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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Nitrapyrin, Qualitative Risk Assessment -
2-Year Fischer 344 Rat Dietary Study

Caswell no.217

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Summary

The qualitative risk assessment of nitrapyrin was based upon 2 two-year chronic toxicity/oncogenicity studies in Fischer 344 rats. The rats were fed 0, 5, 20 and 60 mg/kg of nitrapyrin for 105 weeks.

The study allocated 60 males/females to each dose group and selected 10 of them for an interim sacrifice at week 53.

The statistical evaluation of mortality in the study indicated a significant dose related decreasing trend in survival in male rats. In females there was no incremental mortality with increasing doses of nitrapyrin.

Male rats had a significant dose related increasing trend in kidney renal tubular tumors in adenomas, carcinomas and in the combined rate. Males also had a significant increase in the combined (adenoma and/or carcinoma) kidney renal tubular tumor rates in the pair-wise comparison of controls and the highest dose group.

(1)

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The female rats had no tumors with statistically significant differences among the dose levels of nitrapyrin.

Background

A 2-year chronic toxicity/oncogenicity study in Fischer 344 rats was conducted by Health and Environmental Science for Dow Chemical Company (TXT:K-o31304-023 and MRID no. 413454-03) and issued in December, 1989.

The study design assigned in a random manner groups of 60 males/females to dose levels of 0, 5, 20 and 60 mg/kg of nitrapyrin. An interim sacrifice of 10 males/females was made in each of the sex/dose categories.

Survival Analysis

In male rats, there was a statistically significant increasing trend in mortality with incremental doses of nitrapyrin. The males also had a significant increase in mortality in the pair-wise comparison of controls and the highest (60 mg/kg) dose of the compound (Table 1).

The female rats had no statistically significant dose related changes in mortality (Table 2).

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

Tumor Analysis

Male rats had a significant increasing dose related trend in kidney renal tubular adenomas, carcinomas and in the combination of both of them. Males also had a significant increase in the kidney renal combined tubular adenomas and/or carcinomas in the pair-wise comparison of controls and the highest (60 mg/kg) dose group (Table 3).

Statistical analysis of tumor rates was based upon the Cochran-Armitage Trend test and Fisher's Exact test for pair-wise comparisons of controls and each dose group, instead of the Peto's Prevalence tests (there were too few tumors and they only appeared in the highest dose group) even though there was dose related significant increase in mortality.

Table 1. Nitrapyrin - Fischer 344 Rat Study , Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Weeks

Dose (mg/kg)	1-52	53[a]	53-78	79-105[b]	Total
0	0/60	10/60	2/50	10/48	12/50(24)**
5	0/60	10/60	2/50	8/48	10/50(20)
20	0/60	10/60	1/50	11/49	12/50(24)
60	0/60	10/60	2/50	21/48	23/50(46)*

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

( ) percent

[a] Interim sacrifice at week 53.
[b] Final sacrifice at week 105.

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 $p<.05$ and if ** then $p<.01$.

Table 2. Nitrapyrin - Fischer 344 Rat Study , Female
Mortality Rates[+] and Cox or Generalized
K/W Test Results

	Weeks				
Dose(mg/kg)	1-52	53[a]	53-78	79-105[b]	Total
0	0/60	10/60	2/50	16/48	18/50(36)
5	1/60	9/59	3/50	20/47	24/51(47)
20	1/60	10/59	4/49	11/45	16/50(32)
60	1/60	10/59	2/49	16/47	19/50(38)

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

( ) percent

[a] Interim sacrifice at week 53.
[b] Final sacrifice at week 105.

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 $p<.05$ and if ** then $p<.01$.

Table 3. Nitrapyrin - Fischer 344 Male Rats , Kidney Renal Tubular Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg)			
	0	5	20	60
Tumors				
Adenomas	0/50	0/50	0/50	3[a]/50
(%)	(0)	(0)	(0)	(6)
p=	0.002**	1.000	1.000	0.121
Carcinomas	0/50	0/50	0/50	3[b]/50
(%)	(0)	(0)	(0)	(6)
p=	0.002**	1.000	1.000	0.121
Both	0/50	0/50	0/50	6/50
(%)	(0)	(0)	(0)	(12)
p=	0.000**	1.000	1.000	0.013*

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

[a] First adenoma observed at week 104, dose 60 mg/kg.
[b] First carcinoma observed at week 106, dose 60 mg/kg.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

References

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