

Science paused, and 17 died

At least 17 workers have been killed by vinyl chloride because research over the past 25 years was not followed up. And for over 10 years, workers have been exposed to concentrations of vinyl chloride 10 times greater than the safe limit imposed by one chemical company—Dow Chemical

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In January Dr John L. Creech, a works doctor at a Kentucky chemical plant, made public evidence that has finally forced a full investigation of an industrial health hazard that should have been eliminated many years ago. Creech's discovery was that four former employees of his company (B. F. Goodrich), who had been involved in making polyvinyl chloride (PVC) from vinyl chloride monomer (VCM), had died from a fatal liver cancer so rare that it kills less than 30 people a year in the US. The immediate implication that there is a causal relationship between industrial exposure to vinyl chloride vapour and development of the liver cancer (angiosarcoma) was reinforced less than a month later when an Italian researcher, Cesare Maltoni, revealed that he had found angiosarcomas in the livers of rats exposed to VCM.

That VCM causes angiosarcomas remains to be proved—although the evidence accumulating is so powerful that the chemical industry and government health inspectorates have little option other than to act on the hypothesis. But how to act? And why has action been delayed, perhaps fatally, for over 30 years?

The story could well begin in 1971, with the publication of a paper by another Italian, P. L. Viola. Researching the effects of exposing rats to an atmosphere containing 30 000 parts per million (ppm) of VCM (a massive dose), Viola found that "almost all animals developed tumours of the skin and lungs" and some developed bone cancers. The results came as something of a surprise because no-one had suspected VCM of being a carcinogen, and Viola had not set out to look for tumours. Criticism of the Italian research, as an indicator of VCM's carcinogenicity, was not slow in coming. The dose level was grotesquely high; so high that the rats' defence mechanisms may simply have been overwhelmed—leaving them susceptible to "spontaneous" tumours.

Nevertheless, such is the emotive impact of even a hint of a new carcinogen that four large European PVC makers (ICI, Montedison, Rhone-Progil, and Solvay) decided to sponsor a study by Cesare Maltoni, professor of Oncology at the Bologna Institute of Oncology. Viola allowed access to his raw data and Maltoni concluded that both the skin and lung tumours probably arose in the Zymbal gland, a sebaceous gland in the ear duct which in rats is particularly responsive to many carcinogens. Maltoni therefore began an extensive series of experiments on rats, mice, and hamsters exposed to ever decreasing concentrations of VCM. Simultaneously, ICI started an epidemiological study of workers at its PVC plant.

The exact sequence of events after this

point, and in particular the fate of Maltoni's results, has created a bitter controversy in the US. Following B. F. Goodrich's disclosure of the deaths among its ex-workers, the US Occupational Safety and Health Administration (OSHA) called an informal hearing. At that inquiry Maltoni gave evidence that he had discovered angiosarcomas in the livers of rats exposed to only 250 ppm of VCM. Because VCM was found to be carcinogenic at such low concentrations, Maltoni began a new series of experiments exposing larger numbers of rats to even lower VCM concentrations (250, 150, 100, and 50 ppm). At the time of the OSHA hearings, results from this crucial series of experiments were not available. It was only at a symposium organised by the American Cancer Society and the New York Academy of Sciences on 10-11 May that Maltoni was able to say that he had discovered angiosarcomas in the 50 ppm group of rats. On 15 April, the US Manufacturing Chemists Association (MCA) disclosed that research it had sponsored also showed angiosarcomas at 50 ppm—but this time in mice.

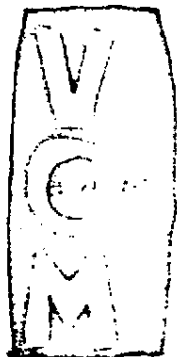
Was there a "cover-up"?

The controversy hinges on a tentative allegation in *Chemical & Engineering News* (20 May, p 16) that the MCA, and individual chemical companies, "held in confidence for at least a year preliminary, albeit significant, scientific findings"—that is, the interim results of Maltoni's work. The MCA replied that it had been given access by the European sponsoring companies to the findings (after "months" of negotiation) only on the understanding that it would make no "unilateral disclosure".

Maltoni observed his first angiosarcomas in rats in August 1972. ICI readily admits that it was aware of these findings in January 1973. In that month the MCA sent a technical delegation to visit Bologna and received reports of the research there. Thus it is undeniable that the chemical industry knew that VCM was carcinogenic in rats at concentrations as low as 250 ppm at the beginning of last year.

ICI and the MCA both say that they passed on this fact to appropriate government agencies in July 1973. But the UK Employment Medical Advisory Service (EMAS) and the Factory Inspectorate say that the first inkling they had of the carcinogenicity of VCM (apart from Viola's paper) was in January 1974 from ICI, which notified them of the Goodrich cases. The US National Institute for Occupational Safety and Health (NIOSH) denies that it knew of the angiosarcoma risk until January 1974.

