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

012548

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **March 19, 1998**

MEMORANDUM

SUBJECT: ***IPRODIONE:*** **- REVISED** Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 3/18/98
Executive Secretary,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, 3/19/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Whang Phang, Branch Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)

PC Code: 109801

On February 25, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicological endpoints selected for acute and chronic dietary as well as occupational and residential (dermal and inhalation) exposure risk assessments in light of a recently submitted prenatal developmental toxicity study in rats (MRID No. 44365001). **This report supersede the previous RfD (4/12/94), TES (5/1/97) and the Hazard ID (12/29/97) Committee reports.**

Committee Members in Attendance

Members present were Karl Baetcke, William Burnam, Robert Fricke, Karen Hamernik, Susan Makris, Mike Metzger, Melba Morrow, John Redden, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Data was presented by Linda Taylor of Reregistration Branch 1.

Other HED members present at the meeting were Sanju Diwan, John Leahy and Christina Scheltema.

Data Presentation: Linda Lee Taylor
Linda Taylor
Toxicologist

Report Preparation: Jess Rowland
Jess Rowland.
Executive Secretary

I. INTRODUCTION

On February 10, 1994 the Health Effects Division's RfD/Peer Review Committee established a Reference Dose (RfD) of 0.06 mg/kg/day based on a NOEL of 6.1 mg/kg/day established in a combined chronic toxicity/carcinogenicity study in rats and an Uncertainty Factor of 100 for inter-species extrapolation and intra-species variability (*Memorandum*: G. Ghali, HED to J. Housenger,, SRRD, dated April 12, 1994).

On May 1, 1997, the Health Effects Division's Toxicology Endpoint Selection (TES) Committee selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments (TES Document dated May 1, 1997).

On October 16, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data to assess the potential enhanced sensitivity of infants and children from exposure to Iprodione as required by the Food Quality Protection Act (FQPA) of 1996 (*Memorandum*: G. Ghali, HED to M. Waller, RD, dated December 29, 1997).

On February 25, 1998, the HIARC met again to re-evaluate the toxicological endpoints for acute and chronic dietary as well as occupational and residential (dermal and inhalation) exposure risk assessments in light of a recently submitted prenatal developmental toxicity study in rats (MRID No. 44365001). The HIARC determined that the application of the FQPA safety factor for the protection of infants and children from exposure to Iprodione, as required by FQPA, will be determined during risk characterization.

This report includes the decisions made at the February 25, 1998 HIARC meeting as well as those made by the previous RfD, TES and HIARC Committee meetings and thus supersedes the previous RfD (4/12/94), TES (5/1/97), and the Hazard ID (12/29/97) Committee reports.

II. HAZARD IDENTIFICATION

A. Acute Dietary : Females 13 +

Study Selected: Developmental Toxicity - Rat §83-3a

MRID No. 44365001

Summary: In a special developmental toxicity study, pregnant Sprague-Dawley rats (25/dose) received Iprodione (97.1%)in methylcellulose via gavage at dose levels of 0, 20, 120, or 250 mg/kg/day during gestation days 6 through 19. A positive control group received Flutamide at 50 mg/kg/day on the same treatment regimen. Maternal toxicity manifested as deaths in three dams at 250 mg/kg/day [days 18-20] and the early sacrifice of 6 additional dams of this group (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 250 mg/kg/day, body weight was 90% of the control value on day 20 of gestation. Body-weight gains were significantly decreased at the 120 mg/kg/day (77% of control) and 250 mg/kg/day (59% of control) throughout the dosing period. Food consumption was decreased at 250 mg/kg/day 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 at 250 mg/kg/day, there was 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 250 mg/kg/day (56%) compared to the control (48%) and other dose groups (46%-48%), and fetal body weights were significantly decreased at 250 mg/kg/day (♂ 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 250 mg/kg/day, 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] in male pups was decreased significantly at 120 mg/kg/day (2.32±0.12) and 250 mg/kg/day (2.10±0.019) when compared to controls (2.43±0.09); the incidence at 20 mg/kg/day was 2.44±0.14.

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

Dose/Endpoint for establishing the Acute RfD: Developmental NOEL=20 mg/kg/day based on decreased anogenital distance (AGD) in male fetuses at 120 mg/kg/day (LOEL).

