Appendix I: Summary of Human Health Effects Data for Iprodione

MEMORANDUM

Subject: Toxicology Review for the Reregistration Eligibility Document on IPRODIONE - **UPDATE**

From: Linda L. Taylor, Ph.D.
Toxicology II Branch, HED (7509C)

Thru: Whang Phang, Ph.D.
Branch Senior Scientist
Reregistration Branch I, HED (7509C)

To: Karen Whitby, Ph.D., Chief
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

Chemical: **IPRODIONE**; [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide]; [3-(3,5-dichloro-phenyl)-N-isopropyl-2,4-dioxo-1-imidazolidine-1-carboxamide]; Case 819434; Reregistration Case No. 2335; Chemical No. 109801; CAS Reg No. 36734-19-7; Caswell No. 470A; **Original** Submission S518295; **Original** DP Barcode D235399. No new DP Barcode with this action.

ACTION REQUESTED: Update Toxicology RED Chapter for Iprodione, in light of the changes made subsequent to Original Toxicology RED Chapter.

Subsequent to my original Tox chapter on Iprodione [dated June 12, 1997], various changes have been made to several aspects. These include the completion of the review of a prenatal developmental toxicity study, two external peer reviews of the data with respect to the issue of carcinogenicity, a revisit to the HED Cancer Assessment Review Committee, and an evaluation of the data by the HED Hazard Identification Committee with specific emphasis on the issues relating to the Food Quality Protection Act [FQPA].

The specific changes to the original chapter are listed below.

1) On the original cover page, the first paragraph has been modified.
2) On page 2 [original document], in Table 1 under 83-3, the prenatal study recently reviewed has been added to the table [MRID 44365001] along with the supplemental analysis [MRID 44422101] of the anogenital distance data; under mechanism-testes, another MRID # has been added [44203401].
3) On page 11 of the original chapter, under 2., the new prenatal study summary has been added [on new page 13].
4) On page 12 of the orignal chapter, the small paragraph above e. Has been deleted [new page 13].
5) On page 13 of the original chapter, an overall conclusion on mutagenicity data has been inserted [on new page 14].
6) On page 14 of the original chapter, under g. **Toxicity Endpoint Selection for Risk Assessment**, some of this has been modified [new page 17]. For the acute dietary risk assessment, the Hazard ID Committee on February 25, 1998 chose the recent prenatal sex differentiation study in which the developmental toxicity NOEL was 20 mg/kg/day, and the developmental toxicity NOEL was 120 mg/kg/day, based on decreased anogenital distance in the male Iprodione pups.

Short term and intermediate term **dermal** occupational/residential exposure risk assessments remain the same; i.e., not required.

Added are the endpoints/NOEL for inhalation exposure [new page 17].

7) Added is a section h. **Consideration of FQPA Issues for Iprodione** new pages 18-19].
8) On page 15 of the original chapter, the Reference Dose paragraph has been modified [new page 19; now under i.].
9) on page 19 of the original chapter, two references have been added to the end of the list on new page 24 [prenatal study - MRID 33365001; statistical analyses of anogenital data - MRID 44422101].

TOXICOLOGY RED CHAPTER FOR IPRODIONE
Based on the currently available toxicology data on Iprodione, a toxicology chapter on Iprodione for the RED has been prepared and is appended. The toxicology data base on Iprodione is not complete, although it is adequate to support the RED. The data gap is a postnatal exposure developmental toxicity study in rats, which was requested by the HED RfD Committee [February 10, 1994] and reiterated by the HED Hazard Identification Committee [February 25, 1998].

The toxicology profile for Iprodione is summarized in Table 1. The standard toxicology database on Iprodione is complete and will support reregistration eligibility.

Table 1. Toxicology Profile

Guideline	Study Type	MRID #	Required	Satisfied
81-1	acute oral - rats	42306301	yes	yes
81-2	acute dermal - rabbits	40567601	yes	yes
81-3	acute inhalation - rats	42946101	yes	yes
81-4	primary eye irritation	41867301	no	yes
81-5	primary dermal irritation	41867302	no	yes
81-6	dermal sensitization	40567602 42524601	no	yes
81-7	acute delayed neurotoxicity - hen	-	no	no
81-8	acute neurotoxicity - rat	-	no	no
82-1	subchronic feeding - rats	42960701	yes	yes
82-1	subchronic feeding - dog	00157377 00157378 00232702	yes	yes
82-2	21-day dermal - rabbits	42023201	yes	yes
82-5	subchronic neurotoxicity - rats	-	no	no
83-1(a)	chronic toxicity - rats	00071997 00128931 00164249 42637801 42787001	yes	yes
83-1(b)	chronic toxicity - dog	00144391 41327001 42211101	yes	yes
83-2	carcinogenicity - mice	00070963 42825002	yes	yes
83-3(a)	developmental toxicity - rat	00162984 40514901 44365001 44422101	yes	yes
83-3(b)	developmental toxicity - rabbits	00155469	yes	yes
83-4	2-generation reproduction - rats	00162983 41871601	yes	yes
83-5	chronic toxicity/carcinogenicity - rat	42637801 42787001	yes	yes
84-2	mutagenicity	41604106 00148207 00148208 00148209 43535001	yes	yes
85-1	metabolism	41346701 42984101 43484901	yes	yes
85-2	dermal penetration	43535003	yes	yes
86-1	domestic animal safety	-	no	no
none	mechanism - testes	43535002 43830601	N/A	N/A

		44171901 44171903 44171904 44203401		
none	mechanism - liver	44171902	N/A	N/A

a. Acute Toxicity

Sufficient data are available on the acute toxicity of Iprodione. Iprodione is not acutely toxic via the oral, dermal, inhalation, or ocular routes of exposure. Acute toxicity values and categories for IPRODIONE are summarized in Table 2.

TABLE 2. Acute Toxicity of IPRODIONE

Guideline	Study Type	MRID #	Results	Toxicity Category
81-1	Acute Oral - rat	42306301	LD_{50} = 4468 mg/kg	III
81-2	Acute Dermal - rabbit	40567601	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation - rat	42946101	LC_{50} = > 5.16 mg/L	IV
81-4	Primary Eye Irritation - rabbit	41867301	mild irritant	III
81-5	Primary Skin Irritation - rabbit	41867302	not an irritant	IV
81-6	Dermal Sensitization - guinea pig	40567602 42524601	not a dermal sensitizer	-

In an acute oral toxicity study with rats, the LD_{50} was 4468 mg/kg, which is toxicity category III [Guideline 81-1; MRID 42306301]. The LD_{50} in an acute dermal toxicity study with rabbits was found to be greater than 2000 mg/kg. This is toxicity category III [Guideline 81-2; MRID 40567601]. In an acute inhalation toxicity study with rats, the LC_{50} was greater than 5.16 mg/L for 4 hours. This is toxicity category IV [Guideline 81-3; MRID 42946101].

In a primary eye irritation study with rabbits, Iprodione was a mild ocular irritant. This is toxicity category III [Guideline 81-4; MRID 41867301]. Iprodione did not induce irritation in a primary dermal irritation study in rabbits. This is toxicity category IV [Guideline 81-5; MRID 41867302].

In a dermal sensitization study in guinea pigs, Iprodione was not found to be a dermal sensitizer [Guideline 81-6; MRID 40567602, 42524601].

b. Subchronic Toxicity

Sufficient data are available on the subchronic toxicity of Iprodione. In a 21-day dermal toxicity study, five New Zealand rabbits/sex/group were administered Iprodione [96.2%] via the skin at dose levels of 0, 100, 500, and 1000 mg/kg/day for 21 days. There were no deaths or clinical signs of toxicity, and no adverse effects were observed on body weight, food consumption, the skin, liver, or kidneys. **The NOEL is 1000 mg/kg/day, the highest dose tested** [Guideline §82-2; MRID 42023201].

