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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Fenbuconazole Qualitative Risk Assessment Based On Charles River Sprague-Dawley Rat and CD-1 Mouse Dietary Studies

Caswell No. 723Q

TO: SanYvette Williams, Pharmacologist
Review Section IV
Toxicology Branch II
Health Effects Division (H7509C)

FROM: Lori L. Brunsman, Statistician
Statistics Section
Science Analysis Branch
Health Effects Division (H7509C)

Lori L. Brunsman 7/19/93

THROUGH: Hugh M. Pettigrew, Section Head
Statistics Section
Science Analysis Branch
Health Effects Division (H7509C)

Hugh M. Pettigrew 7/19/93

Summary

The qualitative risk assessment of Fenbuconazole was based upon chronic feeding/oncogenicity studies conducted in Charles River Sprague-Dawley rats and CD-1 mice. Two rat studies were considered: one tested both males and females; one tested only males. In the first study, both male and female rats were fed 0, 8, 80, or 800 ppm of Fenbuconazole for 105 weeks. In the second study of only male rats, the animals were fed 0, 800, or 1600 ppm of Fenbuconazole for 105 weeks. The male mice were fed 0, 10, 200, or 650 ppm of Fenbuconazole for 79 weeks. The female mice were fed 0, 10, 650, or 1300 ppm of Fenbuconazole for 79 weeks.

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fenbuconazole in male or female rats or mice.

Male rats had significant dose-related increasing trends in thyroid follicular cell adenomas, and combined thyroid follicular cell adenomas and/or carcinomas in both studies. In the low-dose study, there was a significant difference in the pair-wise

comparison of the 800 ppm dose group with the controls for combined thyroid follicular cell adenomas and/or carcinomas. In the high-dose study, there was a significant difference in the pair-wise comparison of the 1600 ppm dose group with the controls for thyroid follicular cell adenomas.

There were no significant compound-related tumors observed in female rats.

Male mice had a significant dose-related increasing trend in hepatocellular carcinomas. There were no significant positive differences in the pair-wise comparisons of the dosed groups with the controls.

Female mice had significant dose-related increasing trends in hepatocellular adenomas and combined hepatocellular adenomas and/or carcinomas. There was also a significant difference in the pair-wise comparison of the 1300 ppm dose group with the controls for combined hepatocellular adenomas and/or carcinomas.

Background

A chronic dietary/oncogenicity study in Charles River Sprague-Dawley rats was conducted by Hazleton Laboratories America, Incorporated, Rockville, Maryland, for Rohm and Haas Company, Spring House, Pennsylvania, and issued August 15, 1990 (HLA Study No. 417-437; MRID Nos. 416353-01 and 416353-02).

The study design allocated groups of 60 rats per sex to dose levels of 0, 4, 40, and 400 ppm of Fenbuconazole for the first two weeks of the study; dose levels of 0, 6, 60, and 600 ppm of Fenbuconazole for weeks 3 and 4 of the study; and dose levels of 0, 8, 80, and 800 ppm of Fenbuconazole for the remainder of the study (weeks 5 through 105). An additional 10 rats per sex per dose were designated for interim sacrifice at week 53.

A second chronic dietary/oncogenicity study in Charles River Sprague-Dawley male rats was conducted by Hazleton Washington, Incorporated, Rockville, Maryland, for Rohm and Haas Company, Spring House, Pennsylvania, and issued July 15, 1991 (HWA Study No. 417-455; MRID No. 420550-01).

The study design allocated groups of 50 male rats to dose levels of 0, 800, and 1600 ppm of Fenbuconazole for 105 weeks. An additional 10 male rats per dose were designated for interim sacrifice at week 53.

A chronic dietary/oncogenicity study in Charles River CD-1 mice was conducted by Hazleton Laboratories America, Incorporated, Rockville, Maryland, for Rohm and Haas Company, Spring House, Pennsylvania, and issued March 20, 1991 (HLA Study No. 417-438; MRID No. 418933-01).

The study design allocated groups of 50 male mice to dose levels of 0, 10, 200, and 650 ppm of Fenbuconazole and 50 female mice to dose levels of 0, 10, 650, and 1300 ppm of Fenbuconazole for 79 weeks. An additional 10 mice per sex per dose were designated for interim sacrifice at week 53.

Survival Analysis

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fenbuconazole in male or female rats or mice. See Tables 1, 2, 3, 4 and 5 for mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analysis

Male rats had significant increasing trends in thyroid follicular cell adenomas, and combined thyroid follicular cell adenomas and/or carcinomas in both studies, all at $p < 0.05$. In the low-dose study, there was a significant difference in the pair-wise comparison of the 800 ppm dose group with the controls for combined thyroid follicular cell adenomas and/or carcinomas at $p < 0.05$. In the high-dose study, there was a significant difference in the pair-wise comparison of the 1600 ppm dose group with the controls for thyroid follicular cell adenomas at $p < 0.05$.

There were no significant compound-related tumors observed in female rats.

Male mice had a significant increasing trend in hepatocellular carcinomas at $p < 0.05$. There were no significant increases in the pair-wise comparisons of the dosed groups with the controls.

Female mice had significant increasing trends in hepatocellular adenomas and combined hepatocellular adenomas and/or carcinomas, both at $p < 0.01$. There was also a significant difference in the pair-wise comparison of the 1300 ppm dose group with the controls for combined hepatocellular adenomas and/or carcinomas at $p < 0.05$.