Comments about Study and Endpoint: The HIARC selected this dose (20 mg/kg/day) as a conservative estimate for risk assessment, however, doubted if this dose represented a "true" NOEL for the following reasons: 1) effects at the next higher dose (120 mg/kg/day, the LOEL), consisted of only marginal decreases; 2) although the decrease in AGD at the

LOEL showed statistical significance, the biological significance is questionable because of the extent of the decreases seen between the NOEL (2.44±0.14) and the LOEL (2.32±0.12) which indicate that the "actual" no effect level could be higher, some where in between these levels (i.e, 20 and 120 mg/kg/day); 3) lack of evaluation of another critical endpoint (i.e., nipple development, characterized as areolas/nipple anlagen in two strains of rats) which was observed along with the decrease in AGD with Vinclozolin, a structurally related compound; and 4) although AGD was not measured, another developmental toxicity study in rats demonstrated a developmental NOEL of 90 mg/kg/day based on delayed fetal development (MRID 00162984).

The HIARC noted that the TES Committee selected the NOEL of 90 mg/kg/day established in the 1986 study along with an additional Uncertainty Factor of 3 due to the lack of data on the androgen deprivation effect. This yielded a dose (90÷3=30 mg/kg/day) which is comparable to the 20 mg/kg/day dose selected for this risk assessment.

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation and 10 x for intra-species variability).

$$\textbf{Acute RfD} = \frac{\text{20 mg/kg/day (NOEL)}}{\text{100 (UF)}} = \textbf{0.2 mg/kg/day}$$

This risk assessment is required.

B. Chronic Dietary

(i). Reference Dose (RfD)

The HIARC concurred with the RfD established in 1994:

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat §83-5

MRID Nos. 43308201 & 43000501

Executive Summary: In combined chronic toxicity/carcinogenicity study, groups of Sprague-Dawley rats were fed diets containing Iprodione at 0, 150, 300 or 1600 ppm for two years. These dose levels were equivalent to 0, 6.1, 12.4, and 69 mg/kg/day for males and 8.4, 16.5 and 95 mg/kg/day for females, respectively. The NOEL was 6.1 mg/kg/day for males and 8.4 mg/kg/day for females and the LOEL was 12.4 mg/kg/day for males and 16.5 mg/kg/day for females based on generalized enlargement of the cells of the zona glomerulose and rarefaction and fine vacuolation of the zona fasciculata in the adrenal cortex in both sexes and histopathological changes in the male reproductive system.

Dose/Endpoint for establishing the RfD: NOEL=6.1 mg/kg/day based on histopathological lesions in the male reproductive system and effects on the adrenal glands in males at 12.4 and in females at 16.5 mg/kg/day (LOEL).

Comments about Study and Endpoint: The HIARC re-affirmed the dose and endpoints selected for establishing the RfD in 1994.

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation and 10 x for intra-species variability).

$$\textbf{Chronic RfD} = \frac{\text{6.1 mg/kg/day (NOEL)}}{\text{100 (UF)}} = \textbf{0.06 mg/kg/day}$$

(ii). Carcinogenic Risk Assessment

HED's Cancer Assessment Review Committee (CARC) in accordance with the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (April 10, 1996), classified Iprodione as a **"likely"** human carcinogen based on the combined hepatocellular adenomas/ carcinomas in mice and testicular tumors in male rats with a linear low-dose extrapolation approach for human risk characterization. For the combined hepatocellular adenomas/ carcinomas, the Q_1*s are 8.7×10^{-3} for the male mouse and 5.07×10^{-3} for the female mouse. For the Leydig cell tumors in male rats, the Q_1* is 4.39×10^{-2}. The CARC determined that of these, the most potent Q_1* of 4.39×10^{-2} should be used for cancer risk assessments. Therefore, the Q_1* of 4.39×10^{-2} should be used for estimating carcinogenic risk from exposure through food and water.

C. Occupational/Residential Exposure

1. Dermal Absorption

MRID No. 43535003

Dermal Absorption Factor: 5% at 10 hours. This factor is necessary ONLY for Long-Term chronic and carcinogenic dermal risk assessments since Short-and Intermediate-Term risk assessments are not required.

2. Short-Term Dermal - (1-7 days)

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: No dermal or systemic toxicity was seen following repeated dermal application of Iprodione at 0, 100, 500 or 1000 mg/kg/day, 6 hours/day, 5 days/week over a three week period to male and female New Zealand rabbits (MRID No. 42032301).

The HIARC concurred with the TES Committee's conclusions that there is no potential hazard via the dermal route because of the lack of systemic toxicity at the Limit-Dose (1000 mg/kg/day) and the demonstration of low (5%) absorption via the dermal route.

This risk assessment is **NOT** required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: See Short-Term

This risk assessment is **NOT** required.

