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March 17, 1997

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ATTN: FYI Coordinator

Re Bis-2-Propylheptyl Phthalate (CASRN 53306-54-0)

Dear Sir or Madam:

Union Carbide Corporation ("Union Carbide") has recently received preliminary data from a rat subchronic feeding study being conducted at The Central Toxicology Laboratory (Macclesfield, Cheshire, U.K.). Union Carbide and Kvaerner Process Technology are co-sponsors of this study.

The results are presented below. Their implications with respect to human health or the environment is very uncertain, as are indeed the biological reliability and relevance of the measurements. The information is herewith submitted for the Agency's information.

In this study, groups of rats have received feed containing bis-2-propylheptyl phthalate (CASRN 53306-54-0) at concentrations of 0, 500, 5000 or 12000 ppm over a 14 week period. Animals were sacrificed immediately after dosing was discontinued. Two additional groups which had received the feed containing 0 or 12000 ppm throughout the study period, were held for 4-weeks without further treatment and then sacrificed.

Significant decreases in body weight gain were noted in animals receiving 12000 ppm in feed. By the end of the dosing period, a 23% and 19% decrease in body weight was seen for males and females respectively when compared to the control group. This difference in weight gain was partially resolved by the end of the 4 week recovery period. Body weights in males receiving 5000 ppm in feed were slightly depressed (6% compared to controls). The decreased

weight gain was accompanied by a decrease in food consumption and hematological changes in the 12000 ppm group. The hematological changes appeared to be associated with decreased hemoglobin. Increased liver weights with concurrent increases in peroxisome enzyme levels were noted in all treatment groups. These latter changes were anticipated based on structure activity relationships with other phthalate esters (DEHP, etc.)

In addition to the observations described above, there appeared to be effects on certain selected sperm measurements from the male rats. These effects were related solely to velocity measurements (Table 1). At the end of the 4 week recovery period similar effects were not observed in any of the velocity indices. Other indices of sperm viability were unaffected by treatment including; total sperm, static count, percent motile, motile count, total sperm concentration and sperm/g tissue (Table 2). There were no effects at any of the dose levels on the stages development in epididymal sperm.

The meaning of the findings on sperm analysis is unclear. The effect of nutritional deficits, as evidenced by decreased body weight gain, on indices of sperm motility are not well studied. This is particularly important with respect to measurements made on epididymal sperm which require fructose as a sole energy source. The limited number of animals on which measurements were conducted coupled with the magnitude of variation, both with and between observation periods, complicate the evaluation of the statistical analysis. Finally, the pattern of response is not typical of that expected from materials causing effects on sperm development. The effects appear to be rapidly resolved after dosing is discontinued and as animals resume a more normal growth pattern. This could indicate the importance of the nutritional state of the animal on motility indices. Therefore, the relevance of these data to hazard evaluation is not clear at this time.

A copy of the final study will be submitted to the Agency promptly after it issues, upon request.

Very truly yours,



William C. Kuryla, Ph.D.
Associate Director
Product Safety
(203/794-5230)

Attachments

Table 1: Bis-2-Propylheptyl Phthalate - 90-Day Dietary Feeding Study in Rats
Sperm Velocity Measurements

	Main Study				Recovery		
	Dietary Concentrations of Bis-2-Propylheptyl Phthalate (ppm)						
	0 (Control)	500	5000	12000	0 (Control)	12000	
Velocity (VSL)	Mean	61.1	57.6	54.4	46.0**	44.1	37.9
	S.D.	8.3	8.9	10.9	11.1	17.8	18.5
	N	6	6	6	6	9	9
Velocity (VCL)	Mean	231	234	215	202.3*	197.6	187.3
	S.D.	17.7	17.1	25.7	26.6	39.1	38.7
	N	6	6	6	6	9	9
Velocity (VAP)	Mean	101.9	97.5	91.8*	85.7**	83.7	78.8
	S.D.	9.9	6.9	8.9	10.8	16.4	17.3
	N	6	6	6	6	9	9
Sperm Motility (%)	Mean	84	81	81	80	68	71
	SD	3.2	5.5	3.8	7.5	19	11
	N	6	6	6	6	6	6

