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

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JUL 27, 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Carcinogenicity Peer Review of Iprodione

FROM: Esther Rinde, Ph.D. E. Rinde
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Science Analysis Branch
Health Effects Division (7509C)

and

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TO: Steven D. Robbins
Product Manager # 21
Fungicide-Herbicide Branch
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and

Kathy Davis, Section Chief
Accelerated Reregistration Branch, Review Section II
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THROUGH: Penelope Penner-Crisp, Ph.D.
Director, Health Effects Division (7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on February 23, 1994 to discuss and evaluate the weight-of-the-evidence on Iprodione with particular reference to its carcinogenic potential. The CPRC concluded that Iprodione should be classified as a Group B2 - Probable Human Carcinogen - based on evidence of tumors in both sexes of the mouse and in the male rat, and that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1^*). The CPRC recommended that a Q_1^* be determined for the hepatocellular combined adenoma/carcinoma for both sexes of the mouse and also separately for the testicular tumors in the male rat.

SUMMARY

Administration of Iprodione in the diet for 99 weeks to Charles River CD-1 mice resulted in statistically significant increases in hepatocellular tumors in both sexes of Charles River CD-1 mice. Female mice also had a statistically significant increase in ovarian luteomas.

Administration of Iprodione in the diet to Charles River Sprague Dawley rats for 2 years resulted in a statistically significant increase in testicular interstitial cell tumors in males. [Details are provided in Section F. "The Weight of Evidence".]

Iprodione was tested in a variety of mutagenicity studies and found to be negative in all but a Bacillus subtilis assay.

Iprodione is structurally similar to Procymidone which was classified by the CPRC as a Group B2 carcinogen, and Vinclozolin (not yet peer reviewed). Both Procymidone and Vinclozolin are associated with testicular tumors in the rat and liver tumors in the mouse (as well as other tumor types).

There were no data provided on hormonal mechanisms to attribute the carcinogenic response as being secondary to the toxicity of the chemical.

The classification of Group B2 was based on evidence of increased incidences of tumors in 2 species: hepatocellular tumors in both sexes of the mouse, ovarian tumors in female mice and testicular interstitial tumors in male rats.

A. Individuals in Attendance at the meetings:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

William Burnam

Karl Baetcke

Marcia Van Gemert

Elizabeth Doyle

Hugh Pettigrew

Esther Rinde

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Linda Taylor[1] 6/23/94

Byron Backus

Clark Swentzel 6/23/94

Lori Brunsman

Lucas Brennecke[2] 6/29/94
(PAI/Clement)

3. Other Attendees:

Karen Whitby, Bernice Fisher (HED)

[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[2]Signature indicates concurrence with pathology report.

B. Material Reviewed:

The material available for review consisted of DER's, one-liners and other data summaries prepared and/or supplied by Dr. Linda Taylor, and tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report.

C. Background Information

Iprodione [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide]; [3-(3,5-dichlorophenyl)-N-isopropyl-2,4-dioxoimidazolidine-1-carboxamide] is a broad spectrum, contact fungicide formulated for use on a variety of crops, among them are fruit trees, berry fruit, vines, vegetable crops, cereals, rice, oilseed rape, sunflower, ornamental crops, and turf. It is known by the tradename Rovral® and Glycophene. The molecular formula is $C_{13}H_{13}Cl_2N_3O_3$ (MW 330.16). Iprodione has a vapor pressure of $< 10^{-6}$ mm Hg at 20° C and a solubility of 13 mg/L in water at 20° C. [See Figure 1 (file copy) for structure].

The Caswell (or Tox Chem) Number of Iprodione is 470A, the Shaughnessey Number is 109801, and the Chemical Abstracts Registry Number (CAS No.) is 36734-19-7.

D. Evaluation of Carcinogenic Evidence

1. Chambers, PR, Crook, D, Gibson, WA, Gopinath, C, and Ames, SA. Iprodione: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats. Study # RNP 346/920808, Huntingdon Research Centre, Ltd., Department of Rodent Toxicology, England; dated December 15, 1992. MRID # 426378-01 [Document # 010570].

Experimental Design: Iprodione was administered in the diet to 60 Sprague-Dawley [Crl:CD(SD)BR] rats/sex/group [main study] for two years at dose levels of 0, 150 [♂♂ 6.1/♀♀ 8.4 mg/kg/day], 300 [♂♂ 12.4/♀♀ 16.5 mg/kg/day], or 1600 [♂♂ 69/♀♀ 95 mg/kg/day] ppm. There was a 52-week interim sacrifice of 10 additional rats/sex/group.

