COMMENTS ON VINYL CHLORIDE

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Carcinogenicity, angiosarcoma: Vinyl chloride's capacity to induce angiosarcomas in animals is established. It has been shown in several laboratories, in several species (including fish, rats and mice) and at all concentrations tested so far.

Vinyl chloride's capacity to produce angiosarcoma in man has not been proven absolutely but the unusually high incidence of angiosarcoma among vinyl chloride workers and the similarity of the tumors in these workers to those produced in animals is as convincing evidence as it is possible to get without deliberate exposure of men. The few parts of the Record that question this conclusion point out that all of the cases have been concentrated in a few factories; seven of them occurred in the Louisville, Kentucky plant alone. This concentration raises the question of whether these workers received a greater exposure or whether other factors were operating in these individuals who succumbed. For instance, were there co-carcinogens present? Were there genetic predispositions to the disease in these individuals? Did regional dietary habits or environmental factors play a role? Was a latent or unknown infection or other disturbance a contributing factor? These are valid questions, but there is no way of knowing whether or not these possibilities influence the carcinogenic potential of vinyl chloride in man. Regardless, it should be

noted that these are only moderating factors. They do not detract from the conclusion that vinyl chloride can cause cancer in man.

Carcinogenicity, other tumors: Vinyl chloride produces several other tumors in animals. Indeed, angiosarcomas were only about one-third of the total tumors produced in the Maltoni and Biotest experiments. Malignant tumors of the kidney, lung and mammary glands each occurred about as often as angiosarcoma. In addition, tumors were found in virtually every other organ. As with angiosarcoma, these tumors have been observed in several laboratories, in several species, and at every concentration of the gas that has been tested so far.

The ability of vinyl chloride to induce tumors other than angiosarcoma in man has not been established. The Tabershaw-Cooper report (Exhibit 132) suggests an increased incidence of death from cancer among vinyl chloride workers but the increase is not statistically significant. On the other hand, detailed searches for other tumors have not been made and it is far more difficult, statistically, to prove the cause of common tumors than of those as rare as angiosarcoma. Hence the production of other tumors in man by vinyl chloride is still an open question. At this time it has been neither proven nor disproven.

Other hazards: The acute hazards of high concentrations of vinyl chloride, fire and anesthesia, have been known for many years. Non-lethal effects of chronic exposure to vinyl chloride also have been apparent for some time. Among the disorders produced are: acroosteolysis, Raynaud's phenomena, portal hypertension, fibrosis of the liver, broncoconstrictive disease, and

a variety of lesser lesions (Lange et al, Exhibit 183). The urgency of the angiosarcoma problem apparently has precluded careful study of other lesions in animals, but damage to brain, liver, kidneys, thyroid, bone, nerves and skin were noted by Viola some years ago and fibrotic changes in the liver are constant concomitants of the angiosarcoma. The Biotest data clearly show early and excess deaths among animals exposed to all concentrations of vinyl chloride tested. Studies of teratogenic effects in animals have not had positive results but hints of possible mutagenic effects in man can be found in the excess chromosome splitting seen in Selikoff's laboratory. The possibility of teratogenicity is raised by Maltoni's observation of angiosarcomas in newborn animals.

Conclusion: The attention that has been given to angiosarcoma of the liver should not encourage a narrow view of the hazard of vinyl chloride. Even the limited data that is available on human toxicity clearly shows the gas to cause changes in virtually every organ in the body. The animal data shows that angiosarcomas are less than one-third of the total number of tumors that can be produced and that other damage is commonplace. In short, the record is replete with evidence that vinyl chloride is a serious potential hazard to the health of man.

Polyvinyl chloride: The Record only touches on the toxicity of polyvinyl chloride, but there are suggestions that it may not be inert. At the least, it is a carrier of the entrapped monomer. In addition the particles are phagocytosed and enter many organs. There are suggestions that they may cause pneumoconiosis

Quantitative aspects of the hazard: The record contains very little data on how much exposure to vinyl chloride it takes to injure workers. With regard to animals, it is clear that 50 ppm, four or seven hours a day, five days a week for a lifetime is a powerful carcinogen but there have been no experiments at lower concentrations and therefore there is no way of knowing whether lower concentrations are also dangerous. I have been told that experiments with lower concentrations have begun but it will be at least a year before significant data are available.

The Record contains no reliable information with regard to the quantity of vinyl chloride that is hazardous to man. Manufacturers did not monitor the concentration of the gas until recently and we don't know what conditions prevailed in their factories. We don't know how much vinyl chloride workers have been exposed to and therefore don't know how much was tolerated safely or how much it took to cause injury. Several exhibits contain estimates, but these are based on memory, odor, and impressions of observers. Attempts have been made to translate these to actual gas concentrations but the results are nothing more than "educated" guesses.

