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

MAY 7 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Bifenthrin - FMC Rebuttal to Regulation by Risk Assessment (Q_1*)

TO: Mr. George LaRocca, Product Manager 15
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THROUGH: K. Clark Swentzel K. Clark Swentzel 5/2/90
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EPA Record No. 243408

Project No. 9-1275

EPA Reg. No. 279-3055

Tox. Chem. 463F

Action Requested:

Review of material submitted by FMC relating to the Agency classification of FMC 54800 (Bifenthrin) as a category C carcinogen with a Q_1*. This material consists of a report by Samuel M. Cohen, M.D., Ph.D., titled "Relevance of Mouse Bladder Tumors to Humans" (MRID No. 410563-01), a report by Walter H. Wilborn, Ph.D., titled "Transmission Electron Microscopy of Formalin-Fixed Chemically-Induced Tumors of the Mouse Urinary Bladder Showing the Origin of the Tumor from Smooth Muscle (MRID No. 410563-02), the Curriculum Vitae of Robert Franklin McConnell, D.V.M., P.A. (No MRID No. assigned), and the Curriculum Vitae of Samuel Monroe Cohen, M.D., Ph.D. (no MRID No. assigned).

Background:

Bifenthrin has been classified as a category C carcinogen, with a risk assessment (Q_1*), primarily on the basis of a mouse study in which highest-dose (600 ppm) males showed a highly significant increased incidence of "leiomyosarcomas" of the urinary bladder. Other findings in this same study (refer to the attached copy of the first peer review summary) included a dose-related trend of increased combined incidences of adenoma and adenocarcinoma of the liver (males only), and increased incidences of bronchio-alveolar adenomas and adenocarcinomas of the lung in females at 50, 200 and 600 ppm (but not 500 ppm) relative to their controls.

Comments and Recommendations:

1. There appears to be agreement that most of the bladder tumors in question originated from smooth muscle cells. This is consistent with the terminology "leiomyosarcoma." The bladder tumors were classified as leiomyosarcomas in the original report received from FMC Corporation, and were considered as such by the Peer Review Committee and FIFRA SAP. In the report by Cohen and that of Wilborn it is simply indicated that the tumors originated from smooth muscle, with no statement in either report as to whether or not the term "leiomyosarcoma" is appropriate. However, the descriptions given by Cohen and Wilborn appear to more readily match the terminology "leiomyoma." According to the Merck Veterinary Manual (4th ed., 1973): "Leiomyomas are benign and arise from smooth muscle cells. They are most frequently found in the gastrointestinal tract, uterus and vagina. These tumors usually form a single, large, spherical mass that has a smooth, translucent grey surface. Although these tumors may reach considerable size, the cut surface appears avascular. Microscopically, the tumor mass is composed of spindle-shaped cells with elongate blunt-ended nuclei arranged in irregular broad fasciculi. Leiomyomas grow slowly by expansion and exhibit little tendency to infiltrate locally. The malignant form of the tumor, leiomyosarcoma, appears in the same locations as the benign counterpart, but metastasizes readily to the regional lymph nodes." However, it is not readily apparent that reclassification of these tumors to "leiomyomas" would be a sufficient reason to bring this chemical before the Peer Review Committee again, particularly as incidences of leiomyoma and leiomyosarcoma for a given site can be combined.

2. It is stated in the report by Cohen that "lesions" of this variety have only been observed in mice, and that no "lesions" of this type have ever been reported in the human urinary bladder. It is also stated (p. 9) that: "A major problem with these lesions is in defining their relevance to humans." The Peer Review Committee's concern was not whether this type of tumor occurs at this site in humans but whether there was a tumorigenic response in the test species associated with

dietary exposure to Bifenthrin. This takes into consideration the possibility that the target organ may vary according to species.

3. Attached are copies of the first and second peer review summaries of Bifenthrin. In the first peer review it was concluded unanimously that a quantitative estimation of the carcinogenic potential for humans should be developed because of the uncommon nature of the urinary bladder tumors seen, and because of the limited but supportive evidence derived from the incidences of both lung and liver neoplasms in the same study. In the second peer review it is noted that the Committee was divided on whether a quantification of risk should be performed, but favored quantification "because of the uncommon nature of the tumor type."

4. The material in MRID Nos. 410563-01 and 410563-02 does not appear to include any information that contradicts or which would significantly change what the Peer Review Committee has previously considered. Therefore, at this time, it does not appear appropriate to have a third Peer Review for Bifenthrin.