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

APR 19 1988

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Benefin 1471-71 (Record Number 212721): Review of the Interim Report of Histopathological Findings in A Two-Year Oncogenic Mouse Study with Benefin (El-110, Compound 54521). Caswell Number 130

From: John H.S. Chen, D.V.M. John H.S. Chen 4/11/88
Review Section I
Toxicology Branch
Hazard Evaluation Division (TS-769C)

To: Robert J. Taylor, PM 25
Herbicide-Fungicide Branch
Registration Division (TS-767C)

Thru: Robert B. Jaeger, Section Head 4/12/88
Review Section I
Toxicology Branch
Hazard Evaluation Division (TS-769C) 4/19/88

Petitioner:

Eli Lilly and Company
Greenfield, Indiana 46140

Action Requested:

Review of the interim report of histopathological findings in a two-year oncogenic mouse study with Benefin (EL-110, Compond 54521). Lilly Research Laboratories Studies M02785 and M02885. June, 1987.

Recommendation:

Toxicology Branch acknowledges receipt of information from Eli Lilly and Company pertaining to identification of the gross liver nodule findings presented in an interim report " Gross pathology findings in a two-year oncogenic mouse study with Benefin " previously submitted (Toxicology Branch Memo 9/21/87 J. Chen). The final report of this study is scheduled to be submitted in January, 1989.

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Three types of proliferative hepatocellular lesions (i.e., hyperplasia, adenoma and carcinoma) have been identified from the gross liver nodule findings presented. Male mice showed no increase in either neoplastic or non-neoplastic hepatocellular lesions while females in the highest dose group (dietary concentration of 0.15%) exhibited an increase in hepatocellular hyperplasia. Although there was no strong evidence for a dose-related trend toward increased carcinomas ($P=0.07$) or adenomas ($P=0.23$) in treated female mice, evidence of a positive trend was present ($P<0.05$) when incidences of adenomas and carcinomas were combined (i.e., 1/60, 3/60, 3/60 and 6/59 for control, low-, mid- and high-dose groups respectively). The evidence of hepatocellular adenomas and carcinomas observed in treated female mice at this point will be carefully evaluated when the final report is submitted. Toxicology Branch will provide a full evaluation when the study is completed and all data, including historical control data, are received. Until then, Toxicology Branch would recommend against the establishment of permanent tolerances or significant new uses (if any) pending a full evaluation (to include Peer Review if necessary) of all relevant toxicological data.

CC: R. Engler, Ph.D
Toxicology Branch

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