8-28-95

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

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Iprodione - Mouse Micronucleus Test, Mechanistic Studies, and a Dermal Absorption Study

TO: Bill Wooge
PM Team Reviewer (52)
Reregistration Branch, SRRD (7508C)

FROM: Linda L. Taylor, Ph.D 8/22/95
Toxicology Branch II, Section II,
Health Effects Division (7509C)

THRU: K. Clark Swentzel 8/28/95
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Karl Baetcke, Ph.D. 8/28/95
Acting Chief, Toxicology Branch II/HED (7509C)

Registrant: Rhone-Poulenc Ag Company
Chemical: [3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide]; [3-(3,5-dichlorophenyl)-N-isopropyl-2,4-dioxoimidazolidine-1-carboxamide]
Synonym: Iprodione; RP26019; Rovral®; Glycophene
Case No.: 816345
Caswell No.: 470A
Submission No.: S485489
Identifying No.: 109801-000264
DP Barcode: D214390
MRID No.: 435350-01, 435350-02, 435350-03

Action Requested: Please review the following studies: Mouse Micronucleus Test; Toxicity Testing of Iprodione on Sprague-Dawley Rats; and Dermal Absorption of Iprodione in Male Rats.

Comment: The Registrant submitted three studies to fulfill promises made for mechanistic studies on Iprodione. These have been reviewed, and the DERs are appended.

1) MRID # 435350-01 Iprodione Mouse Micronucleus Test. Proudlock, RJ and Elmore, EA. In an in vivo mouse micronucleus assay, groups of 5 CD-1 mice per sex were administered single oral gavage doses

of 750, 1500, or 3000 mg Iprodione/kg body weight. Bone marrow cells were collected at 24, 48, or 72 hours after dosing and were examined for micronucleated polychromatic erythrocytes [MOEs]. The test material was delivered to the test animals as suspensions prepared in aqueous 1% methylcellulose. One male and 8 females in the high-dose group succumbed to treatment; the other toxic signs at this concentration included piloerection, hunched posture, ptosis, lethargy, and coma. Dose-related cytotoxic effects on the target tissue were also observed at 48 hours postdosing; the response was significant [$p<0.01$] for the high-dose animals. **There was, however, no evidence of a clastogenic or aneugenic effect at any dose or harvest time.** The positive control induced the expected high yield of MPEs in both sexes. This study is classified Acceptable, and it satisfies the guideline requirement [84-2] for a mouse micronucleus assay.

2) MRID # 435350-02 Toxicity Testing of a Fungicide, Iprodione, in Adult Male CD® Sprague-Dawley Rats Exposed to Oral Iprodione. Fail, PA, Anderson, SA, and Pearce, SW. There are several pieces of evidence that suggest that Iprodione may have similarities to Flutamide, while other information strongly suggests that Iprodione is not the same type of antiandrogen. Poor binding affinity to the androgen receptor was found following Iprodione exposure at very high dose levels, but two metabolites of Iprodione displayed an affinity for the androgen receptor close to that found for Flutamide. While Flutamide caused marked effects on all male sex-related organs [↓ organ weight, microscopic lesions], Iprodione caused no effect on the prostate, but showed a slight effect on the seminal vesicles and epididymidis [↓ organ weight, microscopic lesions]. Increased concentrations of LH, FSH, testosterone, and estradiol were found following 15 and 30 days of exposure to Flutamide compared to vehicle control values. Following Iprodione treatment for 15 but not 30 days, only LH and FSH concentrations were increased relative to the vehicle control. Testosterone concentrations at necropsy were comparable between the Iprodione and pair-fed control rats, but there were subtle changes in the secretion pattern of testosterone and LH between these two groups. Estradiol concentrations were increased in the Iprodione rats at necropsy following 30 days of exposure compared to both the vehicle and pair-fed control groups. A marked effect [increase] on adrenal weight associated with histopathologic lesions [vacuolation] indicative of an alteration of steroidogenesis was observed following 30 days of exposure to Iprodione but not to Flutamide. Although there is 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 the current study suggests that the two compounds share only certain parts of a mechanism of toxicity/carcinogenicity. Compared to Flutamide, Iprodione appears to be a much less active/potent endocrine toxicant. This mechanistic, non-guideline, study is Acceptable.

3) MRID # 435350-03 Dermal Absorption of ^{14}C-Iprodione (Rovral® 4F)

in Male Rats. Cheng, T. Male Crl:CD®BR rats were exposed dermally to Iprodione at dose levels of 0.4, 4.0, and 40 mg/rat for 0.5, 1, 2, 4, 10, and 24 hours. Skin residue 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 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.

CONCLUSION: All three studies are acceptable. The mechanistic studies do not provide sufficient support to the hypothesis on hormonal mechanisms to attribute the carcinogenic response observed following Iprodione exposure to mice and rats as secondary to the toxicity of the chemical. The cover letter from the Registrant indicated that further mechanistic studies are ongoing and will be submitted when completed. The micronucleus assay results are consistent with other mutagenicity data, which demonstrate that Iprodione is not mutagenic, and lend support to the supposition that Iprodione is operating via a mode other than genotoxicity.