

April 14, 1976

TO: Vinyl Chloride Technical Panel

SUBJECT: Protocol for Birth Defect Study by Center for Disease Control and Other Items

Gentlemen:

Enclosed are the following:

1. Subject protocol entitled "Proposed Study of Increased Rates of Central Nervous System Defects in Kanawha Co. West Virginia" and cover letter of March 25 from Dr. Flynt. In compliance with his request, names of participating hospitals have been blocked out.

In a telecon with Dr. Flynt on March 25, I learned the field work was nearly complete and a report was targeted for about one month from then. Their study includes fifty cases (interviews) and a like number of controls. Key aspects of the program are to try to locate residence at conception and occupational history of both parents.

2. Summary of article "Pharmacodynamics and Uptake of Vinyl Chloride Monomer Administered by Various Routes to Rats" by J. R. Withey in Journal of Toxicology and Environmental Health, 1:381-394, 1976.

3. First page, containing summary, of V. J. Feron et al. article "Observations on the Oral Administration and Toxicity of Vinyl Chloride in Rats", in Food and Cosmetic Toxicology, Volume 13, pages 633-638.

4. "Morbidity and Mortality" article of February 28, 1976 citing arsenic and thorium dioxide in addition to vinyl chloride as suspect causative agents of angiosarcoma of the liver in Wisconsin cases.

5. Letter of April 1, 1976 from Mr. G. L. McCowin, Assistant to the Director, Division of Food and Color Additives of FDA indicating that so far they have been unable to detect

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any migration of vinyl chloride at a sensitivity of 1 ppb, from polyvinyl chloride articles.

6. Citations of vinyl chloride research (pages 130, 147; Appendix II, pages V, VI) from Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity, No. 6, March 1976, by the International Agency for Research on Cancer.

7. Dr. Torkelson's letter of April 5 to Dr. Warren R. Muir, without attachments, regarding the Tabershaw-Cooper Associates epidemiology study.

Information

1. The last paragraph of my March 17 letter to the Panel reported on a transplacental study on vinyl chloride at Midwest Research Institute, (MRI). I have since learned this particular study was with vinylidene chloride (VDC), not vinyl chloride. MRI is working with both monomers.

2. NIOSH has published a Recommended Standard for Occupational Exposure to Vinyl Chloride, PB-246-691/OGA. Copies are available at \$3.50 each from:

Office of Technical Publications
National Institute for Occupational
Safety and Health
Post Office Building
Cincinnati, Ohio 45202
(513/684-2723)

Please include a self-addressed mailing label to assist in answering your request.

Sincerely,


Milton Freifeld
Project Manager
Vinyl Chloride Research

MF:ec

Enclosure

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

March 25, 1976

Mr. Milton Freifeld
Manufacturer's Chemist Association
1825 Connecticut Avenue
Washington, D. C. 20009

Dear Mr. Freifeld:

Enclosed is a copy of the protocol for the study presently underway in Charleston, West Virginia. I have made a few marginal notes where changes were made. The main change was the decision from the outset to interview cases and controls (regardless of exposures among the case group). We had at one time considered searching occupational records at the plant for names of cases and controls, but discarded the idea in favor of the interviews.

If you have questions about this, do not hesitate to contact me. I would like to emphasize our desire to maintain the confidentiality of hospitals that participate in the BDMP. This includes, according to our agreement with the Commission on Professional and Hospital Activities, no mention of the number of hospitals in a community which participate in BDMP. We would appreciate your cooperation in this respect. Also note that the data contained in this protocol are preliminary and were compiled only as background for planning of the study. Final data will be part of the finished report.

Sincerely yours,

J. William Flynt, Jr., M.D.
Chief, Birth Defects Branch
Bureau of Epidemiology

Enclosure

cc: Dr. John Finklea
Mr. Larry Edmonds

JWF:crs

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Proposed Study of Increased Rates of Central Nervous
System Defects in Kanawha Co. West Virginia

Introduction

A recent report noted higher rates of CNS defects in Painesville, Ohio, a city with a vinyl chloride polymerization (VCP) plant. This report suggested a causal association between the PVC plant and the higher CNS rate. We conducted a follow-up investigation, including interviews of parents of cases, and found no current or past occupational exposures to vinyl chloride among parents of cases. Comparison of cases with controls suggested no differences in distances of family residence from the vinyl chloride plant. The latter finding has been questioned because cases and controls were based on hospital births rather than resident births in the community.

