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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Oryzalin

FROM: John A. Quest, Ph.D. JAQ
Team Leader, Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: ~~Henry Jacoby~~
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (TS-767C)

The Toxicology Branch Peer Review Committee met on September 16, 1985, to discuss and evaluate the data base on Oryzalin, with particular reference to the oncogenic potential of the chemical.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated).

not John Brantner, Ph.D.

William Burnam, M.S.

Reto Engler, Ph.D.

Louis Kasza, D.V.M., Ph.D.

John A. Quest, Ph.D.

2. Reviewers: (Non-panel members responsible for presentation of data; signatures indicate technical accuracy of panel report).

R. Bruce Jaeger

John Chen, Ph.D.

3. Dr. Farber and Mr. Litt were unable to attend the discussion; their signatures indicate concurrence with the overall conclusion of the panel.

Theodore M. Farber, Ph.D. Theodore M Farber

Bertram Litt Bertram Litt

B. Material Reviewed:

The documents available for review were the Registration Standard Toxicology Chapter, a table of oryzalin's structure and possible metabolites, "one-liner" information on the oryzalin data base, DER's on the rat and mouse studies, a dose-response assessment on the rat study, a summary table of pathologic diagnoses from the 2-year rat study performed at Eli Lilly Co., and a statistical evaluation of tumors in the oryzalin rat and mouse studies (provided by B. Litt and B. Fisher, Toxicology Branch).

C. Overview of Toxicology Issues:

Oryzalin was observed to produce tumors of the skin and thyroid gland in male and female rats and tumors of the mammary gland in female rats in chronic feeding studies conducted by the registrant, Eli Lilly and Company. No apparent tumorigenic effect of oryzalin occurred in similar chronic feeding studies in mice.

The review committee initially met on August 22, 1985, to discuss the adequacy of the oncogenicity studies of oryzalin in rats and mice and to identify any outstanding questions or problems with these studies in order to have them resolved prior to developing a Weight of the Evidence characterization on the chemical (a memorandum of the August 22, 1985 meeting is attached). As a result of this preliminary meeting it was determined that a statistical reevaluation of the rat study be performed for the thyroid gland, mammary gland, and skin tumors. In addition, the committee recommended that the mouse pathology tables be rechecked for individual tumor incidences, since all previous DER information on oncogenicity was reported solely as the incidence of benign and malignant neoplasms between control and treated mice (no differences were reported between treated and untreated mice). The results of the statistical reevaluation of the rat tumor data and the tabulation of individual mouse tumors are attached to this report. The review committee considered this newly developed information along with the

other available toxicity data in developing the Weight of the Evidence position on oryzalin.

D. Evaluation of the Evidence:

Rat Oncogenicity Study: Two identical chronic studies were performed concurrently in rats by Eli Lilly and Company. In each study oryzalin was administered in the diet to 30 rats/sex/dose level at levels of 0, 300, 900, and 2700 ppm for 2 years. The following incidence pattern of tumors, suggestive of a compound-related effect, were observed in male and/or female rats.

Tumor Site and Type	Dose (ppm) 0		300		900		2700	
Thyroid Gland	M	F	M	F	M	F	M	F
foll. cell adenoma	1/59	1/55	6/59	1/60	5/57	3/60	4/56	8/55
foll. cell carcinoma	0/59	0/55	0/59	0/60	0/57	0/60	3/56	1/55
combined	1/59	1/55	6/59	1/60	5/57	3/60	7/56*	9/55*
Skin								
fibroma	3/60	2/60	3/60	2/60	9/60	2/60	11/60	3/60
fibrosarcoma	1/60	0/60	2/60	2/60	4/60	2/60	2/60	2/60
combined	4/60	2/60	5/60	4/60	13/60*	4/60	13/60*	5/60
papillomas	1/60	0/60	3/60	1/60	1/60	0/60	7/59	1/60
Keratoacanthomas	3/60	1/60	3/60	1/60	4/60	3/60	16/59	8/60
sq. cell carcinoma	1/60	0/60	0/60	0/60	1/60	1/60	1/59	0/60
combined	5/60	1/60	6/60	2/60	6/60	4/60	24/59*	9/60*
basal cell adenoma	2/60	0/60	4/60	1/60	2/60	0/60	0/59	1/60
preputial gl. adenoma	4/60	0/60	6/60	0/60	12/60	0/60	8/59	0/60
sebaceous gl. adenoma	3/60	2/60	3/60	4/60	4/60	12/60	5/59	5/60
zymbal's gland adenomas	0/60	0/60	1/60	0/60	2/60	1/60	2/59	4/60
trichoepithelioma	0/60	0/60	0/60	0/60	0/60	0/60	3/59	0/60
combined	9/60	2/60	14/60	5/60	20/60*	13/60*	18/59*	10/60*
Mammary Gland								
adenoma		0/60		1/60		1/60		2/60
fibroadenoma		10/60		20/60		37/60		29/60
adenocarcinoma		0/60		0/60		1/60		1/60
combined		10/60 (16.7%)		21/60* (35%)		39/60* (65%)		32/60* (53.3%)
Liver								
hepatic adenoma	0/60		0/60		0/60		4/59	
bile duct adenoma	0/60		0/60		1/60		0/59	
combined	0/60		0/60		1/60		4/59**	