There is comfort in the fact that there are no cases of angiosarcoma in factories where management was concerned about the potential for toxicity and therefore presumably took more precautions, but the two cases in individuals exposed to low concentrations in Connecticut are extremely disturbing. The only source of comfort in them is in the report that their lesions are not exactly the same as the angiosarcomas in other individuals or in laboratory animals (Exhibit 164) i.e., these may not be vinyl chloride related lesions.

It is even more difficult, if that is possible, to ascertain the amount of vinyl chloride that produces noncancerous lesions. There is virtually no quantitative information for either animal or man and there has been no attempt to quantitate the occurrence of these lesions, or the concentrations of vinyl chloride that cause them. This is a major gap in our knowledge. More workers may suffer from these effects than from the carcinogenic effect.

There is no clue to the villain in the toxicity produced by vinyl chloride. It could be the intact molecule or it could be a metabolite or a reactive intermediate. Several metabolites have been found and several potential routes of metabolism have been illustrated, but which of these, if any, leads to carcinoma and other changes is not known. There is also evidence that the metabolism of vinyl chloride is concentration dependent with one pathway predominating at higher concentrations and another at lower ones. These data obviously would be significant if it were known which route led to the deleterious material, but the critical insight is not available.

The Record contains many discussions of the dose-response relationship between vinyl chloride and its toxicity, but the data needed to establish the critical part of the relationship are absent. Every concentration tested so far has produced tumors and excessive rates of death in animals. Some scientists have taken numbers from these experiments, and have attempted to project the dose response curve below the observed values. Such projection is speculative, at best. Even at the high end of the curve, the data are scanty and give a poor basis for line fitting. They give no grounds for extrapolating to the unknown. More fundamentally,

there is no proven or theoretical reason for extrapolating the curve. We do not know whether there is an absolute threshold for the toxic effects of vinyl chloride or whether the toxicity grades continuously at ever lower doses. Our knowledge of other carcinogens could support either hypothesis and there is no reason to choose one over the other with respect to vinyl chloride. In short, the only factual statement is that 50 ppm is toxic for animals and nothing is known about the effects of less than 50 ppm.

Finally, there is no way of projecting from the animal data to man. The Record shows the mouse to be the most sensitive of the mammalian species tested in the laboratory. The Record also shows that hamsters are substantially more resistant and that there are differences between Wistar and Sprague-Dawley rats. Thus, there is documentation of species and strain differences. Arguments have been made that man has a substantially lower rate of respiration and metabolism and therefore he should be less susceptible than a mouse to the carcinogenic effect. It has also been argued that man's exposure is less intense in that it normally begins in adult life and is not continuous, i.e. workers take vacations, holidays, sick-time, they change jobs and there are variations in factory conditions. There is also a suggestion in the record that factories with generally lower concentrations of vinyl chloride have had no cases of angiosarcoma.

The Record contains many allusions to these facts and innumerable remarks to the effect that a man is not a mouse and that his susceptibility should not be equated with that of a mouse. The implication is that OSHA's standard should not be further reduced without direct evidence on the susceptibility of man. This kind of logic points to a path which is dangerous

to follow. As noted above, it is as clear as it is possible for it to be that a similar set of toxic effects occurs in man and experimental animals. It is also clear that among the experimental animals there is no great difference in the concentrations of the gas that produce effects in the various susceptible species. Under these circumstances, there is only one prudent course to follow: assume that man is at least as sensitive as the most sensitive mammalian species. This assumption is universally applied in assessing the toxic hazard of materials to man. The potential for disaster in any other course is apparent.

Time factors: There is a similar void in our knowledge of the time it takes to produce carcinomas. In animals the tumors do not appear soon after exposure. Instead, there seems to be an inverse relationship between concentration of gas and time to onset of tumors, and in some cases the time to onset approaches the lifespan of the animal. Much has been made in the Record of these facts and the fact that the human victims worked in the vinyl chloride industry for many years before their tumors were diagnosed. However, we have no way of translating these observations into practical guidance. We do not know if this long time to onset is an induction period; that is, a long, continuous exposure to the gas is necessary to produce the fatal change; or whether it is a latency period; that is, the tumor begins its inexorable course very soon after exposure but its initial growth is slow and its recognition is delayed.

