

EXXON CHEMICAL AMERICAS

8EHQ-1296-13844 (A)



8EHQ-96-13844



Safety and Environmental Affairs  
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MANAGER, SAFETY PROGRAMS

December 19, 1996

Document Processing Center (7407)  
Attn: TSCA Section 8(e) Coordinator  
Office of Pollution Prevention and Toxics  
U. S. Environmental Protection Agency  
401 M Street, S. W.  
Washington, D. C. 20460-0001



8897000094

Notification of Substantial Risk  
Under TSCA Section 8(c)

Dear Sir or Madam:

Under the provisions of Section 8(e) of the Toxic Substances Control Act, Exxon Chemical Company is submitting the following preliminary information describing the developmental toxicity of a substance described as 1,2-benzenedicarboxylic acid, di-C<sub>6-8</sub>-branched alkyl esters, C<sub>7</sub> rich (CAS Registry Number 71888-89-6). This substance is currently being manufactured for commercial purposes as defined by TSCA.

While the information presented is considered preliminary, we feel that the toxicity observed thus far warrants reporting under the substantial risk reporting requirements of TSCA §8(e).

The data presented in this submission is from a dose range-finding developmental toxicity study in rats. This study was conducted for the purpose of selecting appropriate dose levels for a definitive developmental toxicity study. Because the study was a dose range-finding study, observations should be considered preliminary until results from the full developmental toxicity study are available. The preliminary results are summarized below and documented in the attachment.

Preliminary Developmental Toxicity Results

The test substance was administered by oral gavage to 7 inseminated female rats/group on gestation days 6-20, at dose levels of 0, 250, 500, 750 and 1000 mg/kg/day. Findings at the 750 and 1000 mg/kg/day levels included a decrease in the number of live fetuses, a concomitant increase in early resorptions, and a slight to moderate decrease in mean fetal body weight. Fetal external malformations were observed in 4 of 20 fetuses from three litters in the 750 mg/kg/day group, and in 3 of 17 fetuses from two litters in the 1000 mg/kg/day groups. Similar observations have been reported in rodent developmental toxicity studies on related chemicals, however this specific chemical has not previously been tested for developmental toxicity potential.

The definitive developmental toxicity study will be underway soon. A copy of the final report from this study will be forwarded to you as soon as it is issued. If you have any questions or need additional information please feel free to contact me on (281) 870-6874.

CSKAD/OPPT  
3/26/97  
mb

Sincerely yours,

Steven G. Hentges

SGH/jad  
Attachment

H:\INFO\WWDATA\SGH\1996\SGH029.DOC

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## Summary Information For A Range-Finding Developmental Toxicity Study in Rats

### Background

A dose range-finding developmental toxicity study was conducted with 1,2-benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7 rich (CAS # 71888-89-6) for the purpose of selecting dose levels for a subsequent definitive study in rats. Because the in-life phase of the range-finding study was just recently completed, a QA'd report is not yet available. It should be emphasized that because this study was a *dose range-finding study*, observations should be considered preliminary -- a more definitive assessment will require completion of a full developmental toxicity study with a larger number of mated females and more indepth fetal evaluations.

The test substance was diluted with corn oil and administered by oral gavage to 7 inseminated female rats/group, on gestation days 6-20, at dose levels of 0, 250, 500, 750, and 1000 mg/kg/day. Control animals received corn oil only. All females were sacrificed on gestation day 21 and subjected to Cesarean section. Uteri were removed, weighed, and examined for the number of live fetuses, dead fetuses, and resorptions. Fetuses were sexed, weighed, and examined for external malformations.

