

W. CLARK COOPER, M.D.
2150 SHATTUCK AVE - SUITE 401
BERKELEY, CALIFORNIA 94704
PHONE (415) 845-3355

March 25, 1980
WCC 1698

Mr. Gershon W. Fishbein
1097 National Press Building
Washington, D.C. 20045

Dear Gershon:

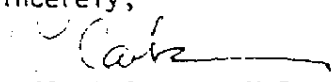
In your report (March 22, 1980) on the vinyl chloride and polyvinyl chloride meeting of March 20 and 21, my views were interpreted in a way that might suggest to some that I do not think that vinyl chloride (VCM) is a human carcinogen. The studies that I reported (which were actually designed and carried out by Tabershaw and Gaffey) detected 8 of the 9 hepatic angiosarcomas that had occurred in the study populations prior to 1973. There is no doubt about the association between vinyl chloride and this rare tumor. While there appeared to be an excess of brain tumors (12 where 5.9 were expected) in 707 deaths among 9,677 workers, it was with respect to this site that the study is still inconclusive as to a causal association with vinyl chloride. Small excesses for other sites could not be ruled out, but if VCM was a causal agent for tumors in multiple other sites, the cumulative effect could not have been very great. The study population had only 4% more deaths than expected from malignancies. This held true even when analysis was confined to those whose exposures had begun prior to 1952 or prior to 1947.

The strongest evidence suggesting that vinyl chloride monomer may cause certain types of lung cancer was in a report by Waxweiler of NIOSH (paper #24), who showed that there was an excess of large cell undifferentiated lung cancer in those who loaded or packed freshly prepared polyvinyl chloride (PVC). A plausible, but unproven, explanation for this would be that it was due to high localized levels of VCM in the lungs resulting from residual amounts in the PVC dust.

Other reports on polyvinyl chloride were extremely reassuring as to the hazards of inhaled PVC. It apparently produces little or no fibrosis in the lungs of animals, although deposited dust remains indefinitely. Workers who had inhaled large amounts of PVC dust showed slight changes by x-ray and slight reduction in lung function, but nothing to indicate that disabling pneumoconiosis would ensue. It appears to act like a relatively inert dust. Clearly, dust control is needed, but in the absence of residual VCM, it is plain that it will not have to be as rigorous as needed for quartz and other fibrosis-producing dusts.

My overall impression was that the meeting did not bring out anything to alter significantly our present stance on vinyl chloride and polyvinyl chloride, although there are many unresolved questions. Some analogues should come under control, but VCM itself would appear adequately controlled with current standards. I will be interested in the opinions of others.

Sincerely,


W. Clark Cooper, M.D.

SCC
5-1538

WCC:bs

DR. MALTONI REPORTS TUMORS IN RATS AT STILL LOWER LEVELS OF VINYL CHLORIDE

Dr. Cesare Maltoni of Italy, whose earlier studies on vinyl chloride exposure figured prominently in the OSHA standard, now reports that tumors have been found in laboratory rats exposed to as low as 25 ppm of vinyl chloride and possibly 10 ppm.

At a meeting called by OSHA, NIOSH and NIEHS to hear and evaluate new data on vinyl chloride for standard-setting purposes, Dr. Maltoni made the following points:

- * In experimental animals, principally Sprague-Dawley rats but including other species as well, tumors have been found at progressively lower levels of vinyl chloride exposure—in a few cases almost down to

Occupational Health & Safety Letter, March 22, 1980

1 ppm. All of the animals were permitted to live a lifespan, none being sacrificed. Newborn rats were especially sensitive.

- * Tumors were found not only in the liver but also in the brain, lung, kidneys and other organs. Dr. Maltoni said this result showed that workers exposed to vinyl chloride should be monitored not only for liver damage, including angiosarcoma, but for other organs as well. In addition to the tumors, cancer precursor dysplasias were found in the livers of many animals.

- * Significant levels of tumors were found in the rats at 50 ppm at various durations of exposure in what Dr. Maltoni believed was a significant dose-response relationship.

Dr. Maltoni's presentation came as we went to press with this issue, and we will continue the discussion of the important meeting in our next issue. Suffice it to say that many in the audience took issue with Dr. Maltoni's findings.

For example, Dr. W. Clark Cooper of Berkeley noted that workers exposed to vinyl chloride have been monitored for multiple sites for a number of years. In his own presentation, Dr. Cooper extended the earlier studies of Drs. Tabershaw and Gaffey which indicated some excess of cancer deaths in workers exposed to vinyl chloride but came to no conclusion on a causal relationship. In his analysis, in which 3,000 additional workers were evaluated in follow-ups, the total number of deaths increased from 343 to 707, with some increase in cancers of the digestive tract, central nervous system and some in the respiratory tract. But Dr. Cooper said that, if anything, his analysis was even more inconclusive on causal relationships with vinyl chloride.

WHERE THE LAW STANDS ON DETERMINING ACCEPTABILITY OF RISK:

A very interesting paper—at least we thought so—on the role of law in determining acceptability of risk was presented by Harold P. Green, professor emeritus of law at George Washington University's National Law Center and now a partner in a prominent Washington law firm whose members include Secretary of HEW Patricia Harris. The scene was a workshop on management of assessed risk for carcinogens, sponsored by the New York Academy of Sciences. We thought his philosophical points on where the law stands worthy of attention.