In a subchronic feeding study, 10 Crl:CD(SD)BR rats/sex/group were administered Iprodione [95.7%] via the diet at dose levels of 0, 1000 ppm [__ 78/__ 89 mg/kg/day], 2000 ppm [__ 151/__ 189 mg/kg/day], 3000 ppm [__ 252/__ 266 mg/kg/day], and 5000 ppm [__ 355/__ 408 mg/kg/day] for 90 days. Signs of toxicity included hunched posture, pilo-erection, pale and/or cold extremities, an emaciated appearance, decreased body weight [__ 75%, 52%, and 39% of control/__ 86%, 70%, and 55% of control at the 2000, 3000, and 5000 ppm

dose levels, respectively], decreased body-weight gain [__ 61% and 26% of control/__ 70% and 38% of control at the 2000 and 3000 ppm dose levels, respectively], negative body-weight gain for both sexes at 5000 ppm, decreased food consumption [81% of control for 2000 ppm males; 69%/79% of control for males/females at 3000 ppm], and decreased food efficiency for both sexes at 2000 and 3000 ppm. The 5000 ppm dose group was terminated early [week 8]. The sex organs, pituitary, and adrenals of both sexes appear to be target organs for Iprodione. In general, the decreases observed in organ weights and the accompanying increases in relative organ weights may be attributed to the decreased body weight, but in females, decreased relative organ weights were observed in the uterus, ovary, adrenal, and pituitary, mainly at the high [3000 ppm] dose. These latter decreases and the decrease in absolute brain weight in females appear to be treatment-related. Dose-related microscopic lesions were observed in the sex organs and adrenals of both sexes at the 2000, 3000, and 5000 ppm dose levels. **The NOEL is 1000 ppm [__ 78/__ 89 mg/kg/day], and the LOEL is 2000 ppm [__ 151/__ 184 mg/kg/day], based on decreased body weight/gain, decreased food consumption/ food utilization, organ weight effects, and microscopic lesions in the sex organs.** This study is classified **Acceptable**, although clinical chemistry and hematology parameters were not monitored. This study was performed to determine appropriate dose levels for the 2-year chronic toxicity/ carcinogenicity study in rats, and these parameters were monitored in the long-term study. Therefore, an additional subchronic feeding study in rats is not required [Guideline §82-1(a); MRID 42960701].

In a subchronic feeding study, 2 Beagle dogs/sex/group were administered Iprodione [technical] via the diet at dose levels of 0, 800 ppm [≈60 mg/kg/day], 2400 ppm [≈ 180 mg/kg/day], and 7200 ppm [≈ 270 mg/kg/day] for 90 days [standard conversion of 0.075 used]. There were no deaths. One high-dose dog displayed general fatigue with muscular atony from week 5 to 13. Body weights were comparable among the groups in both sexes. High-dose dogs displayed a slight anemia during the study, and increased alkaline phosphatase and transaminase [SGOT, SGPT] values compared to the controls. There were no effects reported in clinical chemistry and urinalysis. At necropsy, both females and one male at the high dose displayed slight liver hypertrophy and the other male displayed a pale liver, in addition to anemia and hypertrophy of the prostate and testes. No treatment-related microscopic lesions were observed. **The NOEL is 2400 ppm [≈180 mg/kg/day], and the LOEL is 7200 ppm [≈270 mg/kg/day], based on liver hypertrophy and increased alkaline phosphatase.** This subchronic feeding study in dogs is classified Unacceptable, but there is an acceptable chronic toxicity study in dogs; therefore, an additional subchronic study is not required [Guideline §82-1(b); MRID 00157377, m MRID 00157378, MRID 00232702].

c. Chronic Toxicity and Carcinogenicity

Sufficient data are available to assess the chronic toxicity and carcinogenic potential of Iprodione. Iprodione has been classified as a Group B2 carcinogen, based on evidence of tumors in both sexes of mouse [liver] and in the male rat [Leydig cell]. For the purpose of risk characterization, a low dose extrapolation model was applied to the animal data for quantification of human risk [Q^*_1 = __ 8.7×10^{-3}/__ 5.07×10^{-3} combined hepatocellular adenoma/ carcinoma (mouse) and __ 4.39×10^{-2} testicular tumors (rat)].

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

In the combined chronic toxicity/carcinogenicity study in rats, Iprodione [≈95% a.i.] was administered to 60 Sprague-Dawley rats/ sex/dose via the diet at dose levels of 0, 150, 300, and 1600 ppm [__ 6.1, 12.4, and 69/__ 8.4, 16.5, 95 mg/kg/day, respectively] for 24 months. An additional 10 rats/sex/group were administered Iprodione for 52 weeks [interim sacrifice]. There were no adverse effects on survival or clinical signs in either sex. Body-weight gains were decreased in both sexes at the high-dose level compared to the controls and overall, body-weight gains were 86% and 92% of control values in the high-dose males and females, respectively. At week 12, body-weight gain was 83.6% of the control in males and 80.7% of the control in females at the high-dose level. Food consumption was decreased slightly at this dose level in both sexes also. There were no treatment-related clinical pathology findings in either sex. At the interim sacrifice, high-dose males displayed an increase in the incidence of lesions in the adrenals, and there was an increased incidence of centrilobular hepatocyte enlargement in mid- and high-dose males. High-dose females displayed an increase in centrilobular hepatocyte enlargement and an increase in the incidence of generalized rarefaction and fine vacuolation of the zone fasciculata in the adrenals compared to the control and other dose groups. At the terminal sacrifice, increased liver weight [absolute and relative-to-body] was observed in males at the mid- and high-dose levels [dose-related]. At the high-dose level in males, testes with epididymides and thyroid weights [absolute and relative-to-body] were increased at the terminal sacrifice. At the terminal sacrifice, 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 the mid- and high-dose males. Atrophy of the seminiferous tubules in the testes, with atrophy of the prostate and absence of spermatozoa in the epididymides were observed at the high-dose level. Centrilobular hepatocyte enlargement was increased in males at the high-dose level. Adrenal lesions were observed in both sexes at the mid- and high-dose levels, although the males displayed more lesions than the females. There was an increased incidence of tubular hyperplasia in the ovaries and increased sciatic nerve fiber degeneration in the high-dose females compared to the controls. Hemosiderosis was increased in females at the mid- and high-dose levels. **The NOEL for non-neoplastic changes is 150 ppm [__ 6.1/__ 8.4 mg/kg/day], and the LOEL is 300 ppm [__ 12.4/__ 16.5 mg/kg/day], based on increases in generalized enlargement of the cells of the zona glomerulosa in males and females, in fine vacuolation of the zona fasciculata and in generalized fine vacuolation of the zone reticularis in males in the adrenal cortex, an increased incidence of interstitial cell hyperplasia, reduced spermatozoa in the epididymides, reduced secretion of the seminal vesicles, increased hemosiderosis in the spleen in females, and increased liver weight.**

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 pairwise comparison of the 1600 ppm dose group with controls for testicular tumors, which exceeds the historical control incidence [Guideline §83-5; MRID 42637801; MRID 42787001].

In an earlier 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 ppm [≈6.25 mg/kg/day], 250 ppm [≈12.5 mg/kg/day], and 1000 ppm [≈50 mg/kg/day], respectively [using standard conversion factor of 0.05]. This study is classified Unacceptable, but it was replaced by the study cited above [Guideline §83-5; MRID 00071997; MRID 00128931; MRID 001164249].

2. Chronic Toxicity Study in Dogs

In a chronic feeding study, 6 Beagle dogs/sex/group were administered Iprodione [86.5%] via the diet at dose levels of 0, 100 ppm [__ 4.1/__ 4.3 mg/kg/day], 600 ppm [__ 24.9/__ 28.3 mg/kg/day], and 3600 ppm [__ 145.3/__ 152.5 mg/kg/day] for 12 months. There were no treatment-related deaths, and no adverse effects were observed on body weight, food consumption, or clinical signs in either sex. At the high-dose level, there were increases in absolute and relative liver weight, alkaline phosphatase, SGOT, SGPT and LDH enzyme levels, and increased absolute and relative adrenal weights [both sexes]. At the mid- and high-dose levels, males displayed an increased number of erythrocytes with Heinz bodies and decreased prostate weights. **The NOEL is 100 ppm [__ 4.1/__ 4.3 mg/kg/day], and the LOEL is 600 ppm [__ 24.9/__ 28.3 mg/kg/day], based on decreased prostate weight and an increased incidence of erythrocytes with Heinz bodies** [Guideline §83-1(b); MRID 00144391; MRID 41327001].

