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Attention: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Subject: TSCA Section 8(e) Submission
CASRN 120-55-8
Ethanol, 2,2-oxybis-, dibenzoate

COMPANY SANITIZED

Dear Sir or Madam:

The following report is herewith listed or submitted, pursuant to TSCA Section 8(e) compliance requirements:

Synopsis No. 1, dated 7 July 1997
[ ]: 13-Week Dietary Toxicity Study in Rats with 4-Week Recovery
Huntingdon Life Sciences [ ]

We wish to maintain the identity of our company and the trade name of the product tested, the study number and the identity of the submitter as Confidential Business Information, therefore we have provided both a Confidential Version and a Public Version of this submission, including a sanitized interim study report.

This is a unaudited interim (weeks 0 to 6) synopsis of a 13-week toxicity study with a 4-week recovery period on our product [ ].

The unaudited results contained in this interim study report may meet the criteria in EPA's TSCA Section 8(e) Reporting Guide (June 1991). Since we wish to be conservative in our approach to this regulation, we are submitting this interim report as reportable under TSCA Section 8(e).

In this study the high dose of 2,2-oxybisethanol dibenzoate (CASRN 120-55-8, approximately 90% purity) at 2500 mg/Kg/day clearly exceeds a Maximum Tolerated Dose (MTD). The

ongoing study observations (weeks 0 to 6 of a 13-week dosage study) include convulsions in 2 male rats at this high dose, 1 sacrificed *in extremis* and the other still alive, may well be due to severe toxicity without indication of any neurotoxic effect. This group has shown a 40% to 50% decrease in body weight gain (females and males respectively), body tremors, staining around the urogenital and head/neck area, hunched posture, and overall unthriftness due to severe toxicity. Upon gross necropsy an enlarged testis on the one male rat was observed, but it is of unknown cause. Since the enlarged testis was unilateral, it suggests strongly that it is not relevant to treatment. Since lower doses show a dose related effect in body weight gain only, any conclusions that may be made at this time regarding the scant observations at an exceeded MTD would be purely speculative. I suggest that you wait until sufficient data are available before concluding which effects may be directly related to the treatment and which effects may be secondary to severe toxicity at a high dose which includes lethality.

If desired, we will send you a copy of the quality assured final report when we receive it.

If you have any questions, please contact me at [ ]

Sincerely,

[ ]
[ ]

HUNTINGDON LIFE SCIENCES

SYNOPSIS No.1

7 July 1997

STUDY SCHEDULE NO.:

STUDY TITLE: 13-Week dietary Toxicity Study in Rats with 4-Week Recovery

STUDY DIRECTOR: T G Smith

STUDY SUPERVISOR: J. Blackwell

STUDY MONITOR:

DATE TREATMENT COMMENCED: 12 May 1997

STUDY IN WEEK: 9 (Week 9 commenced 7 July)

WEEKS COVERED IN THIS SYNOPSIS: 0 to 6

STUDY DESIGN:

Group	Treatment level (mg/kg/day)	No. Animals	
		Main group	Recovery group
1	Control	10 m + 10 f	10 m + 10 f
2	250	10 m + 10 f	-
3	1000	10 m + 10 f	-
4	1750	10 m + 10 f	-
5	2500	10 m + 10 f	10 m + 10 f

WATER CONSUMPTION: Week 12 & Recovery Week 3.

OPHTHALMOSCOPY: Predose & Week 13 (plus Recovery Week 4, if treatment-related changes).

LABORATORY INVESTIGATIONS: Week 13 (plus Recovery Week 4, if treatment-related changes).

TERMINAL KILL: Week 14 (beginning 11 August 1997).

RECOVERY KILL: Week R5 (beginning 8 September 1997).

All data and interpretation are provisional, and as such may be subject to alteration in subsequent documents.

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SYNOPSIS No.1

7 July 1997

MORTALITY

Animal 138m (2500 mg/kg/day) was terminated for humane reasons in Week 4 following a series of convulsive-like episodes. Details are as follows:

Clinical findings:

Body tremors on handling were noted from Week 3. Body tremors observed while animal in cage, brown staining on muzzle, wet urogenital region and hunched posture were noted during Week 4. Convulsions were noted on two occasions during Week 4, these episodes were followed by subdued and inactive behaviour.