Non-neoplastic Lesions: At the interim sacrifice, males at the high-dose level displayed an increase in the incidence of lesions in the adrenals, and there was an increase in the incidence of centrilobular hepatocyte enlargement in males at 300 and 1600 ppm. Females at the high-dose level displayed an increase in extramedullary hemopoiesis in the spleen, an increase in centrilobular hepatocyte enlargement, and an increase in the incidence of generalized rarefaction and fine vacuolation of the zona fasciculata in the adrenals compared to the control and other dose groups.

In the rats fed the test material for 2 years, interstitial cell hyperplasia in the testes, reduced spermatozoa in the epididymides, and absent/empty secretory colloid cells or reduced secretion in the seminal vesicles were observed in males at the 300 and 1600 ppm dose levels. Atrophy of the seminiferous tubules in the testes,

with atrophy of the prostate and absence of spermatozoa in the epididymides were observed at 1600 ppm. Centrilobular hepatocyte enlargement was increased in males at the high-dose level. Adrenal lesions were observed in both sexes at the 300 and 1600 ppm dose levels, although the males displayed more lesions than the females. In the high-dose females, there was an increased incidence of tubular hyperplasia in the ovaries and increased sciatic nerve fiber degeneration compared to the controls. Hemosiderosis was increased in females at the two highest dose levels. The NOEL for non-neoplastic changes was 150 ppm [♂♂ 6.1/♀♀ 8.4 mg/kg/day] and the LEL was 300 ppm [♂♂ 12.4/♀♀ 16.5 mg/kg/day].

Neoplastic lesions: There was an increase in the incidence of both unilateral and bilateral benign interstitial cell tumors in the testes of males at the 1600 ppm dose level. There was a dose-related increasing trend and a significant difference in the pair-wise comparison of the 1600 ppm dose group with controls for testicular tumors [Table 1] which exceeds the historical control incidence [Table 2].

Table 1. Testicular Interstitial Cell Tumor Rates♦ and Peto's Prevalence Test Results (p values)

Dose	0 ppm	150 ppm	300 ppm	1600 ppm
Incidence (%)	3♣/51 (6)	7/57 (12)	7/52 (13)	29/59 (49)
p value	0.000**	0.130	0.104	0.000**

♦ # of tumor bearing rats/# of rats examined, excluding those that died or were sacrificed before observation of the first tumor.
♣ First benign tumor observed at week 74, dose 0 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Historical Control Incidence of Testicular Tumors

Tumor/Study #	Incidence [# with tumor/# examined]
Interstitial Cell Tumor	
8901	2/50
8902	4/50
8903	1/50
8904	0/50
8905	0/49
8906	4/50
8907	5/50

Consideration of Adequacy of Dose Level Selection: The statistical evaluation of mortality [Brunsman memo dated 1/27/94] indicated a significant decreasing trend in mortality with increasing doses of Iprodione in male rats. Female rats showed no significant incremental changes with increasing doses of Iprodione.

Body weight gains were decreased in both sexes at the 1600 ppm dose level compared to control values during the 0-12 week interval and at other intervals also. At week 12, body-weight gain was 83.6% of the control value in the males and 80.7% of the control value in females at the highest dose level. Overall, body-weight gains were 86% and 92% of control values in the high-dose males and females, respectively.

Based on the above, the CPRC considered the doses used in this study to be adequate for assessing the carcinogenic potential of Iprodione in the rat.

In the 90-day study [MRID # 429607-01], dose levels of 0, 1000 ppm [78 ♂/89 ♀ mg/kg], 2000 ppm [151 ♂/184 ♀ mg/kg], 3000 ppm [252 ♂/266 ♀ mg/kg], and 5000 ppm [351 ♂/408 ♀ mg/kg] resulted in signs of toxicity [pilo-erection, hunched posture, pale and/or cold extremities, an emaciated appearance, decreased body weight {♂♂ 75%, 52%, and 39% of control and ♀♀ 86%, 70%, and 55% of control at 2000, 3000, and 5000 ppm, respectively}, decreased body-weight gain {♂♂ 61% (2000 ppm) and 26% (3000 ppm) of control; ♀♀ 70% (2000 ppm) and 38% (3000 ppm) of control; negative gain at 5000 ppm for both sexes}, decreased food consumption {81% (♂♂ at 2000 ppm} and 69%/79% {♂♂/♀♀ at 3000 ppm}/food efficiency] leading to the early termination [week 8] of the 5000 ppm dose groups.