The continuing concern about a causal association prompted a review of all 36 counties with VCP plants to determine those with BDMP hospitals. A similar determination had been done previously selecting for analysis those communities with a VCP plant and most likely served by a single hospital also in the BDMP (and having a VCP plant). Painesville, Ohio, and Pottstown, Pennsylvania, were identified in this manner. Pottstown had no excess of malformations while Painesville was noticed to have a twofold increase in CNS defects. On the second review, a total of 17 counties with VCP plants also have at least 1 BDMP hospital. Four of the 17 counties have a significantly higher number of CNS defects than expected, based on a total U.S. rate 1970-73. In two counties BDMP monitors less than 50 percent of the total reported births (Table 1). The 2 remaining counties are Lake Co., Ohio (Painesville),

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the site of previous investigation, and Kanawha County (Charleston), West Virginia. There are 4 hospitals in Kanawha County reporting 4,476 births in 1973 (Table 2). The 2 largest hospitals are enrolled in the BDMP; 1 is located in Charleston and the other in South Charleston, the site of the VCP plant. The current BDMP data show for Kanawha County a significantly higher number of CNS defects than expected (59 observed vs. 37 expected). The expected number of cases are based on the total U.S. rates for 1970-74 (Table 3).

In light of continuing concern regarding the possible teratogenicity of VC monomer; the Kanawha County setting was selected for a second investigation concerning the possible association of increased rates of CNS defects with parental occupation or residential exposure to the S. Charleston VCP plant.

Additional background data on Kanawha County vital statistics are provided in the appendix.

Objectives

The objective of this study will be to further investigate the possible relationship of parental exposure to vinyl chloride and the increased incidence of central nervous system defects. The case-control study method will be used to compare the frequency of maternal and paternal occupational exposure to VCP. Similarly, residential exposure will be examined by comparing distances of parental residences at birth from the VCP plant in South Charleston.

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Methods

A. Case Ascertainment

All cases of Central Nervous System (ICDA NO. 740.0-743.9) defects that occurred among resident live births and fetal deaths in Kanawha County between January 1, 1970 and December 31, 1974 will be identified. Two sources of case identifications will be employed:

1. Birth and fetal death certificates will be reviewed in the West Virginia Department of Vital Statistics.
2. Records at all Kanawha County hospitals will be reviewed. This will include cases reported through the Birth Defects Monitoring Program. A consolidated list of unduplicated cases will be compiled and diagnosis verified according to hospital records. Non-residential and unverified cases will be retained for further comparative analysis, but not matched with controls.

B. Selection of Controls

Controls will be selected from Kanawha County resident birth certificates after all cases have been identified. Two controls will be selected for each case of CNS defects. The controls selected will be the next matched normal live birth preceding and following. The cases and controls will be matched for maternal age (15-19, 20-24, etc.), paternal education (0-8, 9-12, 13 over), and race. A maximum of twenty-five birth certificates will be reviewed preceding and following the case to find the two matching controls. If a preceding (following) age-education-race matched control is not found, then the first preceding (following) birth matched on race

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and either education or age will be chosen, education being the first choice. If there is still no-match, then the first preceding (following) birth matched only on race will be selected.

Data Collection

A. Birth Certificates and Fetal Death Certificates

The information to be collected on case and controls from the birth certificates is contained on page 1 of the work sheet.

B. Hospital Record

The information to be collected on cases from hospital charts is listed on page 2 of the work sheet. Hospital records will be reviewed for controls only in cases where birth certificates information is incomplete.

C. Interview

Parents of cases will be interviewed in standard fashion regarding prior residences and occupations. The information to be obtained is listed on Worksheets 3-5.

