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THE TOXIC AND CARCINOGENIC RISKS OF VINYL CHLORIDE: A SERIOUS CURRENT INDUSTRIAL HYGIENE PROBLEM [Les Risques Toxiques et Cancerogenes du Chlorure de Vinyl: Un Grand Probleme Actuel d'Hygiene Industrielle]

by

R. Truhaut and J. Berrod

of

Toxicological and Industrial Research Center,
Department of Pharmaceutical and Biological Sciences,
Rene Descartes University, France.

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R. Truhaut* and J. Berrod**

I.N.R.S.
30, rue Olivier-Noyer
75680 Paris Cedex 14

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Abstract:

Vinyl chloride or monochlorethylene $CH_2 = CHCl$, discovered by Regnault in 1835 [1] by reacting potassium hydroxide in alcohol with 1,1-dichloroethane or 1,2-dichlorethane, is one of the representatives of the class of halogenated derivatives of the aliphatic hydrocarbons most widely used in industry. After having long been considered as one of the least toxic among the substances of this series, it has recently been proven very dangerous, especia-ly due to its carcinogenic properties, which may be manifested not only in laboratory animals but also in man. The objective of the present article is to clarify this question. It is divided into several parts: 1. Presentation of the compound, indicating the ways in which it is produced and its principal physical and chemical properties, as well as its industrial uses, making it possible to define the conditions and circumstances of exposure which, along with the toxicity, determine the manifestation of the risks. 2. Information on the different forms of vinyl chloride toxicity, with particular attention to the toxic effects over a more or less lengthy period, including the carcinogenic effects which may result from repeated exposure to this chlorinated hydrocarbon. 3. Risk prevention measures to be applied for the protection of occupationally exposed subjects.

*Director of the Toxicological and Industrial Research Center, Department of Pharmaceutical and Biological Sciences of the Rene Descartes University;
**Physician, Rhone-Poulenc Industries.

1. Presentation of Vinyl Chloride $CH_2 = CHCl$

A. Preparation

We shall not discuss laboratory methods or methods abandoned by industry, such as the action of soda on dichlorethane.

The phenomenal growth of the production of PVC is due in large part to the availability of cheap monomer.

Direct synthesis from acetylene and hydrochloric acid has long been the main preparation method. The reaction takes place in the gaseous state between 150 and 200°C and contact with activated charcoal impregnated with mercuric chloride. The yield is 99% with a slight excess of HCl.

$$CH \equiv CH + HCl \rightarrow CH_2 = CH\ Cl$$

Another process for the preparation of vinyl chloride is the dehydrochlorination of 1,2-dichloroethane

$$CH_2Cl - CH_2Cl \xrightarrow{-HCl} CH_2 = CH\ Cl$$

The choice of one method or another is guided by economic considerations (price of acetylene) and the availability of hydrochloric acid.

The process involving acetylene consumes HCl while the process with 1,2-dichloroethane produces it. Sometimes there are two laboratories to equalize the HCl balance.

New processes based on oxychlorination techniques have recently been applied and developed industrially. They are based on the Deacon Process, the hydrochloric acid being oxidized by the air at around 500°C to produce chlorine and water. The reaction takes place in the presence of ethylene, which serves as a chlorine *acceptor* and controls the reaction.

According to this principle, a procedure has been developed allowing the simultaneous synthesis of several C_2 chlorinated compounds in variable proportions, as needed, particularly vinyl chloride, 1,2-di-

chloroethane, which is subsequently transformed by thermal cracking into vinyl chloride, trichloroethylene, perchloroethylene, vinylidene chloride, etc., and tetrachloroethane which is also transformed by cracking. According to the local conditions, the process may be an HCl consumer, an equalizer, or even an HCl producer.

$$C_2H_4 + Cl_2 \rightarrow C_2H_3Cl + HCl$$
$$C_2H_4 + 2\,Cl_2 \rightarrow C_2H_2Cl_2 + 2\,HCl$$
$$C_2H_4Cl_2 \rightarrow C_2H_3Cl + HCl$$
$$C_2H_3Cl_2 \rightarrow C_2H_2Cl_2 + HCl$$

The hydrochloric acid produced in this way is combined with ethylene and oxygen (in the form of air) at 300°C using a copper catalyst. The oxychlorination reactions thus developed mainly produce dichloroethane, which is dehydrochlorinated to give vinyl chloride.

$$C_2H_4 + 2\,HCl + 1/2\,(O_2 + 4\,N_2) \rightarrow C_2H_4Cl_2 + H_2O + 2\,N_2$$
$$C_2H_4Cl_2 \rightarrow C_2H_3Cl + HCl$$

Two points should be emphasized:

1. The operations are conducted continuously in hermetically sealed systems and, as a consequence, without accidents (leaks in particular); exposure of the workers involved is practically nonexistent.

2. The monomer vinyl chloride produced in modern plants has a very high degree of purity. It contains less than 20 ppm by volume of organic impurities checked by gas phase chromatography (1,2-dichloroethane, methyl chloride, propylene..). The vinyl chloride obtained in the form of a gas is liquefied and stored as a liquid under pressure.

With respect to the quantities produced throughout the world, which are very high, we take the liberty of directing our readers to the report of a vinyl chloride study group, which met in Lyon on June 23 and 24, 1974 under the auspices of the International Cancer Research Center [2].

B. Physical and Chemical Properties of Vinyl Chloride

Under normal temperature and pressure, vinyl chloride (molecular weight: 62.5) is a colorless gas, but it is ordinarily used after liquefaction under pressure.

The physical constants are as follows:

Boiling point	-13.9°C
Density of the liquid D_4^{20}	0.9121
Refractive index n_D^{10}	1.4066
Vapor density (air = 1)	2.15
Vapor pressure	2660 mm of mercury at 25°C
Heat of polymerization	23 kcal/mole (400 cal/g)

It is inflammable and forms explosive mixtures with air at concentrations between 4% and 22% by volume [3].

It is slightly soluble in water (0.11% weight/weight at 25°C) [4], soluble in alcohol, and very soluble in ether, carbon tetrachloride, and benzene.

It is also very soluble in lipids.

On the chemical level, it is easily polymerized under the influence of solar rays and/or catalysts. This polymerization reaction has been recognized by Baumann [5] but has been cited in particular by Ostromyslinski [6]. According to Lefaux [7], the catalysts most widely used at the present time are hydrogen peroxide, organic peroxides, ozone, and the persulfates.

By combustion, it produces hydrochloric acid, carbon monoxide, and carbon dioxide gas [8].

Under the effect of strong alkalies at a high temperature, vinyl chloride is released in the form of chlorides.

C. Uses of Vinyl Chloride

According to the information assembled by "Chemical Information Services, Stanford Research Institute, California" and reported to the International Cancer Research Center [2], in the United States, the majority (about 97%) of the vinyl chloride produced was used for the manufacturing of polyvinyl chloride (PVC) or of copolymers in which it is found in combination with other monomers, the principal one of which is vinyl acetate.

The PVC industry came to life in Germany during the thirties and then began its rise in the United States and France around 1940. It developed to a considerable extent after the war.

Numerous applications of vinyl chloride have been put into practice, especially its use as a refrigerant, as an extraction solvent, and particularly as a propellant in the production of preparations for domestic use designed to be dispersed in the form of aerosols, products such as insecticides, cosmetics, or even drugs.

These applications were completely eliminated in France a number of years ago, vinyl chloride having been replaced by non-inflammable fluorinated hydrocarbons. It still appears to be used as a raw material in the manufacturing of 1,1,1-trichloroethane or methylchloroform, a solvent very widely used in industry, and in the manufacturing of monochloracetaldehyde, an intermediate product in the manufacturing of certain drugs of the sulfonamide class.

The manufacture of polymers having a vinyl chloride base (PVC or copolymers), whose annual production on a world scale is about 7 million tons (about 700,000 tons for France), is determined by the quality desired based on the specified purpose. But, from all evidence, the basic process lies in the polymerization of the vinyl chloride. This polymerization is a polyaddition reaction, the macromolecular chain elongating

by end-to-end addition of monomer molecules. It is initiated by chemical compounds capable of decomposing under the effect of heat, producing free radicals. Generally speaking, these radicals are organic peroxides. Polymerization may take place in the presence of a dispersing medium (water) (polymerization in emulsion or in suspension), or in a liquid monomer under pressure (bulk polymerization). In certain cases, it is carried out in the presence of another monomer capable of copolymerizing, for example, vinyl acetate. The temperature (generally ranging between 40 and 70°C), the pressure (6 to 10 bars), and the nature of the catalyst modify the behavior of the reaction. These different factors influence the length of the linear macromolecular chains, and the presence and form of the lateral chains.

The common industrial polymers have average molecular weights ranging between 50,000 and 100,000 [9]. They come in the form of white powders, of low apparent density (0.40 to 0.60).

The thermal degradation of PVC begins at 200°C with the release of hydrochloric acid. The speed of degradation increases rapidly with the temperature. The color of the polymer turns from white to brown and then to black. The decomposition procedure is not yet perfectly understood and there are several conflicting theories. Certain authors [10] suggest the formation of free radicals followed by a molecular rearrangement with the release of HCl; other authors [11] think that the unsaturation activates the adjacent chlorine molecule.