In a second chronic feeding study designed to complement the study cited above, 6 Beagle dogs/sex/group were administered Iprodione [96.1%] via the diet at dose levels of 0, 200 ppm [__ 7.8/__ 9.1 mg/kg/day], 300 ppm [__ 12.4/__ 13.1 mg/kg/day], 400 ppm [__ 17.5/__ 18.4], and 600 ppm [__ 24.6/__ 26.4 mg/kg/day] for 12 months. There were no treatment-related deaths, and no adverse effects were observed on clinical signs, body weight/gain, and food consumption in either sex. At the high-dose level, decreases were observed in the red blood cell parameters [hemoglobin, hematocrit, and red blood cells]. **The NOEL for systemic toxicity is 400 ppm [__ 17.5/__ 18.4 mg/kg/day], and the LOEL is 600 ppm [__ 24.6/__ 26.4 mg/kg/day], based on decreased red blood cell values.** This nonguideline study is classified Acceptable. When both chronic dog studies are considered together, the **NOEL is 400 ppm [≈18 mg/kg/day]** [Guideline §83-1(b); MRID 42211101].

3. Carcinogenicity Study in Mice

In a carcinogenicity study, Iprodione [95.7% a.i.] was administered in the diet to 50 Crl: CD-1 (ICR) BR mice/sex/dose for 99 weeks at dose levels of 0, 160 ppm [__ 23/__ 27 mg/kg/day], 800 ppm [__ 115/__ 138 mg/kg/day], and 4000 ppm [__ 604/__ 793 mg/kg/day]. There was an interim sacrifice group of 15 mice/sex/group.

The statistical evaluation of mortality indicated no significant incremental changes with increasing dose in either sex, although the high-dose group displayed the highest mortality rate for both sexes. Food consumption and clinical signs were comparable among the groups for both sexes. Decreased body- weight gains [overall gain __ 86%/__ 89% of control] were observed in both sexes at the highest dose level. There was an increase in the incidence of liver tumors in both sexes at the high-dose level, which was accompanied by increases in several liver lesions [centrilobular hepatocyte enlargement/ vacuolation, area(s) of enlarged eosinophilic hepatocytes, pigmented

macrophages, centrilobular necrosis, and amyloid deposits]. SGOT and SGPT levels were elevated at the high-dose level in both sexes compared to the controls at the interim sacrifice [only time examined for these enzymes]. Liver weight was increased at the high-dose level in both sexes at both the interim and terminal sacrifices. There was an increase in the incidence of benign ovarian tumors [luteoma] in females at the high dose compared to the control incidence, which was accompanied by an increase in luteinization of the interstitial cells, corpora lutea absent, and prominent granulosa cells. There was also an increased incidence of generalized vacuolation/hypertrophy of the interstitial cells of the testes in the mid- and high-dose males compared to the controls. Dosing was considered adequate, based on an overall decrease in body-weight gain [__ 86%/__ 89% of control]. **The LOEL is 800 ppm [__ 115/__ 138 mg/kg/day], based on the increased incidence of centrilobular hepatocyte enlargement in females and the increased incidence of generalized vacuolation/hypertrophy of the interstitial cells in the testes of males. The NOEL is 160 ppm [__ 23/__ 27 mg/kg/day]** [Guideline §83-2; MRID 42825002].

In a previous chronic toxicity/carcinogenicity study in Carworth CF-1 albino mice, Iprodione was negative for carcinogenicity. The dose levels were 200 ppm [≈30 mg/kg/day], 500 ppm [≈75 mg/kg/day], and 1250 ppm [≈187.5 mg/kg/day] (using standard conversion factor of 0.15), and the duration was 18 months. Only one ovarian tumor [malignant] was reported [mid dose], and the incidence of liver tumors was as follows:

Table . Liver Tumors [# with tumor/# mice examined]

Dose/Tumor Type	Benign	Malignant	Dose/Tumor Type	Benign	Malignant
MALES			FEMALES		
0	0/60	2/60	0	0/60	0/60
200	2/59	0/59	200	0/60	0/60
500	0/60	4/60	500	1/58	2/58
1250	2/59	5/59	1250	0/59	1/59

This study is classified Unacceptable, but in has been replaced by the study cited above [Guideline §83-2; MRID 00070963].

4. Other Carcinogenic issues

Several mechanistic studies on Iprodione are available. These were submitted in support of the premise that both the liver and testicular tumors are threshold phenomena. Following review of these data, which included an Agency external peer review, along with the submission of another external peer review, it was concluded that there is no reason to deviate from the previous conclusion that the mechanistic data available on Iprodione do not provide a definitive mode of action with respect to either the Leydig cell tumors or the liver tumors.

TESTES

In an in vitro study using immature porcine cultured Leydig cells, Iprodione [99.7%] and two of its metabolites [RP36112 (99.2%) and RP36115 (96.7%)] inhibited testosterone secretion when Leydig cells were stimulated with (1) the gonadotropin hCG, (2) with drugs that enhance cAMP production [(a) cholera toxin, which stimulates Gs protein; (b) forskolin, which stimulates adenylate cyclase catalytic unit, and (3) with a cAMP analog [8-bromo-cAMP].

Because there were no effects observed on gonadotropin-stimulated cAMP production with Iprodione, it is hypothesized that the inhibition of testosterone secretion by Iprodione is downstream from cAMP production. At the next step in testosterone biosynthesis, inhibition of testosterone secretion by Iprodione was not observed when the substrate 22ROHCT was added to the culture medium, which indicates that the step that is inhibited is located between the cAMP production and the movement/penetration of cholesterol into the mitochondria. Since 22ROHCT is a cholesterol substrate that passes through the mitochondrial membrane without the need of an active transport system, the sensitive site of inhibition of testosterone synthesis by Iprodione [or RP 36115] maybe the transport/availability of cholesterol substrate for the cholesterol side chain cleavage enzyme. The RP 36112 metabolite appears to act downstream from the cholesterol step; i.e., at the level of steroidogenic enzyme 17 αhydroxylase/17, 20 lyase. Iprodione and its metabolites appear to modulate Leydig cell steroidogenesis by interfering at the level of cholesterol transport and/or steroidogenic enzyme activity. [Non-Guideline; MRID 44171901].

In another in vitro study, the objective was to determine the effect of in vitro Iprodione [99.7%] exposure on basal testosterone secretion and stimulated release from testicular sections in culture media [in vitro Endocrine Challenge Test (ECT) using human chorionic gonadotropin (hCG)]. The effects of prior in vivo exposure of the male rats via the diet [3000 ppm Iprodione for 14 days] was also evaluated. Testicular sections obtained from 12 male CD® Sprague-Dawley rats administered Iprodione via the diet for 14 days at dose levels of 0 ppm or 3000 ppm were incubated with 0, 1, 10, or 100 μg/ml Iprodione for one hour. Half of these testicular sections from each in vitro treatment group were challenged with human chorionic gonadotrophin and the other half of the sections were monitored for basal testosterone secretion. Media testosterone concentrations were monitored at hourly intervals for 3 hours after challenge. There was a dose-related reduction in testosterone secretion from testicular sections incubated in vitro with Iprodione, with and without hCG stimulation. Prior exposure of the rats to Iprodione in vivo for 14 days appeared to have little effect on the secretion of testosterone, with and without hCG stimulation, from testicular sections incubated in vitro other than a slight increase initially. At sacrifice following the 14-day exposure period to Iprodione in vivo, plasma LH concentrations were significantly increased compared to the control and, although plasma testosterone was not significantly affected, the levels were somewhat increased compared to the control [132% of control]. The significant increase in plasma LH at necropsy suggests a possible stimulation of the homeostatic mechanism. Under the conditions of this 14-day study, Iprodione was shown to produce a reduction in testosterone secretion from testicular sections following incubation in vitro with Iprodione. Prior exposure of male rats to Iprodione in vivo via the diet for 14 days did not alter the reduction in testosterone secretion observed in their testicular sections exposed to Iprodione in vitro. Although the in vitro inhibition appeared to be dose-related, it appears that a maximum response may have occurred between the 10 and 100 μg/mL dose levels. The data presented provide pieces to the "puzzle" but not a complete picture of what may be occurring in the testes/rat that ultimately results in testicular tumors. Although it appears that the premise is that Iprodione produces testosterone biosynthesis inhibition, resulting ultimately in the increased incidence of Leydig cell tumors, there are inconsistencies in the in vitro and in vivo data, and the in vitro effects observed in the short-term studies to date have not been demonstrated to occur in long-term studies, nor is it clear that the levels

at which the in vitro effects were observed are attained in vivo. [Non-Guideline; MRID 44171903].