Parents of controls will not be interviewed unless 1 or more parents of cases are found to be employed in the vinyl chloride plant or a significantly greater proportion of the parents of cases live near the vinyl chloride plant. In the event that 1 or more parents of cases works at vinyl chloride plant, only 1 control will be interviewed for each matching case. The control chosen for interview will be the closest match.

*Parents of controls
will not be interviewed
unless 1 or more parents
of cases are found to be
employed in the vinyl
chloride plant or a
significantly greater
proportion of the
parents of cases live
near the vinyl
chloride plant.*

*Parents of cases
will be interviewed
regarding prior
residences and
occupations.*

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Data Analysis

An analysis of matched tri^{ple}s will be made using the method of Mantel and Haenszel.

The possible relationship between parents' occupational exposure and CNS defects in their children will be analyzed 3 ways by dichotomizing cases and controls on employment of mother, father, and either parent in a vinyl chloride plant. Only current employment will be used for controls unless significance is attained. Then past employment data will be obtained from the controls in the same manner as for cases and the resulting data re-analyzed.

The effect of distance of residence from the vinyl chloride plant will be analyzed by dichotomizing on distance in increments of 1 mile in the range 1-10 miles.

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Table I

Counties with Significant Increases in CNS Defects 1970-73
and Reported Births in 1973

	# CNS Defects in BDMP		# Births In BDMP	#Births In AHA*	% Monitored in BDMP
	obs.	exp.			
Oklahoma Co., Oklahoma	68	44.9	4,096 [REDACTED]	8,718 (9 hospitals)	47.0
New Castle Co. Delaware	9	4	366 [REDACTED]	5,634 (3 hospitals)	6.5
Lake Co. Ohio	31	18	1,821 [REDACTED]	1,851 (2 hospitals)	98.4
Kanawha Co. West Virginia	53	31	4,245 [REDACTED]	4,476 (4 hospitals)	94.8

*American Hospital Association Guide to the health care field (1974 edition)

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Table II

Reported Hospital Births in Kanawha County, W. Virginia from AHA Guide

Charleston	3488
"	148
"	93
South Charleston	757
Total birth Kanawha County	4476

*BDMP Hospital

95% of reported hospital births are monitored by BDMP

Vital Statistics Data from West Virginia Vital Statistics Reports
1974 for Kanawha County

Total Births	3348
Hospital Births	3341
White Births (male)	1616
(female)	1471
Non-white Births (male)	126
(female)	135

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Table III
Total Central Nervous System Defects - 1970-1974

	OBS.	EXP.*	RATE+
	43	29.2	31.3
	16	8.2	41.3
Kanawha County	59	37.4	33.5
Total U.S.	7655		21.2

Relative risk = 1.58

Anencephalus-Spina Bifida - 1970-1974

	OBS.	EXP.	RATE
Charleston	27	17.6	19.6
S. Charleston	13	5.0	33.5
Kanawha County	40	22.6	22.7
Total U.S.	4604		12.8

Relative risk = 1.77

BDMP Births - 1970-1974

Charleston	13,754
S. Charleston	3,877
Kanawha County	17,631
Total U.S.	3,606,848

* Expected calculated on BDMP total white U.S. rate 1970-1974

+ Rates per 10,000 total births for whites

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APPENDIX

VITAL STATISTICS, KANAWHA COUNTY, WEST VIRGINIA

POPULATION

Census Population, Kanawha County

	<u>1970</u>	<u>1971</u>	<u>1972</u>	<u>1973</u>	<u>1974</u>
S. Charleston	16,330				
Charleston	71,505				
St. Albans	14,356				
County	229,515	230,400	230,300	226,800	223,700

BIRTH RATE

	<u>1970</u>	<u>1971</u>	<u>1972</u>	<u>1973</u>	<u>1974</u>
Kanawha County	16.3	16.5	15.0	14.4	15.0
West Virginia	17.3	17.8	16.7	15.4	15.4