There are numerous stabilizers which prevent the degradation of PVC, regardless of the origin (thermal or under the effect of ultraviolet rays). These stabilizing agents share the property of reacting with the HCl released at the beginning of decomposition so as to prevent an autocatalysis of the reaction. Certain stabilizing agents can be used alone. These are the

"primary" stabilizers. Others have a synergistic effect with the primary stabilizers but cannot be used alone. These are called "secondary" stabilizers. The main stabilizers used for PVC are the organic metal salts (lead, tin, calcium, barium, cadmium, etc.), epoxidized oils, or phosphites. They are generally used at levels ranging from 0.1% to 3% of the weight of the resin.

Polyvinyl chloride is sometimes supplemented with *plasticizers* which facilitate the work of a plastic material and, in particular, give it a permanent pliability. A large number of plasticizers have been proposed. We shall mention, in particular, the inorganic acid esters (phosphates), the organic acid esters (phthalates, adipates, sebacates, ricinoleates...), polymers (polyesters), and high polymers (butadiene-acrylic nitrile copolymer, for example).

Non-plasticized polyvinyl chloride can be worked at 170-210°C and welded at 200°C in a jet of hot air. Plasticized, it can be worked at a lower temperature (160 to 180°C). The main transformation processes are extrusion, calendering, injection, and extrusion-blowing.

The polymerization of vinyl chloride and the subsequent operations, unlike the manufacturing of vinyl chloride, which takes place continuously, as we have seen, are almost always performed discontinuously and require human participation at various stages in the work: polymerization autoclaves, addition of adjuvants which may have a toxicity of their own, conditioning, bagging of the resins, etc.

Upon stopping polymerization, a fraction of the vinyl chloride whose quantity depends on the polymerization method used (emulsion, suspension, or bulk) and which generally ranges from 3% to 20% of the total charge, is still present in the reactor. This vinyl chloride is eliminated from the

resin by degassing, either directly in the autoclave or in a special apparatus. This operation is performed, first, by connection to a condensation circuit, the vinyl chloride being recovered in liquid form to be reused at the time of another polymerization operation. When the pressure drop is total, the remaining traces of vinyl chloride are eliminated almost completely by repeated vacuum extraction separated by periods in a nitrogen atmosphere. After the last vacuum extraction, the container with the PVC is filled with air. It may be transported either directly to screening installations when bulk polymerization is involved, or to dryers where the water present is eliminsted, in the case of emulsion or suspension processes.

In the chapter dedicated to means of preventing risks which may result from exposure to vinyl chloride we shall see that, following the discovery of the occupational pathology of vinyl chloride, numerous technological improvements were made in the processes used, with a considerable reduction in the degree of exposure as a consequence.

2. *Toxicology of Vinyl Chloride*

Before going into the details, we feel that it would be useful to take an overall look at the history of the development of our knowledge on the toxicity of vinyl chloride, since this compound is a spectacular example of the constant vigilance which must be exercised by toxicologists to detect any chemical agent capable of polluting the occupational or general environment.

A. *Introduction to the Study of the Toxicology of Vinyl Chloride: Historical Review*

Vinyl chloride--undoubtedly the compound most widely used in the plastics industry for more than 20 years--has never been considered as

particularly dangerous on the human toxicological level until relatively recently.

Of course, it was known to be inflammable and explosive, but the precautions taken against the risks deriving from these properties seemed to be largely sufficient.

Nor was there any lack of knowledge as to its narcotic power at high doses, and some cases of coma had been reported during prolonged accidental exposures in a concentrated atmosphere. There was nothing surprising in this, since it was known that, as with the majority of the compounds belonging to the same chemical class, its volatility--affecting pulmonary penetration--permitted rapid access to the central nervous system, although its lipid solubility influenced binding and retention at this level. But, even in this regard, it was considered to be one of the least toxic chlorinated hydrocarbons, which meant the recommendation of a relatively high permissible limit in the atmosphere of working sites: 500 ppm, i.e., under normal temperature and pressure, 1275 mg/cm^3.

But 1963 saw the discovery for the first time of cases of bone disturbances of the osteolytic type, particularly--but not exclusively--striking the hands, with disappearance of bone tissue from the ungual phalanges of several fingers on both hands (acroosteolysis syndrome). The cases reported occurred in practically all the world's producers, and especially in a particular category of workers--*autoclave decrusters*. These workers were responsible for manually removing, with a type of trowel, the inevitable crusty residues of polymerization. The operation lasted about 1/4 hour in a vinyl chloride atmosphere. It sufficed to enter an autoclave at the end of the operation to smell this weakly etheral, but characteristic odor which meant that the workers were inhaling air containing at least 40 ppm--or often more--

of vinyl chloride, which scarcely caused a stir *at the time*.

The proportion of subjects afflicted was in the order of 2 to 3% of the workers. Other subjects presented an abnormal prevalence of circulatory disturbances, similar to those characterizing Raynaud's phenomenon.

It was at the 16th International Occupational Medicine Congress, held in Tokyo in 1969, that the first three reports were presented on this subject, one by Professor Viola, occupational physician of the Solvay Company at Rossignano Solvay (Italy) [12].

The etiology was unknown due to the diversity of the ingredients used in the manufacturing of PVC, but an analysis of the data resulted in the incrimination of vinyl chloride exposure. Furthermore, Professor Viola had reproduced lesions similar to those observed in PVC workers in his experimental investigations on the rat, exposed via the pulmonary route to very high doses of vinyl chloride it is true (30,000 ppm), 5 days per week for 1 year.

Pursuing his experimental studies, he confided to one of us who visited him about his anguish over seeing the development in exposed animals of a number of tumors (skin, lung, and bone, in particular). This was the subject of his report to the 16th International Cancer Congress in Houston (United States) in May, 1970 [13].

These observations, added to those concerning the effects of vinyl chloride on the bone system, had a resounding effect. They led four major European producers of PVC (Montedison, ICI, Rhone-Progil, Solvay) to join forces in consulting an eminent cancerologist, Professor Maltoni of the University of Bologna, concerning the execution of a very strict long-term experimental program. These tests were to be conducted for 2-1/2 to 3 years on several species of animals. The animals were to be exposed by the

pulmonary route to different concentrations of vinyl chloride as purified as possible.

Begun in *July 1971*, these experiments, which unfortunately confirmed the carcinogenic power of vinyl chloride, revealed--in addition to the locations reported by Viola--other specific locations, notably nephroblastomas and especially angiomas and hemangiosarcomas of the liver, which are extremely rare malignant tumors in animal species subjected to experimental tests.

The production of such effects by the pulmonary route disclose a "system pathology" resulting from exposure to vinyl chloride which proved to be a toxic agent having a vascular affinity, as demonstrated by signs similar to Raynaud's disease (with an asphyxia of the extremities), multifocal hepatic tumors or cellular atypia, often combined with vascular ectasia and endothelial hypertrophy.

We were a long way from the microtraumatically induced local action mentioned at the beginning to explain the lesions of the hands of autoclave decrusters!

However, although observations related to human bone pathology had preceded etiological confirmation in the animal as to the culpability of vinyl chloride, it could at least be hoped that the neoplastic pathology of animals would not be found in human subjects exposed to it.

Now, in January, 1974, information from the United States has reduced such hope to nothing. American organizations MCA (Manufacturing Chemists Association), NIOSH (National Institute on Occupational Safety and Health), OSHA (Occupational Safety and Health Administration) informed by the Europeans of the experimental results, had performed an epidemiological study. They were able to confirm the discovery of 13 cases of hepatic hemangiosarcomas in workers exposed to vinyl chloride, including 7 at the

Goodrich Plant in Louisville (Kentucky) where--revealing coincidence--the first cases of acroosteolysis had appeared!

There is no need to stress the consequences of such observations, to which new ones are being progressively added--whether in the United States or in other countries--and to stress their reverberation at all levels (certain ones with passion in the wake of the first emotion) with respect to the protective measures which it was imperative to consider.

We shall only say that the discovery of a carcinogenic effect of vinyl chloride in man presents toxicologists, doctors, and health specialists with a burning problem with respect to the preventive measures to be implemented at numerous levels; first of all, according to all evidence, at the level of PVC production plants.

After this general introduction, we shall now go into greater detail in examining toxicological information concerning vinyl chloride, compiled from experimental studies on laboratory animals or epidemiological observations and surveys of exposed human subjects.

We shall consider successively:

1. Data on acute or subacute toxicity.
2. Data on more or less long-term toxicity.

B. *Acute and Subacute Toxicity of Vinyl Chloride*

The acute toxicity of vinyl chloride, i.e. the series of harmful effects which may result from a single exposure, has been studied by inhalation for different periods of air containing various concentrations of the product in several species of animals:

-- in the *mouse*, by Peoples and Leake (1933) [14] and by the researchers from the Pharmacology and Toxicology Division of the National Institute of Public Health of the Netherlands [15];

— in the *rat*, by H. Danziger (1960) [16] and by Lester et al. (1963) [17];

— in the *guinea pig, rat, and other laboratory animal species* by Mastro-Matteo et al. (1960) [18].

The following table (Table I) summarizes the data obtained on the *guinea pig*.

We must also add to this table the data supplied by Patty [3], according to which the maximum concentrations capable of being survived by the guinea pig for varying exposure periods are the following:

50 to 70,000 ppm for 1 hour;

25,000 ppm for 8 hours,

although exposure to concentrations of 15,000 ppm for 1 hour and 5,000 ppm for 8 hours, respectively, did not cause serious problems..

Patty described pulmonary edema and hyperemia of the kidney and the liver in animals dying of an acute exposure.

In summary, observations in laboratory animals showed an affinity for the central nervous system, with narcotic effects which can represent true anesthesia and, at sufficient doses, cause death from respiratory and cardiac collapse. The rapid reversibility of the narcotic effects after stopping the exposure should also be noted.

