VINYL CHLORIDE—PART 5: MUTAGENICITY IN MAN

Since it is widely accepted that somatic mutation is frequently a step in tumour formation, the demonstrable carcinogenicity of vinyl chloride (VC) indicates that *in vivo* mutagenicity does occur in man. Cytogenetic examination is one means of evaluating this aspect of the monomer's biological profile.

Until recently, studies of this type have given equivocal results, the reports identifying a VC-associated increase in chromosomal aberration being balanced by those showing no effect. Several of the positive studies are of limited value, involving only small and therefore possibly non-representative groups of workers. Ducatman *et al.* (*Mutation Res.* 1975, 31, 163), for example, examined lymphocyte cultures from 11 VC-exposed workers, Kučerová *et al.* (*ibid* 1979, 67, 97) from nine and Funes-Cravioto *et al.* (*Lancet* 1975, I, 459) from seven.

The experiment of Léonard *et al.* (*J. Toxicol envir. Hlth* 1977, 2, 1135), in which lymphocyte cultures were taken from ten "control" individuals, seven men who had worked in the laboratory of a VC plant and who were subjected to only limited VC exposure and 11 workers in a VC polymerization plant, is open to the same criticism. While these authors found that the incidence of chromosomal aberrations, such as chromatid gaps and breaks and chromosome gaps, were comparable in all groups, more severe abnormalities, such as dicentrics, fragments, translocations and rings, were observed in ten of the 11 workers from the polymerization plant but in none of the controls. Levels of VC in the plant were less than 10 ppm at the time of the study, but had been as high as 500 ppm a few years earlier. The authors did not consider that these findings incriminated VC as the causative factor. Many of the workers in the polymerization plant had evidently been given several X-rays of the hands and feet (in order to check on possible acro-osteolysis), while the control group had no similar exposure to radiation, and Léonard *et al.* (*loc. cit.*) considered it likely that the observed cytogenetic changes were attributable to X-rays rather than to VC exposure. They thought that a suitably representative sample of VC workers would be difficult to identify because of the practice in the industry of monitoring the workforce regularly by various scanning techniques. Nevertheless, this is a fairly recent development and in at least one of the earlier studies, that of Purchase *et al*, in 1975 (*Lancet* 1975, II, 410), the test and control groups were said to be comparable in their exposure to radiation. In that study, lymphocyte cultures from 156 workers exposed to VC and from 24 controls were examined and it was found that VC-exposure was associated with an increased incidence of chromosomal aberrations including major chromosomal abnormalities.

On further analysis of essentially the same data (the exposed group had been increased to 57 men), Purchase *et al.* (*Mutation Res.* 1978, 57, 325) found an association between chromosomal aberration and four factors: job category, length of employment, experience of exposure to short-term excursion levels of VC, and smoking habits (as ascertained in an interview 18 months after lymphocyte sampling). It was not possible to estimate which of these parameters was the most important. With respect to job category, the greatest statistically significant increase in both minor and major chromosome abnormalities occurred in autoclave operators/cleaners (17 men in all). Smaller increases in one or more of the types of aberration were commonly seen with other job categories. The autoclave operators were subject to average VC levels of 40–400 ppm for the decade up to 1974, but the levels had been reduced to 15 ppm by mid-1973 and to 5 ppm by 1975. Blood samples for chromosomal analysis were taken in mid-1974.

Heng & Theiss (*J. occup. Med.* 1978, 20, 557) compared lymphocyte cultures from ten workers exposed to VC (but showing no symptoms of VC disease) with those from 20 matched unexposed controls. There were no statistically significant differences between the two groups. However a significantly higher incidence of aberrations was found in a group of 20 workers suffering from various symptoms of VC disease than in the control group of 20 individuals: the control incidence of aberrations of 5·5%, including gaps and 2·1%, excluding gaps being raised to 11·2 and 5·2%, respectively. Furthermore, a 16·6% incidence of chromosomal aberrations (7·3%, excluding gaps) was measured in a 43-yr-old patient, who had developed an angiosarcoma after working in the PVC industry for 13 yr. His exposure to VC in the past few years, resulting from the cleaning of autoclaves, was estimated at between 35 and 150 ppm for about 20–30 hr a month. Surprisingly, there is no specific mention of the X-ray experience of the workers suffering from VC disease and these individuals are likely to have been subjected to X-ray examinations. As for the cancer victim, the authors noted that cancer chemotherapy had been received 9 months before the lymphocyte examination.

