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

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JUN 30 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of additional rat nasal histopathology data for Monsanto Study # PR 80-006; Record no. 223011/223012/223016/223018; EPA ID no. 3F2966/6G3345/524-GUI/524-EUP-AT; Accession No. 40484801; Proj. No. 8-0776; Caswell No. 3B

TO: Robert Taylor/V.P. Waters (PM 25)
Registration Division (TS-769C)

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Hazard Evaluation Division (TS-769C)

ACTION: Expedited review of additional rat chronic histopathology data for Monsanto Study # PR 80-006, May 83; Record no. 223011/223012/223016/223018; EPA ID no. 3F2966/6G3345/524-GUI/524-EUP-AT; Accession No. 40484801; Proj. No. 8-0776; Caswell No. 3B

RECOMMENDATIONS:

There is a dose-related increase in nasal papillary adenomas in male rats with statistically significant differences at the mid (1500 ppm) and high dose (5000 ppm) levels. Papillary adenocarcinomas are present also in two high dose males. A small number of papillary adenomas are also present in the mid and high dose females. However, the lack of dose-related findings for the female adenomas may relate to the significantly lower survival rate observed in these groups.

This data is consistent with the findings of nasal papillary tumors in a second rat chronic feeding study performed for acetochlor (EHL-83107). Results of this report should be considered in the context of its oncogenic classification.

Reviewed By: James N. Rowe, Ph.D.
Section V, Toxicology Branch (TS-769C)
Secondary Reviewer: Quang Bui, Ph.D.
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DATA EVALUATION REPORT

Study type: Partial Chronic Rat Histopathology (nasal tissues)
Test system: Rats, Sprague-Dawley
Guideline: 83-1, 83-2

Study Title: Histopathology Findings in Noses of Rats Administered MON 097 in a Lifetime Feeding Study

EPA ID NOS.: EPA ID NO. 3F2966/6G3345/524-GUI/524-EUP-AT
EPA Accession No. 40484801
Caswell No. 3B
Project No. 8-0776

Sponsor: Monsanto Company
St. Louis, MO 63110

Testing Laboratory: Tegeris Laboratories
9705 N. Washington Boulevard
Laurel, MD 20707
and
Monsanto Environmental Health Laboratory
645 S. Newstead
St. Louis, MO 63110

Laboratory Project No.: ML-86-44/EHL 86027

Final Report Date: 11/4/87

Date of Study Completion: 6/30/86

Study Author: W.E. Ribelin, D.V.M., Study director

Quality Assurance: A statement of Quality Assurance is signed by Arthur F. Uelner, Manager, Quality Assurance at EHL (10/11/87)

Compound: MON-097; chemical name is acetochlor.

CONCLUSIONS:

Based upon the histopathological reexamination, there is evidence for a dose-related increase in nasal papillary adenomas in male rats with statistically significant differences at the mid (1500 ppm) and high dose (5000 ppm) levels. Papillary adenocarcinomas are also present in two high dose males. A small number of papillary adenomas are also present in the mid and high dose females. However, the lack of dose-related findings for female adenomas may relate to the significantly lower survival rate observed in these groups.

Recommendations:

This data is consistent with the findings of nasal papillary tumors in a second rat chronic feeding study performed for acetochlor(MSL-83-200; EHL-83107). Results of this report should be considered in the context of its oncogenic potential and classification.

Background:

In a rat chronic study (Monsanto Study No. ML-83-200; EHL Project No. 83107), treatment related papillary adenomas were noted in the nasal mucosa of the posterior regions of the nasal cavity at 1000 ppm (MTD), a dose considerably lower than the HDT (5000 ppm) in an original study (Monsanto PR 80-006). This prompted a re-analysis of the nasal tissues with histopathological examination focusing on the posterior portion of the nasal cavity which had not been systematically examined in the original study. This submission consists of histopathology data from a rat chronic feeding study performed by Pharmacopathics Research Laboratories at dosage levels of 0, 500, 1500 and 5000 ppm and reported in May, 1983 (Monsanto Study No. PR-80-006; Pharmacopathics Report No. 8004).

Methods:

The nasal tissues were trimmed, processed, sectioned and stained at Tegeris labs. Original blocks of paraffin-embedded tissue were re-sectioned, or wet tissue remnants processed and sectioned, depending on the amount of available tissue. Sections were requested from all three functioning areas of the nose--squamous, respiratory and olfactory--and were generally available. Seventy males and seventy females were used per dose group. Tissues from the following animals were not available: MN068(control male), M2014(1500 ppm male), M3057 (5000 ppm male), FN069 (control female), F1001, F1008 (500 ppm females), F3037 (5000 ppm female). Each animal was re-identified with an EHL number. Survival times for each animal were obtained and plotted as life span tables.

