International Research and Development Corporation

SPONSOR:	Velsicol Chemical Corporation
COMPOUND:	Tetrabromobisphenol A (FM BP-4A)
SUBJECT:	Pilot Teratology Study in Rats.

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I. SYNOPSIS

A pilot study with mated Charles River CD female rats was performed to determine dosage levels for a teratology study. Tetrabromobisphenol A was administered by gavage at dosage levels of 30, 100, 300, 1,000, 3,000 and 10,000 mg/kg/day from gestation day 6 through day 15. A control group received the vehicle, corn oil, at 10 ml/kg/day.

During gestation the females were observed for clinical signs of effect, mortality and body weight changes. The rats were sacrificed on gestation day 20 by carbon dioxide inhalation, and the uterine contents examined for viable and nonviable fetuses, early and late resorptions, and total implantations.

There were no changes in appearance, behavior, or body weights which were attributed to Tetrabromobisphenol A, for those females receiving 3,000 mg/kg/day or less. There were no differences in the mean number of viable or nonviable fetuses, resorptions, implantions, or corpora lutea when compared to the controls which were attributable to treatment at 10,000 mg/kg/day or less. There were slight decreases in body weight gains between gestation days 6 and 15 in the 10,000 mg/kg/day dose group which may be attributed to treatment.

Three of the five rats in the 10,000 mg/kg/day dosage group died. All rats at this dosage level showed signs of toxicity.

A dosage level of 10,000 mg/kg/day is considered too high for meaningful evaluation of the potential teratogenicity of the test material.

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II. COMPOUND

The compound was received from Velsicol Chemical Corporation, Chicago, Illinois on October 28, 1977 as indicated below:

Label	Description		
Tetrabromobisphenol A Lot 1021-85	white powder (Also referred to as BP-4A on packing slip)		

III. METHODS AND PROCEDURES

A. ANIMALS:

Thirty-five female Charles River CD rats (The Charles River Breeding Laboratories, Inc., Portage, Michigan) were used in this pilot teratology study. These rats were approximately 15 weeks old at the time of mating and had been acclimated in this laboratory for a minimum of 5 weeks prior to mating. All rats were individually housed, except during mating, in wire mesh cages and maintained in a temperature, humidity and light controlled room. Purina[®] Laboratory Chow[®] and tap water were available ad libitum.

Mating was initiated on December 1, 1977 and the last sacrifice was on January 6, 1978.

B. MATING:

Male rats of the same strain were used for mating. One female and one male were placed together for mating. The day of mating was determined by daily inspection for the copulatory plug or by vaginal smear for sperm. The day when a plug or sperm was found, was designated day 0 of gestation and the female was returned to its individual cage.

C. ORGANIZATION OF TEST GROUPS AND TREATMENT:

The bred females were consecutively assigned to 6 groups in a block design containing one control and 5 treatment groups of 5 rats each. Due to lack of toxicity at these dosage levels, one additional treatment group of 5 rats was later assigned.

Tetrabromobisphenol A was administered orally by gavage at the dosage levels indicated below:

Dosage Level	Volume Administered
mg/kg/day	ml/kg/day
Control	10
30	10
100	10
300	10
1,000	10
3,000	10
10,000	20

The compound was suspended in Mazola[®] corn oil, with the use of a tissue homogenizer. Compound administration was from day 6 through day 15 of gestation and the control rats received the vehicle on a comparable regimen. Individual dosages were based on body weights on gestation days 6, 12 and 15.

D. MATERNAL OBSERVATIONS:

The females were observed daily for changes in appearance and behavior, and for mortality. Individual female body weights were recorded on days 0, 6, 12, 15 and 20 of gestation.

E. UTERINE OBSERVATIONS:

All females were sacrificed by an overdose of carbon dioxide on the 20th day of gestation and the abdominal and thoracic cavities were examined. The numbers of viable and nonviable fetuses, early and late resorptions, total implantations and corpora lutea were recorded.

IV. RESULTS

A. <u>MATERNAL OBSERVATIONS</u>:

There were no changes in appearance, behavior, or body weight gains which were related to the compound, in those females receiving 3,000 mg/kg/day or less. Survival was 100% for all rats receiving 3,000 mg/kg/day or less. Three rats in the 10,000 mg/kg/day dosage group died. Rats in the 10,000 mg/kg/day dosage group had green, soft stool and an increase in matted hair in the anogenital area when compared to the controls.

There was a slight decrease in weight gains between gestation days 6 and 15 for the rats in the 10,000 mg/kg/day dosage group, upon inspection of individual body weights and group mean body weights (Table 1).

