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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Company Response - Submission of Additional Data to Supplement Two Baythroid™ Neurotoxicity Studies in Rats

EPA No. 3125-GLR
Record No. 169470
Project No. 1436
Tox. Chem. No. 266E

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John E Whalan 5-5-86

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Budd 5/9/86

Concur WTB 5/17/86

Toxicology Branch reviewed two neurotoxicity studies in rats (J. Whalan; EPA No. 4F-3046; May 22, 1985) submitted by Mobay Chemical Corporation. There were a number of deficiencies in both study reports to which the Registrant has now responded. The following are itemizations of the deficiencies and the data submitted. The revised Core status of these studies follows each presentation.

1. Subacute Neurotoxicity of Orally Administered FCR 1272 in Rats, Bayer AG Institut Fur Toxikologie; Bayer Report No. 12338, Mobay Report No. 86305; December 27, 1983.
The response was in the form of an addendum to the report.

   A. This report was lacking the signatures of the participating scientists and pathologist - The Registrant submitted a copy of the signed discussion page (page 24) from the German report. Although this page had no report number to identify it, it did appear to come from this report.

   B. The histopathology tables were lacking all data that pertained to what was described by the authors as "normal variability specific to the species and the animals' ages, and the conventional conditions under which they were kept." - The pathologist, Dr. G. Kaliner, gave a description of what was reported in the histopathology tables as "histopathologically unremarkable. These lesions included such findings as "degenerated, short segments of individual fibers (digestion chambers), and the occurrence of individual round cells and mast cells."

C. The report was lacking a presentation of the gross lesions - The gross pathology data were presented. These data demonstrate that most rats dosed at 50 or 60 mg/kg/day had distended lungs; this was not mentioned in the report, and it is not regarded as a compound-related effect. Further, the four males which died in the 60 mg/kg/day group died on days 6-9, not days 5-8 as reported.

On the basis of these clarifications, the Core classification for this study can now be upgraded to CORE GUIDELINE.

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2. Subacute Neurotoxicity of Orally Administered FCR 1272 in Rats, Nihon Tokushu Noyaku Seizo K. K. Agricultural Chemicals Institute; Mobay Report No. 86427; June 30, 1983. A complete revised report was submitted.

A. This report was lacking the signatures of the participating scientists and pathologist - Dr. Iyatomi did not want to sign the English translation of the report because he believes that only the original (in Japanese) should be signed. This line of logic is flawed, because the purpose of the signatures is not to verify the accuracy of the translation, but rather to verify that the study was actually performed, and the data are correct. More specifically, these signatures assign responsibility for the study to the participating scientists and pathologists, not the translator (who may not know anything about the study). Dr. Iyatomi was the Supervisor of this study. He signed page 12, assuming responsibility for the translation. He also said that he sent a signed Japanese report, but a copy was not received in the Toxicology Branch. This objection will be waived since the report was signed by Dr. Iyatomi, the Study Supervisor.

B. The method of orally dosing the rats was not described - The rats were "forcedly" dosed p.o. Presumably, this means that they were dosed by stomach tube.

C. The schedule for observing clinical signs was not given - "All of rats [sic] were daily inspected on their appearance and behavior through the 14-day administration period and 3-month observation period."

D. No clinical signs were reported for any control animals - There were no clinical signs observed in any control animals.

E. The study protocol, results section, and body weight graph were not consistent in regards to the times of measurement and periods of divergent weights - All of the rats, "were weighed daily on the administration period, and at 1st and 5th day, 2nd week, 1st, 2nd and 3rd month of observation period." The body weight data presented in tables and a graph were reported weekly during the administration period, and as specified during the observation period. This procedure is appropriate.

F. The histopathology tables were lacking all data for lesions that were judged to be not caused by the test article - A complete presentation of histopathology revealed no lesions other than sciatic nerve axonal degeneration (previously reported).

G. There were contradictions between the results section and the pathology tables in regard to the number of animals affected - The results section in the revised report agrees with the pathology tables.

H. The report was lacking a presentation of the gross lesions - There were few gross examinations performed because, "Autopsy was not inspected in all of animals, because the macro-changes in color and/or size occurred by the perfusion fixation." This is a reasonable procedure.

On the basis of these clarifications, the Core classification for this study can now be upgraded to CORE GUIDELINE.

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