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

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

TXR No. 0053709

MEMORANDUM

DATE: August 31, 2005

SUBJECT: **Metconazole**: Qualitative Risk Assessment Based On Fischer 344 Rat and Crl:CD-1(ICR)BR Mouse Dietary Studies

P.C. Code: 125619

TO: Gregory Akernan, Toxicologist
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THROUGH: Jess Rowland, Branch Chief
Science Information Management Branch
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BACKGROUND

The 104-Week Fischer 344 Rat Carcinogenicity Study (MRID 44721611)

A combined chronic toxicity/carcinogenicity study in Fischer 344 rats was conducted by Shell Research Limited, Sittingbourne Research Center, Sittingbourne, Kent, England, for BASF Corporation, Research Triangle Park, North Carolina, and dated June 30, 1992 (Laboratory Report No. SBGR.91.192, MRID No. 44721611).

The study design allocated groups of 50 rats per sex to dose levels of 0, 100, 300 or 1000 ppm (0, 4.6, 13.8 or 46.5 mg/kg/day for males; 0, 5.5, 16.6 or 56.2 mg/kg/day for females) of Metconazole for 104 weeks. There were no compound-related tumors observed in male rats so this document only contains analyses of the females.

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The 91-Week Crl:CD-1(ICR)BR Mouse Carcinogenicity Study (MRID 44721612)

A carcinogenicity study in Crl:CD-1(ICR)BR mice was conducted by Hazelton U.K. North Yorkshire, England, for BASF Corporation, Research Triangle Park, North Carolina, and dated August 26, 1992 (Laboratory Report No. 579/26, MRID No. 44721612).

The study design allocated groups of 51 mice per sex to dose levels of 0, 30, 300 or 1000 ppm (0, 4.4, 43.6 or 144.9 mg/kg/day for males; 0, 5.2, 53.0 or 179.2 mg/kg/day for females) of Metconazole for 92 weeks. An additional 12 mice per sex per dose were designated for interim sacrifice at week 53.

ANALYSES

The 104-Week Fischer 344 Rat Carcinogenicity Study (MRID 44721611)

Survival Analyses

There were no statistically significant incremental changes in mortality with increasing doses of Metconazole in female rats (Table 1).

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

Tumor Analyses

Female rats had significant differences in the pair-wise comparisons of the 100, 300 and 1000 ppm dose groups with the controls, all at $p < 0.05$, for mononuclear cell leukemia at all sites. There was no statistically significant trend. The statistical analyses of the female rats were based upon Fisher's Exact Test for pair-wise comparisons and the Exact Test for trend (Table 2).

The 92-Week Crl:CD-1(ICR)BR Mouse Carcinogenicity Study (MRID 44721612)

Survival Analyses

There were no statistically significant incremental changes in mortality with increasing doses of Metconazole in male or female mice (Tables 3 and 5).

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

Tumor Analyses

Male mice had significant increasing trends, and significant differences in the pair-wise comparison of the 1000 ppm dose group with the controls, for liver adenomas and adenomas and/or carcinomas combined, all at $p < 0.01$. The statistical analyses of the male mice were based upon Fisher's Exact test for pair-wise comparisons and the Exact test for trend (Table 4).

Female mice had significant increasing trends, and significant differences in the pair-wise comparison of the 1000 ppm dose group with the controls, for liver adenomas, carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. The statistical analyses of the female mice were based upon Fisher's Exact test for pair-wise comparisons and the Exact test for trend (Table 6).

Table 1. Metconazole - Fischer 344 Rat Study (MRID 44721611)
Female Mortality Rates¹ and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	53-78	79-106 ¹		
0	0/50	0/50	0/50	17/50		17/50 (34)
100	0/50	0/50	1/50	19/49		20/50 (40)
300	0/50	0/50	1/50	18/49		19/50 (38)
1000	0/50	0/50	0/50	16/50		16/50 (32)

¹Number of animals that died during interval/Number of animals alive at the beginning of the interval.

¹Final sacrifice at weeks 104-106.

