VCM00000177

With J.F. Carney letter of 10th March 1983

R&S 117004

THE EMPIRICAL APPROACH

VINYL CHLORIDE : A CANCER CASE STUDY

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Vinyl chloride monomer (VCM) is a simple organic chemical gas which is normally handled in industry as a pressurised liquid. It was discovered about 1833 and 5 years later its polymerisation was observed. Its main use now is in the manufacture of PVC (polyvinyl chloride) and for this purpose around 12 million tonnes are produced annually throughout the world.

The first evidence of worker health problems with VCM appeared in the early 1960's. Men who entered the PVC autoclaves and were thus exposed to high concentrations of VCM developed acro-osteolysis and as a result of animal studies to investigate this condition, carcinogenic properties were also suspected. Beginning April 1973, Maltoni was reporting the rare tumour, angiosarcoma of the liver (ASL) from his rat experiments. One year later the first human ASL cases were recorded in the USA. These events prompted intense activity throughout the world because a chemical of evident economic importance was recognised as a human carcinogen. The immediate response was a planned reduction in worker exposure to VCM from a previous 500 ppm (TLV) to less than 5 ppm.

There have now been nearly 1000 articles published in the scientific press on all aspects of VCM toxicity and its relevance to man. If such publications are considered with the many on quantitative risk assessment, there are a very large number of answers offered to the all-important question, "what is a safe concentration of VCM for human exposure?" In fact, the question needs refining to be meaningful and it has most frequently become "what is the most precise and accurate estimate of the concentration of VCM in air which increases the lifetime risk of ASL in exposed humans by 1 in 1,000,000?"

There are two main sources of data for such estimates (i) studies in experimental animals and (ii) analysis of effects in humans - or epidemiological studies.

(i) In terms of quantitative risk estimates, the chronic animal bioassay has provided most data. Such studies give information on the numbers of animals in different dose groups which exhibit cancer and permit the application of mathemetical techniques most favoured by the investigator.

Maltoni and co-workers have made the largest contribution with their 17 studies on VCM (Maltoni, Lefemine et al 1981). Carcinogenic effects were observed in mice, rats and hamsters although unavoidable biological variation and changes in procedure complicate the interpretation of these, as many other animal studies.

Lowest concentrations of VCM giving significant excess of tumours in rats (Maltoni et al 1981)

Stomach (papilloma)	30,000 ppm	
Zymbal gland	10,000 ppm	
Neuroblastoma	10,000 ppm	female
Nephroblastoma	250 ppm - female 100 ppm - male	
Liver angiosarcoma	200 ppm - male 50 ppm - female	
Mammary gland	5 ppm - female	

Barr (1982) has compiled a summary table of Maltoni's five main experiments in rats which developed ASL. Four of the five experiments were conducted with Sprague-Dawley strain rats, but one with Wistar strain. The difficulties of analysing such data to determine the highest, non-carcinogenic dose of VCM to rats can be appreciated from figure 2.

Figure 2 ASL Incidence (%) in rats

Dose(ppm)	10000	6000	2500	500	250	200	150	100	50	25	10	1
Expt. No												
1	12	22	10	5					1.7			
2						10	5	0.8				
7*	27	6.6	10	13	3.3				0			
9									4.8			
15										4.2	0.8	0	0

* Wistar strain rats

One important feature of making animal data meaningful to man is to check for the similarity of metabolic pathways for VCM in both species. For the rat it is now accepted that highly reactive intermediates in the metabolic process (particularly chloroethylene oxide and chloracetaldehyde) react with cellular macromolecules, including DNA producing the critical lesions leading to mutation or the induction of cancer. From obviously limited studies using human liver tissue this proposed pathway and end-result is believed to be similar in rodents and man. However, another feature is equally important for extrapolation from animals to man and that is reaction kinetics or whether the end-result is the same irrespective of the dose given; such information is crucial in the risk assessment for VCM. Gehring et-al (1978) discovered that as the dose of VCM administered to rats was increased then a smaller proportion of the dose was actually converted, or metabolised in comparison to the proportion

converted from a low dose and thus the kinetics were non linear at higher concentrations. It was later found that an equilibrium is quickly established between VCM concentrations in the blood and atmosphere and that there was little or no storage of VCM in the body. Therefore factors for accumulation would not have to be incorporated into calculations of risk.

In summary therefore, animal studies have established; a link between VCM and experimental ASL, that the relationship is dose dependent, that the same metabolites of VCM are probably responsible for ASL in the rat and man and that extrapolation from low doses is, at best, uncertain.

(ii) Data from human exposure

Manufacture and use of VCM and PVC could result in potential exposure of 4 groups of the population :

1) The highest exposure category are the workers involved in the manufacture of VCM and its polymerisation to PVC. In this group certain occupations such as autoclave cleaning would have had higher potential exposure than others (although all groups would now be expected to have exposures below 1 to 3 ppm hygiene standards). The evidence suggests that in the past some autoclave workers may have been exposed to extremely high levels of VCM.

2) Workers in the compounding and fabrication of PVC products would have been exposed to levels 10 to 100 times lower than those in group 1. In a study of 4341 deaths from 17 PVC factories in the USA, no cases of ASL or any excess of lung or brain cancers were found, any evidence that intestinal and urinary system cancers were increased in incidence has not been confirmed. In the UK, very similar results were obtained in a study of 707 deaths of male fabrication workers.

