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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: March 27, 2012

SUBJECT: Iprodione. Revision of Endpoint Selection for New Dietary Assessment

PC Code: 109801
Decision No.: 409718
Petition No.: N/A
Risk Assessment Type: Dietary Aggregate
TXR No.: N/A
MRID No.: N/A

DP Barcode: D400304
Registration No.:
Regulatory Action:
Case No.: N/A
CAS No.: 36734-19-7
40 CFR: 180.399

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DeVGen has petitioned the Agency to establish tolerances to support new uses for iprodione on cucurbits and fruiting vegetables. The most recent dietary risk assessment for iprodione was conducted in 2007; therefore, the Iprodione Review Team reviewed the available toxicity data for iprodione as well as considered current policies and determined that a re-evaluation of endpoints for risk assessment was required. As a result of this re-visit, new acute and chronic toxicological points of departure (PODs) were selected for dietary risk assessment. Additionally, the occupational and non-occupational short and intermediate term dermal and inhalation exposure scenarios were re-visited and new endpoints were selected. Lastly, the Q_1* for the parent compound, iprodione, for incorporation into the new dietary assessment, was re-evaluated, and revised.

An acute POD for females 13 – 49 years old was selected from a male rat pubertal assay, with a prenatal developmental study in rats as co-critical, based on reduced serum levels of testosterone as the most sensitive endpoint in the database (Table 1). A chronic POD was selected from the male pubertal assay, with testosterone as the most sensitive endpoint in the database, and the chronic oral toxicity study in the rat was considered co-critical (Table 1). For the occupational and non-occupational short and intermediate term dermal and inhalation exposure scenarios, the endpoint selected is based on reduced serum levels of testosterone as the most sensitive endpoint in the database (Table 2).

An uncertainty factor of 1000X was applied to all endpoints selected for all exposure routes (10X for interspecies extrapolation, 10X for intraspecies variation, 10X FQPA:$UF_{LOAEL \rightarrow NOAEL}$). The FQPA factor accounts for the lack of a NOAEL in the testosterone data. Males are clearly more sensitive than females based on (1) the metabolism data, which show that elimination of iprodione from the blood is slower in males than in females and males absorb a greater percent of the dose than females, and (2) the anogenital distance (AGD) data, which show an effect only in males. Since testosterone is the basis of the acute and chronic risk assessments and is considered the endpoint that is protective of all other downstream effects in males or females, an additional uncertainty factor beyond the FQPA 10X for lack of NOAEL is not warranted at this time.

Iprodione has been classified as a "Likely" human carcinogen, based on the increased incidence of liver tumors in both sexes of the mouse and the increased incidence of Leydig cell tumors in male rats. The registrant previously submitted mode of action (MOA) data for both tumor types; however, the Cancer Assessment Review Committee (CARC) determined that the MOA data do not provide a sufficient basis for establishing an MOA for iprodione for either tumor type (TXR No. 0012523, dated 2/26/1998). Therefore; the Agency determined that it is appropriate to quantify cancer dose response using the linearized low dose extrapolation model (Q1* approach), and Leydig cell tumors were chosen for human health risk assessment as the most sensitive endpoint. Although the basis of the linear low dose extrapolation was changed to the liver tumors Q1* in 2007, this decision was revisited and it was determined that the Q1* based on the more sensitive Leydig cell tumors must be used.

Table 1. Summary of Toxicological Doses and Endpoints for Iprodione for Use in Dietary Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD/PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Females 13-49 years of age)	LOAEL = 50 mg/kg/day	UF_A 10x UF_H 10x FQPA:$UF_{LOAEL \rightarrow NOAEL}$ = 10x Total UF: 1000	aRfD = 0.05 mg/kg aPAD = 0.05 mg/kg	Male pubertal toxicity (rat) MRID 48279201 LOAEL = 50 mg/kg/day, based on significant, dose-related *reductions in serum testosterone levels*; delayed preputial separation (PPS) at 100 mg/kg/day Developmental toxicity (rat) MRID 44365001 LOAEL = 120 mg/kg, based on decreased anogenital distance in male pups (dams dosed on GD 6-19)
Acute Dietary (General Population, including Infants and Children)	No hazard or appropriate acute endpoint was identified in the database. A decline in testosterone levels for a short time period (repeat exposure) during puberty could potentially result in delayed puberty, as well as other adverse effects; however, a delay in puberty or other adverse outcomes would not be expected from an acute (single) exposure. A transient decline in serum testosterone levels for a few hours in an adult animal would not likely cause any adverse, permanent effects.			
Chronic Dietary (All Populations)	LOAEL = 50 mg/kg/day	UF_A 10x UF_H 10x FQPA:$UF_{LOAEL \rightarrow NOAEL}$ = 10x Total: 1000	cRfD = 0.05 mg/kg/day cPAD = 0.05 mg/kg/day	Co-critical studies: Chronic oral toxicity (rat) and Male pubertal toxicity study (rat) Male pubertal toxicity (rat) MRID 48279201 LOAEL = 50 mg/kg/day, based on significant, dose-related *reductions in serum testosterone levels*; delayed PPS at 100 mg/kg/day Chronic oral toxicity (rat) MRID 42637801/42787001 LOAEL = 12.4 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. Leydig cell tumors at 69 mg/kg/day. NOAEL = 6.1 mg/kg/day
Cancer (oral)	Classified as a "Likely" human carcinogen with a low-dose extrapolation approach for human risk assessment.			

Table 2. Summary of Toxicological Doses and Endpoints for Iprodione for Use in Non-Occupational and Occupational Human Health Risk Assessments (Inhalation)				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD/PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal and Inhalation (short- and intermediate-term)	LOAEL = 50 mg/kg/day 5% dermal absorption factor 100% inhalation	UF_A 10x UF_H 10x $UF_{LOAEL \rightarrow NOAEL}$ = 10x	LOC for MOE =1000	Co-critical studies Male pubertal toxicity (rat) MRID 48279201 LOAEL = 50 mg/kg/day, based on significant, dose-related *reductions in serum testosterone levels (↓73%)* Chronic oral toxicity (rat) MRID 42637801/42787001 LOAEL = 12.4 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. NOAEL = 6.1 mg/kg/day
Cancer (oral)	Classified as a "Likely" human carcinogen with a low-dose extrapolation approach for human risk assessment.			