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SCIENTIFIC DATA REVIEWS
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MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

SUBJECT: **Iprodione:** Hazard Identification Committee Report.

CASRN: 36734-19-7
PC Code: 109801
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FROM: George Z. Ghali, PhD. G. Ghali
Executive Secretary, Hazard Identification Committee
Health Effects Division (7509C)

Thru: Clark Swentzel
Chairman, Hazard Identification Committee
Health Effects Division (7509C)

Michael Metzger
Co-Chairman, Hazard Identification Committee
Health Effects Division (7509C)

To: Mary Waller, PM 21
Fungicide-Herbicide Branch
Registration Division (7505C)

The Health Effects Division-Hazard Identification Committee met on October 16, 1997 to evaluate the existing and/or recently submitted toxicology data in support of iprodione re-registration, and to address issues relating to 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)

It should be noted that this chemical has already been discussed by the Health Effects Division-RfD Committee on February 10, 1994 (report dated April 12, 1994), and by the Toxicity Endpoint Selection Committee (TES) on March 27, 1997 (*ad hoc*) and again on May 1, 1997. The Hazard Identification Committee concurred with the conclusions reached by the RfD and TES Committees. The current report emphasizes only the FQPA aspects. For more information, please refer to the reports cited above.

Material available for review consisted of data evaluation records (DERs) for a combined chronic toxicity-carcinogenicity study in rats **(83-5)**, a chronic toxicity study in dogs **(83-1b)**, a carcinogenicity study in mice **(83-2b)**, a reproductive toxicity

study in rats (83-4), developmental toxicity studies in rats and rabbits (83-3a and -3b), subchronic studies in rodents and non-rodent species (82-1a and 82-1b), a 21-day dermal toxicity study in rats (82-2), a battery of mutagenicity studies (84-2), and a series of acute toxicity studies (81-1 through 81-6).

Hazard Identification Committee members present were David Anderson, Karl Baetcke (Senior Science Advisor, HED), William Burnam (Chief, SAB, HED), George Ghali (Executive Secretary, Hazard Identification Committee, HED), Susan Makris, Nancy McCarroll, Michael Metzger (Co-Chair, Hazard ID Committee), Melba Morrow (Alt-Chair), Kathleen Raffaele, John Redden, Jess Rowland, Clark Swentzel (Chairman, Hazard Identification Committee, HED).

Scientific reviewer(s): (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report and concurrence with the hazard identification assessment review unless otherwise stated).

Linda Taylor

A. Hazard Identification:

The following evaluation is provided to address FQPA considerations on the sensitivity of infants and children.

1. Reproductive Toxicity:

In a two-generation reproduction study, 96.2% iprodione was administered to Sprague-Dawley rats at dietary levels of 300, 1000, or 2000/3000 ppm (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) (MRID No. 41871601; Doc. No. 009695). The parental systemic NOEL was 300 ppm (18.5/22.49 mg/kg/day in M/F; approx. 21 mg/kg/day) and the parental systemic LOEL was 1000 ppm (61.4/76.2 mg/kg/day in M/F; approx. 69 mg/kg/day), based on decreased body weight, body weight gain, and food consumption in both sexes and generations. The NOEL for offspring was 1000 ppm (61.4/76.2 mg/kg/day in M/F; approx. 69 mg/kg/day) and the LOEL was 2000/3000 ppm (154.8/201.2 mg/kg/day in M/F; approx. 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 in pups during the lactation period (smallness, reduced mobility, unkempt appearance, hunching, and/or tremors).

