UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Risk Assessment
Captafol - Mouse Oncogenicity Study
Accession Nos. 257492 and 257907
Caswell No. 535

FROM: Bertram Litt, Statistical Team Leader
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

8/1/86

and

Bernice Fisher, Statistician
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Bernice Fisher 8/1/86

TO: Marion Copley, Ph.D., Toxicologist
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Reto Engler, Ph.D., Chief
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Reto Engler

Summary

Survival in mice is severely impaired with increasing doses of Captafol for both sexes. However, it is worse for females. The statistical evaluation of lymphosarcomas in this mouse study indicates that the oncogenic potency estimate, Q_1^* of Captafol, in human equivalents is $5.1 \times 10^{-2}(mg/kg/day)^{-1}$.

Appendix Table A

Captafol - Mortality Trend* - Rats, Males

Dose (ppm)	Time (Weeks) 1-49	50-79	80-104	105-121	Total
0	1/50	2/49	12/47	16/35	31/50
75	2/50	4/48	9/44	10/35	25/50
300	3/50	2/47	12/45	11/33	28/50
1200	1/50	1/49	13/48	8/35	23/50
T	- 506.25	- 1467.36	1275	- 4129.89	- 4828.50
V	1.55×10^6	2.00×10^6	8.17×10^6	7.09×10^6	1.881×10^7
Z	- 0.406	- 1.038	0.446	- 1.551	- 1.113
P	0.658	0.850	0.328	0.940	0.865

Appendix Table B

Captafol - Mortality Trend* - Rats, Females

Dose (ppm)	Time (Weeks) 1-49	50-79	80-104	105-121	Total
0	0/50	6/50	13/44	16/31	35/50
75	0/50	5/50	12/45	13/33	30/50
300	0/50	3/50	10/47	17/37	30/50
1200	0/50	2/50	13/48	11/35	26/50
T	-	- 2625	- 84.78	- 4017.46	- 6727.2426
V	-	3.39×10^6	8.33×10^6	7.65×10^6	1.94×10^7
Z	-	- 1.427	- 0.029	- 1.452	- 1.53
P	-	0.923	0.512	0.927	0.936

* Peto's Mortality Trend Analysis, IARC Supplement II, 1980.

Background

A 2-year Captafol feeding study in Charles River Swiss CL-1 (ICR derived) mice was conducted by the Chevron Chemical Company (SOCAL #1330, January 11, 1980) of Richmond, California (EPA Accession Nos. 257492 and 257907).

Groups of 80 animals of both sexes, were allocated to each of three dose levels (300, 1000, and 3000 ppm) of Captafol and 52 males and 52 females were designated as the controls. The statistical method of sample selection was not specified.

Data summarization/evaluation of survival and tumor occurrences during the study was prepared by Brian Cook, Dynamac Corporation (EPA 68-02-4224, Task 1-25, February 1986).

Qualitative Analysis

Evaluation of survival patterns presented in Table 1 indicate that increasing doses of Captafol significantly reduce longevity of the animals of both sexes in this study.

At the suggestion of Dr. Copley, only lymphosarcomas in both sexes, the most frequent tumor types, were analyzed (see Table 2).

The lymphosarcoma rate adjusted for survival and Captafol doses, analysed by the K/W method of Gehan-Breslow, resulted in a Chi Square of 40.0 for males and 48.5 for females(both had a $p<.0001$).

The evaluation of trend of tumor formation with increasing doses of Captafol by means of the Cochran-Armitage test indicated a highly significant effect (males, $p < .00025$ and females, $p < .0025$).

Comparisons of the controls with the highest dose of Captafol by Fisher's Exact test demonstrated significant differences in the tumor rates (males, $p = .001$ and females, $p = .031$) for both sexes.

Thus, males were more sensitive to Captafol in terms of lymphosarcoma rates. Females were more sensitive to other forces of mortality (i.e., shown by reduced survival at higher doses of Captafol).

