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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Cyproconazole(San 619F)- Qualitative Risk Assessment, Mouse (CD-1) Study

Caswell no. 272E

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Summary

The qualitative risk assessment of cyproconazole is based upon a dietary/oncogenicity study in CD-1 mice. The animals were fed 0, 0, 5, 15, 100, 200 ppm of cyproconazole for 81 weeks (males) and 88 weeks (females).

Mortality was not increased by cypronoazole in mice of either sex. The statistical evaluation of survival indicated that male and female mice had significant decreasing trends in mortality with incremental doses of cyproconozole. In addition both sexes exhibited significant decreases in mortality with increasing doses of cyproconazole in the pair-wise comparison of combined controls and the next to the highest (100 ppm) dose level. The male mice also had a significant decrease in mortality in the pair-wise comparison of combined controls and the highest dose of cyproconazole.

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In male mice, there was a significant dose related increasing trend in hepatocellular adenomas, and in combined hepatocellular (adenoma and/or carcinoma) tumors. Significant differences occurred in the pair-wise comparison of combined controls and the highest dose group in carcinomas and in total liver tumors (adenomas and/or carcinomas). In addition significant differences occurred in the pair-wise comparison of combined controls and the 100 ppm in carcinomas and the combined hepatocellular (adenoma and/or carcinoma) tumors.

In female mice there was a significant dose related increasing trend in hepatocellular adenomas, carcinomas and in combined hepatocellular (adenoma and/or carcinoma) tumors. All of these 3 groups also had significant differences in the pair-wise comparison of combined controls and the highest (200 ppm) dose group.

Background

A dietary/oncogenicity study in CD-1 mice (project 388-M/398-M) was conducted at the Sandoz AG, Agro Division in Basle, Switzerland and issued in May,1989. The study was terminated after 81 weeks for males and after 88 weeks for females.

The study design allocated in a random manner, groups of 50 males/females, to dose levels of 0, 0, 5, 15, 100, 200 ppm of cyproconazole. Sandoz gave no reason for the selection of dual controls (50 mice, both male and female in each of two control groups) included in the design of this study.

Dual Control Analysis

The evaluation of mortality and liver tumor occurrences between the dual controls did not produce any significant differences. Therefore the following qualitative risk assessment was based upon the use of dual controls (50 mice in each group) as one group of combined controls (100 mice) for both males and females separately.

Survival Analysis

In male mice there was a statistically significant dose related trend for reduced mortality. In addition, the pair-wise comparison with combined controls and the highest (200 ppm) dose group resulted in a significant ($p<.01$) difference for reduced mortality. Also a significant ($p<.05$) reduced mortality occurred in the pair-wise comparison of combined controls and the 100 ppm and also the 15 ppm group (Table 1).

In female mice there was a statistically significant ($p<.01$) negative dose related trend in mortality. In addition, the pair-wise comparison with combined controls and the 100 ppm. dose group resulted in a significant ($p<.05$) difference for reduced mortality (Table 2).

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

Table 1. Cyproconazole CD-1 Mouse Study, Male Mortality Rates+ and Cox or Generalized K/W Test Results

Dose (ppm)	Week 1-26	27-52	53-77	78-81a	Total
0b	1/100	6/99	48/93	10/45	65/100(65)n**
5	1/50	0/49	27/49	2/22	30/50(60)
15	0/50	1/50	15/49	6/34	22/50(44)n*
100	1/50	1/49	18/48	1/30	21/50(42)n*
200	1/50	0/49	9/49	2/40	12/50(24)n**

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

( ) percent

a Final sacrifices at weeks 82-83.

b Composed of 2 control groups, 50 animals in each one.

n Decreasing trend or Negative change from control.

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. Cyproconazole CD-1 Mouse Study, Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (ppm)	Week 1-52	53-77	78-88[a]	Total
0[b]	4/100	31/96	24/65	59/100(60)n**
5	0/50	14/50	12/36	26/50(52)
15	2/50	19/48	8/29	29/50(58)
100	2/50	6/48	5/42	13/50(26)n**
200	5/50	6/45	11/39	22/50(44)

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

( ) percent

a Final sacrifices at weeks 89-91.

b Composed of 2 controls, 50 animals in each one.

n Decreasing trend or Negative change from control.

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 $p<.01$.

Tumor Analysis

Male mice had a significant ($p<.01$) positive dose related trend for adenomas, and for combined hepatocellular (adenoma and/or carcinoma) tumors. In the pair-wise comparison of combined controls and the highest (200 ppm.) dose group, there was a significant difference in carcinomas ($p<.01$) and in the combined liver (adenoma and/or carcinoma) tumor group ($p<.05$). In addition, in the pair-wise comparison of combined controls and their respective 100 ppm dose groups, there was a significant difference in adenomas ($p<.05$), in carcinomas ($p<.01$), and in the combined liver (adenoma and/or carcinoma) tumor group ($p<.01$). Also in the pair-wise comparison of combined controls and the 15 ppm. dosed group, male mice had a significant ($p<.05$) difference in liver carcinomas (Table 3).

Female mice had a significant ($p<.01$) positive dose related trend in adenomas, carcinomas and for combined hepatocellular (adenoma and/or carcinoma) tumors. In the pair-wise comparison of combined controls and the highest (200 ppm.) dose group, there was a significant ($p<.01$) difference in adenomas, carcinomas and in the combined liver (adenoma and/or carcinoma) tumor groups (Table 4).

Since there was statistical evidence of differential survival with incremental doses of cyproconazole in both sexes, the above tumor rate statistical analysis was based upon the Peto Prevalence Method.

Table 3. Cyproconazole, CD-1 Mouse- Male Hepatocellular Tumor Rates+ and Peto's Prevalence Test Results (p values)

Tumor	Dose(ppm) 0[a]	5	15	100	200
Liver Adenomas (%)	6/92 (7)	4[b]/49 (8)	5/48 (10)	12/47 (26)	12/48 (25)
p=	0.009**	0.368	0.375	0.013*	0.055
Liver Carcinomas (%)	0/74 (0)	0/38 (0)	3/46 (7)	3[c]/43 (7)	1/41 (2)
p=	0.096	1.000	0.031*	0.008**	0.004**
Both (%)	6/92 (7)	4/49 (8)	8/48 (17)	15/47 (32)	13/48 (27)
p=	0.003**	0.383	0.086	0.001**	0.022*

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

( ) percent

a composed of 2 controls, 50 animals in each one.

b first liver adenoma observed at week 56, dose 5 ppm.

c first liver carcinoma observed at week 68, dose 100 ppm.

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 $p<.01$.

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Table 4. Cyproconazole- CD-1 Mouse, Female Hepatocellular Tumor Rates+ and Peto's Prevalence Test Results (p values)

Tumor	Dose(ppm) 0[a]	5	15	100	200
Liver Adenomas	0/61	0/34	0/28	2/41	6[b]/39
(%)	(0)	(0)	(0)	(5)	(15)
p=	0.000**	1.000	1.000	0.067	0.001**
Liver Carcinomas	0/69	0/41	0/31	0/43	7[c]/40
(%)	(0)	(0)	(0)	(0)	(18)
p=	0.000**	1.000	1.000	1.000	0.000**
Both	0/69	0/41	0/31	2/43	13/40
(%)	(0)	(0)	(0)	(5)	(33)
p=	0.000**	1.000	1.000	0.067	0.000**

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

( ) percent

a composed of 2 controls, 50 animals in each one.

b first liver adenoma observed at week 80, dose 200 ppm.

c first liver carcinoma observed at week 76, dose 200 ppm.

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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