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Problems of Toxicity of Vinyl Chloride Monomer

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INTRODUCTION

This session deals with the problem of the toxicity of vinyl chloride monomer. We propose to have a panel discussion. We believe that most of the audience already have sufficient information about this topic; nevertheless, we think that it would be interesting to have some further discussion of the problem.

This was to have been introduced by myself, but, since most of the audience are English-speaking, and no translation facilities are available, I have asked Doctor Stafford, from the United Kingdom, to give this presentation. Following that, we will have a discussion led by Dr. Stafford, Dr. Praefke, from Germany, and myself. All three of us are members of the European Vinyl Chloride Committee.

Dr. Stafford (I. C. I. Welwyn Garden City, U. K.): The Conseil Europeen des Federations de L'Industrie Chimique (CEFIC) set up a Committee for the Toxicity of VCM in 1974. Three working parties, viz., technical, medical, and packaging, report to this Committee which though it appropriate to offer to IUPAC a few of its members to answer questions on VCM toxicity.

Since VCM/PVC manufacture started in the late 30's, the hazards associated with VCM were fire, explosion and narcosis. We though we were knowledgeable on these hazards and that our assessment of the toxicology of VCM was well founded, sufficiently so for it to be considered as an anaesthetic and even an aerosol propellant. Our

first shock came around 1966 with the discovery of acro-osteolysis (AOL). This was controlled by improving plant hygiene but left a residual worry. Professor Viola of Solvay in Italy attempted to reproduce AOL in animals using concentrations of 30,000 ppm. (Up to 1970 the TLV for VCM was 500 ppm and in 1970 it was reduced to 200 ppm). Viola did not produce AOL but was the first to produce angiosarcomata in experimental animals. This led to Solvay, Rhône-Poulenc, Montedison, and ICI banding together to fund a program of work (still going on) with Professor Maltoni in Bologna, who exposed rats to inhalation experiments for 12 months, 5 days/wk, 4 hr/day to concentrations of VCM ranging from 10,000 ppm to 50 ppm. At all dosages he found a considerable yield of tumors of many types in glands and liver, and there was a linear relationship between log concentrations and number of tumors. At 50 ppm there were signs of the beginning of a no-effect level.

Maltoni's findings were made available promptly by the sponsors to the rest of the interested world and epidemiological studies started. Late 1973/4, the first angiosarcomas of the livers of PVC workers were confirmed by B. F. Goodrich Co., and in the last 2/3 years we have built up knowledge of around 50 deaths due to this rare cancer.

January 1974 was a watershed in the history of occupational medicine. The world's PVC industry came face to face with the stark fact that it was making and using large quantities of a human carcinogen. Should the industry shut down completely and desist from making and handling such vast quantities of a carcinogen? This possibility looked very real early in 1974.

Alternatively could the industry improve its hygiene so that work could continue with risks which were socially acceptable to all branches of the industry, our customers, consumers and neighbors? This was a world problem. The industry's products had become in many cases economic necessities. In different ways in different parts of the world, regulatory bodies, industry, unions, and other interested parties have concluded that if certain improvements in hygiene could be achieved quickly, PVC manufacture could become a socially acceptable risk. By the expenditure of a great deal of effort and money in a large, crash technical program, the hazard has been contained.

It became clear during 1974 that the problems were associated with long exposure (15-20 yr) to high concentrations of VCM (hundreds of parts per million or higher). The main dangers were in VCM polymerization plants where atmospheric concentrations 20 yr ago might have been ca. 1000 ppm and where despite reductions during the years, the 1973 levels were still around 150 ppm. The next in rank of hazard (much lower) were VCM production plants with concentrations of 5 ppm. Thirdly PVC fabrication plants with levels

around 2 ppm. Fourthly at factory boundaries, concentrations in the air were 0.1 ppm and below (in Europe). Fifthly in foodstuffs and beverages, VCM traces remain in food wraps or bottles; as a result minute traces can be detected in parts per billion in the food product.

