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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Oxyfluorfen - Carcinogenicity in Animals

FROM: Penelope Fenner-Crisp, Ph.D.
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TO: Daniel Barolo
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Oxyfluorfen; CAS Registry No. 42874-03-3; Chemical No. 111601

The Health Effects Division (HED) Carcinogenicity Peer Review Committee met on May 24, 1989 to evaluate the carcinogenicity data for Oxyfluorfen. Full details and references are found in the Peer Review files.

A. Animal Carcinogenicity Studies

Male and female CD-1 mice were fed 0, 0 (ethanol), 2, 20, or 200 ppm of oxyfluorfen for 20 months. It is not clear why the ethanol control was used as ethanol was not a vehicle for the test groups. The 2 ppm dosed animals were terminated at 18 months instead of 20 months. The animals in the 200 ppm dose group were dosed at 800 ppm for 2 weeks (weeks 57 and 58) during the study. The Peer Review Committee agreed that the signs observed in this study were not sufficient enough for adequate maximal dosing to fully assess the carcinogenic potential of Oxyfluorfen (i.e. 200 ppm was not high enough for an appropriate top dose).

Oxyfluorfen was associated with significant positive dose-related trends for male hepatocellular adenoma, carcinoma, and combined adenoma/carcinoma. The incidence of these hepatocellular adenomas and carcinomas exceeded the upper range of the testing laboratory's historical controls (for carcinomas at the 20 and 200 ppm doses; for adenomas at the highest dose tested (HDT), 200 ppm). No compound related increase in tumors was observed in female mice.

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Male and female Long-Evans rats were fed oxyfluorfen at "specific dose levels" for 24 months. Initial dose levels were gradually increased over a 4 week period in order to acclimate the animals to compound administration. At week 5, dose levels were established at 0, 2, 40, or 800 ppm. Through a calculation error, animals in the 800 ppm group actually received 685 ppm a.i. in the diet for weeks 5 through 48; upon discovery of the error, dose correction to 800 ppm was made. At week 57, the 800 ppm dose was increased to 1600 ppm in an attempt to establish an "effect" level.

The Peer Review Committee agreed that there was no evidence of carcinogenicity due to Oxyfluorfen in the Long-Evans rat study; however, the Committee did not consider the minimal signs seen to be significant enough for appropriate dose selection to properly assess carcinogenic potential. Based on these data, this rat study was deemed inadequate.

B. Additional Information

Oxyfluorfen is structurally related to four other diphenyl ether herbicides that have carcinogenicity evidence associated with them. These chemicals include lactofen, acifluorfen, nitrofen, and fomesafen. The primary tumors induced by these chemicals include hepatocellular carcinomas and adenomas in mice, similar to that seen in the Oxyfluorfen mouse study. These data provide strong support for the association of liver tumors with this class of chemicals.

Technical grade Oxyfluorfen was found positive for inducing gene mutations in the Salmonella and the mouse lymphoma assays; these data provide evidence that Oxyfluorfen has mutagenic activity. Oxyfluorfen was negative for clastogenicity (rat bone marrow aberrations assay) and other genotoxic effects (unscheduled DNA synthesis assay).

C. Carcinogenicity in Animals

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, it is concluded that exposure to oxyfluorfen results in an increased incidence of hepatocellular adenomas and carcinomas in male CD-1 mice. Although not statistically significant by comparison to control groups, there were statistically significant positive trends for adenomas, carcinomas, and combined adenomas/carcinomas. The Committee felt that the induced tumor incidences of the benign and malignant tumors over control were related to oxyfluorfen exposure as they were above the historical control range of the testing laboratory and are very consistent with this class of structurally related compounds. Also, oxyfluorfen has mutagenic capability. In addition, the fact that oxyfluorfen was tested at doses below those deemed sufficient for maximal top dosing supports the contention that the incidence for benign and malignant tumors was increasing

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and would likely be statistically significant compared to control if more appropriate, higher dosing had been used. The relevance of these data to an evaluation of oxyfluorfen's potential for human carcinogenicity is discussed in the Peer Review document for Oxyfluorfen (September 29, 1989).

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