The Record hints that the former may be the case. There is a suggestion in the recent Maltoni data that long continuous exposure is

needed to produce tumors, but the data are few and preliminary. Some theoretical considerations are in the same vein. Broken strands of DNA are known to be reparable and it is thought that immune processes can kill abnormal cells early in the carcinogenic process. Similarly, Dr. Popper's theory that the angiosarcoma is a result of a precursor fibrosis suggests a critical length of exposure. These observations are enticing, but are not adequate to form a conclusion. There is no way of knowing whether the theories are applicable or if they are, of estimating the time at which the process changes from reversible to irreversible.

In another regard, it is important to realize that the apparent lag time for some of these hazards, particularly carcinogenesis, is so great that improvement in working conditions may not improve morbidity for a decade or more. That is, we can expect to see the consequences of the higher exposures that have existed up until now. In addition to the human tragedy associated with this continuing morbidity and mortality, there is the possibility of misinterpreting the data. Some may not recognize the time lag and may take the failure to reduce morbidity as a sign of failure to set the standard low enough.

As the ultimate irony, the apparent lag time in the production of human disease among those exposed to vinyl chloride is such that the Assistant Secretary will probably never know whether or not he made a correct decision.

Conclusion: Vinyl chloride has to be presumed to be hazardous to man, causing a series of acute, chronic and fatal diseases. All of these

effects have been produced by concentrations that existed in the work place in the past, but virtually nothing is known about the circumstances that produced them. The deficit in our knowledge is so great that there is no hope of getting adequate quantitative data in the foreseeable future and a full explanation of the hazard is probably several decades away. Since we do not and cannot know what concentration of vinyl chloride is dangerous for man, it will not be possible to set a standard on a solid basis of fact. The best that can be done is to try as hard as possible to reduce the potential medical risk without incurring unacceptable economic risk.

Recommended approach--Philosophy and tactics: An important factor is the special terror of cancer in our society. The risk of violent death or injury is accepted by workmen in many industries. The risk of chronic disease has also been accepted in certain industries, (e.g. "black lung"). Cancer is not and will not be viewed as sanguinely by the American public and workman.

The tactics for achieving a reduction in exposure are not in my area of competence, but the following observations may be helpful. To me, it does not seem likely that vinyl chloride can be banned without damage to our economy. It also does not seem likely that human exposure can be eliminated immediately. Therefore, some risk will have to be borne by some individuals. In my view, this risk should be as small as possible and it should be confined to the smallest possible number of people. Those at risk should be fully aware of the risk, accept it voluntarily, have the best means of protecting themselves against it, and be compensated for bearing

it. There should be no risk to the innocent, the ignorant or the unsuspecting.

Since there are several different populations exposed to vinyl chloride, I suggest the following:

1. Reduce the residual vinyl chloride in the polymerized product. The greatest number of people presently exposed to vinyl chloride are those using the polymer. The concentration in their environment is small, but it is not known whether or not this concentration is safe and, accordingly, it should be reduced or, if possible, eliminated. Furthermore, most of the people working in these factories are ignorant of the risk and unsuspecting of the hazard. Almost all of the exposed females are among this group of employees. The companies these people work for are the least capable technically and financially of monitoring and controlling gaseous vinyl chloride. All of these problems can be solved by preventing vinyl chloride from leaving the polymerizing plants. Therefore, I suggest that every effort be made to encourage manufacturers to strip the monomer from their products.

In addition to eliminating or reducing the exposure in the fabricating plants, this approach would have the extra benefit of protecting those who transport polyvinyl chloride. Some of the highest gas concentrations reported in the Record were found in trucks and freight cars that had been filled with polymer, sealed, and shipped through the heat. Workers should be protected against the possibility of exposure if they should enter such a vehicle.

Finally, insisting on clean polymer would reduce the threat of unfair competition from foreign manufacturers whose occupational standards

may be less stringent and, therefore, less costly than those imposed on American companies.

In this regard, the record suggests that little thought has been given to the technology for stripping the monomer. Therefore, this may be an area in which very large gains might be made with relative ease.

2. I suggest a reduction in the emphasis on ventilation as a means of reducing exposure in the monomer and poly plants. Ventilators perforce distribute the gas to the surrounding environment and the Record is filled with observations of significant concentrations in offices, laboratories, open areas and even beyond the fence line. Some of these concentrations are uncomfortably high. The public and unsuspecting workers should not be exposed in this way.

3. Following the theme that the area of risk should be as small as possible, I suggest different standards for different groups of people. I suspect that the general public and workers at end-product plants can be protected much more quickly and easily than those engaged in polymer production. I see no reason why a low concentration standard for these people has to be delayed until more difficult situations in the polymerizing plants can be solved.