### Results

Data tables summarizing maternal and fetal data from the range-finding study are attached. There were no significant clinical observations and all females survived for the duration of the study. Mean maternal body weight and body weight gain were decreased at the 750 and 1000 mg/kg levels during gestation. In addition, mean maternal food consumption appeared to be slightly lower than controls at the 750 and 1000 mg/kg/day levels. However, corrected maternal body weight at termination (i.e., day 21 body weight minus gravid uterus weight) was similar among the groups. A decrease in the number of live fetuses, a concomitant increase in early resorptions, and a slight to moderate decrease in mean fetal body weight were noted at the 750 and 1000 mg/kg/day levels. Fetal external malformations were observed in a total of four fetuses from three litters in the 750 mg/kg/day group, and in three fetuses from two litters in the 1000 mg/kg/day group. Malformations at the 750 mg/kg/day level included one male with encephalocele; one male with cleft palate, filamentous tail, and anal atresia; one female with generalized edema; and one female with exencephaly, cleft palate, and protruding tongue. Malformations at the 1000 mg/kg/day level included one male with anal atresia and no tail; one female with exencephaly and protruding tongue; and one fetus of undetermined sex with cleft palate. No fetal malformations were observed at levels of 500 mg/kg/day and lower.

## Previous Findings

Findings similar to those described above have been previously reported in rodent developmental toxicity studies with phthalate esters in the C4-C7 range, including butylbenzyl phthalate (Ema *et al.*, 1991,1992), di-n-butyl phthalate (Ema *et al.*, 1995), di-n-heptyl phthalate (Nakashima *et al.*, 1977), and di-(2-ethylhexyl) phthalate (Tyl *et al.*, 1988). The types of findings in these studies included increased post-implantation loss, decreased fetal body weight, and increased occurrences of various fatal malformations. These findings were noted both in the presence and absence of overt maternal toxicity.

Phthalate esters by the oral route are readily hydrolyzed to the corresponding phthalate monoester and corresponding aliphatic phthalate alcohol. Prevailing data suggest that the monoester may be the bioactive metabolite of certain phthalate esters.

The definitive teratogenic evaluation of butyl benzyl phthalate (BBP) by Ema *et al* (1992) was similar in design to the present dose range-finding study. Pregnant rats were administered BBP by oral gavage at doses of 0, 500, 750 and 1000 mg/kg/day on days 7-15 of gestation. High maternal lethality and complete resorption were observed at the 1000 mg/kg/day level. Increased embryo-fetal death and decreased fetal weight were detected at the 750 mg/kg/day level. These effects occurred in the presence of maternal toxicity, as demonstrated by reduced maternal body weight gain and food consumption. A significantly increased incidence of fetal malformations was also observed at the 750 mg/kg/day BBP level. Malformations included cleft palate, fusion of sternebrae, and dilatation of the renal pelvis.

Developmental toxicity studies with di-(2-ethylhexyl) phthalate (DEHP) were conducted via the diet in both rats and mice by the NTP (Tyl *et al.*, 1988). Dietary dose level were 0, 0.5, 1.0, 1.5 and 2% for rats, and 0, 0.025, 0.05, 0.10, and 0.15% for mice. In rats, DEHP did not produce any evidence of malformations, although fetal body weight was reduced at dietary levels of 1% and above in conjunction with maternal toxicity. In mice, increased resorption rate, increased fetal death, and decreased fetal body weight were observed in the presence of maternal toxicity at 0.1% and above. There was also an increase in the rate of specific malformations at levels of 0.05% and higher.

The developmental toxicity of di-n-heptyl-phthalate (DHP) was investigated in mice following single oral doses on day 7, 8, 9, 10 or 11 of gestation (Nakashima *et al.*, 1977). Only limited information is available on this study since it was published as an abstract. The authors reported a high degree of embryo-fetal toxicity and increased occurrence of fetal malformations at doses of

2.5 and 7.5 ml/kg. Fetal external malformations included exencephaly, open eye lid, cleft palate, and tail anomalies.

In contrast to the above findings, rat developmental toxicity studies with C9 and C10 phthalate esters (di-isononyl and di-isodecyl phthalate) have shown no effects on post-implantation loss, fetal body weights, or the occurrence of malformations at doses up to and including 1000 mg/kg/day.

