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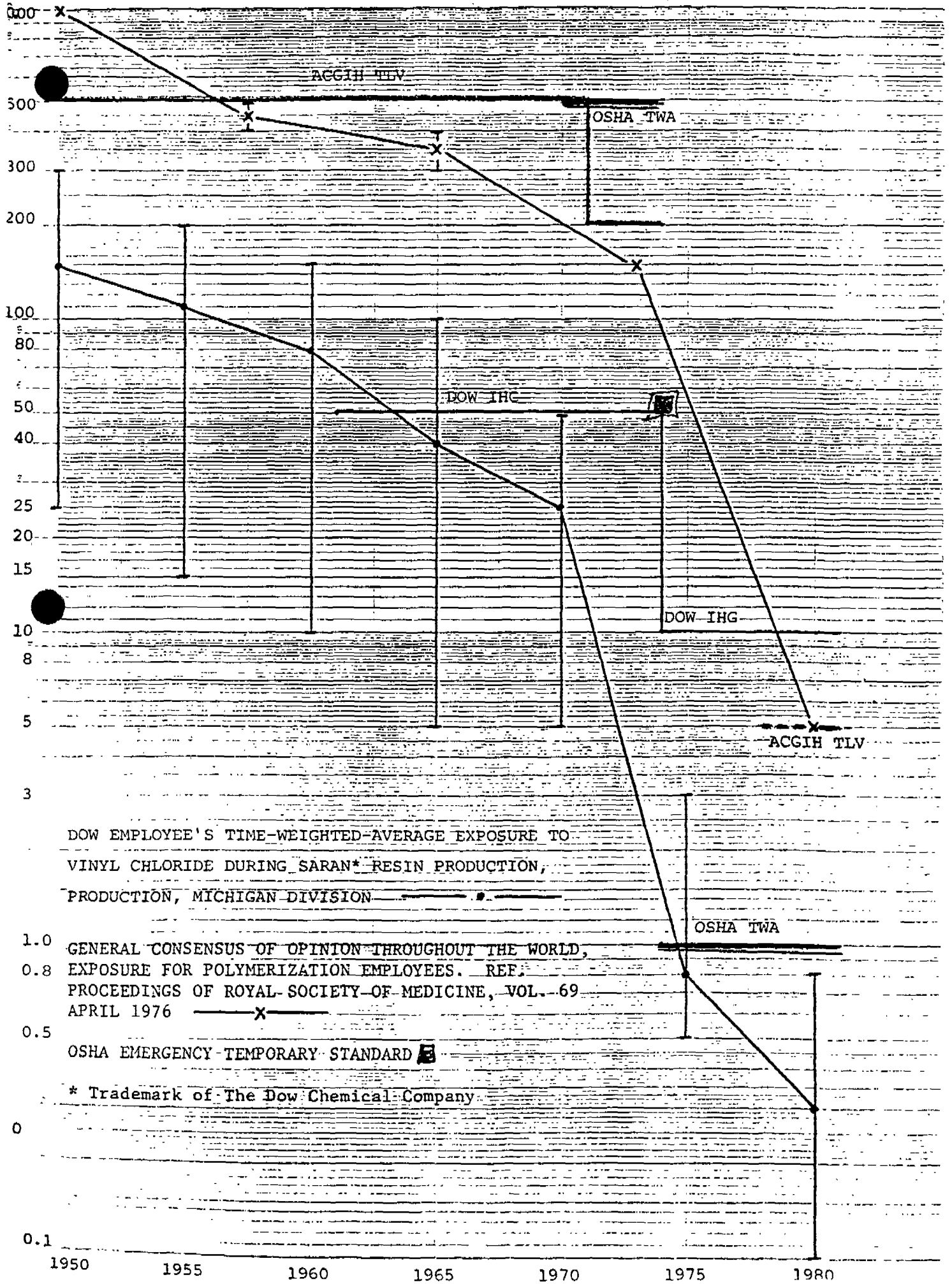
VINYL CHLORIDE EXPOSURES AND GUIDELINES/STANDARDS



HEALTH & ENVIRONMENTAL SCIENCES, U.S.A.

Bob Dostal,

Page 279 contains the estimated concentrations to which PVC workers were exposed.

I can possibly find other places where these same figures have been cited.

TRT

FROM: T. R. TORKELSON
1803 Building
517/636-5197

be due to exposure; he or she should see a supervised worker who has been absent from work more than two weeks owing to illness. These absences should be reviewed on a group and individual basis. If indicated, medical examination should be undertaken at any time. Section 16 provides for the keeping of confidential medical records of all supervised workers; these must not be destroyed without the agreement of the Chief Employment Medical Adviser.

The purpose of the present symposium is to review British experience of the environmental, clinical, epidemiological and pathological effects of exposure to vinyl chloride arising in the course of polymerization of vinyl chloride monomer to polyvinyl chloride, and to exchange information.

The implications of the association of angiosarcoma of the liver with exposure of workers to vinyl chloride monomer have had such a profound effect on industry, workers and governments that these effects must be seen in the wider context of occupational carcinogenesis generally. I think it is necessary to consider what the future may hold in the way of carcinogenic risks. We can, I believe, regard the experience we have gained throughout the world with vinyl chloride as a pilot study on a newly discovered occupational carcinogen. Frank and open discussion between government departments and both sides of industry is indispensable to the achievement of success.

Postscript

The Working Group on Vinyl Chloride Code of Practice for Health Precautions met on 8 October 1975 and adopted a new hygiene standard agreed by the Working Group as 'a ceiling value of 30 ppm and a time weighted average of 10 ppm, allowing that wherever practicable exposure should be brought as near as possible to zero concentrations.' The figures of 30 parts/10^6 and 10 parts/10^6 replace the original figures of 50 parts/10^6 and 25 parts/10^6.

Other requirements of the Code, including medical supervision, are currently being reviewed.

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Mr A W Barnes
(*ICI Plastics Division, Welwyn Garden City, Hertfordshire*)

Vinyl Chloride and the Production of PVC

Polymerization Characteristics of Vinyl Chloride

Vinyl chloride has a boiling point of −13.5°C; under normal pressures and temperatures it is a gas. In its liquefied form under pressure, it can be readily polymerized at temperatures in the range 40–70°C to give polyvinyl chloride (PVC), a white solid material. The addition polymerization of about 500–1500 molecules of vinyl chloride produces one molecule of PVC and the polymerization reaction is strongly exothermic. The polymer itself is insoluble in the liquid monomer and so precipitates out as it is produced. The polymer is, however, capable of absorbing high proportions of monomer (40% by weight) so that as the polymerization reaction proceeds and more polymer is precipitated, so equally is more monomer absorbed by the polymer to the point at about 70% conversion where monomer as a separate liquid phase disappears and the remaining monomer must be polymerized in its dissolved state within the swollen polymer. As this phase of the polymerization proceeds, the concentration of monomer in the polymer decreases and the rate of reaction correspondingly diminishes until at about 92–95% total conversion the speed of polymerization becomes uneconomically slow. These are the fundamental characteristics of vinyl chloride and its polymerization mechanism which decide the principal features of industrial processes for the production of PVC.

The Production Process for PVC

Because it must be polymerized in liquefied form at temperatures above its boiling point, the industrial process must be carried out in pressure vessels (at 50°C the vapour pressure of vinyl chloride is ~7 atmospheres). Because the reaction is exothermic, means must be found for removal of the heat produced so that the temperature of reaction (and thus the pressure, and the properties of the end-product) may be kept under control. In the most widely used process, this control is achieved by dispersing the liquid monomer into tiny droplets (about 100 μm in diameter) in approximately equal quantities of water, by means of mechanical agitation together with the addition of small quantities of surface-active agents which facilitate the breakdown of the monomer into droplets and stabilize it in this form. This fine subdivision of liquid monomer enables the heat evolved from the polymerizing monomer to be rapidly transferred to the surrounding water and then removed by a cooling jacket on the reactor, the process being aided by agitation. The subdivision of the monomer into droplets has also the vital property of ensuring that the polymer, which is produced within each droplet, is presented at the end of the reaction in finely divided, powder form, and not as an intractable horny mass.

As polymerization proceeds, the two phase system of monomer dispersed in water becomes a three phase system of solid polymer precipitated within liquid monomer droplets which are in turn dispersed in a continuous water phase. A great deal of research has been devoted in the past thirty years to the control and stabilization of this rather delicate colloidal system but, even so, small quantities of polymer are still thrown out from it and form a thin continuous film of PVC on the walls of the reactor. If left, this will increase in thickness and, since PVC is a poor thermal conductor, will reduce the heat transfer characteristics of the vessel and make temperature control impossible. At the end of the reaction it is therefore essential that this film should be cleaned away. This is one of the basic reasons why a truly continuous process has never yet been developed for making PVC and why the polymer, the world over, is still made by a batch process in relatively small reactors. This, as we shall see, has a significant influence on the ease of controlling fugitive monomer in a PVC plant.

