OPP#00664
Ref A

HED DOC. NO. 013218

MEMORANDUM February 9, 1999

SUBJECT: Atrazine Qualitative Risk Assessment Based On Female Sprague-Dawley Rat Dietary Study

P.C. Code 080803

TO: Roger Hawks, Toxicologist
Risk Characterization & Analysis Branch
Health Effects Division (7509C)

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

THROUGH: William L. Burnam, Branch Chief
Science Analysis Branch
Health Effects Division (7509C)

Background

A carcinogenicity toxicity study in female Sprague-Dawley rats was conducted by Covance Laboratories, Vienna, Virginia, for Novartis Crop Protection, Greensboro, North Carolina, and dated April 15, 1998 (Lab Report No. 2386-108; MRID No. 445447-01).

The study design allocated groups of 160 female rats to dose levels of 0, 25, 50, 70, or 400 ppm of Atrazine for 105 weeks. Eighty animals per dose group were ovariectomized while the others were left intact. Only the intact animals have been included in this analysis, as there were no compound-related tumors observed in the ovariectomized animals.

Survival Analyses

The statistical evaluation of mortality indicated a significant increasing trend with increasing doses of Atrazine in female rats. See Table 1 for mortality test results.

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

1/8

Tumor Analyses

Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 400 ppm dose group with the controls, for mammary gland carcinomas and fibroadenomas and/or adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 25 and 70 ppm dose groups with the controls for mammary gland fibroadenomas and fibroadenomas and/or adenomas and/or carcinomas combined, all at $p < 0.05$. There were significant differences in the pair-wise comparison of the 50 ppm dose group with the controls for mammary gland fibroadenomas and fibroadenomas and/or adenomas and/or carcinomas combined, both at $p < 0.01$. There was also a significant difference in the pair-wise comparison of the 400 ppm dose group with the controls for mammary gland fibroadenomas at $p < 0.05$.

The statistical analyses of the female rats were based upon Peto's Prevalence Test since there was a statistically significant positive trend for mortality with increasing doses of Atrazine in female rats. See Table 2 for tumor analysis results.

Table 1. Atrazine Sprague-Dawley Female Rat Study
Intact Animals ONLY

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

Dose (ppm)	Weeks 1-26	27-52	53[i]	53-78	79-106[f]	Total
0	1/80	1/79	20/78	9/58	23/49	34/60 (57)*
25	0/80	1/80	21/79	14/58	25/44	40/59 (68)
50	1/80	2/79	21/77	12/56	27/44	42/59 (71)
70	0/80	2/80	20/78	8/58	31/50	41/60 (68)
400	2/80	1/78	22/77	16/55	26/39	45/58 (78)*

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

[f]Final sacrifice at week 105.

[i]Interim sacrifice at week 53.

( )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. Atrazine Sprague-Dawley Female Rat Study
Intact Animals ONLY

Mammary Gland Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	25	50	70	400
Fibro-adenomas (%)	16/78 (21)	25[a]/79 (32)	34/77 (44)	29/78 (37)	25/77 (32)
p =	0.233	0.030*	0.000**	0.014*	0.014*
Adenomas (%)	0/28 (0)	0/24 (0)	1[b]/20 (5)	0/21 (0)	0/15 (0)
Carcinomas (%)	12/80 (15)	18/80 (22)	20/79 (25)	14/80 (18)	27[c]/80 (34)
p =	0.002**	0.112	0.067	0.395	0.007**
Combined[d] (%)	24/80 (30)	34/80 (42)	45/79 (57)	38/80 (48)	43/80 (54)
p =	0.004**	0.025*	0.000**	0.015*	0.000**

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

[a]First fibroadenoma observed at week 53, dose 25 ppm.

[b]First adenoma observed at week 103, dose 50 ppm.

[c]First carcinoma observed at week 19, dose 400 ppm.

[d]The number of animals with multiple tumors are 4, 9, 10, 5 and 9 for the control, 25, 50, 70 and 400 ppm dose groups, respectively.

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.

SignOff Date:	2/9/99
DP Barcode:	D000000
HED DOC Number:	013218
Toxicology Branch:	SAB