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TR-4066

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

004066

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Report Amendment to Mouse Teratology Study on Acrolein; #10707-9

TO: Richard Mounfort
Product Manager (23)
Registration Division (TS-767)

THRU: Christine F. Chaisson, Ph.D. CFC 10/29/84
Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: Chad B. Sandusky, Ph.D. Chad B Sandusky 10/29/84
Pharmacologist
Toxicology Branch
Hazard Evaluation Division (TS-769) 10/30/84

Action Requested:

Magna Corporation previously submitted a mouse teratology study (Accession # 248886) which, upon review, was assessed to be Core Supplementary. In the current submission, Magna has submitted an amendment (Accession #253620) for review and incorporation into the original report. Magna has requested that upon consideration of this amendment the Core Classification of the mouse teratology study be upgraded from supplementary to Minimum. Both the original report and amendment were prepared by Biossay Systems, Inc. who conducted the study.

Review:

The original review of the mouse teratology study outlined numerous deficienies which were discussed in a meeting with Dr. Indu Muni and Mr. Mattew King of Biossay Systems on January 10, 1984. Subsequently, on February 10, 1984 Magna requested a complete copy of the original review prepared by Dr. John DeSesso of the Mitre Corporation. The amendment prepared by Biossay and submitted by Magna was also reviewed by Dr. DeSesso.

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His comments are attached (#1) and summarized below.

Although the amendment addresses 15 changes from the original submission, the majority of these are minor in nature and inconsequential to the evaluation of the data, e.g., changes in terminology, spelling, titles of tables, etc. There were also several changes made in manipulations of the original data, e.g., reclassification of certain malformations or variations and the use of different statistical tests. These manipulations had previously been performed in the preparation of the original, i.e., Mitre, review of the report. Therefore, these changes do not impact upon the Core Classification since they have already been considered.

Two key issues, however, are not resolved concerning the quality of this study. Although the amendment states that all viscerally and skeletally examined fetuses have been rechecked for cleft palate, the low number of pregnant animals precludes definitive evaluation of acrolein for teratologic effects in the mouse. The low number of pregnancies and low pregnancy rates (14 and 46% for controls; 12 and 40% for high dose) was discussed with the representatives of Biossay Systems and raises additional questions concerning animal husbandry, especially since the animals were ordered pregnant.

Conclusion:

Due to the insufficient number of pregnant animals, the Core Classification of the mouse teratology study remains Supplementary. In addition, as discussed in the original review, the number of fetuses with generalized delayed ossificaiton was increased over controls in all treated groups. Although this may be due to "under development" of the fetuses, as stated by Biossay, it is not possible to establish this effect as a nonfetotoxic event or establish a NOEL.

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Attachment # 1

MITRE CONTROL NO. OPP84WC0302
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REVIEWED BY Tom

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ADDENDUM TO MITRE DER 82/611, ACROLEIN TERATOGENICITY IN MICE

In response to both a Data Evaluation Record (DER) and an informal discussion concerning the teratogenicity study of acrolein in mice performed by Bioassay Systems Corporation (Project #10258), a report amendment was submitted to the EPA by the registrant for consideration with the intention of upgrading the Core Classification of the study. The report amendment contains numerous changes in terminology, spelling, titles of tables, and appropriate changes in the table of contents. These changes will not be commented upon in this document.

The authors provided additional information relating to preparation of skeletal specimens. Anomalies were reclassified as either malformations or variations, and new statistical tests were applied to these data. Since these operations had previously been performed during review of the study in the original DER, no further discussion is warranted here.

The authors reclassified findings of hemmorhage into the fetal body cavities as artifactual. Although the suggestion that the hemmorhages may be artifactual was made in the original DER, the authors provided no explanation as to why they were artifactual. Therefore, this point remains unclarified.

The key issue concerning the quality of this study pivoted on two major problems. First, 4 cases of cleft palate were found in treated pups (2 each in the high and mid-dose groups); and second, an insufficient number of animals bore litters.

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The authors have asserted that all viscerally and skeletally examined fetus have been checked for the presence of cleft palate. The total incidence has been verified as 0/167, 0/184, 2/207, and 2/124 for control, low, mild, and high dose groups, respectively. When analyzed by chi-squared analysis, and Fischer's Exact Test, no significant differences are found. However, the low number of pregnancies precludes one from establishing whether or not there is a treatment related effect.

Other data which are usually present in teratology studies remain unsupplied including numbers of corpora lutea and interim maternal body weights (to determine the rate of meternal body weight changes).

In the absence of these data, and with the reduced statistical power caused by insufficient number of pregnant animals, it is recommended that the classification of this study remain supplementary.