4. Long-Term Dermal (Several Months to Life-Time)

(i). Non-Cancer (Chronic) Effects

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat §83-5

MRID Nos. 43308201 & 43000501

Executive Summary: See Chronic Dietary

Dose/Endpoint for establishing the RfD: NOEL=6.1 mg/kg/day based on histopathological lesions in the male reproductive system and effects on the adrenal glands in males at 12.4 and in females at 16.5 mg/kg/day (LOEL).

Comments about Study and Endpoint: This dose was selected since the current use pattern (6 days/week for up to 180 days) indicates potential for Long-Term dermal exposures. This oral NOEL with a dermal absorption factor of 5% should be used **only for non-cancer** dermal risk assessments. Dermal exposure **should not be** combined with inhalation exposure since a Long-Term inhalation risk assessment is not required.

This risk assessment is required.

(ii). Carcinogenic Effects

The Q_1* of 4.39×10^{-2} should be used for estimating carcinogenic risk from occupational exposure. The dermal and inhalation exposures **should be combined** and appropriate dermal (5%) and inhalation (100%) absorption factors should be used in **carcinogenic** risk assessments.

5. Inhalation Exposure (Short and Intermediate-Term ONLY)

Except for an acute inhalation toxicity study, the results of which place Iprodione in Toxicity Category IV (LC_{50} = >3.29.1 mg/L), no other studies are available via this route. The current use pattern (4 days/week up to several weeks) indicate a concern only for Short and Intermediate-Term but not for Long-Term exposures via this route. Therefore, the **HIARC selected the doses only for Short and Intermediate-Term inhalation exposure risk assessments.**

(i). Short-Term Exposure

Study Selected: Developmental Toxicity - Rat §83-3a

MRID No. 44365001

Summary: See Acute Dietary

Dose/Endpoint for establishing the Acute RfD: Developmental NOEL=20 mg/kg/day based decreased AGD in male fetuses at 120 mg/kg/day (LOEL).

Comments about Study and Endpoint: The inhalation exposure component (i.e., µg a.i/lb/day) using a 100% absorption rate (default value) should be *converted to* an *equivalent oral dose* (mg/kg/day). This converted oral dose should then be compared to the NOEL identified above. Inhalation exposure **should not be** combined with dermal exposure since a dermal risk assessment is not required.

This risk assessment is required.

(ii). Intermediate-Term Exposure

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat §83-5

MRID Nos. 43308201 & 43000501

Executive Summary: See Chronic Dietary

Dose/Endpoint for establishing the RfD: NOEL=6.1 mg/kg/day based on histopathological lesions in the male reproductive system and effects on the adrenal glands in males at 12.4 and in females at 16.5 mg/kg/day (LOEL).

Comments about Study and Endpoint: The inhalation exposure component (i.e., µg a.i/lb/day) using a 100% absorption rate (default value) should be *converted to* an *equivalent oral dose* (mg/kg/day). This converted oral dose should then be compared to the NOEL identified above. Inhalation exposure **should not be** combined with dermal exposure since a dermal risk assessment is not required.

This risk assessment is required.

(iii). Long-Term Exposure

The current use pattern does not indicate a concern for Long-Term exposure or risk.

This risk assessment is **NOT** required.

D. Margin of Exposure for Occupational/Residential Exposures:

The appropriate MOEs will be determined during risk characterization.

E. Recommendation for Aggregate Exposure Risk Assessments

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the oral NOEL to calculate the MOE.

For **short and intermediate** aggregate exposure risk assessment, combine the average exposure values from food + water together with the exposure from inhalation route (100% absorption) only and compare it to the oral NOELs to calculate the MOE (dermal risk assessments are not required for these exposure periods).

For **chronic** aggregate exposure risk assessment, combine the average exposure values from food + water together with the exposure from dermal route (5% dermal absorption) only and compare it to the oral NOEL to calculate the MOE (inhalation exposure risk assessment is not required for this exposure period).

IV. FQPA CONSIDERATIONS

1. Neurotoxicity Data

There are no acute and subchronic neurotoxicity studies with Iprodione

2. Developmental Toxicity Data:

In a 1976 prenatal developmental toxicity study, groups of pregnant Sprague-Dawley rats (25-30/dose) received Iprodione (100%) in 1% carboxymethylcellulose via gavage at doses of 0, 100, 200, or 400 mg/kg/day during gestation days 5 through 15. For maternal toxicity, the NOEL was 200 mg/kg/day and the LOEL was 400 mg/kg/day based on slightly decreased body weight gain and significantly decreased food consumption. For developmental toxicity, the NOEL was 200 mg/kg/day and the LOEL was 400 mg/kg/day based on decreased implantation sites. This study does not appear to provide a robust evaluation of fetal effects following *in utero* exposure of Iprodione (MRID 0071324).
In a 1986 prenatal developmental toxicity study, groups of pregnant Sprague-Dawley rats were given oral (gavage) administrations of Iprodione (94.2%) in 0.5% methylcellulose at doses of 0, 40, 90, or 200 mg/kg/day during gestation days 6 through 15. No maternal toxicity was observed (maternal NOEL $\geq$200 mg/kg/day). For developmental toxicity, the NOEL was 90 mg/kg/day and the LOEL was 200 mg/kg/day, based upon delayed fetal development, as evidenced by slightly reduced fetal weights and an increased incidence of space between the body wall and organs in fetuses(MRID 00162984).

