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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

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MEMORANDUM

DATE: March 14, 2007

SUBJECT: **Pyrasulfotole:** Qualitative Risk Assessment Based On C57BL/6J Mouse Carcinogenicity Dietary Study

P.C. Code: 000692

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BACKGROUND

A carcinogenicity study in C57BL/6J mice was conducted by Bayer CropScience, Sophia Antipolis Cedex, France, for the Bayer AG, Bayer CropScience, Monheim, Germany, and completed February 17, 2006 (Study No. SA 03172, MRID No. 46801909).

The study design allocated groups of 60 mice per sex to dose levels of 0, 100, 1000 and 4000 ppm of Pyrasulfotole for 78 weeks. The high dose for the females was 6000 ppm for the first 10 weeks of the study, but was reduced to 4000 ppm from week 11 onward due to excessive mortality. Doses were equivalent to 0, 13.6, 137, and 560 mg/kg/day for males and 0, 16.7, 168, and 713 mg/kg/day for females. Ten mice per sex

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per were designated for interim sacrifice at week 53. These animals did not receive histopathological examinations and, therefore, have not been included in the analyses in this report.

ANALYSES

Survival Analyses

Both male and female mice showed statistically significant increasing trends for mortality with increasing doses of Pyrasulfotole, as well as a significant pair-wise comparison of the 4000 ppm dose group with the controls, all at $p < 0.01$ (Table 1 for males; Table 4 for females).

Tumor Analyses

Male mice had statistically significant trends, and significant pair-wise comparisons of the 4000 ppm dose group with the controls, for urinary bladder transitional cell carcinomas, and papillomas and carcinomas combined, all at $p < 0.01$. There was a statistically significant trend for urinary bladder transitional cell papillomas at $p < 0.05$. In addition, although there was only one urethral transitional cell carcinoma at the high dose, there was a statistically significant trend at $p < 0.05$ due to increased mortality at the high dose. In conversations with Dr. John Pletcher, EPA's consulting pathologist, this urethral transitional cell carcinoma should be considered the same tumor type as the transitional cell carcinomas in the urinary bladder. The statistical analyses of the tumors in male mice were based upon Peto's Prevalence Test since there were statistically significant survival disparities among the dose groups (Tables 2 and 3).

Female mice had statistically significant trends for urinary bladder transitional cell papillomas, carcinomas, and papillomas and carcinomas combined, all at $p < 0.01$. There were significant pair-wise comparisons of the 4000 ppm dose group with the controls for urinary bladder transitional cell papillomas and carcinomas, both at $p < 0.05$, and for urinary bladder transitional cell papillomas and carcinomas combined at $p < 0.01$. The statistical analyses of the tumors in female mice were based upon Peto's Prevalence Test since there were statistically significant survival disparities among the dose groups (Table 5).

Table 1. Pyrasulfotole – C57BL/6J Mouse Study (MRID 46801909)

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

Dose (ppm)	Weeks				Total
	1-26	27-52	53 ⁱ	53-81 ^f	
0	2/60	1/58	9/57	5/48	8/51 (16)**
100	1/60	3/59	9/56	5/47	9/51 (18)
1000	2/59 ^a	3/57	10/54	2/44	7/49 (14)
4000	4/60	10/56	9/46	13/37	27/51 (53)**

ⁱNumber of animals that died during interval/Number of animals alive at the beginning of the interval.

^fInterim sacrifice at week 53.

^fFinal sacrifice at weeks 79-81.

^aOne accidental death at week 20, dose 1000 ppm.

() 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. Pyrasulfotole – C57BL/6J Mouse Study (MRID 46801909)

Male Urinary Bladder Transitional Cell Tumor Rates⁺
and Peto's Prevalence Test Results

	Dose (ppm)			
	0	100	1000	4000
Papillomas (%)	0/46 (0)	0/44 (0)	0/43 (0)	3 ^a /33 (9)
p =	0.02155*	-	-	0.06781
Carcinomas (%)	0/47 (0)	0/44 (0)	0/43 (0)	8 ^b /34 (24)
p =	0.00000**	-	-	0.00011**
Combined (%)	0/47 (0)	0/44 (0)	0/43 (0)	11/34 (32)
p =	0.00000**	-	-	0.00002**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

^aFirst papilloma observed at week 71, dose 4000 ppm.

^bFirst carcinoma observed at week 69, dose 4000 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 3. Pyrasulfotole – C57BL/6J Mouse Study (MRID 46801909)

Male Urethral Transitional Cell Tumor Rates[†]
and Peto's Prevalence Test Results

	Dose (ppm)			
	0	100	1000	4000
Carcinomas#	0/43	0/42	0/42	1 ^a /24
(^a)	(0)	(0)	(0)	(4)
p =	0.01400*	-	-	0.09036

-Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

#No adenomas observed.

^aFirst carcinoma observed at the final sacrifice at week 79, dose 4000 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 4. Pyrasulfotole – C57BL/6J Mouse Study (MRID 46801909)

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

Dose (ppm)	Weeks				Total
	1-26	27-52	53 ⁱ	53-81 ^f	
0	3/60	3/57	10/54	9/44	15/50 (30)**
100	0/60	4/60	9/56	5/47	9/51 (18)
1000	2/60	4/58	9/54	3/45	9/51 (18)
4000	14/60	7/46	7/39	12/32	33/53 (62)**

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

ⁱInterim sacrifice at week 53.

^fFinal sacrifice at weeks 79-81.

()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. Pyrasulfotole – C57BL/6J Mouse Study (MRID 46801909)

Female Urinary Bladder Transitional Cell Tumor Rates
and Peto's Prevalence Test Results

	Dose (ppm)			
	0	100	1000	4000
Papillomas (%)	0/35 (0)	0/40 (0)	0/42 (0)	2 ^a /19 (11)
p =	0.00042**	-	-	0.02632*
Carcinomas (%)	0/35 (0)	0/40 (0)	0/42 (0)	2 ^b /19 (11)
p =	0.00042**	-	-	0.02632*
Combined (%)	0/35 (0)	0/40 (0)	0/42 (0)	4/19 (21)
p =	0.00000**	-	-	0.00260**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

^aFirst papilloma observed at the final sacrifice at week 79, dose 4000 ppm.

^bFirst carcinoma observed at the final sacrifice at week 79, dose 4000 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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