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HEALTH EFFECTS DIVISION
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SCIENTIFIC DATA REVIEWS
EPA SERIES 361
11499

#434A

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: BUTYLATE:---Tox Data Submitted Under MRID 434522-01.

ID # 041405

PCCODE
041405 (434A)
RD Record: S477473
DP Barcode : D209675

FROM: Irving Mauer, PH.D., Geneticist
Toxicology Branch-I
Health Effects Division (7509C)

J. Mauer
03-03-95

TO: Linda Probst/Judith Loranger, PM # 73
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THRU: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I
Health Effect Division (7509C)

Karl P. Baetcke
4/7/95

Registrant: Zeneca Ag Products, Wilmington, DE

Request: Review and evaluate the following subchronic neurotoxicity assay:

(82-7) Butylate: Subchronic Neurotoxicity Study in Rats, performed at Zeneca's Central Toxicology Laboratory (CTL), Cheshire (UK), Final Report No. CTL/P/4423 (of Study No. PR0970), dated September 02, 1994 (MRID No. 434522-01).

TB CONCLUSIONS/EVALUATION: This study is judged ACCEPTABLE in demonstrating no evidence of either structural or functional neurotoxicity in rats fed test article for 13 weeks at doses up to the HDT, 5000 ppm in the diet (providing compound intakes up to 336/mg/kg/da in males, 382 mg/kg/da in females), which caused 10% to 15% reductions in bodyweight and food consumption.

ATTACHMENT: DER

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BUTYLATE

(82-7) SUBCHRONIC NEUROTOXICITY

EPA Reviewer: Irving Mauer, PH.D. *I. Mauer* Date: 03-01-95
 Immediate Office, Toxicology Branch-I (7509C)
 Secondary Reviewer: Karl P. Baetcke, Ph.D. *K.P. Baetcke* Date: 4/7/95
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DATA EVALUATION RECORD

MRID No.: 434522-01
 PC No.: 041405
 RD Record No.: S477473
 EPA ID No.: 041405
 Tox Chem. No.: 434A
 Project No.: D209675

I. SUMMARY

STUDY TYPE: (82-7) Subchronic neurotoxicity screening battery - rat

CHEMICAL: Butylate

SPONSOR: Zeneca Ag Products, Wilmington, DE

TESTING FACILITY: Zeneca Central Toxicology Laboratory (CTL),
Cheshire (UK)

TITLE OF REPORT: Butylate: Subchronic Neurotoxicity in Rats

AUTHOR: A. Brammer

STUDY NUMBER: PRO970 (Report No. CTL/P/4423)

DATE ISSUED: September 02, 1994

EXECUTIVE SUMMARY: Rats were fed test article for 13 weeks at dietary levels of 0, 250, 1000 and 5000 ppm, and assessed for neurological function (FOB, LA) monthly (Study Weeks 5, 9, 14). At termination, neural tissues were processed for gross and histopathological examination.

No evidence of either structural (organic) or functional (FOB/LA) impairment was found up to the HDT, which caused 10-15% reductions in bodyweight and food consumptions (actual mean intakes up to 366 mg/kg/day in males, and 382 mg/kg/day in females).

TB-I EVALUATION: ACCEPTABLE. This study satisfies data requirements for GDLN 82-7 (Subchronic Neurotoxicity)

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(82-7) SUBCHRONIC NEUROTOXICITY

II. DETAILED REVIEW

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A. TEST MATERIAL: Butylate

Description: Amber-colored liquid
 Batches (Lots): Y06370/007
 Purity (%): 95.7%
 Solvent/carrier/diluent: Incorporated in feed (diet)

B. TEST ORGANISM: Rodent

Species: Rat
 Strain: Alpk: APfSD
 Age: 28 days
 Weights - males: 209-211 g
 females: 164-168 g
 Source: Zeneca's (SPF) Animal Breeding Unit, Cheshire (UK)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the neurotoxic potential of the test article when administered in the diet to male and female rats for 90 days, and recording any functional changes in a battery of tests (FOB), and/or histoneuropathological lesions, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Following two weeks' acclimatization, groups of animals (12/sex/dose) were fed diets containing 0, 250, 1000 and 5000 ppm butylate¹ for 13 weeks. Animals were observed daily, weighed weekly, and quantitative assessments of neurological function (functional observation battery, FOB² and locomotor

¹NB: The dose levels for this study were stated to have been selected on the basis of a "preliminary dietary study conducted in this laboratory", but neither bibliographic reference to which, nor results, were included in this Final Report.

²FOB:

Landing foot splay	Piloerection	Ptosis
Tail-flick test	Exophthalmus	Convulsions/tremors
Fore-/hind-limb grip	Urination	Abnormal reactivity to stimuli
Lachrymation	Defecation	Level of arousal
Salivation	Pupillary function	Alterations in sensimotor responses/respiration

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(82-7) SUBCHRONIC NEUROTOXICITY

activity (LA)³ were monitored during the week prior to start of feeding test article, as well as during Study Weeks 5, 9 and 14.

At study termination, one-half of the animals from each group, i.e., six so "designated" per sex per dose group, were anesthetized, and perfusion-fixed with Karnovsky's Fluid; the remainder were exsanguinated, their brains removed, and kept on ice for biochemical analysis (cholinesterase, etc.). From perfusion-fixed animals, neuromuscular tissues (brain; spinal cord and roots; dorsal root ganglia; Gasserian ganglia; sciatic, sural and tibial nerves; gastrocnemius muscle) were removed, and prepared for histological examination as follows: (1) Right-hand portions were dehydrated in alcohol, cleared in toluene, embedded in paraffin wax, sectioned at one micron, and stained with alum hematoxylin/eosin; (2) the remaining (left-hand) portions were post-fixed in osmium tetroxide, dehydrated and cleared in acetone, embedded in resin, and "semi-thin" sections stained with toluidine blue. Only control (Group 1) and high-dose (5000 ppm) perfusion-fixed animals were actually examined microscopically.

At termination, plasma and erythrocyte cholinesterase activities were determined in exsanguinated blood of six rats/sex/dose group; as well, the left half of the (above) ice-cooled brains were submitted for cholinesterase determination, while the right halves were analyzed for "neuropathy" (neurotoxic) target esterase (NTE).

Resultant data were analyzed statistically, separately for males and females, as follows:

Analysis of Covariance: For body weights; brain weight, length and width.

Analysis of Variance (ANOVA): For food consumption and utilization
 -motor activity measurements
 -time-to-tail flick
 -landing foot splay
 -grip strength
 - neuropathy target esterase and cholinesterase activities

³LA: By means of an automated activity recording apparatus; each observation period divided into ten scans of five minute duration each.

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Differences from control values were tested by Student's "t"-test (two-sided).