In an in vivo study, no changes in testicular function, as assessed by measuring testosterone levels in plasma and testicular homogenates from 15 male Sprague-Dawley rats administered Iprodione [97.3%] via the diet at doses levels of 0 ppm and 3000 ppm for 2, 7 or 14 days, were observed. Decreased body weight [95% of control after 2 days, 90-91% of control after 7 days, and 87% of control after 14 days], body-weight gain [negative gain after 2 days, 32% of control after 7 days, 44% of control after 14 days], and food consumption were observed following all exposure intervals. Organ-weight effects included decreased absolute liver, kidney, epididymis, and total accessory sex organs [TASO]; increased absolute and relative adrenal; and decreased relative TASO. The objective of this study was to assess the effects of in vivo Iprodione exposure on plasma and testicular homogenate testosterone concentrations in the male rat following a human chorionic gonadotrophin [hCG] Endocrine Challenge Test (ECT). There were no significant differences in either peripheral plasma or testicular homogenate testosterone levels observed in samples collected one hour after human chorionic gonadotrophin [hCG] challenge. Under the conditions of this study, Iprodione did not produce alterations in testicular function following dietary exposure at 3000 ppm for up to 14 days [Non-Guideline; MRID 44171904].

In a mechanistic study in male rats designed to (a) assess the competitive binding affinity of Iprodione to the androgen receptor; (b) establish an effective dose and dosing regimen and quantify testosterone, luteinizing hormone [LH], follicle-stimulating hormone [FSH], and estradiol concentrations in a single plasma sample; and (c) describe testosterone, LH, and FSH profiles during a 4-hour baseline occurring after 30 days of Iprodione exposure, Iprodione was shown to have poor binding affinity to the androgen receptor following exposure at very high dose levels. LH and FSH concentrations were increased after 15 days exposure but not after 30 days of exposure to Iprodione. At necropsy, testosterone concentrations were comparable between the Iprodione and the pair-fed rats, and estradiol concentrations were increased at necropsy following 30 days of exposure. A marked increase in adrenal weights was accompanied by histopathological lesions [vacuolation] indicative of an alteration of steroidogenesis was observed following the 30-day exposure period. Although there was some evidence to suggest that Iprodione interferes with sex/steroid hormone regulation, the difference in the spectrum of effects observed between Iprodione and Flutamide in this study indicate that the two compounds share only certain parts of a mechanism of toxicity/carcinogenicity. [Non-Guideline; MRID 43535002; MRID 44203401].

In an in vitro study using porcine cultured Leydig cells, Iprodione [99.7%] and two of its metabolites were shown to inhibit gonadotropin-stimulated testosterone secretion in a concentration range of 1-10 μg/mL. Inhibition by Iprodione was observed after short-term exposure [3 hours], and the inhibitory effects were similar to those observed with the fungicide Ketoconazole. The inhibitory effects do not appear to be related to Leydig cell damage because the removal of Iprodione from the culture medium for 72 hours resulted in the recovery of the cells ability to secrete testosterone following hCG stimulation. There was no discussion as to how the concentrations of Iprodione used in this study relate to the levels attained within the testicular cells following oral dosing in the rat carcinogenic study where testicular tumors were observed. [Non-Guideline; MRID 43830601].

LIVER

In a 3-day and 14-day oral exposure study, groups of CD1 male mice [15/dose/group/chemical; 7 weeks old on arrival] were administered (1) **IPRODIONE** via the diet at dose levels of 4000 ppm [696 mg/kg/day] or 12000 ppm [2138 mg/kg/day]; (2) **KETOCONAZOLE** via the diet at a dose of 2000 ppm [341 mg/kg/day]; (3) **PHENOBARBITAL** via gavage at a dose level of 75 mg/kg/day; and (4) **CYPROTERONE ACETATE** via gavage at a dose level of 40 mg/kg/day. The control for the dietary studies was basal diet, and 0.5% methylcellulose was the control of the gavage studies. The objective of the study was to examine the potential liver effects of Iprodione in mice and to compare these effects with those produced by well characterized liver enzyme inducers and/or rodent liver carcinogens. Ketoconazole was selected as a positive control for its potential to inhibit testosterone secretion; Phenobarbital and Cyproterone acetate were selected for their potential to induce early liver changes and subsequent liver tumor formation in rodents. All of the liver effects produced by Ketoconazole, Phenobarbital, and/or Cyproterone acetate [increases in liver weight, alanine aminotransferase, aspartate aminotransferase, # hepatocytic mitoses, total cytochrome P-450 content, staining for isoforms CYP 2B and CYP 3A, benzoxyresorufin [BROD], ethoxyresorufin [EROD], pentoxyresorufin [PROD] enzyme activities, and hepatocyte proliferation, in addition to increases in the incidence of liver enlargement, centrilobular hypertrophy, diffuse hypertrophy, centrilobular/midzonal fine vacuolation] were exhibited by Iprodione at 12000 ppm. An effect observed following Iprodione exposure that was not observed following any of the other test material exposures was an increase in lauric acid hydroxylation. Although several of the effects observed in the liver following Iprodione exposure are analogous to those observed following the positive controls, especially Phenobarbital [centrilobular hypertrophy, liver weight, increased BROD, PROD, and EROD activities, cell proliferation after 3 days], in several cases the liver effect observed was most pronounced in the Iprodione mice compared to the positive controls [centrilobular/midzonal fine vacuolation, increased number of mitoses, cell proliferation at day 15].
This study demonstrates that Iprodione, at dose levels that are 5- and 15-fold greater than the LOEL for liver effects observed in the mouse carcinogenicity study, induces (1) liver cell proliferation, (2) increased microsomal enzyme activities, (3) an increase in total cytochrome P-450 content, and (4) centrilobular hypertrophy. These observations most closely resemble the pattern of liver effects observed following Phenobarbital exposure. Hepatocytic hypertrophy was observed at the high-dose level of Iprodione following both the 3- and 14-day exposure periods but only following the 14-day exposure period at the low dose. Liver cell proliferation was observed after both the 3-day and 14-day exposure periods at both dose levels of Iprodione. Increased cytochrome P-450 content and increased microsomal enzyme activities were observed at both dose levels of Iprodione following the 14-day exposure period, but neither analysis was performed following the 3-day exposure period. The dose level where liver tumors were observed in the mouse carcinogenicity study [604 mg/kg/day] is comparable to the low dose used in the current study. The findings in this study support the Registrant's arguments that the liver tumors observed in the Iprodione mouse carcinogenicity study may be secondary to liver toxicity. However, several pieces of data are lacking. The current study does not address whether cytochrome P-450 content and the microsomal enzyme activities are increased initially [after the 3-day exposure period]; therefore, one cannot determine whether the cell proliferation and hepatocytic hypertrophy observed after 3-days exposure to Iprodione is due to a direct effect of

Iprodione on the liver or the result of adaptive processes. Additionally, the current study does not identify a NOEL for the liver effects monitored over a 14-day exposure period or address the question of whether these liver effects occur initially at the lower doses utilized in the mouse carcinogenicity study. Another outstanding question is whether the liver effects [hepatocytic hypertrophy, increased total cytochrome P-450 content, increased microsomal activities, cell proliferation] observed in the current study persist throughout a long-term exposure. It is to be noted that Phenobarbital produces a short-term increase in hepatocyte proliferation that is not sustained [Jirtle, et al. 1991, Standeven and Goldsworthy, 1993]. In a paper on proliferation and liver tumor development [CIIT Activities, vol. 15 (8), August, 1995], it is stated that the proliferative response seen after acute exposure does not always reflect the proliferative response observed after chronic exposure [Non-Guideline; MRID # 44171902]].