BIRTHS, KANAWHA COUNTY

	<u>1970</u>	<u>1971</u>	<u>1972</u>	<u>1973</u>	<u>1974</u>
White Male	1724	1805	1658	1624	1616
White Female	1726	1694	1535	1436	1471
TOTAL	3450	3499	3193	3060	3087
Nonwhite Male	148	116	134	120	126
Nonwhite Female	137	162	107	147	135
TOTAL	285	278	241	267	261

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162.89

NUMBER OF BIRTHS					
<u>City</u>	<u>1970</u>	<u>1971</u>	<u>1972</u>	<u>1973</u>	<u>1974</u>
Charleston			1035	972	1031
S. Charleston			245	240	227
St. Albans			200	218	198

BIRTHS BY AGE OF MOTHER, KANAWHA COUNTY							
	<u>10-14</u>	<u>15-19</u>	<u>20-24</u>	<u>25-34</u>	<u>35-44</u>	<u>45</u>	<u>Unk</u>
1970	7	711	1504	1309	201	3	
1971	9	761	1553	1274	180		
1972	6	723	1360	1186	156	3	
1973	14	743	1247	1186	136	1	
1974	10	671	1290	1252	124	1	

RESIDENT DEATHS, KANAWHA COUNTY					
	<u>1970</u>	<u>1971</u>	<u>1972</u>	<u>1973</u>	<u>1974</u>
Fetal Deaths	59 (15.8)	60 (15.9)	53 (15.4)	37 (11.1)	28 (8.4)
Congenital Anomaly	25 (10.9)	25 (10.9)	20 (8.7)	15 (6.5)	11 (4.9)
Premature Births	12 (5.2)	3 (1.3)	8 (3.5)	9 (3.9)	7 (3.1)

FAMILIES WITH INCOME LESS THAN POVERTY LEVEL IN 1969 BY COUNTY		
	<u># Families</u>	<u>% Of All Families</u>
Kanawha County	8020	13.0
West Virginia	81697	18.0

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PHARMACODYNAMICS AND UPTAKE OF VINYL CHLORIDE MONOMER ADMINISTERED BY VARIOUS ROUTES TO RATS

Jim R. Withey

Toxicology Division, Bureau of Chemical Safety
(Foods), Health Protection Branch, Ottawa, Canada

Finding at least 2-3 ppm and occasionally as much as 10-20 ppm of vinyl chloride monomer in a wide range of foodstuffs has prompted concern for a possible human health hazard. The recognition of vinyl chloride as a carcinogen to humans in April 1974, following the discovery of angiosarcoma as the cause of death in at least 25 workers who had been engaged in the manufacture of polyvinyl chloride, enhanced this concern with respect to the presence of vinyl chloride monomer in foods.

To assess the hazard presented by the oral ingestion of vinyl chloride monomer, rats that had been surgically prepared with an indwelling jugular cannula were dosed by intragastric intubation with aqueous solutions containing up to 2.0 mg/ml vinyl chloride. Time-concentration curves were obtained from sequential samples of blood. The uptake of vinyl chloride by this route was found to be extremely rapid; peak concentrations were achieved less than 10 min after administration of the dose. Elimination from the blood compartment appeared to be biexponential.

Studies with the same animal model in a single restraint cage that allowed a "head only" exposure to concentrations of vinyl chloride up to 7,000 ppm in the gas phase have shown a similar rapid uptake followed by a plateau blood concentration during several hours of exposure. On removal from the vinyl chloride atmosphere, blood levels fell rapidly to barely detectable concentrations after 2 hr.

The precise kinetic coefficients that describe the distribution and elimination rates of vinyl chloride from the blood compartment were also determined from the blood concentration data after the administration of an intravenous dose of aqueous or vegetable oil solution.

INTRODUCTION

Prior to the discovery of a connection between the induction of angiosarcoma in humans and the exposure to vinyl chloride monomer (VCM) in January 1974 (Falk et al., 1974; Thomas et al., 1975), the U.S. Food and Drug Administration had already withdrawn their prior sanctioned use of

This paper was presented in part at the 14th Annual Meeting of The Society of Toxicology, Williamsburg, Virginia, March 9-13, 1975.