* = $p < 0.05$ (Fishers Exact Test); ** = $p = 0.057$

Comments on Tumors Observed in Rats:

a. Thyroid Gland: A statistically significant positive trend occurred in female rats for follicular cell adenomas and follicular cell carcinomas combined. The combined tumor incidence was significantly elevated at the highest dose level tested (2700 ppm) in both males and females, and was primarily due to an increase in the adenomas. The incidence of the adenomas produced by oryzalin in females (8/55, 14.5%) exceeded the historical control incidence of follicular cell adnomas in female (0.56%, range 0 to 3.6%) F344 rats in studies performed at the registrant's laboratory. However, the incidence of adenomas produced by oryzalin in males (4/56, 7.1%) did not exceed the range of these tumors in male (1.68%, range of 0 to 10%) F344 rats at Eli Lilly (Note: this historical data was obtained from 24 studies conducted at Eli Lilly, and in 22 of these 24 tests the incidence of oryzalin - induced adenomas did exceed Lilly's historical control range). In addition, the incidences of the adenomas produced by oryzalin in males (4/56, 7.1%) and females (8/55, 14.5%) also exceeded the historical control incidences of follicular cell adenomas in male (1.0%, range 0 to 5%) and female (0.4%, range 0 to 4%) F344 rats in recent NTP studies.

   The elevated incidence of thyroid tumors observed in high dose male and female rats was accompanied by focal follicular hyperplasia of the thyroid gland in males (control, 2/59; low dose 2/59; mid dose, 4/57' high dose, 15/56) and females (control, 0/55; low dose, 1/59; mid dose, 5/57; high dose, 14/55).

b. Skin:

   1) A statistically significant positive trend for skin fibromas and fibrosarcomas combined occurred in male rats. The combined tumor incidence was significantly elevated at dose levels of 900 and 2700 ppm in male rats and was primarily due to an increase in the fibromas. Historical control data from Eli Lilly was not available for fibromas in male mice. The incidences of fibromas produced by oryzalin in males (11/60, 18.3%) exceeded the historical incidences of fibromas/neurofibromas in male (4.5%, range 0 to 12%) F344 rats in recent NTP studies. No changes in these tumor types occurred in female rats.

2) A statistically significant positive trend for skin papillomas, keratocanthomas, and squamous cell carcinomas combined occurred in both male and female rats. The combined tumor incidence was significantly elevated at the highest dose level (2700 ppm) in both males and females, and was primarily due to increases in papillomas and keratoacanthomas in males and to an increase in keratoacanthomas in females. The incidence of papillomas produced by oryzalin in males (7/59, 11.8%) and the incidence of keratoacanthomas produced by the compound in males (16/59, 27.1%) and females (8/60, 13.3%) exceeded the historical incidences of squamous cell papillomas (males 1.1%, range of 0 to 10%) and keratoacanthomas (males 2.1%, range 0-10%; females 0.4%, range 0 to 3.3%) in F344 rats in studies performed at the registrant's laboratory. Furthermore, the incidences of these tumors also exceeded the historical incidences of squamous cell papillomas (males, 1.2%, range 0 to 5%) and keratoacanthomas (males, 0.9%, females, 0.3%; no range data available) in F344 rats in recent NTP studies.

3) A statistically significant positive trend for skin basal cell adenomas, preputial gland adenomas, sebaceous gland adenomas, zymbal's gland adenomas and trichoepitheliomas combined occurred in both male and female rats. The combined tumor incidence was significantly elevated at doses of 900 and 2700 ppm in both males and females, and was primarily due to increases in preputial gland adenomas, sebaceous gland adenomas and trichoepitheliomas in males and sebaceous gland and zymbal's gland adenomas in females. The historical control data from both the registrant's laboratory and from the NTP that were available to the panel did not identify these tumor types

c. Mammary Gland: A statistically significant positive trend for adenomas, fibroadenomas and adenocarcinomas combined occurred in female rats. The combined tumor incidence was significantly elevated at doses of 300, 900, and 2700 ppm and was due to an increase in fibroadenomas. Historical control data from Eli Lilly was not available for fibroadenomas in female mice. The incidence of mammary gland fibroadenomas produced by oryzalin in females (29/60, 48.3%) exceeded the historical incidence of fibroadenomas in female (24.1%, range 2 to 44%) F344 rats in recent NTP studies.