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.

C&EN staff photo

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 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

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[a]	Hamsters
Prestomach papilloma	Rats, hamsters
Melanoma[a]	Hamsters
Lymphoma[a]	Hamsters

[a]Data less certain. Source: Cesare Maltoni, Istituto di Oncologia, Bologna, Italy

grouped these categories from all plants for the overall study. This procedure is not very accurate for providing a quantitative view of vinyl chloride exposure, Cooper says. The study is very important, however, because it includes essentially all people in the U.S. who have been exposed to high levels of vinyl chloride in their work.

The most significant finding of this study is that workers with high exposure to vinyl chloride do not die earlier than the control population, nor are they more likely to die of cancer. However, certain types of cancers are found at levels higher than expected among vinyl chloride workers. Among these are cancers of the brain and central nervous system and cancers of the digestive system, which includes the liver. Both digestive and respiratory system cancers were more common in workers placed in the high exposure category.

A followup study is being planned, Cooper says, that will include worker deaths since 1973. This study also will try to separate data from older plants (those built before 1960) from newer ones and distinguish among exposures to vinyl chloride, polyvinyl chloride, and various copolymers.

Many studies have been conducted on the effects of exposure to polyvinyl chloride dust. David Groth of NIOSH and Chris Wagner of the British Medical Research Council in Penarth, Wales, reported separate studies showing that polyvinyl chloride particles can be picked up by the lungs of animals and man. The particles can remain there for years but, in Groth and Wagner's studies, caused little change in respiratory function. However, a study of 818 British polyvinyl chloride workers conducted for Imperial Chemical Industries by Anthony Seaton and coworkers at the University of Edinburgh showed changes in lung x-rays and in some lung functions in the workers most exposed to polyvinyl chloride dust. Similar findings have been seen in studies conducted by Ruth Lillis and associates at Mt. Sinai School of Medicine in New York.

These studies show that lungs can be changed by exposure to polyvinyl chloride, Seaton says. "We haven't made a case that these minor x-ray changes are going to cause people to die sooner or become ill," he says. "We don't think they will." Lillis, however, says some cases of lung disease may have been caused by exposure to polyvinyl chloride.

Another area of concern about vinyl chloride is reproductive hazards. Jackie John, a toxicologist from Dow Chemical, described an extensive study she conducted that found no effects on the offspring of mice, rats, and rabbits at levels of vinyl chloride high enough to cause toxicity in the mothers.

Other studies, however, according to Jill Fabricant of the University of Texas, Galveston, show that vinyl chloride does cause mutations in bacteria and that fertility levels drop in mice exposed to vinyl chloride at the 50-ppm level, although there is no effect on the health of the offspring.

The question of whether vinyl chloride is a reproductive hazard has not yet been answered, concludes statistician Maureen Hatch of Columbia University. Although none of the studies conducted so far have shown clearly that it does cause reproductive damage, none would have been able to detect an effect any smaller than a doubling of birth defects.

Rebecca Rawls, Washington

Enantiomer resolution by preparative HPLC

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Preparative high-performance liquid chromatography (HPLC) may become the method of choice over the next few years to resolve racemic mixtures in quantities of tens of grams as a result of work by organic chemists John M. Finn and William H. Pirkle of the University of Illinois, Urbana. Potential applications of their work include preparation of chiral (right- or left-handed) derivatizing reagents, solvating agents, and HPLC column stationary phases.

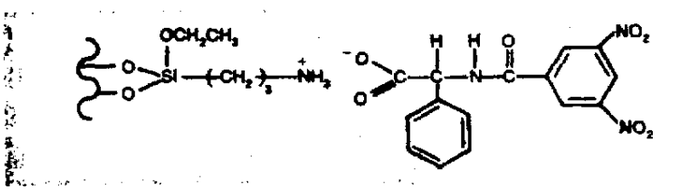
Resolution of enantiomers (dissymmetric, optically active compounds) by HPLC or other column methods has been done before. In fact, resolution of dihydroxyphenylalanine (dopa) is a commercial process. L-Dopa and the stationary phase that resolves it are tailored to one another, however.

In those column methods that have achieved some generality, amounts were limited to 100 mg, and separation efficiencies were only about 70%. In contrast, HPLC stationary phases developed by Finn and Pirkle promise resolution of a wide variety of compound types in significantly larger amounts, with optical purities approaching 100%.

Finn told the Division of Organic Chemistry that they have separated several grams of a limited class of compounds using a chiral HPLC stationary phase made by reacting (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine with a 40- to 60-micrometer silica gel functionalized with γ-aminopropyltriethoxysilane. Use of an ionic linkage to the gel eliminated problems of racemization and side reactions.

Although the range of compounds that could be resolved preparatively by this ionic stationary phase was limited, one compound type that could be resolved includes 10-substituted 2,2,2-trifluoro-1-(9-anthryl)ethanols. The Illinois researchers previously had found that these fluoroalcohols yield stationary phases with potential to resolve a much wider range of compound types

One stationary phase resolves fluoroalcohols...



...used in more versatile stationary phases