It is a pleasure to acknowledge the technical assistance of Mr. Peter Collins in this work. The interest, skill, and dedication of Mr. Henry James, who surgically prepared the animals used in this study, is also appreciated.

Requests for reprints should be sent to Jim R. Withey, Toxicology Division, Bureau of Chemical Safety (Foods), Health Protection Branch, Ottawa, Canada.

OBSERVATIONS ON THE ORAL ADMINISTRATION AND TOXICITY OF VINYL CHLORIDE IN RATS*

V. J. FIRON, A. J. SPIJK, MARIANNE I. WILLEMS,
D. VAN BATTUM and A. P. DE GROOT

Central Institute for Nutrition and Food Research (CIVO) TNO,
Utrechtseweg 48, Zeist, The Netherlands

(Received 1 April 1975)

R. E. Shapiro
2/26/76

1975

Abstract. Various possibilities were studied for administering vinyl chloride monomer (VCM) orally to rats. Upon storage, solutions of VCM in soya-bean oil appeared to be stable with respect to their VCM content and the fatty acid composition of the oil. In addition no oligomers of vinyl chloride or reaction products of VCM with components of the oil were detected. Stomach intubation of such solutions was considered an acceptable method of oral administration of VCM to rats in short-term toxicity studies. Within a period of 4 hr following intragastric intubation of VCM in soya-bean oil (300 mg VCM/kg body weight), over 92% of the VCM administered was recovered from the gases excreted (mainly exhaled) by the animals. Eructation did not appear to be involved in the excretion of VCM.

VCM dissolved in soya-bean oil was administered by gavage to male and female rats at levels of 0 (controls), 30, 100 and 300 mg/kg body weight, once daily on 6 days/wk for a period of 13 wk. Several haematological, biochemical and organ weight values differed to a statistically significant degree from those of the controls, but these differences were considered to have only minor, if any, toxicological significance. A slight increase in liver-to-body weight ratio occurred in males and females on the highest dose level. This increase was not accompanied by liver damage, as was evident from histological examination, enzyme histochemistry and electron microscopy. The no-effect level in this 90-day study was conservatively placed at 30 mg VCM/kg body weight, but was probably higher since the effects occurring at 100 and 300 mg/kg body weight were of doubtful toxicological significance.

Indications were obtained that the feeding of rats on diets containing polyvinyl chloride (PVC) powder with a high VCM content is a more practical method for the long-term oral exposure of rats to VCM than is stomach intubation of VCM in oil. VCM was almost completely released from PVC powder during passage through the digestive tract.

INTRODUCTION

Vinyl chloride monomer (VCM) is used in the manufacture of the resin, polyvinyl chloride (PVC). Industrial exposure to VCM has been associated with several disorders, including acro-osteolysis (Dinman, Cook, Whitehouse, Magnuson & Ditchcock, 1971; Harris & Adams, 1967; Lange, Jühe, Stein & Veltman, 1974; Markowitz, McDonald, Fethiere & Kerzner, 1972) and non-malignant liver diseases (Kramer & Mutchler, 1972; Marsteller, Lelbach, Müller, Jühe, Lange, Rohner & Veltman, 1973; Sacu, Drejman & Valaskat, 1967) and, only recently, also with angiosarcoma of the liver (Block, 1974; Creech & Johnson, 1974; Lee & Harry, 1974) and tumours of the brain and lungs (Monson, Peters & Johnson, 1974). Degenerative changes in the liver, kidneys, bone and brain were detected in rats and rabbits following exposure to VCM inhalation (Basalac, Vazin & Kochetkov, 1972; Jaeger, Reynolds, Conolly, Moslen, Szabo & Murphy, 1974; Torkelson, Oyen & Rowe, 1961; Viola, 1970). Moreover, VCM inhalation was found to induce tumours in both rats and mice (Mañóni & Lefemine, 1974; Viola, Bigotti & Caputo, 1971).