B. UTERINE OBSERVATIONS:

The cesarean section data are presented in Table 2. One rat in the 300 mg/kg/day group delivered 17 viable pups after 9 days of treatment. This is attributed to an inaccurate determination of copulation. There are no compound related differences for the mean number of viable or nonviable fetuses, resorptions, implantations or corpora lutea for dosage levels of 10,000 mg/kg/day or less. An increase in post implantation losses was seen in the 1,000 mg/kg/day group; however, this was due to only one rat and not considered to be treatment related. Tetrabromobisphenol A:

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TABLE 1.	Individual Body Weights, grams.						
Dosage Level,	Day of Gestation						
Dam Number	0	6	12	15	20		
Control:							
73716	207	243	257	265	217		
73717	294	325	347	202	517		
73745	246	282	284	300	420		
73795	241	273	304	344	392		
77311	253	308	31 2	330	202		
Mean	248	286	301	319	408		
30 mg/kg/day:		200	201	519	204		
73603	207	207					
79767	287	327	323	356	430		
73707	227	259	284	282	348		
73799	216	256	275	273	328		
73820	233	280	280	293	365		
//315	242	287	286	329	390		
Mean	241	282	290	307	372		
100 mg/kg/day:							
73803	217	254	271	267	33%		
73832	225	268	297	306	224		
73854	226	260	286	202	200		
73862	292	336	321	234	330		
77316	226	265	268	300	420		
Masz	220	200	200	300	355		
	237	277	289	305	365		
<u>300 mg/kg/day</u> :							
73834	276	319	360	Delivered			
73856	287	320	328	352	422		
73858	243	275	320	309	360		
77301	235	290	306	329	402		
77328	247	301	245	295	334		
Mean	253	297	300	321	380		
1,000 mg/kg/day:							
73787	229	264	2 2 /				
73957	226	264	284	310	376		
74034	280	323	331	345	420		
77306	341	369	399	394	496		
77330	230	271	283	311	372		
Neer	243	291	310	332	368		
Mean	266	304	321	338	406		
3,000 mg/kg/day:							
73682	262	280	289	315	380		
73788	296	324	337	348	430		
73812	239	272	285	305	368		
77307	246	303	314	352	412		
77352	245	294	309	350	412		
Mean	258	295	307	334	400		
10,000 mg/kg/dav:				224	400		
77/1/b	220	2/0		D			
77421	220	248	Died, Gestat	tion Day II			
77/310	225	258	255	268	342		
774460	220	254	224	Died, Gestat	ion Day 15		
77447	221	250	230	209 Died, Ge	station Day 17		
// ••• /	245	305	313	318	400		
Mean	235	282	284	293	371		

a delivered, not used in calculation of means. died, not used in calculation of means.

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TABLE 2.		Cesar	ean Section Data	for Individual	Females.		
Dosage Level, Dam Number	Viable Fetuses	Nonviable Fetuses	Late Resorptions	Early Resorptions	Post Implantations Loss	Implan- tations	Corpora Lutea
Control:							
73716 73717 73745 73795 77311	10 16 16 16 15			1 0 1 0 2	1 0 1 0 2	11 16 17 16	11 16 18 17
Total	73	0	0	4	4	77	80
Mean	14.6	0.0	0.0	0.8	0.8	15.4	16.0
30 mg/kg/day:							1010
73693 73767 73799 73820 77315	15 11 10 15 14		0 0 0 0	1 0 2 0 0	1 0 2 0 0	16 11 12 15 14	18 11 12 15 14
Total	65	0	0	3	3	68	70
Mean	13.0	0.0	0.0	0.6	0.6	13.6	14.0
<u>100 mg/kg/day</u> : 73803 73832 73854 73862 77316	12 15 13 16 13	0 0 0 0	0 1 0 0	1 0 0 0		13 16 13 16	13 17 13 17
Total	69	0	1	1	2	71	73
Mean	13.8	0.0	0.2	0.2	0.4	14.2	14 6
300 mg/kg/day: 73834 ^a 73856 73858 77301 77328 Total	15 13 13 14 55					15 13 13 14 55	15 14 13 15 57
1 000 mg/hg/dawn	12.0	0.0	0.0	0.0	0.0	13.8	14.3
73787 73857 74036 77306 77330 Total	13 15 18 15 4 65		1 0 0 0 0 1	0 1 0 7 8	1 0 0 7 9	14 16 18 15 11 74	14 16 20 15 12 77
Mean	13.0	0.0	0.2	1.6	1.8	14.8	15.4
3,000 mg/kg/day: 73682 73788 73812 77307 77352	14 16 11 13 14	0 0 0 0		0 0 4 0	0 0 4 0	14 16 11 17 14	14 17 11 17 15
Total	68	0	0	4	4	72	74
Mean	13.6	0.0	0.0	0.8	0.8	14.4	14.8
10,000 mg/kg/day: 77414 77421 77431 77446 77447	Died gest 12 Died gest Died gest 13	ation day 11 - 0 ation day 15 - ation day 17 - 0	Gravid O Gravid Gravid O	0	0	12	12
Total	25	0	0	0	0	13	13
Mean	12.5	0.0	0.0	0.0	0.0	12.5	20 12.5

^adelivered, sacrificed not used in calculation of means.