E. RESULTS: Determination of test article in diets used in this study were considered satisfactory in terms of concentration (mean within 4% of nominal/range, 1% to 7% - Report Tables 2, 3); homogeneity (3% - Report Table 4), and stability (within the period of repeat preparation - Report Table 5).

There were no treatment-related deaths, and no apparent clinically significant adverse effects in butylate-treated animals (Report Table 9). One mid-dose (1000 ppm) female (F83) was sacrificed during Week 13 "due to the presence of an abscess." Both high-dose (5000 ppm) males and females lost weight throughout the study, maximally 9% and 12%, as did 1000 ppm females (up to 7%), but not mid-dose males (Report Table 6; Figs. 1-4). Comparable reductions in food consumption (10-20%) were noted in both high-dose groups as well as mid-dose females, greatest (15-25%) during Study-Week 1 (Report Table 7), suggesting to the investigator, a "palatability effect." A smaller (non-significant) reduction was also noted during Study Week 1 in mid-dose males. Reductions in food utilization were statistically significant in affected female groups only (Report Table 8).

The actual intakes of test article were calculated in terms of mg butylate/kg body weights/day, and revealed a rapid decline during the study, due to "period of rapid growth to week 5" (Report APPENDIX I; Fig. 5). Mean doses of butylate received were 18.7, 76.0 and 366.1 mg/kg/day for the low, mid and high-dose male groups; 21.5, 80.6 and 382.5 mg/kg/day for the comparable female groups.

There were no observable treatment related effects in any dose group in any of the FOB tests (Report Tables 10/landing-foot splay; 11/time-to-tail flick; 12/grip strength), nor in LA measurements (Report Table 13/Fig. 6-9). Additionally, there were no compound-related changes recorded in brain, plasma or erythrocyte cholinesterase activities (Report Table 14⁴), nor in neuropathy target esterase activity (Report Table 15). Brain measurements (weight, length, width) in treated groups were no different from controls (Report Table 16), and no macroscopic (Report Table 17) or microscopic (Report Table 18) changes from controls were discernible in treatment groups.

Since the HDT, 5000 ppm, was fairly close to, if not at an MTD, as indicated by the significant weight loss at that level, the

⁴The singular statistically significant increase in the female high-dose (5000 ppm) mean erythrocyte cholinesterase activity was discounted by the investigator as "of no biological significance".

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investigator concluded there was no evidence of neurological or structural impairment of the nervous system, and the assay providing a NOEL for neurotoxicity > 5000 ppm.

F. TB EVALUATION: ACCEPTABLE.

ATTACHMENTS: Report Tables

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(82-7) SUBCHRONIC NEUROTOXICITY

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BUTYLATE : SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 2
 ACHIEVED DIETARY CONCENTRATION SUMMARY

Group No.	Nominal Conc. (ppm)	Number of batches analysed	Mean Conc. (ppm)	% of Nominal Conc.	Concn. range (ppm)
1	Control	4	ND		
2	250	4	258	103.2	246 - 267
3	1000	4	967	96.7	879 - 1014
4	5000	4	5070	101.4	4710 - 5318

Limit of detection 15ppm ND - not detected

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BUTYLATE : SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 3
 ACHIEVED DIETARY CONCENTRATION

Preparation Date	Group No.	Nominal Concn. (ppm)	Analysed Concn. (ppm)			Mean Concn. (ppm)	% of Nominal Concn.
10/11/93	1	Control	ND				
	2	250	265	254	267	262	104.8
	3	1000	1011	1010		1011	101.1
	4	5000	5460	5270	5223	5318	106.4
22/11/93	1	Control	ND				
	2	250	256	253		255	102.0
	3	1000	1009	1018		1014	101.4
	4	5000	5305	5322		5314	106.3
15/12/93	1	Control	ND				
	2	250	246	246		246	98.4
	3	1000	944	985		965	96.5
	4	5000	4850	5027		4939	98.8

Limit of detection 15ppm ND - not detected.

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BUYLADE : SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 3
 ACHIEVED DIETARY CONCENTRATION

Preparation Date	Group No.	Nominal Conc. (ppm)	ND	Analysed Conc. (ppm)	Mean. Conc. (ppm)	% of Nominal Conc.
4/ 2/94	1	Control	ND			
	2	250	249	285	267	106.8
	3	1000	851	906	879	87.9
	4	5000	4698	4722	4710	94.2

Limit of detection 15ppm ND - not detected.

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BUTYLATE : SUBCHRONIC NEUROTOXICITY STUDY IN RATS

TABLE 4
HOMOGENEITY OF BUTYLATE IN DIET

Preparation Date: 10/11/93

30kg batch size

Nominal Conc'n. (ppm)	Sampling Point	Analyzed Conc'n. (ppm)			Mean Conc'n. (ppm)	Overall Mean Conc'n. (ppm)	Z Deviation
250	BOTTOM	287	287	283	286	310	-11.7
	MIDDLE	351	343	237			
	TOP	373	381	377			
5000	BOTTOM	7021	6889	7194	7035	5487	+28.0
	MIDDLE	5399	5895	5168			
	TOP	4084	3835	3996			
					3972	5498	-27.8

Z Deviation = Deviation of mean concentration from overall mean concentration.

BUTYRATE : SUBCHRONIC NEUROTOXICITY STUDY IN RATS

TABLE 4
HOMOGENEITY OF BUTYRATE IN DIET

Preparation Date: 22/11/93

30kg batch size

Nominal Conc'n. (ppm)	Sampling Point	Analysed Conc'n. (ppm)	Mean Conc'n. (ppm)	Overall Mean Conc'n. (ppm)	\bar{x} Deviation
250	BOTTOM	229	248	239	-1.6
	MIDDLE	248	239	244	+0.4
	TOP	249	244	247	+1.6
5000	BOTTOM	5083	4994	5039	-2.2
	MIDDLE	5122	5176	5149	+0.0
	TOP	5262	5265	5264	+2.2

\bar{x} Deviation = Deviation of mean concentration from overall mean concentration.

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BUTYLATE : SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 4
 HOMOGENEITY OF BUTYLATE IN DIET

Preparation Date: 15/12/93

15kg batch size

Nominal Concn. (ppm)	Sampling Point	Analysed Concn. (ppm)	Mean Concn. (ppm)	Overall Mean Concn. (ppm)	Σ Deviation
250	BOTTOM	255	252	251	+0.4
	MIDDLE	259	257		+2.4
	TOP	263	246		-2.4
5000	BOTTOM	5005	4993	4955	+0.8
	MIDDLE	4904	4916		-0.8
	TOP	4977	4935		+0.0

Σ Deviation = Deviation of mean concentration from overall mean concentration.