*This study was sponsored by a group of co-operating European industries, including Verband Kunststoff-zeugende Industrie e.V. (Federal Republic of Germany), Shell Nederland Chemie, Dutch State Mines, Akzo Zout Chemie Nederland B.V. and Dow Chemical Europe S.A.

Certain formulations of PVC are used widely as food-packaging materials. Residual VCM present in the extruded polymeric product was shown to be liable to migration into PVC-packed foods and drinks, especially distilled spirits (Randolph, 1973). Since no data on the oral toxicity of VCM appeared to be available, studies were initiated to examine the subacute toxic properties of this compound when administered orally to rats. Oral administration is greatly hampered by the fact that VCM is a gas at room temperature (b.p. $c.$ -13.8°C) and therefore preliminary experiments were carried out to find an acceptable way of administering the compound orally to rats.

Administration in the drinking-water was considered in this respect but was rejected because of the rather poor solubility of VCM in water (Hardie, 1964) and, more significantly, because of the difficulties to be expected in handling the solutions and in estimating the quantities of VCM actually ingested by the animals.

As VCM is lipophilic, we investigated the possibility of administering VCM as a solution in edible oil either by gastric intubation or by incorporation into the diet. Another possibility studied was the addition to the diet of a PVC powder containing an unusually high concentration of VCM.

The present report describes tentative experiments on the oral administration of VCM and presents some observations on the fate of VCM in rats. In addition, the results are given of a subacute toxicity

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

April 1, 1976

Mr. Albert C. Clark
Manufacturing Chemists Assn.
1825 Connecticut Avenue, N.W.
Washington, DC 20009

Dear Mr. Clark:

This is to acknowledge receipt of your letter of March 23, 1976, transmitting the final report entitled, "The Effects of Maternally Inhaled Vinyl Chloride on Embryonal and Fetal Development in Mice, Rats and Rabbits."

This information will be considered in our evaluation of the use of vinyl chloride polymers in contact with food. Accordingly, as you are aware, it may be necessary to place this report on public display at the Hearing Clerk when final regulations are published.

We have not been conducting any animal studies on the potential toxicity of FD&C Red No. 2. We have been analyzing various samples of PVC coatings, gasket material, plasticized film, and flexible tubing. To date, we have been unable to detect any migration of vinyl chloride from these types of articles at a level of sensitivity of 1 part per billion. We are looking forward to the receipt of further reports of the studies being sponsored by MCA.

Sincerely yours,

Gerard L. McCowin
Assistant to the Director
Division of Food and
Color Additives, HFF-334

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Name of substance (Synonyms)	Species (Strain)	Exposure	Stage of experiment	Principal investigators
5. <u>Furfural</u> (CAS Reg. No.: 98-01-1; 2-Furaldehyde; 2-Furancarboxal; α-Furole)	Hamster (Syrian Golden)	inhalation	histology in progress	Feron, V.J. & Kruysse, A.
6. <u>Iron oxide</u> (CAS Reg. No.: 1309-37-1; Ferric oxide; C.I. 77491; Ferric sesquioxide; Jeweler's rouge; Hematite)	Hamster (Syrian Golden)	i.tr. alone & in combination with Diethyl- nitrosamine (inhal. & i.tr.)	completed published ¹	Feron, V.J.
7. <u>γ-Irradiated chicken</u>	Rat (Wistar)	p.o. in the diet	completed to be published	Til, H.P.
8. <u>Methylbenzocyanate</u>	Rat (Wistar)	p.o. in the diet	in progress	Til, H.P.
9. <u>3-Methylthio-2-butanone-O- [(Methylamino)carbonyl]oxime</u>	Rat (Wistar)	p.o. in the diet	in progress	Til, H.P.
10. <u>N-Nitrosodiethylamine</u> (CAS Reg. No.: 55-18-5; Diethylnitrosamine; DEN; DENA)	Hamster (Syrian Golden)	i.t.	completed published ¹	Feron, V.J.
11. <u>Vinyl chloride</u> (CAS Reg. No.: 75-01-4; Chloroethene; Chloethylene; Chloroethene; Chloroethylene; Ethylene monochloride; VC; VCM)	Rat (Wistar)	p.o. in the diet & inhal.	in progress	Feron, V.J. Til, H.P. & Kruysse, A.
12. <u>Yeast (grown on gas-oil)</u>	Rat Mouse	p.o. -d i t t o-	completed -d i t t o-	Feron, V.J.
13. <u>Yeast (grown on pure n-paraffins)</u>	Rat (Wistar) Mouse	p.o. -d i t t o-	completed -d i t t o-	Feron, V.J.