As polymerization nears 90–92% conversion, the rate of reaction slows down markedly and at about 95% conversion has become so slow as to be quite uneconomic. There is no possibility therefore of continuing polymerization to 100% conversion and solving some of the problems connected with vinyl chloride toxicity in this way. At the termination point of the reaction, therefore, the 5–6% residual monomer (still at a pressure of 4–5 atmospheres) is vented back to a gasholder and a slurry of PVC particles (100–150 μm diameter), suspended by stirring in water, is left in the reactor.

Now to a description of the process in engineering rather than chemical terms: polymerization is carried out in cylindrical, stirred, jacketed pressure vessels. To begin, water, surfactive agents and free radical catalyst are added to the reactor: the air space above this liquid phase is purged of oxygen (which inhibits polymerization) and liquid vinyl chloride is then injected into the reactor. (In the UK, reactor sizes range from 10m³ to 40m³ and the monomer charge per batch ranges up to about 15 tons.) The reactor contents are then heated to and maintained at reaction temperature. After a reaction time of the order of eight hours, excess monomer is vented to a gasholder (for recycling) and the reactor is evacuated, at elevated temperature, to strip as much monomer as possible from the polymer on which it is absorbed. The polymer slurry is then transferred to closed tanks prior to the next stage in the process.

Meanwhile the empty autoclave, which still contains vinyl chloride gas at a low partial pressure is further evacuated before opening to atmosphere, and automatic high pressure water cleaning jets are activated to remove polymer scale from the walls. At this stage, the cycle is complete.

Vinyl chloride monomer has a strong affinity for PVC and the last traces of it are difficult to remove from the polymer; the polymer in the slurry after stripping therefore still contains around 500 parts/10^6 of vinyl chloride. This slurry is centrifuged to remove the water phase and the wet powder is then dried in continuous driers; during this process further vinyl chloride is removed in the drier gases and the final dried powder currently contains about 50 parts/10^6 of monomer.

Interfaces between Vinyl Chloride and People

This description of the production process gives some indication of the relative potentials of different parts of the process for creating significant exposures of people to vinyl chloride. If we take a plant capable of making 100 000 tons per annum (tpa) of PVC then the polymerization building will, during the course of a year, have handled over 100 000 tons of vinyl chloride in

liquefied form under pressure. Into the drying section will have passed 50 tons of vinyl chloride in a form strongly absorbed on the polymer and at a concentration on polymer of about 0.05%. In the finished product, 5 tons of vinyl chloride will leave the factory, each year, still absorbed on the polymer at a concentration of 0.005%. Although strictly outside the scope of this paper it is worth proceeding further and pointing out that in further fabrication operations on the polymer, some of this small residual concentration of monomer is driven off so that in the final fabricated article only ~5 parts/10^6 of monomer remain or 0.5 tons out of the original annual total of 100 000 tons. In fabricated articles which are used for foodstuffs packaging (bottles, film and foil), and which represent about 10% of total UK production, the monomer concentration is still lower, and the pro rata amount absorbed on foodstuff containers from a 100 000 tpa plant would be 50 lb. Of this quantity 3½ lb might migrate into the foodstuff where its average concentration is unlikely to exceed 10 parts per thousand million. Since total UK production is about 400 000 tpa this means that the annual ingestion by the average UK citizen cannot exceed 0.0001 g, a figure which agrees well with calculations based on diet analysis.

A final potential interface arises because at points in the production process, vinyl chloride is exhausted to atmosphere. On a typical PVC plant and with current levels of achievement, 0.3% of the monomer is lost to atmosphere: with this performance ground level concentrations at the factory boundary are well below 0.1 parts/10^6 and even these low amounts decay very rapidly with distance. In the band ¼–1 mile (0.4–1.6 km) around one factory, for instance, the concentrations determined are in the range 0.01–0.0001 parts/10^6.

These figures should make clear that by far the biggest potential for exposure exists in the polymerization section of the plant, since here 100 000 tons per year of a liquefied gas under pressure are handled in a confined space, in contrast to other parts of the process and to the later downstream operations of the plastics industry. In these downstream operations the corresponding quantities, this time in the form of absorbed vapour at a low partial pressure and not confined to a single geographic situation, range from 5 tons down to 3 lb per year. That the polymerization section is in fact the area where hazard has existed in the past is confirmed by the fact that all the authenticated cases of vinyl chloride-related angiosarcoma of the liver throughout the world have been of workers engaged in plants where liquid vinyl chloride under pressure was used in large quantities.

The nature of the polymerization process, as described above, illustrates why exposures in the past could have been large. The plants are composed of a large number of batch reactors of small capacity per batch, relative to the total annual throughout. In each reactor, two complete cycles per day are carried out and each cycle requires vinyl chloride to be injected under pressure, heated, contained, stirred and polymerized almost completely: at the end of the cycle unpolymerized monomer has to be removed and the reactor opened and cleaned. The possibilities of small leakages from pumps, valves, stirrer glands and from the opened reactor at the end of the cycle were obviously significant: and the manual cleaning of reactors gave further opportunity for high exposures. This was particularly true during the long period in the 1940s to 1960s when vinyl chloride was thought to be harmless and when a recommended exposure limit did not exist or, late in the 1950s, was set by regulatory authorities, industrial hygienists, &c., at a level of 500 parts/10^6.

The general consensus of opinion throughout the world, today, is that average atmospheric exposure for polymerization workers between 1940 and 1970 might have been of the following orders: 1945–55, ~1000 parts/10^6; 1955–60, ~400–500; 1960–70, ~300–400; mid-1973, ~150; 1975, ~5 parts/10^6. Across the world, there will have been variations around these figures because of differences in plant design r process operation. Even the way in which jobs were organized can have caused variations. In some countries or on some plants workmen were employed specifically to clean out autoclaves (where exposures could have been very high) while in others autoclave cleaning was part only of a whole range of jobs carried out by individual work people. Some spokesmen have suggested, perhaps for full-time cleaners, exposure levels as high as 3000 parts/10^6 in the early days of the industry.

With these very high figures as background, the progress made by the PVC industry in the UK in reducing atmospheric concentrations since the carcinogenic hazard of vinyl chloride became known in early 1974 is shown in Table 1, which also shows improvements made at all the other interfaces described earlier in this paper. Although, as we have seen, the exposure levels in these other places are many orders of magnitude lower than on the polymerization plants, industry has aimed to reduce fugitive vinyl chloride levels

at every point in order to eliminate concern wherever it might exist. With work still in progress, all these figures will be reduced further though, in view of the effort already put in, it is likely that the polymerization plant atmospheres are approaching a limiting value of 2–5 parts/10^6.

Table 1

Vinyl chloride monomer levels in UK industry

	January 1974 (parts/10^6)	*July 1975 (parts/10^6)*
Polymerization		
VCM in plant atmosphere (weekly average)	~150	~5
VCM emissions	0.75% of output	0.3% of output
VCM in product	200–500	< 50 for most grades
Fabrication and Use		
VCM in plant atmospheres	2–15	<2
VCM in PVC bottles	~50	~2
VCM in beverages	0.1	0.01

Finally a few rough calculations of the daily dosages at the current exposure levels and at the higher atmospheric levels which previously could have existed on PVC plants may be helpful in putting current plant performance and present downstream exposures into perspective, one with another, and in comparison with earlier figures (Table 2).

Table 2

Daily dosages at current and earlier exposure levels

	Daily dose (g/kg body weight)
Polymerization plant operator at 1000 parts/10^6	0.36
Polymerization plant operator at 500 parts/10^6	0.18
Polymerization plant operator now at ~5 parts/10^6	0.0018
Fabrication plant operator at 1 part/10^6	0.0004
Average UK citizen through ingestion in food	0.000000004

In later papers to this conference, a wide range of diseases or symptoms which have been associated with or attributed to exposure to vinyl chloride will be discussed. It is important to note that most, if not all, of these have been contracted by people who worked under conditions represented by the highest figures in the above table. Today no one is exposed to doses at this level. The exposure of workers in industry is now at least two orders of magnitude lower, while the general public in the UK absorbs, through foodstuffs, a quantity which is some fifty million times lower.

While the conference will be concentrating primarily on problems which have occurred in the past, I hope it may find some time to consider whether there remains any possibility of similar effects occurring at the markedly lower – and in some areas almost incomprehensibly lower – levels which prevail today. For it is on this, quite properly, that industry, and society generally, have focused their attention in the past eighteen months.

