

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

5



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

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

TXR No. 0054152

MEMORANDUM

DATE: March 15, 2006

SUBJECT: **Metrafenone:** Qualitative Risk Assessment Based On CrI:CD-1(ICR)BR Mouse and Sprague-Dawley Rat Carcinogenicity Dietary Studies

P.C. Code: 000325

TO: Alan Levy, Physiologist
Registration Action Branch 2
Health Effects Division (7509C)

FROM: Lori L. Brunzman, Statistician
Science Information Management Branch
Health Effects Division (7509C)

THROUGH: Jess Rowland, Branch Chief
Science Information Management Branch
Health Effects Division (7509C)

BACKGROUND

Mouse Study

A carcinogenicity study in CrI:CD-1(ICR)BR mice was conducted by BASF Agro Research, Princeton, New Jersey, for BASF Corporation, Research Triangle Park, North Carolina, and dated March 12, 2002 (Laboratory Project ID No. T-1130, MRID No. 46415731).

The study design allocated groups of 65 mice (66 in the high dose) per sex to dose levels of 0, 250, 1000 or 7000 ppm (0, 39, 156 or 1109 mg/kg/day for males; 0, 53, 223 or 1493 mg/kg/day for females) of Metrafenone for 78 weeks. There were no compound-related tumors

in the females so only the analyses of the males are presented in this document.

Rat Study

A combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats was conducted by Huntingdon Life Sciences, East Millstone, New Jersey, for BASF Corporation, Princeton, New Jersey, and dated April 1, 2002 (Laboratory Project ID No. 98-2606, MRID No. 46415732).

The study design allocated groups of 65 rats per sex to dose levels of 0, 500, 5000 or 20,000 ppm (0, 24.9, 260 or 1068 mg/kg/day for males; 0, 30.4, 320 or 1419 mg/kg/day for females) of Metrafenone for 104 weeks. At week 69, the high dose of 20,000 ppm was reduced to 10,000 ppm for females only (equivalent to 593 mg/kg/day for females) due to toxicity. An additional 10 rats per sex per dose were designated for interim sacrifice at week 53.

ANALYSES

Survival Analyses

Mouse Study

Male mice showed negative pair-wise comparisons of the 250 (at $p < 0.05$) and 1000 ppm (at $p < 0.01$) dose groups with the controls with increasing doses of Metrafenone (Table 1). There was not a statistically significant trend for mortality.

Rat Study

There were no statistically significant incremental changes in mortality with increasing doses of Metrafenone in male rats (Table 3). Female rats showed a statistically significant decreasing trend for mortality, as well as a negative pair-wise comparison of the 20,000 ppm dose group with the controls, both at $p < 0.01$ (Table 5).

Tumor Analyses

Mouse Study

Male mice had statistically significant trends in liver adenomas ($p < 0.01$), carcinomas ($p < 0.05$) and adenomas and/or carcinomas combined ($p < 0.01$). There were statistically significant pair-wise comparisons of the 7000 ppm dose group with the controls for liver adenomas ($p < 0.05$) and adenomas and/or carcinomas combined ($p < 0.01$). The statistical analyses of the male mice were based upon the Exact test for trend and Fisher's Exact test for pair-wise comparisons (Table 2).

Rat Study

Male rats had a statistically significant trend for liver adenomas at $p < 0.05$. There were no statistically significant pair-wise comparisons of the dosed groups with the controls. The statistical analyses of the male rats were based upon the Exact test for trend and Fisher's Exact test for pair-wise comparisons (Table 4).

Female rats had statistically significant trends, and statistically significant pair-wise comparisons of the 20,000 ppm dose group with the controls, for liver adenomas and adenomas and/or carcinomas combined, all $p < 0.01$. The statistical analyses of the female rats were based upon Peto's Prevalence test due to a statistically significant decreasing trend for mortality with increasing doses of Metrafenone (Table 6).

Table 1. Metrafenone - CrI:CD-1(ICR)BR Mouse Study (MRID 46415731)

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

Weeks

Dose (ppm)	1-26	27-52	53-79 ^f	Total
0	2/65	7/63	12/56	21/65 (32)
250	0/65	2/65	10/63	12/65 (18)*n
1000	0/65	1/65	9/64	10/65 (15)**n
7000	1/66	3/65	8/62	12/66 (18)

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

^fFinal sacrifice at week 79.

*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 2. Metrafenone – CrI:CD-1(ICR)BR Mouse Study (MRID 46415731)
 Male Liver Tumor Rates^a and Fisher's Exact Test and Exact Test for Trend Results

	Dose (ppm)			
	0	250	1000	7000
Adenomas (%)	4/56 (7)	2/63 (3)	8/64 (13)	14 ^a /62 (23)
p =	0.00074**	0.92129	0.25300	0.01750*
Carcinomas (%)	2 ^b /56 (4)	1/63 (2)	1/64 (2)	5/62 (8)
p =	0.03976*	0.89877	0.90130	0.26364
Combined (%)	6/56 (11)	3/63 (5)	9/64 (14)	19/62 (31)
p =	0.00006**	0.94314	0.39320	0.00697**

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

^aFirst adenoma observed at week 71, dose 7000 ppm.