We must point out that, according to the figures shown in the table, exposure of the guinea pig to a concentration of 10,000 ppm did not cause any apparent disorder; but it is not without interest to recall that Viola's experiments [12], rats exposed to concentrations of 30,000 ppm 4 hours per day and 5 days per week for a period of 1 year, did not present disturbances immediately. Although we are talking about longer exposure times, to be sure, we would also like to mention Torkelson who, in 1961, exposing rats to vinyl chloride doses of 500, 200, and

Table 1. Experimental data related to the acute toxicity of vinyl chloride in the guinea pig.

Concentrations		Duration of Exposure	Observations
Parts Per Million by Volume (p.p.m.)	mg/liter		
400,000	1024	15 seconds	animal lying on its side
"	"	10 to 20 minutes	dead
150,000 to 200,000	384 to 640	1 minute	animal lying on its side
"	"	16 to 20 minutes	deep narcosis
"	"	18 to 35 minutes	dead
100,000	256	2 minutes	animal lying on its side
"	"	60 minutes	deep narcosis
"	"	120 to 340 minutes	greatly retarded respiration, but not dead
50,000	128	50 minutes	deep narcosis
"	"	360 minutes	greatly retarded respiration, but not dead
10,000	25.6	480 minutes	no signs of narcosis

100 ppm for 4 to 5 months, observed lesions of the liver and kidneys without tumorous manifestation on anatomo-pathological examination [19].

The narcotic effect of vinyl chloride is found in man. Two accidental deaths have been reported [16]. They occurred during work performed in a local vineyard (fermenting chamber) where the vinyl chloride content must have been high and the surveillance nonexistent.

One member of our group succeeded in obtaining information from a large chemical product company, concerning observations made in two workers who had gone into the initial stage of anesthesia in decrusting vats that

they had entered before degassing and who owed their health only to the prompt intervention of the supervisors. The doses must have been greater than 10,000 ppm.

At lesser doses, vinyl chloride has an irritating effect on the eye (conjunctivitis, keratitis) and skin (erythema and even phlyctenae in the case of spurting of liquid vinyl chloride), in these cases justifying immediate,heavy and prolonged washing--an emergency procedure imperative for any chemical burn.

As a supplement to the observations concerning the acute toxicity of vinyl chloride, we thought that it would be a good idea to indicate the few data unearthed in the specialized scientific literature on subacute toxicity, i.e. on the toxic effects which may eventually be produced by repeated exposure to vinyl chloride during a short period and at very short intervals.

Indications on this subject have been given in a monograph from the National Institute of Public Health of the Netherlands [15].

Rats and mice, exposed for 4 hours per day for 5 to 8 consecutive days to a concentration of vinyl chloride sufficient to induce signs of mild narcosis, did not present any signs of liver or kidney pathology.

In their study of the effects of vinyl chloride on the rat, Lester et al. [17] exposed the animals to concentrations of 50,000 ppm for 8 hours per day during a period of 19 days and 20,000 ppm for 8 hours per day during a period of 92 days. They did not observe any effect on growth, hemoglobin level, hematocrit, prothrombin level, or on the macroscopic and microscopic characteristics of the principal organs. However, at two concentrations, they observed an increase in the liver weight/body weight ratio and a decrease in the white blood cell count and, at a concentration of

50,000 ppm, an increase in the red blood cell count.

In man, Lester et al. [17] observed 3 men and 3 women exposed for 5 minutes 2 times per day at 6-hour intervals for a period of 3 consecutive days, at concentrations of 4,000, 8,000, 16,000, and 20,000 ppm, respectively. They observed that only levels above 6,000 ppm caused mild symptoms of intoxication: vertigo, nausea, and decreases in visual and auditory acuity.

Baretta, Stewart et al. (1969) [20] followed the behavior and reactions of human subjects exposed for 7-1/2 hours to vinyl chloride concentrations of 50, 250, and 500 ppm, respectively. It was only at the highest concentration of 500 ppm that 2 of the exposed subjects developed dryness of the mucous membranes of the eyes and nose. Two of the 6 subjects exposed to 50 ppm were exposed 2 days later to 500 ppm for a period of 3-1/2 hours, without manifesting any harmful effects.

C. More or Less Long-Term Toxicity of Vinyl Chloride

As we indicated in our general look at the history and evolution of knowledge on the danger of vinyl chloride--which we included in the introduction to the study of the toxicology of this chlorinated hydrocarbon--two prominent facts have been disclosed during the past 12 years.

1. The production of bone and angioneurotic lesions in workers exposed to vinyl chloride during the manufacturing of PVC.

2. The demonstration--first by experiment on laboratory animals and then by epidemiological investigations of occupationally exposed groups--of the carcinogenic power of vinyl chloride.

We will examine these two points in turn:

1. *Bone and angioneurotic lesions* caused by occupational exposure to vinyl chloride.

The first cases of bone lesions were discovered in 1963,

occurring simultaneously in different countries, all in autoclave decrusters. A Russian publication [21] dating from 1968, reported these problems, which had been observed for several years in personnel working with PVC in suspension. Some workers complained of subjective disturbances, similar to those characterizing Raynaud's phenomenon: asphyxia of the extremities followed by intense vasodilatation, sometimes followed by distrubances having an affinity for the skin. Sometimes, at most, a condition was observed resembling *scleroderma*, a collagen (connective tissue) disease consisting of a thinning of the skin which, atrophied and sometimes ulcerated, "sticks" to the underlying bones, sometimes considerably interfering with movement [22-33].

Other vascular disorders have been reported, in particular myocardial infarction and arteritis of different sites. One case of this type was reported by a member of our group at the International Occupational Medicine Congress held at Buenos Aires in 1972 [34].

Other workers, not having any subjective symptoms or any apparent disturbances, nevertheless presented bone lesions which could only be revealed by *systematic radiological surveys* after the discovery of other affected subjects working at the same occupation.

The *typical lesions found* which will always be pathognomonic for the disorder, involve the hands (one or both) and consist of lysis of the ungual phalanges, first of all of the index and middle fingers, but often of all the fingers on the hand. These cases of bandlike osteolysis have been and remain the principal symptom of the disease. The terminal phalanges definitely look fractured, but the characteristic would be very large in such an event.

This is not the only bone lesion. Notches resembling "halberds"

have frequently been found on the edge of the phalanx, resembling the bony lesions of gout, also amputations of the distal phalanx ("barley-sugar" images). Microgeodes have also been observed elsewhere on the skeleton: the ribs, the pelvis, the iliac crest, the bones of the tarsus, and the phalanges of the toes. As a result, incrimination of a local action is not very plausible, all the more so since subjective manifestations were nonexistent in certain cases. It was not really possible under these conditions to state that a bone disorder of this magnitude, if it was induced by a local trauma, was not *always* accompanied by significant skin disturbances.

Moreover, studies on the absorption of vinyl chloride have since shown the very cutaneous skin absorption of this compound.

The currently reported cases of acroosteolysis, do not make it possible to suggest any predisposing factor, because of their disparity, such as age, sex, race, duration of exposure (cases appearing rapidly within a few months), or the beneficial effect of certain individual protective measures, in particular, the wearing of gloves. The polymerization process is no longer an intervening factor. Cases have been reported with all types of processes.

It is therefore definitely inevitable to consider a *systemic disorder*, predominantly caused by penetration through the lungs.

Furthermore, American researchers have made a careful study, in particular of workers suffering from bone disturbances, and the biological tests performed on these subjects have not proved to be very conclusive. Phosphorus and calcium levels, in particular, were not disturbed.

According to Lefevre [35], toxicologists at the Solvay Company, who studied the chronology of the lesions in detail, everything begins with distal

amputation of the phalanx. The classical band of osteolysis is, according to him, a false sign, since repair by recalcification begins at the end and continues proximally, thinning the band until it disappears upon "restitutio ad integrum".

Thus, whether or not the bone lesions are accompanied by asphyxic vascular disturbances (the most frequent cases), generalized disorders are very definitely involved. It can be stated that these problems are linked to paripheral vascular disorders, with or without subjective disturbances, and sometimes to dermal sclerosis recalling scleroderma.

It should also be remarked that reported cases of acroosteolysis have diminished very significantly in recent years, certainly due to the preventive measures which have been taken, in particular the application of hydraulic decrusting apparatus.

In any case, this indisputable occupational pathology has been recognized by French law, which has set up a new table of occupational diseases subject to compensation (Table 52) which we have reproduced here:

No. 52. Disorders attributed to vinyl chloride polymerization operations. (Decree No. 73-215 of 23 February 1973). Exposure time : 6 months.

Designation of the Diseases	Time Taken by the Disorder	List of the Main Occupations Capable of Provoking these Diseases
Angioneurotic disturbances of fingers. Osteolysis of the ungual phalanges of the hands confirmed radiologically.	2 months 3 years	Work performed in vinyl chloride polymerization shops, especially: manual decrusting of autoclaves and polymerization.

The course of the reported cases of acroosteolysis has always been favorable when the stricken subjects were removed from the risk as soon as the diagnosis was made.

Recalcification (which, as we have seen, begins in the distal part of

the phalanx) continues smoothly, but "restitutio ad integrum" always takes fairly long and rarely requires less than 10 months, sometimes clearly more. Few radiological scars remain. Sometimes, small "collar-stud" phalanges accompany cicatricial deformities (shortening of the previously afflicted ungual phalanges) and curved nails.