It was obvious that top priority had to be given to improvement of conditions in PVC polymerization plants, particularly in the autoclave/autoclave cleaning area. This is a marvellous lecture in itself and it is interesting that despite regional variations in law, public claims and counter-claims, everyone is working in the same ball-park. We hope our rough assessment of margins gives a great improvement in the casualties in future years. In the meantime we have to bear with the fact that some (we hope a small number) of us and our colleagues with past high exposures will develop angiosarcomas over the next 15-20 years.

In all the other areas VCM manufacture, PVC conversion, factory neighborhoods and food packaging great improvements have been made in the past two years and these continue.

We think that the greatest (and perhaps only risk) is to autoclave men exposed in the past to high concentrations. Of the roughly 50 angiosarcoma deaths, ten have been at one plant in the U. S. A., nine in one Canadian plant, and perhaps in all 27 of 28 in North America. This clustering is strange. Some plants elsewhere have had multiple deaths; some plants have had no deaths. How does one account for this? We do not have any answer as yet, and in saying this we should like to be clearly understood that no criticism is implied or intended of any of the PVC factories which have had the misfortune to experience a high cluster of deaths. On the present form we are confident that little risk exists except to some autoclave workers exposed in past.

For many good reasons, the PVC industry has been allowed to survive, and indeed the PVC industry itself has made a sober judgment that it should allow itself to continue. All human activity is risky. We have found courage enough to start again to put up new PVC plants. But as industrial scientists we can only be dissatisfied with our present state of knowledge. We know more than we did in 1975 and previous years. However, despite years of expensive animal experimentation, there are gaps which must be filled by results of experiments still going on or still to be designed. Despite what I have said about improved hygiene, we have only made some educated guesses and we hope overreacted. Perhaps the overreaction has gone too far and we could be running into other dangers? Professor Maltoni has still to do a lot of statistical analysis of his inhalation studies on rats, etc. In the PVC industry, we all have or could collate or synthesize a lot of useful data on human exposures; even if these data are somewhat inaccurate, they could still teach us valuable lessons for VCM and

other chemicals. We have still to adapt the experience of the radiation industry to our VCM story. We have to analyze, refine, and establish data on dose response and time relationships, and establish thresholds. The metabolism of VCM is beginning to be understood and work continues here. Epidemiological studies continue but regretfully many are of dubious quality. There is a real need to get good professional, scientific work done with the minimum of interference from political and pressure groups with their penchant for selecting only those data which suit their purposes.

Since the problem has been successfully contained, the high priorities of resources devoted by industry, governments, unions and academia are tending to become lower priorities, and I fear much of the work outlined above will not be done or will be done more slowly.

The VCM events of 1974 formed a watershed in the history of occupational medicine. I hope the sense of urgency and cooperation built up since then will continue so that in the coming years we can put together all the pieces in this fascinating jigsaw puzzle and develop a much fuller understanding of the long-term health effects of VCM. We shall be glad to have your comments and questions. In particular we would be glad if our colleagues from Eastern Europe would participate in this discussion.

GENERAL DISCUSSION

Dr. J. C. Thomas (Rhône-Poulenc, France): One general question that a layman might ask is why PVC polymerization is a batch process and not a continuous one? Everyone knows that health risks are less in a continuous unit than in batch one. As Dr. Stafford mentioned, exposure of the workers to vinyl chloride is less in the monomer plant than in the polymerization plant. I will try to answer the question myself. First, we must keep in mind the batch process of polymerization of vinyl chloride. There are several processes of polymerization—but in all cases, the polymer is insoluble in the monomer and precipitates out. A very small amount of this polymer is either thrown to the walls of the reactor or polymerized directly in the reactor. It is absolutely essential to clean the reactors between polymerizations in order to have a good heat transfer at the walls of the reactor.

I think this is the main reason why the batch process is used. There are one or two special adaptations of a continuous process carried out in Germany. They are emulsion polymerizations. Most of the processes used today, however, are batch processes. I cannot foresee any real possibility for a generalization of a continuous

process for polymerization of vinyl chloride, so we must live with the batch processes. A second problem is the affinity of vinyl chloride monomer for PVC and the very great difficulty in removing the last traces of vinyl chloride from PVC. These two factors explain the problem with which we are faced.