3) Consumers who eat food and drink beverages which have been packed in PVC may ingest unreacted VCM which has migrated from the package. Since 1974 stringent controls have ensured that average daily intakes of VCM in food and drink are lower than 1 microgram/kg/day. (In a severe life-time study, Feron et al induced ASL in rats by ensuring there was absorption from the stomach for 24 hr/day. The minimum dose leading to ASL was 5,000 times the 1 microgram/kg/day limit)

4) This group would be those who live in the vicinity of VCM or PVC plants. The levels in ambient air around a factory are very low (in the parts per billion of air) but of course, large populations of all age and health groups are involved. At least 10 major studies have been made of th general population using ASL as the marker, but none of these has shown a connection between general ambient exposure and increased incidence of cancer (Barr 1982).

For risk assessment purposes therefore the relationship between ASL and VCM must be examined in group 1. ASL is a rare - but not unknown - cancer in unexposed populations so its presence in VCM/PVC workers can reasonably be attributed to VCM exposure. The data-base for this purpose is the ASL Register; from 1974 cases from around the world have been recorded and categorised. The register is now maintained by Dr John Stafford of Imperial Chemical Industries who has updated and circulated it to interested parties in Universities, Governments, Trade Unions and research organisations etc. At the end of 1982, 99 cases had been included and following analyses by country, company and plant etc, some important conclusions emerge :

* The majority of ASL cases are PVC autoclave cleaners or men who worked in or around the autoclaves.

* ASL tends to occur in larger numbers in some plants than in others, 87% of USA cases originate from just 4 plants, whereas 40 plants have not so far recorded one case.

* The average latent period between starting work in an occupation with VCM exposure and death from ASL for the 99 cases is 21.9 years.

* All 99 cases were first exposed before the mid 1960's which coincides with discovery of acro-osteolysis and improved procedures for autoclave cleaning.

  Therefore we have yet no information about whether these improvements have had any effect on the incidence of ASL in exposed populations.

Risk Assessment from animal and human data

Maltoni's experiments have been the basis for many estimates of a 10^{-6} lifetime risk to man which cover a substantial range (up to 10^{8}), depending on the mathematical model and the inherent assumptions. Even after more 'selective' estimates have been derived - for instance, by correcting for the non-linear kinetics of metabolism at high doses - a large range of 10^{3} in 'low risk dose estimate' is obtained. Clearly at this stage in their development we can have little confidence in mathematical models for quantitative risk estimates from animal studies. At a joint NIOSH and OSHA conference in 1980 to "Re-evaluate the Toxicity of Vinyl Chloride and PVC" the conclusion was reached that no reliable estimate of human risk can be obtained from raw animal data alone, but it must include biological adjustments.

Turning to the human data therefore, about 19 epidemiological studies of cancer associated with VCM have been undertaken since 1974. Several have been criticised, but when considered alongside the animal data to estimate the exposure for a 1 in 1,000,000 lifetime risk, some 15 different values have emerged. The estimates have ranged from 0.00000039 to 1,400.0 parts per billion depending on, amongst other things, which theory of cancer response is chosen (eg. probit, logit, Weibull, one-hit, multi-hit etc.)

Accordingly, it seems that empirical, quantitative risk assessments have contributed little definitive guidance. It is certainly reasonable to suggest that the present VCM hygiene levels of 1 to 3 ppm applied in most industrialised countries represent an achievable best practice rather than the outcome of an acceptable and clearly defined risk assessment. The Gehring/Anderson estimate - generally regarded as the most meaningful - of a 1 ppm for 10^{-6} lifetime risk was not proposed until 1980, well after the 1 to 3 ppm standards had been common industrial practice. Yet these conclusions are not to imply the irrelevance of empirical risk analysis for VCM, rather they illustrate that there is still very much to learn about the analyses and their application. For instance, almost all cases of ASL are associated with VCM exposure but relatively few of those exposed have developed ASL and this applies as much to rats as humans. The models leave this observation unexplained although it is clearly important in risk estimation.

The empirical information is available - the theory must be developed so that the true risk can be presented for judgement.

(I wish to record my thanks to Drs Purchase, Paddle and Stafford of Imperial Chemical Industries PLC for their help in preparing this presentation).

Paper by Dr. Ian F Cooney
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JS 12/3/83

References

1 Barr J T, Hazard Evaluation and Risk Assessment for vinyl chloride. prep. for AIHC Risk Assess. Sub-committee March 1982.

2 Feron V J, Hendrikson C F M, Speek A J, Til H P and Spit B J (1981) Fd. Cosmet Toxicol 19 317-333.

3 Gehring P J, Watanabe P G and Park C N (1978) Tox. Appl. Pharmacol. 44 581-591.

4 Maltoni C, Lefemine G, Cilibert A, Cotti G and Carretti D (1981) Environ. Health Perspectives 41 3-29

VCM

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R&S 117010

Your ref	Our ref	Tel ext	Date
	JS/SEN/DSO-16	7535	18 March 1983

VCM - PAPER BY DR IAN CARNEY

Dr I F Carney of CTL gave a paper on VCM on 15 March to the "First International Risk Seminar" 13-15 March in London. The seminar was entitled "Risk in Society, Risks from Chemicals and The Acceptable Risk, does it exist?" The seminar was run by a group called "Information Transfer International" located at PO Box 62, Beaconsfield, Bucks, UK (Tel 04946-2837). I enclose a copy of Dr Carney's paper. The proceedings of the seminar will be published around November 1983.

Although Mr Clive Jenkins (ASTMS) was billed as a star speaker and was as usual provocative/political/controversial, the audience was smaller than expected (100 instead of 200) and consisted of professional and academic types who did not necessarily warm to Mr Jenkins' polemics.

I thought you may like to be aware of this seminar and have a pre-publication copy of Dr Carney's paper.

J Stafford