fat vacuolation of zona fasiculata	0	0	0	1	1	0	1	6
pallid zona glomerulosa	2	0	3	6	0	0	1	6
Gall Bladder-enlarged	0	0	0	2	0	0	0	1
Kidney								
Lipofuscinosis in proximal tubular epithelium	2	1	2	4	2	0	4	4
Liver								
Occasional centrilobular Hepatic cord atrophy	0	0	0	3	0	0	0	4
Urinary Bladder								
Submucosal granuloma	0	0	0	4	0	0	0	5
Submucosal crystals within giant cells	0	0	0	4	0	0	0	4

Adrenal Cortex
The study text described changes seen in the zona glomerulosa and zona fasiculata as zones with increased depth and the cells as being large, with pale "watery" cytoplasm. In table 3 these are described as "pallid zona glomerulosa" and "deep pallid zona fasiculata". The zona fasiculata changes in the high dose were considered "occasionally marked." These changes according to the study text were associated with foci of cells which were largely represented by vacuoles, tabulated in table 3 as "fatty vacuolization, zona fasiculata. The increased pallor of the zona glomerulosa were associated with high dose animals. Mid dose group males had 3/6, however, there were two animals seen in control group males.

Urinary Bladder
high dose males and females showed treatment-related granulomata, considered small, in the immediate submucosa of the urinary bladder. These were "virtually all" associated with bladders containing crystals. The crystals were described as having a constant shape which was described as tall pyramidal with a circular base. The crystals were only present within the cytoplasm of phagocytic giant cells. The study text states that two of the six male dogs in the high dose had small foci of polymorphonuclear leucocyte infiltration within the transitional epithelium.

Liver
The study text stated that there was an increase in the size and frequency of agglomerates of pigmented macrophages in the liver of animals receiving high dose iprodione. They stated that these phagocytic cell associations are a usual feature of canine liver, representing a record of minor tissue damage. 9/12 high dose animals showed these changes as compared to none seen at these

levels of severity in the control animals. High dose male and female livers also had "hepatic cord atrophy" or a "rounding" of hepatocytes seen in occasional centriacinar zones. They state that this is probable evidence of previous hepatocyte necrosis in the liver sections seen at termination.

Kidney

In kidneys there was a slight trend towards increased frequency of slight or moderate lipofuscinosis of the epithelium of the proximal convoluted tubules. This is considered a fairly common occurrence.

Discussion:

Iprodione produced a number of changes such as in the eye, liver prostate, kidneys, red blood cells, adrenals, gall bladder and urinary bladder.

In the red blood cells, Heinz bodies were evident at 600 ppm and 3600 ppm in males with increased severity seen at 3600 ppm. The appearance of Heinz bodies correlates with some of the other hematological changes seen, such as a decrease in the high dose of hemoglobin, MCHC, PCV and RBCs. Heinz bodies are the produce of the degradation of unstable hemoglobin. The erythrocytes containing Heinz bodies are cleaned from the system by the spleen, and this might account for the increased plasma protein concentrations seen.

In the liver, both male and female high dose absolute and relative weights were increased, with an increase in the size and frequency of agglomerates of pigmented macrophages. High dose males and females also showed "hepatic cord atrophy", indicative of hepatic necrosis. This hepatic damage correlates with the blood enzyme changes seen at the high dose, such as increased alkaline phosphatase alanine amino transferase, aspartate aminotransferase, and lactate dehydrogenase activities; prolonged partial prothrombin times, and raised platelet counts.

In the eye, there was a slight increase in hyperreflection seen mostly in the high dose animals. However, this phenomen was seen very erratically, and it would be hard to call this occurrence a toxicological consequence of iprodione administration. 2/6 male high dose dogs shoed finely scattered opalescent particles (asteroid bodies) in the vitreous humor. This phenomen may be treatment-related since no controls showed these asteroid bodies.

In the prostate, high dose males had both decreased absolute and relative weights. Mid dose absolute weights were significantly decreasd with a definite trend seen in relative weights, although the mid dose was not quite significantly different from controls.

In the urinary bladder of high dose males and females, small granulomata were seen in the immediate submucosa with foci of polymorphonuclear leucocyte infiltration seen in the transitional epithelium. The granulomata contained tall pyramidal crystals within the cytoplasm of phagocytic giant cells according to the study text.

In the adrenals both absolute and relative high dose males and females were increased. Microscopically the changes seen were described as zones in the zona glomerulosa and zona fasiculata with increased depth and the cells were large with pale "watery"

cytoplasm. Fatty vacuolization of the zona fasiculata was also seen, along with increased pallor of the zona glomerulosa. In the kidneys, there was a slight trend towards increased frequency of slight or moderate lipofuscinosis of the epithelium of the proximal convoluted tubules.

NOEL = 100 ppm (4.2 mg/kg)
LEL = 600 ppm based on prostate weight reductions and Heinz bodies seen in the erythrocytes.

Core classification = minimum