(2) Confidential

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Vinyl Chloride Content of Subcutaneous Adipose Tissue from Vinyl Chloride Polymerization Workers

Abstract: Significant levels of vinyl chloride monomer were found in subcutaneous fat depots of workers exposed to the gas during the manufacture of polyvinyl chloride. The compound was not detected in a control group of unexposed workers.

Vinyl Chloride Monomer (VCM) is a fat soluble, sweet smelling gas at room temperature which is used in the production of polyvinyl chloride (PVC). Although PVC has been known since 1830, little attention has been given to the possible toxic effects involved in its production until recently when exposure to the monomer was found to be associated with the occurrence of angiosarcoma of the liver and other malignancies in both man and animal (1-3). The neoplastic potential of this substance has been demonstrated in rats and mice by Maltoni (4,5). He exposed animals to air containing varying concentrations of vinyl chloride and was able to produce tumors at levels as low as 50 parts per million (ppm). In man the evidence is less direct, although chromosome abnormalities have been found in circulating lymphocytes of exposed workers (6), and mutagenic effects in bacterial test systems have been reported (7).

To date little is known about the concentrations of VCM to which workers are exposed since relatively few measurements have been made in polymerization or other manufacturing facilities. Currently, the Occupational Safety and Health Administration of the U.S. Department of Labor has proposed an exposure standard for VCM of 1 ppm averaged over an 8 hour work day (8).

Currently, no specific biochemical evidence of exposure to VCM has been demonstrated in workers engaged in the production of PVC, although liver damage has been demonstrated (9,10). Indeed, it is not known whether or not VCM exists in its original form after inhalation by exposed subjects. It was therefore of interest to explore the possibility of identifying VCM in tissues of man. If this were possible it could provide the means for further studies of the metabolic fate of the monomer. Furthermore such a study could provide the basis for a sensitive monitoring system of individuals potentially exposed to the monomer in its production, the preparation

of the polymer, the fabrication of a large variety of PVC products or the use of a number of consumer products (11).

Since VCM is a fat soluble substance we postulated that fat depots of exposed workers might serve as an important indicator of monomer body burden similar to that used for other fat soluble toxic substances (12). The analyses reported in the present communication are based on samples of fat obtained by means of needle aspiration (13) from workers with widely varying degrees of exposure ranging from none to 32 years. Analyses of VCM were accomplished by gas liquid chromatographic techniques after extraction from the lipid sample (14). Total lipid in the sample was determined by measurement of carboxyl esters according to the method of Rappaport et al (15). Results in figures 1-4 are expressed as PPM in air and as PPM/lipid in table 1. In all cases, standards of VCM were run before and after each determination. Samples were analyzed without prior knowledge of exposure, which was coded and known only to the physicians who examined the workers.

Fig. 1 depicts a typical standard run ranging from 0.4 to 2.0 PPM in air of VCM gas obtained from the Matheson Gas Company. Responses were linear and standards as low as 0.1 PPM can be detected. Fig. 2 depicts the analysis of a fat sample from a subject with a long history (over 20 years) of exposure in the production area of his plant. In this subject a distinct peak with a retention time identical with that of VCM standards can be seen. In addition, 4 other peaks were found, the nature of which are currently under investigation. The examination of a sample from a subject with no exposure to VCM is shown in figure 3. Here one can see 4 peaks; however, no VCM peak was noted. In figure 4 one can see that in a subject exposed for a period of 8 months prior to biopsy at a PVC production plant, no significant levels of VCM were detected in his fat depot. A summary of the

results of 14 subjects studied thus far is shown in table 1. A correlation between exposure time and levels of VCM in the fat depot existed in these subjects. It was of interest that subject 7, who had a history of heavy and prolonged exposure showed only modest amounts of VCM in his tissue. However, his exposure to VCM ended 5 years ago, and the lower levels may be related to the turnover of VCM from his fat stores during that time. This would suggest that both total exposure and duration from last exposure are important in this regard. It is likely that intensity of exposure will be found to have similar relevance.