DISCUSSION

Dr M D Kipling (*Employment Medical Advisory Service, Birmingham*) said that it was known that workers bagging the PVC powder were sometimes covered with the dust and that this powder contained a percentage of vinyl chloride monomer. He asked whether any information was available on the particle-size of the dust produced in differing processes throughout the world and the incidence of vinyl chloride disease.

Mr A W Barnes replied that the particle sizes of PVC powder did vary very widely, depending on the application for which the PVC powder was made. However, most manufacturers produced all grades of polymer so that it was unlikely that any medical conditions peculiar to a particular manufacturing site could be explained in terms of the polymer and its particle size. Moreover, it should be remembered that all the significant medical effects under discussion at this conference (angiosarcoma, acro-osteolysis &c.) had, throughout the world, been observed exclusively in workers on polymerization plants or, in two cases, plants handling liquid vinyl chloride under pressure. Features common to all these workers were that they were exposed to vinyl chloride vapour in the atmosphere but were not exposed to PVC dust since the polymer was maintained in aqueous suspension throughout this stage of the process.

It was in the drying and bagging sections of the PVC-producing process that exposure to solid PVC particles could arise but, despite extensive medical investigation, no significant abnormalities had been found among drier operators or packers. It was perhaps worth noting, too, that the greater proportion of PVC powder was of a particle size similar to sand so it did not generally pose an airborne dust problem. For those powders which might cause true dust exposures it had been customary in industry, because of the nuisance and discomfort factors alone, to provide some form of respiratory protection.

Dr C S Darke (*Royal Infirmary, Sheffield*) said that he had investigated 14 cases of breathlessness in workers exposed to vinyl chloride monomer. The findings were: no abnormal physical signs; chest radiographs normal; routine respiratory function tests difficult to evaluate but some results slightly below predicted values, especially impaired CO diffusion in 6 individuals; perfusion and ventilation scans showed striking abnormalities as illustrated by one slide revealing marked perfusion defects of upper lobes. One patient underwent open biopsy of each of the three lobes of the right lung. Histology revealed focal alveolar wall thickening with macrophages in the alveolar spaces and increased reticulin and collagen

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formation seen on electron microscopy. No obvious vascular abnormality except on fluorescent examination. It might be of importance that some of the worst affected men were concerned in a polymerization process that yielded 'plastisol', a very fine PVC powder with particle size around 0.5 μm. These particles, containing vinyl chloride monomer, could be carried to the alveolar walls where they might be retained and thus set up a reaction of the type seen on light microscopy.

Professor I J Selikoff (*Mount Sinai School of Medicine, City University of New York*) said that pulmonary abnormalities had been unexpectedly common findings among some 1200 vinyl chloride polymerization workers in his studies. Obstructive pulmonary function defects were noted in approximately 50%. Neither age nor cigarette smoking served to explain the findings. For those under age 40, obstructive findings were predominantly among cigarette smokers, as expected. After that age, however, the prevalence of changes was very much the same among smokers and nonsmokers. Of course, age correlated strongly with duration of employment. These two factors were analysed separately and it was found that the changes were generally among smokers with less than 20 years from onset of exposure, but that thereafter they were present in both smokers and nonsmokers. Radiographic changes were less common. Overall, 13.3% of 985 chest films showed linear, reticular or nodular changes characterized as 1/0 or 1/1 in the ILO U/C Classification. Dyspnœa was uncommon and signs or symptoms of chronic bronchitis were not striking (Miller *et al.* 1975, Miller 1975).

The pathogenesis of these abnormalities was not clear. It was not known, for example, whether they reflected another biological change associated with exposure to vinyl chloride monomer, or another factor. Mr A W Barnes had noted that manufactured PVC might currently contain 5 parts/10^6 of retained vinyl chloride monomer, as well as other agents added in the polymerization process. Inhalation of such PVC particles might be associated with adverse effect. Frongia and his colleagues (1974) had reported significant histopathological changes in the lungs of guinea-pigs exposed to PVC powder in a PVC plant. In the polymerization facilities investigated by Professor Selikoff, there had usually been opportunity for PVC dust exposure as well as vinyl chloride exposure, either by a period of work with the polymer during the employment span and/or as the result of incomplete separation of the various parts of the production process. PVC dust was often to be found in several parts of the plants.

It would seem of interest to study further the influence of vinyl chloride and PVC in the experimental animal, as well as the pulmonary status of workers producing vinyl chloride monomer but not exposed to PVC during or after the polymerization process.

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Dr K S Williamson
(ICI Ltd, Central Medical Group, Fulshaw Hall, Wilmslow, Cheshire, SK9 1QB)

Review of Animal Studies

Since vinyl chloride is a gas at normal temperature and pressure, inhalation is the important route of exposure in industry, and most animal studies have used this method of dosing. Many experimental studies have demonstrated the very low acute toxicity of the compound. The acute inhalation toxicity was studied by Mastromatteo *et al.* (1960), who found that the lethal concentration for mice, rats and guinea-pigs exposed for 30 minutes was between 200 and 300 000 parts/10^6. In long-term studies few toxic effects were reported, though Torkelson *et al.* (1961) found that inhalation of vinyl chloride resulted in minimal microscopic changes in the liver and kidneys of several species of experimental animals exposed seven hours a day to 500–200 parts/10^6 for six-month periods. No significant changes were found in any species exposed to 50 parts/10^6 for six months.

In 1971, however, Viola *et al.* reported that while attempting to produce acro-osteolysis in rats, they had found tumours of the ceruminous glands, lungs and bones in animals exposed for 4 hours a day, 5 days a week, for 12 months to 30 000 parts/10^6 of vinyl chloride. Viola's findings, which are the earliest to be published describing the oncogenic effect of vinyl chloride, caused considerable concern throughout the world and led to further epidemiological and animal studies, many of which are still incomplete. The most complete series of animal studies available to us are those conducted by Maltoni and his co-workers (Maltoni 1973, Maltoni & Lefemine 1974). In these experiments groups of rats were exposed to vinyl chloride vapour concentrations ranging from 10 000 to 50 parts/10^6 for 4 hours a day, 5 days a week, for 12 months. The animals were then maintained for the rest of their lives unless they became ill. Tumours of the ceruminous glands, angiosarcomata of liver and other organs, nephroblastomata and a variety of other tumours were found in animals exposed to vinyl chloride. In animals exposed to 50, 250 and 500 parts/10^6 the logarithms of the numbers of animals having angiosarcomata and the total tumour-bearing animals are linearly related to the dose of vinyl chloride, but in animals exposed to higher concentrations, this relationship is not found. Tumours have also been found in mice and hamsters by Maltoni and by Keplinger *et al.* (1975), who reported the findings of angiosarcomata and lung adenomata in mice exposed

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ESTABLISHMENT OF PAST EXPOSURE CONCENTRATION IN VCM/PVC PLANTS
June 25, 1977

Many, including Dr. David Rall of NIEHS, have noted that rodents appear more susceptible to vinyl chloride induced angiosarcoma than humans. If this were not true the exposures of workermen to vinyl chloride in previous years would have resulted in hundreds of angiosarcomas in the U.S. rather than the 19-20 cases reported since 1961. This is extremely important to the vinyl industry since future animals studies will no doubt result in cancer at lower and lower levels of exposure.

It would be most useful if we could at least semi-quantitatively ascribe numbers to previous exposures. These need not be precise estimates, ~~estimates~~, orders of magnitude will be adequate. Therefore, it is requested that each company thoroughly investigate all the methods which it can to realistically evaluate previous exposures of their employees included in the Equitable Environmental Health (MCA) study.

It must be remembered that prior to 1962 there was no accepted industrial hygiene guide for vinyl chloride. In 1962, the ACGIH suggested a time weighted average (TWA) of 500 ppm. Until 1963, there was no limit on peak exposures; thus a worker could have experienced less than 500 ppm as a TWA but have had peak exposures of several thousand parts per million for several minutes.

The following are suggested as possible ways of documentating past vinyl chloride exposures. Each has serious limitations but please remember we only need to establish whether exposures were nearer 10, 100, 1000, 10000 or even 100,000 ppm in order to show a difference between people and rodents.

SPEECH ON VINYL CHLORIDE GIVEN BY V. K. ROWE AT THE FOURTEENTH ANNUAL INDUSTRIAL HYGIENE CONFERENCE, FONTAINEBLEAU HOTEL, MIAMI, FLORIDA, MAY 15, 1974.