In a previous chronic toxicity/carcinogenicity study in Charles River CD outbred albino rats, no treatment-related tumors were reported, although the incidence of testicular interstitial cell tumors was 2, 2, 4, and 5 out of 60 rats/group at dose levels of 0, 125, 250, and 1000 ppm, respectively.

2. Chambers, PR; Crook, D; Gibson, WA; Read, RM; and Gopinath, C. May 10, 1993. IPRODIONE Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice. Study No. RNP 359/921240; dated May 10, 1993. MRID No. 428250-02 [Document # 010570].

Experimental Design: Iprodione was fed to Crl:CD®-1 (ICR) BR mice (50/sex/group-Main study) at dose levels of 0, 160 [♂♂ 23/♀♀ 27 mg/kg/day], 800 [♂♂ 115/♀♀ 138 mg/kg/day], or 4000 [♂♂ 604/♀♀ 793 mg/kg/day] ppm for at least 99 weeks [or until the 52-week interim sacrifice of 15 additional mice/sex/group].

Non-Neoplastic Lesions: **Interim Sacrifice** - In the liver, mice of both sexes displayed an increase in the incidence and degree of centrilobular hepatocyte enlargement compared to the controls, and centrilobular hepatocyte vacuolation was observed in the majority of high-dose females compared to the control incidence. These findings are consistent with the increases in liver weight and plasma GPT and GOT observed in the groups. Although the incidence and degree of fat in the hepatocytes were similar among the groups, a difference in distribution was noted; i.e., control, low- and mid-dose mice displayed fat in all zones while in the high-dose mice, fat was confined to the periportal hepatocytes.

The majority of high-dose females displayed hypertrophy of the cells of the zona fasciculata of the adrenal gland. No other group displayed this lesion. The lesion correlates with the increased adrenal weight observed in these females, but no morphological correlation was observed to account for the increased adrenal weight observed in high-dose males.

Only high-dose males displayed generalized vacuolation and hypertrophy of the interstitial cells of the testes. In females, only high-dose mice displayed luteinization of the interstitial cells of the ovary. In the cervix and vagina, epithelial thickening, usually with keratinization, was observed more frequently in the treated females compared to the controls, but no dose-response was evident.

Terminal - LIVER - At the high-dose level (both sexes), there was a significantly increased incidence of single and multiple areas of enlarged eosinophilic hepatocytes and focal fat-containing hepatocytes compared to the control values. The incidence and degree of centrilobular hepatocyte enlargement were increased significantly at the high-dose level in both sexes, and the incidence of minimal centrilobular hepatocyte enlargement was increased at the mid-dose level in females compared to the control mice. Additionally, at the high-dose level, the incidence and degree of pigmented macrophages and the degree of centrilobular hepatocyte vacuolation were increased significantly in male mice compared to the control male mice. TESTES - There was an increased incidence of generalized vacuolation/hypertrophy of the interstitial cells of the testes in the mid- and high-dose mice. OVARIES - There was a dose-related increase in female mice displaying luteinization of the interstitial cell of the ovary, but statistical significance was not attained at any dose level. The NOEL for non-neoplastic changes was 160 ppm [♂♂ 23/♀♀ 27 mg/kg/day], and the LEL was 800 ppm [♂♂ 115/♀♀ 138 mg/kg/day].

Neoplastic Lesions: **Interim** - Very few tumors were observed at the interim sacrifice. Pulmonary adenoma [benign] was observed in one low-dose female and one mid-dose female, and pulmonary adenocarcinoma [malignant] was observed in one control male and one high-dose male. One male in the mid- and one male in the high-dose groups displayed a benign liver cell tumor. One benign cystadenoma in the Harderian gland was observed in the low-dose male group.