"In considering the relevance of law to the determination of acceptable levels of risk, it is well to understand more generally the role of law in a democratic society such as the United States," he said. "Societal actions take place within a framework of laws that, not necessarily with clarity, establish the acceptable ambit of individual action and define the possible consequences if the limits are exceeded.

"The basic philosophy underlying the legal system is that every individual should be free to act as he or she perceives to be in self-interest, subject only to limits established to protect the interests of others. The basic function of the legal framework is, therefore, to resolve the conflict that inevitably arises as individuals pursue their respective self-interest.

"The laws that exist at any given moment—whether made by legislature, administrative agency, or courts—reflect societal values that have reached expression through a complex socio-economic-political process. They are not immutable, but are always subject to change. They may be changed by legislative action, by executive implementation, by judicial application and interpretation, and/or by a combination of these, again reflecting the values that emerge from the socio-economic-political process.

What, however, is the nature and function of the legal system is not always well understood by many,

500
5-1559

IMPERIAL CHEMICAL INDUSTRIES LIMITED
PLASTICS DIVISION
HEALTH AND ENVIRONMENT PROTECTION

SUMMARY REPORT

REPORT OF CONFERENCE TO RE-EVALUATE THE TOXICITY OF VCM, PVC AND STRUCTURAL ANALOGUES - BETHESDA 20-21 MARCH 1980

1 Introduction

This Symposium sponsored by NIEHS, NIOSH and OSHA was a poorly attended, not very well organised event as might have been expected from the unseemly haste evident in its preparations. Even the printed programme was scrappily done - I have seen better quality printing for church bazaars. Many of the speakers changed the titles of their papers and some speakers were substitutes for those listed. Dr A Robbins the Director of NIOSH did not turn up to chair the final session and Dr Selikoff did not attend to take part in the final panel discussion. The press and TV were certainly not visible. The papers were rushed and the discussion periods hopelessly short; no attempt was made to distinguish between what was old and what was new and deserving more time for discussion. The whole affair went off in low key with an attendance of 150-200 max with 400-600 expected. The Proceedings will be published officially in due course - the SPI have arranged for an earlier transcript plus photos of slides to be circulated.

2 Maltoni

Maltoni had worked on his Paris lecture and gave a different set of slides, many of them simplified for easier assimilation and understanding. A discussion of the implications for human hygiene standards and human health was nipped in the bud principally by Dr Saffiotti who said the VCM hygiene standard was based on technical feasibility and not extrapolation from rodent to man. This alas will keep cropping up because there are diverse views held about the relative potency of VCM to different animal species and many believe VCM to be a potent human carcinogen. OSHA are still keen to incriminate target organs other than liver in humans. Their standard response used throughout is that too little time has elapsed to be certain that organs other than liver in man are not target sites. The same argument is used regarding the lack of proven ASL in the PVC fabrication industry and in "neighbourhood cases".

3 PVC Dust

The Seaton paper was one of the few original papers giving new information at this meeting. Dr Mastroangelo gave a surprisingly good paper but there was no time for Dr Mattiussi to challenge him at the discussion period. Dr C Wagner was mainly inaudible and the playback from one or two later speakers/questioners showed that he was not understood and was being misquoted unfortunately with no opportunity for correction of the record. There was a great deal of interest in PVC dust but the reception was in the main good and moderate. Some change in hygiene standard in the USA seems inevitable. I was worried by the use of the word "pneumoconiosis" in its original Greek sense as "dust in the lung". While scientists may understand this, others may wish to confuse this literal usage with the medico-legal usage which implies (disabling?) fibrotic disease in the lung resulting from the habitual inhalation of excessive quantities of (fibrogenic?) dusts. We will have to take care that we use the word accurately in all our discussions.

4 Reproductive effects

This tended to be dominated by active feminists restating the Infante/Wagoner line. One was left wondering at the miracle whereby any human foetus in the USA survived to term and puzzled by the fact that so much of the US population is, against all the odds, not deformed. We learned something of "power" considerations in analysing studies. From this we gather that "not all negative results are equal - some are less negative than others". This was a more plausible line than the normal Infante/Wagoner assertions regarding their findings and some of their colleagues' previous tendencies to end up studies by saying "we haven't quite managed to prove X is carcinogenic but next time we will nail it". Dr Jackie John of Dow spoke about her experimental work on transplacental teratogenic effects of VCM and ethyl alcohol on rabbits, rats and mice - I missed a large part of it because of a discussion outside the meeting but I got the impression in her summary that effects were found in rats, mice and rabbits when VCM and alcohol are administered together. There seemed to be some doubts about the effects of 2,500 ppm VCM on its own. I suggest waiting for her paper to be printed. Overall I doubt whether there was sufficient evidence adduced in this series of talks to make any agency keen to do anything other than suggest more, properly designed studies on potential reproductive hazards of VCM.

5 Epidemiology

Nothing new was presented but plenty of old stuff was regurgitated in tables/slides which will need checking when the proceedings become available. This is particularly true of Infante's presentation on brain, lung, lymphatic etc tumours where he was merely restating his personal position of certainty on liver, brain and lung and (query) lymphatic. "Power considerations" came in again and there were wide disagreements re the potency of VCM in man. Waxweiler said we could not rule out the possibility that PVC fabricators with low exposures would in the fullness of time develop ASL. He also added "anabolic steroids" to the list of carcinogens which cause ASL. (Do we know of this?) There were also suggestions that there may be other carcinogens which give rise to ASL! (I am still worried that there is such a factor beginning to show up in the UK plastics fabrication industry). Despite clever detective work by Waxweiler and Falk, it was clear that there was nothing really new and we were all waiting for the quinquennial update on 1974 studies from the USA, UK and elsewhere. (The emphasis on longer and longer latency periods being found with Thorotrast is a worrying feature of the papers presented).