What I am going to try do do is to give you a chronological picture, at least as I know it, from away back up until today. Things are happening so fast, that I am not even sure about today.

Years ago, and this goes back to the 40's and perhaps even before that, no one was particularly concerned about vinyl chloride. The acute work that was done toxicologically, certainly indicated that it was nothing more than a darn poor anesthetic, as a matter of fact everybody knew it was a central nervous system depressant, but people tried it out as an anesthetic and it didn't work very well. In some applications along the way in the use and manufacture of it some people did find out that it was a fairly potent anesthetic.

Back in 1949, there apparently was a Russian article dealing with vinyl chloride, which most of us have never seen. It has recently come to light and I have yet to see this article. I am told that it tells us that the Russian's had found the material to be a liver toxin. I don't think there is anything in there with respect to carcinogenesis, but I haven't seen the article. Perhaps someone who has can add to that information later.

In 1958 and 9, I can become a bit more realistic, because during the preceding years in our laboratory we had been studying a series of chlorinated hydrocarbons and at that particular time we decided that we were handling a lot of vinyl chloride so we thought we would introduce it into our inhalation program. Back in those days, the typical inhalation experiment involved several species of animals not too large a number, and exposures of 7 hours/day, for 5 days/week for a period of six months. Then the animals were sacrificed and examined to see what had happened to them. That was the typical thing we did back in those days. We studied concentrations of 500, 200, 100, and 50 ppm during the period of 1958 and 9. We found out that, in our rat colonly at least, these were Wistar rats in those days, that we had liver and kidney injury at 500, we had slight liver weight increases at 200, we had liver weight increases at 100 and nothing at 50. At the 200 ppm level, we also exposed guinea pigs, rabbits, and dogs and we found only liver injury at 200 with the rabbits, nothing in the other two species, either at that level, 100 or at 50 ppm.

Nevertheless, we had the basic philosphy, I think that one kept the industrial hygiene limits and guidelines as low as he could practically and we set for ouselves the guideline of 50 ppm on a time-weighted average basis at that time with

a maximum of 100 ppm. As I've said publicly before, we didn't always achieve that, but that was at least our goal. That paper was published in 1961 in the AIHA journal.

In 1963 and 4, the problem of acroosteolysis came to be known in Europe. People hadn't recognized it, to my knowledge, in this country but very shortly after that, as a matter of fact in 1967 and 8 if I am not mistaken, U. S. industry, through the Manufacturing Chemists Association (MCA) undertook an epidemiological study on PVC workers to see whether there was a significant amount of acroosteolysis in this country. Now that job was undertaken by some of our good friends from the University of Michigan. The result was that they did find some acroosteolysis in some kettle cleaners in some of the PVC industries. We felt fortunate at that particular time because we didn't find any in our workers but we were also using different technology than some of the others and this was perhaps the explanation for it.

Nevertheless, we were somewhat concerned about the picture with regard to vinyl chloride, so John Mutchler who is now with Clayton Associates, and Dr. Kramer who was in our Division Medical Department at that time undertook a study of all the clinical records that we had relative to people who had been employed in vinyl chloride, vinyl chloride polymers

Oct 1961

The Toxicity of Vinyl Chloride as Determined by Repeated Exposure of Laboratory Animals

T. R. TORKELSON, M.S., F. OYEN, and V. K. ROWE, M.S.

Biochemical Research Laboratory, The Dow Chemical Company, Midland, Michigan

Groups of laboratory animals were exposed repeatedly for up to six months to either 500, 200, 100 or 50 ppm vinyl chloride in air. Detectable changes occurred at all but the lowest concentration. The results are discussed and handling precautions suggested.

Introduction

VINYL chloride (CH_2=$CHCl$) is a chemical of great industrial importance. It is used in the preparation of polyvinyl chloride resin, as a copolymer in saran and other plastics, as a chemical intermediate and as a solvent. Because of the flammability of vinyl chloride, it has been generally assumed that the greatest hazard associated with vinyl chloride is that due to its flammability rather than its toxicity.[1]

The toxicity of vinyl chloride has been reviewed by von Oettingen[2] and more recently by Mastromatteo *et al.*[3] von Oettingen concluded that the gas was anesthetic in high concentrations and that considerable interest had been shown in the use of vinyl chloride as a surgical anesthetic. However, its effect on the circulatory system has discouraged exploitation of this property. No doubt the hazard from flammability has also hindered this use. Only limited repeated exposures which were reported by Schaumann[4] were discussed by von Oettingen. These repeated exposures indicated little or no chronic effects even from anesthetic concentrations.

Mastromatteo *et al.*[3] also discussed the published data and reported the results of single exposures of mice, rats and guinea pigs which confirmed the low acute toxicity of vinyl chloride. Mastromatteo reported that only two human fatalities due to vinyl chloride had been reported.

It can be concluded from the published toxicological data that anesthesia is the only significant effect of acute exposure. Sufficient repeated exposures have not been reported to draw conclusions about chronic toxicity. The Threshold Limit Value of 500 ppm suggested by the American Conference of Governmental Industrial Hygienists (ACGIH)[5] is reported by Smyth[6] to be based on single animal exposures and human experience.

The following report summarizes the results of repeated exposures of laboratory animals to either 500, 200, 100 or 50 ppm of vinyl chloride. The significance of the results is discussed and recommendations for a threshold limit value are made.

Experimental Procedures

Materials Tested

Vinyl chloride, CH_2=$CHCl$, is a colorless gas. It has a boiling point of −13.35°C (+7.97°F) and a freezing point of −154°C (−244.82°F). The material polymerizes readily and hence is sometimes inhibited with phenol or tertiary butylcatechol. Vinyl chloride is very flammable, its flashpoint being −78°C (−108°F). The explosive limits are from 4% to 22% by volume. It has little odor although high concentrations may smell faintly sweet.

A single, uninhibited sample was used in these studies. It was shown by mass spectrographic analysis to be essentially pure CH_2=$CHCl$, being the only impurity detected in gas phase samples.

Source and Feeding of Animals

The rats and rabbits used in this study were obtained from the stock colony of this laboratory, the guinea pigs were obtained from a commercial grower[7] and the dogs were purebred beagles obtained from a local kennel. The rats and dogs were fed Purina Laboratory Chow[8] or Famo Laboratory Ration.[9] The rabbits and guinea pigs received Famo Rabbit Ration. The guinea pig diet was supplemented with carrots.

Experimental Protocol

The experiments were continued in two phases. In the first phase, groups of 10

TABLE IX

Summary of Average Hematological Values for Dogs Receiving Repeated 7-Hour Exposures to Vinyl Chloride

Dog #	Sex	Concentration in ppm	Months on Experiment	No. of Animals	Hemoglobin g/100 g	Hematocrit	WBX × 10^3	Neutrophils	Lymphocytes	Monocytes	Eosinophils
Dog #152	M	Unexposed control	0	1	11	43	12.9	54	41	1	4
Dog #152	M	Unexposed control	3	1	15	52	19.4	42	50	4	4
Dog #152	M	Unexposed control	6	1	15.5	54	15.4	52	40	5	3
Dog #156	M	Air exposed control	0	1	—	—	—	—	—	—	—
Dog #156	M	Air exposed control	3	1	14.5	50	13.4	45	50	2	3
Dog #156	M	Air exposed control	6	1	14	50	11.1	55	28	5	12
Dog #162	M	50	0	1	10.5	39	13.6	48	48	2	2
Dog #162	M	50	3	1	14.5	54	12.7	48	48	3	1
Dog #162	M	50	6	1	15.5	53	11.2	43	50	4	3
Dog #151	F	Unexposed control	0	1	11	48	13.3	59	30	3	8
Dog #151	F	Unexposed control	3	1	14.5	52	23.6	67	25	0	8
Dog #151	F	Unexposed control	6	1	15.5	58	15.5	46	42	3	9
Dog #155	F	Air exposed control	0	1	13	46	14	61	37	0	2
Dog #155	F	Air exposed control	3	1	16	59	18.2	60	33	5	2
Dog #155	F	Air exposed control	6	1	15.5	56	17.0	53	31	5	11
Dog #161	F	50	0	1	10.5	35	15.3	55	40	5	0
Dog #161	F	50	3	1	15.5	58	13.4	56	42	2	0
Dog #161	F	50	6	1	15.5	56	12.3	43	43	3	11

adjacent to the leaks. The flammability of vinyl chloride precludes such severe leaks if this hazard of vinyl chloride is to be controlled.

Industrial Hygiene Standard

The data presented indicate that little likelihood of injury would be expected if repeated daily 7- to 8-hour exposures are limited to 100 ppm or less.