¹ See Appendix I

URL 19658

Name of substance (Synonyms)	Species (Strain)	Exposure	Stage of experiment	Principal investigators
20. <u>Span 60</u> (CAS Reg. No.: 1338-41-6; Sorbitan monostearate)	Mouse (TFI)	p.o. in the diet	histopatho- logical exami- nation to be carried out	BIBRA staff
21. <u>Stearoyl lactic acid, sodium & calcium salt</u>	Rat		planned	
22. <u>Tartrazine</u> (CAS Reg. No.: 1934-21-0; C.I. Acid Yellow 23, trisodium salt; 5-Hydroxy-1-(p-sulpho- phenyl)-4-[(p-sulphophenyl)- azolpyrazole-3-carboxylic acid, trisodium salt; C.I. 19140; C.I. Food yellow 4; FD & C yellow 5; Tartar yellow N)	Mouse (CSI)	p.o. in the diet	completed to be published ¹	BIBRA staff
23. <u>γ-Undecalactone</u> (CAS Reg. No.: 104-67-6)	Mouse		discontinued	
24. <u>Vinyl chloride</u> (CAS Reg. No.: 75-01-4; Chlorethene; Chlorethylene; Chloroethene; Chloroethylene; Ethylene monochloride; VC; VCM)	Rat (Wistar)	p.o. in drinking water	in progress	BIBRA staff

¹ See Appendix I

URL 17208

Chemical	Principal Investigator	Name of Department/Laboratory & Address
19. <u>Testosterone & dihydrotestosterone</u>	Habib, F.K.	Division of Steroid Endocrinology, 26-28 Hyde Terrace, Leeds LS2 9LN, UK
20. <u>Titanium dioxide</u> (CAS Reg. No.: 13463-67-7; Titanium oxide; Ilmenite; Rutiox cr; Titania; Unitane)	Selikoff, I.J.	Environmental Sciences Laboratory, Mount Sinai School of Medicine, The City University of New York, 100th Street & 5th Avenue, New York, N.Y. 10029, USA
21. <u>Trichloroethylene</u> (CAS Reg. No.: 79-01-6; 1- Chloro-2,2-dichloroethylene; Ethynyl trichloride; Tri- chloroethene; Algylen; Germalgene; Trichloran; Tri- clene; Westrosol)	Axelson, O.	Department of Occupational Medicine, Regional Hospital, S-70185 Orebro, Sweden
22. <u>Vinyl chloride</u> (CAS Reg. No.: 75-01-4; Chlor- ethene; Chlorethylene; Chloro- ethene; Chloroethylene; Ethylene monochloride; VC; VCM)	Thiess, A.M.	Medical Department, Badische Anilin- und Sodafabrik, BASF-AG, Brunchstrasse, Ludwigshafen, Federal Republic of Germany
	Bartalini, E.	Medicina e Igiene del Lavoro, Montedison & Consociate, Via A. Appiani, 12, 201212 Milan, Italy
	Duncan, K.D.	Employment Medical Advisory Service, Health & Safety Executive, Baynard's House, Chepstow Place, London W2, UK
	Selikoff, I.J.	Environmental Sciences Laboratory, Mount Sinai School of Medicine, The City University of New York, 100th Street & 5th Avenue, New York, N.Y. 10029, USA