2. Developmental Toxicity:

In a 1976 prenatal developmental toxicity study in Sprague-Dawley rats (25-30/group) (MRID 0071324; Doc. 000614, 001519, 004078), 100% iprodione was administered at doses of 100, 200, or 400 mg/kg/day by gavage in 5 mg/kg of 1% carboxymethylcellulose on gestation days 5-15. The maternal NOEL was 200 mg/kg/day, based on slightly decreased body weight gain and significantly decreased food consumption at the maternal LOEL of 400 mg/kg/day. The developmental NOEL was 200 mg/kg/day, based upon decreased implantation sites at the developmental LOEL of 400 mg/kg/day. This study does not appear to provide robust evaluation of fetal effects and was eventually graded Supplementary for multiple reasons.

In a 1986 prenatal developmental toxicity study in Sprague-Dawley rats (MRID 00162984; Doc. 006359, 007008), 94.2% iprodione was administered at doses of 40, 90, or 200 mg/kg/day by gavage in 10 mg/kg of 0.5% methylcellulose on gestation days 6-15. No maternal toxicity was observed (maternal NOEL $\geq$200 mg/kg/day). The developmental NOEL was 90 mg/kg/day and the developmental 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.

A prenatal developmental toxicity study (MRID 00155469; Doc. 005214) was conducted in pregnant New Zealand white rabbits

(18/group), in which 95% iprodione was administered by gavage in 1 ml/kg at doses of 20, 60, or 200 mg/kg/day in 0.5% Methocel on gestation days 6-18. The maternal NOEL was 20 mg/kg/day. The maternal 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. The developmental NOEL was 60 mg/kg/day. The developmental 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).

3. Data Gaps:

A postnatal developmental toxicity study was recommended due to the close structural similarity of iprodione to procymidone and vinclozolin and by effects on the male reproductive system in the long-term feeding study in Long Evans rats. The postnatal study has been submitted to the Agency and is currently in the process of review. It appears that effects in the offspring, including the evaluation of anogenital distance, occur only at doses which are maternally toxic.

4. Developmental Neurotoxicity:

The Committee did not recommend that a developmental neurotoxicity study be required for iprodione. The following information was considered in the weight-of-evidence evaluation.

a) Evidence that a developmental neurotoxicity study should not be required:

Overall, iprodione does not appear to be a frankly neurotoxic chemical. For the most part, 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.

Preliminary evaluation of the postnatal developmental toxicity study did not reveal any endpoints of concern that would trigger a developmental neurotoxicity study.

b) Evidence that would suggest the need for a developmental

neurotoxicity study:

There were findings in the database that were suggestive of neurotoxicity as shown below:

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 90-day subchronic study in rats, absolute brain weight was significantly decreased for females only at the HDT (3000 ppm). Clinical signs of toxicity in this study included piloerection and hunched posture at 3000 and 5000 ppm (the 5000 ppm treatment group was terminated early due to severe toxicity).

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.

c) Other Unknown Factors:

Because of the lack of acute and subchronic neurotoxicity studies in rats and delayed neuropathy studies in chickens, 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.

B. <u>FQPA Considerations</u>:

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 for the pesticide chemical residue and other sources of exposure 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, the Administrator may use a different 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); this study has been submitted to the Agency and is currently in review. 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.

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 or equivalent 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 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.

Uncertainty factor: The Committee determined that for iprodione, the 10-fold uncertainty factor for the protection of

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infants and children would be removed for the following reasons:

1. There were no data gaps for the standard assessment of potential effects on offspring following *in utero* and/or postnatal exposure to iprodione. In addition, a confirmatory postnatal developmental study in rats was submitted to the Agency. It is noted that at the last FQPA review of iprodione by an *ad hoc* committee in March, 1997, this postnatal study was still considered a data gap.

2. Although the prenatal developmental toxicity study in rabbits and the two-generation reproduction study data 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 developmental toxicity study in rats were not judged to be an appropriate measure of potential sensitivity following *in utero* exposure to iprodione.

cc: Stephanie Irene
Michael Ioannou
Linda Taylor
Clark Swentzel
Michael Metzger
William Burnam
Chritina Sheltema
Karen Whitby
Jess Rowland
Amal Mahfouz (OW)
Hazard ID file
Caswell File