Although the level of 100 ppm may not appear to offer any margin of safety since rats exposed repeatedly to this level were very slightly affected, the vast amount of human experience that is available while operating under an MAC of 500 ppm indicates that injury is not likely. Likewise the effects of even rather severe overexposure are not serious, hence this level seems reasonable.

A time-weighted average for all exposure should probably not exceed 50 ppm.

Summary

Vinyl chloride (CH_2=CHCl) is a monomer used in very large quantities in the production of plastics. Repeated exposures of laboratory animals to several concentrations of vinyl chloride in air were conducted to determine the chronic toxicity of this material towards animals in order to assess the hazard to humans. Vinyl chloride was found to have a slight capacity to cause liver and kidney injury on repeated exposures. Male and female rats showed micropathological changes after repeated daily 7-hour exposures at 500 ppm for 4.5 months. Repeated 7-hour exposures at 200 ppm for six months resulted in micropathological changes in the livers of rabbits and statistically significant increases in the average weight of the livers of male and female rats but no detectable changes in dogs and guinea pigs. Repeated 7-hour exposures at 100 ppm resulted in slight increases in the average weight of rat livers, the other species were not affected. All species studied tolerated repeated daily 7-hour exposures to 50 ppm for six months with no detectable injury.

Repeated daily 1-hour exposures at 200 and 100 ppm of vinyl chloride were without effect, longer exposures caused a slight increase in liver weight.

The standard for evaluating regular daily 7- to 8-hour exposures may be defined as the concentration below which practically all analytical results must fall. The value of 100 ppm is suggested as this standard for vinyl chloride, with a time-weighted average for all exposures not to exceed 50 ppm.

References

1. Manufacturing Chemists Assoc. Chemical Safety Data Sheet SD-56 (1954).
2. VON OETTINGEN, W. F.: *The Halogenated Hydrocarbons—Toxicity and Potential Dangers.* (U. S. Public Health Service. Publication No. 414.) Government Printing Office. Washington, D. C. (1955).
3. MASTROMATTEO, E., A. M. FISHER, H. CHRISTIE, AND D. DANZIGER: Acute Inhalation Toxicity of Vinyl Chloride to Laboratory Animals. *Am. Ind. Hyg. Assoc. J. 21:* 394 (1960).
4. SCHAUMANN, O., cited by K. B. LEHMAN AND F. FLURY.

Material	IHG	Date
V9/DOA (Dioctyl adipate V9)	500 ppm	1975
Vinyl chloride	10 ppm	1974
Vitamin C	10 mg	1976
Voranol CP700	10 mg	1975
Z-6	1 mg	1977
Z-11 methyl ester	1 ppm	1977
Z-200	0.5 ppm	1977
Zinc bromide	5 mg	1980
Zinc stearate	10 mg	1975
Zinc sulfide diffuser 2693	10 mg	1975

GLOSSARY

Ceiling - This concentration should not be exceeded, even for brief periods.

Excursion - An excursion guide establishes a maximum excursion concentration above the IHG. Although no duration or frequency limitations have been assigned to these excursion guides, the 8-hour time weighted average (TWA) exposures should be controlled within the IHG recommendation. These excursion guides have been approved for a few chemicals which may have acute adverse effects and for which information is available as a basis for a specific excursion recommendation.

IHG - The Industrial Hygiene Guide (IHG) is the internal Dow guideline for 8-hour TWA exposures to airborne concentrations of materials. These guidelines were prepared by industrial hygienists in cooperation with toxicology, medical, production and product department representatives and approved by the Dow Industrial Health Board.

Skin - This material may be absorbed through the skin in amounts sufficient to cause toxic effects. Although the IHG is for inhalation exposures, skin contact can contribute to the overall exposure to this and invalidate the TWA exposure evaluations. It is recommended that skin contact be avoided.

Tentative - This IHG has been approved only on a temporary basis and must be reviewed in one year.

M. G. Swank
Industrial Hygiene Laboratory
1803 Building - Midland
517/636-3976

ED SCHNEIDER

DOCUMENTATION

OF THE

THRESHOLD LIMIT VALUES

for

Substances

in

Workroom Air

WITH
SUPPLEMENTS FOR THOSE SUBSTANCES
ADDED OR CHANGED
SINCE 1971

AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS

Third Edition 1971

3RD PRINTING 1976

PREFACE TO THIRD EDITION

The issuance in 1971 constitutes the third edition of the Documentation of the Threshold Limit alues for Substances in Workroom Air. The second edition (1966) comprised 367 substances; iis edition contains almost 500. The documentation for each substance has been updated and xpanded to include information through 1970, selected from the scientific literature for its relevance to the TLVs. The general format of the 1966 edition has been retained, but chemical formulae ıave been added for precise identification of each substance, more than 100 substances have been :ross referenced, and the size of the substances' captions has been greatly enlarged for more ready :eference. Specific statements on the toxicity and hazard, culled from the literature, or from the :ollective experience of the TLV Committee members, have been referenced for further examiniıtion and a clear, summarizing statement on precisely what basis the TLV has been selected is ıncluded in most documentations. This latter has been felt by the Committee to be a highly impor:ant adjunct for industrial hygienists administering the TLVs.

This edition was placed in the capable hands of Dr. Hervey B. Elkins, Director, Massachusetts Division of Occupational Hygiene, and long-time member of the TLV Committee of the American Conference of Governmental Industrial Hygienists. Although the minutiae of the editorial work was entrusted to Andrew D. Hosey, much devoted care and attention to proper arrangement and content was given by TLV Committee recording secretary, William D. Wagner, and my secretary Eileen Fangmeyer.

H. E. Stokinger, Ph.D. Chairman
Threshold Limits Committee

PREFACE -- SECOND PRINTING

This second printing, three years after publication of the third edition, was occasioned by the relatively large number (72) new additions or updating of old documentations. The printing thus contains all the documentations of the third edition and as a supplement, the new and revised documentations since 1971. These additions or revisions are noted by a ★ and are arranged alphabetically as in the main text.

The edited, supplemental documentations represent the efforts of all members of the various TLV subcommittees. Accordingly, it would be appreciated if readers would call to the attention of the TLV Committee Chairman any errors or discrepancies in the supplement, as the documentations of the entire TLV listing are undergoing revision for the fourth edition.

H. E. Stokinger, Ph.D.
Chairman
Threshold Limits Committee

★★ denotes 1974-1975 changes.

A star ★ preceding the name of a substance in the main body of the text indicates that this documentation has been revised and is to be found in the Supplement.

metabolism. The dominant response, however, was irritation of the eyes with evident lacrimation. Industrial experience has revealed severe irritation of the skin with blister formation(1).

Acute toxicity is moderate; about 4,000 ppm represents a four-hour LC_{50} for rats, 1,550 ppm for mice, and about 2,500 ppm for rabbits. Although 240 ppm for four hours caused some eye irritation (blinking and reddening of the sclera) in a beagle dog, 106 ppm caused no observable effects(2). Rats exposed at this latter level exhibited normal growth and behavior after 15 daily six-hour exposures, but exposures at two and one-half times this level showed retarded growth in females. No hematologic or pathologic abnormalities attributable to exposures as high as 630 ppm were found(3).

Vinyl acetate is moderately hazardous by mouth. 2.5 g/kg was found to be the LD_{50} for rats as a single oral dose(4).

Gage(5) found rats unaffected by repeated exposures at 100 ppm, and recommended 50 ppm as a working standard.

A report of 15 years industrial experience(3) with 21 chemical operators in vinyl acetate production exposed at levels from 5 to 10 ppm indicated that vinyl acetate is not a significant upper respiratory tract irritant at 10 ppm, but around 22 ppm slight irritation was observed in the form of cough and hoarseness. This level produced a significant subjective response in all three subjects tested. Medical records and multiphasic examinations revealed no evidence of chronic effects from levels of 5 to 10 ppm. Vinyl acetate was not considered to be a serious skin irritant, or a producer of contact dermatitis, or a serious eye injurant provided prompt flushing of the affected part was carried out. At levels of less than 5 ppm, vinyl acetate is detectable by odor by most individuals, and by some at about one-tenth this value(3). Olefactory fatigue may occur in a matter of a few minutes at levels around 20 ppm. Recovery is rapid, however(2).

In light of the above evidence that neither acute or chronic effects occur from repeated daily exposures after many years, and that irritation may be experienced at around 20 ppm, but not at 10 ppm, a TLV of 10 ppm is recommended.