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BUFLAITE : SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 5A
 CHEMICAL STABILITY OF BUFLAITE IN DIET AT ROOM TEMPERATURE

Nominal Conc'n. (ppm)	Preparation Date	Analysis Date	Analysis Interval (Days)	Analysed Conc'n. (ppm)	Mean Conc'n. (ppm)	% of Initial Conc'n.			
250	22/11/93	23/11/93	0	256	253	255	100.0		
		30/11/93	7	215	217	216	84.7		
		7/12/93	14	219	215	217	85.1		
		9/12/93	16	230	225	228	89.4		
		15/12/93	0	246	246	246	100.0		
		18/12/93	3	245	245	245	99.6		
		21/12/93	6	248	249	249	101.2		
		9/ 2/94	56	248	248	248	100.8		
		5000	22/11/93	23/11/93	0	5305	5322	5314	100.0
				30/11/93	7	4782	4754	4768	89.7
7/12/93	14			4992	4819	4906	92.3		
9/12/93	16			4877	4670	4774	89.8		
15/12/93	0			4850	5027	4939	100.0		
18/12/93	3			5059	4962	5011	101.5		
21/12/93	6			4742	4916	4829	97.8		
9/ 2/94	56			4297	4459	4378	88.6		

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BUYLATE : SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 5B
 CHEMICAL STABILITY OF BUYLATE IN DIET AT -20°C

Nominal Conc. (ppm)	Preparation Date	Analysis Date	Analysis Interval (Days)	Analysed Conc. (ppm)	Mean Conc. (ppm)	% of Initial Conc.		
250	22/11/93	23/11/93	0	256	253	100.0		
		30/11/93	7	214	214	83.9		
		7/12/93	14	222	235	89.8		
		9/12/93	16	229	228	89.8		
		21/12/93	28	231	241	92.5		
		15/12/93	0	246	246	100.0		
		9/ 2/94	56	263	249	104.1		
		5000	22/11/93	23/11/93	0	5305	5322	100.0
				30/11/93	7	4991	4744	91.6
				7/12/93	14	4782	4897	91.1
9/12/93	16			4913	4679	90.3		
21/12/93	28			4440	4471	83.9		
15/12/93	0			4850	5027	100.0		
9/ 2/94	56	4663	4637	94.1				

BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS

GLOSSARY FOR STATISTICAL TABLES

Key to results of statistical tests:

- ** Statistically significant difference from the control group mean at the 1% level (Student's t-test, two-sided).
- * Statistically significant difference from the control group mean at the 5% level (Student's t-test, two-sided).

The following results were excluded from statistical analyses :

Table 6	Bodyweights	Male 15 , Week 3.
Table 16	Brain Parameters	Female 61 , brain weight.

BUTYRATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 6
 INTERGROUP COMPARISON OF BODYWEIGHTS (G) - MALES

Week	MEAN S.D. N	Dietary Concentration of Butyrate (ppm)		
		0(Control)	250	1000
Week 1	211.4 9.7 12	211.7 13.4 12	209.1 10.2 12	211.1 14.7 12
Week 2	263.3 13.4 12	263.3 17.8 12	257.7 10.9 12	248.1** 18.0 12
Week 3	308.6 18.0 12	312.8 17.3 11	304.1 12.4 12	288.8** 18.5 12
Week 4	343.9 19.5 12	348.3 20.6 12	341.8 15.6 12	321.3** 18.5 12
Week 5	376.6 20.6 12	380.9 22.0 12	373.8 19.8 12	350.6** 22.5 12
Week 6	399.7 23.9 12	407.9 27.3 12	400.6 23.7 12	374.0** 23.1 12
Week 7	427.3 28.6 12	430.8 28.3 12	426.7 24.9 12	396.9** 27.9 12
Week 8	446.8 28.4 12	449.0 27.7 12	445.0 28.7 12	408.9** 27.3 12
Week 9	464.8 33.0 12	469.6 29.0 12	463.3 32.5 12	424.7** 29.5 12
Week 10	484.3 36.5 12	485.2 30.8 12	483.8 34.9 12	443.8** 30.6 12
Week 11	497.3 39.8 12	499.3 33.8 12	496.7 39.0 12	454.6** 32.8 12
Week 12	512.0 40.8 12	519.1 38.4 12	512.8 42.3 12	468.3** 38.1 12
Week 13	517.9 38.1 12	527.3 38.7 12	523.0 42.7 12	474.0** 41.4 12
Week 14	523.4 37.9 12	536.4 39.7 12	529.9 45.1 12	479.6** 42.0 12

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BUTYRATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
TABLE 6
INTERGROUP COMPARISON OF BODYWEIGHTS (g) - FEMALE

Week	Dietary Concentration of Butyrate (ppm)			
	0 (Control)	250	1000	5000
Week 1	MEAN	167.9	164.3	164.8
	S.D.	5.8	9.7	7.9
Week 2	MEAN	192.0	186.8	183.0*
	S.D.	10.9	10.1	8.9
Week 3	MEAN	209.4	202.8	199.2*
	S.D.	13.4	9.6	7.8
Week 4	MEAN	224.1	217.8	207.6**
	S.D.	12.0	14.4	8.6
Week 5	MEAN	234.3	228.5	215.3***
	S.D.	11.8	13.0	8.0
Week 6	MEAN	247.0	241.5	228.9***
	S.D.	13.9	13.5	8.0
Week 7	MEAN	260.3	250.7	238.7***
	S.D.	15.7	11.1	9.9
Week 8	MEAN	259.8	255.0	241.6***
	S.D.	13.6	13.2	11.4
Week 9	MEAN	264.8	257.8	244.9***
	S.D.	13.1	12.5	11.7
Week 10	MEAN	273.1	267.3	253.3***
	S.D.	15.6	11.4	9.2
Week 11	MEAN	273.7	269.6	257.0***
	S.D.	13.4	12.1	12.0
Week 12	MEAN	276.7	279.4	259.3***
	S.D.	12.2	13.9	13.7
Week 13	MEAN	282.7	277.2	261.9***
	S.D.	15.8	12.3	11.9
Week 14	MEAN	285.4	277.8	263.9***
	S.D.	17.5	12.3	11.2

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BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 7
 INTERGROUP COMPARISON OF FOOD CONSUMPTION (g/RAT/DAY) - MALES