Based on these mechanistic studies, it is concluded that the data available do not provide a definitive mode of action with respect to either the Leydig cell tumors or the liver tumors.

d. Reproduction and Developmental Toxicity Studies

1. Two-Generation Reproduction Study in Rats

In a 2-generation reproduction study, 28 Crl:CD®BR/VAF/PLUS rats/sex/group were administered Iprodione [96.2%] via the diet at dose levels of 0, 300 ppm [__ 18.5/__ 22.5 mg/kg/day], 1000 ppm [__ 61.4/__ 76.2 mg/kg/day], and 3000/2000 ppm [__ 154.8/__ 201.2 mg/kg/day] for two generations [2 litters per generation]. **The systemic maternal/parental NOEL was 300 ppm [__ 18.5/__ 22.5 mg/kg/day], and the LOEL was 1000 ppm [__ 61.4/__ 76.2 mg/kg/day], based on decreased body weight, body-weight gain, and food consumption in both sexes and both generations. The reproductive [offspring] NOEL was 1000 ppm [76.2 mg/kg/day], and the reproductive [offspring] LOEL was 2000 ppm [201.2 mg/kg/day], based on decreased pup viability [as evidenced by an increased number of stillborn pups and decreased survival during postnatal days 0-4], decreased pup body weight throughout lactation, and an increased incidence in clinical signs in pups during the lactation period [smallness, reduced mobility, unkempt appearance, hunching, and/or tremors]** [Guideline §83-4; MRID 00162983; MRID 41871601].

2. Developmental Toxicity Study in Rats

In a developmental toxicity study, 20 pregnant Sprague-Dawley CD rats [mated 1:1] were administered Iprodione [94.2%] at dose levels of 0 [0.5% methylcellulose], 40, 90, and 200 mg/kg/day via gavage from day 6 through 15 of gestation. On day 20 of gestation, the dams were sacrificed via CO_2 inhalation. There were no deaths. Body weights were comparable among the groups. There were no significant differences observed in the mean number of viable fetuses, implantations, corpora lutea, resorptions, and pre- and postimplantation losses were comparable among the groups. There was no evidence of maternal toxicity at any dose level. **The developmental NOEL was 90 mg/kg/day, and the developmental toxicity LOEL was 200 mg/kg/day, based on delayed fetal development [slightly reduced fetal body weight and increased incidences of space between the body wall and organs in the fetuses].** [Guideline §83-3(a); MRID 00162984; MRID 40514901].

In a prenatal developmental toxicity study, 25 naturally-mated female Sprague-Dawley Crl: CD [SD] BR rats/group were the administered Iprodione [97.1% a.i.] via gavage at dose levels of 0 [methylcellulose], 20, 120, and 250 mg/kg/day from days 6 through 19 of gestation. Three deaths occurred at the high-dose level during days 18-20, and the early sacrifice of 6 additional high-dose dams occurred during days 15-20 due to the severity of clinical signs [prostration, reduced motor activity, and facial/urogenital staining]. All dams in the other groups [except one vehicle control dam on day 11] survived until study termination. Clinical signs observed included staining of the skin/fur in the facial and anogenital area in three mid-dose dams [12%] and in all of the high-dose dams [100%], prostration in six high-dose dams, reduced/no motor activity in 10 high-dose dams, and staggering step in one high-dose dam. At the high-dose level, body weight was 90% of the control value on day 20 of gestation. Body-weight gains were significantly decreased at the mid- [77% of control] and high-dose [59% of control] Iprodione levels throughout the dosing period, and the corrected body weight [89% of control at the high dose] and corrected body-weight gain [71% (mid-dose)/30% (high-dose) of control] were decreased significantly compared to the vehicle control. Food consumption was decreased at the high-dose Iprodione level from day 9, with the magnitude of the decrease increasing with time. There were no treatment-related gross pathology findings at the low-dose level, but there was a dose-related increase in enlarged adrenals at the mid- and high-dose levels at study termination. There were no abortions or premature deliveries, and no dams had 100% intrauterine deaths. All surviving dams had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, and live fetuses per dam among the groups. Only the high dose Iprodione group had dead fetuses [15 in one litter]. There was no significant increase in pre- or postimplantation losses, but the high-dose Iprodione group displayed an increase in late resorptions compared to the control group and postimplantation loss was approximately double that of the control [13.5% vs 6.8%]. The percent males was slightly greater at the high-dose level [56%] compared to the control [48%] and other dose groups [46%-48%], and fetal body weights were significantly decreased at the high-dose Iprodione level [__ 85%/__ 86% of control] compared to the control. There was no treatment-related increase in the incidence of any external malformation [only malformation found was in a mid-dose Iprodione pup (cleft palate, partial)]. At the high-dose level, there was an increase in the number of runts and in the number of litters with runts compared to the vehicle and positive controls and the low- and mid-dose groups. Anogenital distance [AGD] was decreased significantly in the mid- and high-dose Iprodione group males [dose-related] compared to the vehicle control males. A similar decrease was noted in the mid- and high-dose Iprodione males when anogenital distance was divided by fetal body weight taken to the 1/3 power. Additionally, statistical significance was attained for the covariance analyses using fetal body weight and the cubed root of fetal body weight as covariate factors [MRID 44422101]. Iprodione was toxic to the maternal rats at a dose level of 250 mg/kg/day, as evidenced by the death of 3/early sacrifice of 6 of the 25 high-dose dams and decreased corrected body-weight gain [30% of control].

The maternal NOEL is 20 mg/kg/day, the LOEL is 120 mg/kg/day, based on decreased body-weight gain and decreased food efficiency. At the high-dose level [250 mg/kg/day], deaths occurred [9 out of 25] in addition to decreased body-weight gain and food consumption/efficiency. The developmental toxicity NOEL is 20 mg/kg/day, and the developmental toxicity LOEL is 120 mg/kg/day, based on decreased anogenital distance in the males Iprodione pups. This perturbation in sexual development is independent of overall reductions in

fetal growth.

This nonguideline [§83-3(a)] prenatal developmental toxicity study in the rat is classified Acceptable. However, this study cannot satisfy the guideline requirements [§83-3] since neither visceral nor skeletal fetal examinations were performed.

3. Developmental Toxicity Study in Rabbits

In a developmental toxicity study, 18 artificially inseminated New Zealand female rabbits were administered Iprodione [95.0-99.3%] at dose levels of 0 [0.5% aqueous methylcellulose], 20, 60, and 200 mg/kg/day via gavage from day 6 through 18 of gestation. On day 29 of gestation, the does were sacrificed. Seven high-dose does aborted between days 17 and 23 of gestation, and prior to aborting all had displayed decreased urination and defecation. One mid-dose doe [day 28] and one control doe [day 20] also aborted. All other does survived until study termination, and nine of the high-dose does that did not abort displayed decreased urination and defecation. During the dosing period, the mid-dose does gained less weight than the control, and the high-dose does lost weight. A negative net body-weight gain was observed at the mid- and high-dose levels. The high-dose does displayed decreased food consumption during the dosing period. Gravid uterine weight was decreased at the high-dose level [90% of control] compared to the control. **The maternal NOEL is 20 mg/kg/day, and the maternal LOEL is 60 mg/kg/day, based on decreased body-weight gain. At the highest dose tested [200 mg/kg/day], maternal toxicity was demonstrated by an increased rate of abortions [7 does], body-weight loss, decreased food consumption, and decreased defecation and urination in females that aborted. The developmental toxicity NOEL was 60 mg/kg/day, and the developmental toxicity LOEL was 200 mg/kg/day, based on an increased incidence of skeletal variations [13th full rib, malaligned sternebrae, and/or 27 presacral vertebrae, with or without delayed ossification].** [Guideline §83-3(b); MRID 00155469].

e. Mutagenicity Studies

Sufficient data are available to satisfy data requirements for mutagenicity testing [§84-2]. Overall, the data do not demonstrate any consistent evidence for a genotoxic concern for Iprodione.