References:

1. Haskell Laboratory: Report of Toxicity of Vinyl Acetate (January, 1967).
2. Communication from Mellon Institute to TLV Committee (October 14, 1968).
3. Industrial Hygiene Foundation of America: Repository of Anonymous Industrial Hygiene Data, Summary Report of Exposures to Vinyl Acetate (April, 1969).
4. Union Carbide and Carbon Corp.: Dept. of Ind. Med. & Tox., Toxicology Range-finding Tests (December, 1956).
5. Gage, J.C.: Brit. J. Ind. Med. 27, 1 (1970).

★★VINYL CHLORIDE

CH_2=CHCl

200 ppm (Approximately 770 mg/m^3)

Vinyl chloride is a flammable gas with anesthetic properties at high concentrations. At anesthetic concentrations (8 to 12%) it has serious effects on cardiac muscle resulting in arrythmias and sensitization in dogs(1,2). There is a wide margin between anesthetic and lethal concentrations (30-40%)(3). Torkelson, Oyen and Rowe(4) reported that repeated seven-hour exposures for six months at 200 ppm resulted in histologic changes in the central lobular region of the livers of rabbits, but not in rats, guinea pigs and dogs. At 100 ppm there was only slight liver enlargement. A subsequent report by Lester, Greenberg and Adams(5) on the effects of repeated exposure of rats to vinyl chloride assaying 99 + percent purity at 2 and 5% concentration stated that, although liver changes were noted, they were not considered to be of pathological significance. In their opinion, a recommended TLV of 500 ppm was satisfactory for worker exposure.

APPENDIX A
CARCINOGENS

The Committee lists below those substances in industrial use that have proven carcinogenic in man, or have induced cancer in animals under appropriate experimental conditions. Present listing of those substances carcinogenic for man takes two forms: Those for which a TLV has been assigned (1a) and those for which environmental conditions have not been sufficiently defined to assign a TLV (1b).

A1a. *Human Carcinogens*. Substances, or substances associated with industrial processes, recognized to have carcinogenic or cocarcinogenic potential, with an assigned TLV:

	TLV
† Acrylonitrile	2 ppm
††Asbestos	
Amosite	0.5 fiber > 5μm/cc
Chrysotile	2 fibers > 5μm/cc
Crocidolite	0.2 fiber > 5μm/cc
Other forms	2 fibers > 5μm/cc
bis (Chloromethyl) ether	0.001 ppm
Chromite ore processing (chromate)	0.05 mg/m^3, as Cr
Nickel sulfide roasting, fume & dust	1.0 mg/m^3, as Ni
Coal tar pitch volatiles	0.2 mg/m^3, as benzene solubles
†† Vinyl chloride	5 ppm

* * *

A1b. *Human Carcinogens*. Substances, or substances associated with industrial processes, recognized to have carcinogenic potential without an assigned TLV:

**. Acrylonitrile
4-Aminodiphenyl (p-Xenylamine)
† Benzidine — Skin
** Chloromethyl methyl ether
** Ethylene dibromide
β-Naphthylamine
4-Nitrodiphenyl

†1980 Addition.
††1980 Adoption.
**See Notice of Intended Changes.

For the substances in 1b, no exposure or contact by any route — respiratory, skin or oral, as detected by the most sensitive methods — shall be permitted. The worker should be properly equipped to insure virtually no contact with the carcinogen.

A2. *Industrial Substances Suspect of Carcinogenic Potential for MAN*. Chemical substances or substances associated with industrial processes, which are suspect of inducing cancer, based on either (1) limited epidemiologic evidence, exclusive of clinical reports of single cases, or (2) demonstration of carcinogenesis in one or more animal species by appropriate methods.

3-Amino 1, 2, 4-triazole	
†† Antimony trioxide production*	——
†† Arsenic trioxide production	——
Benzene	10 ppm
Benzo(a)pyrene	——
Beryllium	2.0 μg/m^3
** Cadmium oxide production	——
Carbon tetrachloride	5 ppm
Chloroform	10 ppm
† Chloromethyl methyl ether	——
Chromates of lead and zinc, as Cr	0.05 mg/m^3
3, 3'-Dichlorobenzidine	——
Dimethylcarbamyl chloride	——
1, 1-Dimethyl hydrazine	0.5 ppm
Dimethyl sulfate — Skin	0.1 ppm
† Ethylene dibromide — Skin	——
† Hexachlorobutadiene	0.02 ppm
Hexamethyl phosphoramide — Skin	——
Hydrazine	0.1 ppm
4, 4'-Methylene bis (2-chloroaniline) — Skin	0.02 ppm
Methyl hydrazine	0.2 ppm
Methyl iodide	2 ppm
††C 2-Nitropropane	25 ppm
n-Nitrosodimethylamine	——
n-Phenyl-beta-naphthylamine	——

*Cigarette smoking can enhance the incidence of respiratory cancers from this or others of these substances or processes.
†1980 Addition.
††1980 Adoption.
**See Notice of Intended Changes.

SUPPLEMENTS

FOR THOSE SUBSTANCES

ADDED OR CHANGED

YEARS 1974 and 1975

Information made available by the Eastman Kodak Company reveals that no injuries have occurred as a result of handling of the compound and that no special precautions are necessary other than those used for the routine handling of organic compounds(1).

References:

1. Personal communication from Robert L. Roudabush, Director of Health and Safety Laboratory, Eastman Kodak Company. Letter dated April 12, 1973.

VINYL CHLORIDE

CH_2=CHCl

APPENDIX A1c

Since vinyl chloride (chloroethene, CH_2=CHCl) is a gas at room temperature and pressure, the common route of toxic exposure is by inhalation. As with many liquified gases, contact of the skin or eyes with escaping compressed vinyl chloride can produce freezing and frostbite(1).

Vinyl chloride has long been considered to be very low in toxicity by acute inhalation. Lehmann and Flury(2) summarized the literature and reported work by Schauman who considered vinyl chloride to be a candidate surgical anesthetic. Schauman reported little pathological change even after repeated exposure to anesthetic concentrations. Further work on the anesthetic potential of vinyl chloride indicated that vinyl chloride was unsafe for use as a surgical anesthetic in dogs and that because of its flammability, poor efficacy and its ability to cause cardiac irregularities at anesthetic concentrations vinyl chloride was not suitable for use as an anesthetic in humans.

Despite the early reports ascribing low toxicity to vinyl chloride, injury during the production of polyvinyl chloride (PVC) resins was reported as early as 1949. Significantly this report came from Europe where production of PVC in Europe preceded U.S. production by several years and today the quantity produced in Europe still exceeds U.S. production by about two fold. In 1949, Tribuhk et al.(3) reported numerous effects in PVC workers in what by today's standards must be considered as primitive production facilities. These authors found a "considerable number of cases of hepatitis among workers" but were more concerned with other hepatotoxic chemicals such as chlorinated diphenyl and chlorinated naphthylene (Holowax (sic)) than they were with vinyl chloride.

As a result of two deaths in Canada, the acute inhalation toxicity of vinyl chloride was studied by Mastromatteo et al.(4) who reported that exposure of mice, rats, and guinea pigs to 10, 20, and 30 volume percent vinyl chloride caused the following mortality:

NUMBER OF DEATHS IN DIFFERENT GROUPS OF FIVE MICE, RATS AND GUINEA PIGS EXPOSED FOR THIRTY MINUTES TO VARYING CONCENTRATIONS OF VINYL CHLORIDE IN AIR

Vinyl Chloride concentration (percent by volume in air)	Laboratory animal			TOTAL
	Mice	Rats	Guinea pigs	
10	0/5	0/5	0/5	0/15
20	1/5	0/5	0/5	1/15
30	5/5	5/5	1/5*	11/15
40	—	—	2/5*	2/5

*A delayed death occurred within 24 hours following exposure.

Some pulmonary hyperemia and engorgement was observed by these investigators, but liver and kidney injury were remarkably low. Deaths were due to narcosis.

The first report of studies to determine the effect of long-term repeated exposure (6 months) were summarized by Torkelson, Oyen and Rowe(1) as follows:

"Repeated exposures of laboratory animals at several concentrations of vinyl chloride in air were conducted to determine the chronic toxicity of this material towards animals in order to assess the hazard to humans. Vinyl chloride was found to have a slight capacity to cause liver and kidney injury on repeated exposures. Male and female rats showed micropathological changes after repeated daily 7-hour exposures at 500 ppm for 4.5 months. Repeated 7-hour exposures at 200 ppm for six months resulted in micropathological changes in the livers of rabbits and statistically significant increases in the average weight of the livers of male and female rats, but no detectable changes in dogs and guinea pigs. Repeated 7-hour exposures at 100 ppm resulted in slight increases in the average weight of rat livers, the other species were not affected. All species studied tolerated repeated daily 7-hour exposures at 50 ppm for six months with no detectable injury.