6 Hygiene

The data presented were all pre-1977. OSHA must have plenty of up-to-date material but NIOSH were using old field study reports. Some of the detailed data is nevertheless interesting especially about the PVC fabrication industry and PVC dust measurements. If OSHA had hoped to have a go at regulating PVC fabrication more closely, the hygiene measurements presented even of pre-1977 vintage did not offer them any support or justification.

7 Medical monitoring

There were no surprises and there is no real difference between the USA and Europe on the value of various tests. In fact there is astonishing unanimity that the tests mandated in government regulations are of little utility. I was astonished to learn that 124 BFG's Louisville employees have had liver biopsies!!

SCC
5-1541

8 Vinyl bromide (VBM)

Results were presented to show that VBM causes ASL in rats and the effect is dose related in male rats. Other tumours were found but not brain, mammary or kidney tumours. The TLV for VBM is given as (250 ppm) which seems unrelated to present day realities. The need for urgent regulatory action was stressed.

9 Other compounds related to VCM

Dr Ken Chu of the NCI put up slides comparing the results of various inhalation and ingestion experiments on animals with VCM, VDC, TCE, PCE, 1:2 DCE, 1:2 DBE and ECH. (Oddly enough no mention was made of the CIVO study). The paper gave rise to two discussion points. Maltoni stated that tabulation of results from different labs was misleading - not all results are equal! Before doing such comparisons, results should be critically re-evaluated to eliminate laboratory differences before talking of biological differences!! The second point related to the use of technical versus pure grades of chemicals - needless to say the argument centred round TCE and defence of the NCI practice of using technical grades.

A review of epidemiology studies in this area by Ms Apfeldorf from OSHA was hopeless - not one of her slides was readable!

10 Final Panel discussion

Dr Haddis of MIT thought VCM a mature model for tackling health hazards. He felt reassured that human data did not so far suggest the large problem originally forecast by the pessimists. He thought nuisance dusts needed to be looked at generally rather than PVC dust in particular and more data were necessary about lung functions in the background general population. On reproductive hazards he said there was a need for a generic approach and need to look at mutagenesis broadly. He advocated the withdrawal of M&F workers from hazardous exposures in plenty of time before mating to allow elimination of chemicals from their bodies!

Mr Wodka of OCAW gave a diatribe against the Schweiker Bill, advocated the strengthening of OSHA and enumerated at length specific examples of hazards inflicted by multinational oil companies in the PVC dust and benzene areas without proper regulation/punishment.

Dr Johnson of BFG advised against the raising of false hopes in early diagnosis and intervention.

Dr Nicolson of Mt Sinai quite rightly complained of the lack of up-to-date information at the Symposium especially on epidemiology, ASL cases and medical surveillance/industrial hygiene. He took the view that VCM is a potent human carcinogen and human exposure should be kept to the absolute minimum.

Dr Wagoner sounded off giving out-of-date information on ASL cases and criticising epidemiological studies in PVC fabrication as being subject to a "dilution factor" which reminded him of similar so-called "negative" studies in the steel industry which had delayed the findings on coke ovens and the promulgation of coke oven standards. He sneeringly mentioned one town where a PVC producer pays to have cars coated with PVC dust washed free of charge - and swimming pools in the neighbourhood are permanently coated with PVC dust! It was a myth that PVC

was a nuisance dust and it needed to be controlled. Dr W did not believe the negative findings on neighbourhood ASL cases in New York State.

As Chairman in place of the Director of NIOSH, Dr Landrigan said the major topics emerging for further study were:-

- a) liver, brain, lung and lymphatic tumours in man as a result of VCM exposure
- b) reproductive hazards of VCM
- c) PVC dust
- d) the hazards of VCM analogues like VBM

In so doing he was merely restating the four subjects which were the backbone of the programme for the Symposium, and not the conclusions of any rational discussion.

11 Observations on the Symposium

The US VCM/PVC industry kept a low profile throughout and in the main left interventions to consultants like Dr Cooper. By comparison, the European VCM/PVC industry representatives were vocal and intervened frequently, particularly Dr Tassignon who had numerous good points to make. In private conversation with members of the US industry, one sensed a continued underlying concern that this low key, somewhat dull symposium should not be under-rated - there was a clear warning that some rule-making was intended and only time will show where OSHA will act. While hearing this message from our US colleagues, I find it difficult to visualise anything happening beyond regulation of PVC dust and vinyl bromide.

J Stafford

JS/SEW/DSO-16

1 April 1980

inspection and citation of a Lansdale, Pa., firm in which Schweiker has a financial interest (Current Report, March 20, p. 965).

Schweiker again rebutted the allegations, and condemned efforts by PHILAPOSH to picket his home in Pennsylvania and to print "a wanted poster with my picture on it — stating I was wanted for conspiracy to injure, maim, and kill thousands of American workers."

The union reaction, Schweiker said, stands in contrast to efforts by "key people in the Senate, Democrats and Republicans, liberals and conservatives," to "put an end to a decade of divisive polarization." Similarly, "we have the vast majority of the business community looking for a positive approach for a constructive government safety and health program," he maintained.