1. Gene Mutation

Iprodione was **negative** for induction of reverse gene mutations at the histidine locus in Salmonella typhimurium strains TA 98, TA 100, TA1535, TA 1537, and TA 1538, both in the presence and absence of S9 activation. There was sufficient cytotoxicity, as evidenced by reductions in mean numbers of revertants and background lawn, at the highest dose in the absence of S9, and a slight to moderate precipitate was observed at doses ≥ 250 μg/plate in the presence and absence of S9. In the presence of S9, Iprodione was assayed to the limit dose [Guideline §84-2; MRID 41604106].

Iprodione **did not induce mutation with or without metabolic activation** in the in vitro forward gene mutation [CHO/HGPRT] assay at adequate dose levels [Guideline §84-2; MRID 00148206].

2. Chromosomal Aberration Assay

Iprodione was **negative** in an in vitro chromosomal aberration assay in Chinese hamster ovary [CHO] cells both in the presence and absence of metabolic activation at adequately high dose levels [doses of 40, 150, 400 μg/mL with; doses of 15, 75, 150 μg/mL without S9]. There was precipitation at exposure levels ≥150 μg/mL both with and without S9. [Guideline §84-2; MRID 00148207].

In an in vivo mouse micronucleus assay, 5 CD-1 mice/sex/group were administered Iprodione [96.1%] suspensions [1% aqueous methylcellulose] via oral gavage once at dose levels of 750, 1500, and 3000 mg/kg. Bone marrow cells were collected for micronucleated polychromatic erythrocytes [MPEs]. One male and eight females died at the high dose, and signs of toxicity at this dose level included piloerection, hunched posture, ptosis, lethargy, and coma. Dose-related cytotoxic effects on the target tissue were also seen at 48 hours postdose; the response was significant at the high dose. The positive control induced the expected high yield of MPEs in both sexes. **There was no evidence of a clastogenic or aneugenic effect at any dose or harvest time** [Guideline §84-2; MRID 43535001].

3. Other Genotoxic Effects

Iprodione was **negative in a sister chromatid exchange assay in Chinese hamster ovary cells both with and without metabolic activation** [Guideline §84-2; MRID 00148209].

Iprodione was tested against 19 strains [including 2 wild type] of Bacillus subtilis both with and without metabolic activation at dose levels of 20.6-1670 μg/disc. Iprodione was **positive both with and without metabolic activation** [Guideline §84-2; MRID 00148208].

f. Metabolism

Sufficient data are available on the metabolism of Iprodione in the rat.

^{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/day] doses. Peak blood levels were observed at 4 and 2 hours, respectively, in the low-dose males and females and at 6 hours in the high-dose rats of both sexes. The elimination of ^{14}C from the blood was slower in males than in 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 ≤ 0.5% of the total amount administered. It is to be noted that the testes of the low-dose males [both single and repeat] 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/day. 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 dealyklated 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 than that of the males. Several urinary metabolites were not identified. The feces contained much larger amounts of unchanged parent 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%] were major routes of excretion, and the majority of the radiolabel was excreted within the first 24 hours post dose in both sexes. Approximately 80% of the 24-hour urine sample radiolabel [≈24% of the dose] and ≈91% of the 24-hour fecal radiolabel [≈49% of the dose] were characterized. Overall, ≈72% of the dose was identified, which accounted for nearly 90% of the total radiolabel found in the samples. 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; 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 [Guideline §85-1; MRID 41346701; MRID 42984101; MRID 43484901].

g. Dermal Penetration Study

In a dermal penetration study, 4 male Crl: CD®BR rats/group/time point were exposed dermally to a single dose of Iprodione at dose levels of 0.4, 4.0, and 40 mg/rat for 0.5, 1, 2, 4, 10, and 24 hours. Skin residues increased with the duration of exposure to 5-10% of the applied dose, although there was no apparent dose response. The portion of the test material absorbed increased with the duration of exposure to 7.41%, 3.16%, and 0.19% of the applied dose at 0.4, 4.0, and 40 mg/rat, respectively. Absorption appears to be saturated at the two highest dose levels. Following a 10-hour exposure period, ≈5% Iprodione is absorbed [Guideline §85-2; MRID 43535003].

g. Toxicity Endpoint Selection for Risk Assessment

An acute dietary risk assessment is required for females 13+ years. No appropriate endpoint was determined for all population groups, including infants and children, and a separate acute dietary risk assessment for this group is not required. The **acute dietary risk assessment** for **females 13+ years of age** should be based on the developmental toxicity study in rats in which the developmental NOEL was 20 mg/kg/day and the developmental LOEL was 120 mg/kg/day, based on decreased anogenital distance in male fetuses exposed to Iprodione *in utero*.

For the **short term [1-7 days] and intermediate term [1 week to several months] dermal occupational/residential exposure risk assessments**, no appropriate endpoint or dose of concern was identified, based on the 21-day dermal toxicity study in which no systemic or dermal toxicity was demonstrated at the limit dose [1000 mg/kg/day]. Neither of these assessments is required.

Inhalation Exposure. Except for an acute inhalation toxicity study [MRID 42946101], no other inhalation studies are available. Based on the LC50 of > 5.16 mg/L, Iprodione is placed in Toxicity Category IV. Based on the use pattern, there is potential for exposures *via* this route and thus inhalation risk assessments are required for short-term and intermediate-term exposure scenarios. The Hazard Identification Committee determined that a **long-term inhalation exposure risk assessment** was not required.

Because of the lack of appropriate inhalation studies, the selected oral NOEL of 20 mg/kg/day [based on decreased anogenital distance in male fetuses] for **Short-Term** and 6.1 mg/kg/day [based on histopathological changes in the male reproductive system and effects on the adrenal glands [both endpoints of concern] in both sexes at 12.4 mg/kg/day] for **Intermediate-Term** should be used for these exposure risk assessments. Since the doses identified for inhalation risk assessments are from oral studies [i.e., use of oral NOEL], the risk assessment should follow the appropriate route-to-route extrapolations, as shown below.

Step 1: The inhalation exposure component [i.e., mg/L] using a 100% absorption rate [default value] should be converted to an **equivalent oral dose** [mg/kg/day]. Step 2: The converted dose from Step 1 should then be compared to the oral NOEL of 20 mg/kg/day for **Short-Term** and 6.1 mg/kg/day for **Intermediate** exposures to calculate the Margins of Exposure.

The **chronic occupational/residential exposure [several months to lifetime] risk assessment** is required and should be based on the chronic rat feeding study [on which the RfD is based]. The systemic NOEL is 6.1 mg/kg/day, based on histopathological changes in the male reproductive system and effects on the adrenal glands [both endpoints of concern] in both sexes at 12.4 mg/kg/day. Since the NOEL is from an oral study, a dermal absorption factor of 5% should be used for risk assessment. The risk assessment is appropriate only for the non-carcinogenic effects. For carcinogenic effects, the Q^*_1 should be used.

h. Consideration of FQPA Issues for Iprodione

Under the Food Quality Protection Act [FQPA], P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA] and the Federal Food, Drug and Cosmetic Act [FFDCA], the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for Iprodione was evaluated by the Hazard Identification Committee.

Adequacy of data package: An acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits have been submitted to the Agency, meeting basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. A postnatal study in rats was required by the Agency [RfD meeting of April 12, 1994] but to date has not been submitted. In a recent prenatal sex differentiation study in rats, no increase in susceptibility was demonstrated, but the male fetuses displayed a decrease in anogenital distance. Following a weight-of-the-evidence review, the Hazard Identification Committee did not recommend that a developmental neurotoxicity study in rats be required. There are no identified data gaps for the assessment of potential effects on offspring following *in utero* and/or postnatal exposure to Iprodione under the old guidelines. However, there are outstanding questions with regard to postnatal exposure that remain to be address in light of the observed effects of Iprodione on the testes and its proposed mode of action [disruption of testosterone biosynthesis]; aspects that can be addressed in the required postnatal exposure study, using the new 2-generation reproduction study guidelines for assessing sperm parameters.