"Repeated daily 1-hour exposures at 200 and 100 ppm of vinyl chloride were without effect, longer exposures caused a slight increase in liver weight.

"The standard for evaluating regular daily 7- to 8-hour exposures may be defined as the concentration below which practically all analytical results must fall. The value of 100 ppm is suggested as this standard for vinyl chloride, with a time-weighted average for all exposures not to exceed 50 ppm."

Lester, Greenberg, and Adams(5) took exception to the conclusion of Torkelson et al. (1961) that 50 ppm should be a maximum time weighted average exposure for workers. On the basis of 3 months exposure of rats to 2 volume percent and 19 days to 5 volume percent, they concluded that 500 ppm was acceptable as a TLV despite minor changes which they observed in rat livers and which they considered "were within the normal range and were not pathologic in nature."

Since 1949 numerous articles describing conditions and problems in PVC production plants have appeared particularly in the Eastern European literature. Filatova and Gronsberg(6), Gabor et al.(7), Suciu et al.(8), Gabor et al.(9), Grigorescu and Toba(10), Antonyuzhenko(11), and Kudryavtseva(12), have all described the effects of apparently gross chronic exposure. These papers and abstracts are difficult to interpret since there are generally inadequate descriptions of the exposure conditions and analysis of the workroom air, so no dose-response relationship can be determined. The injuries and effects described by the authors are not consistent with the levels of exposures claimed by the authors nor are the levels of exposure consistent with past or even present-day chemical technology. Furthermore, mixtures of chemicals are involved making it possible to ascribe the effect to any one of them.

For example, Suciu et al.(8) (through translation) described nervous disorders including euphoria with whistling and laughing, incoordination and dizziness similar to alcohol intoxication. However, Suciu et al. ascribes these results to exposure of the order of 5.5 mg/m^3 (2 ppm v/v) which is not consistent with other publications which indicate these effects will be apparent only if concentrations greatly exceed 10,000 to 20,000 ppm v/v. Therefore, the following conclusions by the authors can be construed as being the result of massive and apparently repeated exposures:

1. Vinyl chloride and the vinyl monomers possess a narcotic action and produce, depending upon concentration, in addition to characteristic neurologic manifestation, a state of euphoria (12%), followed by a state of inebriation similar to that of alcohol intoxication. In certain cases narcosis can appear.

   After leaving the working environment, a state of somnolence (45%) persists, with hypersomnia. Vinyl chloride acts on the skin and produces a sensation of formication and of heat.

2. After repeated exposure, a neurologic asthenia sets in in which somnolence predominates.

3. After a variable period of time, dyspeptic disturbances are added to the neurologic manifestations; these are at first not characteristic; they are in the form of epigastric pains (16%), swelling, discomfort, feeling of heaviness in the right hypochondrium (7%) or the left (5%) with anorexia, particularly for fats.

   In 30.2% of the cases, congestive hepatomegaly appears, which may mimic toxic hepatitis without jaundice; some cases may become chronic.

   In 6% of the cases, the hepatomegaly is accompanied by splenomegaly. The proteinogram and the aldolases are the most sensitive tests and show changes similar to those of acute hepatitis: increase in α-globulins and of the β- and γ-globulins; and thymol test, Greenstedt's reaction and the zinc sulfate test are positive only in few of the cases.

4. After 3 years of exposure in 9% of the cases a syndrome typical of ulcer without radiologic changes becomes manifest.

5. In 6% of the cases the Raynaud syndrome has appeared, particularly among the young men. Plethysmography shows in half of the cases an inhibition of the vasomotor centers.

6. In addition, allergic dermatitis in 4.4% of the cases, and scleroderma in 3.6%, has been observed.

7. The clinical and laboratory findings are of great importance in occupational pathology because in numerous cases diseases appear in man that cannot be reproduced in the animal (Raynaud's syndrome and scleroderma).

The sudden and frequent appearance of these manifestations in the PVC division of several plants, and in certain divisions in normal individuals who are still relatively young, and their disappearance in the majority of the cases after the institution of protective measures and change of work, have shown us decisively that vinyl chloride and the vinyl monomers have played a part in the production of these manifestations. (End of author's summary).

In 1967, reports appeared in the literature describing a condition known as acroosteolysis in workmen engaged in polymerization of vinyl chloride to polyvinyl chloride. Harris and Adams(13) reported on two cases in Europe. Wilson et al.(14), reported on 37 cases in the B. F. Goodrich Company. Jühe et al.(15) described a syndrome consisting of (arranged in decreasing order of occurrence) thrombopenia, splenomegaly, liver damage, obstruction of ventilation, circulatory obstruction, and skin and bone alteration.

As a result of this problem, the University of Michigan in 1967 was retained by the Manufacturing Chemists Association to investigate acroosteolysis in sponsoring American companies. The results of a large scale epidemiological study of workers then currently employed in vinyl chloride and polyvinyl chloride production were reported in three publications by this group Dinman et al.(16), Cook et al.(17), and Dodson et al.(18).

Dinman et al.(16) summarized the study as follows:

"An epidemiological study was performed covering 5,011 employees with 21,510 man-years experience in various phases of vinyl chloride (VC) and polyvinyl chloride (PVC) manufacturing in 32 plants throughout the United States and Canada. The total number of definitive cases of acroosteolysis (AOL) was 25; 16 other individuals were under suspicion. This condition is clearly associated with the hand cleaning of polymerizers. Workers engaged in other phases of VC or PVC manufacturing do not appear to be at risk of developing AOL. The importance of Raynaud's phenomenon as a concomitant of AOL is emphasized. Several statistical approaches for rapid medical survey are suggested. Acroosteolysis appears to be a systemic rather than local disease. Presently, neither the etiological agent nor its portal of entry is known."

Cook et al.(17) describes the polyvinyl chloride production process in considerable detail. They concluded that although no etiological agent could be identified, "There appeared to be a correlation between the extent of degassing prior to entry into the reactor" and the incidence of acroosteolysis.

Mutchler and Kramer(19) presented a paper at the 1968 Gordon Research Conference which was subsequently published (1972), which reported on "The Correlation of Clinical and Environmental Measurements for Workers Exposed to Vinyl Chloride." The authors drew the following conclusion:

"Our findings suggest that repeated exposure to vinyl chloride at TWA levels of 300 ppm or above for a working lifetime together with a very low level of vinylidene chloride may result in slight changes in certain physiologic and clinical laboratory parameters. The possibility of some impairment in liver function tests must be considered, even though no overt clinical disease was evident in any of the individuals studied. We shall continue our study, but suggest that similar studies to help clarify the effects of this material be performed for other worker populations exposed to vinyl chloride alone."

P. L. Viola, in an attempt to produce acroosteolysis in animals, exposed rats 4 hours per day, 5 days per week to 30,000 ppm (3%) vinyl chloride vapor. In his first report on the results of 12 months exposure, he described metaplastic changes in the bones which he considered similar to the human disease acroosteolysis. He made no mention of having observed cancer in these animals until the Tenth International Cancer Congress in May, 1970. In the abstracts of this meeting, and subsequently in May, 1971, Viola, Bigotti and Caputo(21) reported tumors of the skin, lungs and bones occurring first after 10 months of exposure. The authors summarized this work as follows:

"Rats (Ar/IRE Wistar strain) exposed for 12 months to vapors of vinyl chloride developed tumors of the skin, lungs, and bones. The cutaneous tumors, which always appeared in the area in which submaxillary and parotid glands are located, have been histologically recognized as epidermoid carcinomas, papillomas, and mucoepidermoid carcinomas. The morphological characteristics of lung tumors, which occurred in a lower percentage, were mainly of the adenocarcinoma type, with the exception of a single epidermoid tumor originating from the epithelial covering cells. In a minor number of rats, a large proliferation of cartilaginous tissue diagnosed as osteochondroma developed in the metacarpal and metatarsal regions of the four limbs."

The report by Viola et al.(21) is apparently the earliest publication in which carcinogenic activity has been ascribed to vinyl chloride in man or animals. Although there were obvious deficiencies in Viola's study, such as his very impure sample, the presence of food and bedding in the exposure chamber, the excessive exposure concentration as well as in the statistical evaluation and interpretation of the lesions, the report was of serious concern and resulted in additional animal and epidemiological studies which are currently underway in Italy Maltoni(22). Maltoni and and Lefemine(23,24) and the U.S., Keplinger et al.(25).