Dr. Vinson (Brasivil Resinas Vinilicas, Saõ Paulo, Brazil): Dr. Stafford has mentioned that further studies are under way by Prof. Maltoni in Italy. Can he give us an idea of the direction in which those studies are going? I am especially interested, for example, in the effect of VCM entering by breathing or through diffusion through the skin. We know that today in cleaning autoclaves, where high VCM concentrations are still encountered, workers generally wear masks. Is there any information available, or study planned about the effect of VCM entering the body through skin diffusion?

Dr. Stafford: Prof. Maltoni's experiments are related to extending the range of concentrations. As I mentioned, his original experiments went from 10,000 ppm down to 50 ppm. He is now looking at much lower concentrations—when investigations were started, 50 ppm seemed a very low concentration. He is also studying ingestion of vinyl chloride monomer and he is varying parameters such as length of time of exposure and so on, all complicated variants on the original experiments.

Dr. Thomas: I think that the absorption of vinyl chloride through the skin is extremely small. I have tried to find some reference to this, but I understood yesterday in going through medical papers that doctors are agreed that the amount absorbed through the skin is very small and not affecting appreciably the total intake.

Dr. Ernst (Berufsgenossenschaft der Chemische Industrie, Nurnberg, West Germany): In addition to Prof. Maltoni's group, are there any other research groups carrying out experiments with animals on this problem?

Dr. Stafford: Experiments are going on at TNO in the Netherlands, sponsored by one of the German companies. These are believed to be directed mainly at feeding rats with PVC compounds containing known concentrations of VCM. Some experiments are also going on in England at the research association known as BIBRA. I should imagine that within about a year we should have some results from their experiments.

Dr. Vinson: I have just spent a few weeks in Germany at Chemische Werke Huls, and my company is trying to reach the same standards as it has.

Dr. Stafford: Have you noticed any peculiar health effects on the workers?

Dr. Vinson: No effect on health has been observed. However, the factory is relatively new, and exposures have not been of great duration.

Dr. Nettesheim (Wacker Chemie, Cologne, West Germany): Are any substances known which may inhibit the effect of vinyl chloride monomer?

Dr. Stafford: There are no substances known to do this, but there is a lot of speculation that by keeping up the sulhydryl level in the liver, it might be possible to reduce the effect of vinyl chloride monomer or the metabolite which causes the trouble. But this is speculation only. Dr. Stockinger in the States recommended that more brassica should be eaten in order to get more cysteine into the system. But there is no suggestion of any real knowledge about this. Of course, we get right into the controversy which is going on now with Dr. Linus Pauling, whether massive doses of vitamin C prevent cancers developing in the body. As I say, all this is pure speculation, nothing is known.

Dr. Thomas: May we turn now to something different. When most people talk about the cancer agents, they do so from a qualitative viewpoint. I think it is interesting to have the other approach, the quantitative one. This is a new way of thinking, and even in the United States, there is no reference to any quantitative level. What usually happens in the States is that if a product is thought to be a carcinogen it is prevented from being used for various purposes - a purely qualitative approach. We now have a table, published this year in a document by CEFIC. It is interesting to present Table 1 because it shows, on one hand, the known effects of vinyl chloride in man together with the present situation. On the other side, is shown the effect on rats. All that we really know are the results from animal experimentation, mainly the experiments by Prof. Maltoni, in Italy, because as has been said previously, we are still waiting for the results from TNO, in Holland, and from BIBRA in England. There have also been some epidemiological studies, but as Dr. Stafford said, it is extremely difficult to make really good large-scale epidemiological studies.