^bFirst carcinoma observed at week 68, dose 0 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. Metrafenone - Sprague-Dawley Rat Study (MRID 46415732)

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

Dose (ppm)	Weeks								Total
	1-26	27-52	53 ¹	53-78	79-105 ¹				
0	1/75	3/74	10/71	14/61	21/47			39/65 (60)	
500	1/75	3/74	10/71	16/61	25/45			45/65 (69)	
5000	2/75	0/73	10/73	13/63	31/50			46/65 (71)	
20,000	1/75	1/74	10/73	12/63	30/51			44/65 (68)	

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

²Interim sacrifice at week 53.

³Final sacrifice at weeks 104-105.

() 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 ⁴, then $p < 0.05$. If ⁵, then $p < 0.01$.

Table 4. Metrafenone – Sprague-Dawley Rat Study (MRID 46415732)

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

	Dose (ppm)			
	0	500	5000	20,000
Adenomas (%)	1 ^a /61 (2)	0/61 (0)	1 ^a /63 (2)	4 ^b /62 (6)
p =	0.0224*	1.0000	0.7600	0.1874
Carcinomas (%)	1/61 (2)	3/61 (5)	1 ^b /63 (2)	1/62 (2)
p =	0.3248	0.3094	0.7600	0.7561
Combined (%)	2/61 (3)	3/61 (5)	2/63 (3)	5/62 (8)
p =	0.1135	0.5000	0.7027	0.2265

^aNumber of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

^bFirst adenoma observed at week 104 in final sacrifice animals simultaneously at 0, 5000 and 20,000 ppm.

^cFirst carcinoma observed at week 95, dose 5000 ppm.

Note: Significance of trend denoted at control.

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

If ^a, then p < 0.05. If ^b, then p < 0.01.

Table 5. Metrafenone – Sprague-Dawley Rat Study (MRID 46415732)

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

Weeks

Dose (ppm)	1-26	27-52	53 ¹	53-78	79-105 ¹	Total
0	0/75	2/75	10/73	6/63	31/57	39/65 (60)**n
500	0/75	0/75	10/75	7/65	29/58	36/65 (55)
5000	0/75	1/75	10/74	8/64	24/56	33/65 (51)
20,000	0/75	0/75	10/75	3/65	17/62	20/65 (31)**n

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 104-105.

¹Negative trend and/or 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 ¹, then p < 0.05. If **, then p < 0.01.

Table 6. Metrafenone - Sprague-Dawley Rat Study (MRID 46415732)

Female Liver Tumor Rates and Peto's Prevalence Test Results

	Dose (ppm)			
	0	500	5000	20,000
Adenomas (%)	1/53 (2)	0/50 (0)	6/54 (11)	10 ^a /57 (18)
p =	0.00042**	0.85454	0.07461	0.00701**
Carcinomas (%)	0/26 (0)	0/29 (0)	0/32 (0)	1 ^b /45 (2)
p =	0.08716	-	-	0.22359
Combined (%)	1/53 (2)	0/50 (0)	6/54 (11)	10 ^a /57 (18)
p =	0.00042**	0.85454	0.07461	0.00701**

^aNumber of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

^bFirst adenoma observed at week 88, dose 20,000 ppm.

^cFirst and only carcinoma observed at week 105 in a final sacrifice animal, dose 20,000 ppm.

^dOne animal in the 20,000 ppm dose group had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in these analyses. Two interim sacrifice animals in the 20,000 ppm dose group had adenomas.

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

- Cox, D.R. (1972) Regression Models and Life Tables (with discussion). J. Royal Stat. Soc. Ser. B. 34, 187-220.
- Gart, J.J., D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf (1986) The Design and Analysis of Long-Term Animal Experiments. In: Statistical Methods in Cancer Research, Volume III. IARC Scientific Publications No. 79. Lyon, France: International Agency for Research on Cancer, p. 18.
- Peto, R., M. Pike, N. Day, R. Gray, P. Lee, S. Parish, J. Peto, S. Richard, and J. Wahrendorf (1980) Guidelines for Simple, Sensitive, Significant Tests for Carcinogenic Effects in Long-Term Animal Experiments. In: Monographs on the long-term and short-term screening assays for carcinogens: a critical appraisal. IARC Monographs, Supplement 2. Lyon, France: International Agency for Research on Cancer, pp. 311-426.
- Thomas, D.G., N. Breslow, and J.J. Gart (1977) Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research 10, 373-381.



13544



R124163

Chemical: METRAFENONE

PC Code:
000325

HED File Code: 13000 Tox Reviews

Memo Date: 3/15/2006

File ID: TX0054152

Accession #: 412-06-0013

HED Records Reference Center
3/30/2006

