4

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

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

TXR No. 0050179

MEMORANDUM

October 4, 2001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **Acetamiprid** Qualitative Risk Assessment Based On Crl:CD®BR Rat Dietary Study

P.C. Code 099050

TO: Pamela Hurley, Acting Branch Chief
Registration Action Branch 2
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

A chronic toxicity/oncogenicity study in Crl:CD®BR rats was conducted by MPI Research, Inc., Mattawan, Michigan, for Nippon Soda Company, Ltd., Tokyo, Japan, and issued September 28, 1999 (Study No. 449-015; MRID Nos. 44988429 and 45245304).

The study design allocated groups of 50 rats per sex to dose levels of 0, 160, 400, or 1000 ppm (0, 7.1, 17.5, or 46.4 mg/kg/day for males; 0, 8.8, 22.6, or 60.0 mg/kg/day for females) of Acetamiprid for 105 weeks. An additional 10 rats per sex per dose were designated for interim sacrifice at week 53.

Survival Analyses

The statistical evaluation of mortality indicated no statistically significant incremental changes with increasing doses of Acetamiprid in male or female rats. See Tables 1 and 2 for mortality test results.

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

1

Tumor Analyses

Male rats had a significant increasing trend in testes interstitial cell tumors at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Female rats had a significant increasing trend in mammary gland adenomas and/or adenocarcinomas combined at $p < 0.05$. There were significant differences in the pair-wise comparisons of the 400 ppm dose group with the controls for pituitary adenomas, and adenomas and/or adenocarcinomas combined, both at $p < 0.05$.

The statistical analyses of the male and female rats were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 3 through 5 for the tumor analyses results.

Table 1. Acetamiprid - Crl:CD®BR 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	4/48	14/44	20/50 (40)
160	0/60	0/60	10/60	2/50	8/48	10/50 (20)*n
400	1/60	1/59	10/58	4/48	11/44	17/50 (34)
1000	1/60	0/59	10/59	1/49	8/48	10/50 (20)*n

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

[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. Acetamiprid - Crl:CD®BR 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	0/60	0/60	10/60	8/50	19/42	27/50 (54)
160	0/60	1/60	10/59	2/49	21/47	24/50 (48)
400	1/60	2/59	10/57	4/47	14/43	21/50 (42)
1000	0/60	1/60	10/59	5/49	15/44	21/50 (42)

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

[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. Acetamiprid - Crl:CD®BR Rat Study

Male Testes Interstitial Cell Tumor Rates[†] and
Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	160	400	1000
Tumors (%)	1/47 (2)	2/50 (4)	0/48 (0)	5[a]/48 (10)
p =	0.0261*	0.5234	0.4947	0.1067

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

[a]First tumor observed at week 85, 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. Acetamiprid - Crl:CD®BR Rat Study

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

	Dose (ppm)			
	0	160	400	1000
Adenomas (%)	38[a]/60 (63)	41/59 (69)	48/59 (81)	44/60 (73)
p =	0.1377	0.3028	0.0227*	0.1633
Adeno-carcinomas (%)	1/60 (2)	0/59 (0)	2[b]/59 (3)	2/60 (3)
p =	0.1720	0.5042	0.4936	0.5000
Combined (%)	39/60 (65)	41/59 (69)	50/59 (85)	46/60 (77)
p =	0.0731	0.3722	0.0111*	0.1140

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 43.

[a]First adenoma observed at week 53, dose 0 ppm.

[b]First adenocarcinoma observed at week 43, dose 400 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 $p < 0.01$.

6

Table 5. Acetamiprid - Crl:CD®BR Rat Study

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

	Dose (ppm)			
	0	160	400	1000
Adenomas (%)	1/59 (2)	0/60 (0)	4/59 (7)	3[a]/60 (5)
p =	0.0888	0.4958	0.1821	0.3157
Adeno-carcinomas (%)	10/59 (17)	11[b]/60 (18)	16/59 (27)	17/60 (28)
p =	0.0543	0.5171	0.1333	0.1029
Combined (%)	11/59 (19)	11/60 (18)	17[c]/59 (29)	19[d]/60 (32)
p =	0.0294*	0.5760	0.1396	0.0768

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 31.

[a]First adenoma observed at week 53, dose 1000 ppm.

[b]First adenocarcinoma observed at week 31, dose 160 ppm.

[c]Three animals in the 400 ppm dose group had both an adenoma and an adenocarcinoma.

[d]One animal in the 1000 ppm dose group had both an adenoma and an adenocarcinoma.

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 $p < 0.01$.

7

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.