Schweiker reasserted his position that the bill would direct OSHA's enforcement resources toward high-hazard workplaces, and would encourage strong employer safety and health programs. Statements by labor leaders that the measure would weaken OSHA authority and infringe on the statutory rights of workers are "false," he declared.

The Senator said he urges labor leaders "to cut the non-sense, and come work with us in good faith to develop positive improvements in the OSHA program." He added, "I frankly do not have much hope that they will, because I have been asking for this since last August, four months before we introduced S 2153."

Business leaders should "get involved, get others involved, and ask members of Congress to read the bill and look at the facts," Schweiker urged.

NAM Urges Support

Member companies of the National Association of Manufacturers were urged March 20 by NAM President Alexander B. Trowbridge to support the Schweiker bill. Though NAM is "concerned with some of the specific provisions of the legislation," the bill warrants support in concept at least as a "positive first step toward meaningful amendment" of the Occupational Safety and Health Act, the association stated.

Trowbridge said that, "while we all can agree with the general objectives" of the Act, "the manner in which OSHA has administered the law has, in too many instances, been counterproductive and overly punitive in approach."

Trowbridge said the bill is the first "OSHA reform" measure to have bipartisan support, and as a result has the best chance of passage of any of these bills.

Vinyl Chloride

ALCOHOL INCREASES TUMOR INCIDENCE IN RATS, RESEARCHER TELLS MEETING

Alcohol drinkers may have increased susceptibility to the carcinogenic affects of vinyl chloride vapors, a Government-sponsored conference was told March 20.

Martha Radike, of the University of Cincinnati, reported the results of a study in which laboratory rats were given water containing 5 percent ethanol and were exposed to vinyl chloride.

The animals that received alcohol had a much higher incidence of vinyl-chloride-induced malignant tumors than the rats exposed to vinyl chloride alone, she said.

The test animals were exposed to a concentration of 600 parts per million vinyl chloride vapor, four hours each day, five days a week for one year.

Control groups exposed to vinyl chloride alone and to alcohol alone had elevated tumor rates in comparison with a

control group not exposed to either substance, Radike reported.

The tumors in the alcohol-only group tended to be benign, rather than malignant, she said.

Radike compared the level of alcohol given to the test animals to a moderate drinking level, similar to a six-pack of beer or a few glasses of wine.

She said the experiment was suggested by the fact that ethanol and vinyl chloride are known to share a step in the metabolic pathway.

Radike suggested that epidemiological studies should be carried out on human populations exposed to vinyl chloride to determine whether chronic alcohol use is related to cancer incidence.

The two-day conference on vinyl chloride toxicity was sponsored by the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health, and the Occupational Safety and Health Administration (Current Report, February 28, p. 906).

The conferees heard reports from 37 researchers, including Caesar Maltoni, of the Institute of Oncology and Tumor Center in Bologna, Italy.

Inhalation Studies

Maltoni reported the results of extensive inhalation studies in rodents at various dose levels ranging from one to 30,000 ppm.

In long-term studies, test rats developed increased incidences of cancer at levels as low as 10 ppm, Maltoni said.

The OSHA standard for worker exposure to vinyl chloride sets a maximum limit of one ppm, averaged over an eight-hour period.

Maltoni's experiments involved exposure of test animals for four hours a day, five days a week, for varying periods.

He reported that the test animals exposed to vinyl chloride suffered a variety of tumors, including cancer of the liver, lung, kidney, stomach, skin, brain, mammarys, and Zymbal's gland.

May Affect Fetus

Maltoni also reported a study suggesting that exposure of a pregnant animal to vinyl chloride can increase the incidence of cancer in her offspring.

He described experiments in which female rats were exposed during pregnancy to vinyl chloride vapors at concentrations of 6,000 and 10,000 ppm.

The offspring of the exposed rats later developed a higher incidence of liver cancer than the offspring of unexposed control rats, Maltoni said.

The increase was over 30 percent in all exposed groups, according to the researcher.

Short Exposures

Robert Hehir of the Consumer Product Safety Commission reported the results of experiments involving relatively brief exposures to vinyl chloride.

He described studies in which test rodents were given between one and 100 one-hour exposures to vinyl chloride vapors.

No statistically significant response resulted from single one-hour exposures, even at concentrations as high as 50,000 ppm, Hehir said.

However, a significant increase in lung tumors did occur in a group of animals given 49 one-hour exposures to 500 ppm of vinyl chloride over a 10-week period.

He told the conference that a comparison of this result with other published reports suggests that vinyl-chloride-induced cancer incidence is related to the total dosage received.

Studies update vinyl chloride hazards

Extensive study affirms compound is potent animal carcinogen; epidemiological studies show elevated rates of certain human cancers

It has been six years since data first began surfacing linking vinyl chloride exposure to a rare form of liver cancer both in laboratory animals and in vinyl chloride workers. Those years have seen an explosion of studies, both in humans and in the laboratory, on the effects of this compound, so that now it is very likely the most studied compound ever in terms of its effects on human health. Thus, the time seemed right for a re-evaluation of the toxicity of vinyl chloride, its polymers, and its structural analogs.