Table 1. Captafol - Mouse Data Survival Patterns

Weeks	Males Deaths - Incidence Dose (ppm) 0	300	1000	3000
< 28	0/52	2/80	0/80	0/80
28-51	2/52	4/78	0/80	22/80
52-77	3/50	13/74	9/80	55/58
78-109	22/47	38/61	51/71	3/3
109,110 (survivors)	25	23	20	0

Weeks	Females Deaths - Incidence Dose (ppm) 0	300	1000	3000
< 28	0/52	0/80	1/80	2/80
28-51	1/52	1/80	3/79	52/78
52-77	6/51	7/79	20/76	26/26
78-109	14/45	28/72	55/56	-
110,111 (survivors)	31	44	1	0

Table 2. Captafol Mouse Oncogenicity Study - Lymphosarcomas

Males

Weeks	Dose (ppm) 0	300	1000	3000
< 28	0	0	0	0
28-51	0	0	0	10
52-77	0	0	0	3
78-110	0	3	4	0
Total Tumor Bearing Animals	0	3	4	13
Total Animals Examined	52	80	80	80

Females

Weeks	Dose (ppm) 0	300	1000	3000
< 28	0	0	1	2
28-51	0	0	2	19
52-77	1	2	5	0
78-111	5	6	2	0
Total Tumor Bearing Animals	6	8	10	21
Total Animals Examined	52	80	80	80

Quantitative Analysis

Lymphosarcoma tumor data from both males and females were used independently to estimate the potency, Q_1^* of Captafol by K. Crumps "Global 83" program (Multi-Stage procedure). However, because survival problems were evident in both sexes with increasing doses of Captafol, the Q_1^* was modified in the following manner: For the "Global 83" program all animals that died before the detection of the first tumor and also all animals with tumors that occurred after the date of the last death in the highest dose group were removed from the data of both sexes[1]. Since this modified potency estimate understates the 2-year risk, Druckery's[2] correction, $(L/LE)^3$ was used to compensate for early high dose mortality.

Another program designed by Crump,Weibull-85, was used to compute low-dose extrapolations of time to death-with tumor and cancer potency from the data base. See Table 3 for the comparison of potency estimate results based upon the two methods.

It appears that the two methods produce very similar Q_1^*'s.

Table 3. Captafol - Mice, Lymphosarcomas-Risk Assessment Estimates, Q_1^* $(ppm)^{-1}$

Males

Week	Weibull Model $(Q_1^*)(ppm)^{-1}$	Global 83-Modified $(Q_1^*)(ppm)^{-1}$
26	7.7×10^{-7}	
52	2.2×10^{-5}	
78	7.0×10^{-5}	8.4×10^{-5}
110	1.5×10^{-4}	

Females

Week	Weibull Model $(Q_1^*)(ppm)^{-1}$	Global 83-Modified $(Q_1^*)(ppm)^{-1}$
26	1.4×10^{-6}	
52	9.2×10^{-6}	
66	1.65×10^{-5}	5.5×10^{-4}
111	5.7×10^{-5}	

[1]Suggested by Personal Communication with John C. Bailar III

[2]This correction is based upon the following--L is the total length of the study and is divided by LE, which is length of time from the beginning of the study to last death in the highest dose group. This ratio (L/LE) is then raised to the third power and multiplied by Q_1^*.

In order to evaluate dose-related tumor incidence of Captafol, the dose for mice was converted to mg/kg/day as shown in (a) and for human equivalence as shown in (b) below (See Table 4 for results of conversion.).

a. For mice, Lehman's Tables show that 7 ppm in the mouse diet is equivalent to 1 mg of chemical per kg of body weight (Lehman 1959, Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, Association of Food Drug Officials of the U.S.).

b. For estimating human carcinogenicity, Mantel and Schneiderman show that to convert mouse mg/kg/day to human mg/kg/day equivalents by surface area, a first order approximation of tissue dose may be obtained by dividing the average mouse body weight by the one-third power of the human weight divided by the animal weight (Mantel and Scheiderman, J. Cancer Research, June 1975, page 1385).

The potency estimate, Q_1^* $(mg/kg/day)^{-1}$ of Captafol for humans based on male mice is 7.9×10^{-3}, and for humans based on female mice is 5.1×10^{-2}. Female mice are more sensitive to increasing doses of Captafol than males, primarily due to the shortening of their lifespan.

Table 4. Captafol, Mouse Oncogenicity Study
Risk Assessment of Lymphosarcomas in Terms of Mice and Human Equivalents

$Q_1^*(mg/kg/day)^{-1}$

	Mouse 95% Upperbound	Human Equivalents 95% Upperbound
Male	5.9×10^{-4}	7.9×10^{-3}
Female	3.8×10^{-3}	5.1×10^{-2}