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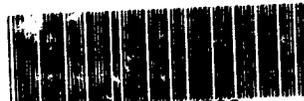
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December 7, 1992

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8EHQ-92-8589  
INIT 12/08/92

Attention: Section 8(e) Coordinator

Dear Sir:

Enclosed you will find a draft report of a rat teratology study with Santovar A Antioxidant - 2,5-di(tert-amyl) hydroquinone (CAS No. 79-74-3).

Santovar A was administered in a corn oil vehicle to pregnant rats at dosage levels of 0, 20, 70, 175 mg/kg/day on gestation days 6-15. Clinical signs of maternal toxicity reported in this draft study data, including post-dosing salivation, were observed at 70 and 175 mg/kg/day. Indications of fetal toxicity that were reported concurrent with the maternal toxicity at 175 mg/kg/day included statistically significant body weight loss and litters with ossification variations. The ossification variation finding was judged to be of questionable biological significance inasmuch as the concurrent control ossification variation data was unusually low when compared with the historical control range for this laboratory (reported to be as high as 82% for this finding). The no observable effect level (NOEL) for maternal effects was judged to be 20 mg/kg/day, and the NOEL for fetal effects was judged to be 70 mg/kg/day.

Although these findings are not considered to be indicative of substantial risk, we are providing the preliminary results in order to satisfy any reporting obligations that the Agency may consider necessary.

Sincerely,

Ronald D. Hogue, Ph.D.  
Manager, Product Safety

Enclosure



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### SUMMARY

This study was performed to detect and evaluate the potential embryotoxic or teratogenic effects of Santovar A when administered orally to pregnant rats during the period of major organogenesis. The study design consisted of a vehicle control and three treatment groups. Each group contained twenty-five mated female Sprague-Dawley rats. The test article was mixed with corn oil and administered at levels of 20.0, 70.0 and 175.0 mg/kg/day from gestation day 6 through gestation day 15. All doses were given at a constant volume of 5 ml/kg. Control animals were administered corn oil under the same experimental conditions and at an equivalent dose volume. The animals were observed daily for clinical signs of toxicity. Body weights and food consumption were measured on gestation days 0, 6, 9, 12, 16 and 20. All females were sacrificed on gestation day 20 and subjected to cesarean section. Fetuses were individually weighed, sexed and examined for external, visceral and skeletal abnormalities.

Oral administration of Santovar A produced slight maternal toxicity at the 70.0 mg/kg/day level and substantial maternal toxicity at the 175.0 mg/kg/day level. The toxicity was characterized by an increase in the incidence of reddish colored vaginal discharge and post-dose salivation at the 70.0 mg/kg/day level and more frequent and severe clinical signs, body weight loss and reduced food consumption at the 175.0 mg/kg/day level. No adverse clinical signs were observed in the 20.0 mg/kg/day group. Similarly, no treatment-related differences in mean body weights, body weight gain or food consumption were observed at the 20.0 or 70.0 mg/kg/day levels. Mean fetal body weight was slightly, but statistically reduced at the 175.0 mg/kg/day level when compared to the control group. All other cesarean section parameters were comparable among the groups. No apparent treatment-related malformations or developmental variations were observed at the 20.0 or 70.0 mg/kg/day levels. A slight, nonstatistical increase in the incidence of skull anomalies and 7th cervical ribs was observed in the 175.0 mg/kg/day group and the number of litters with sternbrae #5 and/or #6 unossified was statistically increased at this level when compared to the control group. The number of litters in the control group with unossified sternbrae in this study is unusually low when compared to SLS historical control data. Therefore, it is not clear if the increase in the number of litters with sternbrae #5 and/or #6 unossified at the 175.0 mg/kg/day level in this study was spontaneous or associated with the reduced fetal body weights observed at this level.

Based on the results of this study, a dosage level of 20.0 mg/kg/day was considered a no-observed-effect level (NOEL) for maternal toxicity and a dosage level of 70.0 mg/kg/day was considered a NOEL for developmental toxicity. Santovar A at a dosage level of 175.0 mg/kg/day produced substantial maternal toxicity with minimal developmental toxicity.

SLS STUDY NO.: 3044 230  
 CLIENT: MONSANTO  
 CLIENT NO.: SB-91-433

TABLE 10  
 TERATOLOGY STUDY IN RATS WITH SANTOVAR A  
 SUMMARY OF FETAL OBSERVATIONS - VARIATIONS  
 (ABSOLUTE)

LEVEL (MG/KG/DAY):	P E T U S E S				L I T T E R S			
	1	2	3	4	1	2	3	4
	0.0	20.0	70.0	175.0	0.0	20.0	70.0	175.0
NUMBER EXAMINED EXTERNALLY NUMBER WITH FINDINGS	347 0	396 0	362 0	365 0	23 0	24 0	24 0	25 0
NUMBER EXAMINED VISCERALLY DISTENDED UTER(S)	173 4	197 3	180 2	180 4	23 3	24 3	24 2	23 3
NUMBER EXAMINED SKELETALLY	174	199	182	185	23	24	24	23
STERNURA(E) MALIGNED(SLIGHT OR MODERATE)	51	53	45	54	21	22	20	22
14TH RUDIMENTARY RIB(S)	39	36	43	44	14	15	16	16
27 PRESACRAL VERTERRAE	4	2	3	2	3	2	2	2
STERNURA(E) #5 AND/OR #6 UNOSSIFIED	1	9	7	19	1	4	4	8*
14TH FULL RIB(S)	0	1	0	2	0	1	0	2
7TH CERVICAL RIB(S)	1	2	2	9	1	2	1	5
REDUCED OSSIFICATION OF THE 13TH RIB(S)	0	1	2	1	0	1	1	1
REDUCED OSSIFICATION OF THE SKULL	3	1	1	4	3	1	1	3
BENT RIB(S)	1	0	1	0	1	0	1	0
HYOID UNOSSIFIED	2	3	3	4	1	2	3	3
COSTAL CARTILAGE POSITION VARIATION	0	0	1	3	0	0	1	2
ACCESSORY SKULL BONE(S)	0	1	0	0	0	1	0	0

SIGNIFICANTLY DIFFERENT FROM CONTROL: \* = P<0.05

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TABLE 8  
 TERATOLOGY STUDY IN RATS WITH SANTOVAR A  
 SUMMARY OF CESAREAN SECTION DATA

SEX M / F	GROUP : LEVEL :			
	1 0.0 MG/KG/DAY	2 20.0 MG/KG/DAY	3 70.0 MG/KG/DAY	4 175.0 MG/KG/DAY
TOTAL	180 167	193 203	173 189	179 186
MEAN	7.8 7.3	8.0 8.5	7.2 7.9	7.8 8.1
S.D.	2.9 2.4	1.7 2.2	2.5 2.9	2.0 2.5
GRAVID UTERUS WEIGHT (G)	MEAN 88.5	95.2	91.0	89.3
	S.D. 14.6	9.7	22.2	12.5
FETAL WEIGHT (G)	MEAN 3.9	3.8	4.0	3.6**
	S.D. 0.2	0.3	0.3	0.4

SIGNIFICANTLY DIFFERENT FROM CONTROL: \*\* = P<0.01

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