First, I will explain how we have managed to present Table 1. We have been obliged to make a common evaluation–which is g/kg body weight per year. This is because there are results from inhalation studies, on the one hand, and from ingestion studies on the other. We

TABLE 1

Man		Rat	
Finding	Annual intake (g/kg body wt)[a]	Finding	Annual intake (g/kg body wt)
Angiosarcoma confirmed in polymerization operators	45-90	Very high angiosarcoma	75-180
No cases among other PVC production operators	9	High angiosarcoma incidence	4-15
No cases in PVC fabrication workers	1.8-4.5	Low angiosarcoma incidence	1.5
Current regulated levels for industrial workers	0.2-0.9	No effect level for rats	<1.5
Current performance in European industry	0.5	Possible metabolic threshold for rats	>0.3
Typical ingestion through food in Europe	0.00001 to 0.0000015		

[a]250 ppm VCM inhaled in air = 22.5 g/kg/pa (g VCM/kg body wt/yr); U. S. regulations demand 1 ppm = 0.09 g/kg/yr.

have tried to put all the results on the same table. Perhaps we can give some explanation later of the way in which our calculations were made.

Dr. Stafford: These figures related to annual intake in g/kg body weight. In man, we are reasonably certain that angiosarcomas do arise when man is exposed to 45 to 90 g/kg body weight. With rats, we know that there is a very high rate of angiosarcomas in the 75-180 g/kg body weight range. We have found no angiosarcoma in man so far at 9 g/kg, whereas with rats there is still a high rate of angiosarcomas in the 4 g/kg to 15 g/kg range. The question arises whether rats are more sensitive than man, or have some different mechanism going on in the body. There have been no authenticated cases so far of angiosarcomas among PVC fabrication workers. The intake that they might have had in the past is 2-5 g/kg. In rats, there is still a low rate of angiosarcomas at 1.5 g/kg. In Europe the current regulations in most countries are such that PVC polymerization workers are exposed to between 0.2 and 0.9 g/kg–this is a range, and it tends to be on the high side. The no-effect level in rats is known to be below 1.5 g/kg. Current performance in Europe plants is such that workers can be said to be exposed to about 0.5 g/kg. We wonder whether the threshold for rats is somewhere between 0.3 and 1.5 g/kg. To put these figures in perspective, I mentioned threshold limit values (TLV) earlier. When people are working at about, say 250 ppm, this is 22.5 g/kg exposure, so it can be seen that there has been a considerable improvement. Twenty years ago, the intake might have been several times that figure. If we look at foodstuffs, the intake of VCM is in the range of 0.00001-0.000001 g/kg body weight per annum. We can do the arithmetic required to see the difference between the exposure of the man to VCM in foodstuffs and of the man who has been exposed to VCM in a manufacturing plant. One more figure worth mentioning is that in U. S. law at the present time, 1 ppm, i.e., 0.09 g/kg, is allowed. As can be seen, therefore, there has been quite a change in recent years.

Dr. Thomas: I should mention that it is extremely difficult to present a precise figure because there have been some differences from one plant to another. The habits are different: for instance, in some plants, the workers are autoclave cleaners, and only autoclave cleaners, and some of them have had extremely high exposure for many years, whereas in other plants the workers might be autoclave cleaners for a while, then conductors or baggers and so on. This makes it difficult to compare one plant with another. It should also be mentioned that when it was possible to smell VCM some people liked that rather

agreeable sweet smell. I personally know several people in polymerization plants who used to smell the vinyl chloride monomer, and of course have inhalated a lot more VCM than the average. We must remember this when we consider the previous position of VCM toxicity in plants.

Dr. Martiny (Rohm and Haas France, Paris, France): What is the significance of the different levels between U. S. and European laws in respect of the maximum quantity allowed, as given by Dr. Stafford?