On January 22-23, 1974, the B. F. Goodrich Company notified its employees, NIOSH, the Kentucky State Department of Labor, and the public, that three workers had died of angiosarcomas of the liver. The case reports of the first subject has been published by Creech and Johnson(26). The subject, a 36 year old male, was hospitalized January 5, 1970 and subsequently succumbed September 27, 1971. He had worked in PVC production from November 1955 until his illness. The history, clinical course and pathologic findings are consistent with the others who died of angiosarcoma.

The work of Maltoni and Lefemine(23,24) has been reported publicly at the OSHA hearing, Washington, D.C., February 15, 1974, and included in the 1974 publication of the Second International Symposium on Cancer Detection and Prevention, Bologna, Italy, April 9-12, 1973. In these studies groups of rats as well as mice and hamsters have been exposed at concentrations of 10,000 to 50 ppm vinyl chloride vapor. Maltoni and Lefemine (1974) reported carcinomas of the Zymbal glands, nephroblastoma and angiosarcomas of the livers of rats at concentrations of 250 ppm to 10,000 ppm but not at 50 ppm. Subsequent unpublished information (August 31, 1974) reported "1 liver angiosarcoma, 1 extrahepatic angiosarcoma and 1 nephroblastoma, in three animals of the first experiment, exposed at 50 ppm of VC for 1 year, and surviving 135 weeks from the beginning of the treatment." The authors conclude that "a dose-response relationship clearly emerges, as far as angiosarcomas and nephroblastomas are concerned, in the lower dose ranges: from 500 ppm to 50 ppm for angiosarcomas, and from 250 ppm to 50 ppm for nephroblastomas. A comparison of the results available at the present moment in rats exposed for 12 months and 4 months (BT1 and BT3 experiments) shows that the neoplastic response, as far as angiosarcomas and nephroblastomas are concerned, is affected by the length of exposure to VC."

In their experiment BT3 Maltoni and Lefemine reported possible in utero production of angiosarcomas in offspring of pregnant rats exposed at 10,000 and 6,000 ppm.

Keplinger et al.(25) in a study sponsored by American companies have confirmed the findings of Maltoni and Lefemine. In this study groups of 100 rats, mice and hamsters of each sex are being exposed seven hours per day, five days per week to either 2,500, 200 to 50 ppm vinyl chloride monomer. After seven months of exposure angiosarcoma and lung adenomas have been observed in mice at all exposure levels. Although the data are preliminary in nature and require confirmation, angiosarcomas were apparently also observed in rats at 2,500 and 200 ppm and in a single hamster at 2,500 ppm. This study is still in progress and will not be completed until 1976 or 1977.

Epidemiological studies on U.S. workers have been conducted by Tabershaw-Cooper Associates for the Manufacturing Chemists Association(27). The summary of this study is as follows:

1. This historical prospective mortality study of 8384 men who had at least one year of occupational exposure to vinyl chloride before December 31, 1972, demonstrated that cancers of the digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure. The mortality from other cancers was lower than that of the general male population, with the exception of cancers of the buccal cavity and pharynx. The explanation for the latter finding is not apparent.

   The other major findings of the study are: (1) The overall mortality of the study population was approximately 75% of what would be expected in a comparable population of U.S. males; (2) No cause

of death showed a statistically significant excess over what would be expected in a comparable U.S. male population; and (3) No deaths identified as angiosarcoma of the liver were found other than those previously identified.

This is the first epidemiological study which suggests that in humans vinyl chloride may also be associated with cancer of multiple sites.

Vinyl chloride is tentatively assigned to Appendix A1c, "Substances awaiting reassignment of TLV because of recently discovered carcinogenicity."

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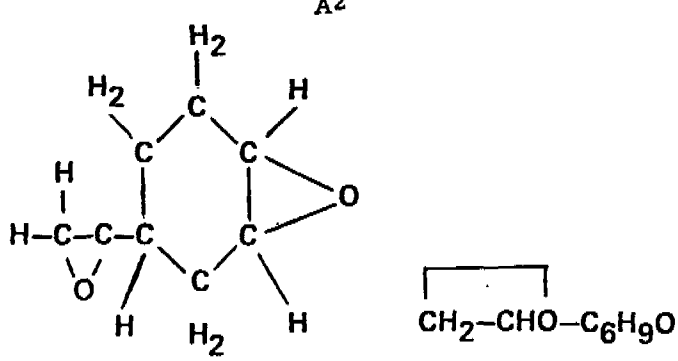
VINYLCYCLOHEXENE DIOXIDE - Skin

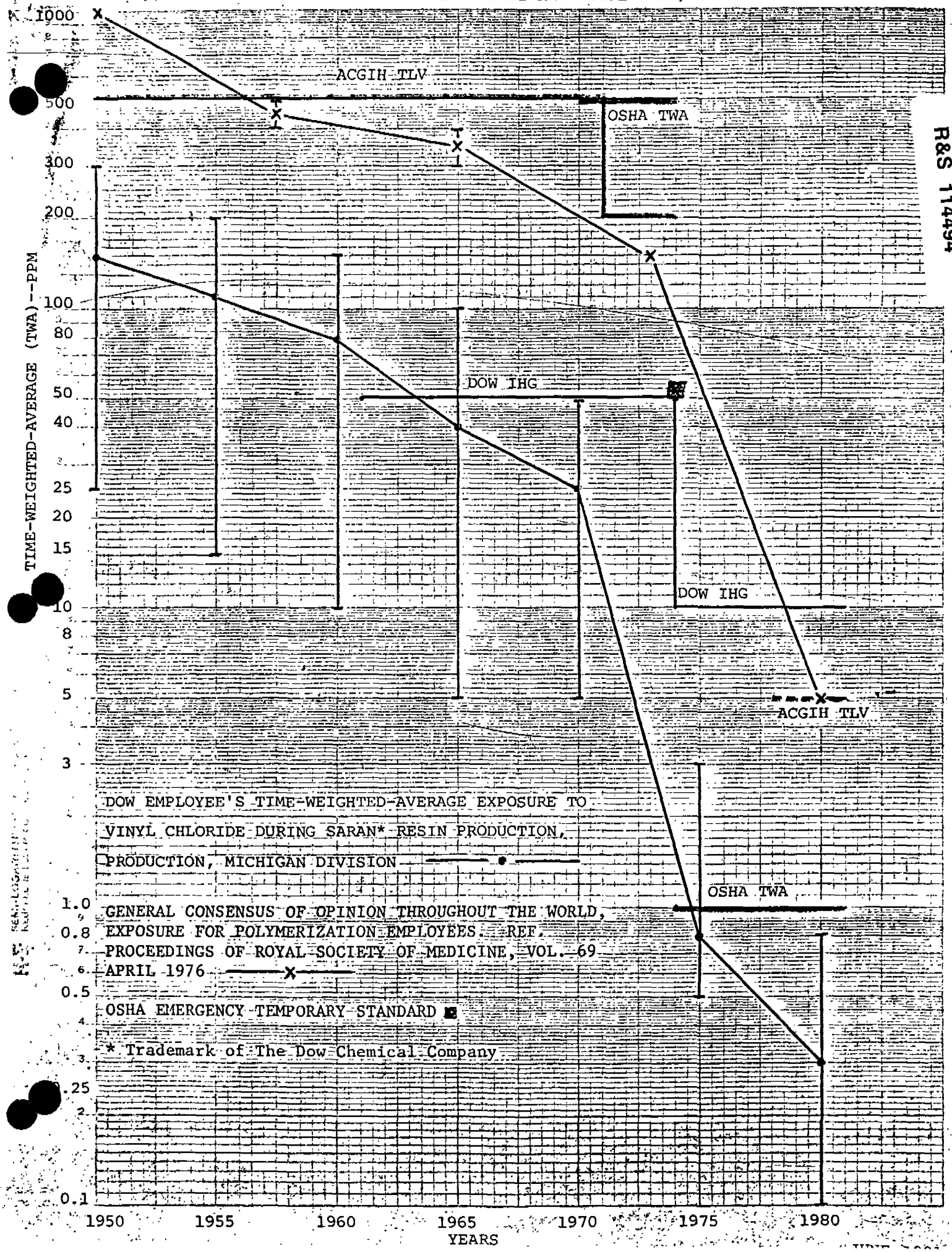
10 ppm (Approximately 60 mg/m^3)

A2



This compound may also be referred to as vinylhexane dioxide. It has a molecular weight of 140, is a colorless liquid and has a specific gravity of 1.098 (20/20°C). Its freezing point is - 108.9°C and the boiling point is 228°C. The flash point (open cup) is 230°F and the viscosity is 7.77 centipoise (20°). The

VINYL CHLORIDE EXPOSURES AND GUIDELINES/STANDARDS



VINYL CHLORIDE EXPOSURES AND GUIDELINES/STANDARDS