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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Richard Mountfort
PM-23
Registration Division (TS-767)

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Hazard Evaluation Division (TS-769)

SUBJECT: Review of Two Protocols for "Oncogenicity Test(s) in Rats (and Mice) with Acrolein". Action #10707-9.

Action Requested

Review of 2 protocols:

1) "Oncogenicity Test in Rats with Acrolein", and

2) "Oncogenicity Test in Mice with Acrolein".

Background

Two protocols for "chronic/oncogenicity" studies were submitted by Magna Corporation for review. One study will be done using rats and one using mice.

The chemical being tested was identified as Magnacide H Herbicide. The protocols further identify the common/chemical names for this substance as arcolein; acrylic aldehyde; acraldehyde; and 2-propenal. The purity of the test substance to be tested is specified in the protocol to be "greater than 96%".

Protocol Review:

The protocols submitted by Magna Corporation are consistent with the Agency's proposed testing guidelines for oncogenicity studies (FR, Vol. 43, No. 163, Section 163.83-2, published 1978). However, the following observations are pertinent to the review of both protocols:

1) Neither protocol includes blood chemistry determinations. Therefore, the protocols, as submitted do not fully meet the Agency's proposed testing guidelines for

chronic studies (FR, Vol 43, No. 163, Section 163.83-1, published in 1978). The sponsor should be aware of this deficiency with respect to chronic testing (see Section 163.83-1, C(11)ii-iv of the above referenced guidelines).

2) Both protocols incorrectly cite "43 FR 37336, part 163.83-4" (reproduction and teratology testing) as guidelines for chronic/oncogenicity testing.

3) In the mouse protocol, Appendices A,D,E, and F are missing. Appendix A is missing from the rat protocol. Therefore, they were not reviewed.

4) With respect to the selection of species for both studies, the sponsor should be aware of 43 FR 163-2, section d (1) (i) page 37380, concerning background information on the test species.

5) With respect to group housing of animals (5/cage), care should be exercised to avoid cannibalism of dead or moribund animals (Section 6.2.1 of both protocols).

6) The sponsor should exercise care in the selection of doses (Section 7.1 of both protocols) to insure the intent of the proposed guidelines for oncogenicity testing is met (Section 163.83-2, C(7) page 37379). The rationale for the selection of doses indicated by Magna does not insure that a Maximally Tolerated Dose (MTD) will be used. In addition, with respect to chronic oral studies, there is no evidence that the proposed doses would allow selection of a No Obserable Effect Level nor establish dose-response relationships for any effects observed.

7) According to Section 11 of both protocols, the original data will be retained "for not less than two years after complexion of the study...." These data should be retained at least until all issues of potential toxicity of this chemical have been resolved.

8) The schedule of interim sacrifices (the number and the intervals) is not specified. Interim sacrifices and collection of hematology data are only referred to in section 7.6.7 of both protocols.

Summary

It is unclear if the protocols are intended to meet the proposed testing guidelines 43 FR (published 1978) for both chronic (Section 163.83-1) and oncogenicity (Section 163.83-2) studies. Both protocols do meet the intent of the requirements for oncogenicity testing but do not fully meet the requirements for chronic studies (see comment 1 above). In addition, particular attention should be given in the selection of doses for both oncogenicity and chronic studies (see comment 6 above).

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