Week	MEAN S.D. N	Dietary Concentration of Butylate (ppm)		
		0 (Control)	250	1000
Week 1	28.8 1.2 3	28.2 1.8 3	27.6** 1.1 3	24.5** 1.0 3
Week 2	30.9 1.8 3	30.7 1.3 3	29.9 1.1 3	27.6** 0.2 3
Week 3	30.6 1.0 3	30.9 1.6 3	29.8 0.8 3	27.3** 0.4 3
Week 4	31.9 1.1 3	31.5 2.6 3	30.8 1.6 3	28.3** 0.7 3
Week 5	29.5 0.3 3	29.8 2.6 3	29.6 1.1 3	26.9 0.8 3
Week 6	30.2 0.7 3	29.7 3.0 3	30.4 1.4 3	27.8 1.3 3
Week 7	29.7 0.4 3	29.0 1.9 3	29.6 1.3 3	26.5* 1.5 3
Week 8	29.2 0.9 3	28.7 2.4 3	29.1 1.1 3	25.9* 1.5 3
Week 9	29.7 1.5 3	28.3 2.4 3	29.5 1.2 3	26.3* 1.1 3
Week 10	30.0 1.3 3	29.7 1.8 3	30.3 1.4 3	27.0* 1.5 3
Week 11	30.4 0.8 3	30.4 2.3 3	30.6 1.4 3	27.4* 1.6 3
Week 12	29.8 0.4 3	30.0 2.0 3	31.1 1.5 3	26.9* 1.4 3
Week 13	29.9 0.4 3	30.1 2.2 3	31.1 1.6 3	26.9* 1.1 3

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BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 7
 INTERGROUP COMPARISON OF FOOD CONSUMPTION (G/RAT/DAY) - FEMALES

Week	Dietary Concentration of Butylate (ppm)			
	0 (Control)	250	1000	5000
Week 1	MEAN 21.5 S.D. 0.5 N 3	21.4 1.1 3	19.0** 1.2 3	16.6** 0.6 3
Week 2	MEAN 21.6 S.D. 0.7 N 3	20.7 1.5 3	19.3* 0.3 3	19.0** 0.8 3
Week 3	MEAN 21.2 S.D. 0.9 N 3	21.0 2.0 3	18.1** 0.7 3	17.4** 0.9 3
Week 4	MEAN 21.9 S.D. 1.4 N 3	21.2 1.2 3	18.8** 1.1 3	17.5** 0.7 3
Week 5	MEAN 20.6 S.D. 1.7 N 3	20.2 1.9 3	18.0** 0.9 3	16.5** 1.2 3
Week 6	MEAN 21.9 S.D. 1.2 N 3	21.0 1.9 3	19.0** 1.1 3	17.2** 1.0 3
Week 7	MEAN 20.9 S.D. 0.3 N 3	20.6 2.2 3	18.2** 0.8 3	16.6** 0.7 3
Week 8	MEAN 19.9 S.D. 0.4 N 3	19.2 1.4 3	17.6** 0.5 3	15.7** 0.6 3
Week 9	MEAN 20.1 S.D. 1.4 N 3	19.6 1.2 3	17.6* 0.1 3	15.9** 1.2 3
Week 10	MEAN 20.7 S.D. 1.6 N 3	20.6 1.8 3	18.3** 0.8 3	17.0** 1.5 3
Week 11	MEAN 19.8 S.D. 0.8 N 3	21.1 2.0 3	17.6** 0.6 3	16.3** 1.3 3
Week 12	MEAN 20.6 S.D. 1.0 N 3	19.7 1.4 3	18.1** 0.5 3	16.5** 1.4 3
Week 13	MEAN 20.8 S.D. 1.1 N 3	19.5 1.7 3	17.9** 0.6 3	16.6** 1.7 3

BITYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 8
 INTERGROUP COMPARISON OF FOOD UTILISATION (g GROWTH / 100g FOOD)

	Dietary Concentration of Bitylate (ppm)				
	250 0(Control)	1000			
Males					
Weeks 1-4	MEAN	19.3	20.0	19.9	18.5
	S.D. N	1.8 3	1.1 3	0.5 3	2.1 3
Weeks 5-8	MEAN	10.6	10.8	10.8	9.9
	S.D. N	1.4 3	1.3 3	1.0 3	0.8 3
Weeks 9-13	MEAN	5.6	6.4	6.2	5.8
	S.D. N	0.7 3	0.3 3	0.6 3	1.0 3
Overall (Weeks 1-13)					
	MEAN	11.4	12.0	11.8	11.0
	S.D. N	1.1 3	0.7 3	0.5 3	1.1 3
Females					
Weeks 1-4	MEAN	11.0	10.9	9.6**	9.4**
	S.D. N	1.1 3	0.5 3	0.5 3	1.3 3
Weeks 5-8	MEAN	5.2	5.2	5.8	4.7
	S.D. N	0.6 3	0.7 3	1.4 3	0.1 3
Weeks 9-13	MEAN	2.9	2.9	2.7	2.6
	S.D. N	0.5 3	0.1 3	0.5 3	1.0 3
Overall (Weeks 1-13)					
	MEAN	6.2	6.1	5.9	5.5*
	S.D. N	0.3 3	0.4 3	0.6 3	0.5 3

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BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS

GLOSSARY FOR TABLE 9

CLINICAL OBSERVATIONS

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Key:

- NO. - number
- OBS. - observations
- INCR/D - increased
- INCONTIN - incontinence
- AREA 20 - underside of tail
- SEE FREE TEXT - Female 83 (1000ppm) - Head leaning to left hand side.

LAC904-09/02

BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 9
 CLINICAL OBSERVATIONS

SEX: MALE	0 PM	250 PM	1000 PM	5000 PM
KILLED TERMINATION				
NO. OF ORS.	12	12	12	12
NO. OF ANIMALS	12	12	12	12
WEEKS FROM - TO	14	14	14	14
SCABS (CODED BY AREA 20)				
NO. OF ORS.	1	7	4	
NO. OF ANIMALS	1	1	1	
WEEKS FROM - TO	5	6	5	8
INCR/SD RESPONSE TO TOUCH				
NO. OF ORS.			1	1
NO. OF ANIMALS			1	1
WEEKS FROM - TO			14	14
REDUCED SPRAY REFLEX				
NO. OF ORS.		2		1
NO. OF ANIMALS		1		1
WEEKS FROM - TO		5	6	14
TAIL BLEEDING				
NO. OF ORS.	1			
NO. OF ANIMALS	1			
WEEKS FROM - TO	6	6		
TAIL DAMAGED				
NO. OF ORS.	28		11	9
NO. OF ANIMALS	4		2	2
WEEKS FROM - TO	5	14	5	14
TEETH TRIMMED				
NO. OF ORS.	1			
NO. OF ANIMALS	1			
WEEKS FROM - TO	14	14		

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BUYLADE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
TABLE 9
CLINICAL OBSERVATIONS

SEX: FEMALE	0 PPM	250 PPM	1000 PPM	5000 PPM
EPITHELIUMS NO. OF ORS. NO. OF ANIMALS WEEKS FROM - TO			1 1	13 13
HAIR LOSS (GENERAL) NO. OF ORS. NO. OF ANIMALS WEEKS FROM - TO	12 2			
HUNCHED NO. OF ORS. NO. OF ANIMALS WEEKS FROM - TO		1 1	2 2	9 9
KILLED FOR HUMANE REASONS NO. OF ORS. NO. OF ANIMALS WEEKS FROM - TO		14 14	5 5	
KILLED TERMINATION NO. OF ORS. NO. OF ANIMALS WEEKS FROM - TO	12 12	12 12	11 11	12 12
PALE NO. OF ORS. NO. OF ANIMALS WEEKS FROM - TO			1 1	
REDUCED SPINAY REFLEX NO. OF ORS. NO. OF ANIMALS WEEKS FROM - TO	2 2	9 1	13 13	7 3