When they exist (alone or in combination), circulatory disturbances require a rather long period to disappear. Rather often, they produce a particularly annoying sensitivity to cold, occasionally during the winter.

Treatment consists of administering calcium (intravenously) and vitamin C.

Several cases have given one member of our group the impression that the oral administration of hydroxyproline was capable of accelerating the healing process.

As far as Raynaud's syndrome is concerned, its existence justifies the implementation of a classical vascular therapy.

2. Carcinogenic power of vinyl chloride.

In the case of this toxic potential, the experimental facts have preceded the revelations of epidemiological studies in exposed human subjects. We shall examine presently available information in that order.

a) The experimental facts.

The first observations of a carcinogenic activity of vinyl chloride in laboratory animals were made by Viola [13, 36]. This author exposed Wistar rats, 4 hours per day and 5 days per week for 1 year, to air containing 30,000 ppm of vinyl chloride. Seventeen animals out of 26 survived or were sacrificed during the period extending between the 40th and the 54th week after the initiation of treatment. They all presented skin tumors (14 epidermoid carcinomas, 2 mucoepidermoid carcinomas, 1 papilloma) which were subsequently identified by Maltoni and Lefemine (1974) as tumors of Zymbal's gland,

corresponding in the rat to the parotid gland in man and particularly rich in fatty tissue. In addition, 7 animals showed pulmonary tumors (5 adenocarcinomas, 1 adenocanthoma, 1 spinocellular carcinoma), subsequently identified by Maltoni and Lefemine [37] as being metastases of the skin tumors although in 5 animals had osteochondromas.

The skin tumors were exclusively located in the region of the submaxillary glands and Zymbal's glands, although the bone tumors had developed in the metacarpal and metatarsal regions of the 4 limbs. No tumors appeared in the 25 control animals sacrificed at the same time as the treated animals.

Table II summarizes the results obtained.

We previously emphasized the concern evoked by these results, which were the subject of a preliminary report at the International Cancer Congress held in Houston (May, 1970), and we indicated that they led a group of European PVC producers to entrust Professor Maltoni with carrying out a program of experiments on a large scale. The investigations of the Italian cancerologist and his team were conducted in 3 animal species: the mouse, the rat, and the hamster.. The animals were exposed for 4 hours per day, 5 days per week, for periods ranging from 30 weeks to 52 weeks, to the inhalation of air containing vinyl chloride concentrations ranging from 50 to 10,000 ppm.

Tables III, IV, and V summarize the results obtained.

They show that the carcinogenic potentiality of vinyl chloride begins to be manifested, although to a slight degree, starting at a concentration of 50 ppm under these experimental conditions. These results (which, in the case of the mouse and the hamster, represent those obtained in experiments which had not yet been completed when we last heard about them) have been discussed in several recent articles by Maltoni et al. [38, 39, 40].

Interested readers will find here, in addition to references of previous

Table II. Experiments of Maltoni et al. (1971). Protocol similar to that of P.L. Viola. Sprague-Dawley rats exposed 4 hours per day, 5 days per week for 43 weeks to a concentration in the air of 30,000 ppm of vinyl chloride. Results after 68 weeks (end of experiment).

Groups and Treatment	Rats			Animals with Tumors							
	Number of Animals at the Beginning of the Experiment	Number of Survivors upon Appearance of the First Tumor and at the 24th Week	Survivors	Carcinomas of Zymbal's Gland			Nephroblastomas	Angiosarcomas		Other Types or Locations	Animals with 2 or More Tumors
				Number	%	Latency Time (Weeks)		Liver	Other Locations		
								Number	Number	Number	Number
30,000 p.p.m. of vinyl chloride	60	60	-	31	52	43	-	14	1	7	38

Table III. First stage experiments of C. Maltoni et al. on Sprague-Dawley rats. Animals exposed 4 hours per day, 5 days per week for 52 weeks. Beginning of experiment: July, 1971. Results after 135 weeks (end of experiment).

Groups and Treatment (Concentrations in p.p.m. of Vinyl Chloride)	Sprague-Dawley Rats		Animals with Tumors															
			Carcinomas of Zymbal's Gland			Nephroblastomas			Angiosarcomas				Subcutaneous Angiomas	Cutaneous Carcinomas	Hepatomas	Neuroblastomas	Other Types or Locations	Animals with Four or More Tumors
									Liver			Others						
	Number of Animals	Number of Survivors Upon Appearance of the First Tumor* and at the 26th Week	Number	%	Latency Time (Weeks)	Number	%	Latency Time	Number	%	Latency Time	Number	Number	Number	Number	Number	Number	Number
10000	69	61	18	26	50	5	8	59	9	15	64	3	4	3	1	7	7	28
6000	72	60	7	12	62	4	7	65	13	22	70	3	3	1	1	3	8	31
2500	74	59	2	3	33	6	10	74	13	22	78	3	3	1	2	5	4	32
500	67	59	4	7	79	4	7	83	7	12	81	2	1	1	3	—	4	22
250	67	59	—	—	—	6	10	80	4	7	79	2	—	4	—	—	3	6
50	64	59	—	—	—	1	2	135	1	2	135	1	1	1	—	—	9	19
VA 2500**	65	49	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Controls	68	58	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10	6
Total	577	464	29	—	—	26	—	—	47	—	—	14	12	11	7	15	45	155

*Zymbal's gland.
**VA-Vinyl acetate "as a control".

Table IV. Experiments of C. Maltoni et al. in Swiss mice. Exposure: 4 hours per day, 5 days per week for 30 weeks. Results after 70 weeks (January 1975).

Groups and Treatment (Concentrations in p.p.m. of Vinyl Chloride)	Animals									Animals with Tumors										
	Number of Animals at the Beginning of the Experiment			Number*			Survivors			Pulmonary Tumors			Mammary Carcinomas			Angio-sarcomas of the Liver	Vascular Tumors (Other Types of Locations)	Skin Tumors	Other Types or Locations	Animals with 2 or more Tumors
	♂	♀	♂♀	♂	♀	♂♀	♂	♀	♂♀	Number	%	Latency Time (Weeks)	Number	%	Latency Time	Number	Number	Number	Number	Number
10000	30	30	60	22	28	50	–	–	–	35	70	35	13	47	31	8	9	3	2	36
0000	30	30	60	26	28	54	–	–	–	38	70	38	6	28	33	5	9	0	4	39
2500	30	30	60	23	30	53	–	–	–	30	57	43	9	30	35	11	12	3	2	31
500	30	30	60	29	29	58	–	–	–	38	66	41	7	24	37	11	17	1	1	43
250	30	30	60	29	29	58	2	–	2	33	57	45	11	32	30	11	15	2	3	40
50	30	30	60	27	30	57	–	6	6	2	3	58	11	37	40	1	11	–	2	3
Controls	60	70	150	74	67	141	15	30	45	5	3	58	–	–	–	–	–	–	1	5
Total	260	250	510	230	241	471	17	36	53	181	–	–	59	–	–	47	73	15	15	212

*Animals alive after 16 weeks when the first tumor was reported (carcinoma of the mammary gland) (the percentage is indicated).

Table V. Experiments of C. Maltoni et al. on hamsters. Exposure: 4 hours per day, 5 days per week for 30 weeks. Results after 57 weeks (January, 1975).

Groups and Treatment (Concentrations in p.p.m. of Vinyl Chloride)	Animals (Golden Hamsters)		Animals with Tumors						
	Total	Survivors	Angiosarcomas of the Liver	Trichoepithelliomas and Basocellular Epitheliomas of the Skin	Melanomas	Lymphomas	Papillomas and Acanthomas of the Stomach	Other Types or Locations	Animals with 2 or More Tumors
			Number	Number	Number	Number	Number	Number	Number
10000	35	6	–	4	–	–	1	–	5
6000	32	5	–	2	1	2	3	1	6
2500	33	9	–	1	–	–	4	2	6
500	33	11	2	1	–	1	1	1	5
250	32	6	–	2	–	1	–	–	3
50	33	11	–	3	1	1	–	–	5
Controls	70	30	–	2	–	1	–	–	3
Total	268	78	2	15	2	6	9	4	28

publications of the Maltoni team, more precise comments on the results obtained, as well as supplementary information, especially data concerning the positive results obtained during the experiments conducted on the Wistar rat which proved to be more resistant than the Sprague-Dawley rat. However, we must emphasize the negative results obtained with vinyl acetate.

We think it is important to point out that positive results, roughly confirming those of the Maltoni team, were obtained in experiments conducted

by "Biotest Laboratory" in the United States, notably on mice subjected for 7 hours per day and 5 days per week to vinyl chloride concentrations of 50, 200, and 2,500 ppm. We were not able to obtain sufficiently precise information on this subject to be in a position to analyze the results in the present article. We shall limit ourselves to indicating that:

after 8 months of exposure, although no tumor had been observed in the controls, the following were noted:

- *in the group exposed to 2,500 ppm*, 28 angiosarcomas of the liver, 28 pulmonary adenomas, and 6 mammary adenocarcinomas, including 1 with pulmonary matastases;
- *in the group exposed to 200 ppm*, 11 angiosarcomas of the liver, 12 pulmonary adenomas, and 3 mammary adenocarcinomas, including 1 with pulmonary matastases;
- *in the group exposed to 50 ppm*, 2 angiosarcomas of the liver, 2 pulmonary adenomas, and 2 mammary adenocarcinomas with pulmonary matastases.

Each group included 50 animals. The experiments will be finished at the end of 1975.

