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

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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(VCM) in January 1974 (Falk et al., 1974; Thomas et al., 1975), the U.S. Food and Drug Administration had already withdrawn their prior sanctioned use of

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

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2/26/76

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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 & Ditcheck, 1971; Harris & Adams, 1967; Lange, Jühe, Stein & Veltman, 1974; Markowitz, McDonald, Fethiere & Kerzner, 1972) and non-malignant liver diseases (Kramer & Mutchler, 1972; Marsteller, Leibach, Müller, Jühe, Lange, Rohner & Veltman, 1973; Saeed, Drejman & Valaskar, 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 (Bastiaev, Vazin & Kochetkov, 1972; Lester, Reynolds, Conolly, Mosley, Szabo & Murphy, 1974; Torkelson, Oyen & Rowe, 1961; Viola, 1970). Moreover, VCM inhalation was found to induce tumours in both rats and mice (Maltoni & Lefemine, 1974; Viola, Bigotti & Caputo, 1971).

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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EPIDEMIOLOGIC NOTES AND REPORTS

ANGIOSARCOMA OF THE LIVER – Wisconsin

In the period June 1973-November 1975, 4 cases of angiosarcoma of the liver (ASL) were diagnosed at the Marshfield Clinic, Marshfield, Wisconsin. One was based on hepatic arteriography and 3 on tissue findings later confirmed by pathologic review at the National Cancer Institute (NCI).

An additional 6 cases, confirmed on pathologic review at NCI and identified through a national ASL case surveillance project initiated at CDC in 1974, have been diagnosed since 1964 in Wisconsin residents. This total of 10 cases is roughly twice as large as might be expected (5.5 cases), based on CDC surveillance estimates of crude ASL incidence for the entire United States. (Five additional cases had been reported for Wisconsin; 4 were not confirmed, and 1 was in a resident of another state.)

In view of this relative frequency of cases, together with the recent succession of cases at the Marshfield Clinic, epidemiologic information concerning each of these 10 cases

TABLE I. CASES OF SPECIFIED NOTIFIABLE DISEASES: UNITED STATES
(Cumulative totals include revised and delayed reports through previous weeks)

DISEASE	WEEK ENDING		MEDIAN	CUMULATIVE, FIRST 8 WEEKS		
	February 28 1976	February 22 1975	1971-1975	February 28 1976	February 22 1975	MEDIAN 1971-1975
Aseptic meningitis	28	35	33	307	292	292
Brucellosis	7	2	2	38	21	15
Chickenpox	5,764	4,311	---	39,288	29,693	---
Diphtheria	4	14	6	62	64	23
Encephalitis, Primary	13	17	15	129	96	120
Encephalitis, Post-Infectious	4	7	5	32	33	33
Hepatitis, Viral, Type B	242	210	172	1,935	1,568	1,314
Hepatitis, Viral, Type A	726	707	890	5,409	5,428	7,619
Hepatitis, Viral, Type unspecified	133	150		1,365	1,123	
Malaria	3	6	6	43	42	42
Measles (rubeola)	805	578	622	4,318	2,668	4,767
Meningococcal infections, total	53	41	41	284	270	270
Civilian	53	41	40	281	263	263
Military	–	–	1	3	7	9
Mumps	1,366	1,425	1,892	9,366	11,136	14,246
Pertussis	22	24	---	194	201	---
Rubella (German measles)	449	285	645	1,870	1,837	3,534
Tetanus	2	–	–	6	9	8
Tuberculosis	570	505	---	4,572	4,105	---
Tularemia	1	1	1	21	8	13
Typhoid fever	3	2	4	58	29	37
Typhus, tick-borne (Rky. Mt. spotted fever)	–	–	–	3	10	9
Venereal Diseases:						
Gonorrhea, Civilian	18,313	17,273	---	151,748	141,258	---
Gonorrhea, Military	562	419	---	4,708	4,776	---
Syphilis, primary and secondary, Civilian	528	531	---	4,132	3,938	---
Syphilis, primary and secondary, Military	8	3	---	64	52	---
Rabies in animals	39	45	56	249	284	448

TABLE II. NOTIFIABLE DISEASES OF LOW FREQUENCY

	Cum.		Cum.
Anthrax:	2	Poliomyelitis, total:	2
Botulism:	4	Paralytic: N.Y.C. 1	2
Congenital rubella syndrome:	5	Psittacosis: Ohio 1, Calif. 3	19
Leprosy: Pa 1, Calif 2	20	Rabies in man:	–
Leptospirosis:	7	Trichinosis: N.J. 1	33
Plague:	–	Typhus, murine: Tex. 1	2

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†Delayed Report for week ending 2/21/76

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ANGIOSARCOMA – Continued

has been assembled through medical record review and family interview (Table 1). Particular attention has been given to potential occupational or environmental exposure to chemicals known to induce ASL (vinyl chloride, arsenic, and thorium dioxide).

