



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

TXR No. 0051321

MEMORANDUM

November 12, 2002

SUBJECT: Ziram Qualitative Risk Assessment Based On 1983 F344/DuCrj/SPF Rat  
Dietary Study

P.C. Code 034805

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Background

A combined chronic toxicity/carcinogenicity study in F344/DuCrj/SPF rats was conducted by Mitsukaido Research Laboratories, Institute of Environmental Toxicology, Ibaragi, Tokyo, Japan, for Ouchi-Shinko Chemical Industrial Company, LTD, submitted by the Ziram Task Force and dated September 23, 2002 (ZTF Project No. ZTF-02001, MRID No. 457702-01, study dated April 20, 1983).

The study design allocated groups of 56 rats per sex to dose levels of 0, 20, 200, or 2000 ppm of Ziram for 104 weeks. An additional 8 rats per sex per dose per time period were designated for interim sacrifice at weeks 26, 52, and 78.

Survival Analyses

The statistical evaluation of mortality indicated a significant increasing trend with increasing doses of Ziram in male rats. There were no statistically significant incremental changes in mortality with increasing doses of Ziram in female rats. See Tables 1 and 2 for the mortality test results.

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

#### Tumor Analyses

Male rats had a significant increasing trend in preputial gland adenomas at  $p < 0.05$ . There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

There were no compound-related tumors observed in female rats.

The statistical analyses of the male rats were based upon Peto's prevalence test. See Table 3 for the tumor analyses results.

Table 1. Ziram - 1983 F344/DuCrj/SPF Rat Study

Male Mortality Rates\* and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>							Total
	1-26	26	27-52	52	53-78	78	79-106 <sup>f</sup>	
0	0/80	8/80	0/72	8/72	3/64	8/61	12/53	15/56* (27)
20	0/80	8/80	1/72	8/71	3/63	7/60	9/53	13/57 (23)
200	0/80	8/80	1/72	8/71	2/63	8/61	12/53	15/56 (27)
2000	0/80	8/80	0/72	8/72	4/64	8/60	18/52	22/56 (39)

\*Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>f</sup>Final 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. Ziram - 1983 F344/DuCrj/SPF Rat Study

Female Mortality Rates<sup>\*</sup> and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>							Total
	1-26	26	27-52	52	53-78	78	79-106 <sup>f</sup>	
0	0/80	8/80	0/72	8/72	8/64	8/56	13/48	21/56 (38)
20	0/80	8/80	2/72	8/70	5/62	8/57	10/49	17/56 (30)
200	0/80	8/80	4/72	8/68	13/59 <sup>a</sup>	8/46	6/38	23/55 (42)
2000	0/80	8/80	2/72	8/70	11/61 <sup>b</sup>	8/50	8/42	21/55 (38)

<sup>\*</sup>Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>f</sup>Final sacrifice at week 105.

<sup>a</sup>One accidental death at week 78, dose 200 ppm.

<sup>b</sup>One accidental death at week 72, dose 2000 ppm.

( ) 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. Ziram - 1983 F344/DuCrj/SPF Rat Study

	<u>Dose (ppm)</u>			
	0	20	200	2000
Adenomas#	3/61 (5)	3/61 (5)	4/61 (7)	8/60 (13)
p =	0.02679*	0.47589	0.35019	0.06577

\*Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

\*First adenoma observed at week 78, dose 200 ppm.

#No carcinomas were observed.

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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References

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- 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.
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November 20, 2002

Ziram

Male Rats Testes Interstitial Cell Tumors

Fisher's Exact Test/Cochran-Armitage trend test

DOSE(ppm)	0.0000	20.0000	200.0000	2000.0000
	51/80 (64)	54/80 (68)	55/80 (69)	64/80 (80)
	p= 0.0096**	p= 0.3697	p= 0.3081	p= 0.0171*
	CHI-SQUARE    DF    P VALUE			
LINEAR TREND (Ho: no trend)	5.2645	1	0.0103* (one-sided)	
DEPARTURE (Ho: linear)	0.3307	2	0.8461 (two-sided)	