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Chemical	Principal Investigator	Name of Department/Laboratory & Address
22. <u>Cont'd</u>	Bertazzi, P.A.	Clinica del Lavoro "L.Devoto", Università degli Studi, via S. Barnaba 8, Milan, Italy
23. <u>Vinyl chloride polymers</u> (CAS Reg. No.: PM9002-86-2; Chloroethylene polymer; Poly- vinyl chloride; Blacar; Opalon; Vynon)	Bertazzi, P.A.	Clinica del Lavoro "L. Devoto", Università degli Studi, via S. Barnaba 8, Milan, Italy
	Ottevanger, C.F.	Department of Industrial Health, Shell Co., P.O. Box 7000, Rotterdam, The Netherlands
	Duncan, K.D.	Employment Medical Advisory Service, Health & Safety Executive, Baynard's House, Chepstow Place, London W2, UK
24. <u>Vinylidene chloride</u> (CAS Reg. No.: 75-35-4; 1,1- Dichloroethylene; asym- Dichloroethylene)	Pell, S.	Medical Division, E.I. du Pont de Nemours & Co., 11400 Nemours Building, Wilmington, Delaware 19898, USA

09961 780



THE DOW CHEMICAL COMPANY

BENNETT BUILDING
2030 DOW CENTER
MIDLAND, MICHIGAN 48640

April 5, 1976

Warren R. Muir, Ph.D.
Senior Staff Member for
Environmental Health
Executive Office of the President
Council on Environmental Quality
722 Jackson Place, N.W.
Washington, D.C. 20006

Dear Dr. Muir:

The attached correspondence is relative to reanalysis of the July 1974 Tabershaw-Cooper study conducted for the companies sponsoring research on vinyl chloride administered by the Manufacturing Chemists Association. We discussed this at the SOT meeting in Atlanta and you requested replacement copies for your files.

I personally feel that this study has been unjustly criticized.. Because of their great importance, the available data were pulled together for the New York Academy of Science meeting in May 1974. They were subsequently published in the Journal of Occupational Medicine to make them publicly available while the work was being extended and reanalyzed. Industry has been damned on one hand for withholding data and on the other for releasing it before it is completed. It is not possible to do both.

Industry has been accused of "diluting" the data by including workers with only one years exposure or more. Since the study was a study of all causes of death it was essential that the study include these workers. Without them, deaths due to non-cancerous causes could not have been studied.

As would be expected, table 9 of Dr. Gaffey's letter of July 12 illustrates the problem of most epidemiological studies; that is, the total number of workers is small. In this study the number is so small that when the total is split into a lot of cells, the number per cell is minute. It is expected that when the total study is completed this spring we may have enough older workers exposed long ago (15-25 years ago) to draw some conclusions.

This was among the first studies of this type conducted by such a large group of companies. It was admittedly incomplete when it was thought necessary to release the data. There was no intent to dilute the data



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or minimize the problem. In fact the authors concluded that "by these criteria, mortality from digestive cancer, respiratory cancer, cancer of other and unspecified sites and lymphomas, appear to be related to exposure as defined in the study" p 513, JOM, Aug 1974. (copy attached). The MCA panel has expressed concern for these other possible cancers and acknowledged the limitation of the data.

It is further of interest that the MCA has received little guidance from government in this study. Several persons and agencies have been asked to comment on the table that I included in my letter to you dated August 12, 1975. To my knowledge no one has done so.

Industry has attempted to maintain the open communications and scientific cooperation necessary for society to deal with these important problems. I suggest your office do all it can to encourage the government agencies and organization to be more understanding of the limitations under which we all work and to foster a better spirit of cooperation.

Sincerely yours,

T. R. Torkelson (cc)

T. R. Torkelson

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Attachment - Letter from T.R.Torkelson to W. R. Muir dated Aug 12, 1975
Letter from W. R. Muir to K. D. Johnson dated June 21, 1974
Letter from K. D. Johnson to W. R. Gaffey dated July 2, 1974
Letter from K. D. Johnson to W. R. Muir dated July 3, 1974
Letter from K. D. Johnson to Tech Task Group on VC Res Mgmt
dated July 22, 1974
Letter from W. R. Gaffey to W. R. Muir dated July 12, 1974

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