Although the title of this article clearly indicates that our objective in writing it was to stress the dangers involved in occupational exposure to vinyl chloride, we feel that it is appropriate to mention in Table VI the preliminary results obtained by Professor Maltoni et al. from his experiments on the oral administration of vinyl chloride to the Sprague-Dawley rats. These experiments are of prime interest for food toxicology, because of the possible existence of vinyl chloride residues in polyvinyl chloride food wrappers and the possibility of its migrating into the food. This particular problem will be the subject of an article by

one member of our group, when we have learned the results of the long-term experiments in rats currently underway in various European or American laboratories.

Table VI. Preliminary results of an experiment by C. Maltoni et al. involving administration by stomach catheter (5 days per week) of vinyl chloride in solution in olive oil to Sprague-Dawley rats. (Duration of the experiment at the end of April 1975: 58 weeks).

Number of Animals	Experimental Conditions (Doses of VC in mg/kg of Body Weight)	Angiosarcomas of the Liver	Other Angiosarcomas	Other Locations
80 (half male and half female)	50	3	1 (thymus)	1 (Zymbal's gland)
80	16.65	1	-	-
80	3.33	-	-	-

Remark: The first positive results (1 angiosarcoma of the thymus in a female animal of the group exposed to a dose of 50 mg/kg; 1 angiosarcoma of the liver in a male animal of the group exposed to a dose of 16.65 mg/kg) were announced by Maltoni et al. at the end of February 1975 [41].

It is a well-known fact that numerous carcinogenic chemicals have mutagenic properties. The joint use of microorganisms or mammalian cells and of *in vitro* and *in vivo* metabolic activation systems has made it possible to demonstrate this. In this context, it was natural to investigate whether vinyl chloride had a mutagenic potential. In this regard, positive results have been obtained by various authors, among others by Rannug et al. [42] and by the researchers of the International Cancer Research Center of Lyon [43, 44, 45].

Without going into a detailed critical examination of the results, it is interesting to note that vinyl chloride manifests mutagenic activity only after metabolic activation. In this regard, according to the indications of Malaveille, the strong mutagenic capacity of monochloroethylene oxide and

Country	Date of Diagnosis	Age at Diagnosis	Number of Years Between the First Exposure and the Diagnosis	Total Number of Years of Exposure	Occupation
USA	June 1952	43 years	15	15	Polymerizer
USA	Aug. 1961	41 years	15	15	"
USA	April 1964	52 years	20	18	"
USA	1968	45 years	24	18	"
USA	May 1968	55 years	17	17	"
USA	March 1969	41 years	19	4	"
USA	May 1969	50 years	20	15	"
USA	March 1970	61 years	23	23	"
USA	May 1960	36 years	14	13	"
USA	July 1972	47 years	10	10	Bookkeeper in a plant manufacturing PVC
USA	March 1973	49 years	22	16	Polymerizer
USA	June 1973	60 years	36		Insulation of electric wires containing PVC
USA	Dec. 1973	58 years	28	28	Polymerizer
USA	Feb. 1974	45 years	12	12	"
USA	March 1974	43 years	19	17	"
USA	May 1974	53 years	30	30	"
USA	Oct. 1974	43 years	19	19	"
England	Feb. 1970	55 years	24	11	Pourer of oil mixtures with PVC on raw materials
England	Dec. 1972	71 years	26	20	Polymerizer
England	1974	36 years	9	3-1/2	"
Sweden	Feb. 1970	43 years	19	18	"
Sweden	May 1972	61 years	27	23	Production of vinyl chloride
Norway	Dec. 1971	56 years	22	21	Polymerizer
W. Germany	Sept. 1968	38 years	12	12	"
W. Germany	1971	40 years	14	12	"
W. Germany	March 1973	43 years	21	21	Filler of pesticide cans with vinyl chloride as a propellant
W. Germany	1974	44 years	17	17	Polymerizer
W. Germany	July 1974	49 years	17	11	"
W. Germany	1975	43 years	13	12	"
France	Feb. 1967	43 years	19	19	"
France	Jan. 1975*	63 years	16	13	"
Italy	April 1971	36 years	6	3	Production of PVC bags
Italy	Dec. 1972	43 years	15	6	Polymerizer
Romania	1970**	27 years	11	5-1/2	"
Czechoslovakia	No data currently available.				
Canada	7 cases confirmed quite recently, but we have not received any details so far.				

*E. Ravier, J.-N. Diter, and J. Pialat: A case of hepatic angiosarcoma in a worker exposed to monomer vinyl chloride. Report presented to the Society of Occupational Medicine and Biotechnology of Lyon on 12/13/1974. *Arch. Mal. Prof.*, 1975, 36 No. 3, pp. 171-179.

**It was diagnosed as a mixed hepatocarcinoma and angiosarcoma.

Note: It may perhaps appear surprising to the reader that cases of angiosarcoma of the liver are reported for the years preceding 1974. But this is explained by the fact that it is only when the carcinogenic power of VC was disclosed in animals that retrospective epidemiological studies were conducted throughout the world, which made it possible to find these cases (diagnosis always operative). These epidemiological studies are much harder to carry out in our country, where death certificates are not kept and where there is no cancer registry, in contrast to the US, for example.

monochloracetate make them good candidates for the last carcinogenic form of vinyl chloride. Nevertheless, additional studies are necessary to permit conclusions which can clarify the mechanism of action of vinyl chloride.

It is not without interest to note at this point that various structural analogues of vinyl chloride or its metabolites have manifested carcinogenic properties in certain experiments. This is the case with epichlorohydrin or 1,2-epoxy 3-butene. Monochloracetic acid, the terminal metabolite of vinyl chloride, was shown to be inactive in this regard, in the experiments of Van Duuren (cited by Malaveille).

Recently, Viola and Caputo showed that vinylidene chloride (VDC) or 1,1-dichloroethylene ($CCl_2 = CH_2$) was carcinogenic in the rat. This compound has been recognized experimentally as having mutagenic properties (cf. among others Malaveille [46]), while vinyl acetate lacks these properties.

A very recent item of information is also very disturbing: researchers at the chemical carcinogenisis division of the National Cancer Institute in the United States have demonstrated the carcinogenic potential of trichloroethylene after repeated oral administration to mice, at doses which were actually relatively high. The rat is apparently not sensitive, which would confirm the negative results obtained about 10 years ago in investigations conducted independently by G. Rudali and by our own group [47].

Of course, interpreting results of this type requires a proper perspective. It is nonetheless true that they must lead to epidemiological investigations in workers exposed to these various chlorinated hydrocarbons and to a reinforcement of preventive measures aimed at reducing the degree of exposure.

b) Results of epidemiological investigations in subjects occupationally exposed to vinyl chloride.

As we have pointed out in our introduction to the study of the toxicology of vinyl chloride, the disclosure of the carcinogenic potential of vinyl chloride in experimental animals prompted investigations, starting at the beginning of 1974, into whether this potential could be manifested in man, especially workers involved in cleaning autoclaves in PVC manufacturing plants who could have been exposed repeatedly to inhalations of relatively high doses of the chlorinated hydrocarbon. To the first cases of angiosarcoma of the liver, rapidly discovered in the United States in such subjects, other cases are progressively being added, not only in the United States but also in Canada and in various European countries. To our knowledge, there are currently 41 cases. We have compiled them in Table VII indicating, among other items, the age of the subjects at the time of diagnosis, the number of years between the first exposure and diagnosis, the total number of exposure years, and the occupation of the subjects exposed; notice that the vast majority had jobs in polymerization shops.

Unfortunately, this list is likely to be lengthened as epidemiological investigations are continued, causing certain deaths in occupationally exposed subjects to be attributed to angiosarcoma of the liver. A certain latency period is known to be required before this disease appears, as in the case of many other occupational cancers.

3. Preventive Measures to be Implemented for the Protection of Exposed Subjects

The information acquired in recent years makes it evident that, in addition to its other toxic properties, vinyl chloride has carcinogenic potency in man. Because of the resulting formidable risk, if it is desired to continue using this compound as a raw material in the chemical industry, it becomes

imperative to set up very strict methods of technical prevention and to have truly adequate methods available to enforce their implementation as well as the effectiveness of their application.

In addition, individual protective measures must be clearly recommended, taking care--by providing adequate information and a true health education--to draw the workers' attention to the major importance of compliance with the instructions given with respect to the precautions to be taken for the protection of their health.

Finally, technical preventive measures and individual protective measures must be completed by a strict medical surveillance.

We shall take up these various points one by one, in a necessarily very general manner.

A. Technical Preventive Measures

These concern, first of all, the industrial conditions under which vinyl chloride is used, and constitute the decisive factor as to the degree of exposure.

Next, they are concerned with surveillance over the work environment. In this respect, there is the very important problem of establishing permissible limits and controlling them by adequate methods of analysis.