Terminal - LIVER: At the high-dose level, there was a significant increase in the incidence of benign and malignant liver cell tumors in both sexes compared to the control. The adenomas found at the control, low-, and mid-dose levels in males were all in mice at the interim or terminal sacrifice, while 6 of the 25 adenomas in the high-dose males, 1 of 2 in the mid-dose females and 5 of 21 in the high-dose females were found in mice dying on test. In the Qualita-

tive Risk Assessment memo, analysis indicates that male mice had significant increasing trends and significant differences in the pair-wise comparisons [all at $p < 0.01$] of the 4000 ppm dose group with the controls, for liver adenomas, carcinomas, and combined adenomas and/or carcinomas [Table 3]. Female mice had significant increasing trends in liver adenomas, carcinomas, and combined adenomas and/or carcinomas also [all at $p < 0.01$], and there were significant differences in the pair-wise comparisons of the 4000 ppm dose group with the controls for liver adenomas and combined adenomas and/or carcinomas [both at $p < 0.01$]. The incidence of both benign and malignant liver tumors in females at 4000 ppm is outside the historical control data, as is the incidence of carcinoma in the high-dose males [Table 4]. It is to be noted that all male groups [including the concurrent control] displayed a higher incidence of carcinomas than observed in the historical control.

Group Dose Tumor	Table 3. Liver Tumor Rates¦ and Exact Trend Test & Fisher's Exact Test Results -(p values)			
	0	160	800	4000
MALES				
adenoma (%)	4/62 (6)	4/62 (6)	8♦/62 (13)	25/63 (40)
p value	0.000**	0.641	0.182	0.000**
carcinoma (%)	4/62 (6)	3/62 (5)	6/62(10)	15♦/63 (24)
p value	0.000**	0.500♥	0.372	0.006**
combined (%)	7/62 (11)	6/62 (10)	11/62 (18)	27/63 (43)
p value	0.000**	0.500♥	0.223	0.000**
FEMALES				
adenoma (%)	1/47 (2)	1/49 (2)	2/49 (4)	21⊜/48 (44)
p value	0.000**	0.742	0.516	0.000**
carcinoma (%)	1/47 (2)	1♣/49	0/49 (0)	6/48 (12)
p value	0.003**	0.742	0.490♥	0.059
combined (%)	2/47 (4)	2/49 (4)	2/49 (4)	21/48 (44)
p value	0.000**	0.676	0.676	0.000**

¦ # of tumor bearing mice/# of mice examined, excluding those that died before week 52.
♥ Negative change from control.
♦ First ♂ adenoma observed at week 52, dose 800 ppm.
♦ First ♂ carcinoma observed at week 83, dose 4000 ppm.
⊜ First ♀ adenoma observed at week 75, dose 4000 ppm.
♣ First ♀ carcinoma observed at week 79, dose 160 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Historical Control Incidence of Liver Tumors

Tumor/Study #	# males with tumor/# examined(%)	# females with tumor/# examined(%)
Benign Tumor only		
8911	5/52 (10)	0/52
8912	7/52 (13)	1/52
8913	5/52 (10)	0/52
8914	6/52 (12)	0/52
8915	9/52 (17)	0/52
8916	11/50 (22)	0/50
8917	6/50 (12)	0/50
8918	10/56 (18)	0/56
Malignant Tumor only		
8911	1/52 (1.9)	0/52
8912	0/52 (0)	0/52
8913	1/52 (1.9)	0/52
8914	2/52 (3.8)	0/52
8915	1/52 (1.9)	0/52
8916	1/50 (2.0)	0/50
8917	1/50 (2.0)	0/50
8918	2/56 (3.6)	0/56
Any Liver Tumor		
8911	6/52 (11.5)	0/52
8912	7/52 (13.5)	1/52
8913	6/52 (11.5)	0/52
8914	8/52 (15.4)	0/52
8915	10/52 (19.2)	0/52
8916	12/50 (24)	0/50
8917	7/50 (14)	0/50
8918	12/56 (21.4)	0/56

OVARIES: The incidence of luteoma of the ovaries was increased [difference in pairwise comparison significant at $p<0.05$], and there was a significant increasing trend in ovarian luteomas [Table 5]. All tumors were found at terminal sacrifice. The incidence at the high dose is slightly greater than observed in the historical control data [Table 6].

Group Dose (ppm) Lesion	Table 5. Ovarian Tumor Rates¦ and Exact Trend Test & Fisher's Exact Test Results (p values)			
	0	160	800	4000
FEMALES luteoma (%) p=	0/47 (0) 0.012*	2♦/48 (4) 0.253	1/49 (2) 0.510	5/48 (10) 0.030*

¦ # of tumor bearing mice/# of mice examined, excluding those that died before week 53.
♦ First luteoma observed at week 99, dose 160 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If , then $p < 0.05$. If , then $p < 0.01$.