Emaciated appearance, unsteady gait, yellow stained urogenital region, curled toes on fore and hindlimbs and loss of use of hindlimbs were noted prior to termination in Week 4.

Macroscopic findings:

Fur - genital region , yellow stained and moist.
- forelimbs and ventral cervical region, moist
Cervical lymph nodes - enlarged
Adipose tissue - minimal
Testes - left, enlarged
Stomach - antum mucosa, 2 white nodules near to limiting ridge

CLINICAL SIGNS (Appendix 1)

Clinical signs considered to be related to treatment to date include yellow stained fur in the urogenital region, brown stained fur (generally in the head/cervical region), hairloss, a hunched posture, body tremors and convulsive-like episodes. In general, the incidence of clinical signs has been greatest in the rats assigned to Group 5 late in the predose period. Late re-allocation of these rats (involving individual re-arrangement of the cage structure) may have placed them under some additional stress, which could possibly account for the higher incidence of clinical signs

Convulsive-like episodes were recorded for Rat 138m (2500 mg/kg/day) prior to its early termination in Week 4 and a single episode (lasting approximately 35 seconds) was also seen in Rat 58m (2500 mg/kg/day) in Week 5.

Slight to moderate body tremors have been noted in a number of rats of both sexes receiving 2500 mg/kg/day (most frequently in Rats 47m, 137m, 146f, 147f and 148f). In the more severe cases, these have been noticeable merely be visual inspection of the animals

Hunched posture was noted on isolated occasions from Week 4 for some rats receiving 2500 mg/kg/day.

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SYNOPSIS No.1

7 July 1997

Yellow or brown stained fur has been noted in some rats receiving 2500 mg/kg/day, generally from Week 4 of treatment.

A few Control rats have developed areas of hairloss, which is not unusual in this species. However, hairloss has also been noted for a number of rats receiving 2500 mg/kg/day at an incidence notably in excess of that of Controls in Weeks 6 to 7 of treatment.

BODYWEIGHTS (Data sent previously)

A dosage-related reduction in weight gain was noted to Week 6 for both sexes receiving 1750 or 2500 mg/kg/day and in females receiving 1000 mg/kg/day, achieving levels of statistical significance at the higher dosage levels. These intergroup differences have been in place since Week 1 of treatment. Weight change of other treated groups is considered essentially comparable to that of Controls.

Group mean bodyweight change to Week 6 was as follows:

	Group/dosage (mg/kg/day)									
Weeks	1m	2m	3m	4m	5m	1f	2f	3f	4f	5f
	Control	250	1000	1750	2500	Control	250	1000	1750	2500
0-6	170	164	162	141**	86**	76	80	71	66*	48**
sd	24.0	39.2	26.2	19.9	23.6	11.3	11.3	11.3	6.5	13.0
% Control	-	96	95	83	51		105	93	87	63

* $p<0.05$; ** $p<0.01$

FOOD CONSUMPTION (Data sent previously)

Group mean food consumption by males receiving 1750 or 2500 mg/kg/day was notably reduced in Week 1 and slightly reduced in Week 2. Since Week 3, food consumption by these groups has been essentially comparable to that of Controls.

Females receiving 2500 mg/kg/day showed a marginally lower consumption during Week 1 only.

Group mean cumulative food consumption to Week 6 is shown overleaf:

	Group/dosage (mg/kg/day)									
Weeks	1m	2m	3m	4m	5m	1f	2f	3f	4f	5f
	Control	250	1000	1750	2500	Control	250	1000	1750	2500
1-6	1117	1101	1164	1059	1057	896	879	916	873	883
sd	59.6	89.0	3.9	0.0	57.0	43.2	53.3	28.3	14.5	39.7
% Control	-	99	104	95	95	-	98	102	97	99
$p>0.05$										

EFFICIENCY OF FOOD UTILISATION (Data sent previously)

The efficiency of food utilisation (assessed by calculation of the food conversion ratios (FCR's)) has been notably below that of Controls for both sexes receiving 2500 mg/kg/day. A slight reduction in the efficiency of food utilisation has also noted in females receiving 1000 or 1750 mg/kg/day, mainly reflecting intergroup differences in bodyweight performance.