Most cases (7 of 10) were diagnosed since 1970, probably reflecting better case ascertainment in recent years. Ages ranged from 36-71 (mean age 58 years). All but 1 patient were male, and all but 1 were white. Places of usual residence for all cases were widely scattered across the state, roughly corresponding with the state's population (Figure 1).

One patient had a history of prior thorium dioxide exposure. For none of the remaining cases was tumor etiology obvious. Occupations and histories of exposure to potential environmental toxins differed widely, with no more than 1 case associated with any particular industry or mode of exposure. In several instances, however, individual patient occupations or exposures were suggestive of possible oncogenicity (Table 1). Patient 10 had had exposure to a vinyl compound; he had worked in paper and plywood products with potential contact with various chemicals, including polyvinyl acetate. Two other patients gave histories of possible exposure to arsenic: patient 9, who had exposure to insecticides while farming, and patient 8, who worked with wood probably treated with arsenic preservatives in the manufacture of bleachers. All but 3 of the 10 patients were known to have lived on farms during their lifetimes, 2 for all of their lives (Table 1).

(Reported by J Fiechtner, MD, C Reyes, MD, Marshfield Clinic; K Rentmesster, MPH, HG Skinner, MD, State Epidemiologist, Wisconsin State Dept of Health and Social Services; Office of Extramural Coordination and Special Projects, National Institute of Safety and Health; and the Cancer and Birth Defects Div, Bur of Epidemiology, CDC.)

Editorial Note

These data indicate no obvious common-source origins among recent cases of ASL in Wisconsin. The marked male preponderance among cases, however, suggests occupational exposure as the potential origin for at least some of the cases. Anecdotal histories of occupational and environmental exposures in several of the cases may warrant further investigation, particularly in relation to contact with arsenic. Although at present only vinyl chloride monomer (*1*), thorium dioxide (*2*), and arsenic (*3,4*) are clearly implicated as causes of ASL, investigations such as the one described here may well provide useful leads in defining further causes.

Figure 1
GEOGRAPHIC DISTRIBUTION OF CONFIRMED CASES OF ANGIOSARCOMA OF THE LIVER IN WISCONSIN RESIDENTS, 1964-1975, BY PLACE OF USUAL RESIDENCE

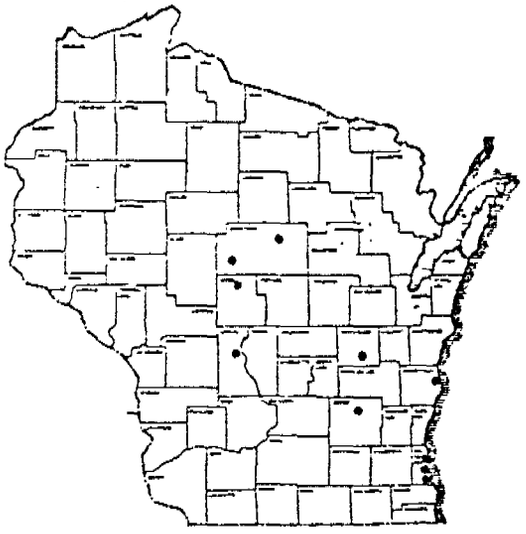

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Table 1
Cases of ASL in Wisconsin Residents 1964–1975

Case Number	Month and Year Diagnosis	Month and Year Death	Usual Town Of Residence	Age at Diagnosis	Race	Sex	Occupation	Comments	Farm Residence
1	4/64	2/65	Sheybogan	71	W	M	University Teacher	Lived near a chemical company which made plastics and resin	Youth
2	2/67	2/67	Oshkosh	61	W	M	Foundry Welder	Exposure to welding materials and resins	None
3	6/67	6/67	Necedah	36	W	F	Secretary	Infectious hepatitis in childhood, mother and sister had liver disease	Youth
4	7/71	7/71	Milwaukee	68	B	M	Hog Scalder		None
5	4/72	4/72	Milwaukee	64	W	M	Unknown	Exposure to thorium dioxide	Unknown
6	4/74	6/74	Brown Deer	46	W	M	Lutheran Pastor	Lived near a paper mill, 1955-1959	Youth
7	7/74	7/74	Wausau	57	W	M	Rock Crusher; Glue-Liner for rubber raincoats, 1940s	Exposure to silica dust, rubber cement	Youth
8	9/74	9/74	Waupun	46	W	M	Postal Mail Carrier formerly employed by company that made bleachers	Contact with lumber, paints, wood preservatives, (ammoniacal-copper-arsenate wood preservative) (?)	Lifetime
9	8/74	8/74	Stratford	66	W	M	Retired Farmer	No tissue diagnosis; ASL diagnosed by hepatic arteriography	Lifetime
10	11/75	11/75	Marshfield	65	W	M	Press operator for paper and plywood company (23 years)	Contact with wood, plywood, glues, polyvinyl acetate, others	Youth

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