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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM

2 pages

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

TO: Mr. John A. McCann, Coordinator
National Laboratory Audit Program (TS-768-C)
Office of Pesticides Program

THROUGH: John Seitz, Chief
Compliance Monitoring Unit (EN 342)

FROM: Dexter S. Goldman, Head
Laboratory Data Integrity Program (EN 342)

SUBJECT: Proposed Audits at Hazleton (Raltech) on Metolachlor

I have reviewed the correspondence leading to this proposed priority site visit at HRT and suggest that a study audit may not be the most appropriate way of resolving the issues raised in the HED review.

Dr. Gary Burin (HED, OPP) has carefully reviewed the chronic rat study of Metolachlor submitted by HRT. Dr. Burin raised certain questions on the study and concluded that a laboratory audit was warranted based on two issues:

1. The report indicated no increased incidence of hepatic neoplastic lesions in treated animals, male and female. Dr. Burin pointed out however (pg 5), that if the neoplastic nodules and the hepatocellular carcinomas are combined the incidence becomes significant.

2. In an earlier letter (Dec. 9, 1982), Registrant indicated a liver tumor incidence that differed from the incidences presented in the final report. Dr. Burin felt that the explanation given by the Original Pathologist was not adequate.

I feel you should be aware of the following points:

1. It is common practice and acceptable practice to give a complete histopathologic examination to animals dying during the course of a 2-year study and then to rediagnose these animals when <u>all</u> the study animals are read at one time at the end of the study. It is common to take a second look at the earlier diagnoses; changes to earlier diagnoses are acceptable if all animals are diagnosed using the same criteria. Dr. Terry Jackson, the Original Pathologist has provided an explanation of the histologic criteria used in has final interpretation; this explanation appears reasonable and adequate.

2. There will never be an end to the controversy of conbining or not combining neoplastic nodules with hepatocellular carcinomas and achieving a different statistical significance to the incidence of lesions. I will only point out that basing a judgement of carcinogenicity on a combination of hepatic lesions in one sex of one species in a 2-species study is considered to be questionable, at best.

3. Testicular atrophy is a common finding in male rats of this age. Dr. Burin makes the point that while the incidence of atrophy in test and control animals is the same at termination it was higher in test animals that died during the conduct of the test. As the cause of interim death is not known it is not clear if the observed atrophy is compound related. An inspection of the weight changes and patterns of weight changes of interim death males, compared to their cage-mates, might provide some useful information on whether the atrophy was, perhaps, compound related or, instead a secondary sign of some wasting process in these animals.

4. The repeat mouse study, submitted earlier, was negative.

I suggest that an audit in the sense recommended by HED would not resolve these issues. A better way might be to ask for an independent and blind review of the rat liver slides with a new pathology narrative prepared from this review. This can be done by the Registrant quickly and should help in the decision process.

I have discussed these issues with Dr. Burin.

These comments are for your consideration and have no bearing on a future decision to audit this study as part of the data integrity program prior to making a regulatory decision.

Dexter S. Goldman, Ph.D.

cc: Dr. Gary Burin TS-769C
Dr. William L. Burnham TS-769C
Mr. A. E. Conroy, II EN-342