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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: ATRAZINE - Updated Qualitative and Quantative Risk Assessment from a Rat 2-Year Chronic Oral Toxicity /Oncogenicity Study. Caswell No. - 63

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SUMMARY:

In female rats, a significant increasing trend in mortality was observed with increasing doses of atrazine. Mortality was significantly increased in the 1000 ppm group compared to controls. The incidence of malignant mammary gland tumors and combined malignant and benign mammary gland tumors had significant dose related trends. The incidence of each of these tumor groups was significantly increased compared to controls at the 70 ppm, 500 ppm, and 1000 ppm dose groups.

The unit risk at week 106 is 2.22x10-1 [mg/kg/day]-1 using the female rat combined mammary gland benign and malignant tumors. For comparison purposes, the Global86 unit risk estimate using the effective proportions of the combined mammary gland tumors is 1.02x10-1 [mg/kg/day]-1, a factor of 2 smaller than the Weibull82 estimate.

The estimates remain essentially unchanged from the Dynamac memo.

1

BACKGROUND:

This is an update on a previous qualitative and quantitative risk assessment memo done by Dynamac and dated 1-19-88. The data for female rats was corrected and verified by Marion Copley. Only tables that changed are reported in this memo.

SURVIVAL ANALYSIS:

In female rats, a statistically significant increasing trend in mortality was observed with increasing doses of Atrazine by Cox's test ($p = 0.0005$) and by the generalized K/W test ($p = 0.0014$). Mortality was significantly increased in the 1000 ppm dose group compared to controls by Cox's test ($p = 0.0028$) and by the generalized K/W test ($p = 0.0045$). These results are only slightly smaller than the previous results. (Table 2).

Survival was evaluated using the computer program of Thomas, Breslow, and Gart.

TUMOR ANALYSIS:

Tumors were analyzed by the Peto Prevalence method since survival differences were observed in the females rats. In these analyses only mammary tumors were analyzed. Fibroadenomas and adenomas were analyzed as benign tumors. Adenocarcinoma and carcinosarcoma were analyzed as malignant tumors. The benign and malignant were combined and a third analysis run (Table X).

In the female rats, the incidence of benign mammary tumors had no pair-wise significant differences between the controls and treated groups, and there was not a significant trend with increasing dose. The incidence of malignant mammary tumors in the 70 ppm, 500 ppm, and 1000 ppm dose groups had significantly higher pair-wise differences when compared to the controls, and there was a significant trend with increasing dose. The incidence of combined malignant and benign mammary tumors had significantly higher pair-wise differences when compared to the controls, and there was a significant trend with increasing dose.

QUANTITATIVE ANALYSIS:

Since mortality in the female rats was significantly impaired with increasing doses of atrazine, the unit risk (the slope of the dose response curve in [mg/kg/day]-1) estimate was obtained using the Weibull82 program of Howe and Crump. This program incorporates time-to-death with tumor and produces an estimate of unit risk that is adjusted for the observed differences in survival. Unit risk's were calculated for both the incidence of combined benign and malignant female rat mammary gland tumors and the incidence of malignant female rat mammary

gland tumors (Table X). Animal risks in ppm were first converted to mg/kg/day using Lehman's tables and then to human equivalents by use of the surface area correction as recommended by the EPA Cancer Guidelines (Table Y).

The most conservative resulting unit risk for humans is

2.22x10-1 [mg/kg/day]-1

using the female rat mammary gland benign and malignant tumors combined. The unit risk is an estimate of the upper (95%) bound on risk. The true value of the risk is unknown and may be as low as zero. The assumption of linearity at low doses was made.

In following the recommendations of the EPA Guidelines for Carcinogen Risk Assessment to indicate the contribution of the benign tumors to total risk, the quantitative models are first fit to the malignant tumors and then fit to the combined tumors. The difference in the unit risk between the combined and the malignant is the result of considering the benign tumor to progress to malignant.

For comparison purposes the Global86 unit risk estimate using the effective proportions (animals alive at the observance of the first tumor) of the combined mammary gland tumors is 1.02x10-1 [mg/kg/day]-1, a factor of 2 smaller than the Weibull82 estimate.

Both of these estimates remain essentially unchanged from the estimates in the Dynamac memo.

TABLE 2. ATRAZINE, RAT Study-- FEMALE Mortality Rates+ and Cox or Generalized k/W Test Results

DOSE(PPM)		WEEK 1-2o	27-52	52 a	53-57	57 a	58-78	79-106 a	TOTAL	
0.		0/89	1/89	10/10	2/78	10/10	7/66	24/59	34/69	
	(%)	(0)	(1)		(3)		(11)	(41)	(49)	**
10.		1/70	4/69		0/65		12/65	22/53	39/70	
	(%)	(1)	(6)		(0)		(18)	(42)	(56)	
70.		0/70	1/70		0/69		11/69	28/58	40/70	
	(%)	(0)	(1)		(0)		(16)	(48)	(57)	
500.		1/70	2/69		2/67		9/65	30/56	44/70	
	(%)	(1)	(3)		(3)		(14)	(54)	(63)	
1000.		0/89	2/89	10/10	2/77	10/10	12/65	36/53	52/69	
	(%)	(0)	(2)		(3)		(18)	(68)	(75)	**

\+ Number of animals that died/number of animals alive at the beginning of the interval.
a Interim sacrifice was conducted at 52 & 57 weeks. Final sacrifice occurred at week 106.

Note: Time intervals were selected for display purposes only. Significance of trend denoted at Control. Significance of pairwise comparison with control denoted at Dose level.
* $p < 0.05$ and ** $p < 0.01$.

TABLE X. ATRAZINE, RAT Study— FEMALE Mammary Tumor Rates+ and Peto's Prevalence Test Results

DOSE		0.	10.	70.	500.	1000.
BENIGN		20/88	24/65	21/69	21/68 a	20/89 b
	(%)	(23)	(37)	(30)	(31)	(22)
	(p)	0.446	0.110	0.373	0.373	0.468
MALIGNANT		15/88	16/67 c	27/69	27/68	45/89 d
	(%)	(17)	(24)	(39)	(40)	(51)
	(p)	0.000 **	0.390	0.024 *	0.019 *	0.000 **
BENIGN AND MALIGNANT COMBINED		35/88	40/67	48/69	48/68	65/89
	(%)	(40)	(60)	(70)	(71)	(73)
	(p)	0.000 **	0.111	0.017 *	0.015 *	0.000 **

\+ Number of tumor bearing animals/Number of animals at risk. (Excluding animals that died before the observation of the first tumor or animals not examined).
( ) Per cent

a) First adenoma occurred at 81 weeks in dose 500 ppm.
b) First fibroadenoma occurred at 45 weeks in dose 1000 ppm.
c) First adenocarcinoma occurred at 34 weeks in dose 10 ppm.
d) First carcinosarcoma occurred at 69 weeks in dose 1000 ppm.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

TABLE Y. ATRAZINE, RAT Study— FEMALE Mammary Gland Tumors Unit Risk Estimates

SPECIES	Combined Benign and Malignant		Malignant	
	RAT	HUMAN Equivalent	RAT	HUMAN Equivalent
	(mg/kg/day)-1		(mg/kg/day)-1	
FEMALES (Weibull83)	4.19x10-2	2.22x10-1	1.72x10-2	9.16x10-2

\+ Surface area correction = $\left[\frac{\text{Human Weight (60 kilograms)}}{\text{Rat Weight (400 grams)}}\right]^{1/3}$

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