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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No. 0053189

MEMORANDUM

DATE: April 12, 2005

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

P.C. Code: 097801

TO: William Dykstra, Toxicologist
Reregistration Branch 4
Health Effects Division (7509C)

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

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

BACKGROUND

The 104-Week Crl:CD BR Rat Carcinogenicity Study (MRID 43601601)

A combined chronic toxicity/carcinogenicity study in Crl:CD BR rats was conducted by Hazleton Washington, Vienna, Virginia, for Roussel UCLAF Corporation, Montvale, New Jersey, and dated December 28, 1994 (Study No. HWA 2623-104, MRID No. 43601601).

The study design allocated groups of 65 rats per sex to dose levels of 0, 250, 1000 or 2500 ppm (0, 10.4, 41.8 or 107.2 mg/kg/day for males; 0, 12.8, 51.7 or 131.4 mg/kg/day for females) of SB-1382 (Resmethrin, 85% a.i.) for 104 weeks. There were no compound-related increases in tumors in male rats so only analyses of female rats are presented in this document.

The 104-Week Swiss Crl:CD-1(ICR)BR Mouse Carcinogenicity Study (MRID 43052101)

A carcinogenicity study in Swiss Crl:CD-1(ICR)BR mice was conducted by Bio-Research Laboratories, Ltd., Senneville, Quebec, Canada, for Roussel UCLAF Corporation, Montvale, New Jersey, and dated January 8, 1992 (Study No. 83754, MRID No. 43052101).

The study design allocated groups of 50 mice per sex to dose levels of 0, 300, 600 or 1200 ppm (0, 43.4, 84.3 or 169.3 mg/kg/day for males; 0, 52.9, 105.5 or 208.9 mg/kg/day for females) of Resmethrin (technical 84.8% a.i.) for 104 weeks. Two control groups of 50 mice per sex were combined for these analyses as there were no statistically significant differences in mortality, mean body weight, total body weight gain or food consumption between these two control groups. There were no compound-related increases in tumors in female mice so only analyses of male mice are presented in this document.

ANALYSES

The 104-Week Crl:CD BR Rat Carcinogenicity Study (MRID 43601601)

Survival Analyses

Female rats showed statistically significant differences in mortality in the pair-wise comparisons of the 250 and 1000 ppm dose groups with the controls, both at $p < 0.05$ (Table 1). There was no statistically significant increase in the trend for female rat mortality with increasing doses of Resmethrin.

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

Tumor Analyses

Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for liver carcinomas, liver adenomas and/or carcinomas combined, and uterine endometrial stromal polyps, all at $p < 0.01$. There was a significant increasing trend at $p < 0.01$, and a significant difference in the pair-wise comparison of the 2500 ppm dose group with the controls at $p < 0.05$, for liver adenomas. There was a significant difference in the pair-wise comparison of the 1000 ppm dose group with the controls for uterine endometrial stromal polyps at $p < 0.05$. The statistical analyses of the female rats were based upon Peto's Prevalence Test (Tables 2 and 3).

The 104-Week Swiss Crl:CD-1(ICR)BR Mouse Carcinogenicity Study (MRID 43052101)

Survival Analyses

Male mice showed a significant increasing trend in mortality, at $p < 0.01$, with increasing doses of Resmethrin, as well as significant differences in the pair-wise comparisons of the 600 and 1200 ppm dose groups with the controls, both at $p < 0.05$ (Table 4).

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 comparisons of the 1200 ppm dose group with the controls, for liver adenomas, carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 600 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, both at $p < 0.01$. There were also significant differences in the pair-wise comparisons of the 300 ppm dose group with the controls for liver adenomas and adenomas and/or carcinomas combined, and of the 600 ppm dose group with the controls for liver carcinomas, all at $p < 0.05$. The statistical analyses of the male mice were based upon Peto's Prevalence Test (Table 5).

Table 1. Resmethrin - Crl:CD BR Rat Study (MRID 43601601)

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

Weeks

Dose (ppm)	1-26	27-52	53-78	79-105[f]	Total
0	0/65	1/65	10/64	22/54	33/65 (51)
250	0/65	3/65	13/62	31/49	47/65 (72)*
1000	0/65	1/65	13/64	32/51	46/65 (71)*
2500	0/65	1/65	15/64	20/49	36/65 (55)

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

[f]Final sacrifice at week 104.

( )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. Resmethrin - Crl:CD BR Rat Study (MRID 43601601)

Female Liver Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	250	1000	2500
Adenomas (%)	0/56 (0)	0/52 (0)	1/54 (2)	3[a]/54 (6)
p =	0.00679**	-	0.09718	0.03430*
Carcinomas (%)	1/51 (2)	0/45 (0)	0/48 (0)	11[b]/45 (24)
p =	0.00000**	0.77337	0.77337	0.00047**
Combined (%)	1/56 (2)	0/52 (0)	1/54 (2)	14/54 (26)
p =	0.00000**	0.77337	0.35324	0.00008**

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

[a]First adenoma observed at week 75, dose 2500 ppm.
[b]First carcinoma observed at week 83, dose 2500 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. Resmethrin - Crl:CD BR Rat Study (MRID 43601601)

Female Uterine Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	250	1000	2500
Endometrial Stromal Polyps (%)	0/54 (0)	1/50 (2)	3[a]/52 (6)	5/50 (10)
p =	0.00520**	0.22713	0.04555*	0.00725**

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

[a]First endometrial stromal polyp observed at week 78, dose 1000 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. Resmethrin - Swiss Crl:CD-1(ICR)BR Mouse Study (MRID 43052101)

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

Weeks

Dose (ppm)	1-26	27-52	53-78	79-105[f]	Total
0	2/100	3/98	17/95	36/78	58/100 (58)**
300	2/50	4/48	11/44	13/33	30/50 (60)
600	1/50	2/49	17/47	15/30	35/50 (70)*
1200	0/50	5/50	14/45	18/31	37/50 (74)*

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

[f]Final sacrifice at week 104.

( )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. Resmethrin - Swiss Crl:CD-1(ICR)BR Mouse Study (MRID 43052101)

Male Liver Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	300	600	1200
Adenomas (%)	9[a]/96 (9)	9/45 (20)	12/47 (26)	15/47 (32)
p =	0.00001**	0.03189*	0.00075**	0.00005**
Carcinomas (%)	2/85 (2)	2[b]/39 (5)	4/35 (11)	6/37 (16)
p =	0.00231**	0.20688	0.01569*	0.00214**
Combined (%)	11/96 (11)	10/45 (22)	14/47 (30)	18/47 (38)
p =	0.00000**	0.03151*	0.00026**	0.00001**

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

[a]First adenoma observed at week 50, dose 0 ppm.
[b]First carcinoma observed at week 69, dose 300 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

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.