In fact, Maltoni's angiosarcoma discoveries were first made public, not at the February



OSHA hearings, but at the Second International Symposium on Cancer Detection and Prevention held in Bologna on 9-12 April, 1973. At that meeting, Maltoni read a general paper about occupational oncology, during which he showed a table of preliminary results. There for all to see were angiosarcomas in the 250 ppm group of rats (as well as Zymbal gland carcinomas and nephroblastomas). It seems unlikely that the European companies sponsoring Maltoni's research would have allowed him to announce preliminary findings at this symposium, while denying the same data to MCA.

The impact of the results contained in the Bologna paper seems to have been minimal. The published version of the paper became available only three weeks ago. One British participant has no recollection of the report of angiosarcomas, despite a personal conversation with Maltoni at the symposium.

It is probably impossible to say whether the chemical industry deliberately and maliciously hid unfavourable research findings. It is, however, likely that, even if this were not the case, the results would not have caused much of a stir. For by this time, the epidemiological survey was showing negative results. ICI had found no deaths from angiosarcomas among ex-employees. Thus in January 1973 there was no human evidence of VCM's carcinogenic properties. Because extrapolating from animals about carcinogenicity is notoriously problematic, epidemiological evidence carries greater weight in the minds of industry and UK regulatory bodies. Thus it is unlikely that animal studies alone would have been convincing enough to force a re-appraisal of industrial exposure standards. "Firm" evidence only arose after the Goodrich report, when other cases of deaths from angiosarcoma were unearthed. ICI updated its survey and found one ex-employee who died from liver cancer in 1973. Other cases were found in Sweden and the US; the total now stands at 19.

Twenty-five years' evidence

However, the history of the research on VCM's toxicity is much more disturbing than any allegation of a 12 month cover-up. "There has been evidence of potentially serious disease among vinyl chloride-polyvinyl chloride workers for 25 years that has been incompletely appreciated and inadequately approached by medical scientists and by regulatory authorities". That is how Irving Selikoff, director of the environmental sciences laboratory at Mount Sinai Medical School in New York, sums up the history.

The evidence he quotes goes back a long way. In a 1949 Russian study, 30 per cent (15 out of 48) of a group of PVC workers examined showed evidence of liver disease. The very fact that VCM was once considered as an anaesthetic, but rejected because it was found to be a cardiac irritant should, says Selikoff, have meant a closer examination of its industrial usage. Experiments in Britain in the 1960s linked VCM to acro-osteolysis—an ugly, but seemingly reversible, bone disease characterised by distortion of

the skin and bones of the toes and fingers. In 1961 toxicologists from the Dow company published reports of an extensive research programme using rats, rabbits, guinea pigs, and beagle dogs. After three months exposure to concentrations of VCM between 100 and 500 ppm, animals showed various kinds of liver damage. Even at the "low" concentration of 100 ppm, livers of subject rats were abnormally enlarged.

None of these studies even hinted that VCM is carcinogenic. They did, however, indicate a cause for great concern. Selikoff says, "We had evidence here and there that a number of organ systems and tissues were affected by VCM. . . . Most of us did not draw the appropriate conclusions—that it should be carefully studied."

Anomalies between limits

Nevertheless, restrictions on the concentrations of VCM allowed in plants have existed for some time. The first (500 ppm in both the US and UK) were imposed because of VCM's inflammability, not its toxicity. But once limits were created on the basis of medical and animal studies, gross international anomalies arose. In the UK, a threshold limit value (TLV) of 200 ppm was set after the discovery of the causal link with acro-osteolysis; incomprehensibly, the 500 ppm limit remained in the US. Even more baffling, the Germans set a maximum workplace concentration of 100 ppm in 1970 on the basis of the 1961 Dow research. But Dow itself restricted exposures in its factories to 50 ppm as long ago as 1961—on exactly the same evidence on which the Germans based their 100 ppm limit. No other section of the US or European industry followed Dow's lead. The reasons for this international confusion are obscure.

Maltoni's evidence at the OSHA hearings threw the whole question into the melting pot. A US temporary limit of 50 ppm was rapidly decided and the UK Factory Inspectorate suggested an interim limit of 50 ppm maximum exposure, and a time weighted average exposure of 25 ppm. But both UK and US limits were devised before it was known that rats exposed to 50 ppm VCM developed angiosarcomas. Now a permanent standard of 1 ppm has been proposed by OSHA—in effect that no worker should be exposed to any detectable VCM vapour. In the UK, it is unlikely that the permanent limit (shortly to be announced) will be less than 25 ppm.

Whatever final limit is accepted, there will be a fight between industry and the trade unions—particularly in the US. The zero exposure limit is strongly backed by Selikoff. "It is evident," he says, "that no threshold is known that would serve to prevent cancer among exposed workers." Not only does he believe it to be the only safe limit (as do other experts), he also thinks it practicable—if expensive. "I don't believe a zero limit will involve closing down the vinyl chloride factories," he states, "I have great confidence that engineers will be able to solve the problems." The industry, of course, does not agree.