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

MAR 20 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: EPA Reg. No. 3125-347, Pesticide Petition No. 8E3642. Baytan; Additional Information on the Developmental Toxicity Study in the Rabbit.

FROM: George Z. Ghali, PhD. G. Ghali 3.19.91
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Susan Lewis, PM 21
Registration Division (H7505C)

THRU: John Quest, PHD.
Science Analysis and Coordination Branch
Health Effects Division (H7509C)
and
Reto Engler, PhD.
Chief, Science Analysis and Coordination Branch
Health Effects Division (H7509C)

In the process of reviewing the toxicology data submitted in support of baytan registration, the Agency determined that the tow developmental toxicity studies in the rat and the rabbits did not meet the Agency's current standards, and therefore were both classified as supplementary. The Agency concluded that the rat study was seriously deficient and should not be upgraded, while the rabbit study might be upgraded to Core-minimum data upon the receipt and evaluation of additional information requested by the Agency.

In compliance with the Agency's request, the registrant has submitted a new developmental toxicity study in the rat (Mobay Report No. 100175, MRID No. 414984) and additional information on the rabbit developmental toxicity study (Mobay Report No. 94762-2, MRID No. 412697-00). This memo is confined to addressing the additional information submitted by the registrant regarding the developmental toxicity study in the rabbit.

The additional information on the subject study was referred to L. Chitlik, SACB/HED for evaluation. A self explanatory memorandum by L. Chitlik, outlining the Agency's position on the subject study and the additional information submitted by the registrant, is attached to this letter.

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CONCLUSIONS:

The study was classified as Core-supplementary data. However, although the Agency has concluded that the current study can not be upgraded due to protocol limitation and the associated limitations of data presented, the Agency still requesting that data on individual findings should be submitted along with the appropriate statistical analysis on the per litter and per fetus basis.

Attachments

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

March 15, 1991

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Supplemental Submission to Baytan "Embryotoxicity (Including Teratogenicity) Study with KWG 0519 in the Rabbit", Report # 94762, (EPA Accession No. 403078)

FROM: Laurence D. Chitlik, D.A.B.T.
Senior Scientist, SACB
Health Effects Division (H7509C)

TO: George Ghali, Ph.D.
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

As per your request, I have reviewed the registrant's addendum submission of 10/10/89, to a rabbit Baytan developmental toxicity study (Report # 94762). It is assumed that the registrant response was submitted as per your memo to RD of 6/29/89. In this memo both studies were classified as Core Supplementary Data and the registrant was requested to resubmit all rat and rabbit study data with a complete statistical assessment on a per fetus and and per litter basis. After review of this registrant submission (consisting of Parts I and II) and which refers only to the rabbit study, the following comments/conclusions are provided:

Part I

The registrant apparently misunderstood the Agency request for a statistical analysis of ALL study findings on a per litter and per fetus basis. The one page analysis that was submitted was titled "Statistical Analyses of All the Findings on a Per Fetus and Per Litter Basis". This table apparently only included external and skeletal malformations totaled together. Such a response has only very limited utility and is not what was requested. The Agency request was for each and every study finding including reproduction data and variation data and not just an assessment of the combined total of only malformations.

Following this table, are additional tables of skeletal variations (with statistical evaluation) presented on a fetal and litter basis. Unfortunately, these data are further limited for a number of reasons. First, they do not include any findings for the skull. Variations in skull development would be expected in a study of this size and it appears from examination of the study methodology that clearing and staining of even a fraction of the heads was not performed. The examination of the skull after

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clearing and staining is especially important in this case since encephalocele was noted after external and soft tissue examination of litters of both the 8 and 40 mg/kg dose groups. Due to this protocol limitation, and the associated limitations in the data presented for the skull, this study cannot be upgraded to an acceptable status.

Secondly, the statistical analyses failed to consider combinations of both incomplete or non-ossification for the same ossification site. In addition, it is not possible or meaningful to simply add the two sets of data together as this will not correctly reflect findings on a litter basis nor resolve questions of the significance of effects upon any specific site. Therefore, it is not possible to reach definitive conclusions relative to NOEL's for developmental toxicity based upon these data.

Finally, as these data tables are labeled "Skeletal Examination Summary", they include no soft tissue variation findings. Certainly, in a study of this size some such findings should be expected ... but none are reported in this addendum.

Although the skeletal data were limited (as noted above), an examination of these data revealed the following:

1. There are a number of new table entries which are simply listed as "unlisted findings". In the case of the sternum, for example, one such finding occurs in 4 out of 14 litters at the the high dose level (or 29% of the litters) without any indication as to what the finding is or whether there is statistical significance even with a 0 incidence in the controls. One fetus in one litter of the low dose also elicited this same "unlisted finding". On this basis, there may be reason to request an audit of this study.

2. Numerous high dose findings are noted at statistically significant levels on a fetal basis. At lower dose levels, biologically significant effects appear more readily as trends (e.g. medial phalanx of forelimb and hindlimb) especially as noted in the underlined sections of the attached tables. Some few findings do appear at statistically significant levels especially for non-ossified or incompletely ossified toe 4, medial phalanx. Looking at these variation data collectively, it appears that developmental delay occurs at all dose levels in this study although such conclusions must be considered tentative due to the limitations of these data.

Part II

This portion of the supplemental submission attempted to clarify problems with a previous addendum dated November 14, 1988. In that earlier addendum, dose levels for the rabbit study were reported to include a 120 mg/kg/day dose level instead of the

reported Group 4 level of 200 mg/kg/day. The registrant indicated that a typographical error was the source of the discrepancy. This explanation may resolve the previous question, but erroneous reporting of dose levels has often been adequate justification for a data audit.

Possibly this dose level discrepancy has been adequately explained, but coupled with the the addition of "unlisted findings" to the tables, the lack of reporting for the skull, and questions associated with the absence of soft tissue variation data, may still support the need for a data audit. I defer on this issue to Dr. Ghali.

cc: Reto Engler