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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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SUBJECT: Preliminary Risk Assessment for Bromacil
Based on Haskel Study #893-80 in CD-1 Mice, CAS# 111

SUMMARY

The data in the mouse study discussed below indicate that Bromacil is a liver carcinogen in CD-1 mice. The weight of this evidence and its relevance to humans is a determination to be made by the Toxicology Branch Cancer Review Committee.

The number of male mice surviving one year or longer on the study, and examined for liver tumors with either carcinoma and/or adenoma, (see Table 1) yielded a potency estimation $Q^*_1 = 3.8 \times 10^{-3}$.

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Description of the Study

This is an 18-month feeding study of 95% Bromacil IN 976 (MR-3155) in CD-1 strain of mice, Haskel study # 893-80, Accession No. 244069. The reviewer of this study was Alex Arce, TOX Branch (TS-769), 10/83.

The study sample consisted of 640 mice, who were stratified by sex and weight and then randomly assigned to groups of 80 males and females of equivalent weights. Bromacil was mixed into their diets in concentrations of 0, 250, 1250 and 5000 ppm. Evaluation of the toxicological results were to be made at the end of a two-year period but because "the rate of mortality observed during test weeks 52-76, particularly among male mice,...it was terminated 18 months after its initiation." See page 27 of the Haskel Report (Attachment 1).

Food consumption data were not used for evaluation because the initial feeder caused a wide variation in spillage from 0 - 28 weeks and was subsequently replaced by another one, see page 23 of the Haskel Report. (Attachment 2).

Qualitative Evaluation -

No significant differences were observed in male mice in the survival rates with the use of Peto's[1] "Death Rate" method of statistical analysis. While in female mice, there was a significant ($P \leq .05$) increase in the number of animals that died on the higher doses of Bromacil. (See Tables I and II).

Weekly weight gains for males were consistently and mostly significantly ($p \leq .05$) lower on the highest dose of Bromacil as compared with the controls. See Table I in the Haskel report. Females also exhibited similar patterns, however, their percent differences were less than the males. See Table III in the Haskel Report. (Attachments 3 and 4.)

1. Peto et al. - IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 1980 - Supplement 2 - Annex pages 311-385.

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Table. I. Bromacil - Trend Analysis of Mortality; Male Mice

Dose (ppm)	Time (Days) 0-189	190-364	365-544	545-569	Total
0	1/80	7/79	35/72	8/37	51/80
250	1/80	3/79	44/76	2/32	50/80
1250	2/80	5/78	33/73	6/40	46/80
5000	0/80	6/80	31/72	7/41	44/80
T	-3750.	2625.79	-22257.7	2673.33	-20708.58
V	159 x10^7	7.97 x10^7	2.92 x10^8	8.21 x10^7	4.70 x10^8
Z	-0.940	0.294	-1.303	0.295	-0.956
p	0.826	0.384	0.904	0.384	0.830

Table II. Bromacil - Trend Analysis of Mortality, Female Mice

Dose (ppm)	Time (Days) 0-189	190-364	365-544	545-569	Total
0	0/80	6/80	27/74	4/47	37/80
250	3/80	3/77	29/74	8/45	43/80
1250	2/80	6/78	35/72	7/37	50/80
5000	1/80	7/79	41/72	2/31	51/80
T	-1500	7394.9	44212.3	-7140.63	42966.57
V	2.37 x10^7	8.29 x10^7	2.90 x10^8	6.35 x10^7	4.60 x10^8
Z	-0.308	0.812	2.598	-0.896	2.004
p	0.621	0.208	0.005	0.815	0.023

T is the sum of the weighted differences between observed and expected frequencies.

V is the variance of the weighted differences between observed and expected frequencies.

$Z = T/\sqrt{V}$

P is the probability associated with the Z Statistic.

The changes in the rate of liver tumors over the 18 months of the study were analyzed by means of the "Prevalence and Trend" method of Petol. See Tables III and IV.

The dose related trend for liver carcinoma and/or adenoma was statistically significant (P .02) at the final kill. Thus, even though the analysis of the total data, the trend was significant (P .03), it was mainly affected by the data at the end of the study (568 days - see table III).

For the males, with the use of the X^2 statistic, there was a significant ($P \leq .05$) increase in liver tumors, comparing the highest dose of Bromacil with the controls.

In addition, the combination of 0, 250 and 1250 doses and then comparing this total with the 5000 dose group yielded a signifcant difference (P _ .02) in the application of Fisher's Exact Test.

Females did not exhibit any dose related effect for liver tumors.