### References

- Ema, M., Itami, T. and Kawasaki, H. (1991) Evaluation of embryoletality of butyl benzyl phthalate by conventional and pair-feeding studies in rats. *J Appl. Toxicol.*, 11:39-42.
- Ema, M., Itami, T. and Kawasaki, H. (1992) Teratogenic evaluation of butyl benzyl phthalate in rats by gastric intubation. *Toxicol. Lett.*, 61:1-7.
- Ema, M., Kurosaka, R., Amano, H. and Ogawa, Y. (1995) Developmental toxicity evaluation of mono-n-butyl phthalate in rats. *Toxicol. Lett.*, 78:101-106.
- Nakashima, K., Kishi, K., Nishikiori, M., Yamamoto, N., and Fujiki, Y. (1977) Teratogenicity of di-n-heptyl phthalate in mice. *Teratology*, 16:117.
- Tyl, R.W., Price, C.J., Marr, M.C. and Kimmel, C.A. (1988) Developmental toxicity evaluation of dietary Di-(2-ethylhexyl)phthalate in Fischer 344 rats and CD-1 mice. *Fund. Appl. Toxicol.*, 10:395-412.

DEVELOPMENTAL TOXICITY RANGE-FINDING STUDY IN RATS  
 WITH MRD-96-676: 167633

TABLE 1 -- INCIDENCE OF GESTATION OBSERVATIONS

GESTATION DAY:	TOTAL (A)																						
	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2
0 MG/KG	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
250 MG/KG	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
500 MG/KG	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
750 MG/KG	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
1000 MG/KG	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
NO OBSERVABLE ABNORMALITIES																							
0 MG/KG	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
250 MG/KG	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
500 MG/KG	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
750 MG/KG	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
1000 MG/KG	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
RED MATERIAL VAGINA																							
0 MG/KG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
250 MG/KG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
500 MG/KG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
750 MG/KG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1000 MG/KG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

NOTE: (A) -- NONPREGNANT ANIMALS EXCLUDED

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DEVELOPMENTAL TOXICITY RANGE-FINDING STUDY IN RATS  
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TABLE 2 - MEAN GESTATION BODY WEIGHT AND BODY WEIGHT CHANGE (CONT'D)

	D		D		D		D		D		D		D	
	Y	A	Y	A	Y	A	Y	A	Y	A	Y	A	Y	A
FEMALE	6	9	1	2	1	5	1	8	2	2	1	2	1	2
0 MG/KG	12.6	18.6	23.0	42.6	41.1	24.7	96.7	204.0	92.9	204.0	96.7	204.0	92.9	204.0
MEAN	4.2	8.3	6.4	10.2	9.0	7.8	11.9	14.7	18.9	14.7	11.9	14.7	18.9	14.7
STD. DEV.	(N)													
250 MG/KG	12.6	20.0	25.0	47.7	44.1	21.6	105.3	213.7	97.7	213.7	105.3	213.7	97.7	213.7
MEAN	2.6	5.7	3.6	7.0	7.4	3.6	4.8	12.2	11.8	12.2	4.8	12.2	11.8	12.2
STD. DEV.	(N)													
500 MG/KG	10.8	24.0	28.5	45.7	45.0	22.2	109.0	221.3	105.5	221.3	109.0	221.3	105.5	221.3
MEAN	5.3	4.3	5.5	5.2	6.4	5.5	12.9	17.1	11.2	17.1	12.9	17.1	11.2	17.1
STD. DEV.	(N)													
750 MG/KG	9.7	20.3	19.8	33.3	29.3	19.7	83.2	169.3	93.2	169.3	83.2	169.3	93.2	169.3
MEAN	8.7	1.6	9.2	9.7	9.9	5.5	12.9	24.2	22.2	24.2	12.9	24.2	22.2	24.2
STD. DEV.	(N)													
1000 MG/KG	6.0	14.3	19.7	24.0	21.0	12.1	64.0	138.9	85.1	138.9	64.0	138.9	85.1	138.9
MEAN	12.6	5.1	7.0	10.2	21.9	7.5	19.3	46.8	18.9	46.8	19.3	46.8	18.9	46.8
STD. DEV.	(N)													

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TABLE 3 - MEAN GESTATION FOOD CONSUMPTION  
 (GRAMS)