Dr. Stafford: I think that the differences in the figures are more apparent than real. I do not think that there is all that much difference in practice between Europe and the United States, no matter what figures are used. There are great differences in the ways in which these exposures are measured and computed to assess the actual dose being experienced by the plant operator. I do not think that we know anything in this area sufficiently accurately to distinguish between a figure of 1 ppm in the States and, say, 0.5 ppm here. I am not sure that there is any significance in these figures. I would say that they are in the same order - that may be sufficient. One of the aspects of this that has concerned us several times is that we may have overreacted and gone too far. The figures which were chosen in most countries, although perhaps they should not be described as "political" figures, reflect politics to some extent. In answering the question about the threshold and susceptibility to cancer like angiosarcoma and tying it up with some of the other questions, I must emphasize, as a layman in medical matters, that there are great difficulties in talking about cancer and threshold levels. I mentioned the fact that there was a clustering in the deaths, and all we can say is that we do not know of any angiosarcomas which have arisen in people exposed to 9 g/kg body weight. We know that angiosarcomas have arisen in people exposed to massive doses of vinyl chloride monomer for years, while some of their colleagues in the same polymerization plants with longer exposures have not developed them. We do not know about susceptibility of individuals. Some of the experiments now being done by Prof. Maltoni are related to this sort of aspect. If someone has been exposed to a massive dose 20 years previously for, say a year or two, is this damage "stored up" or does someone have to be exposed continuously over a longer period of time? There are many other similar questions which for the moment remain unanswered.

Dr. Ernst: Has there been any attempt to correlate the living habits of those people who developed angiosarcomas, such as smoking and alcohol consumption? Is anything known about this?

Dr. Stafford: I think there is partial knowledge about it. In all questionnaires which are sent to people who have had liver damage or angiosarcomas and who are still living, these questions are asked. But, again, we do not necessarily know what it signifies. There appears to be a natural incidence of angiosarcomas, but there is an additional incidence of angiosarcomas caused by VCM, oil, and other agents. I think it is significant that in England some testing of chromosomes in white blood cells has been done in people who have been exposed to vinyl chloride, and aberrations were found in the people with high exposure. There were fewer aberrations in the medium exposures and none at all in the lowest ones. This has been confirmed in the U. S. for the low exposures. But we will have to go back over all the data on cigarette smoking, personal habits, looking closely at the aberrations and to try and discover relationships. It is very complicated.

Dr. Thomas: I will now ask Dr. Praefke, as Chairman of the works practices' group of the European Vinyl Chloride Committee to tell us about the achievements of the group.

Dr. Praefke (Chemische Werke Huls, Marl, West Germany): As mentioned before, industry has to work at a socially acceptable risk and the PVC industry is continuing production under this aspect.

There are four groups that may be exposed to vinyl chloride: men in VC monomer and polymer production; men in PVC fabrication; people living in the neighborhood of these plants; consumers of PVC goods. The industry assumes the responsibility for protecting these four groups against risks arising from vinyl chloride as well as from other sources. As you have heard, there have been no authenticated cases of illness in the big groups of fabricators, neighbors, and consumers, and since there have only been isolated cases of illness in monomer plants and polymer plants with the exception of autoclave cleaners, it appears that there must be a safe route for further production under previous conditions for the remaining groups. It is the aim of the VC and PVC industry to increase the safety margin as far as possible for human beings involved.

What has been done in the last two years?

The problem was to decrease the emissions as far as possible as this would reduce the working area concentration and the emissions to the neighborhood. The biggest source of emission was the polymer plant, so let me take this plant as an example.

As you all know, the polymerization cycle is feeding, polymerizing, degassing, drying, cleaning.

Feeding and polymerizing are no major problems in this connection because they are carried out in pressure-proof facilities and

only fugitive emissions occur. The degassing is the crucial point, as nearly all unpolymerized and undegassed VC subsequently excapes into the atmosphere, mostly with the drying air at the stack, in minor proportions during processing, or in very small quantities from fabricated PVC into the environment and possibly into food. So a degassing technology had to be developed for lowest monomer contents. This had to be done for the different types and grades of PVC polymers. The European PVC producers decided that instead of combining their efforts, each process should be evaluated separately, in full competition, thereupon offering licenses for the best method. This was the quickest way of solving the problem. About 80% of the suspension grades of PVC, for example, can be degassed to or below 500 ppm VC in PVC instead of concentrations of several thousand parts used before, and the same dry PVC resin grades can have less than 20 ppm VC instead of several hundred parts they had before. At present, the degassing facilities of most of our European plants are being reconstructed which will result in a dropping of the VC content in PVC down to approximately 5% of the former level.