In a 1997 special prenatal developmental toxicity study, pregnant Sprague-Dawley rats (25/dose) received Iprodione (97.1%)in methylcellulose via gavage at dose levels of 0, 20, 120, or 250 mg/kg/day during gestation days 6 through 19. For maternal toxicity, the NOEL was 20 mg/kg/day, the LOEL was 120 mg/kg/day, based on decreased body-weight gain and decreased food efficiency. At 250 mg/kg/day, deaths occurred [9 out of 25] in addition to decreased body-weight gain and food consumption/ efficiency. For developmental toxicity, the NOEL was 20 mg/kg/day and the LOEL was 120 mg/kg/day, based on decreased anogenital distance in the male pups (MRID No. 44365001).

In a prenatal developmental toxicity study, pregnant New Zealand white rabbits (18/group), were given oral (gavage) administration of Iprodione (85%) in 0.5% Methocel at doses of 0, 20, 60, or 200 mg/kg/day during gestation days 6 through 18. For maternal toxicity, the NOEL was 20 mg/kg/day and the LOEL was 60 mg/kg/day based on decreased body weight gain. Also at 200 mg/kg/day, the following were observed:

increased numbers of abortions, body weight loss, decreased food consumption and decreased defecation and urination. For developmental toxicity, the NOEL was 60 mg/kg/day and the LOEL was 200 mg/kg/day based upon increased skeletal variations (13th full rib, malaligned sternebrae, and 27 presacral vertebrae, occurring alone or in combination with each other or accompanied by delayed ossification) (MRID No. 00155469).

3. Reproductive Toxicity Data

In a two-generation reproduction study, male and female Sprague-Dawley received diets containing Iprodione (96.2%) at 0, 300, 1000, or 2000/3000 ppm (0, 18.5, 61.4, or 154.8 mg/kg/day for males and 22.49, 76.2, or 201.2 mg/kg/day for females) For parental systemic toxicity, the NOEL was 300 ppm (21 mg/kg/day) and the LOEL was 1000 ppm (69 mg/kg/day), based on decreased body weight, body weight gain, and food consumption in both sexes and generations. For offspring toxicity, the NOEL was 1000 ppm (69 mg/kg/day) and the LOEL was 2000/3000 ppm (178 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 (smallness, reduced mobility, unkempt appearance, hunching, and/or tremors) in pups during the lactation period. (MRID No. 41871601).

4. Determination of Susceptibility

The prenatal developmental toxicity study in rabbits, the special prenatal study in rats, and the two-generation reproduction study in rats demonstrated no indication of increased susceptibility to *in utero* and/or postnatal exposure to Iprodione.

In the 1986 prenatal developmental toxicity study in rats, however, developmental effects in the fetuses (a slight dose-related decrease in fetal 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 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. Also, the fetal findings 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 this study were not judged to be an appropriate measure of potential sensitivity following *in utero* exposure to Iprodione.

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 this study were not judged to be an appropriate measure of potential sensitivity following *in utero* exposure to Iprodione.

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

5. Recommendation for a Developmental Neurotoxicity Study

Based on the following weight-of-the-evidence considerations, the HIARC determined that a developmental neurotoxicity study in rats is **not** required for Iprodione.

(i) Evidence that support requiring a developmental neurotoxicity study:

- Overall, Iprodione does not appear to be a frankly neurotoxic chemical. There were no effects on brain weight or histopathology (nonperfused) of the nervous system in the chronic studies in rats, mice, and dogs. Findings that were suggestive of neurotoxicity (see below) were often equivocal, unsupported by data from other studies, and/or observed only at doses which compromised the survival of the animals.

- No evidence of developmental anomalies of the fetal nervous system was observed in the prenatal developmental toxicity studies in either rats or rabbits, at developmentally and/or maternally toxic oral doses up to 200 mg/kg/day.

- Evaluation of the special postnatal developmental toxicity study did not reveal any endpoints of concern that would trigger a developmental neurotoxicity study.

