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

REVIEWER

MAY - 8 1996

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Iprodione - Comments/Response to Rhone-Poulenc's Discussion of the Weight of Evidence Regarding the Induction of Cancer

TO: William Burnam
Science Analysis and Coordination Branch
Health Effects Division (7509C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 4/25/96
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THRU: K. Clark Swentzel K. Clark Swentzel 4/25/96
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and

Stephanie R. Irene, Ph.D. Stephanie R. Irene 5/3/96
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
Caswell No.: 470A
Submission No.: none
Identifying No.: 109801
DP Barcode: D224824
Action Requested: Review Rebuttal and integrate information with what we already know about Iprodione and new mechanism of action research.

Comment: Submitted to TB II for review were pages 28-36 of a document apparently from the Registrant. Section submitted for review is titled: The Weight Of The Evidence Demonstrates That Iprodione Does Not "Induce Cancer". The first argument is that the 1978 mouse and rat studies did not demonstrate an increased incidence of tumors. Additionally, it is stated that Iprodione has been shown to be nongenotoxic in several assays. TB II points out that the 1978 studies were performed at dose levels that are not considered adequate for assessing the carcinogenic potential of

Iprodione, and a positive response was observed in the Bacillus subtilis assay for DNA damage without metabolic activation. According to the Registrant, the only positive results [for tumor formation] were in studies that the Registrant believes are not appropriate for the evaluation of safety of Iprodione "either because (1) the tumor type seen is not relevant to humans; or (2) the tumors were the secondary effect of a mechanism operative only at the high test doses." This latter statement is speculation at present, since no data have been presented to demonstrate this. And the relevancy of Leydig cell tumors to humans is the subject of debate. In an assessment of similar data on another chemical [Procymidone], Dr. L. Earl Gray, Jr. [NHEERL] stated that the assertion that testicular cell tumors in male rats have little or no relevance to humans is often stated by industry, but only weakly supported by a very small data base. Additionally, he stated that there are "many hormonal and nonhormonal mechanisms responsible [for] testicular tumor formation, some of which may have relevance to man." He states further that " testicular cancers have doubled in man over the last few decades and environmental mechanisms have been proposed as the cause of this increase. The specific mechanism of action of the hormonal alteration for a chemical must be clearly characterized before one can speculate about the relevance to man."

With regard to the statement on page 31 of the Registrant's document: "The absence of any action by FDA to prevent the marketing of lactitol confirms the lack of relevance of rat Leydig tumors to humans.", Leydig cell tumors are not viewed as irrelevant by the FDA/Center for Food Safety and Applied Nutrition [personal communication]. In the second paragraph on page 31, it states that a recent study indicates that Iprodione "could cause a decrease in normal testosterone production by the rat testes. Decreased testosterone production could result in benign or testicular lesions by promoting compensatory mechanisms such as sustained cellular stimulation. Such cellular stimulation over a long period of time is believed to lead to Leydig cell hyperplasia and ultimately to tumor formation in these cells." TB II points out that in the mechanistic study submitted [MRID 43535002], a decrease in testosterone was observed during a 10-hour sampling period following Iprodione administration for 30 days, but an increase was observed at necropsy [day 31]. It should also be noted that the dose level in this study was 600 mg/kg/day; the highest dose in the rat carcinogenicity study was 69 mg/kg/day. In a second mechanistic study [MRID 43830601] in cultured porcine Leydig cells, Iprodione was shown to inhibit hCG-stimulated testosterone secretion at dose levels of 1 μg/mL and above. However, there was no indication of how the dose levels utilized in this in vitro study relate to the concentrations of Iprodione attained in the target organ cells in the in vivo studies.

With regard to the ovarian tumors observed in the female mouse, the Registrant states that the toxic effect produced by Iprodione on the female reproductive system "suggests that the slight increased incidence of luteomas observed at 4000 ppm is secondary to a prolonged and profound perturbation of sex hormone regulation at

the target organ level... ." The Registrant further states that it is "probable that high dietary levels of iprodione in the mouse result in elevated circulating and ovarian levels of LH, which in turn may lead to hyperplasia of the ovarian interstitial cells and tumor formation." However, to date no data have been generated to demonstrate this perturbation of sex hormone regulation in the female mouse.

With regard to the liver tumors in mice, the data show a progression in effects in the liver, such that comparable non-neoplastic lesions are observed in the control and low-dose mice, while an increasing incidence of these lesions is observed in the mid- and high-dose mice [both sexes]. TB II notes that hepatocellular hyperplasia was <u>not</u> observed at any dose level.

With respect to the issue of MTD and the Registrant's contention that tumors were observed only at the MTD, the HED CPRC considered the high dose in both the rat and mouse studies in question to be adequate [**not excessive**] for assessing the carcinogenic potential of Iprodione. In this type of study [carcinogenic], one wants to test a compound at a high enough dose level to produce some toxic effect(s) in order to optimize the opportunity to identify a carcinogenic effect. In neither case is the high-dose level in the Iprodione studies considered excessive and, therefore, the tumors observed are considered a result of Iprodione exposure.

The Registrant has indicated that there are three additional studies addressing the cancer issue that are ongoing: (1) a hepatotoxicity study in mice; (2) a study in porcine cells to identify the site of testosterone inhibition; and (3) a study to assess the inhibition of testosterone secretion in the rat. Studies (1) and (3) are scheduled for completion July 1, 1996 and the other study is scheduled for October 1, 1996.

To date, the Registrant's mechanistic studies have shown that Iprodione has poor binding affinity to the androgen receptor at very high levels and has very weak antiandrogen activity. The levels at which effects were observed in the 30-day endocrine toxicology screen study far exceed the high-dose level at which testicular tumors were observed in the rat carcinogenicity study. Additionally, in porcine Leydig cells, Iprodione was shown to inhibit hCG-stimulated testosterone secretion at dose levels of 1 µg/mL and above.

<u>CONCLUSION</u>: From the data currently available on Iprodione, no specific mechanism of action of the hormonal alteration has been clearly characterized. Although Iprodione was shown to inhibit testosterone secretion in porcine Leydig cells, the testicular tumors were observed in rats and a similar study in rat Leydig cells has not been completed to date. To be consistent with what has been done with Procymidone, there does not appear to be a compelling reason [scientific-wise] to warrant reconsideration by the HED Cancer Peer Review Committee at this time.