All this degassed vinyl chloride monomer is recovered and again fed to the autoclaves with fresh monomer.

This extensive degassing protects the four groups mentioned before. There is no emission of the degassed and recycled monomer into the working area, the VC content of the plant atmosphere is considerably lower, thus providing better protection for the workers. The vent stream of the dryer has such a low VC content that it is not practical to purify the wet and warm air, which is contaminated by PVC dust, by adsorption or absorption methods; the emission is considerably lower and owing to extremely low emissions, the people living in the neighborhood are much less exposed to VC. The PVC resin has a lower monomer content of which in the course of processing the resin into the finished product, about 50-90% is emitted into the atmosphere. This emission is again reduced, so that better protection of workers and neighbors is afforded, thus also providing better protection for the consumers.

In addition to this extensive degassing, all other measures are of second rank, e.g., degassing of wastewater streams containing VC, purification of vent streams having a high VC content, especially the inert gas stream after liquefying the recovered VC.

All this work has to be checked by analytical instruments. Fixed-point monitors detect and print out the actual VC level at several points of the working area supported by transportable leak detectors and in some countries completed with personal monitors which with a time lag indicate the average concentration in the inhaled air and adjusted by grab samples of the air analyzed in the laboratory. So

TABLE 2. History of Exposure of Workers in the PVC Industry (Typical Ranges)

	VCM exposure level, ppm		
Years	VCM polymerization plant operators	PVC fabrication operators	VCM production plant operators
1945-1960	≥1000	?	≥500
1960-1970	~300-400	possibly 10-20	>5
1973	~150	~5	~5
Now	~5	<2	<2

we know that in most of our monomer and polymer plants the area concentration is about 5 ppm VC, and the concentration of the inhaled air averages 1-3 ppm VC. This has been the concentration in fabricating plants in the past where no authenticated cases occurred (Table 2). Industry is still trying to reduce this concentration in order to increase the safety margin for labor protection.

As you know, only a few cases of acro-osteolysis and angiosarcoma of the liver have occurred in the group of autoclave cleaners. To a large extent this problem has been solved by a combination of various factors. Special groups of autoclave cleaners have been broken up and the length of time spent by men in the autoclave has been reduced. Antifouling recipes have been developed which allow polymerization of several batches without manual cleaning. The autoclave atmosphere is purged by inert gases fed into the VC recovery system, and the air in the autoclaves before and during the stay of the workers is analyzed. Manual cleaning is replaced by mechanical cleaning with water under high pressure; in large autoclaves this is done automatically without having to open or enter the reactor.

The PVC producers carried out some measurements of the working area of fabricators. Well-equipped processing plants working with PVC resins of a VC content below 100 ppm have area concentrations below 2 ppm, mostly below 1 ppm.

With these combined efforts we are confident that we can handle large quantities of the toxic substance called vinyl chloride monomer at a socially acceptable risk. Poly(vinyl chloride) will survive.

Dr. Thomas: We have now come to the end of the session. I will try to add just a few words on the lessons to be learnt from these problems. The emphasis placed on the problem of toxicity of vinyl chloride is not directly related to the number of deaths but specifically to the aspect that if angiosarcomas had not been found to be nearly specific to exposure to vinyl chloride, no one would have heard about this vinyl chloride problem. If, instead of angiosarcomas, it had been cancer of the lung or of the larynx, we would not have been aware of the number of tumors arising as a result of vinyl chloride exposure. I do not want to say that there are no more problems with vinyl chloride, but what we have achieved can reassure us about the future of PVC industry. However, we must return to the quantitative aspect and try to consider this. All the emotion aroused about vinyl chloride came from qualitative findings throughout the world. That was emotional, arising from specific angiosarcoma development. We should now think about the other things, because vinyl chloride is only an example, not only for the chemical industry but for the people who are responsible for legislation all over the world. Everybody will now look at the PVC industry and what has been done there. I think that nothing will be the same now in the chemical industry as a whole, and with everything connected with all these problems as a result of the vinyl chloride toxicity problem.