UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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MEMORANDUM

SUBJECT: FMC 54800 (BIFENTHRIN)

TO: Mr. George LaRocca, PM 15
Registration Division (TS-767C)

FROM: Byron T. Backus, Toxicologist Byron T. Backus 10/29/86
Toxicology Branch (TS-769C)

THROUGH: Marcia van Gemert, Ph.D.
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Toxicology Branch (TS-769C) Marcia van Gemert 10/28/86

and

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EPA Reg. No. 279-3055

Project No. 1900

Tox. Chem. 463F

Action Requested:

Review of a submission (material from the open literature) sent in response to an Agency request for historical control data on spontaneous neoplasms (particularly pulmonary tumors) in Swiss-Webster mice. This relates to a previously reviewed mouse oncogenicity study involving dietary exposure to FMC 54800.

Comments and Recommendations:

1. None of the submitted articles gives tumor incidences in Swiss-Webster mice from Taconic Farms (the source of the mice used in the FMC 54800 oncogenicity study).

2. The 28% (14/50) incidence of pulmonary tumors (adenomas and adenocarcinomas) in controls in the FMC 54800 study was in the general range of incidences reported for these tumor types in the literature, but the incidences for females receiving FMC 54800 (ranging from 38% in the 500 ppm mice to 52% at 50 ppm) were somewhat higher than what has usually been reported for Swiss-Webster mice, although in one part of the study by Buening et al. (1980) a control incidence of 57% (12/21?) for these tumor types was reported.

3. It is noteworthy that the article by Sher (1974) includes the statement (p. 338) that: "Tumor incidence was also relatively low in Swiss-Webster mice, varying from 10 to 43% in 18-month studies. Lymphomas or leukemia was infrequent in this strain, varying from 1.7 to 7%." The incidence in the control females in the FMC 54800 mouse study was at least 12/50 (24%). This alone suggests some differences between Taconic Farms Swiss-Webster mice and those from other sources.

4. As indicated in the review of August 8, 1986 of the mouse oncogenicity study, there was a greater incidence of combined bronchioalveolar adenocarcinomas and adenomas in female mice fed the FMC 54800. For most dosage levels incidences were significantly higher than for controls. While no dose-related trend was apparent for females fed FMC 54800, this may be indicative of an extremely low slope in a dose-response curve.

5. The conclusion remains then that exposure to FMC 54800 must be considered associated with an increased incidence of pulmonary tumors in females in the mouse oncogenicity study.

Discussion:

In a previously reviewed mouse oncogenicity study (males, 87 weeks; females, 92 weeks) utilizing Swiss-Webster Tac(SW)fBR mice from Taconic Farms, all female groups receiving FMC 54800 in their diet showed elevated incidences (relative to controls) of combined bronchioalveolar adenomas and adenocarcinomas of the lung.

Lung - females:	Group 1 0 ppm	Group 2 50 ppm	Group 3 200 ppm	Group 4 500 ppm	Group 5 600 ppm
bronchioalveolar adenomas	0/50	1/50†	0/50†	3/50†	1/48†
bronchioalveolar adenocarcinomas	14/50	25/50†	23/50†	16/50†	22/48†
combined bronchioalveolar adenomas and adenocarcinomas	14/50 (28%)	26/50* (52%)	23/50* (46%)	19/50 (38%)	23/48* (48%)

†statistical calculations not done.
*statistically significant at $p < 0.05$ relative to control incidence.

This was the first mouse oncogenicity study conducted by this particular laboratory, so there were no in-house historical control data. Because of this the registrant has submitted material from the open literature consisting of copies of the following:

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Prejean, J. D., Peckham, J. C., Casey, A. E., Griswold, D. P., Weisburger, E. K. and Weisburger, J. H. (1973). Spontaneous Tumors in Sprague-Dawley Rats and Swiss Mice. Cancer Research 33, 2768-2773.

Buening, M. K., Levin, W., Wood, A. W., Chang. R. L., Lehr, R. E., Taylor, C. W., Yagi, H., Jerina, D. M. and Conney, A. H. (1980). Tumorigenic Activity of Benzo(e)pyrene Derivatives on Mouse Skin and in Newborn Mice. Cancer Research 40, 203-206.

Sher, S. P. (1974). Tumors in Control Mice: Literature Tabulation. Toxicology and Applied Pharmacology 30, 337-359.

The following incidences are reported for "pulmonary tumors" in female Swiss-Webster control mice in a number of studies:

Report	Strain Designation and Source	Study Duration	Incidence
Prejean et al.	SPF Swiss (Webster derived) from Manor Farms, Staatsburg, NY.	540 days	21/153 13.7%
Buening et al.	Swiss-Webster BLU: Ha(ICR) from Blue Spruce Farms, NY	62-66 wks	12/21 "57%"
Buening et al.	Swiss-Webster BLU: Ha(ICR) from Blue Spruce Farms, NY	62-66 wks	12/30 "40%"
Sher, S. P.	CFW (Carworth Farms)	18 months	4/100 (4%)
"	CFW (Carworth Farms)	18 months	10/203 (4.9%)
"	CFW (Carworth Farms)	80 weeks	19/60 (31.7%)
"	Swiss-Webster Carworth Farms	2 years	28/100[a,b]
"	Swiss-Webster Carworth Farms	2 years	26/101[a,b]
"	Swiss-Webster Carworth Farms	2 years	23/99[a,c]
"	Swiss-Webster	18 months	1/46 (2.2%)
"	"	18 months	3/34 (8.8%)

a - sex not specified
b - carcinomas only
c - presumably carcinomas only

Although there is a fairly wide range of pulmonary tumor incidences (to some extent dependent on source) in Swiss-Webster mice, the range is usually from 0 to about 30%. Even with uncertainties from the lack of data for Swiss-Webster mice from Taconic Farms, it seems that the 14/50 (28%) incidence for pulmonary tumors in female controls in the FMC 54800 study fits in with what has been reported in the literature about as reasonably well as can be expected. The higher incidences (ranging from 38 to 52%) in female mice receiving FMC 54800 are not as easily explicable, and must presently be considered as exposure-related, especially as most of these values are significantly different from the control incidence at $p < 0.05$.