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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

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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.

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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 - Cr1:CD®BR Rat Study

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

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	53 ⁱ	53-78	79-105 ^f	
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) ^{**}
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) ^{**}

[†]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 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^a and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	53 ⁱ	53-78	79-105 ^f	
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)

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

ⁱInterim sacrifice at week 53.

^fFinal 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 $p < 0.01$.

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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)

	<u>Dose (ppm)</u>			
	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.

^aFirst 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.

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Table 4. Acetamiprid - Crl:CD®BR Rat Study
Female Pituitary Tumor Rates[†] and Exact Trend Test
and Fisher's Exact Test Results (p values)

	<u>Dose (ppm)</u>			
	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.

^aFirst adenoma observed at week 53, dose 0 ppm.

^bFirst 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 $p < 0.01$.

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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)

	<u>Dose (ppm)</u>			
	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.

^aFirst adenoma observed at week 53, dose 1000 ppm.

^bFirst adenocarcinoma observed at week 31, dose 160 ppm.

^cThree animals in the 400 ppm dose group had both an adenoma and an adenocarcinoma.

^dOne 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.

References

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