I recognize that setting different standards for different groups may be taken by some as callousness, i.e. a different concern for one group of workers than for another. This isn't the case. The purpose of separate standards is to reduce the exposure for everyone at the rate that is possible in each area. Permitting exposure of some workers to high concentrations

may be unpalatable, but the converse is even more unpalatable to me, i.e. that all workers shall be permitted to be exposed to high concentrations. Similar "double standards" are commonplace in our society. An obvious example is found by comparing the TLV's for workers to EPA's standards for the populace.

When considering separate standards, it is most important to remember that there is no known risk in American factories. All injuries that have been documented are presumed to have been caused by conditions that are different from present ones. At the hearing, many stated their opinion that the Temporary Standard provides conditions that are perfectly safe. Thus, a lower standard is being considered, not because the present one is known to be inadequate, but because it might be. In this context, different standards for different segments would not require anyone to work in a place known to be dangerous. They would instead, be a prudent way of operating in a potentially risky situation, much like evacuating non-essential personnel from a potential danger area while permitting essential personnel to remain.

Approach to a standard: Clearly a standard cannot be set on the basis of factual medical, toxicologic, epidemiologic, or pharmacologic data. Such data do not exist. All that can be proven is that 50 ppm inhaled for several hours a day for many months is extremely toxic to rodents. Traditional toxicologic reasoning would prohibit comparable exposure of human beings. Therefore, the upper limit of any standard should be well below 50 ppm TWA.

Unless vinyl chloride is banned outright, the lower limit of a standard will be dictated by analytic technology. The practical lower

limit is one that can be observed, monitored, and enforced. This means it must be within the capability of current analytic technology. The hearings were not specifically directed at this, but the concensus seems to be that the NIOSH recommendation is probably a good appraisal of the equipment that is available for routine field use today and that this equipment is capable of one ppm. Therefore, one ppm becomes the lowest reliably detectable and enforceable limit.

The term "no detectable amount" deserves comment. It has substantial appeal, but it is fraught with potential mischief because what is or is not detectable will vary from circumstance to circumstance and from time to time. The mere existence of such a term is a challenge to the analytic chemist to sharpen his tools and push the frontier downward, and the state of the art of organic analysis is such that major advances can be made in a short time. Thus a "no detectable amount" standard becomes infinitely elastic and subject to constant redefinition. The manufacturer who in good faith purchases and installs the best equipment available today may find himself challenged tomorrow by someone with a new technology. Even worse, the present wording is extremely ambiguous. Almost everyone at the hearing interpreted it to mean a standard of 1 ppm, but that is not what the document says. It says "no detectable amount, as determined by a . . . method capable of detecting . . . 1 ppm". Thus, this standard really doesn't specify a vinyl chloride concentration; it specifies the minimum sensitivity of the analytic equipment. This seems to me to be an illogical way to set a standard.

If the standard is to be this low, a better approach would be to state it in accord with reality. That is, determine the lowest concentration that can be detected by equipment that is: available now, available from several manufacturers, adaptable to the purposes to which it will be put, reliable under field conditions, and can be operated by technicians of ordinary competence and use this level as the standard until such time as instruments with the same qualities but greater sensitivity are produced.

Medical Surveillance: Regular examinations would be of questionable value if their only purpose were to detect angiosarcoma. Reasonable people can easily disagree on the virtue of early detection of an untreatable and fatal disease. However, there are other reasons for desiring medical examinations of workers who are regularly exposed to vinyl chloride. One is epidemiologic; we need to know more about the human experience in this industry. The more compelling reason stems from the evidence that vinyl chloride may cause a variety of disorders, some of which (e.g. bronchoconstrictive disease, vascular hyperactivity, fibrosis of the liver) might be reversed or, at least, arrested if detected early.

For these same reasons, the medical examination should not be aimed exclusively at tumors of the liver, as that in the Proposed Standard seems to be. It should be broad and complete. Specific recommendations follow, but it should be clearly understood that these are suggestions for minimum examinations. The regulations should be written so that there is no way of missing the intent and interpreting the stipulated tests as the only things a physician should do. Attention should be

given to the major potential target organs, but it should not be limited to them.

History-complete; including previous illnesses, previous employment, exposures to toxic materials, alcohol intake and dietary habits.

Physical-complete; including skin; limbs; vascular system; lungs; heart; abdominal organs.

Laboratory; chest x-ray; complete blood count including smear for differential and estimation of platelets; urinalysis including microscopic examination; chemical analysis of blood, including SMA-12; liver function and serum enzyme determinations; hepatitis associated (Australian) antigen, and (where available) carcinoembryonic antigen and alpha fetoprotein; pulmonary function tests (FEV_1 and FVC).