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BUTYLATE; SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 9
 CLINICAL OBSERVATIONS

	0 PM	250 PM	1000 PM	5000 PM
SEX: FEMALE				
SIGNS OF URINARY INCONTINENCE				
NO. OF OBS.				4
NO. OF ANIMALS				1
WEEKS FROM - TO				6 14
TAIL REDDING				
NO. OF OBS.			1	
NO. OF ANIMALS			1	
WEEKS FROM - TO			5 5	
TAIL DAMAGED				
NO. OF OBS.		6	11	
NO. OF ANIMALS		1	1	
WEEKS FROM - TO		9 14	4 14	
SCALY TAIL				
NO. OF OBS.				1
NO. OF ANIMALS				1
WEEKS FROM - TO				14 14
SEE FREE TEXT				
NO. OF OBS.			5	
NO. OF ANIMALS			1	
WEEKS FROM - TO			9 13	
TIP TOE GAIT				
NO. OF OBS.			1	
NO. OF ANIMALS			1	
WEEKS FROM - TO			9 9	

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BUTYRATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 10
 INTERGROUP COMPARISON OF LANDING FOOT SPLAY (mm)

	Dietary Concentration of Butyrate (ppm)			
	0(Control)	250	1000	5000
Males				
Week -1	MEAN S.D. N	58.6 17.1 12	60.3 13.8 12	56.7 12.8 12
Week 5	MEAN S.D. N	71.5 12.3 12	76.2 14.8 12	71.5 15.6 12
Week 9	MEAN S.D. N	65.5 16.2 12	74.1 19.6 12	68.7 20.8 12
Week 14	MEAN S.D. N	68.6 15.5 12	64.6 11.6 12	69.2 14.2 12
Females				
Week -1	MEAN S.D. N	43.3 9.0 12	43.3 7.8 12	47.0 9.7 12
Week 5	MEAN S.D. N	61.2 12.8 12	57.3 12.1 12	66.3 20.9 12
Week 9	MEAN S.D. N	60.6 8.6 12	59.2 12.5 12	54.0 10.0 12
Week 14	MEAN S.D. N	56.6 15.3 12	50.6 3.0 12	52.4 10.9 11
				53.6 11.1 12

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BUYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 11
 INTERGROUP COMPARISON OF TAIL FLICK (s)

	Dietary Concentration of Butylate (ppm)						
	0 (Control)	250	1000	5000			
Males	Week -1	MEAN	6.4	9.5	7.6	6.4	
		S.D.	4.1	6.7	4.6	4.3	
	Week 5	MEAN	8.7	9.2	5.8	6.6	
		S.D.	4.8	6.8	2.3	6.3	
	Week 9	MEAN	10.2	14.0	8.5	8.8	
		S.D.	6.1	6.7	5.2	5.5	
	Week 14	MEAN	10.9	8.9	6.8	9.0	
		S.D.	6.8	6.8	3.7	7.1	
	Females	Week -1	MEAN	5.9	8.3	5.1	5.3
			S.D.	3.1	5.0	2.5	3.1
		Week 5	MEAN	3.0	3.5	6.3**	3.7
			S.D.	2.2	1.9	4.1	2.1
Week 9		MEAN	4.6	6.2	5.2	4.8	
		S.D.	1.5	3.4	3.0	2.2	
Week 14		MEAN	6.3	4.5	5.1	4.3	
		S.D.	4.0	1.4	2.6	1.9	

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BUTYLATE, SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 12A
 INTERGROUP COMPARISON OF GRIP STRENGTH (g) - FORELIMS

	Dietary Concentration of Butylate (ppm)			
	0 (Control)	250	1000	5000
Males				
Week -1	MEAN S.D. N	646 102 12	696 67 12	671 107 12
Week 5	MEAN S.D. N	1306 133 12	1369 277 12	1392 209 12
Week 9	MEAN S.D. N	1575 164 12	1563 192 12	1581 187 12
Week 14	MEAN S.D. N	1929 193 12	1890 188 12	1867 455 12
Females				
Week -1	MEAN S.D. N	635 81 12	640 91 12	638 78 12
Week 5	MEAN S.D. N	1215 93 12	1185 158 12	1090* 140 12
Week 9	MEAN S.D. N	1310 183 12	1313 162 12	1275 112 12
Week 14	MEAN S.D. N	1548 170 12	1517 193 12	1455 102 11
				1471 171 12

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BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 12B
 INTERGROUP COMPARISON OF GRIP STRENGTH (g) - HINDLIMBS

	Dietary Concentration of Butylate (ppm)			
	0 (Control)	250	1000	5000
Males				
Week -1	MEAN S.D. N	319 118 12	279 58 12	377 76 12
Week 5	MEAN S.D. N	602 160 12	627 85 12	544 132 12
Week 9	MEAN S.D. N	840 96 12	863 203 12	854 174 12
Week 14	MEAN S.D. N	879 154 12	983 291 12	960 261 12
Females				
Week -1	MEAN S.D. N	304 66 12	294 73 12	306 82 12
Week 5	MEAN S.D. N	506 109 12	423 129 12	410 134 12
Week 9	MEAN S.D. N	546 141 12	565 127 12	550 131 12
Week 14	MEAN S.D. N	623 193 12	515 186 12	559 175 11

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BITYLATE, SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 13
 INTERGROUP COMPARISON OF MOTOR ACTIVITY - WEEK -1 Males

	Dietary Concentration of Butylate (ppm)			
	0 (Control)	250	1000	5000
Minutes 1-5	MEAN	40.8	42.1	46.3
	S.D.	20.2	16.4	20.6
Minutes 6-10	MEAN	40.0	46.0	48.1
	S.D.	21.4	15.4	11.9
Minutes 11-15	MEAN	30.6	36.8	42.0
	S.D.	20.4	22.8	17.0
Minutes 16-20	MEAN	19.1	17.1	20.8
	S.D.	20.5	23.7	21.6
Minutes 21-25	MEAN	5.3	11.9	11.8
	S.D.	7.8	21.2	26.2
Minutes 26-30	MEAN	3.6	5.2	3.2
	S.D.	7.6	12.2	9.4
Minutes 31-35	MEAN	1.8	2.3	2.8
	S.D.	4.7	6.3	6.2
Minutes 36-40	MEAN	5.4	3.3	1.3
	S.D.	13.4	9.4	4.3
Minutes 41-45	MEAN	2.1	2.8	6.4
	S.D.	3.9	3.6	12.7
Minutes 46-50	MEAN	1.8	1.6	4.1
	S.D.	5.2	3.4	10.0
Overall (1-50)	MEAN	150.3	169.0	166.8
	S.D.	76.4	63.2	75.9