1. Conditions of the industrial use of vinyl chloride.

We have mentioned the basic concepts in this regard in the first part of this article, dedicated to the presentation of vinyl chloride. We have emphasized that these concepts are essential for defining the conditions and exposure circumstances which, together with the qualitative and quantitative aspects of toxicity, determine the manifestation of the risks. The capacity of VC to polymerize and the production of PVC or copolymers constitute by far the principal use of this chlorinated hydrocarbon. But we now wish to stress

that, with the progressive disclosure of the health risks that may result from the exposure of workers involved in this production, especially during recent years, a very large number of chemical and technological refinements have been made in the processes used. A better knowledge of the kinetics of the reactions involved, both in the production of vinyl chloride and - particularly in its polymerization, combined with considerable progress made in the field of chemical engineering, have made it possible to reduce the degree of exposure to vinyl chloride considerably, while improving the output. An increase in the size of the autoclaves (from 1 cubic meter to 50 cubic meters and even 200 cubic meters), combined with execution of the decrusting process under hydraulic pressure and prolonged degassing, as well as progress in the area of automation, have made it possible to work continuously with closed systems. For these reasons, the technology of modern polymerization shops has considerably reduced the possibilities of the workers' being exposed to vinyl chloride, particularly eliminating the possibility, which was frequent 10 or 15 years ago, of inhaling toxic puffs of air while manually decrusting the polymerization autoclaves. Of course, the situation has been improved much more in the recent, modern installations than in those that are already old.

2. *Surveillance of the working environment.*

In this regard, in the case of toxic substances that may be found in the air of working areas, the very important problem of determining the permissible limits comes up as always [48].

In the case of vinyl chloride, about 30 years ago, the major concern was the risk of explosion at concentrations greater than 30,000 ppm. Following a study on the dose-response relationship with respect to the manifestation of such an effect in laboratory animals and in man, the disclosure of the

neurotoxic potential of vinyl chloride led to the recommendation of a permissible limit of 500 ppm, which is essentially equivalent to 1.275 mg/cm^3 under normal temperature and pressure conditions. This value was much greater than the value for the perception threshold of the slightly ethereal odor of chlorinated hydrocarbon--a threshold which, moreover, varies according to the individual. It was notably less than the concentrations (1,000 ppm and more) to which workers involved in cleaning autoclaves might have been exposed before 1960.

We would like to emphasize that it was a question of a *mean value integrated with respect to time*, valid for repeated exposures day after day under industrial working conditions, 8 hours per day and 5 days per week.

The discovery that repeated exposure to vinyl chloride can induce vascular effects and the acroosteolysis syndrome which we described above, led to a lowering of the permissible limit, defined as previously, to 200 ppm, which is equivalent to 5 mg/cm^3 under normal temperature and pressure conditions. This value had been especially recommended by the American Conferences of Government Industrial Hygienists in the list of *Threshold Limit Values* adopted in 1973 [49].

The revelation of the fact that vinyl chloride has a carcinogenic potential in various laboratory animal species and the recognition of its carcinogenic potency in man led the same organization, in May 1974, to revise its position drastically and to postpone the establishment of a permissible limit for this human carcinogen.

This a ticklish problem, since there is a very widespread concept that there is no threshold for carcinogens, either physical or chemical, and that, under these conditions, it is not possible to establish permissible limits for them other than on the basis of the concept of *socially*

permissible risks.

However, certain objections of a scientific nature have formulated in recent years against such a rigid theory. Since it is not possible for us to expand on this subject here, we take the liberty of referring the reader to the report of a scientific group of the World Health Organization [50] and to an article by one member of our group [51].

We would only like to point out that, even if the experimental data used by H. Druckrey, the German specialist on chemical carcinogenesis, as the basis of his proposed theory on the formation of totally irreversible reactions to carcinogenic substances were recognized as being exact, a certain number of theoretical considerations or experimental facts would lead us to consider the possibility of establishing thresholds at least for certain carcinogens. The present problem is that, for such a determination, it is necessary to have recourse to adequate quantitative data on the minimal doses of carcinogens, so as to establish doses without effect. In the vast majority of cases, these data are completely lacking at the present time.

Whatever may be the case, a certain number of national or international organizations have focused on the problem. This has been especially true of the O.S.H.A. (Occupational Safety and Health Administration) of the Department of Labor of the United States of America which, following the guidelines of its committee of expert consultants (N.I.O.S.H.), published in "U.S. Federal Register" (issue of 5 April 1974, 39, 12342) a regulation establishing, for a period of 6 months, a preliminary ceiling value (a value not to be exceeded even for short durations of exposure to a vinyl chloride concentration in the atmosphere of working areas) of 50 ppm. It was specified in this regulation, in all operations where the vinyl chloride concentrations

exceeded this figure, respiratory equipment was indisensable for the exposed subjects and that everything has to be done to reduce these concentrations to the limit provisionally considered permissible.

At the same time, the Chemical Industries Association of the United Kingdom recommended 50 ppm as a ceiling value and 25 ppm as an average value.

At the beginning of October 1974, in a regulation appearing in "U.S. Federal Register" for October 1974 (39, 194, pp. 35890-97), O.S.H.A. adopted a much more restrictive attitude. This regulation went into effect starting on January 1, 1975.

It is stipulated, in effect, that no worker should be exposed to an average concentration in a given period (one 8-hour work day) greater than 1 ppm of vinyl chloride, i.e., 3 mg/cm^3 at 25°C. A ceiling value of 5 ppm for a duration of exposure not exceeding 15 minutes was simultaneously selected.

Up to December 31, 1975, provided that the vinyl chloride concentrations never exceed 25 ppm, the regulation allows manufacturers the possibility to provide the exposed subjects with respiratory masks, whose type is defined according to the concentrations present in the air of the shops. But this is only a temporary measure until the concentrations have been reduced to the limits previously mentioned.

Many other points are found in a long text published in the "Federal Register".

We shall limit ourselves here to mentioning that no worker should be exposed to direct contact with liquid vinyl chloride and, furthermore, areas affected by this regulation should have signs indicating that vinyl chloride is an agent capable of producting cancer.

These provisions were discussed at an international symposium held in Milan on October 28 and 29, 1974, under the auspices of a subcommittee of the International Association for Occupational Medicine (MEDICHEM). Representatives of industry have become aware of the fact that it is not realistic to schedule their application without allowing a sufficient period to alter their installations.

One member of our group, who presided over this meeting, at the end of the discussion gave his own opinion, shared by the cosigner of this article. It is summarized as follows: if vinyl chloride is considered to be a carcinogen for man, all efforts must be taken to eliminate the exposure of workers to this compound in practice. As far as the average limit of 1 ppm and the ceiling value of 5 ppm for brief durations of exposure are concerned, these are reasonable on theoretical grounds.

Actually, even if the possibility is acknowledged of considering a threshold for carcinogenic chemical agents of the vinyl chloride type whose mechanism of action, after metabolic activation, may well be alkylation of certain sites on the nucleic acid macromolecule, it is indispensable to establish, in long-term investigations on laboratory animals, an ineffective concentration, to which a sufficiently high safety factor should then be applied for extrapolation to man. However, as we have seen, in experiments conducted until this time, the lowest tested concentrations of vinyl chloride in the air (50 ppm) caused the appearance of tumors and especially angiosarcomas of the liver. From all evidence, it is wise to recommend to industry that they do everything to meet the standards adopted by the American authorities.

But, fully conscious of our responsibilities, we think that to be realistic, industry should be permitted sufficient time to attain

this objective.

This is why we have pragmatically proposed the following permissible limits *on a temporary basis*, for 2 years starting on 1 January 1976, *pairing this recommendation with the need for strict individual protective measures:*

Average value for a given period (8 hours per day—5 days per week):	5 ppm.
Ceiling value for an exposure duration not exceeding 15 minutes:	15 ppm.

Meanwhile, industry can prepare itself to confront stricter requirements, if the experiments currently being conducted on laboratory animals subjected to concentrations in the air less than 50 ppm reveal the appearance of tumors and, in particular, of angiosarcomas of the liver.

An important problem arises with respect to these permissible limits: the necessity of controlling their observance. Towards this objective, it is indispensable to provide analytical methods of adequate specificity, sensitivity, and accuracy.

In this regard, up to 1973, the methods generally used to estimate vinyl chloride concentrations in working areas relied on the use of exposure meters equipped with tubes having a reagent producing a color with vinyl chloride. But the sensitivity of these methods did not go beyond 100 ppm under normal conditions of usage.

With the need for considerably reducing the value of the permissible limits, it becomes necessary to establish much more sensitive methods. Without going into detail, we wish to mention that the specialists then turned toward infrared spectrometry and gas phase chromatography. The results of infrared spectrometry are influenced by external parameters (humidity of the

air). Therefore, gas phase chromatography, generally with a flame ionization detector, was selected. Analytical methods based on the application of this technique make it possible to achieve a sensitivity on the order of 0.1 ppm with an accuracy of 6%. An entire series of techniques has been proposed. The establishment of a standarized method is currently being studied in the "Air Quality" section of the applied chemistry department of the International Union of Pure and Applied Chemistry (IUPAC).

Two types of control may be implemented:

On the one hand, permanent surveillance by means of a fixed apparatus sampling the atmosphere at several characteristic points in the shop [6-10].

On the other hand, determination of individual exposure at each working site by means of a portable micropump apparatus accompanying the worker in all his movements. This apparatus is equipped with an appropriate adsorbent (silica gel, activated charcoal, etc.) for capturing the vinyl chloride, which is then absorbed by a suitably chosen solvent (carbon disulfide, ethyl acetate). The analysis is then performed by gas phase chromatography and makes it possible to determine the vinyl chloride level present in the volume of air sampled during the course of the work day by the micropump.

B. Individual Protective Measures

No matter how effective, collective protective measures could not permit us to dispense with the classical hygienic and individual protective measures of the chemical industry (washing of hands, special soaps, double cloakroom for separating work clothes) on which we cannot elaborate in this article. Nevertheless, we must stress that the use of an independent open-circuit respiratory unit is indespensible when checking and repairing polymerization installations.

