

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000930

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DATE: July 24, 1979

SUBJECT: Trifluralin Reproduction and Teratology Studies

FROM: Laurence D. Chitlik, Toxicologist  
TOX/HED TS-769

*LC*

TO: Marcia Williams, Director  
Special Pesticide Review Division TS-791

and

Douglas Campt, Director  
Registration Division TS-767

THRU: M. Adrian Gross, Chief  
TCX/HED TS-769

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THRU: Peter E. McGrath, Ph.D.  
Director  
Hazard Evaluation Division TS-769

Your memo to Dr. McGrath was forwarded to Toxicology Branch for our response (attachment).

Toxicology Branch has re-reviewed both of the following studies referred to in the memo of D. Kuroda, 5/8/79:

1. Rat, Multi-generation reproduction, Trifluralin, H.M. Worth, K.M. Small, W.R. Gibson, W.J. Griffing, E.C. Pierce and P.N. Harris, The Lilly Toxicology Laboratory, Greenfield, Indiana, Oct. 1966.
2. Rabbit, Teratology, Trifluralin, H.M. Worth, R.M. Small, W.R. Gibson and E.C. Pierce, The Lilly Toxicology Laboratory, Greenfield, Indiana, Oct. 1966.

In reference to the Reproduction Study, it was determined that stresses induced by severe temperature regulation problems within the Laboratory and moving the animals from one facility to another during the study could very likely have resulted in very low reproductive indices in some test and control litters; additionally, an inadequate number of rats were used. This study has therefore been classified as "supplementary" as per the Core concept and shall no longer fulfill the regulatory requirement for an acceptable reproduction study.

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The rabbit teratology study had only 8 rabbits assigned per group and, of these, only 6 or 7 were pregnant. Dosing by gavage was from the 8th through the 16th day of gestation rather than days 6 through 18 which is considered as the period of major organogenesis in the rabbit. Of even greater concern than the above listed problems, is the fact that only one finding related to soft or skeletal tissue examination was noted (and this was explained as artifact due to over clearing of 2 fetuses). The normal incidence of variations and anomalies would indicate that a number of such findings should have been reported. Furthermore, not only did control dam weights essentially remain unchanged, but test group dam weights actually decreased during gestation. Dams were also sacrificed 4-5 days prematurely (day 25 of gestation) which resulted in unusually low fetal weights (i.e., mean control fetal weight of 17.67 grams). For many of the listed reasons, this study shall also be classified as "supplementary" and shall no longer fulfill the regulatory requirement for an acceptable teratology study.

In conclusion, Toxicology Branch finds neither of these studies adequate to meet regulatory requirements; but it must also be emphasized that no RPAR triggers were noted in either of these studies and Registration Division should be notified as to their status so that these data gaps may be addressed.

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

JUL 18 1979

OFFICE OF TOXIC SUBSTANCES

SUBJECT: Trifluralin Reproductive and Teratogenicity  
Studies

FROM: Marcia Williams, Director *Marin*  
Special Pesticide Review Division

TO: Peter McGrath, Director  
Hazard Evaluation Division

As we discussed, we are on a PD 2/3 schedule for Trifluralin (Treflan) that would result in a DAA briefing by July 24 and an AA briefing by July 31. We circulated the document for PCRC review last month. We received extensive comments from OGC and both our staffs are now working to incorporate those comments. (I mentioned to you last week our request to put Treflan priority above Maleic Hydrazide priority for the next two weeks.)

We have just received another set of PCRC comments from Donna Kuroda. She suggests that there are significant inadequacies in the existing trifluralin reproduction and teratogenicity studies. Although the time frame is short, we would appreciate it if HED could review the referenced studies and let us know whether these studies are adequate. If new studies are necessary, we should indicate this in the PD 2/3 for trifluralin.

Is a response by COB 7/20/79 a possibility?

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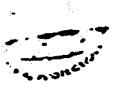
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5/30/79



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

000930

May 8, 1979

OFFICE OF  
RESEARCH AND DEVELOPMENT

SUBJECT: Trifluralin

From: Donna Kuroda, Physical Science Administrator

TO: Tom Miller, Project Officer Special Pesticide  
Review Division

The 3 generation reproduction study for trifluralin has some very serious deficiencies such as a lone survivor in the third generation for one of two dose levels. Also, the rabbit teratology is seriously flawed by using small numbers of animals, unexplained failures to conceive, etc. It would be prudent to have the registrant re-do these studies following standards in the Guidelines for Registering Pesticides.

PCRC Comments

Elanco Studies:  
① H.M. Worth, R.M. Small, W.R. Gibson and  
E.C. Pierce  
Teratology studies with  
Trifluralin. Lilly Toxicology  
REC. Greenfield, IN. 5/9/79

② H.M. Worth, R.M. Small, W.R. Gibson and  
W.S. Griffing, E.C. Pierce and P.P. Harris  
Effect of trifluralin treatment  
on reproduction in rooster dogs.  
Lilly Toxicology. Oct 1966

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