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BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 13
 INTERGROUP COMPARISON OF MOTOR ACTIVITY - WEEK -1 FEMALES

	Dietary Concentration of Butylate (ppm)				
	0(Control)	250	1000	5000	
Minutes 1-5	MEAN S.D. N	47.8 8.2 12	49.1 18.6 12	44.5 16.9 12	51.6 8.3 12
Minutes 6-10	MEAN S.D. N	56.0 9.5 12	44.8 24.8 12	48.3 19.9 12	52.8 10.8 12
Minutes 11-15	MEAN S.D. N	40.8 18.2 12	32.0 24.4 12	47.3 17.6 12	35.3 17.1 12
Minutes 16-20	MEAN S.D. N	21.8 25.4 12	23.9 28.6 12	30.5 26.8 12	15.8 18.9 12
Minutes 21-25	MEAN S.D. N	11.8 18.3 12	8.1 15.6 12	17.9 21.7 12	7.6 14.4 12
Minutes 26-30	MEAN S.D. N	5.4 10.9 12	5.8 11.0 12	4.7 7.8 12	6.3 15.7 12
Minutes 31-35	MEAN S.D. N	0.4 1.2 12	1.5 3.3 12	8.3 16.3 12	5.5 17.2 12
Minutes 36-40	MEAN S.D. N	1.3 2.4 12	2.4 5.4 12	9.4 16.6 12	7.2 19.3 12
Minutes 41-45	MEAN S.D. N	4.0 4.0 12	6.2 15.6 12	12.8 19.0 12	4.5 9.7 12
Minutes 46-50	MEAN S.D. N	3.3 8.1 12	0.4 0.8 12	11.8 20.3 12	0.3 0.8 12
Overall (1-50)	MEAN S.D. N	189.8 72.6 12	174.2 109.6 12	235.8 75.3 12	186.8 84.2 12

BUTYRATE: SYNCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 13
 INTERGROUP COMPARISON OF MOTOR ACTIVITY - WEEK 5 MALES

Minutes	Dietary Concentration of Butyrate (ppm)			
	0 (Control)	250	1000	5000
Minutes 1-5	MEAN	59.5	60.6	58.2
	S.D.	9.8	10.5	6.2
Minutes 6-10	MEAN	57.8	60.3	58.3
	S.D.	10.6	10.9	16.2
Minutes 11-15	MEAN	61.7	52.8	45.3*
	S.D.	14.1	14.9	20.6
Minutes 16-20	MEAN	53.8	42.2	39.3
	S.D.	25.7	23.1	25.0
Minutes 21-25	MEAN	48.5	39.7	48.4
	S.D.	17.4	22.2	23.3
Minutes 26-30	MEAN	47.4	31.8	25.5*
	S.D.	28.2	23.0	22.0
Minutes 31-35	MEAN	37.8	26.3	28.3
	S.D.	27.9	23.7	27.9
Minutes 36-40	MEAN	30.0	18.3	23.8
	S.D.	26.3	26.0	28.4
Minutes 41-45	MEAN	27.2	15.2	15.8
	S.D.	30.8	27.8	20.1
Minutes 46-50	MEAN	17.7	11.4	8.7
	S.D.	26.5	21.5	14.5
Overall (1-50)	MEAN	441.3	358.4	351.3
	S.D.	156.3	151.6	159.2

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BITTATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 13
 INTERGROUP COMPARISON OF MOTOR ACTIVITY - WEEK 5 FEMALES

	0(Control)		250		1000		5000	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Minutes 1-5	51.9	6.2	54.2	8.0	54.6	7.3	57.6	9.0
Minutes 6-10	50.8	6.9	61.3**	12	58.0	12	53.8	12.2
Minutes 11-15	43.6	12	49.3	12	60.6*	12	53.1	12
Minutes 16-20	39.3	12	35.8	12	62.9**	12	46.2	12
Minutes 21-25	43.3	12	48.3	12	53.5	12	49.9	12
Minutes 26-30	41.3	12	49.5	12	54.5	12	48.5	12
Minutes 31-35	35.7	12	42.4	12	50.4	12	52.8	12
Minutes 36-40	30.0	12	22.5	12	24.0	12	18.3	12
Minutes 41-45	35.1	12	38.0	12	45.9	12	53.3	12
Minutes 46-50	28.8	12	25.8	12	27.8	12	22.9	12
Overall (1-50)	430.8	167.7	464.8	153.7	523.2	109.9	527.0	107.6

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ESTIMATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 13
 INTERGROUP COMPARISON OF MOTOR ACTIVITY - WEEK 9 MALES

Minutes	MEAN S.D. N	Dietary Concentration of Butylate (ppm)		
		0(Control)	250	1000
Minutes 1-5	61.2 10.1 12	60.7 8.4 12	55.4 10.5 12	64.0 8.2 12
Minutes 6-10	57.4 10.5 12	56.0 8.5 12	59.3 11.0 12	55.7 12.5 12
Minutes 11-15	47.0 21.1 12	43.3 20.8 12	53.7 8.0 12	54.4 14.8 12
Minutes 16-20	48.5 20.5 12	42.0 25.6 12	40.8 14.1 12	52.1 11.0 12
Minutes 21-25	38.3 22.7 12	30.7 24.8 12	41.9 20.7 12	40.7 17.1 12
Minutes 26-30	34.4 27.7 12	35.4 28.4 12	42.2 21.5 12	36.3 31.0 12
Minutes 31-35	44.1 27.6 12	38.9 23.2 12	32.4 27.4 12	26.5 27.2 12
Minutes 36-40	34.8 25.3 12	34.3 29.6 12	21.8 20.2 12	20.9 22.7 12
Minutes 41-45	30.3 29.9 12	17.2 20.4 12	16.0 22.3 12	20.0 24.5 12
Minutes 46-50	25.1 25.9 12	22.6 27.2 12	13.4 17.9 12	24.7 29.6 12
Overall (1-50)	421.1 154.5 12	381.3 141.2 12	378.9 108.0 12	395.2 159.6 12

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EUTILATE: SYNCHRONIC NEUROTOXICITY STUDY IN RATS
TABLE 13
INTERGROUP COMPARISON OF MOTOR ACTIVITY - WEEK 9 FEMALE