* P<.05

** P<.01

**Table 2: Bis-2-Propylheptyl Phthalate - 90-Day Dietary Feeding Study in Rats
Other Sperm Measurements**

		Dietary Concentrations of Bis-2-Propylheptyl Phthalate			
		0 (Control)	500	5000	12000
Total Sperm	Mean	439.0	335.8	376.5	461.2
	S.D.	163.9	97.7	106.0	150.9
	N	6	6	6	6
Static Count	Mean	67.0	62.5	72.0	93.7
	S.D.	18.5	16.3	23.7	64.4
	N	6	6	6	6
Motile Count	Mean	372.0	273.3	304.5	367.5
	S.D.	148.3	91.8	88.9	116.3
	N	6	6	6	6
Total Concentration	Mean	35.5	28.2	32.5	40.1
	S.D.	14.0	8.0	9.0	12.8
	N	6	6	6	6
Sperm/g Tissue	Mean	161.0	132.2	156.7	197.4
	S.D.	69.7	37.2	43.9	71.5
	N	6	6	6	6



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FYI - 0198 - 1292

UNION CARBIDE CORPORATION 39 OLD RIDGEBURY ROAD, DANBURY CT 06817-0001



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January 15, 1998

TSCA Document Processing Center (7407)
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U.S. Environmental Protection Agency
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Washington, DC 20460

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ATTN: TSCA 8(e) FYI Coordinator

**RE: Union Carbide Corporation's TSCA 8(e) FYI Submission of
March 17, 1997 Concerning Bis-2-Propylheptyl Phthalate
(CASRN 53306-54-0) [FYI-0597-001292]**



85980000007

Dear Sir or Madam:

As a follow-up to the above-referenced submission, Union Carbide recently received a copy of a draft report concerning a 90-day rat feeding study with bis-2-propylheptyl phthalate (CASRN 53306-54-0).

Previously we had submitted to the EPA preliminary results from this study regarding treatment related effects on sperm motility measurements. Review of the draft report indicates that additional information may be reportable to the agency in particular information of histopathology finding on the adrenal glands and liver, and certain hematologic findings in rats treated with this material.

In this study groups of 12 rats of each sex (Alpk:APfSD strain) received bis-2-propylheptyl phthalate in feed at concentrations of 0, 500, 5000 or 12000 ppm. These concentrations provided dosages of approximately 40, 420 and 1000 mg/kg body weight respectively. The rats were kept on this regimen for 90 days at which time they were killed, and organs and tissues collected and processed for histological examination. In addition, blood was obtained and standard hematological and clinical chemistry analyses were performed.

Histological examination of the adrenal glands revealed a characteristic lesion in the adrenals described as vacuolation of the *zona glomerulosa*. The lesion was evident in both sexes and at all treatment levels. The severity of the lesion was a clearly dose related predominantly described as minimal in the 500 ppm, slight in the 5000 ppm and moderate in the 12000 ppm concentration groups, respectively. Clinical chemistry finding in both sexes of the 12000 ppm concentration group included decreased plasma sodium

concentrations and increased plasma potassium concentrations likely associated with the adrenal lesions. Similar changes were not seen in the 500 or 5000 ppm concentration groups suggesting that the adrenal lesions at these dose administration levels were not functionally significant.

Histopathological lesions were also seen in the livers of both sexes in the 12000 and 5000 ppm concentration groups consistent with peroxisome proliferation, a known and anticipated effect of phthalate esters. The peroxisome proliferation hypothesis was further supported by finding of increased cyanide insensitive palmitoyl CoA activity, an enzyme specifically associated with this effect and decreases in plasma cholesterol and triglycerides, changes also associated with peroxisome proliferation.

In addition to the histology findings, effects were seen in hematology evaluations in both sexes of the 12000 ppm and in males of the 5000 ppm concentration groups. These findings included a reduction in red blood cell count, hemoglobin and hematocrit with, in some instances, associated changes in red blood cellular indices and an increase in platelet count.

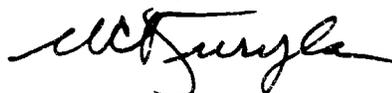
It is significant that the adrenal *zona glomerulosa* is associated with the synthesis of a number of steroid hormones including aldosterone, a hormone involved in the regulation of sodium balance. Steroid hormones are metabolized by mixed function oxidases, enzymes implicated in proliferation of peroxisomes. It is possible that the effects in the *zona glomerulosa* of the adrenals are also linked to the peroxisome proliferating potential of this phthalate.

A copy of the final report will be sent to the Agency promptly after it issues.

Finally, we are not clear if these results qualify for submission under TSCA 8(e), and would appreciate the Agency's guidance in this regard.

Please contact the undersigned with questions, if any, at 203/794-5230.

Very truly yours,



William C. Kuryla, Ph.D.
Associate Director
Product Safety