Table 6. Historical Control Incidence of Luteoma

Tumor/Study #	# with tumor/# examined (%)
Luteoma	
8911	2/51 (3.9)
8912	0/52
8913	0/52
8914	1/51 (2)
8915	1/52 (2)
8916	2/50 (4)
8917	4/50 (8)
8918	0/56

KIDNEY: Clear cell carcinoma (malignant) was observed in the kidney of one high-dose male at termination.

Consideration of the Adequacy of Dose Selection: There was no apparent effect of treatment on survival, although the high-dose group displayed the highest mortality rate for both sexes. The statistical evaluation of mortality [memo from Brunsman to Taylor, dated 1/27/94] indicated no significant incremental changes with increasing dose in either sex. The most frequently occurring probable cause of death was amyloidosis, with the high-dose males and all treated female groups (dose-related) displaying a greater incidence than their respective controls (Table 7).

Table 7. Incidence of Amyloidosis in Mice Dying on Test

Sex	MALES				FEMALES			
Dose level (ppm)	0	160	800	4000	0	160	800	4000
# dying due to amyloidosis (%)	11 (48)	13 (50)	8 (44)	18 (62)	7 (26)	13 (45)	16 (55)	17 (53)

During the first 18-week interval, body-weight gains were comparable among the groups for both sexes. During the 18 to 45 week interval, the high-dose mice [both sexes] displayed a statistically significant decrease in body-weight gain compared to their respective control group [56 (♂) and 53 (♀) % of control value]. Overall, mice at the high-dose level [♂♂-86%; ♀♀-89%] displayed a lower body-weight gain compared to their respective control group.

Based on the above, the CPRC considered the doses used in this study to be adequate for assessing the carcinogenic potential of Iprodione in the mouse.

In a previous chronic toxicity/carcinogenicity study in Carworth CF-1 albino mice [Accession # 097201; Document # 001519], Iprodione was negative for carcinogenicity. The dose levels were 200, 500, and 1250 ppm, and the duration of the study was 18 months. Only one ovarian tumor [malignant] was reported [500 ppm]. Liver tumors were reported as follows [Table 8]:

Table 8. Liver Tumors		
Group/Tumor Type	Benign	Malignant
MALES		
0	0/60	2/60
200	2/59	0/59
500	0/60	4/60
1250	2/59	5/59
FEMALES		
0	0/60	0/60
200	0/60	0/60
500	1/58	2/58
1250	0/59	1/59

E. Other Relevant Toxicology Information:

1. Genotoxicity

Iprodione has been tested in several mutagenicity studies. With the exception of the Bacillus subtilis assay for DNA damage, Iprodione was negative in the (1) Ames assay; (2) CHO/HGPRT mammalian cell forward mutation assay, with and without metabolic activation; (3) in vitro chromosome aberration assay in CHO cells; (4) in vitro sister chromatid exchange assay in CHO cells; and (5) dominant lethal test in mice. Iprodione was positive in the Bacillus subtilis assay for DNA damage without metabolic activation.

2. Metabolism

^{14}C-Iprodione was absorbed readily from the gastrointestinal tract, metabolized, and excreted by rats of both sexes following single low [50 mg/kg] and high [900 mg/kg] oral doses and 14 repeated low [50 mg/kg] doses. Peak blood levels were observed at 4 and 2 hours, respectively, in low-dose males and females and at 6 hours in high-dose rats of both sexes. The elimination of ^{14}C from the blood was slower in males than females. There were both dose and sex-related differences noted in absorption: males absorbed a greater percentage of the low and repeated doses than females. Although levels of ^{14}C were found in most tissues monitored, the levels were $\leq$ 0.5% of the total amount administered. It is to be noted that the testes of the low-dose [50 mg/kg] males showed no detectable amount of ^{14}C; the high dose in the rat chronic toxicity/carcinogenicity study where testicular tumors were observed was 69 mg/kg. The primary route of elimination of ^{14}C following single and repeat low dose exposure was the urine, and the feces was the primary route following high-dose exposure. Dealkylation and cleavage of the hydantoin ring were the two primary steps in the metabolism of Iprodione. Hydroxylation of the phenyl ring and oxidation of the alkyl chain also occurred. The primary metabolites recovered from

the urine [both sexes] included a dealkylated derivative of Iprodione and 2 polar but unidentified compounds. Males produced larger amounts of a hydantoin ring-opened metabolite than females, and the urine of the females contained a higher proportion of unchanged parent compound than that of the males. Several urinary metabolites were not identified. The feces contained much larger amounts of unchanged parent compound than the urine, which the authors suggested was unabsorbed Iprodione and metabolites or hydrolyzed conjugates of absorbed material.