Susceptibility issues: The prenatal developmental toxicity study in rabbits and the two-generation reproduction study in rats demonstrated no indication of increased sensitivity to *in utero* and/or postnatal exposure to Iprodione. In these studies, maternal and parental NOELS were lower than or equal to developmental or offspring NOELs. In the prenatal developmental toxicity study in rats, however, developmental effects in the fetuses [a slight dose-related decrease in fetal body weight and increased incidence of fetuses with a space between the body wall and the internal organs] were noted in the absence of maternal toxicity. It is noted that the fetal findings were suggestive of fetal toxicity but not conclusive of fetal toxicity. Fetal weights were not altered in a statistically-significant manner and were well within historical values. The incidence of space between the body wall and organs was also not apparently statistically significant. This finding may have been supportive [as were the c-section observations of "small fetus"] of weight decrements in fetuses at the LOEL, but it could also be an artifact of

preservative techniques.

Based on the weight-of-the-evidence of all available studies, it was concluded that there was no increased susceptibility to rat and rabbit fetuses following *in utero* and/or postnatal exposure to Iprodione.

1. There were no data gaps for the standard assessment of potential effects on offspring following *in utero* and/or postnatal exposure to Iprodione.

2. Although the data from the prenatal developmental toxicity study in rabbits and the two-generation reproduction study in rats demonstrated no indication of increased sensitivity to *in utero* and/or postnatal exposure to Iprodione, apparent sensitivity to prenatal exposure with Iprodione was observed in the prenatal developmental toxicity study in rats. However, the fetal findings identified by this study were marginal and not statistically significant, within ranges of historical control values, and were not supported by data from other studies. Therefore, due to the lack of confidence in these data, the findings of the prenatal develpmental toxicity study in rats were not judged to be an appropriate measure of potential sensitivity following *in utero* exposure to Iprodione.

Uncertainty factor: The application of an FQPA factor to ensure the protestion of infants and children from exposure to Iprodione, as required by FQPA, will be determined during risk characterization.

i. Reference Dose [RfD]

The RfD for Iprodione was established at 0.06 mg/kg/day, based on a NOEL of 6.1 mg/kg/day in a chronic toxicity study in rats [MRID 42637801]. The LOEL was 12.4 mg/kg/day in males and 16.5 mg/kg/day in females, based on histopathological lesions in the male reproductive system, generalized enlargement of the cells of the zona glomerulosa in males and females, and rarefaction and fine vacuolation of the zona fasciculata in the adrenal cortex in males. An uncertainty factor of 100 was applied to account for both inter-species extrapolation and intra-species variability. The Health Effects Division-Hazard Identification Committee concurred with these conclusions reached by the Health Effects Division-RfD/Peer Review Committee. It should be noted that this chemical has been reviewed by the FAO/WHO Joint Committee Meeting on Pesticide Residues [JMPR] and that an acceptable daily intake [ADI] of 0.3 mg/kg/day was established by the World Health Organization [WHO] in 1977 and was then revised in 1992 [0.2 mg/kg/day].

REFERENCES

MRID No.

00070963 Hastings, S.E.; Kiggins, E.M.; Page, J.G.; et al. (1978). Chronic Toxicologic and Carcinogenic Study with RP 26019 in Mice. Report No. SEH 75:133. Unpublished study submitted by Rhône-Poulenc Chemical Co..

00071997 Hastings, S.E.; Kiggins, E.M.; Page, J.G.; et al. (1978). Chronic Toxicologic and Carcinogenic Study with RP 26019 in Rats. Report No. SEH 76:57. Unpublished study submitted by Rhône-Poulenc Chemical Co..

00128931 Brooks, P. and Roe, F. (1983). Two Year Chronic Oral Toxicity Study with Antor Technical in Albino Rats: Grading of Histopathological Lesions. FBC Report Tox/83/178-2. Unpublished study prepared by FBC Limited, England.

00144391 Broadmeadow, A. (1984). Iprodione: 52-Week Toxicity Study in Dietary Administration to Beagle Dogs: Final Report. LSR Report No. 84/RH0022/179. Unpublished study prepared by Life Sciences Research, Ltd.

00148206 Godek, E. (1985). CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay: Iprodione: Final Report. Study No. PH 314-B0-001-84. Unpublished study prepared by Pharmakon Research International, Inc.

00148207 SanSebastian, J. (1985). CHO Metaphase Analysis In Vitro Chromosome Aberration Analysis in Chinese Hamster Ovary Cells (CHO): Final Report: PH 320-B0-001-84. Unpublished study prepared by Pharmakon Research International, Inc.

00148208 Worthy, B. (1985). DNA Damage in Bacillus Subtilis with Iprodione Technical: Final Report; Project No. 2214. Unpublished study prepared by Borriston Labs, Inc.

00148209 SanSebastian, J. (1985). In Vitro Sister Chromatid Exchange in Chinese Hamster Ovary Cells (CHO): Final Report: PH 319-B0-001-84. Unpublished study prepared by Pharmakon Research International, Inc.

00155469 Rodwell, D. (1985). A Teratology Study in Rabbits with Iprodione: Final Report. Project No. WIL-21028. Unpublished study prepared by WIL Research Laboratories, Inc.

00157377 Centre de Recherche et d'Elevage des Oncins (1976). # Month Study of Toxicity of 26,019 RP Orally in the Dog: 731008. Unpublished study.

00157378 Ganter; Girard, M. (1977). Product 26 019 R.P.: Histological Examination of Ocular Toxicity in Dog after Three Months Treatment: 19357. Unpublished study prepared by Rhône-Poulenc, Inc..

00162983 Tesh, J.; McAnulty, P.; Deans, C. (1986). Iprodione (Technical Grade): Effects of Oral Administration upon Pregnancy in the Rat. 1. Dosage Range-Finding Study. LSR Report No. 85/RHA063/752. Unpublished study prepared by Life Science Research.

00162984 Tesh, J.; McAnulty, P.; Deans, C.; et al. (1986). Iprodione (Technical Grade): Teratology Study in the Rat. LSR Report No. 85/RHA064/765. Unpublished study prepared by Life Science Research.

00164249 Microscopy for Biological Research, Ltd. (1978). Chronic Toxicologic and Carcinogenic Study with RP 26019 in Rats. Project No. CH-41, Report No. SEH 76:57. Unpublished study submitted by Rhône-Poulenc Chemical Co.

00232702 Beurlet, J. and Goldman, C. (1978). Three-month study of Toxicity of RP 26019 Orally in the Dog. Report No. IC-DREB 731008. Unpublished study submitted by Rhône Poulenc.

40514901 Tesh, J.; McAnulty, P.; Lambert, E.; et al. (1987). Iprodione (Technical Grade): Teratology Study in the Rat: Supplementary Litter Data. Laboratory Identification No.: 87/RHA064/755. Unpublished study prepared by Life Science Research.

40567601 Plutnick, R. (41987). Iprodione (Technical) - Acute Dermal Limit Test in the Rabbit; Project No. 209806/MRD-87-098. Unpublished study prepared by Exxon Biomedical Sciences, Inc.

40567602 Trimmer, G. (1987). Iprodione (Technical)--Dermal Sensitization Test in the Guinea Pig (Buehler Method); Project No. 209821/MRD-87-098. Unpublished study prepared by Exxon Biomedical Sciences, Inc.

41327001 Blacker, A. and Broadmeadow, A. (1989)> Iprodione: 52 Week Toxicity Study in Dietary Administration to Beagle Dogs - Addendum to Study Assigned MRID N. 00144391. Lab. Project No. NS 12/14. Unpublished study prepared by Life Sciences Research, Ltd. in association with Rhône-Poulenc Ag Co.