Statistical methods:

Mean survival times for each treatment group were compared and survival rates were analyzed using the method of Breslow (Generalized Wilcoxon Procedure) and the method of Mantel (Generalized Savage procedure). Frequencies of lesions and tumors were analyzed with Fisher's Exact test with the Bonferroni Inequality Procedure. The relationship of time and dose to tumor was analyzed using the Peto test for linear trend.

Results:

Mean survival times with their statistical significance are presented below (taken from p. 5 of report):

Dose group:	Survival (days)	Breslow p =	Mantel p =
Males			
0 ppm	699	----	----
500 ppm	720	0.580	0.719
1500 ppm	722	0.191	0.159
5000 ppm	706	0.963	0.882
All treated	---	0.501	0.349
Females			
0 ppm	660	----	----
500 ppm	617	0.027	0.067
1500 ppm	645	0.574	0.768
5000 ppm	593	0.001	0.002
All treated	---	0.004	0.006

Mean survival time for compound-treated males were not different from control times. Female survival times were statistically significantly lower for the low and high dose groups as well as for all treated females as compared to the controls.

A summary of selected histopathology findings is presented below along with trend analysis data:

There was a dose-related increase in papillary adenomas in treated males with the mid and high dose groups being statistically significantly different from the control group (control/0, 500 ppm/1, 1500 ppm/6, 5000 ppm/18). Two males in the high dose group(not present in animals with papillary adenoma) also had papillary adenocarcinoma. There was an apparent increase in all compound-treated males of inflammation of the nasal mucosa which was statistical significant in the 5000 ppm dose group (control/3 vs 5000 ppm/16; $p<.01$). For all but three high dose animals, there was no association between nasal inflammation and the presence of papillary adenomas in the males. Statistically significant treatment-related trends in males were calculated for nasal papillary adenomas and adenocarcinomas as well as for all nasal malignancies.

There were papillary adenomas observed in the female mid and high dose groups (control/0, mid/2, high/1) which approached statistical significance ($p<0.055$) with the Peto trend analysis. The lack of a clear dose-related elevation in nasal papillary adenomas among treated females may relate to the significantly lower survival rate observed in the groups.

Selected Histopathology findings (from pp. 1 and 2 of pathology section)

No. tissues examined: Dose group:	(69) 0ppm	(70) 500ppm	(69) 1500ppm	(69) 5000ppm
(MALES)				
NOSE/TURBINATES				
-autolysis	2	0	0	0
-inflammation, nasolacrimal duct	1	8	5	6
-inflammation, nasal mucosa	3	9	7	16**
-inflammatory epithelial hyperpl.	1	0	3	2
-papillary adenomas	0	1	6*	18**
-Squamous cell carcinoma	0	1	0	1
-Squamous papilloma	0	0	1	0
-osteoma, maxillary (benign)				
-papillary adenocarcinoma	0	0	0	2
-Esthesioneuroma (benign tumor)	0	0	0	1
No. tissues examined: (FEMALES)	(69)	(68)	(70)	(69)
NOSE/TURBINATES				
-inflammation, nasolacrimal duct	5	1	2	2
-inflammation, nasal mucosa	2	8	6	8
-inflammatory epithelial hyperpl.	1	0	2	0
-Papillary adenomas	0	0	2	1
-Squamous cell carcinoma	1	2	1	0
-carcinoma in-situ	0	0	1	0
-epithel. inflamm. squamous metaplasia	0	0	1	0
-submucosal glandular hyperplasia	0	0	0	2

* significantly different (p< or = 0.05) from control using Fisher's Exact Test with Bonferroni Inequality
** significantly different (p< or = 0.01) from control using Fisher's Exact Test with Bonferroni Inequality

Peto test* for trend:	"p"
nasal papillary adenoma, males	0.000
nasal papillary adenoma, females	0.055
nasal papillary adenoma, both sexes	0.000
papillary adenocarcinoma, males	0.027
esthesioneuroma, males	0.062
all nasal malignancies, males	0.031

* taken from p. 5 of EHL 86027 report

Summary/Conclusions:

Reanalysis of all acceptable nasal tissues (squamous, respiratory, and olfactory portions of the nose) from a rat chronic feeding study (Monsanto PR 80-006) conducted at dietary levels of 0, 500, 1500 and 5000 ppm of acetochlor were performed. Based upon the histopath-ological examination, there is evidence for a dose-related increase in papillary adenomas in male rats which is statistically significant at the mid and high dose levels. A statistically significant increase in nasal inflammation was also observed in high dose males but is not generally present in males having the papillary adenomas. Papillary adenocarcinomas are present also in two high dose males. A small number of papillary adenomas are also present in the mid and high dose females. The lack of dose-related findings for female adenomas may relate to the significantly lower survival rate observed in females.

Compound-related findings of nasal papillary adenomas/carcinomas in this study (Monsanto PR 80-006) at 1500 and 5000 ppm in males, thus, corroborate the similar findings at 1000 ppm in Monsanto Study ML 83-200.