Last month, a two-day conference at the National Institutes of Health in Bethesda, Md., sponsored by the National Institutes of Environmental Health Sciences, the National Institute for Occupational Safety & Health, and the Occupational Safety & Health Administration, pulled together 35 scientists to update the picture on vinyl chloride and its possible hazards.



Maltoni: doesn't imply a threshold

Some of the most important early evidence of a link between vinyl chloride and cancer came from the work of Cesare Maltoni of the Istituto di Oncologia in Bologna, Italy. Maltoni showed in experiments with rats that inhalation of vinyl chloride could cause the formation of a rare liver tumor, angiosarcoma, that had earlier been found in vinyl chloride workers.

Since then Maltoni has been conducting what he believes is the most extensive animal study ever done on a chemical. He has examined the effects of vinyl chloride and a few structurally similar compounds in mice, hamsters, and two species of rats. Altogether 7000 animals and more than 3 million rodent-days have gone into the study, final results of which will be published later this spring.

The study's main findings are that vinyl chloride is unquestionably an animal carcinogen. It is what Maltoni calls a multipotent carcinogen, which means it produces tumors in many different organs and, in some cases, different types of tumors in a single organ.

The Maltoni study also provides quantitative data on the health effects of vinyl chloride. Liver angiosarcomas and other tumors are found in animals treated by inhalation with as little as 10 ppm of vinyl chloride and by ingestion with as little as 0.3 mg per kg body weight. This inhalation level is much lower than the common workplace exposure level for the compound before 1974. OSHA's exposure level for inhalation of this compound is now 1 ppm.

Maltoni finds a dropping off in the incidence of tumors in animals receiving less than 10 ppm vinyl chloride by inhalation or 0.3 mg per kg by ingestion. He is quick to point out, however, that he does not interpret this decline as evidence for a threshold level below which vinyl chloride does not present a hazard to animals. "After 10 ppm, the effects seem to fall down, but in my own view this does not imply at all that there is a threshold in theoretical, biological terms," he says. For one thing, tumors are found below this level.

In humans, too, the effects of vinyl chloride exposure do not appear to be

Animal data show vinyl chloride is a multipotent carcinogen

This tumor type . . .	is found in . . .
Liver angiosarcoma	Rats, mice, hamsters
Hepatocarcinoma	Rats
Extrahepatic angiosarcoma	Rats, mice
Zymbal gland (sebaceous) carcinoma	Rats
Nephroblastoma	Rats
Neuroblastoma	Rats
Mammary carcinoma	Rats, mice
Pulmonary tumor	Mice
Skin tumor*	Hamsters
Prestomach papilloma	Rats, hamsters
Melanoma*	Hamsters
Lymphoma*	Hamsters

* Data test certain. Source: Cesare Maltoni, Istituto di Oncologia Bologna, Italy

limited to the liver. Peter Infante, director of the carcinogen identification program at OSHA, summarized data from various human epidemiological studies on vinyl chloride. These studies show wide variations in findings, but taken together they indicate an even greater incidence of brain cancers than liver cancers among workers exposed to vinyl chloride. Lung cancers, too, occurred at more than twice the predicted incidence among vinyl chloride workers in four of the studies.

Probably the most extensive epidemiological study concerning exposure to vinyl chloride is that conducted for the Chemical Manufacturers Association by Tabershaw-Cooper Associates and Equitable Environmental Health Inc. This study included 10,173 workers in 37 of the 43 plants that either made vinyl chloride or produced polyvinyl chloride in the U.S. in 1973. The study, described by W. Clark Cooper, a consultant with Tabershaw-Cooper Associates, attempted to include all male employees who had been exposed to vinyl chloride for at least one year prior to the end of 1972.

It classified exposure to vinyl chloride subjectively as high, medium, or low at each plant, and then

SCC
5-1545

rules are not hard and fast, and use of such light-sensitive reagents still depends on a case-by-case evaluation.

Efforts to use polymers to protect residues in sugars during synthesis have often ended in frustration, several chemists admitted at the symposium. But Fréchet clearly is more optimistic about the efficacy of using polymers.

Perhaps the impetus for trying polymers as blocking groups comes, in part, from the success of peptide chemists (and, more recently, chemists who make oligonucleotides for recombinant DNA end uses) in exploiting that strategy. But peptide chemists have usually one and almost never more than two functional groups to block, whereas carbohydrate chemists typically must deal with four or five highly similar groups.

One of the more attractive polymer applications enables one to block two hydroxyl groups simultaneously. A matrix consisting of polystyrylboronic acid is useful for protecting hydroxyls that are in a cis configuration, according to Fréchet. The system can be very efficient, particularly for fishing out certain dideoxy sugars, which have an appropriate cis diol group, from a complex reaction mixture. The

polymer-sugar adduct then can be disrupted simply by adding water to free the sugar and regenerate the polymer. The problem with such systems, Fréchet says, is that the boronate is difficult to purify in the first place, a factor that causes problems in scaling up the procedure.

An entirely different way of exploiting polymers during carbohydrate syntheses is extremely clever in principle, if difficult in practice. The basic idea is to use the rigidity of polymers to construct a template for making chiral sugars. The work has been pioneered by German chemist Gunther Wolff, Fréchet notes.

A chiral sugar (that is, a sugar having a particular "handedness," a complicating factor for most synthetic schemes involving natural products, particularly those containing several sugars) is attached to a monomer that is bifunctional. Thus, instead of a boronate monomer, for example, a diboronate monomer might be used. Once the sugars are fixed to the monomers, the material is polymerized through the other functional groups of the monomers. When the sugars are removed, the "holes" that remain are fixed within the polymerized matrix—and presumably may be used to separate

from a mixture sugars having the correct chirality.