41346701 Hallifax, D. (1989). Iprodione: Absorption, Distribution, Metabolism and Excretion Study in the Rat. Project No. 89/rpm005/1013. Unpublished study prepared by Rhône-Poulenc Ag Co..

41604106 Lawlor, T. and Valentine, D. (1990). Mutagenicity Test on Iprodione (Technical) in the Salmonella/Mammalian Microsome Assay: Final Report. Lab Project No. HLA 11092-0-401R. Unpublished Study prepared by Hazelton Laboratories America, Inc..

41867301 Bonnette, K. (1991). Primary Eye Irritation Study in Rabbits with Iprodione: Final Report. Project No. 3147/109. Unpublished study prepared by Springborn Laboratories, Inc.

41867302 Bonnette, K. (1991). Primary Skin Irritation Study in Rabbits with Iprodione: Final Report. Project No. 3147/108. Unpublished study prepared by Springborn Laboratories, Inc.

41871601 Henwood, S. (1991). Two-Generation Reproduction Study with Iprodione Technical in Rats: Final Report. Project No. HLA 6224-154. Unpublished report prepared by Hazleton Laboratories America, Inc.

42023201 Siglin, J. (1991). 21-Day Dermal Toxicity Study in Rabbits with Iprodione Technical: Final Report. Project No. 3147.107. Unpublished study prepared by Springborn Laboratories, Inc.

42211101 Kangas, L. (1991). A 52 Week Dietary Toxicity Study of Iprodione in the Beagle Dog. Lab Project No. 84296. Unpublished study prepared by Bio-Research Labs., Ltd.

42306301 Cummins, H. (1989). Iprodione: Acute Oral Toxicity Study in the Rat. Project No. RHA/255:89/RHA155/0391. Unpublished study prepared by Life Science Research Ltd.

42524601 Blacker, A.; and Bars, R. (1992). Additional Data to Support MRID No. 40567602: Dermal Sensitization Study with Iprodione. Project No. RB/AB-92. Unpublished study prepared by Rhône-Poulenc Ag Co..

42637801 Chambers, P.; Crook, D.; Gibson, W.; et al. (1992). Iprodione: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats. Project No. RNP 346/920808. Unpublished study prepared by Rhône-Poulenc Agrochimie and ADME Bioanalyses.

42787001 Larochelle, D. (1993). Letter Sent to B. Chambliss and K. Davis dated May 12, 1993: (Histopathology from Oncogenicity Study of Iprodione in Rats). Prepared by Rhône-Poulenc AG Co..

42825002 Chambers, P.; Crook, D.; Gibson, W.; et al. (1993). Iprodione: Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice. Project No. RNP 359/921240. Unpublished study prepared by Rhone-Poulenc Agrochimie, Huntingdon Research Centre Ltd and ADME Bioanalyses.

42946101 Nachreiner, D. (1993). Iprodione: Acute Dust Inhalation Toxicity Study in Rats. Project No. 93N1216. Unpublished study prepared by Bushy Run Research Center, Union Carbide.

42960701 Fryer, S.; Duckworth, J.; Gibson, W.; et al. (1993). Iprodione Sub-Acute Toxicity to Rats by Dietary Administration for 13 Weeks: Amended Report. Project No. RNP 322/90767. Unpublished study prepared by Hazleton Europe.

42984101 D'Souza, G. (1993). (Carbon 14)-Iprodione: Absorption, Metabolism and Excretion in the Rat: Addendum to MRID 41346701. Project No. 198/61-1011:198/61:P7558D Unpublished study prepared by Hazleton Europe.

43484901 Fisher, P. (1994). (Carbon 14)-Iprodione: Absorption, Metabolism and Excretion in the Rat: Supplementary Response to MRID #42984101 and #41346701. Project No. 600450. Unpublished study prepared by Rhône-Poulenc Ag Co.

43535001 Proudlock, R. and Elmore, E. (1994). Iprodione: Mouse Micronucleus Test: Final Report. Lab Project No. RNP 442/941483: RPA/IPR/94031. Unpublished study prepared by Huntingdon Research Centre, Ltd. and ADME Bioanalysis.

43535002 Fail, P.A.; Anderson, S.A.; and Pearce, S.W. (1994). Toxicity Testing of a Fungicide, Iprodione, in Adult Male CD® Sprague-Dawley Rats. (Part I): Chemistry Binding and Dose-Range Finding in Adult Male CD® Sprague-Dawley Rats Exposed to Oral Iprodione; (Part II): 30-Day Endocrine Toxicology Screen in Adult Male CD® Sprague-Dawley Rats Exposed to Oral Iprodione. RTI Identification # 65C-5703. Unpublished study prepared by Laboratory of Reproductive Endocrinology Center of Life Sciences and Toxicology Chemistry and Life Sciences Research Triangle Institute.

43535003 Cheng, T. (1994). Dermal Absorption of (Carbon 14)- Iprodione (ROVRAL 4F) in Male Rats: (Preliminary and Definitive Phases): Final Report. Lab Project No. HWI 6224-208. Unpublished study prepared by Hazleton Wisconsin, Inc.

43830601 Benahmed, M. (1995). Effects of Iprodione and Its Metabolites on Testosterone Secretion in Cultured Leydig Cells. Report INSERM/U407/95001. Unpublished study prepared by Communication Cellulaire en Biologie de la Reproduction. Laboratoire de Biochimie, France.

44171901 Benahmed, M. (1996). Effects of Iprodione and Its Metabolites RP 36112 and RP 36115 on Testosterone Secretion in Cultured Leydig Cells: Sites of Action. Project No. INSERM U 407. Unpublished study prepared by Communication Cellulaire en Biologie de la Reproduction. Laboratoire de Biochimie, France.

44171902 Bigot, D. (1996). Iprodione Exploratory 14-Day Toxicity Study in the Mouse by Dietary Administration. Project No. SA 95131. Unpublished study prepared by Rhône-Poulenc Agrochimie.

44171903 Fail, P.A.; Anderson, S.A.; and Pearce, S.W. (1996). Toxicity Testing of a Fungicide, Iprodione: Endocrine Toxicology Studies of Testes From Adult Male CD® Sprague-Dawley Rats Exposed to Iprodione In Vitro. Project No. 65C-6169, Rt95-IPDB, RTI-532. Unpublished study prepared by Laboratory of Reproductive and Endocrine Toxicology/Center for Life Sciences and Toxicology/Chemistry and Life Sciences/Research Triangle Institute.

44171904 Fail, P.A.; Anderson, S.A.; and Pearce, S.W. (1996). Toxicity Testing of a Fungicide, Iprodione: Endocrine Toxicology Studies of Testes From Adult Male CD® Sprague-Dawley Rats Exposed to Iprodione In Vivo. Project No. 65C-6169, Rt95-IPDA, RTI-527. Unpublished study prepared by Laboratory of Reproductive and Endocrine Toxicology/Center for Life Sciences and Toxicology/Chemistry and Life Sciences/Research Triangle Institute.

44203401 Eldridge, S. (1996). Cell Proliferation in Rat Testes. Supplement to MRID # 43535002, Toxicity Testing of a Fungicide, Iprodione, in Adult Male CD Sprague Dawley Rats. Report No. PAI SN 94-4247. Unpublished study prepared by Pathology Associates International.

44365001 Repetto-Larsay, M. (1997). Iprodione. Toxicology Study in Pregnant Rat by Gavage to Examine Sex Differentiation. Report No. SA 96448. Unpublished study prepared by Rhône-Poulenc Agrochimie Centre de Recherche.

44422101 Bars, R.G. (1997). A Response to the EPA Review of the Protocol for Iprodione - Toxicology Study in Pregnant Rat by Gavage to Examine Sex Differentiation [Addendum to MRID # 44365001]. Report No. DAL 1097. Unpublished study prepared by Rhône-Poulenc Agrochimie Centre de Recherche.

SignOff Date:	3/12/1998
DP Barcode:	D235399
HED DOC Number:	012529
Toxicology Branch:	RRB1