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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chlorothalonil - Rat Study, Qualitative and Quantitative Risk Assessment caswell no. 215

FROM: Bernice Fisher, Biostatistician Bernice Fisher 7/20/87
Scientific Mission Support Staff
Toxicology Branch
Health and Evaluation Division (TS-769C)

TO: David Ritter, Toxicologist
Section I, Toxicology Branch
Health and Evaluation Division (TS-769C)

THRU: for Richard Levy, M.P.H., Leader-Biostatistics Team c Julian 7/20/87
Scientific Mission Support Staff
Toxicology Branch
Health and Evaluation Division (TS-769C)

and

for Reto Engler, Ph.D C. Rinde
Chief, Scientific Mission Support Staff
Toxicology Branch
Health and Evaluation Division (TS-769C)

SUMMARY

The potency estimate, Q_1^* of Chlorothalonil is 1.1×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents $[B_2]$. This estimate is based upon female rat renal tumors (carcinomas and adenomas).

In female rats there was a significant survival disparity in the pairwise comparison of controls with the mid dose group.

In males rats, there was a significant increase in mortality with dose increments of the chemical, primarily due to the significant increase of deaths in the high dose group as compared with controls.

(1)

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Background

The May 28, 1987 Peer Review Committee for Chlorothalonil decided that a qualitative and quantitative Risk Assessment was needed and should be based upon the renal tumor formations in rats of the SDS Biotect study of Fisher 344 strain, dosed with 0, 40, 80 and 175 mg/kg of the chemical.

Qualitative Review

Survival analysis was prepared by the use of the D.G. Thomas, H. Breslow and J.J. Gart computer program. The results of the analysis indicated that mortality did not significantly increase with increasing doses of Chlorothalonil in female rats. However, in the pairwise comparison of conrols with the mid dose (80 mg/kg) group, there was a significant ($p = .02$) difference.

In male rats, survival was significantly ($p<.02$) decreased with dose increments of Chlorothalonil. In addition the pair wise comparison of control with the highest dose (175 mg/kg) was also statistically significant ($p=.03$). See Table 1. for details.

In spite of the fact that survival was a problem in the study, the renal tumor formations only started to appear at the beginning of the 79th week of the study and most of the tumors were found in the final kill of the study in both sexes. In addition deaths on the study began about one year after it started.

Because of the late appearance of both deaths and also renal tumors, the use of the Cochran-Armitage Trend test and Fisher's Exact pairwise comparisons with controls were deemed most appropriate+ for the qualitative evaluation of the data.

The Cochran-Armitage Trend test on renal carcinomas, renal adenomas, and combined renal carcinomas and adenomas for both sexes, were all highly significant ($p<.02$). Also, all of the aforementioned groups for both sexes showed consistently significant diferences in tumor rates in the pairwise comparisons (Fisher Exact test) of controls with the highest dose (175 mg/kg) group. See Table II. for details.

+ There is no appropriate way to adjust for the survival disparties since the Peto Prevalence test would be collapsed onto too few time intervals.

Dose- Response Review

On the basis of the qualitative evaluation of renal tumors in rats, the potency estimate, Q_1^* of Chlorothalonil was based upon the proportions in females, which were the most sensitive to the chemical. This estimate was obtained from the Multi-Stage (K. Crump's computer program) Model in terms of rat mg/kg/day doses and then converted to human equivalents by the interspecies surface area adjustments as recommended by EPA Cancer Guidelines. See Table IV. for details.

Table I. Chlorothalonil - Rat Study, Mortality Rates+ and Life Table Analysis Resulta

A. Males

Dose	Weeks				
mg/kg	0-52	53-78	79-104	105-115[a]	Total
0	0/66	3/66	10/63	15/53	28/66 (42)*
40	0/61	1/66	10/60	16/50	27/61 (44)
80	2/60	1/58	14/57	9/43	26/60 (43)
175	0/60	1/60	16/59	21/43	38/60 (63)*

B. Females

Dose	Weeks				
mg/kg	0-52	53-78	79-104	105-128[b]	Total
0	0/60	1/60	10/59	18/49	29/60 (48)
40	0/60	0/60	11/60	28/49	39/60 (65)
80	1/61	3/60	6/57	33/51	43/61 (70)*
175	0/59	1/59	11/58	22/47	34/59 (58)

+ Number of animals died/ Number of live animals at beginning of interval

( ) percent
a final sacrifice at 115 weeks.
b final sacrifice at 128 weeks.

Note: The above time intervals were selected for display only. Significance of Trend Analysis denoted at Control. Significance of pairwise comparison with control denoted at Dose level.

* $p < .05$, ** $p < .01$

Table II - Chlorothalonil - Rat Study, Renal Tumor Rates Cochran-Armitage Trend test and Fisher Exact test Results

A. Males

Dose mg/kg Renal Tumor Rates[1]	0	40	80	175
Carcinomas	1/66(2)*	3/61(5)	1/60(2)	6/60(10)*
Adenomas	0/66(0)**	2/61(3)	5/60(8)*	12/60(20)**
Both Carcinomas and Adenomas	1/66(2)**	5/61(8)	6/60(10)*	18/60(32)**

B. Females

Dose mg/kg Renal Tumor Rates[1]	0	40	80	175
Carcinomas	0/60(0)**	1/60(2)	3/61(5)	12/59(20)**
Adenomas	0/60(0)**	1/60(2)	4/61(7)	7/59(12)**
Both Carcinomas and Adenomas	0/60(0)**	2/60(3)	7/61(11)**	19/59(32)**

1 Number of tumor bearing animals/number of animals examined
( ) per cent

Significance of Cochran-Armitage Trent test denoted at Control. Significance of Fisher Exact test of pairwise comparison with control denoted at Dose level.

* $p < .05$, ** $p < .01$

Table III. Chlorothalonil - Rat Study, Stomach Tumor Rates+
(Gastric Squamous Mucosa - Papilloma and Carcinoma)
Cochran-Armitage Trend test and Fisher Exact test Results

A. Males

Tumor	Dose - mg/kg 0	40	80	175
Stomach Gastric Squamous Mucosa				
Carcinoma	1/66/(2)	0/60(0)	0/60(0)	1/60(2)

B. Females

Tumor				
Stomach Gastric Squamous Mucosa				
Carcinoma	0/60	0/60	1/61	1/59
Papilloma	0/60	1/60	2/61	2/59
Both	0/60(0)*	1/60(2)	3/61(5)	3/59(5)

+ Number of tumor bearing animals/Number of animals examined

( ) Percent

Significance of Trent test denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.

* $p < .05$, ** $p < .01$

Table IV. Chlorothalonil - Rat Study - Potency Estimate, Q_1^* $(mg/kg/day)^{-1}$

	Rat	Human Equivalents
Female	2.0×10^{-3}	1.1×10^{-2}
Male	2.3×10^{-3}	1.2×10^{-2}

References

Armitage, P. (1955) Tests for Linear Trends in Proportious, Biometrics 11, 375-386.

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Cox, D.r. (1972) Regression Models and Life Tables (with discussion) J. Roy. Stat. Soc. Ser. B. 34, 187-220.

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