(ii) Evidence that would suggest the need for a developmental neurotoxicity study:

- In the chronic toxicity study in rats, degeneration of the sciatic nerve was observed after 2 years of dietary exposure to Iprodione. This finding was also observed at a relatively high incidence in control animals, although the incidence doubled for females at the highest dose tested (1600 ppm).

- In the carcinogenicity study in mice, absolute brain weight was slightly decreased and adjusted brain weight was significantly decreased at the HDT (4000 ppm).

- In the two-generation reproduction study in rats, clinical observations in pups included reduced mobility, unkempt appearance, hunching, and/or tremors at the HDT (2000/3000 ppm = 178 mg/kg/day). At this treatment level, severe toxicity was observed in the parental animals, pup body weight was reduced, and pup survival was compromised.

- Iprodione causes endocrine disruption, affecting the reproductive system, pituitary, adrenals, and/or thyroid in various studies.

(iii) Other Unknown Factors:

- Because of the lack of acute and subchronic neurotoxicity studies in rats, there was no evaluation of the nervous system following perfusion. Findings in other studies that were suggestive of neurotoxicity could not be confirmed or refuted.

6. Determination of the FQPA Factor:

The application of an FQPA factor to ensure the protection of infants and children from exposure to Iprodione, as required by FQPA, will be determined by the FQPA Safety Factor Assessment Review Committee.

VI. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. In 1994, the RfD Committee recommended a postnatal developmental toxicity study in rats due to the close structural similarity of Iprodione to Vinclozolin and because of the effects seen in the reproductive system of male rats as well as in the adrenal glands of both sexes of rats in the combined chronic toxicity/ carcinogenicity study. In response to the above recommendation, the Registrant in 1997 submitted a special study that examined the sex differentiation of offspring from in pregnant rats exposed orally to Iprodione (MRID No. 44365001).

The HIARC determined that there are outstanding questions with regard to postnatal exposure that remain to be addressed in light of the observed effects of Iprodione on the testes and its proposed mode of action (disruption of testosterone biosynthesis). Iprodione has been shown to alter anogenital distances in male fetuses following exposure during late gestation and there is evidence of toxicity to the male reproductive organs in chronic studies in rats. Also, no data are available on the effect of Iprodione on sperm count, motility or morphology in rat or other species. Therefore, the HIARC concluded that an assessment of effects on the male reproductive system following pre and/or postnatal exposure is required and these aspects can be addressed by conducting the study as described in OPPTS 870.3800

VII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	Developmental NOEL=20	Decreased anogential distance in male pups.	Developmental- Rat
	UF=100	**Acute RfD = 0.2 mg/kg/day**	
Chronic Dietary	NOEL=6.1	Histopathological lesions in the male reproductive system and the adrenal glands in both sexes.	Combined Chronic Toxicity/ Carcinogenicity -Rat
	UF=100	**Chronic RfD = 0.06 mg/kg/day**	
Carcinogenicity (Dietary)	Q_1*= 4.39×10^{-2}	Iprodione is classified as a **"Likely"** human carcinogen with a low-dose extrapolation approach for human risk assessment.	
Short-Term (Dermal)	Not Applicable	No dermal or systemic toxicity seen at the Limit-Dose in a 21-da dermal toxicity study in rabbits. This risk assessment is not required.	
Intermediate-Term (Dermal)	Not Applicable	No dermal or systemic toxicity seen at the Limit-Dose in a 21-da dermal toxicity study in rabbits. This risk assessment is not required.	
Long-Term (Dermal)[a] **Non-Cancer**	Oral NOEL=6.1	Histopathological lesions in the male reproductive system and the adrenal glands in both sexes.	Combined Chronic Toxicity/ Carcinogenicity Rat
Long-Term (Dermal)[a] **Cancer**	Q_1*= 4.39×10^{-2}	Iprodione is classified as a **"Likely"** human carcinogen with a low-dose extrapolation approach for human risk assessment.	
Short-Term (Inhalation)[a]	Developmental NOEL=20	Decreased anogential distance in male pups.	Developmental-Rat
Intermediate-Term (Inhalation)[a]	Oral NOEL=6.1	Histopathological lesions in the male reproductive system and the adrenal glands in both sexes.	Combined Chronic Toxicity/ Carcinogenicity Rat
Long-Term (Inhalation)	Not Applicable	Based on the use pattern, there is no concern for exposure or risk This risk assessment is not required.	

a = Appropriate route-to-route extrapolation should be performed (i.e., a dermal absorption factor of 5% and an inhalation absorption factor of 100% used for conversion to oral equivalent doses and then compared to the oral NOELs).