The medical examination should be done by a licensed physician, preferably one experienced in industrial hygiene, and the laboratory work by an accredited and licensed laboratory. (Physicians familiar with the toxic potential of vinyl chloride should be available to all of the monomer and polymer manufacturers. They are not as likely to be available to the many processers of the polymer--another reason for trying to contain the monomer within the confines of the major plants.)

Annual examinations should be adequate. Abnormal findings should be checked as quickly as possible and appropriate additional examinations should be done to find the cause of abnormalities.

Records should be maintained at least for the lifetime of the employee, preferably for several years longer; it would be very helpful

to establish a central repository if appropriate means of doing so can be found.

Since there is no knowledge of the course of the toxic effects produced by vinyl chloride, there is no way of knowing whether or not an employee who developes abnormalities should be removed from contact with the material. On the one hand, the processes may be reversible and removal from contact would be beneficial; on the other hand, the processes might not be reversible and removing one worker and filling the job with someone else may only multiply the number at risk. There will be no means of resolving this dilemma until we know more about the course of vinyl chloride toxicity. For now it would probably be best to assume that early stages are reversible and act accordingly.

Miscellaneous: Other parts of the proposed standard also call for comment. The requirement for impermeable clothing seems to me to be excessive. There are few studies of the penetration of skin by vinyl chloride but those few that are available (see Dow Report) suggest that while vinyl chloride can enter by this route, it does so in very small amounts and at a very low rate. This is in keeping with theory which would predict that a gas of moderate lipid solubility (such as vinyl chloride) would be able to penetrate the skin but at a rate vastly slower than through the lungs. On the other hand, a gas with solubility in water as low as that of vinyl chloride would be expected to be exhaled almost as soon as it entered the blood stream. Thus, a man respiring clean air should retain virtually none of whatever little gas enters through his

skin. Therefore, I do not see any need for impervious suiting under anything except the most extreme conditions (prolonged exposure to many thousands of parts per million of vinyl chloride). The use of ordinary protective clothing to reduce the exposure to polymer and entrapped liquid vinyl chloride would be desirable.

The Record suggests that there is a fortuitous relationship between polymer and air such that a polymer containing, for example, 50 ppm of monomer can produce an air concentration that is also 50 ppm. This relationship should not be allowed to confuse the reader. A careful distinction should be made between gas concentration in air and monomer concentration in polymer. Both may be expressed in the same units, but their importance is entirely different. For example, an upper limit of 1 ppm of gas in air may be a necessary and attainable goal for major segments of the industry, but 1 ppm of monomer in polymer is probably neither necessary nor attainable. Therefore, if a purity standard for polymer is set, it should be different from that set for air. The Record suggests that plants handling polymer with 50-100 ppm of monomer are having little or no difficulty maintaining less than 1 ppm in the working area.

The Record suggests to me that area monitoring is feasible and desirable. It also suggests that personal monitoring should also be done, particularly for those whose jobs cause them to move from one area to another.

I am not competent to choose among the various types of respiratory protection equipment, but to me it seems that a strong case has been made

for permitting cannister-type equipment for emergencies and for short term use by those whose jobs require mobility.

With regard to air supplied equipment, it should go without saying that the air should not be contaminated, but given present factory environments some precautionary words may be in order.

There should be careful distinction among contact with liquid monomer, gaseous monomer and polymer contaminated with monomer. The Proposed Standard seems to equate them, but each has a different problem and a vastly different hazard. The final regulations should distinguish among them and prescribe protective clothing, hygenic practices, and medical treatment and surveillance that is appropriate to the hazard.

In this regard, it should be remembered that vinyl chloride is a gas which will not cling to skin or clothing and, therefore, is different from solid or liquid industrial hazards which stay until washed off. It should also be remembered that the toxic effects of the gas are extremely delayed in onset. They will not be detected or prevented by prompt medical examination.

The requirement for an immediate shower after exposure also is unnecessary. Washing the exposed part and being prepared to deal with freezing injury are worthwhile, but the volatility of vinyl chloride is such that none would be expected to remain on the skin for a significant time after exposure. On the other hand, anyone exposed to liquid vinyl chloride to the extent that there is skin damage should receive

immediate medical attention. The "within twenty-four hours" requirement is not adequate.

I am sympathetic with those who object to the proposed signs and labels in that they are frightening without telling the individual what it is he should be frightened of, or how to avoid danger. The label should contain the name of the material, recognize that cancer is not the only (or even the most likely) form of health hazard, and give instructions or precautions for avoiding the hazard.

A final expression of a personal prejudice: "Level" is laboratory jargon. It would be nice if the final document could refer to concentrations instead of levels.