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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Assessment of Acute Risk due to Atrazine - Recommendations from the Ad Hoc Committee Regarding the Use of the Developmental Toxicity Studies.

FROM: Marion Copley, DVM, Section Head
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TO: George Ghali
RfD/Mini Peer Review Committee
SAB/HED (H7509C)

THRU: Karl Baetcke, PhD
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CONCLUSIONS

The following are the recommendations and conclusions of this Committee concerning the developmental toxicity of Atrazine and acute risk assessment:

- RAT Developmental Toxicity Study[1]

Maternal NOEL = 10 mg/kg/day
Maternal LEL = 70 mg/kg/day based on decreased body weight, weight gain and food consumption. At 700 mg/kg/day there was maternal death and other clinical signs.

Developmental NOEL at least 10 mg/kg/day or greater (see limitations).
Developmental LEL at least 70 mg/kg/day or greater (see limitations) based on delayed development as characterized by delayed or no ossification at several sites. Runting was present at 700 mg/kg/day.

Limitation of the study: inability of the Committee to determine the significance of delayed skeletal development from the DER. Since this NOEL is greater than the Rabbit NOEL, this limitation does not alter the recommendation for acute risk assessment below.

- RABBIT Developmental Toxicity Study[3]

  Maternal NOEL = 5 mg/kg/day
  Maternal LEL = 75 mg/kg/day based on decreased body weight and food consumption.

  Developmental NOEL = 5 mg/kg/day
  Developmental LEL = 75 mg/kg/day based on increased resorptions, decreased live fetuses, due to an increased post-implantation loss and a decrease in mean fetal weight.

  Limitation of the study: definitive determination of significance of increased skeletal variations and runting at the high dose could not be determined from the DER. This will not alter the recommendations of the Committee with regard to the NOEL to be used for acute risk assessment.

- **Acute Risk Assessment: use NOEL = 5 mg/kg/day (rabbit) for exposures of 1 or more days.**

- It was concluded that the above issues did not need to be presented to the full HED Developmental Peer Review Committee since the Ad Hoc group had many of the full Committee's members in attendance.

ACTION REQUESTED

On March 18, 1993, the Ad Hoc Committee (attendees: D. Anderson, K. Baetcke, M. Beringer, M. Copley, R. Gardner, G. Ghali, K. Hamernik, J. Rowe and H. Spencer) met to discuss the rat and rabbit developmental studies conducted using Atrazine with respect to the maternal NOEL/LEL and developmental NOEL/LEL and adequacy of the reviews to support the endpoints of concern. Following this evaluation it was determined which endpoints were appropriate for acute risk assessment, taking exposure patterns into consideration.

BACKGROUND

The HED RfD Committee met on 1/15/92. Conclusions of the 1/15/92 RfD meeting established that the RfD be based on the NOEL of 2.5 mg/kg/day from the reproduction study. At a meeting on 9/28/92 it was determined that the reproductive study should not be used to establish the RfD. As a result of that meeting, the RfD is currently based on 70 ppm (3.5 mg/kg/day) from a long-term study in rats.

The Committee, in a memorandum dated 1/16/93, was requested to address the following in their summary of the meeting.

- Justify not using the NOEL of 1 mg/kg/day from the rabbit developmental study.
- Address the maternal and developmental NOELs in both the rat and rabbit studies as they relate to use in acute toxicity risk evaluations.

Although the HED RfD Committee met again on 2/11/93 to address the above issues, they were not all resolved at that time.

Atrazine is being considered by SRRD for special review based on cancer, cardiac toxicity and possibly developmental toxicity.

DISCUSSION

RAT DEVELOPMENTAL TOXICITY STUDY - The information examined by the Ad Hoc Committee included the DER by H. Spencer[1] and memo from J. Hauswirth[2]

The Committee determined that the **maternal NOEL/LEL** was 10/70 mg/kg/day based on decreased body weight and weight gain and food consumption. there was high maternal mortality and other clinical signs at 700 mg/kg/day. The **developmental NOEL/LEL** was considered to be at least 10/70 mg/kg/day based on possible skeletal variations indicating delayed ossification (skull not completely ossified; presphenoid, teeth, metacarpals and distal phalanx not ossified; and metacarpals bipartite. The Committee could not confirm this since the data tables (listed as #s 8 and 9) for this effect was not in the DER or in the Hauswirth memo. Although this will not change the recommendation for acute risk assessment, it was recommended that the raw data be examined to confirm this endpoint. At 700 mg/kg/day there was decreased fetal weight (possibly related to runting).

Runting was discussed and it was determined that the incidence of runts at the low and mid doses were not treatment related since the incidence of litters effected was the same as controls and values were within historical control limits. The occurrence of runting at 700 mg/kg/day was treatment related. This is consistent with the memo by J. Hauswirth.

RABBIT DEVELOPMENTAL TOXICITY STUDY - The information examined by the Ad Hoc Committee included the DER by H. Spencer[3] and memos from J. Hauswirth[4] and, S. Dapson[5].

The Committee concurred with the conclusions reached in the S. Dapson memorandum that the **maternal NOEL/LEL** was 5/75 mg/kg/day based on decreased body weight and food consumption. It was noted in that memo that the NOEL may be higher but due to the wide spread between the mid and high doses (5, 75 mg/kg/day) this could not be determined. The **developmental NOEL/LEL** was considered to be 5/75 mg/kg/day based on the Cesarean data (increased total resorptions and resorptions per dam, decreased total live fetuses and live fetuses per dam, an increased post-implantation loss and a decrease in mean fetal weight) presented in the table on page 6 of the Dapson memo. Concern was expressed as to whether the increase in skeletal variations was real since there were no tables in either the DER or either the Dapson or Hauswirth memo. Although the Committee recommended that the raw data be examined to evaluate this endpoint, it was felt that it would not have any impact on the risk assessment since the other developmental endpoints were of much greater concern. The Committee also discussed the occurrence of runts. Concern was expressed that the criteria for "runts" in the DER of "body weight less than 30 grams" was not adequate; standard deviations were not given. They felt that the effect may have only been treatment related at the high dose.

Use of endpoints for acute risk assessment: It was the opinion of the Committee that the developmental endpoints including resorptions, decreased live fetuses and post-implantation loss could have been due to a single day exposure. The NOEL of 5 mg/kg/day in the rabbit study is therefore considered appropriate for acute risk assessment for any use that has one or more days exposure.

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1. DER by H. Spencer for "A teratology study of Atrazine Technical in Charles River Rats", dated 8/19/93, Ciba-Geigy study number 60-84 (MRID 405663-02, HED doc. # 006131).

2. Atrazine - Company response to Toxicology Branch reviews of the rat and rabbit teratology studies. Submitted March 25, 1988 by Ciba-Geigy Corporation., dated 6/24/88, from J. Hauswirth to R. Taylor (HED doc. # 006761).

3. DER by H. Spencer for "A teratology study of Atrazine Technical in New Zealand White Rabbits", dated 8/19/93, Ciba-Geigy study number 68-84 (MRID 405663-01, HED doc. # 006131).

4. Atrazine - Company response to Toxicology Branch reviews of the rat and rabbit teratology studies. Submitted March 25, 1988 by Ciba-Geigy Corporation., dated 6/24/88, from J. Hauswirth to R. Taylor (HED doc. # 006761).

5. Atrazine - re-evaluation of the maternal toxicity in the rabbit teratology study (MRID # 405663-01)., dated 4/24/92 from S. Dapson to G. Ghali.