It's an extremely clever scheme, one that can provide separations with yields of greater than 90%, Fréchet says. It's not perfect because the initial binding and polymerization steps don't always put molecules into the hypothetical configurations that are needed. Nonetheless, such results are promising enough that Fréchet and his colleagues as well as several other research groups are actively developing the chemistry that could bring this strategy into wider use. □

Activity correlated to structure by computer



179th ACS Meeting
HOUSTON

Once, when compounds were less numerous than today, and regulations less stringent, screening new drugs, cosmetics, food additives, and the like was much less of a problem. Today, for instance, the Environmental Protection Agency is charged with making regulatory decisions on up to 43,000 compounds under the Toxic Substances Control Act. Meanwhile, several hundred thousand compounds are backlogged in the files of pharmaceutical companies, waiting to be checked for drug action.

Inevitably, chemists slogging through this molecular landslide have turned to the computer. The general idea is to teach the machine to look at a given compound, and from its structure and physical chemical properties predict whether it is toxic, carcinogenic, biodegradable, or even particularly effective in its hoped-for application.

Difficult as that may sound, practitioners of the art have developed programs over the past few years that can predict, say, carcinogenicity, with an accuracy of up to 95%—albeit on very limited compound lists. Efforts in this direction come under the general heading of Quantitative Structure/Activity Relationships (QSAR). Such work was discussed at a number of sessions in Houston, and within the Division of Chemical Information, QSAR was the topic of a day-long symposium.

By far the most ambitious effort in this field is EPA's Health Effects & Environmental Data Analysis system (HEEDA).

"EPA has been interested in the use of computerized structure/activ-

SWITCHING TO HYDROCARBONS IN PLASTIC FOAM PRODUCTION?

Hydrocarbon foaming agents are a proven substitute for chlorofluorocarbons in the production of polystyrene beads and polystyrene foam sheet. If you're considering the switch, we direct your attention to Phillips N-Butane, N-Pentane, and Isopentane. As hydrocarbons, they have a high degree of purity and are particularly well suited to food contact products.

Typical Properties

Composition, Mol %	N-Butane	N-Pentane	Isopentane
Isobutane	2.0	—	—
N-Butane	97.6	—	0.2
Isopentane	0.3	0.5	97.1
N-Pentane	0.1	98.8	2.7
Other Hydrocarbons	—	0.7	—
	100.0	100.0	100.0
Vapor Pressure (PSIA at 100°F)	52	15.2	20.1
Sulfur Content, ppm	2	1	1

Phillips is a leading producer of these foaming agents and our vast feedstocks assure you of continuous supply. Put Phillips resources, technology, and manpower to work for you. Specify Phillips hydrocarbon foaming agents. We'll ship promptly. For more information, write: Specialty Chemicals, 14C4 Phillips Building, Bartlesville, Oklahoma 74004. Or call: 918 661-5361. For pricing and orders, call 800 858-4327. (In Texas 800 692-4054).



PHILLIPS CHEMICAL COMPANY
A DIVISION OF PHILLIPS PETROLEUM COMPANY
The Performance Company

FOAMING AGENTS



HSE more involved with major hazards, less with carcinogens

GIVING local authorities advice, particularly in Scotland, regarding the safety of proposed oil, gas and other major industrial installations is becoming an increasingly important function of the UK Health and Safety Executive, according to its 1978/79 annual report. In fact, the increasing involvement with planning of major facilities created a backlog of work during 1978 which led to complaints about the time taken by the HSE's new Major Hazards Assessment Unit (MHAU) to give advice. Requests from local authorities for advice on planning permission rose by 50 per cent over 1977/78, for example, the report states, many of these coming from Scotland and concerning North Sea oil and gas-related projects, totalling 500 in all.

The MHAU and its risk appraisal group which services local authority enquiries were brought under the same HSE umbrella as nuclear installations following a reorganization in 1978. This was because of the similarities between the techniques of assessment for the safety of nuclear and non-nuclear installations. In its major involvements during 1978/79, the non-nuclear section was involved with the Canvey Island, St Fergus, Braefoot Bay and Moss Morran developments.

Besides demanding some hardware modifications and hazard analyses to be carried out at Canvey, the group also requested the re-routing of two NGL pipelines from St Fergus and made suggestions to mitigate the hazards associated with radio frequency emissions

at Braefoot Bay and Moss Morran.

Work on the proposals for notification of toxic properties of substances was the main work of the important Advisory Committee of Toxic Substances (ACTS). Also mentioned in the HSC/HSE report, however, is progress on controls on carcinogens and VCM, in particular. A draft approved code of practice for VCM (still not published) was developed in order to implement the 1978 EEC directive. And although not mentioning the EEC aspect (which it is understood will delay further development of UK proposals), "draft regulations and an approved code of practice" on the control of carcinogenic substances are briefly referred to. Proposals for regulations were approved in June 1978, according to the report.

Ecococ approves directive

ECOSOC the EEC Economic and Social Committee has approved the Commission's proposals for the "post-Seveso" major accident hazards directive, though with some reservations. The committee has asked the Commission to look at the possibility of extending the scheme beyond industrial activity to transport and laboratory activities and says that implementation could be hampered by inadequate definitions of such terms as "industrial activity" and "dangerous substances".