In another single oral administration study in rats using 50 mg/kg, no sex differences were apparent in the excretion profile, and both urinary elimination [≈37%♂/28%♀] and fecal excretion [56%♂/50%♀] are major routes of excretion. The metabolism of Iprodione was extensive and characterized by the large number of metabolites formed. In the urine, RP 36115, RP 32490, RP 36112, RP 36119, and RP 30228 were either confirmed or indicated. The feces contained a large proportion of parent compound; the major fecal metabolites were RP 36115, RP 36114, RP 32490, and RP 30228. A general metabolic pathway for Iprodione in the rat indicates that biotransformation results in hydroxylation of the aromatic ring, degradation of the isopropylcarbamoyl chain and rearrangement followed by cleavage of the hydantoin moiety. Additionally, structural isomers of Iprodione resulting from molecular rearrangement, as well as intermediates in the pathway, were detected.

3. **Acute, Subchronic, and Chronic Toxicity Data**

The acute oral LD_{50} for Iprodione Technical in rats was > 2.5 mg/-kg, Tox. Cat. III. An acute oral study in mice gave an LD_{50} of 4 ♂/4.4 ♀ g/kg, Tox. Cat. III. In a 5-month feeding (150, 500, 1000 ppm) study [Accession # 232702; Document # 001519] in rats, the NOEL was set at 1000 ppm [HDT]. In a 3-month dog study [Accession # 232702; Document # 001519], the NOEL was set at 2400 ppm, the LEL at 7200 ppm, based on liver hypertrophy and increased SAP [doses of 800, 2400, and 7200 ppm]. No significant systemic toxicity was observed in a 3-week dermal study [MRID # 420232-01; Document # 009575] at dose levels of 100, 500, and 1000 mg/kg. The NOEL was set at 1000 mg/kg [HDT].

Two one-year dog studies have been performed. In the first study [Accession # 255951; Document #'s 004439 and 005882], the NOEL was set at 100 ppm, the LEL at 600 ppm, based on decreased prostate weight and an increased number of erythrocytes with Heinz bodies in males. The dietary levels tested were 0, 100, 600, and 3600 ppm. In the second study [MRID # 422111-01; Document # 009548], performed as a bridging study to establish a higher no-effect level, dose levels of 0, 200, 300, 400, and 600 ppm were tested. The NOEL was

set at 400 ppm [17.5 ♂♂/18.4 ♀♀ mg/kg], the LEL at 600 ppm [24.6 ♂♂/26.4 ♀♀ mg/kg], based on depressed red blood cell parameters.

4. Structure-Activity Correlations

Iprodione is structurally similar to Procymidone and Vinclozolin.

a) **Procymidone** - [N-(3,5-dichlorophenyl)-1,2-dimethylcyclopropane-1,2-dicarboximide)], a fungicide, has been tested in a rat chronic toxicity/carcinogenicity study and a mouse carcinogenicity study. In the rat [Osborne-Mendel] study, Procymidone was associated with the appearance of tumors in both sexes. In males, there was a statistically significant increase in testicular interstitial cell adenomas at the 1000 and 2000 ppm dose levels, and a statistically significant dose-related increasing trend in these tumors, which appeared earlier than in the controls. In females, there was a statistically significant increasing trend in pituitary adenomas, as well as a significant difference in the pair-wise comparison of controls and both the 1000 and 2000 ppm dose groups for pituitary adenomas. Additionally, there was an increase in stromal hyperplasia of the ovaries at the 2000 ppm dose level, but no dose-related increase in ovarian tumors. In males, there was a dose-related increase in testicular interstitial cell hyperplasia at the 1000 and 2000 ppm dose levels. Liver cytomegaly occurred in treated rats only and it was dose-related in both sexes. In the mouse [$B_6C_3F_1$], there was a significant dose-related positive trend in hepatoblastomas [rare variant of hepatocellular carcinoma] in males, and significant dose-related positive trends in hepatocellular adenomas and in combined adenomas and/or carcinomas, with a significance in the pair-wise comparison of controls and the highest dose groups in both hepatocellular adenomas and in the combined adenomas and/or carcinomas in females. Procymidone was negative in the <u>in vitro</u> UDS assay, the <u>in vitro</u> chromosome aberration [CHO cells] assay, and the Ames assay.

