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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Butylate (Sutan) - Qualitative Risk Assessment,
Rat (Sprague-Dawley CD) Study
caswell no. 434A

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Summary

The qualitative risk assessment of butylate is based upon a 2-year chronic/oncogenicity study in Sprague-Dawley CD rats, fed 0, 50, 100, 200 and 400 mg/kg/day of butylate.

The statistical evaluation of these data indicated that neither male nor female rats had mortality differences with incrementatal doses of butylate.

In male rats, there was a significant dose related increasing trend in hepatocellular adenomas and also a significant difference in the pair-wise comparison of control and the 400 mg/kg/day dose level.

In female rats there was a significant dose related increasing trend in hepatocellular carcimomas.

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Background

A 2-year dietary chronic toxicity/oncogenicity study in Sprague-Dawley CD rats was conducted by Stauffer Chemical Company (registration no.476-2156, accession no. 249390-249403) and reported in April,1982.

The study design allocated groups of 70 males and 70 females, each to groups of 0, 50, 100, 200 and 400 mg/kg/day of butylate for 24 months. An interim sacrifice of 10 per sex/dose group was indicated to have occurred after 12 and 18 months. However the individual animal data for the males showed that interim sacrifices occurred at 52, 53, 69, 70, 71, 72, 73, 74, and 80 weeks for the dose level of 50 mg/kg/day; and at 52, 53, 75, 80, 83, and 89 weeks for the dose level of 100 mg/kg/day; and at 52, 53, 75, and 80 weeks for the dose levels of 200 and 400 mg/kg/day.

Survival Analysis

In both male and female rats there were no statistically significant mortality differences with increments of butylate (Tables 1 and 2 respectively).

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

Table 1. Butylate - Rat (Sprague-Dawley CD) Study, Male Mortality Rates+ and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Week 1-26	27-52	52-53[a]	53-78	78[b]	79-106[c]	Total
0	0/70	1/70	10/10	7/59	10/10	15/42	23/50(46)
50	0/70	2/70	7/7	5/61	15/15	19/41	26/48(54)
100	1/70	2/69	10/10	9/57	12/12	14/36	26/48(54)
200	0/70	0/70	10/10	8/60	11/11	15/41	23/49(47)
400	1/70	1/69	10/10	8/58	11/11	9/39	19/49(39)

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

( ) percent

a Interim sacrifice at week 52 and 53.

b Interim sacrifice for dose 0, week 80; for dose 50, weeks 69-74, & 80; for dose 100, weeks 80, 83 & 89; for doses 200 and 400, weeks 75 & 80.

c Final Sacrifice at week 107.

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 $p<.01$.

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Table 2. Butylate - Rat (Sprague-Dawley CD) Study, Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Week 1-26	27-52	52-53[a]	53-79	80[a]	80-106[b]	Total
0	0/70	0/69	10/10	24/59	11/11	0/24	24/48(50)
50	0/70	0/70	10/10	25/60	10/10	0/25	25/50(50)
100	1/70	3/69	10/10	22/56	10/10	0/24	26/50(52)
200	0/70	0/70	10/10	23/60	10/10	0/27	23/50(46)
400	0/70	3/70	10/10	22/57	9/9	0/26	25/51(49)

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

( ) percent

a Interim sacrifices at weeks 52, 53, 80, & 95 for dose 0; at weeks 52, 53, 80 for doses 50, 100, 200, & 400.

b Final sacrifice at weeks 106-107.

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 $p<.01$.

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Tumor Analysis

Male rats had a significant (p=.015) increasing trend in liver adenomas with increasing doses of butylate and also a significant (p=.045) difference in the pair-wise comparison of controls and the 400 mg/kg/day dose group. There were no other statistically significant findings in tumorigenicity for the males (Table 3).

Female rats had a significant (p=.034) increasing trend in liver carcinomas with increasing doses of butylate. There were no other statistically significant findings in tumorigenicity for the females (Table 4).

Since there was no statistical evidence of differential survival with incremental doses of butylate, the above tumor rate statistical analysis was based upon the Cochran- Armitage Trend test and the Fisher Exact test for the pair-wise comparison of controls and each dose group.

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Table 3. Butylate - Male Rat, Hepatocellular Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results

Tumor	Dose(mg/kg/day) 0	50	100	200	400
Liver Adenomas (%)	2/61 (3)	5[a]/62 (8)	1/59 (2)	1/62 (2)	8/60 (13)
p=	0.015*	0.226	0.513	0.494	0.045*
Liver Carcinomas (%)	2[b]/69 (3)	3/70 (4)	4/67 (6)	3/70 (4)	2/68 (3)
p=	0.387	0.507	0.326	0.507	0.695
Both (%)	4/69 (6)	8/70 (11)	5/67 (7)	4/70 (6)	10/68 (15)
p=	0.075	0.190	0.481	0.633	0.074

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

( ) percent

a first liver adenoma observed at week 53, dose 50 mg/kg/day.
b first liver carcinoma observed at week 52, dose 0 mg/kg/day.

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. Butylate - Female Rats, Hepatocellular Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results

Tumor	Dose(mg/kg/day) 0	50	100	200	400
Liver Adenomas	5/57	7/58	4/55	5/59	7[a]/55
(%)	(9)	(12)	(7)	(8)	(13)
p=	0.294	0.393	0.523	0.606	0.356
Liver Carcinomas	1/69	2/70	0/67	1/70	4[b]/67
(%)	(1)	(3)	(0)	(1)	(6)
p=	0.034*	0.505	0.507	0.748	0.174
Both	6/69	9/70	4/67	6/70	11/67
(%)	(9)	(13)	(6)	(9)	(16)
p=	0.083	0.303	0.391	0.608	0.135

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

( ) percent

a first liver adenoma observed at week 52, dose 400 mg/kg/day.
b first liver carcinoma observed at week 52, dose 400 mg/kg/day.

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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