Quantitative Risk Assessment

The data in table III and IV have shown that no liver tumors appeared until the second year of the study and therefore animals dying during the first year were not considered to be at risk of liver tumors. Accordingly, 8 controls, 4 low, 7 middle and 6 high dosed males and 6 controls, 6 low, 8 middle and 8 high dosed females have been deleted from the total animals used for the low-dose extrapolation procedure. As there was no evidence of increased liver tumor incidence in females, only the males were used for the Bromacil quantitative risk assessment.

Since the study diet of Bromacil was reported in ppm and as food consumption could not be accurately estimated, Lehman's Tables have been used to adjust the ppm of Bromacil in the diet to mg (7 ppm = 1 mg/kg/day for mice). The surface area adjustment described by N. Mantel and M. Schneiderman (Cancer Research, Vol. 35, 1975 June, pages 1379-1386) has been used to estimate exposures and doses in human equivalents expressed in mg/kg/day.

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Table III. Bromacil, Trend Analysis of Liver Tumors in Males Examined

Dose (ppm)	Time (days)			
	0-365	366-567	568	Total
0	0/8	4/43	4/29	8/72
250	0/4	2/46	9/30	11/76
1250	0/7	2/39	5/34	7/73
5000	0/6	3/38	14/36	17/74
T	0	1417.17	21445.7	22862.87
V	0	3.96×10^7	1.02×10^8	1.42×10^8
Z	0	0.225	2.119	1.918
p	0	0.411	0.017	0.027

Table IV. Bromacil, Trend Analysis of Liver Tumors in Females Examined

Dose (ppm)	Time (days)			
	0-365	366-567	568	Total
0	0/6	0/31	1/43	1/74
250	0/6	1/37	2/37	3/74
1250	0/8	0/42	0/30	0/72
5000	0/8	0/48	1/24	1/72
T	0	-1659.81	522.39	-1137.42
V	0	4.38×10^6	1.29×10^7	1.73×10^7
Z	0	-0.793	0.146	-0.274
p	0	0.786	0.442	0.608

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The data below were fitted to the Multi-stage, One-hit, Weibull, Probit and Logit models using the assumptions of Independent background (i.e. control rate) effect and separately for the additive background. The independent assumption provided a smaller confidence band and the best fitting results (See Table V).

Bromacil - Males

Human Equivalent Doses (Mg/kg/day)	0	3	15	60
Number at risk	72	76	73	74
Number of Tumor bearing animals	8	11	7	17

Table V. Bromacil - Male Mice, Liver Tumors
Estimation of Dose Associated in mg/kg/day with Risk
(via Independent Assumption)

Risk	Models					
	Multi-Stage		Weibull		Probit	
	MLE	Lower 95% Bound	MLE	Lower 95% Bound	MLE	Lower 95% Bound
10^{-4}	1.6	2.6×10^{-2}	46.	4.2×10^{-4}	38.	1.6×10^{-5}
10^{-6}	1.6×10^{-1}	2.6×10^{-4}	38.	2.1×10^{-4}	31.	9.5×10^{-6}

As there are no metabolic or other data indicating that there is a basis for the use of a particular extrapolation model, the Multistage model was used as recommended by the Agency for estimating human risks. The Multistage model when fitted to the above data estimated the carcinogenic potency as $Q_1^* = 3.8 \times 10^{-3}$ for mg/kg/day.

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Characterization of Risks

The only exposure data available are the published tolerances CFR 180.210 (Code of Federal Regulations 40, Parts 150-189, July 1, 1983 page 359) for citrus fruits and pineapples. These tolerances have been adjusted by their contribution to the human diet, 3.81 percent and 0.3 percent of 1.5 kg intake. The dietary intake is then divided by 60 kg (average human weight - See Table VI) in order to obtain the exposure in mg/kg as shown in Table VII.

Table VI

Food	Tolerances (ppm)	% of Diet	Amount of Exposure (1.5 kg/day) x % of Diet
Citrus fruits	0.1	3.81	5.7×10^{-3}
Pineapples	0.1	0.30	4.5×10^{-4}
Total			6.2×10^{-3}

Table VII. Bromacil - Male Mice - Estimation of Human Exposure and Risk

Food	Amount of Human Exposure[1] mg/kg/day	Upper 95% Bound on Risk[2]
Citrus fruit	9.5×10^{-5}	10^{-7} to 10^{-6}
Pineapples	7.5×10^{-6}	10^{-8}
Total	1.0×10^{-4}	10^{-7} to 10^{-6}

1 Amount of Exposure divided by 60 kg (avg. human wt.)

2 Q^*_1 (3.8×10^{-3}) x Amount of Exposure

Bromacil RIN: 1607-93

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