These statistical analyses were based upon the Exact trend test and Fisher's Exact test for pair-wise comparisons due to the relatively small numbers of tumors observed. See Tables 6, 7, 8 and 9 for tumor analysis results.

Table 1. Fenbuconazole - Charles River Sprague-Dawley Low-Dose Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	2/69[a]	3/67	10/64	9/54	25/45	39/59 (66)
8	0/70	2/70	10/68	8/58	31/50	41/60 (68)
80	0/70	3/70	10/67	7/57	21/50	31/60 (52)
800	0/70	2/70	10/68	7/58	28/51	37/60 (62)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[a]One accidental death at week 23, dose 0 ppm.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Fenbuconazole - Charles River Sprague-Dawley Low-Dose Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	0/70	1/70	10/69	8/59	25/51	34/60 (57)
8	2/70	2/68	10/66	9/56	20/47	33/60 (55)
80	1/70	1/69	10/68	15/58	25/43	42/60 (70)
800	0/69[a]	3/69	10/66	5/56	17/50[a]	25/58 (43)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[a]One accidental death each at weeks 14 and 79, dose 800 ppm.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Fenbuconazole - Charles River Sprague-Dawley High-Dose Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	0/60	2/60	10/58	6/48	21/42	29/50 (58)
800	2/60	1/58	10/57	8/47	19/39	30/50 (60)
1600	2/60	3/58	10/55	6/44[a]	11/38	22/49 (45)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[a]One accidental death at week 75, dose 1600 ppm.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Fenbuconazole - Charles River CD-1 Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose(ppm)	1-26	27-52	53[i]	53-80[f]	Total
0	0/60	3/60	10/57	8/47	11/50 (22)
10	0/60	3/60	10/57	7/46[a]	10/49 (20)
200	0/60	2/60	10/58	8/48	10/50 (20)
650	0/60	5/60	10/55	6/45	11/50 (22)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[a]One accidental death at week 70, dose 10 ppm.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 79.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. Fenbuconazole - Charles River CD-1 Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose(ppm)	1-26	27-52	53[i]	53-80[f]	Total
0	2/59[a]	3/56[a]	10/53	8/43	13/48 (27)
10	1/60	2/58[b]	10/56	6/46	9/49 (18)
650	0/58[c]	5/57	10/52	6/41[c]	11/47 (23)
1300	1/60	2/59	10/57	8/47	11/50 (22)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[a]One accidental death each at weeks 15 and 28, dose 0 ppm.

[b]One accidental death at week 30, dose 10 ppm.

[c]One accidental death each at weeks 3, 4 and 64, dose 650 ppm.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 79.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 6. Fenbuconazole - Charles River Sprague-Dawley Low-Dose Rat Study

Male Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	8	80	800
Adenomas	1/54	2[a]/58	3/57	6/58
(%)	(2)	(3)	(5)	(10)
p =	0.023*	0.527	0.330	0.069
Carcinomas	0/54	3[b]/58	0/57	4/58
(%)	(0)	(5)	(0)	(7)
p =	0.058	0.135	1.000	0.068
Combined	1/54	5/58	3/57	8/58
(%)	(2)	(9)	(5)	(14)
p =	0.022*	0.120	0.330	0.021*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First adenoma observed at week 89, dose 8 ppm.

[b]First carcinoma observed at week 75, dose 8 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 7. Fenbuconazole - Charles River Sprague-Dawley High-Dose Rat Study

Male Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)		
	0	800	1600
Adenomas (%)	2/59 (3)	5[a]/58 (9)	9/55 (16)
p =	0.013*	0.212	0.020*
Carcinomas (%)	2/59 (3)	0/58 (0)	2[b]/55 (4)
p =	0.596	0.252[n]	0.664
Combined (%)	4/59 (7)	5/58 (9)	10/55 (18)
p =	0.038*	0.489	0.058

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 51.

[n]Negative change from control.

[a]First adenoma observed at week 51, dose 800 ppm.

[b]First carcinoma observed at week 67, dose 1600 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 8. Fenbuconazole - Charles River CD-1 Mouse Study

Male Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	10	200	650
Adenomas (%)	8/57 (14)	1/57 (2)	8[a]/58 (14)	6/55 (11)
p =	0.293	0.016[n*]	0.591	0.416
Carcinomas (%)	1/57 (2)	1/57 (2)	3/58 (5)	5[b]/55 (9)
p =	0.023[*]	0.752	0.316	0.095
Combined (%)	9/57 (16)	2/57 (4)	10/58 (17)	10/55 (18)
p =	0.077	0.026[n*]	0.517	0.466

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative change from control.

[a]First adenoma observed at week 53, dose 200 ppm.

[b]First carcinoma observed at week 62, dose 650 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 9. Fenbuconazole - Charles River CD-1 Mouse Study

Female Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	10	650	1300
Adenomas (%)	0/43 (0)	0/46 (0)	0/43 (0)	4[a]/47 (9)
p =	0.004**	1.000	1.000	0.070
Carcinomas (%)	0/43 (0)	1/46 (2)	0/43 (0)	1[b]/47 (2)
p =	0.330	0.517	1.000	0.522
Combined (%)	0/43 (0)	1/46 (2)	0/43 (0)	5/47 (11)
p =	0.004**	0.517	1.000	0.035*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First adenoma observed at week 77, dose 1300 ppm.

[b]First carcinoma observed at week 79, dose 1300 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

References

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