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

SEP 13 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: 2nd Peer Review Meeting to Determine Risk Quantification Method for Oryzalin.

To: Robert Taylor
Product Manager #25
Registration Division (H7505c)

From: John A Quest, Ph.D. JA Quest
Head, Science Support Staff
Science Analysis and Coordination Branch
Health Effects Division (H7509c)

The Health Effects Division Peer Review Committee met on June 13, 1990, to review the toxicological data base on Oryzalin for the purpose of determining the quantitative approach to be used in assessing risk for the chemical.

A. Individuals in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated).

Penelope A. Fenner-Crisp Penelope A Fenner Crisp

William L. Burnam Wm L Burnam

Reto Engler

Marcia Van Gemert Marcia Van Gemert

Karl Baetcke

Kerry Dearfield Kerry Dearfield

John Quest John A. Quest

Esther Rinde Esther Rinde

William Sette

Yin-Tak Woo Yin tak Woo

2. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Robert Beliles for _____

Marion Copley Marion P. Copley

Julie Du —

George Ghali G. Ghali

Richard Hill —

B. Material Reviewed:

The material available for review consisted of a summary of the toxicology data on oryzalin contained in HED files.

C. Background Information:

The initial weight-of-evidence toxicological review of oryzalin was performed by the HED Peer Review committee on September 16, 1985. The chemical was also considered by the Science Advisory Panel on February 11, 1986. Although both groups viewed oryzalin as a group C carcinogen, neither one described how the compound's risk should be assessed. This issue was resolved by the Peer Review Committee at the present meeting. The toxicology information contained in the 1985 peer review memorandum on oryzalin was discussed and agreement was reached that a low dose, non-threshold (i.e., $Q1^*$), approach should be used for risk assessment proposes rather than the threshold or reference dose (RFD) method.

D. Determination of Risk Quantification Method:

The toxicology data base on oryzalin that was used to decide the risk assessment approach was a 2-year study in F344 rats (dietary doses of 0, 300, 900 and 2700 ppm). Oryzalin produced statistically significant increases in the following tumor types: (1) benign mammary tumors in female rats at all 3 dose levels; (2) benign thyroid tumors in both sexes at the high dose level; and (3) benign tumors at several skin sites at the mid and high dose levels. In this study, the 2700 ppm dose of oryzalin was considered to be excessively toxic due to increased mortality and weight loss, whereas the other doses were considered to be adequate for testing. In a second long-term study in $B6C3F_1$ mice, oryzalin was not found to be carcinogenic. With this data in mind, the Committee considered factors that primarily supported either the threshold (RFD) or the non-threshold ($Q1^*$) approaches to risk assessment.

The RFD approach was supported by data showing that oryzalin evoked tumors in only a single species and strain of animal, and that the majority of the observed neoplasms were non-malignant in nature. In addition, oryzalin was not mutagenic in the Salmonella assay, a rat dominant lethal assay and an unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes. While oryzalin induced a small increase in sister chromatid exchanges in female chinese hamster bone marrow after an i.p. exposure, the response was not great (less than twice background) and there were negative results after an oral exposure.

The $Q1^*$ risk assessment approach was supported by observations that the observed tumors occurred in both sexes of rats, that multiple sites of neoplasia (mammary gland, thyroid gland, and skin) were involved, that all of the statistically significant elevated tumor incidences exceeded available historical control ranges for the same tumor types, and that tumors not only occurred at a dose of oryzalin that was excessively toxic (2700 ppm) but also at doses that were below this level (i.e., mammary tumors occurred at 300 ppm and 900 ppm in female rats, and skin tumors at 900 ppm in rats of both sexes). Finally, oryzalin was structurally similar to other chemicals that were carcinogenic in rodents. These analogues included 2,4 - diaminoanisole sulfate (thyroid and skin tumors), sulfamethoxazole (thyroid tumors), trifluralin (thyroid and renal pelvis tumors), and ethalfluralin (mammary gland tumors).

E. Conclusions:

The Peer Review Committee concluded from the above information that the weight of the toxicological evidence on oryzalin best supported the use of the low dose, non-threshold, linearized risk extrapolation method for quantification of risk. The mammary gland tumors (adenomas, fibroadenomas, and adenocarcinomas combined) induced by oryzalin in female rats were used for this purpose since they occurred in a generally dose-related manner, and with the highest tumor incidence when compared to the other tumor types. The $Q1^*$ value calculated from the mammary gland tumor data was 1.3×10^{-1} $(mg/kg/day)^{-1}$, as described in the attached memorandum (Engler to Quest) of June 20, 1990.