It is quite obvious that educating the workers as to the nature

and degree of the risks to which they are exposed constitutes, in the case of vinyl chloride, as generally speaking in the case of toxic substances responsible for occupational exposure, an essential factor in prevention, permitting them to play an active role in this control. Thus, a great deal of significance is attached to their health education, which must be extended to the foremen, engineers, chemists, and administrative personnel. It is very important to display, in full view in the shops, a set of instructions, written in simple and clear terms, specifying the preventive measures to be observed against the risks of vinyl chloride exposure.

C. Medical Surveillance

Today, thanks to the progressive use of absolutely indispensable technical prevention measures, bone pathology due to vinyl chloride exposure is in the process of disappearing. We are justified in hoping that the same will be true as far as the carcinogenic risk is concerned.

Of course, an explosion of hepatic angiosarcoma cases in the future may be feared, since it cannot be forgotten that they may occur in workers who have been subjected to exposures at levels known to be high, 10 to 15 years ago and even more.

The present atmospheric concentrations in PVC manufacturing shops are fortunately considerably lower, and we must continue to make an effort in this area. Nevertheless, can the physician responsible for monitoring the workers at such a plant rely only on these measurements?

It may be difficult for all levels of the hierarchy to understand this, even at a time when the whole importance of preventive medicine is justifiably recognized. As a consequence, it is a good idea to define the basis for the medical surveillance of workers exposed to vinyl chloride.

Everything we know concerning the pathology linked to exposure to this

compound must direct the attention of the occupational physician:

-- towards the vascular system and bones;

-- towards the liver;

-- towards the nervous system;

-- towards the skin.

Employment medicals.

This attention must first of all be given at the time of the employment medical. In our opinion, candidates with the following histories should not be assigned to jobs possibly involving exposure to VC:

-- confirmed hepatic insufficiency (recent history of viral hepatitis, in particular, within the past year);

-- a hematological disorder or blood coagulation disturbance (acrocyanosis, angiohemophilia, hemoglobinopathy, leukopenia, etc.);

-- vascular disturbances suggesting--even mildly--Raynaud's syndrome;

-- history of bone disease;

-- diabetes, chronic nephropathy;

-- history of epilepsy;

-- atopic eczema (this is also valid for any exposure to industrial chemicals).

Thus, an accurate interview of the subject is necessary, as well as a thorough clinical examination (but isn't this true of any serious hiring test?).

The data obtained in this clinical examination should be supplemented by biological tests of such a nature as to define the health profile of the candidate.

Which tests?

We feel that it is reasonable to require the following:

-- blood count;

-- blood picture;

-- platelet count;

-- determination of the blood transaminases (SGOT and SGPT) (to identify a possible viral hepatitis);

-- urine test (reactive strips)

and, naturally,

-- a lung X-ray;

-- X-rays of both hands (placed quite flat on the plate).

These will subsequently be very useful as a reference source, since the number of small traumatic sequelar lesions which may cause the change will be known if their existence had not previously been demonstrated.

Of course, as always, there will be subjects representing borderline cases. After they have been assigned to jobs, they should be followed up subsequently.

Furthermore, there should be no question of limiting the occupational physician to a fixed list of examinations.

This clinical examination, which remains the medical act par excellence, will sometimes prompt him to request additional tests.

We feel that it is useful to remind the reader here that it is well worthwhile to be strict during the hiring test--this test being the responsibility of the occupational physician and influencing the subsequent fitness of the worker.

Follow-up examinations of workers admitted at the time of the hiring examination.

Interval: twice a year.

Clinical and radiographic examination of the hands (in certain cases, the speed with which the bone lesions appear is known).

The appearance of these lesions will be cause for a change of job and,

as we know, will bring about a remission of the lesions. The problem here is relatively simple.

On the other hand, in the area of prevention of carcinogenic risks, in the present state of knowledge we do not have any biological test furnishing a sufficiently early warning. Many biological tests have been proposed, and the number of blood parameters which have been the subject of discussions between physicians definitely proves the problem of establishing a typical list. However, we cannot abstain from discussing this.

Of course, if the clinical examination shows a palpable liver (a large liver is always pathological), the worker should be sent to his physician or to a specialized department.

In the contrary case, as far as we are concerned, we think it is reasonable to require the following biological tests:

-- blood count;

-- blood picture;

-- platelet count;

-- two liver function tests (cholestasis tests):

- determination of alkaline phosphatases;
- determination of the blood fibrin;

-- *once a year*, a thoracic-abdominal X-ray, a pulmonary checkup and examination for possible splenomegaly, which is undoubtedly the best sign of portal fibrosis syndrome, which we know to be frequent;

-- a determination of the blood sedimentation rate: definitely not a specific test but one which, if the result reveals a significant elevation (on the order of 70 mm and higher during the first hour), confirmed by a second test, practically always indicates a serious active disorder and justifies interruption of work and strict medical surveillance;

-- finally, two tests merit particular attention:

- *examination of the ocular fundis*, of a certain usefulness;
- *sulfobromophthalein test* (BSP).

We feel that determination of the level of dye retention in the serum after 45 minutes is the best test of hepatic cholestasis; it could even be the only one to be performed in monitoring workers who may possibly have been exposed to vinyl chloride. Unfortunately, it is difficult to apply and takes a good deal of time.

The testing of a number of other biological parameters is advised in the list of items to be monitored by certain foreign occupational physicians (Americans, in particular). As far as we are concerned, it seems impossible to recommend these tests routinely, since certain ones would require highly specialized laboratories beyond the reach of the occupational medical departments of many plants.

In particular, we wish to mention enzymatic determinations which, when positive, indicate an established tumor which has already reached an advanced stage.

In this case, moreover, the clinical examination would very probably have outstripped these positive findings due to the observation of a large liver. One exception may be the determination of blood ornithine carbemyltransferase--relatively easy to do—which is considered as one of the most sensitive hepatic function tests.

As far as we are concerned, we would not insist on the abovementioned tests.

We finish by pointing out that angiosarcoma of the liver will soon be added to Table No. 52 of occupational diseases reproduced in this article.

4. *Conclusions*

Concluding this article, in which we attempted to analyze the information

currently available on the risks that may result from occupational exposure to vinyl chloride, mainly during the manufacturing of vinyl polychlorides and subsequent operations, we feel that a certain number of points should be strongly emphasized:

1. About 10 years ago, the danger for workers exposed to vinyl chloride appeared to result only from its inflammability combined with its explosive nature between certain concentration limits, its mixing with the air, as well as its narcotic effects. The disclosure that it is capable of causing an acroosteolysis syndrome and especially, more recently, is carcinogenic effects in man, are a spectacular example of the vigilance that must constantly be exerted by toxicologists, occupational physicians, and epidemiologists with respect to the possible toxic potential of chemical agents that may be found in working environments.

2. The disclosure of the carcinogenic potential of vinyl chloride by experiments on animals, followed by its recognition as a human carcinogen epidemiological investigations in occupationally exposed groups, show the major importance of conducting adequate experimental investigations on laboratory animals for any chemical compound manufactured industrially, for which practical applications are planned, and paying the greatest attention to the results thus obtained with respect to technical prevention and individual protective measures, as well as the medical surveillance of the workers exposed.

3. Many investigations still remain to be done, in an attempt to clarify the mechanisms of toxic action and especially carcinogenic action of vinyl chloride. In this regard, we feel that it is appropriate to emphasize that many facts already known suggest that the initial attack point lies in the vascular system, and that this affinity must be affected by biochemical factors

which are still unknown.

4. On the practical level of prevention, the determination of permissible limits of vinyl chloride in the air of working environments constitutes a burning current problem whose study, in our opinion, requires experiments involving the exposure of various species of laboratory animals to a range of concentrations sufficiently low to enable us to establish concentrations without effect. In this regard, the thorny and controversial problem of the existence of thresholds for carcinogenic agents should not be forgotten, especially for compounds recognized as being carcinogenic in man.

5. While awaiting the accumulation of the scientific information indispensable to an objective discussion of the decisions to be made, it becomes necessary to require industry (which has, moreover, already extended considerable effort in this direction, leading to the practical disappearance of bone pathology) immediately to implement preventive measures and especially technical preventive measures, making it possible to reduce the degree of exposure of the workers to the lowest possible level.

It is in such a spirit that in the present article, while taking into account certain pragmatic aspects which we feel affect the entire community, we recommended the immediate application, for a limited period of time, of permissible limits which would represent a considerable advance over the current situation.

REFERENCES

[1] Regnault: *Ann. chim. phy.*, 1835, 58, p. 308.

[2] I.A.R.C.: Intern. technical report No. 74/005. Report of a working group on vinyl chloride, 1974.

[3] Patty, F.A.: Industrial hygiene and toxicology, Interscience publishers. New York/London, 1963, Vol. 2, pp. 1303-1305.

[4] Hardie, D.W.F., in: Kirk, R.E. and Othmer, D.F.: *Encyclopedia of Chemical Technology*, 2nd ed., 1964, 5, New York, John Wiley & Sons, pp. 171-178.

[5] Baumann: *Annal.*, 1872, 163, p. 37.

[6] Oatromyslinski: *J. Soc. Physico. Chimique Russe*, 1916, 48, p. 32, cited by F. Swartz in Grignard, V., *Treatises on Organic Chemistry*, 3, p. 361.

[7] Lefaux, R.: Plastic Materials in the Food Industry. Associated Technical Publications Edition--Group of the French Editions Company, 1972, p. 44.

[8] O'Mara, M.M., Crider, L.B., Daniel, R.L.: Combustion Product from Vinyl Chloride Monomer, *Amer. Industr. Hyg. Assoc. J.*, 1971, 32, p. 153.

