CASWELL FILE

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

MEMORANDUM

DEC 12 1989

SUBJECT Industry Response to Trifluralin Carcinogenicity mouse Study Review of July 14, 1987.

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

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Chemical Trifluralin

Caswell No: 889

In response to the deficiencies noted in the July 14, 1987 Toxicology branch memo on the Trifluralin (IPICI) mouse study Hoechst-Celanese Corp. (HCC) has submitted the following data:

1. Historical control data for hepatocellular neoplasms in NMRI mice,
2. Statistical calculations of the liver tumor data,
3. Summary calculations of gross pathology findings for both interim and terminal sacrifices,
4. Time-to-liver tumor analyses,
5. Possible explanations for the liver carcinoma incidence levels in group 4 males.

The submitted information will be discussed in the above order.

1. Historical Control Data:
HCC had the performing laboratory RCC (Research and Consulting Co. AG) compile historical control data from mouse carcinogenicity studies performed in their laboratory. In these studies, the incidence of hepatocellular adenomas in untreated males ranged from 4 to 16%. The incidence in the trifluralin study in males was 10, 16, 14 and 12% for groups 1 through 4 respectively, well within the historical control range. The historical incidence for hepatocellular carcinomas in males ranged from 0 to 8%. The incidence in the trifluralin study was 2, 6, 14 and 3% for groups 1-4 respectively.

EPA Response:
EPA agrees with HCC concerning the adenomas and carcinomas being within historical control values.

2. Statistical Calculations:
HCC used the Peto prevalence analysis method to test for a positive trend with respect to dose rates, and found no positive trend.

EPA Response:
EPA also performed its own statistical analyses, and a pair-wise comparison of total liver tumors between the control and mid-dose gives a value of P=0.039. The Peto trend analysis performed by EPA indicated that there is no significant trend for either the adenomas, carcinomas or combined adenomas and carcinomas.

3. Summary Tabulation of Gross Pathology Findings:
HCC has submitted the summary tables for gross pathology of the interim and final sacrifices. These tables were missing from the original report.

EPA Response:
There do not appear to be any compound-related increased incidences of gross pathology findings.

4. Time-To-Tumor Analysis:
HCC has submitted a table of days under test and diagnoses of liver tumors.

EPA Response:
There does not appear to be a decrease in time-to-tumor with increasing dose of trifluralin.

5. Possible Explanations for the Liver Carcinoma Incidence Level in Group 4 males.
HCC has submitted several possible explanations for the apparent increased incidence of liver tumors in male mice.

EPA Response:
After examining the submitted historical control data the EPA has concluded that the incidence of male liver tumors was not sufficiently high to warrant a more thorough review of the tumor data by the Peer Review Committee.

Conclusions:
The requested information has been submitted by HCC and the liver tumors do not appear to be treatment-related. The study may be upgraded to core minimum.