

SUBJECT: PROTOCOL FOR A STUDY OF THE EFFECTS OF MATERNALLY
INHALED VINYL CHLORIDE ON RAT AND RABBIT EMBRYONAL
AND FETAL DEVELOPMENT. FIRST SUPPLEMENT: SECOND
STAGE STUDIES

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DATE: September 18, 1974 (original was dated December, 1973):

FILE NUMBER: NB T3.4-16-10

K-NUMBER: K-1711

PROBLEM NUMBER: 998-0060100

*any questions
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COPY: Preliminary _____

Final X

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SUPPLEMENTAL PROTOCOL (1), VINYL CHLORIDE TERATOLOGY STUDIES

INTRODUCTION

This supplemental protocol describes the second part of a multi-stage teratology study on vinyl chloride. In the first stage, pregnant mice, rats and rabbits were exposed to 500 ppm vinyl chloride 7 hours daily throughout organogenesis (see NB T3.4-16-10 issued on Dec. 11, 1973). A summary of the results of this first stage is included in this protocol. The examination of the skeletons of some of the mice and rabbits remains to be completed, but enough of the study has been completed to design the second stage of this experiment. As noted in the summary, maternal toxicity was not observed in either rats or rabbits. Deaths were observed among the mice, however. No teratogenic effects were observed in any species, based on the external and soft tissue examinations. One group of mice exposed to vinyl chloride was allowed 15% ethanol as their source of liquids. This experimental group was included to determine whether or not simultaneous ingestion of ethanol would enhance the teratogenic potential of vinyl chloride. This treatment combination did result in an increase in the maternal toxicity as well as an increase in the incidence of cleft palate, a teratogenic response.

EXPERIMENTAL PROCEDURES

Based on the above observations, it is recommended that in the second stage of this experiment an additional group of mice be exposed to vinyl chloride at a concentration of 50 ppm 7 hr/day on days 6-15 of gestation. Half of the group of mice will receive 15% ethanol while the others will receive tap water and no ethanol. The purpose of this study is to determine if the teratogenic potential of vinyl chloride at 50 ppm is also enhanced by simultaneous ingestion of ethanol. In addition to this study in mice, additional groups of rats and rabbits will be exposed to 2500 ppm vinyl chloride on the same treatment schedule as in the first experiment. In each species, half of the group will receive ethanol in the drinking water and the remaining half will receive no ethanol. In addition to these groups of rats and rabbits receiving 2500 ppm vinyl chloride with or without ethanol, an additional group of rats and rabbits will be given 15% ethanol alone. These groups will serve as controls for the vinyl chloride-exposed animals that also receive ethanol.

The methods of exposure of the animals and examination of the fetuses for evidence of a teratogenic effect will be the

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same as those described in the original protocol. A summary of the completed studies and the proposed second stage is indicated below. The estimated cost of this second stage of experiments is \$17,900.

TERATOLOGY STUDIES

STAGE 1

	<u>Vinyl Chloride</u>	<u>Ethanol</u>	
mice	500 ppm	0	} done
mice	500 ppm	15%	
mice	0	15%	
rats	500 ppm	0	
rabbits	500 ppm	0	
mice, rats, rabbits	0	0	

STAGE 2

rats	2500 ppm	0	
rats	2500 ppm	15%	
rats	0	15%	
rabbits	2500 ppm <i>0428</i>	0	✓
rabbits	2500 ppm <i>0428</i>	15%	?
rabbits	0	15% (done)	✓
mice	50 ppm	15%	
mice	50 ppm	0	

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SUMMARY - VINYL CHLORIDE TERATOLOGY STUDIES

	Rats	Rabbits	Mice	
Vinyl chloride, 500 ppm, 7 hr/day	yes	yes	yes	yes
Ethanol - 15% in drinking water	no	no	no	yes
Gestation days of treatment	6-15	6-18	6-15	6-15
No. maternal deaths/No. treated	0/33	0/19	6/30 (20%)	4/30 (13%)
% Pregnancy	94 (control = 96)	95 (control = 100%)	72 (control = 88)	31 (control = 88)
No. litters examined	31	18	19	5
Maternal weight gain	-- ^a	--	sl. dec.	dec.
Maternal food consumption	--	dec.	--	dec.
Maternal liver weight - absolute	--	--	sl. dec.	dec.
- relative	--	--	--	dec..
Implantation sites/dam	--	sl. dec.	--	dec.
% Resorptions	--	--	sl. inc.	--
Litters totally resorbed	0/31	1/19	0/19	2/7
Litter size	--	sl. dec.	sl. dec.	dec.
Fetal body weight	dec.	--	sl. dec.	dec.
Fetal crown-rump length	inc.	--	--	dec.
External malformations	--	--	--	--
Visceral malformations	--	--	--	inc. ^b
Skeletal malformations	NC	NC	NC	NC

^a-- = no change, dec. = decrease, inc. = increase, sl. = slight, NC = exam not completed

^bcleft palate

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VINYL CHLORIDE - ESTIMATED COSTS OF STAGE 2

<u>Hours</u>	<u>Salaried</u>	<u>Hourly</u>
Fetal exam (60 rats + 36 rabbits + 40 mice @ 2 hr)	272	50
Exposure	150	150
Data Evaluation	30	
Report	30	
	482	200
	X \$24	X \$14
	\$11568	\$2800
	SUBTOTAL	\$14368

Animals

40 rabbits @ \$15.00	600
50 mice @ \$0.50	25
75 rats @ \$7.00	525

Chambers

2 chambers, 2 weeks each	305
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Space

½ room for 1 mo.	262
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Cage Wash

\$18/rack X 9 racks	162
	\$16247
+ 10%	1625
TOTAL	\$17872

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439 }
611 }
71 }
1-615 }
139 }
503 }

8

603 }
1-560 }
1-625 }
464 }
164 }
68 }
1-799 }
502 }

1011

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139

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