Group mean FCR's to Week 6 were as follows:

	Group/dosage (mg/kg/day)									
Weeks	1m	2m	3m	4m	5m	1f	2f	3f	4f	5f
	Control	250	1000	1750	2500	Control	250	1000	1750	2500
1-6	6.6	6.7	7.2	7.5	12.3	11.8	11.0	12.9	13.3	18.5

ACHIEVED INTAKES OF BENZOFLEX 2-45 (Data sent previously)

Overall achieved intakes to Week 6 have been in acceptable agreement with the nominal dosage levels.

	Group/dosage (mg/kg/day)									
Weeks	1m	2m	3m	4m	5m	1f	2f	3f	4f	5f
	Control	250	1000	1750	2500	Control	250	1000	1750	2500
1-6	-	241	951	1669	2431	-	260	1025	1788	2565

HUNTINGDON LIFE SCIENCES

SYNOPSIS No.1

7 July 1997

We apologise for two minor typographical errors in the Achieved Intake and Dietary Concentration tables in our previous facsimile of 4 July. Achieved intake for Group 4m, Week 5 should have read 1827 mg/kg/day, dietary inclusion level should have read 25200 ppm.

WATER CONSUMPTION

Will first be assessed in Week 12.

OPHTHALMOSCOPY

Only predose data is available. The next scheduled investigations will be carried out in Week 13.

LABORATORY INVESTIGATIONS

Will first be performed in Week 13.

Signed:.....
Study Director

.....
Study Supervisor

Date: 7 July, 1997

APPENDIX 1

Clinical signs - incidence summary

Incidence of Hunched posture
(No. of animals affected)

Group	Dosage (mg/kg/day)	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	R1	R2	R3	R4
1 m	Control																	
2 m	250																	
3 m	1000																	
4 m	1750																	
5 m	2500				1	1												
1 f	Control																	
2 f	250																	
3 f	1000																	
4 f	1750																	
5 f	2500				2	2	2	2										

Incidence of body tremors
(No. of animals affected)

Group	Dosage (mg/kg/day)	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	R1	R2	R3	R4
1 m	Control																	
2 m	250																	
3 m	1000																	
4 m	1750																	
5 m	2500			5	5	6	7	5										
1 f	Control																	
2 f	250																	
3 f	1000																	
4 f	1750																	
5 f	2500			3	4	4	4	5										

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Clinical signs - incidence summary

Incidence of yellow stained urogenital region
(No. of animals affected)

Group	Dosage (mg/kg/day)	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	R1	R2	R3	R4
1 m	Control																	
2 m	250																	
3 m	1000																	
4 m	1750																	
5 m	2500				1	2	4	3										
1 f	Control																	
2 f	250																	
3 f	1000																	
4 f	1750																	
5 f	2500				2	2	5	5										

Incidence of brown stained fur
(No. of animals affected)

Group	Dosage (mg/kg/day)	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	R1	R2	R3	R4
1 m	Control																	
2 m	250																	
3 m	1000																	
4 m	1750																	
5 m	2500				1	1	3	3										
1 f	Control																	
2 f	250																	
3 f	1000																	
4 f	1750																	
5 f	2500			2	2	2	4	4										

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Incidence of hairloss
(No. of animals affected)

Group	Dosage (mg/kg/day)	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	R1	R2	R3	R4
1 m	Control	1	1	2	2	2	2	2										
2 m	250																	
3 m	1000																	
4 m	1750																	
5 m	2500			1	1	3	7	9										
1 f	Control		1	1	1	1	1	1										
2 f	250																	
3 f	1000																	
4 f	1750	2	2	2	2	1												
5 f	2500			1	3	3	4	5										