Minutes	MEAN S.D. N	Dietary Concentration of Bacylate (ppm)			
		0 (Control)	250	1000	5000
Minutes 1-5	MEAN S.D. N	58.6 9.0 12	55.1 10.4 12	58.2 9.9 12	59.8 7.0 12
Minutes 6-10	MEAN S.D. N	60.3 15.4 12	51.8 12.0 12	57.3 13.7 12	54.3 13.8 12
Minutes 11-15	MEAN S.D. N	59.5 9.5 12	51.1* 16.4 12	57.8 8.8 12	58.1 9.7 12
Minutes 16-20	MEAN S.D. N	50.8 14.8 12	55.1 14.6 12	57.0 20.6 12	51.6 19.7 12
Minutes 21-25	MEAN S.D. N	44.5 26.8 12	35.8 22.5 12	43.4 23.4 12	51.8 21.7 12
Minutes 26-30	MEAN S.D. N	44.4 23.2 12	33.7 21.0 12	50.3 26.3 12	54.5 21.7 12
Minutes 31-35	MEAN S.D. N	52.8 15.1 12	54.4 14.2 12	41.6 24.4 12	52.3 16.4 12
Minutes 36-40	MEAN S.D. N	40.3 28.3 12	45.4 17.2 12	59.8* 21.5 12	52.2 19.6 12
Minutes 41-45	MEAN S.D. N	43.8 25.7 12	47.8 25.5 12	61.7* 10.4 12	58.1 19.3 12
Minutes 46-50	MEAN S.D. N	51.9 18.7 12	46.8 23.0 12	51.5 26.4 12	47.5 16.8 12
Overall (1-50)	MEAN S.D. N	506.9 117.6 12	476.9 82.8 12	538.6 134.0 12	540.0 121.5 12

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BUYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 13
 INTERGROUP COMPARISON OF MOTOR ACTIVITY - WEEK 14 MALES

Minutes	MEAN S.D. N	Dietary Concentration of Butylate (ppm)		
		0(Control)	250	5000
Minutes 1-5	48.8 19.5 12	56.3 10.1 12	53.0 17.4 12	55.4 18.3 12
Minutes 6-10	37.3 22.9 12	45.0 17.6 12	49.5 16.2 12	52.4* 21.9 12
Minutes 11-15	31.4 26.7 12	35.2 19.2 12	38.4 32.6 12	37.8 23.6 12
Minutes 16-20	15.8 19.3 12	17.2 18.1 12	18.0 19.7 12	33.1* 27.9 12
Minutes 21-25	14.9 16.0 12	16.0 19.9 12	19.7 26.1 12	21.8 22.0 12
Minutes 26-30	11.9 16.9 12	13.3 12.7 12	9.8 12.8 12	12.3 17.6 12
Minutes 31-35	8.3 14.1 12	15.6 23.2 12	6.8 8.3 12	8.7 17.7 12
Minutes 36-40	5.8 7.8 12	11.3 12.4 12	2.7 3.7 12	5.7 10.6 12
Minutes 41-45	8.2 15.3 12	3.7 5.8 12	1.8 4.6 12	2.7 6.9 12
Minutes 46-50	8.9 18.0 12	2.2 3.9 12	3.3 6.4 12	1.0* 1.6 12
Overall (1-50)	191.3 108.0 12	215.6 65.4 12	202.8 86.2 12	230.8 128.0 12

BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 13
 INTERGROUP COMPARISON OF MOTOR ACTIVITY - WEEK 14 FEMALES

Minutes	0(Control)		250		1000		5000	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Minutes 1-5	51.7	7.3	56.3	9.5	58.0*	7.9	52.6	7.5
	N	12	N	12	N	11	N	12
Minutes 6-10	52.9	18.9	56.6	7.2	58.8	7.8	58.4	7.6
	N	12	N	12	N	11	N	12
Minutes 11-15	53.8	19.6	49.0	20.3	62.8	13.3	50.3	19.0
	N	12	N	12	N	11	N	12
Minutes 16-20	47.3	23.5	40.8	19.9	46.8	22.5	48.3	19.0
	N	12	N	12	N	11	N	12
Minutes 21-25	36.8	27.2	35.4	29.0	51.7	27.5	47.8	20.5
	N	12	N	12	N	11	N	12
Minutes 26-30	32.4	29.3	29.0	28.4	43.5	30.3	46.1	25.6
	N	12	N	12	N	11	N	12
Minutes 31-35	35.5	26.7	35.0	21.6	51.8	21.4	53.5*	11.8
	N	12	N	12	N	11	N	12
Minutes 36-40	42.8	29.6	31.1	24.7	56.5	19.7	51.6	9.6
	N	12	N	12	N	11	N	12
Minutes 41-45	45.8	20.9	28.3	24.6	57.1	27.4	46.2	24.8
	N	12	N	12	N	11	N	12
Minutes 46-50	41.3	28.0	21.7*	24.5	45.5	25.4	46.1	17.6
	N	12	N	12	N	11	N	12
Overall (1-50)	440.2	164.6	383.1	133.2	532.6	143.6	500.8	103.7
	N	12	N	12	N	11	N	12

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BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 14
 INTERGROUP COMPARISON OF CHOLINESTERASE ACTIVITY

	Dietary Concentration of Butylate (ppm)				
	0 (Control)	250	1000	5000	
Males					
Brain Cholinesterase (micromoles/1/min/g)	MEAN	10.31	10.85	10.95	11.09
	S.D.	1.10	1.07	0.24	1.36
Erythrocyte Cholinesterase (U/l)	MEAN	2128	2072	2483*	2168
	S.D.	300	178	326	246
Plasma Cholinesterase (U/l)	MEAN	547	528	525	606
	S.D.	54	35	80	95
Females					
Brain Cholinesterase (micromoles/1/min/g)	MEAN	11.34	10.99	11.77	11.90
	S.D.	0.33	0.61	0.39	0.70
Erythrocyte Cholinesterase (U/l)	MEAN	2177	2336	2440	2496*
	S.D.	246	299	321	213
Plasma Cholinesterase (U/l)	MEAN	1508	1672	1781	1654
	S.D.	243	252	352	232

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BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 15
 INTERGROUP COMPARISON OF NEUROPATHY TARGET ESTERASE ACTIVITY

Activity (nmoles/min/g wet weight)	Dietary Concentration of Butylate (ppm)			
	0 (Control)	250	1000	5000
Males				
MEAN	967	1032	1092*	1060
S.D.	126	85	144	63
N	3	3	3	3
Females				
MEAN	979	1060	1021	999
S.D.	103	101	34	144
N	3	3	3	3

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BUYLANE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 16
 INTERGROUP COMPARISON OF BRAIN PARAMETERS

