

THE APME REGISTRY OF CASES OF ANGIOSARCOMA OF THE LIVER (ASL) - AN UPDATED REPORT

Introduction

The Association of Plastics Manufacturers in Europe (APME) maintains a register of all cases of angiosarcoma of the liver (ASL) resulting from exposure to vinyl chloride monomer (VCM).

The register has been described in two publications, Purchase et al incorporated data from it in their chapter 'Vinyl Chloride - A Cancer Case Study' in 'Toxicological Risk Assessment' Volume 2 edited by Clayson et al. They subscribed the view that it was the most exhaustive compilation of ASL cases attributable to VCM. The paper by Forman et al is entirely devoted to the register and its contents. They described it as the most comprehensive tabulation of such cases available. Both papers used the information in the register as a means of forecasting future cases, and as a source of data for characterising the risk of ASL in different jobs, in different factories, in different countries, at different times.

Report

The latest version of the register reviews reported cases up to October 1993. It contains 173 histologically confirmed cases of ASL. The cases are tabulated by year of diagnosis, country, latent period, duration of exposure, age at diagnosis and survival after diagnosis. Further tables list the producers and their factories by country and start-up date. The review is a factual document that makes little attempt to draw conclusions or to make predictions from its many tabulations. It does state in the introduction, however, that 'a few more cases can be expected during the next years. But it may be hoped that, in the near future, the ASL linked to VCM will become an illness of the past'.

Prediction of the number of VCM related ASL cases to be expected in the future is an inexact science because the basic information, the population at risk and the level of risk attached to each individual, is unavailable. It has to be assumed that this information can be estimated from the case register, or, putting the same idea a different way, that future cases will be proportional to past cases in some sense. Forman et al based their prediction on a particularly neat and simple version of this assumption. Table 1 is a 10 year update of Table 5 in their paper. (Although 10 years has not yet elapsed it is simplest to use 10 years and the calculation is not materially affected). Table 1 excludes the 6 cases from Eastern Europe and 1 case with missing dates. The model assumes that the numbers to be estimated can be calculated from the numbers in the same row and column compared to numbers in previous rows and columns (to the left and above in the Table). For examples, the figure for the ((35-39), 35-) box is calculated as:

$$(8+2) * (0+4+8+8+12+6) / (0+3+2+8+12+7+0+0+4+11+6+8) = 10 * 38/61 = 6 = 2 (+4)$$

This updated calculation shows that a further 64 cases are to be expected for latent periods up to 44 years. The figures for latent periods of greater than 44 years cannot yet be predicted. The cases from Eastern Europe were excluded because it is not yet known whether they are likely to be a complete ascertainment of cases.

Discussion

A registry of cases of ASL related to VCM exposure has been maintained by the industry since 1976. It is regarded both by the industry and by academic researchers as the most comprehensive list of such cases available. Registers of all cases of ASL in the population at large are also kept in the UK and USA, but these have different bases and different objectives.

The registry has been used on two occasions as a means of predicting future VCM related cases and one of these predictions has been updated in this report. At the end of 1982 when the register contained 99 cases, Purchase et al predicted a further 150 cases assuming no risk after 1964 and a further 323 cases assuming no risk after 1974. Based on the 118 cases reported to the end of 1984, Forman et al predicted a further 155 cases would occur plus 0 or 61 cases among recent recruits, depending on when the risk was eliminated, and an unknown number with latency greater than 35 years. In this report based on 166 cases reported to the end of 1992, a further 64 cases is predicted plus an unknown number with latency greater than 44 years and an unknown number in Eastern Europe. Compared with the Forman et al report this latest prediction contains elements that are both encouraging and discouraging. On the encouraging side, the presence of only one case first exposed after 1970 suggests that the best prediction for cases recruited after 1970 is much nearer to 0 than to 61. On the discouraging side, the number of cases with a latency of over 35 years suggests that cases will continue to occur for very long latent periods and that they will only be restricted by old age and consequent deaths from other causes. The other discouraging feature is the emergence of cases from Eastern Europe and a resultant unpredictable element in the equation.

The problems that beset the prediction of all future VCM related cases become even more extreme if an attempt is made to relate cases, and, therefore, risk, to exposure level. This is a problem that can really only be approached by characterising populations, as in a cohort study, rather than by characterising cases.

The International Agency for Cancer Research (IARC) has carried out a multinational cohort study, primarily to determine whether tumours at sites other than the liver are associated with VCM exposure. In collaboration with a team of industrial hygienists they attached VCM exposure levels to each job in each participating country in each year of their study, and derived risk estimates for ASL based on job and exposure. These are shown in Table 2.

TABLE 2
ASL STANDARDISED MORTALITY RATES (SMR) BY
EXPOSURE LEVEL IN IARC COHORT STUDY

HIGHEST EXPOSURE (ppm)	SMR	CUMULATIVE EXPOSURE (ppm yrs)	SMR
0-50	119	0-1999	99
50-499	161	2000-6000	351
500-	567	6000-9999	800
Not Known	317	10000-	1429
		Not Known	357

In comparison, Purchase et al state that the 'majority' of their 99 cases occurred in autoclave workers, who experienced the highest exposures, and Forman et al show that 51 of their 118 cases had the job of autoclave cleaner at some time and 69, overlapping with the 57, were production workers or operators. The latest version of the register contains occupational records that reveal that 81 of the cases worked at some time as autoclave cleaners and a further 46 worked in polymerisation plants.

There are however 39 cases with indefinite job descriptions and 7 who worked only on monomer plants. Whilst it can be said that the data from the cohort study and the register are reasonably compatible, it would not be wise to try to draw conclusions about exposure based risk estimates from the register.

Conclusions

The register of ASL cases related to VCM maintained by the APME has a good reputation in the field of occupational epidemiology. It has been used to provide informative tabulations of the cases as they arise, to predict future cases, and to permit qualitative statements about the concentration of the highest levels of risk in certain jobs and in certain factories. Bearing in mind the absence of key information, the predictions have proved so far to be reasonably reliable and the findings about jobs and exposure have been supported by an international cohort study conducted by IARC.

It is essential that the register continues to be maintained and, where possible, improved, not least because it is viewed by the outside world as a worthy attempt to chronicle and manage a unique industrial epidemic. The need for continued vigilance is underlined by the reports of cases in Eastern Europe and the occurrence of cases with very long latency (greater than 40 years). One element of the registry that needs to be improved is the process of accepting or rejecting cases when they are reported. A process that permits vacillation is not scientifically acceptable and it creates doubts about integrity if one review of the contents of the register differs materially from a previous one.