	D		A		D		A		D		A		D		A	
	Y	6	9	1	2	5	8	1	1	1	1	1	1	1	1	1
FEMALE	162.5	76.8	78.0	80.7	88.1	88.3	233.3	570.7	158.0	72.4	77.7	78.1	90.4	89.6	228.3	566.3
0 MG/KG	18.6	10.2	7.5	7.9	8.2	4.8	22.9	49.9	10.4	8.5	5.0	5.4	4.6	5.6	17.4	31.8
MEAN																
STD.DEV.																
(N)																
250 MG/KG	164.7	76.3	80.3	84.0	92.5	92.5	240.7	590.3	154.2	70.8	72.3	74.7	82.5	87.7	217.8	542.2
MEAN	12.2	9.1	8.0	9.8	9.5	7.4	26.0	52.2	13.0	7.9	6.8	8.5	6.1	2.9	21.1	38.7
STD.DEV.																
(N)																
500 MG/KG	160.4	69.3	71.0	77.7	90.1	84.4	218.0	553.0	12.6	8.3	10.8	8.9	17.6	17.1	25.6	55.7
MEAN																
STD.DEV.																
(N)																

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TABLE 4 - INCIDENCE OF GROSS POSTMORTEM OBSERVATIONS

FEMALES

	0 MG/KG	250 MG/KG	500 MG/KG	750 MG/KG	1000 MG/KG
TOTAL AT TERMINAL SACRIFICE	7	7	7	7	7
NO OBSERVABLE ABNORMALITIES	7	7	7	6	6
KIDNEY: Dilated renal pelvis	0	0	0	1	0
STOMACH/GASTROINTESTINAL TRACT/PANCREAS/SPLEEN: Situs inversus	0	0	0	0	1
ANIMAL NOT PREGNANT (No evidence of uterine implantation sites)	0	0	1	1	0

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TABLE 5 - MEAN UTERINE IMPLANTATION DATA

	TOT LIVE	M ALE FET	F E M A L E F E T	R E S O R P T	I M P L A N T S	C O R P L U T	T O T A L	F E T / I M P	R E S / I M P	D E A D / I M P
FEMALE										
0 MG/KG	14.86	6.57	8.29	1.71	16.57	17.29	0	0.90	0.10	0
MEAN	2.67	3.21	1.80	2.06	2.30	1.80	0	0.13	0.13	0
STD.DEV.										
(N)	7	7	7	7	7	7	7	7	7	7
250 MG/KG	16.00	7.43	8.57	0.86	16.86	19.71	0	0.95	0.05	0
MEAN	1.00	2.88	3.10	0.90	0.90	4.64	0	0.05	0.05	0
STD.DEV.										
(N)	7	7	7	7	7	7	7	7	7	7
500 MG/KG	15.83	6.50	9.33	1.33	17.17	20.00	0	0.93	0.07	0
MEAN	1.17	2.88	3.50	1.37	2.32	2.53	0	0.07	0.07	0
STD.DEV.										
(N)	6	6	6	6	6	6	6	6	6	6
750 MG/KG	10.83	3.33	7.50	5.00	15.83	16.67	0	0.69	0.32	0
MEAN	3.87	2.34	3.62	3.74	1.33	1.63	0	0.23	0.23	0
STD.DEV.										
(N)	6	6	6	6	6	6	6	6	6	6
1000 MG/KG	7.43	2.43	4.86	9.86	17.29	17.71	0	0.43	0.57	0
MEAN	5.44	2.23	4.14	5.43	1.11	3.09	0	0.32	0.32	0
STD.DEV.										
(N)	7	7	7	7	7	7	7	7	7	7

NOTE: TOT - TOTAL  
FEM - FEMALE  
FET - FETUSES  
RESORP OF RES - RESORPTIONS  
IMPLANTS OF IMP - IMPLANTATION SITES  
CORP. LUT - CORPORA LUTEA

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TABLE 5 - MEAN UTERINE IMPLANTATION DATA (CONT'D)

