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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Imazalil, Reregistration Case No. 2325. Review of Protocols for Combined Chronic Feeding/Carcinogenicity Study in Rats and Concurrent Study to Develop Contemporary Historical Control Data.

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Case 816389 | PC Code 111901
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Action Requested

Review and comment on two protocols submitted by Janssen Pharmaceutica for 1) a 2-year combined chronic feeding/ carcinogenicity study in rats using Imazalil base (R023979) as the test material (protocol 3817), and 2) a 2-year concurrent study to develop contemporary historical control data. The Wistar (Hannover substrain) rat is to be used in both studies. The studies are to be sponsored by Janssen Pharmaceutica N.V. (Beerse, Belgium) and conducted at the Department of Toxicology, Jannsen Research Foundation (Beerse, Belgium).

Comments

1. The new 2-year study (protocol 3817) should be conducted in accordance with the EPA Pesticide Assessment Guidelines, Subdivision F, Guideline 83-5 (combined chronic toxicity/carcinogenicity study), November 1984.

2. Janssen Pharmaceutica has proposed that the following dose levels be used in the new 2-year study: 0 (control), 50, 200, 800 and 2400 ppm. The following comments on these dose levels are offered for consideration by the registrant.

   a. Based on evaluations of all available rat subchronic and chronic oral studies on Imazalil, and particularly on the recently submitted 3-month oral dose range-finding study and mechanistic toxicity study on Wistar (Hannover substrain) rats (Experiment No. 3672, MRID 439657-05), Toxicology Branch I concurs with Janssen Pharmaceutica that 2400 ppm appears to be an appropriate highest dose level to be tested for both male and female rats in the new 2-year combined chronic feeding/carcinogenicity study.

   b. Regarding the next highest dose level proposed by the registrant to be used in the same study (800 ppm), it is recommended that this dose level be increased to at least one-half of the highest dose level tested (i.e. to at least 1200 ppm). The reason for this recommendation is that if excessive mortality and/or serious life-threatening toxicity were to occur at 2400 ppm, then 1200 ppm would still be acceptable as a highest dose level, whereas a highest dose level of less than 1200 ppm most likely would not be acceptable.

   c. Regarding the remaining lower dose levels proposed by the registrant (200 and 50 ppm), Toxicology Branch I has no comment other than a NOEL should be established in the study.

3. Regarding the proposed duration of the study, the EPA Guidelines require that the study duration for rats ordinarily should not be less than 24 months or longer than 30 months. The number of rats in <u>any</u> group should not fall below 50% at 18 months and at termination of the study the survival in <u>any</u> group should not fall below 25%.

4. Detailed clinical exminations should be conducted on each animal at least once each week.

5. Gross pathology examinations should be conducted on all animals in the study regardless of time or cause of death.

6. Ophthalmological examinations should be conducted prior to administration of the test material and at least at termination of the study on all animals in the control and high-dose group. If changes in the eyes are detected, then all animals in all dose groups should be examined. In the protocol, there is a discrepancy between the frequency of eye examination between page 9 and page 17.

7. It is not clear in the protocol precisely which animals will be histopathologically examined. The EPA Guidelines (83-5) require that full histopathologic examinations be conducted on at least 1) all animals in the control and high-dose group <u>and</u> all animals that died or were killed during the study, 2) all gross lesions in all animals, 3) target organs in all animals, and 4) lungs, liver and kidneys of all animals.

8. Regarding the protocol for the 2-year concurrent study to develop contemporary historical control data for the Wistar (Hannover substrain) rats, experimental conditions in this study should mimic as closely as possible those in the study using Imazalil base as the test material (protocol 3817). Therefore, the above comments on protocol 3817, except for comments on dose levels of test material, are also applicable to this study.

9. The above comments are provided to assist the registrant in planning, conducting and reporting a study(ies) that will be acceptable and fulfill the Guideline requirements (83-5) for a combined chronic toxicity/carcinogenicity study in rats. The registrant should be reminded, however, that the responsibility for submitting an acceptable study rests not with EPA, but rather with the registrant.

Discussion

The above comments on dose levels in the new 2-year rat study were based, in large part, on the following considerations.

1. In the 3-month dose range-finding study in rats (MRID 439657-05), none of the toxic effects observed in this study at dose levels up to 3200 ppm in male and female rats, other than effects on body weight which are discussed below, are considered to be potentially life-threatening or of serious toxicologic concern. Although the incidences of some effects in both males and females (e.g. hepatocellular hypertrophy, small and/or large vaculoes in hepatocytes) observed at higher dose levels were high, the corresponding severity scores for the same effects at the same dose levels were relatively low.

2. In the same 3-month rat study, the body weight data were very difficult to interpret because it was not possible to determine how much of the dose-related decreased body weights and body weight gains observed in the treated rats was a toxicologically significant effect directly attributable to the test material and how much was a manifestation of the poor palatability/food wastage phenomenon that was observed in the study. It was clear, however, that the palatability/ food wastage problem would preclude the use of diets containing dose levels higher than 3200 ppm.

3. An oral gavage study (daily dosing for 2 years) for this test material is considered to be impractical and not feasible.

4. In the same 3-month study, the nearly identical results observed at dose levels of 3200 ppm and 2400 ppm suggested that in the new 2-year study toxic effects would not be seen at a dose level of 3200 ppm that would not also be seen at 2400 ppm.