	Dietary Concentration of Butylate (ppm)			
	0(Control)	250	1000	5000
BRAIN				
MALES				
Terminal Bodyweight (g)	MEAN 524.4 S.D. 35.0 N 12	MEAN 535.8 S.D. 41.1 N 12	MEAN 529.8 S.D. 44.9 N 12	MEAN 481.5 S.D. 41.4 N 12
Organ Weight (g)	MEAN 2.13 S.D. 0.07 N 12	MEAN 2.17 S.D. 0.08 N 12	MEAN 2.18 S.D. 0.08 N 12	MEAN 2.15 S.D. 0.07 N 12
Organ to Bodyweight Ratio (Z)	MEAN 0.41 S.D. 0.03 N 12	MEAN 0.41 S.D. 0.02 N 12	MEAN 0.41 S.D. 0.04 N 12	MEAN 0.45 S.D. 0.03 N 12
Organ Weight Adjusted For Bodyweight	2.13	2.15	2.17	2.18
FDWALS				
Terminal Bodyweight (g)	MEAN 285.0 S.D. 17.7 N 12	MEAN 275.3 S.D. 12.8 N 11	MEAN 260.4 S.D. 12.4 N 11	MEAN 249.7 S.D. 20.0 N 12
Organ Weight (g)	MEAN 1.98 S.D. 0.06 N 12	MEAN 1.97 S.D. 0.09 N 11	MEAN 1.97 S.D. 0.08 N 11	MEAN 1.95 S.D. 0.05 N 12
Organ to Bodyweight Ratio (Z)	MEAN 0.70 S.D. 0.03 N 12	MEAN 0.72 S.D. 0.04 N 11	MEAN 0.76 S.D. 0.04 N 11	MEAN 0.79 S.D. 0.07 N 12
Organ Weight Adjusted For Bodyweight	1.97	1.97	1.97	1.96

BUYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 16
 INTERGROUP COMPARISON OF BRAIN PARAMETERS

	Dietary Concentration of Buylate (ppm)				
	0 (Control)	250	1000	5000	
BRAIN LENGTH					
MALES					
Terminal Bodyweight (g)	MEAN	524.4	535.8	529.8	461.5
	S.D.	35.0	41.1	44.9	41.4
	N	12	12	12	12
Brain Length (mm)	MEAN	28.1	28.6	28.3	28.6
	S.D.	2.1	2.1	1.9	2.1
	N	12	12	12	12
Brain Length to Bodyweight Ratio (Z)	MEAN	5.4	5.4	5.4	6.0
	S.D.	0.5	0.6	0.6	0.6
	N	12	12	12	12
Brain Length Adjusted For Bodyweight		28.1	28.6	28.2	28.6
FEMALES					
Terminal Bodyweight (g)	MEAN	265.0	275.0	260.4	249.7
	S.D.	17.7	12.2	12.4	20.0
	N	12	12	11	12
Brain Length (mm)	MEAN	26.9	27.3	27.3	27.0
	S.D.	2.3	2.3	2.1	1.8
	N	12	12	11	12
Brain Length to Bodyweight Ratio (Z)	MEAN	9.5	9.9	10.5	10.9
	S.D.	0.7	1.0	0.9	1.2
	N	12	12	11	12
Brain Length Adjusted For Bodyweight		27.0	27.3	27.2	27.0

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BUTYLATE: SUBCHRONIC NEUROTOXICITY STUDY IN RATS
 TABLE 16
 INTERGROUP COMPARISON OF BRAIN PARAMETERS

	Dietary Concentration of Butylate (ppm)			
	0 (Control)	250	1000	5000
BRAIN WIDTH				
MALES				
Terminal Bodyweight (g)	MEAN 524.4 S.D. 35.0 N 12	MEAN 535.8 S.D. 41.1 N 12	MEAN 529.8 S.D. 44.9 N 12	MEAN 481.5 S.D. 41.4 N 12
Brain Width (mm)	MEAN 15.7 S.D. 0.5 N 12	MEAN 15.5 S.D. 0.5 N 12	MEAN 15.5 S.D. 0.7 N 12	MEAN 15.4 S.D. 0.8 N 12
Brain Width to Bodyweight Ratio (X)	MEAN 3.0 S.D. 0.2 N 12	MEAN 2.9 S.D. 0.2 N 12	MEAN 2.9 S.D. 0.2 N 12	MEAN 3.2 S.D. 0.3 N 12
Brain Width Adjusted For Bodyweight	15.7	15.5	15.5	15.5
FEMALES				
Terminal Bodyweight (g)	MEAN 285.0 S.D. 17.7 N 12	MEAN 275.0 S.D. 12.2 N 12	MEAN 260.4 S.D. 12.4 N 11	MEAN 249.7 S.D. 20.0 N 12
Brain Width (mm)	MEAN 14.9 S.D. 0.5 N 12	MEAN 14.8 S.D. 0.6 N 12	MEAN 15.0 S.D. 0.6 N 11	MEAN 14.8 S.D. 0.7 N 12
Brain Width to Bodyweight Ratio (X)	MEAN 5.3 S.D. 0.4 N 12	MEAN 5.4 S.D. 0.3 N 12	MEAN 5.8 S.D. 0.5 N 11	MEAN 6.0 S.D. 0.6 N 12
Brain Width Adjusted For Bodyweight	14.9	14.8	15.0	14.8

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 TABLE 17
 INTERGROUP COMPARISON OF MACROSCOPIC FINDINGS

	MALES				FEMALES			
	0	250	1000	5000	0	250	1000	5000
ANIMALS ON STUDY	12	12	12	12	12	12	12	12
ANIMALS COMPLETED	12	12	12	12	12	12	12	12
KIDNEY NO. WITH FINDINGS BUT NOT SUBMITTED	0	0	0	1	0	0	0	1
Pelvic dilatation	0	0	0	1	0	0	0	1
SKIN NO. WITH FINDINGS BUT NOT SUBMITTED	0	0	0	0	2	0	0	0
Hair loss	0	0	0	0	2	0	0	0
TAIL SUBMITTED	1	0	1	1	0	0	0	1
NO. WITH FINDINGS	1	0	1	1	0	0	0	1
NO. WITH FINDINGS BUT NOT SUBMITTED	1	0	1	1	0	0	1	0
Transected	0	0	0	1	0	1	0	0
Kinked	2	0	2	0	0	1	0	0
Scaly	0	0	0	0	0	1	1	0
Scab/s	0	0	0	1	0	0	0	0
URINARY BLADDER NO. WITH FINDINGS BUT NOT SUBMITTED	0	0	0	0	0	0	0	1
Distended	0	0	0	0	0	0	0	1
Firm deposit/s	0	0	0	0	0	0	0	1

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 TABLE 18
 INTERGROUP COMPARISON OF MICROSCOPIC FINDINGS

REMOVAL REASON: TERMINAL	MALES				FEMALES			
	0	250	1000	5000	0	250	1000	5000
ANIMALS ON STUDY	12	12	12	12	12	12	12	12
ANIMALS COMPLETED	6	0	0	6	6	0	0	6
BRAIN EXAMINED.....	6	0	0	6	6	0	0	6
NO ABNORMALITIES DETECTED.....	4	0	0	3	5	0	0	6
Neuronal cell necrosis (TOTAL).....	2	0	0	3	1	0	0	0
minimal.....	2	0	0	3	1	0	0	0

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