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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

RELEASABLE

JAN 16 1987

005670

MEMORANDUM

SUBJECT: Linuron Data Call-In, Reanalysis of Hematological Data from Rat Chronic Study; Caswell 528; EPA I.D. # 035506; Project 7-0133; Record No. 183736

TO: Michael McDavit, Review Manager
Special Review Branch (TS-767C)
and
Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division/HED (TS-769C)

James N. Rowe
12/15/86

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)

Laurence D. Chitlik for LOC
12/13/86
11/16/87

ACTION: Review of Du Pont submission for reanalysis of hematological data from previous chronic rat study with Linuron (study #100-80, 1980; EPA Accession # 241897); Caswell 528; EPA I.D. # 035506; Project 7-0133; Record no. 183736

CONCLUSIONS/RECOMMENDATIONS:

A rat chronic study was previously submitted and reviewed by the Agency (J.W. Holder; Linuron Toxicology Chapter for Registration Standard; 9/15/82). based on data gaps noted in the Registration Standard, the registrant submitted data regarding blood pigments and hematology data, in addition to the present submission. The hematology submission was meant to clarify the issue of a NOEL for general hematology effects observed in chronic exposure of rats to linuron in a three-generation reproduction test (see Accession #s 26053 and 25913). The blood pigment data (sulf- and methemoglobin following dietary exposure) was required in the registration standard for certain substituted phenyl urea compounds such as linuron. The present re-analysis was intended to show that a NOEL for general hematology had been established in the two-year rat study, and to support the Company's position that an additional chronic rat study was unnecessary.

The submitted re-analysis of the hematological data was evaluated by Bernice Fisher of the Biostatistics Team of the Toxicology branch at the reviewer's request (see attached memo). It was determined that the Company's re-analysis

failed to evaluate the total data set over the time of the study and an additional analysis was suggested to du Pont's statistician, Jay Graepf. It is recommended that the requested analysis, as stated on p. 2 of the attached memo, be performed in the near future.

Based upon the findings of the additional company analysis of the hematology data from the rat chronic study and the additional hematology data submitted by the registrant which are presently under review, a final EPA recommendation for the necessity of a repeat of the two-year rat study will be made.

ATTACHMENT



005670

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Linuron, Comments on Statistical Re-evaluation of
Blood Data from the Two Year Rat Study.

FROM: Bernice Fisher, Statistician *Bernice Fisher 12/3/86*
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

and

Bertram D. Litt, Leader, Biostatistics Team
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769) *Bertram D. Litt*

TO: James Rowe, Ph.D., Pharmacologist
Toxicology Branch/HED (TS-769)

THRU: Reto Engler, Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769) *Reto Engler*

Dr. Rowe requested an evaluation of the repeat Statistical Analysis in the E.I. Du Pont's Evaluation of Clinical Laboratory Data report based upon the 2-year rat study with Linuron (INZ-326), 9/8/86.

The Company's report specified that for each of the five designated time periods (3, 6, 12, 18 and 24 months) 10 animals were selected for examination of selected blood factors.

It became evident during the examination of individual animal data that the blood data of the same 10 animals were used in at least three of the five aforementioned time periods, while in the last two of them, animal substitutions were made where ever it was necessary, in order to maintain a 10 animal group.

Therefore, the standard approaches to statistical evaluation of time as related to dose differences in this study was not feasible due to the inconsistencies in the use of same or different animals in the selected time periods.

The Company's report presented statistical evaluations for each time period alone and did not attempt to evaluate the total data set over the time of the study.

EPA suggested via a phone call to the statistician (Jay Graepl) at E.I. Du Pont that a profile or repeated measures analysis could be prepared for the first three time periods under two assumptions; one, that the animals were the same 10 in each of the 3 groups and the other, that the 10 were different in each of the time groups. If the statistical outcome under each of the above two assumptions were similar, then all the five periods with blood data could be evaluated under the assumption of independence among the time periods. However, if statistical results differed and if five or more of the same animals' blood data were available for all of the time periods, a repeated measurements ANOVA could be performed for each of the selected observations made. Otherwise the statistical findings from the three time period profile and the remaining individual time periods could be compared by '-2 log P' or other procedures to test for homogeneity of overall significance or individual contrasts for outcomes of interest.

cc Jay Graepl

#15 12/2/86 sb