b. **Vinclozolin** - [3-(3,5-dichlorophenyl)-5-methyl-5-vinyl-1,3-oxazolidin-2,4 dione] is a fungicide, bactericide, and wood preservative. Vinclozolin is being tested in both a rat chronic toxicity/carcinogenicity study and a mouse carcinogenicity study; previous studies were found unacceptable. In an interim report of the new rat [Wistar] study, testicular and ovarian masses have been observed at 1500 and 4500 ppm, liver tumors [masses] at 4500 ppm, and ophthalmic lesions have been observed at all dose levels. In a subchronic study, increased liver [both sexes], adrenal [both sexes], pituitary and testes [male], and ovary [female] weights were observed at 1000 and 4500 ppm. The interim report of the mouse [C57BL/6N] study indicated that liver carcinomas were observed at 8000 ppm [HDT] in females, a dose where excessive mortality occurred. In the subchronic study in mice, hyperplasia of

testicular Leydig cells at 1000 ppm and ovarian stromal cells at 5000 ppm was observed. Increased adrenal weight was observed in dogs in both a 6-month and 1 year studies. Vinclozolin was negative in the sister chromatid exchange assay [hamsters], the in vivo reverse mutation assay, CHO/HGPRT assay with and without metabolic activation, Ames assay with and without metabolic activation, and UDS assay in rat hepatocytes. In the mouse lymphoma (forward mutation) assay, a significant reproducible increase in mutation frequency was observed with metabolic activation at insoluble concentrations.

6. **Mechanism of Action - Hormonal Effects and Tumor Induction**

The Registrant put forth an hypothesis on the mechanism of tumor formation by Iprodione, suggesting a perturbation of sex hormone regulation. A causal relationship between a possible hormonal imbalance and tumor formation is discussed in their document entitled: IPRODIONE: Carcinogenicity in Rodents, dated June 16, 1993. In light of the negative results in various genetic toxicity tests, the Registrant states that Iprodione clearly is not a genotoxic carcinogen, and the increased incidence of tumors in both rats and mice occurred only at the MTD. Considering the non-neoplastic findings in the reproductive system of male rats and female mice and the lack of genotoxic potential, the Registrant proposes that the "nongenotoxic mechanism of carcinogenesis results from a perturbation in sex hormone regulation. Tumor formation is therefore likely to be secondary to prolonged and profound hormonal imbalance at the target organ level which only occurs when animals are exposed to high dietary levels of iprodione. Such a mechanism would be expected to occur above a threshold which would need to be exceeded to overcome the powerful normal hormonal homeostasis. Consequently, quantitative carcinogen risk assessment based on the "linearized" multistage model is inappropriate in the case of iprodione. Instead, safety factors are considered to be an appropriate and adequate method for risk assessment of threshold carcinogens." The Registrant has indicated that mechanistic studies will be conducted to demonstrate the effect of Iprodione on sex hormone regulation in order to establish a link between this hormonal perturbation and the increased incidence of tumor formation.

Since no data to support the hypothesis on hormonal mechanisms were provided, the CPRC had no basis for attributing the carcinogenic response as being secondary to the toxicity of the chemical.

F. **Weight of Evidence Considerations:**

The Committee considered the following facts regarding the toxicology data on Iprodione in a weight-of-the-evidence determination of carcinogenic potential.

1. **Male and female Sprague-Dawley [Crl:CD(SD)BR] rats were fed Iprodione for two years at dose levels of 0, 150 [♂♂ 6.1/♀♀ 8.4 mg/kg/day], 300 [♂♂ 12.4/♀♀ 16.5 mg/kg/day], or 1600 [♂♂ 69/♀♀ 95 mg/kg/day] ppm.**

   In male rats, there was a significant [$p<0.01$] dose-related increasing trend and a significant [$p<0.01$] difference in the pair-wise comparison of the 1600 ppm dose group with the controls for testicular interstitial cell benign tumors. The incidence of both unilateral and bilateral benign interstitial cell tumors was increased at this dose level compared to the control.

   In male rats, the increased incidence of testicular tumors noted at 1600 ppm exceeds the historical control incidence for these tumors in this strain of rat.

   In female rats, there were no significant compound-related tumors observed.