These preliminary investigations indicate that measurable amounts of VCM can be found in fat depots of workers exposed to VCM gas. Although the results of the present studies do not purport to correlate levels of body burden with manifestation of disease, the method may serve to investigate such relations. The technique is simple and safe and would permit surveillance of exposed individuals over time. It can be readily utilized as a routine clinical procedure. The ability to detect small amounts of VCM in the body prior to the onset of overt liver disease or chemical abnormalities could provide early warning of potentially harmful effects.

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BIBLIOGRAPHY

1. J.L. Creech, L. Makk, J.G. Whelan and C.H. Tomburno, Gasteroenterology (abs) 67 (4):786 (1974)

2. D.E. Gordon, L.B. Thomas, G. Kent, J. Calandra, R. Bahu and H. Popper, Gasteroenterology (abs) 67 (4):794 (1974)

3. J.F. Martin, J.G. Waggoner and P.D. Berk, Gasteroenterology (abs) 67 (4):814.(1974)

4. C. Maltoni and G. Lefemine, Environ. Res. 7:381,(1974)

5. C. Maltoni and G. Lefemine, Ann. N.Y. Acad. Sc. Vol 246,(1975)(in press)

6. A. Ducatman. K. Hirschhorn and I.J. Selikoff (Submitted for publication) (1975)

7. U. Rannug, A. Johanson, C. Ramel and C. Wachtmeister. Ambio 3(5):194,(1974)

8. Federal Register 39(194):35890, October 4,(1974)

9. H.J. Marsteller, W.K. Lelbach, R. Muller and P. Gedigk, Ann. N.Y. Acad. Sc. Vol 246,(1975)(in press)

10. L.B. Thomas, H. Popper, P.D. Berk, I.J. Selikoff and Falk, H., New Eng. J. Med.,(1975)(in press)

11. B.W. Gay, Jr., W.A. Lonneman, K. Bridbord and J. Moran, Ann. N.Y. Acad. Sc. Vol 246,(1975)(in press)

12. M.F. Ortele, AMA Archives of Industrial Medicine, 18:433 (1958)

13. G. Christakis. Journal of Lipid Res. 6:427 (1965)

14. Hewlett-Packard Application Note: ANGC 8-74

15. M.M. Rapport and N. Alonzo, J. Biol. Chem. 217:1963 (1955)

Table 1 Summary Of Exposure History And Vinyl Chloride Monomer Burden In Fat Depots Of Subjects Studied.*

Subject	Age	Length of Exposure	Time Since Last Exposure	Vinyl Chloride Levels (PPM/µg lipid)
1.	59	32 yrs.	80 days	120
2.	54	25 yrs.	80 days	160
3.	49	27½ yrs.	currently exposed	120
4.	60	28 yrs.	currently exposed	160
5.	41	20 yrs.	80 days	120
6.	42	19 yrs.	80 days	180
7.	47	19 yrs.	80 days	150
8.	48	16 yrs.	5 yrs.	40
9.	57	11 yrs.	80 days	160
10.	52	8 mos.	80 days	0
11.	25	6 mos.	80 days	0
12.	48	never exposed	-------	0
13.	55	never exposed	-------	0
14.	22	never exposed	-------	0

* These workers were all employed in the manufacture of polyvinyl chloride by polymerization of Vinyl Chloride Monomer. Their integrated exposure experience is not known.

Figure Legends

Fig. 1 Chromatogram of standard run of vinyl chloride monomer. A Hewlett-Packard Model 5750 gas chromatograph was used for all chromatography, calculations and reports. The flame ionization detector gas flows were 60 ml/min. H_2, 480 ml/min. Air. The separation is achieved by using a two foot Porapak Q column, VCM retention time 1 min. and 30 seconds. Injection was performed by using gas tight syringes.

Fig. 2 Chromatogram of a sample of subcutaneous fat from a worker exposed over 20 years during polymerization. A VCM peak is noted with retention time of 1 min. and 30 seconds. Conditions of injection are as described in fig. 1.

Fig. 3 Chromatogram of a sample of subcutaneous fat from an un-exposed worker. No VCM peak was detected. Conditions of injection are as described in fig. 1.

Fig. 4 Chromatogram of a sample of subcutaneous fat from a worker exposed for only 8 months. No VCM was detected. Conditions of injection are as described in fig. 1.