()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. Metconazole - Fischer 344 Rat Study (MRID 44721611)

Female Mononuclear Cell Leukemia Rates and Fisher's Exact Test and Trend Test Results

	Dose (ppm)		
	0	100	300
Mononuclear Cell Leukemia - All Sites (%)	5/50 (10)	8*/22# (36)	7/20# (35)
p =	0.06482	0.01136*	0.01850*

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

*First mononuclear cell leukemia observed at week 78, dose 100 ppm.

#Only decedents in the 100 and 300 ppm dose groups were examined for all tissues. Although these groups exhibit statistical significance, they are not biologically significant when compared to the control and high dose groups.

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. Metconazole - Cri:CD-1(ICR)BR Mouse Study (MRID 44721612)

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

Weeks

Dose (ppm)	1-26	27-52	53 ¹	53-78	79-92 ¹	Total
0	1/63	9/62	11/53	10/42	8/32	28/52 (54)
30	4/63	11/59	11/48	7/37	8/30	30/52 (58)
300	1/63	11/62	10/51	7/41	11/34	30/53 (57)
1000	4/63	4/59	9/55	14/46	9/32	31/54 (57)

¹Number of animals that died during interval/Number of animals alive at the beginning of the interval.

¹Interim sacrifice at week 53.

¹Final sacrifice at week 92.

()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. Metconazole - CrI:CD-1(ICR)BR Mouse Study (MRID 44721612)

Male Liver Tumor Rates and Fisher's Exact Test and Exact Test for Trend Test Results

	Dose (ppm)			
	0	30	300	1000
Adenomas (%)	11 ^a /53 (21)	17 ^a /48 (35)	16 ^a /51 (31)	35 ^a /55 (64)
p =	0.00000**	0.07753	0.15604	0.000001**
Carcinomas (%)	4 ^b /53 (8)	4/48 (8)	7/51 (14)	7/55 (13)
p =	0.1952	0.58527	0.24092	0.28516
Combined (%)	13 ^c /53 (25)	17 ^d /48 (35)	19 ^d /51 (37)	38 ^d /55 (69)
p =	0.00000**	0.16409	0.11631	0.00000**

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

^aFirst adenoma observed simultaneously in interim sacrifice animals at week 53 in all dose groups.

^bFirst carcinoma observed at week 68, dose 0 ppm.

^cTwo animals in the control group had both an adenoma and a carcinoma.

^dFour animals in each of the 30, 300 and 1000 ppm dose groups had both an adenoma and a carcinoma.

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 5. Metconazole - CrI:CD-1(ICR)BR Mouse Study (MRID 44721612)

Female Mortality Rates¹ and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>							Total
	1-26	27-52	53 ¹	53-78	79-93 ¹			
0	1/62	6/61	12/55	11/43	6/32		24/50 (48)	
30	0/63	3/63	12/60	12/48	10/36		25/51 (49)	
300	0/63	2/63	12/61	5/49	8/44		15/51 (29) [#]	
1000	1/63	2/62	11/60	10/49	7/39		20/52 (38)	

¹Number of animals that died during interval/Number of animals alive at the beginning of the interval.

¹Interim sacrifice at week 53.

¹Final sacrifice at weeks 92-93.

[#]Negative change from control.

() 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. Metconazole - Ctrl:CD-1(ICR)BR Mouse Study (MRID 44721612)

Female Liver Tumor Rates and Fisher's Exact Test and Exact Test for Trend Test Results

	Dose (ppm)		
	0	30	1000
Adenomas (%)	0/56 (0)	1/61 (2)	50 ^a /61 (82)
p =	0.00000**	0.52137	0.00000***
Carcinomas (%)	0/56 (0)	1/61 (2)	20 ^b /61 (33)
p =	0.00000**	0.52137	0.00000*#
Combined (%)	0/56 (0)	2/61 (3)	52 ^c /61 (85)
p =	0.00000**	0.26967	0.00000***

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 46.

^aFirst adenoma observed at week 46, dose 1000 ppm.

^bFirst carcinoma observed at week 46, dose 1000 ppm.

^cEighteen animals in the 1000 ppm dose group had both an adenoma and a carcinoma.

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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Chemical: Cyclopentanol, 5-[(4-chlorophenyl)methyl]

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