Under the terms of the proposed directive planning approach for hazardous plant would not be granted until a detailed report on associated risks had been submitted.

IChemE supports Finniston proposals

PRIORITY should be given to the setting up of a new engineering authority to provide a sound reference framework for the profession in the UK, according to the Institution of Chemical Engineers (IChemE). In its response to the government's request for comments on the recent Finniston report on the committee of inquiry into the engineering profession, the IChemE endorses Finniston's hope that such an authority will raise the image of engineers both in the UK and abroad and will enable them to become more effective.

The support is qualified somewhat in that the IChemE lays great emphasis on the need for any new authority to liaise closely with the four existing chartered institutions, covering the different fields of interest. In order that the four institutions can give support, their memberships must be maintained, so provision must be made for this. In addition, the IChemE says there is no evidence that an overall body would succeed in raising status where the existing bodies have allegedly failed.

One of the key functions of the new

maintenance of a register of engineers. In the chemical industry, the institution says, problems with lack of interest in registration has not historically been a problem, as it has in some other sectors. It therefore disagrees that there is a serious weakness but supports the idea of a register and the reservation of work for engineers on it, as proposed in the report.

The IChemE, whose members work largely within the process industries or organizations serving them, comments that the history of the process industries does not show the loss of competitiveness and markets to such an extent as described in the Finniston report. It considers that such problems which it does encounter are not due to the lack of skills of the engineers but to a number of other factors such as attitude to work and bad human relationships. Such problems are self-perpetuating in that they discourage others from entering the industry. The Institution therefore feels that it would be a dangerous over-simplification to assume that the proposals alone would make a marked con-

Osha reopens VCM hazards debate...

THE US Occupational Safety and Health Administration is opening up the vinyl chloride monomer (VCM) debate again by initiating a meeting with industry, research institutions and unions to discuss 'new' health hazards associated with the product. Stressing that the meeting does not imply that any changes in the current regulations, which impose an eight hour time-weighted average of 1 ppm, the agency say that it is seeking further information on three major topics.

Firstly, Osha would like to see documentation which could open the way for workers to receive compensation for diseases other than angiosarcoma caused by VCM. Recently, reports have been published showing that the product can cause lymph, brain and lung cancers.

Pneumoconiosis, the lung disease more usually associated with asbestos, has also been connected with VCM and PVC recently. The problem appears to be caused by PVC dusts, according to reports, but it has not yet been shown whether it is due to the dust itself or residual monomer.

Finally, a number of tests have been carried out recently to assess the effect of VCM on the reproductive system and foetuses of rats. Osha wishes to know more details of the results of these.

...Vinatex settles VCM damages claims

VINATEX, the UK producer of PVC, has settled 15 claims for damages from former employees suffering from the effects of vinyl chloride monomer (VCM). One of the claimants was awarded £3 500 by a court and the others settled out of court for sums up to £40 000, according to the lawyer representing the men involved.

The company, jointly owned by Norsk Hydro and Stavley Chemicals, itself a 45:45:10 venture between the National Coal Board, British Steel and the Norwegian major, declined to reveal the total amount of damages paid, but this is believed to be in the region of £500 000. Three further claims are pending.

ABSORPTION of lead from petrol fumes is a relatively minor contribution to overall absorption in most areas according to a report from a committee set up to look at the effects of lead on environmental health by the UK Department of Health and Social Security. The progressive reduction of lead emissions from traffic and industrial sources should, nevertheless, be a major priority in the efforts to reduce lead in the atmosphere, the report says.

These reductions could be made in a number of ways, such as reducing the lead content of petrol, already being done in many countries; improving vehicle exhaust systems; changing traffic management and relocating industry or housing; the commit-

EVIDENCE OF CANCER ASSOCIATED WITH POLYVINYL CHLORIDE DUST PRESENTED:

What may be the first evidence suggesting that polyvinyl chloride (PVC) dust may be carcinogenic was presented by Dr. Richard Waxweiler of NIOSH to a meeting called to consider new health data on vinyl chloride. The meeting was co-sponsored by NIEHS, NIOSH and OSHA.

Dr. Waxweiler actually presented the results of three studies: a retrospective cohort study of a chemical plant that included PVC polymerization; a worker-case vs. community comparative case study which compared histologic distributions of lung cancer cases from the same community; a serially-additive expected dose study, comparing doses of different chemicals that lung cancer cases in the cohort received, as against doses of chemicals that the controls in the cohort received.

In the latter study, the observed and expected doses of 19 different chemicals used in the plant were examined for lung cancers, specifically adenoma, carcinoma and large cell undifferentiated cancers. The chemicals rated at the company were acrylic acid, acrylonitrile, chlorinated solvents, vinyl chloride,

Occupational Health & Safety Letter, April 8, 1980

5

vinylidene chloride, vinyl acetate and PVC dust.

In all of the substances, PVC dust proved positive in the excess of 15 lung cancer cases—adenoma and large cell undifferentiated.

In reply to a question by Dr. W. Clark Cooper, Dr. Waxweiler suggested that there may be some residual monomer in the PVC dust, or perhaps the dust itself, which served as the primary agent. The major consideration, he said, is that at this plant a different cell type distribution is being seen, a cell type that has not been related to cigarette smoking.