A study of a large number of PVC workers of Dow Chemical USA, conducted by Picciano *et al.* (*J. occup. Med.* 1977, 19, 527), suggests that VC exposures below 15 ppm do not induce chromosomal aberrations. When lymphocyte cultures taken from a group of 209 workers who had worked in the plant for periods ranging from 1 to 332 months (average 48·3 months) were compared with those from a control group of 295 pre-employment examinees, no significant cytogenetic differences were observed. The workers had been exposed to maximum levels of 15·2 ppm VC before 1960, 11·4 ppm from 1960 to 1972 and 8·7 ppm between 1973 and 1974. The two groups were not comparable in age, the controls, averaging 25·1 yr, being some 14 yr younger than the VC workers, and apparently no attempt was made to standardize with respect to X-ray exposure. Again there was no indication of any VC-associated changes in the chromosomes when the data were analysed with respect to monomer exposure, the 209 workers being divided for this purpose into three sub-groups, those exposed on average to less than 1 ppm, 1–5 ppm and above 5 ppm VC, respectively.

Further support for VC as the real cause of the chromosomal damage comes from Hansteen *et al.* (*Mutation Res.* 1978, 51, 271). In 1974 this group found that at 3·41%, the mean chromosome breakage frequency in lymphocyte cultures from a group of 39

workers from a PVC plant was significantly higher than that seen in the 16 controls (1·79%). However, when 35 of the original 39 workers were re-examined 2·2–5·3 yr later, a period during which they had only minimal VC exposure, the frequency of chromosome breakage was down to control levels, suggesting that visible chromosomal changes may reflect only recent industrial experience.

It has been shown that the frequency and type of somatic chromosomal aberration seen in any particular worker may vary markedly over a period of time during which there is continual exposure to VC (Kuberová *et al. loc. cit.*). A wide inter-subject variability has also been observed (Hansteen *et al. loc. cit.*). The biological implications of somatic mutations are as yet unknown—the time-scale of chromosomal change is an area particularly in need of further study—although such changes may eventually prove to be of value in the early identification of groups at high risk from cancer and they may have some potential for screening individuals (one subject with a high breakage frequency in this group's original study was subsequently found to have cancer). It is reassuring, however, that on the present evidence workers exposed to VC at levels up to the TLV of 5 ppm probably do not develop visible cytogenetic changes in the cells of the peripheral blood.

While somatic mutation is expressed in exposed individuals, alterations of the genetic material in the germ cells will not become apparent until the next generation and perhaps even later. One possible consequence of a chromosomal aberration in germ cells is the induction of dominant lethal mutations, which in many would be observed as early foetal loss. A study by Infante *et al.* (*Lancet* 1976, I, 734) of the pregnancy outcome among wives of workers exposed to VC suggests that the monomer may possess just such activity. A group of 95 polymerization workers (primary VC group) was compared with an age-matched control group made up of 158 rubber and PVC-fabrication workers (with very low or no VC exposure); these numbers reflected group participation rates of 62–77%. Age-adjusted foetal deaths per 100 pregnancies in the primary VC group were 6·9 before and 15·8 after VC exposure, compared with corresponding foetal losses of 6·9 and 8·8% in the controls. The statistically significant ($P < 0·02$) difference between the primary VC group after VC exposure and the controls was found to reflect a greater foetal loss in the wives of men under 30. In this age group, foetal loss after VC exposure was 20%, compared with 5% in the controls, whereas the foetal loss of wives of men over 30 yr old was comparable in the exposed and control groups (13 and 12%, respectively). A VC-associated increase was still apparent when women with more than one abortion were excluded from the analysis. The lack of details of the method of data collection and the age-adjustment procedure used in this study were queried by Paddle (*ibid* 1976, I, 1079). Responding with details of their interview procedures and with a further explanation of the age-adjustment method, Infante *et al.* (*ibid* 1976, I, 1289) tentatively suggested that their findings for the under-30 age group might have reflected the placing of newly-hired personnel in categories involving the worst levels of VC exposure.

These findings in particular raise doubts over the possible genetic risks of VC. More studies of this type are badly needed. It is to be hoped that future studies will include direct information both on maternal age at conception and on occupational exposure levels.

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