	PREI		POSTI		MALAR		VAR		AFF	
	MEAN	STD. DEV.	MEAN	STD. DEV.	MEAN	STD. DEV.	MEAN	STD. DEV.	MEAN	STD. DEV.
0 MG/KG	4.3	10.3	0	0	0	0	0	0	0	0
MEAN	6.6	13.3	0	0	0	0	0	0	0	0
STD. DEV.	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)
250 MG/KG	11.3	5.0	0	0	0	0	0	0	0	0
MEAN	15.9	5.3	0	0	0	0	0	0	0	0
STD. DEV.	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)
500 MG/KG	13.4	7.0	0	0	0	0	0	0	0	0
MEAN	13.6	7.0	0	0	0	0	0	0	0	0
STD. DEV.	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)
750 MG/KG	4.9	31.6	0.67	0.2	0.2	0.4	0.6	0.6	0.6	0.6
MEAN	2.4	23.3	0.82	0.4	0.4	0.6	0.6	0.6	0.6	0.6
STD. DEV.	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)
1000 MG/KG	0.8	57.0	0.43	0.1	0.1	0.4	0.7	0.7	0.7	0.7
MEAN	12.4	32.4	0.79	0.4	0.4	0.7	0.7	0.7	0.7	0.7
STD. DEV.	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)	(N)

NOTE: PREI - PRE IMPLANTATION LOSS = (CORPORA LUTEA - IMPLANTATION SITES)/CORPORA LUTEA X 100  
 POSTI - POST IMPLANTATION LOSS = (IMPLANTATION SITES - TOTAL LIVE)/IMPLANTATION SITES X 100  
 TOT - TOTAL  
 MALAR - FETUSES WITH MALFORMATIONS  
 VAR - FETUSES WITH VARIATIONS  
 AFF - AFFECTED = (RESORPTIONS + DEAD + MALFORMED) FETUSES

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TABLE 6 -- MEAN FETAL BODY WEIGHT  
 (GRAMS)

	MALE	FEMALE
0 MG/KG		
MEAN	5.52	5.43
STD. DEV.	0.47	0.50
(N)	46	58
250 MG/KG		
MEAN	5.37	5.13
STD. DEV.	0.35	0.34
(N)	52	60
500 MG/KG		
MEAN	5.47	5.25
STD. DEV.	0.49	0.60
(N)	39	56
750 MG/KG		
MEAN	4.54	4.58
STD. DEV.	0.45	0.55
(N)	20	45
1000 MG/KG		
MEAN	4.73	4.58
STD. DEV.	0.50	0.68
(N)	17	34

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TABLE 7 - INCIDENCE OF FETAL EXTERNAL OBSERVATIONS

	0 MG/KG	250 MG/KG	500 MG/KG	750 MG/KG	1000 MG/KG
MALES					
TOTAL AT CESAREAN SECTION	46	52	39	20	17
NO OBSERVABLE ABNORMALITIES	46	52	39	18	15
STUNTED (a)	0	0	0	2	2
HEMATOMA (HEAD)	0	0	0	0	1
DEVELOPMENTAL MALFORMATIONS: ENCEPHALOCELE	0	0	0	1	0
CLEFT PALATE	0	0	0	1	0
FILAMENTOUS TAIL	0	0	0	1	0
ATRESIA ANI	0	0	0	1	1
CAUDIA	0	0	0	0	1
FEMALES					
TOTAL AT CESAREAN SECTION	58	60	56	45	34
NO OBSERVABLE ABNORMALITIES	58	60	56	43	31
STUNTED (a)	0	1	0	6	7
HEMATOMA (HEAD)	0	0	0	0	2
DEVELOPMENTAL MALFORMATIONS: EXENCEPHALY	0	0	0	1	1
CLEFT PALATE	0	0	0	1	0
ANASARCA	0	0	0	1	0
DEVELOPMENTAL VARIATIONS: PROTRUDING TONGUE	0	0	0	1	1
SEX NOT RECORDED					
TOTAL AT CESAREAN SECTION	0	0	0	0	1
DEVELOPMENTAL MALFORMATIONS: CLEFT PALATE	0	0	0	0	1

NOTE: (a) - INCLUDED IN NO OBSERVABLE ABNORMALITIES TOTALS.