   In female rats, although there was no increase in the incidence of ovarian tumors, tubular hyperplasia was increased at the 4000 ppm dose levels compared to the control incidence.

   The doses used in both sexes of the rat were considered to be adequate.

2. **Male and female Crl:CD®-1 (ICR) BR mice were fed Iprodione at dose levels of 0, 160 [♂♂ 23/♀♀ 27 mg/kg/day], 800 [♂♂ 115/♀♀ 138 mg/kg/day], or 4000 [♂♂ 604/♀♀ 793 mg/kg/day] ppm for at least 99 weeks.**

   In male mice, Iprodione was associated with significant [$p<0.01$] dose-related increasing trends in liver adenomas, carcinomas, and combined adenomas and/or carcinomas.

   In male mice, there were significant [$p<0.01$] differences in the pair-wise comparisons of the 4000 ppm dose group with the controls for liver adenomas, carcinomas, and combined adenomas and/or carcinomas.

   In male mice, the increased incidences of hepatocellular tumors noted at 4000 ppm generally exceeded the available historical control incidences for these same tumor types in

mice of this strain.

In male mice, although there was no increase in the incidence of testicular tumors in the male CD-1 mice, there was a dose-related increase in the incidence of interstitial cell hyperplasia at the 300 and 4000 ppm dose levels.

In female mice, Iprodione was associated with significant [$p<0.01$] dose-related increasing trends in liver adenomas, carcinomas, and combined adenomas and/or carcinomas.

In female mice, there were significant [$p<0.01$] differences in the pair-wise comparisons the 4000 ppm dose group with the controls for liver adenomas and combined adenomas and/or carcinomas.

In female mice, the increased incidences of hepatocellular tumors noted at 4000 ppm generally exceeded the available historical control incidences for these same tumor types in mice of this strain.

In female mice, Iprodione was associated with a significant [$p<0.05$] increasing trend in ovarian luteomas, and there was a significant [$p<0.05$] difference in the pair-wise comparison of the 4000 ppm dose group with the control for ovarian luteomas.

In female mice, the increased incidence of ovarian luteomas noted at 4000 ppm in CD-1 mice exceeds the historical control incidence for these tumors in this strain of mouse.

The doses used in both sexes of the mouse were considered adequate.

3. From submitted studies, Iprodione was not mutagenic in the Ames assay, the CHO/HGPRT mammalian cell forwarded mutation assay, with and without metabolic activation, the in vitro chromosome aberration assay in CHO cells, the in vitro sister chromatid exchange assay in CHO cells and the dominant lethal test in mice. However, Iprodione was positive in the Bacillus subtilis assay for DNA damage withiut metabolic activation.

4. Iprodione is structurally related to Vinclozolin and Procymidone. Procymidone was associated with the appearance of tumors in both sexes in the sex organs and the liver, but was negative for mutagenicity. Vinclozolin, which is currently being tested for its carcinogenic potential, has been associated with adverse effects on the sex organs and liver. With the exception of the mouse lymphoma (forward mutation) assay, Vinclozolin was negative for mutagenicity.

5. Carcinogenicity in animals -- Iprodione

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concludes that exposure to Iprodione resulted in an increased incidence of hepatocellular malignant carcinomas in males and combined heptocellular adenomas/carcinomas in both sexes of mice, ovarian luteomas in female mice, and testicular interstitial cell tumors in male rats. Structural analogs closely related to Iprodione are also carcinogenic and induce cancer and adverse effects at the same sites (liver, ovary and testis) as Iprodione. The relevance of these data to an evlaluation of Iprodione's potential for human carcinogenicity is discussed elsewhere in this document.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The Peer Review Committee agreed that Iprodione should be classified as a Group B2 - probable human carcinogen and that a low-dose extrapolation methodology (Q*) be applied to the animal data. This decision was based on evidence of increased incidences of tumors in 2 species: hepatocellular tumors in both sexes of the mouse, ovarian tumors in female mice and testicular interstitial tumors in male rats. Iprodione was tested in a variety of mutagenicity studies and found to be negative in all but a Bacillus subtilis assay. Iprodione is structurally similar to Procymidone which was classified by the CPRC as a B2 carcinogen, and Vinclozolin (not yet peer reviewed). Both Procymidone and Vinclozolin are associated with testicular tumors in the rat and liver tumors in the mouse (as well as other tumor types). There were no data provided on hormonal mechanisms to attribute the carcinogenic response as being secondary to the toxicity of the chemical.