7-14-87

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EPA: 68-02-4225
DYNAMAC No. 230
July 14, 1987

ATRAZINE--QUALITATIVE AND QUANTITATIVE RISK ASSESSMENT

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SUMMARY:

In female rats, survival was significantly reduced with increasing doses of atrazine. In addition, pairwise comparisons with the control group showed significant decreases in survival in the high dose group. Using the Peto Prevalence Method, the incidence of mammary gland adenocarcinomas exhibited an increasing dose-related trend and was significantly increased at all but the low dose compared to control by pairwise comparisons.

The cancer potency estimate, Q_1^*, of atrazine is 1.24×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents based on the incidence of mammary adenocarcinomas in female mice using the Weibull82 multistage procedure incorporating time-to-death with tumor.

BACKGROUND:

A 24-month chronic oral toxicity and oncogenicity study was conducted at American Biogenics Corporation, Decatur, IL, on Sprague-Dawley CD and BR rats from Charles River Breeding Laboratories. Atrazine was administered at 10, 70, 500, or 1000 ppm in the diet to the test animals. Each dose group contained 50 males and 50 females with the exception of the control and high-dose groups, which contained 70 males and 70 females each. A chronic toxicity subgroup was used, which contained 20 males and 20 females per dose group. This resulted in 90 animals in the control and high-dose groups and 70 animals in the low and mid-dose groups. Interim sacrifice of 20 animals in the control and high-dose group was performed.

QUALITATIVE ANALYSIS:

Significant differences in survival were observed with increasing doses of atrazine by the Cox Test for Life Table Data ($p<0.01$) and the Generalized K/W Analysis (Gehan-Breslow) ($p<0.01$). Pairwise comparisons indicated a significant decrease in survival in the high dose group compared to controls by both the Cox Test ($p<0.01$) and the Generalized K/W Analysis ($p<0.01$) Table 1. Survival was evaluated using the computer program of Thomas, Breslow and Gart (Thomas et al., 1977).

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TABLE 1. Survival Rates in Female Rats Dosed with Atrazine

Dose (ppm)	Weeks				
	0-26	27-52	53-78	79-106	Total
0	90/90	89/90	79/89	56/79	56/90**
10	69/70	65/69	53/65	31/53	31/70
70	70/70	69/70	58/69	30/58	30/70
500	69/70	67/69	56/67	26/56	26/70
1000	90/90	88/90	74/88	39/74	39/90**

Note: Significance of trend by Cox test and generalized K/W test denoted at the control level.
Significance of pairwise comparisons by Cox test and generalized K/W test denoted at each dose level.

*p <0.05.

**p <0.01.

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Since significant survival differences between dose groups were observed the tumor analysis of mammary adenocarcinoma incidence was conducted by the Peto Prevalence Method. This procedure is an adjusted analysis for time-to-death with tumor. Table 2 shows the mammary adenocarcinoma incidence rates by selected time intervals. By the Peto Prevalence Method a significant dose-related trend was observed for mammary adenocarcinomas ($p<0.01$) and significant increases in tumors were observed at the 70 ppm, 500 ppm and 1000 ppm dose groups compared to controls, $p<0.01$.

QUANTITATIVE ANALYSIS:

Mammary gland adenocarcinoma incidence data were used to estimate the cancer potency, Q_1^*, of atrazine. Since significant survival differences were observed, the Weibull82 multistage procedure incorporating time-to-death with tumor, was used to determine the cancer potency, Q_1^*. The linearized multistage model (Global83, Howe and Crump, 1983) was also used to estimate cancer potency for comparison. Doses were converted to mg/kg/day and conversions were made to human equivalents using an interspecies surface-area adjustment as recommended by EPA cancer guidelines. Q_1^* was determined to be 1.24×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents by the Weibull82 multistage procedure and 6.27×10^{-2} $(mg/kg/day)^{-1}$ by the Global83 multistage procedure.

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TABLE 2. Peto Prevalence Analysis[a] of Mammary Gland Adenocarcinomas in Female Rats Dosed with Atrazine by Week of Death with Tumor

	Weeks					
Dose (ppm)	34[b]-60	Interim Kill	61-78	79-105	Final Kill	Total
0	0/3	0/20	1/8	8/23	6/35	15/89**
10	1/3		3/11	5/21	7/33	16/68
70	1/2		4/10	12/28	10/30	27/70**
500	0/3		3/9	13/30	11/26	27/68**
1000	2/7	6/20	7/10	20/36	8/17	43/90**

NOTE: Significance of trend denoted at control group. Significance of pairwise comparison denoted at dose level.

[a]Number of tumor bearing animals/number of animals at risk, excluding animals that died prior to appearance of the first tumor.

[b]Appearance of first tumor--10 ppm group.

**$p<0.01$.

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