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CASWELL FILE

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Peer Reviews of Ronilan Mouse Oncogenicity Study
Caswell No. 323C

Study Identification:
Chronic Toxicity and Oncogenicity of Vinclozolin (Ronilan) in Mice. F. Leuschner, Laboratory for Pharm. & Toxicol, Hamburg, FRG. Dec. 15, 1977.

Background: The mouse study has been submitted to OPP in support of registration of Ronilan and has been reviewed by the Toxicology Branch (several memos 1982-83). The reviews, inter alia, concluded that there was a trend showing increased incidences of lung adenomas. The registrant (BASF) contended in its submission of Feb. 9, 1984, that the lung adenomas observed were within the range of historical controls, and therefore not compound-related.

On August 30, 1984, Dr. Ernest E. McConnell, NIEHS, North Carolina, peformed a peer review of the findings, conclusions and rebuttals. He was provided with a copy of the mouse study, the reviews of the Toxicology Branch, and the rebuttal argument (historical control data) of the registrant.

After the reviews, Dr. McConnell, debriefed Dr. Reto Engler and Mr. Bruce Jaeger of the Toxicology Branch as follows:

Conclusions:

1. The mouse study is acceptable for evaluating oncogenic effects, in particular the MTD for the test compound has been reached (very significant liver weight increases).

2. Leukemias:

    1. Incidences in control groups are fortuitously low.
    2. Incidences in treated groups are well within the expected (historical) rate.
    3. No dose response trend was established.
    4. Therefore, the conclusion by Tox Branch that leukemias were not compound-related can be corrobated.

3.. Liver Tumors

    1. Show a low incidence, barely significant.
    2. They are, however, above historical controls.
    3. They are only seen at study termination.
    4. There are only benign tumors
    5. The conclusion by Tox. Branch that liver tumors were not likely to be compound-related was corroborated.

4. Lung Tumors

1. No effects in males were seen.
2. Adenomas (non-lethal) increased with dose in females, however with low incidence (10%).
3. Lung adenomas did not progress to carcinomas.
4. The historical range of lung adenomas is 4-11% in this mouse strain in studies conducted in the same laboratory. However, it is concluded that the incidence in the Ronilan mouse study are only exceeded by one historical data point and therefore cannot be considered "average." The trend of increases of lung adenoma, therefore, cannot be discounted based on the historical data alone. Furthermore, the historical control data, especially for pulmonary lesions, should only include those performed in the same laboratory and preferably by the same pathologist, and it is not clear that both these criteria are fulfilled for the data presented by BASF (i.e. same pathologist).

5. Dr. McConnell finally suggested that the study should be evaluated to define the incidence of alveolar hypyplasias (a presumed precursor stage of alveolar adenomas). This evaluation could significantly affect the weight of evidence (Tox Branch is now undertaking this effort).

Prepared by

Reto Engler, Ph.D.
Toxicology Branch
Hazard Evaluation Div.

Concurred by

Ernest E. McConnell, D.V.M.
Acting Director
Toxicology Research and Testing Program

cc: R. Jaeger
R. Gessert
W. Burnam
H. Jacoby