Dr. Peter F. Infante of OSHA commented that Dr. Waxweiler's data has extended to PVC dust the "net of carcinogenicity" which had previously covered vinyl chloride and polyvinyl chloride.

In his own paper on multiple site risk analysis, Dr. Infante said epidemiological evidence clearly demonstrates that the carcinogenic effects of vinyl chloride in humans extends beyond the liver, and that the brain and lung should also be considered target organs. Some studies, he added, indicate that the lymphohematopoietic system is also involved.

Dr. Infante documented his observation with an analysis of several major studies conducted between 1973 and 1977 to assess the site-specific cancer risks among workers exposed to vinyl chloride. All, he said, point to the conclusion that other organs besides liver are at risk of cancer.

Dr. W. Clark Cooper of Berkeley, Cal., clarifying and elaborating on our brief report on his presentation in the March 22 issue of *OCCUPATIONAL HEALTH & SAFETY LETTER*, said there is no doubt about the association between vinyl chloride and angiosarcoma of the liver but that the association with other organ sites must still be considered inconclusive.

His report was an extension of studies designed and carried out initially by Drs. Tabershaw and Gaffey. While there appeared to be an excess of brain tumors (12 vs. 5.9 expected) in 707 deaths among 9,677 workers, the study is still inconclusive with respect to a causal relationship with vinyl chloride, Dr. Cooper said.

"Small excesses for other sites could not be ruled out, but if VCM was a causal agent for tumors in multiple other sites, the cumulative effect could have been very great," Dr. Cooper said. "The study population had only 4 percent more deaths than expected from malignancies. This held true even when analysis was confined to those whose exposures had begun prior to 1952 or prior to 1947."

F1 28/3/80

T
a
of
fa
ga
po
y
re
te
m
es
de
m
su
sp
go
Of
ab
su
ve
pe

y
r
t
m
e
d
m
s
s
g

Of
ab
su
ve
pe

1

1

A
lat
Ab

Gu
pr
Me
for
Be

**You
and
me
th**

St
wi
pa
in
P.

of
52

EW

June
26/3/80

2000
 1999
 1998
 1997

berty
 Jack
 food.
 Ram-
 330.
 0.1

Handl-
—
11 1
151 2
-11 3
11th.
ay-Rail
E. Tex.
E1 OM.

2686:
14
11 7

21 2
11 3
in with
Tears
16-1
y Val

200.
21.39.
kland.

Hunt-
d.
by
-d-
1 1
2 2
3 3

He added: "The treatment of the symptoms of vinyl chloride disease, of which all these plaintiffs suffer, is still in its infancy and the prognosis for the long term is simply unknown."

Mr Alan Stuart, aged 38, father of two children, who worked as a bagger at the plant until August, 1973; said he left when he began to suffer chest pains and suspected his working conditions were to blame.

He said he had become bad tempered and suffered migraine attacks. "Over the last two or three years the least little thing upsets me and I take it out on the wife and kids which I know is wrong", he added. "I still get severe chest pains, tiredness and aching limbs if I try to do manual work."

Dr. Ann Walker, a skin specialist, who made a special study of the men at Chesterfield Royal Hospital, and has now become an expert on vinyl chloride disease, told the court: "The men are extremely worried about their health and some have, in fact, been referred to a psychiatrist."

The hearing continues today.

future.

Times 27-3-80
**Plastics plant to
pay £500,000 to
stricken workers**

From Our Correspondent
Sheffield

A plastics plant where workers suffered health disorders including sexual difficulties after being exposed to poisonous fumes agreed yesterday to pay a total of nearly £500,000 in damages.

The money was shared among 15 workers who brought claims against Vinatex Ltd. of Staveley, near Chesterfield. All but one of them settled out of court while the case was proceeding at Sheffield Crown Court.

Mr Justice Woolf was told that the men were all exposed to fumes from vinyl chloride, used in the making of the artificial leather material, PVC, while they were working at the plant in the early 1970s.

It resulted in some men becoming impotent.

Those awarded damages included: Mr Stanley Pritchard, aged 41, of Chesterfield, £70,000; Mr Colin Jack Hadfield, £65,000; Mr George Naylor, aged 39, of Staveley, £57,500; and Mr Keith Redfern, aged 46, of Temple Normanton, near Chesterfield, £57,500.

Mr Jeffrey Ansell, aged 53, of Bridlington, who receives £32,500, said: "At one time I thought I was dying."

DAILY TEL. 27-3-80

**PVC FIRM
TO PAY £½m
DAMAGES**

A PLASTICS plant, where workers suffered health disorders, including sex problems, after being exposed to poisonous fumes, yesterday agreed to pay nearly £500,000 in damages.

The money is shared among 15 workers who brought claims against Vinatex Ltd. of Staveley, near Chesterfield. All but one of the men settled out of court while the case was proceeding at Sheffield Crown Court.

Mr Justice Woolf was told that the men were all exposed to fumes from vinyl chloride, used in the making of PVC, while they were working at the plant in the early 1970s.

Some of the men became impotent, and others suffered bone disease, breathlessness, aching joints, stomach disorders, clubbing of the fingers and headaches.

Mr CHRISTOPHER ROSE, Q.C., for the men, said the long-term effects of the disease were still unknown.

Some of the men were unable to work at all. Others had taken light jobs with a drop in pay.

KELLER AND HECKMAN (SPI LAWYER) CY+10
06-K-004 MAY-JULY 1980

SCC
5-1551