[9] Fuross, R.M. and Mead, D.J.: *Journal Phys. Chem.*, 1953, pp. 47-59.

[10] Stromberg, R.P. et al.: Thermal Decomposition of PVC, *J. Polym. Sci.*, March 1959, 35, No. 129, p. 355.

[11] Boyer, R.F.: A Statistical Theory of Discloration of Halogen Containing Polymers., *J. Phys. and Colloid. Chemistry*, January 1947, 51, No. 1, p. 80.

[12] Viola, P.L.: Pathology of Vinyl Chloride, Communication of the XVIth International Congress of Occupational Health, Tokyo, September 1969, Proceed. pp. 296-297.

[13] Viola, P.L.: Carcinogenic Effect of Vinyl Chloride, Xth International Cancer Congress, Houston, [illegible] session 3, Chemical carcinogenesis various [illegible] Proceed, 29, 4 p.

[14] Peoples, A.S., Leake, C.D.: The Anesthetic Action of Vinyl Chloride, *J. Pharmacol. Experim. Therap.*, 1933, 48, p. 284.

[15] Monograph. National Institute of Public Health, The Netherlands, 6 April 1964, p. 2.

[16] Danziger, H.: Accidental Poisoning by Vinyl Chloride, Report of two cases, *Canada Med. Assoc. J.*, 1970, 82, p. 828.

[17] Lester, D., Greenberg, L.A. et al.: *Amer. Ind. Hyg. Assoc.*, 1963, 24, pp. 165-275.

[18] Mastromatteo, E., Fisher, A.M. et al.: *Am. Ind. Hyg. Assocl. J.*, 1960, 21, pp. 394-398.

[19] Torkelson, T.R., Oyen, F. and Rowe, V.K.: The Toxicity of Vinyl Chloride as Determined by Repeated Exposure of Laboratory Animals, *Amer. Industr. Hyg. Assoc. J.*, 1961, 22, pp. 354-361.

[20] Baretta, E.D., Stewart, R.D. et al.: *Amer. Ind. Hyg. Assoc. J.*, 1969, 30, pp. 536-544.

[21] Antonjuzkenko, V.A.: Occupational Poisoning by Vinyl Chloride, *Gigiena truda i prof. Zabolev.*, 1968, 13, pp. 50-52.

[22] Cordier, J.M., Fierez, C., Lefevre, M.J., Sevrin, A.: Acroosteolysis and Associated Skin Lesions in Two Workers Affected during Autoclave Cleaning, *Cahiers de medecine du travail*, 1966, 4. p. 3.

[23] Harris, D.K., Adams, W.G.F.: Acroosteolysis Occurring in Men Engaged in the Polymerization of Vinyl Chloride, *Brit. Med. J.*, 1967, pp. 712-714.

[24] Chatelain, A., Motillon, P.: A Syndrome of Acroosteolysis of Occupational Origin Newly Observed in France, *J. radiol. electrol*, 1967, 49, pp. 277-280.

[25] Marin, A., Strauss, J. Michiels, R., Benoit, J.P., Baltie, R. and Pierre, C.: Acroosteolysis of Occupational Origin, *Revue rhumatisme*, 1967, 6, pp. 340-351.

[26] Sciu, I., Drejman, I. and Valaskai, M.: Studies of Diseases Due to Vinyl Chloride, *Med. lav.*, 1967, 58, pp. 261-271.

[27] Wilson, R.H., McCormick, W.E., Tatum, C.F. and Creech, J.L.: Occupational Acroosteolysis, Report of 31 cases, *Journ, Amer. Med. Assoc.*, 1967, 201, pp. 577-581.

[28] Benoit, J.P.: Acroosteolysis: A New Pathological Manifestation in Industry of Plastic Materials, *Cahiers de notes documentaires*, 1969, 54.

[29] Dinman, B.D., Cook, W.A., Whitehouse, W.M., Magnuson, H.J. and Ditcheck, T.: Occupational Acroosteolysis. I. An Epidemiological Study, *Arch. Environm. Health*, 1971, 22, pp. 61-73.

[30] Cook, W.A., Giever, P.M., Dinman, B.D. and Magnuson, H.J.: Occupational Acroosteolysis. II. An Industrial Hygiene Study, *Arch. Environm. Health*, 1971, 22, pp. 74-82.

[31] Mazella Di Bosco, M. Faccini, E.: The Occupational Pathology of Vinyl Chloride with Particular Reference to Acroosteolysis in Operated Subjects Employed in the Cleaning of Polymerization Autoclaves, *Riv. di clin. tossi*, 1973, 3, fasc. 1-2.

[32] Lange, C.E., Juhe, S., Stein, G. and Veltman, G.: The So-called Vinyl Chloride Sickness--an Occupationally Induced Systemic Sclerosis? *Internationales Archiv. fur Arbeitsmed.*, 1974, 32, No. 1-2, pp. 1-32.

[33] Moulin, G., Rety, J., Paliard, P., Vouillon, G. and Guttin, G.: Sclerodermal Aspects of Occupational Acroosteolysis (Polymerization of Vinyl Chloride), *Ann. dermatol.*, 1974, 101, No. 1, pp. 33-44.

[34] Berrod, J., Bourichon, J., Lazard, P. and Rety, J.: Acroosteolysis and Vascular Disturbances Related to Vinyl Chloride. With Respect to a Clinical Observation. XVIII International Work Congress, Buenos Aires, September 1972, Summary p. 43.

[35] Lefevre, M.J.: Radiological and Evolutional Diagnosis of Cases of Acroosteolysis. "MEDICAM". First International Symposium of Occupational Physicians in the Chemical Industry, Ludwigshafan, 27-29 April 1972, Report pp. 260-266.

[36] Viola, P.L., Bigotti, A. and Caputo, A.: Oncogenic Responses of Rat Skin, Lungs and Bones to Vinyl Chloride, *Cancer Research*, 1971, 31, pp. 516-522.

[37] Maltoni, C. and Lefemine, G.: Carcinogenicity Bioassays of Vinyl Chloride. I. Research Plan and Early Results, *Environmental Res.*, 1974, 7, No. 3, pp. 337-405.

[38] Maltoni, C. Lefemine, G., Chieco, P. and Carretti, D.: Environmental and Occupational Carcinogenesis in the Light of the Carcinogenesis of Vinyl Chloride, *Gli ospedali delle vite*, 1974, 1, No. 5-6.

[39] Maltoni, C. and Lefemine, G.: The Potentiality of Experimental Tests in the Prediction of Oncogenic Environmental Risks. An Example: Vinyl Chloride, *Rend. Sci. Fis. Mat. Nat.* (uncei), 1974, fasc. 3, serie VII, vol. 56.

[40] Maltoni, C. Lefemine, G., Chieco, P. and Carretti, D.: Vinyl Chloride Carcinogenesis: Current Results and Perspectives. *Med. del lav.*, 1974, 65, No. 11-12, pp. 421-444.

[41] Maltoni, C., Ciliberti, A., Brauni, L. and Chieco, P.: Insurgence of Angiosarcoma in Rats Following Oral Administration of Vinyl Chloride., *Gli ospedale della vita*, 1975, 2, No. 1, pp. 65-66.

[42] Rannug, U., Johansson, A., Ramel, C. and Machtmeister, C.A.: The Mutagenicity of Vinyl Chloride after Metabolic Activation. Second International Symposium on Chromosomic Abberations Caused by Chemical Substances Used in Industry, Milan, 28-29 October 1974, cf. also No. 3, 1974.

[43] Malaveille, C.: Communication Presented to the Ninth Session of the French Association of Chemical Carcinogenesis, Paris, Curie Institute (24 May 1975) and Bartsch, H., Malaveille, C. and Montesano, R.: Tissue Mediated. *Int. Cancer J.*, 1975, 15, p. 429.

[44] Bartsch, H., Malaveille, C. and Montesano, R.: Mutagenic and Carcinogenic Effects of Vinyl Chloride (to appear in Autumn 1975) *Mutation Research* (Review in genetic toxicology).

[45] Malaveille, C., Bartsch, H., Montesano, R., Barbin, A., Camus, A.M., Croizy, A. and Jacquignon, P.: *Biochem. biophys. res. common.* 1975, 63, p. 363.

[46] Malaveille, C.: Tissue Mediated Mutagenicity of Vinyl Chloride and Chloro 2-Butadiene, *Nature*, 1975, (at press).

[47] Truhaut, R.: Carcinogenic Hazards from Drugs. Account from a symposium of the International Union Against Cancer, Paris, November 1965, Ed. Springer Verlag, 1967.

[48] Truhaut, R.: Present State of the Problem of Allowable or Tolerable Limits for Potentially Toxic Chemical Agents in Occupational Environments, *Arch. mal. prof.*, 1971, t. 32, No. 4-5, pp. 353-370.

[49] Threshold Limit Values for Chemical Substances and Physical Agents in the Working Environment with Intended Changes for 1973. Booklet published by the American Conference of Governmental Industrial Hygienists.

[50] Report of a Scientific Group of the W.H.O. on the Carcinogenicity and Mutagenicity of Chemical Agents, Geneva, 13-17 August 1973, series of reports of the W.H.O., 1974, No. 346.

[51] Truhaut, R.: Can Permissible Levels of Carcinogenic Compounds in the Environment be Established? Account of the International Congress on Cancer, Florence, October 1974, ed. *Excerpta medica*, Amsterdam, 1974.