



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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: November 18, 1981

SUBJECT: Response to Ciba-Geigy Comments re Metolachlor Chronic Rat
Feeding Study. Tox. Chem. #188DD

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THRU: William Burnam, Acting Chief
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The following Toxicology Branch comments are offered in response to the November 2, 1981 letter from Dr. Gene Holt of Ciba-Geigy. In that letter, Ciba-Geigy presented four separate considerations which are relevant to this interpretation of the study. Those considerations, and the Agency responses, are as follows:

1. "The inclusion of hyperplastic nodules as an oncogenic response is not universally accepted..."

TB Response: True - their inclusion of hyperplastic nodules as an oncogenic response is not universally accepted. However, that classification was the consensus of an NCI-sponsored workshop held in December of 1974 (Cancer Research, Vol. 35, 3214-3223, 1975) and is currently recommended by the National Academy of Sciences (see "Histologic Typing of Liver Tumors of the Rat", JNCI, Vol. 64, No. 1, 1980, p. 185).

The NCI workshop recommended that the term "neoplastic nodule" replace "hyperplastic nodule" based upon the experimental and biological evidence available. The report on the workshop stated that "such nodules are proliferative lesions and are known to be induced by carcinogens, and, at the least, they indicate an increased probability for the development of hepatocellular carcinoma."

The National Academy of Sciences has concluded that "The neoplastic nodule is a manifestation of the process of hepatocarcinogenesis... It is induced by a variety of hepatocarcinogens but not by noncarcinogenic agents."

Thus, both NCI and NAS concur with the Agency policy of classifying hyperplastic nodules as neoplasms. The classification is not merely semantic but is an evaluation of the biologic significance of the lesions.

Furthermore, as is noted in the letter of November 2, 1981 from Ciba-Geigy, "The synonyms hyperplastic nodule, nodular hyperplasia, hyperplastic nodule, adenoma, etc., denote the same lesion and Dr. Robert Jacoby, the pathologist making the audit review, has used the term "hyperplastic/hypertrophic nodule" in this sense."

Based on this statement, the Agency is unable to conclude that the term "hyperplastic/hypertrophic nodules" does not refer to a neoplastic lesion.

2. "The incidence of hepatic hypertrophic and hyperplastic lesions is not influenced by metolachlor."

TB Response: True. However, the lesion of interest, hepatocellular neoplasia, is influenced by treatment as evidenced by the increased number of animals bearing primary liver tumor in the high dose female group ($p < 0.005$). As Ciba-Geigy notes in their letter, the increase in neoplasia is probably due to a shift in the nature of existing hyperplastic lesions i.e. from focal hyperplasia to focal neoplasia.

Although Ciba-Geigy states that the "observed results (liver neoplasia) would not expected to be relevant to man", Toxicology Branch cannot make a regulatory decision based on this interpretation.

3. "Only animals with pituitary adenomas were observed to have hyperplastic liver nodules."

TB Response: True but irrelevant. Pituitary chromophobe adenomas are extremely common in aging rats. In this study pituitary adenomas were found in 38, 42, 46, 40 and 49 of the 60 females in the 0, 30, 100, 1000 and 3000 ppm groups (not significant at $p < 0.05$). An association between metolachlor treatment and pituitary adenomas or between pituitary adenomas and neoplastic nodules is not apparent. Although academically interesting, the hypothesis that metolachlor indirectly caused hepatocellular neoplasia by way of pituitary hypersecretion is not likely to be proven or disproven in the near future and is irrelevant to the oncogenic assessment of metalachlor.

4. "In the interpretation of the results of this study, it is inappropriate to combine cholangiomas and cystic cholangiomas or angiosarcomas with hepatocellular lesions because of the difference in cell type from which each of these lesions arises."

TB Response: Partially true. An angiosarcoma is a tumor of connective tissue and is therefore different in origin than the parenchymally - derived tumors i.e. neoplastic nodules, cholangiomas and hepatocellular carcinomas. This tumor will not be grouped with the other tumor types for risk assessment purposes.

However, there is a basis on which the cholangioma and hepatocellular neoplasms can be combined as a single group of liver tumors. As is illustrated in the following except from A.W. Ham, Histology,* the origin of hepatocytes and the cells which line the bile ducts is identical;

"In the development of exocrine glands the terminal outgrowths become secretory units, and the epithelial cells that connect these with the site from which the gland originates form the ducts... The cells closer to the site of origin of the outgrowth begin to differentiate to form tubules;... Farther away from the origin of the outgrowth the cells become arranged into thick irregular clumps and plates... At this time there is no difference in the appearance of the cells that form the tubules or the plates. Later their appearance changes, and the cells that... are forming tubules become the epithelial cells of bile ducts (ductular cells), whereas those (forming plates) become the cells of the exocrine secretory units of the liver; these cells are called hepatic cells or hepatocytes."

On the other hand, other compounds may induce either cholangioma or hepatocyte neoplasia. Therefore, the grouping of these tumor types either together or separately is acceptable for risk assessment.

*Ham, A.W., Histology, Seventh Edition, J.P. Lippincott Co., Philadelphia and Toronto, 1974, p. 714.