



Pier Luigi Viola

**(Arezzo 1917 –
Rosignano Solvay 1985)**

Alla Solvay dal 1945

Direttore dell'Ospedale Aziendale Solvay dal 1960 al 1972

Sino al 1979 Dirigente dei Servizi sanitari Solvay in Italia

Quaranta pubblicazioni scientifiche

**Due libere docenze, nel 1964 all'Università di Perugia in Patologia
generale, nel 1972 in Medicina del lavoro, presso l'Università di Pisa**



Viola, nel 1969, descrive una *Malattia da cloruro di vinile*, unitaria, sulla scorta della propria esperienza di medico “competente” e sulla base della preesistente letteratura

- una *sintomatologia soggettiva di carattere neurologico* (vertigini, sonnolenza, cefalea, nausea, formicolii agli arti, pesantezza delle gambe);
- *acroosteolisi con localizzazione più frequente nelle falangi distali delle dita delle mani;*
- *alterazioni cutanee di tipo sclerodermico localizzate più spesso al dorso delle mani;*
- *manifestazioni circolatorie periferiche tipo Raynaud con alterazioni della microcircolazione prevalentemente alle dita delle mani;*
- *epatopatia con epato e splenomegalia e possibile evoluzione in fibrosi, cirrosi ed ipertensione portale;*
- *alterazioni ematologiche non costanti e semmai, più spesso, con leucopenia, anemia ipocromica e trombocitopenia;*
- *alterazioni polmonari e ventilatorie con fibrosi intestiziale, possibile pneumoconiosi “benigna” ed alterazione della funzione ventilatoria come effetto determinato, in alcuni casi, da esposizioni complesse, a CVM, a polimero e ad altri tipi di composti.*

L'Abstract di Tokio di Viola del 1969, riporta anche dei dati sperimentali ottenuti su animali intossicati cronicamente, riguardanti principalmente dei quadri patologici dell'encefalo, del fegato e delle ossa, ma non fa cenno ad eventuali effetti cancerogeni riscontrati negli stessi animali.

Si conclude dicendo: *“Therefore according to these studies we like to stress that some precautions should be taken in the manufacturing plants polymerizing vinyl chloride, as to the reduction of the threshold limit value of monomer, and substitution of manual cleaning of autoclaves by automatic devices.”*
(Viola, 1969, pag. 297)

L'Abstract di Houston di Viola del 1970 trasmette un messaggio molto chiaro, a partire dal suo titolo sulla cancerogenicità del CVM e conclude sostenendo che in base ai dati sperimentali ottenuti *“vinyl choride is an effective carcinogenic agent for the rat”*;

l'ultima frase dell'abstract recita: *“No implications to human pathology can be extrapolated from the experimental model reported in this paper.”*
(Viola, 1970, pag. 4)

XVI. INTERNATIONAL CONGRESS
ON OCCUPATIONAL HEALTH

XVI^e CONGRES INTERNATIONAL
DE MEDECINE DU TRAVAIL



September 22-27, 1969 Tokyo, Japan

PATHOLOGY OF VINYL CHLORIDE

Piero Luigi VIOLA Italy

During the last years a syndrome among the workmen associated with vinyl chloride polymerization process has been observed. This syndrome was characterized by alterations of the skeleton, teguments, nervous system and hepatic function (1); (2); (3); (4); (5); (6). In this communication we refer to the results of a medical research carried out in several European plants where this work is performed and the results of the experimental toxicologic study of vinyl chloride. Six hundred people working in 6 plants polymerizing vinyl chloride have been under strict medical control. The hygienic conditions of the work were investigated and the concentration of the monomer in the air have been ascertained by means of an infrared rays instrument (UNOR). Twenty-five Wistar male albino rats were exposed to vapours of vinyl chloride (3% in the air) 4 hours a day for 5 days a week during 12 months to study the pathogenesis of this sickness.

Comprehensive medical examinations in 4 plants revealed among the workmen involved in cleaning the autoclaves 14 cases of osteolysis. In the other two plants no alterations of the skeleton occurred. Seven of these cases have been described previously (1), (2), (3). The lesions of the bone were localized above all in the distal phalanges of the hands. At the beginning of the illness the X-ray examination sometimes showed a slight thinning of the cortical zone. After which a decalcification process in layers of the distal part took place. In many cases the phalanges were tapered and sharper in the distal parts, occasionally it was noted osteolysis or thickening in the central zone of the bone. In two cases existed osteolysis in the feet. The bone lesions were diagnosed by means of X-ray examination after about 30 months from the beginning of the work. Several of the patients had skin lesions of the hands and to some extent bling those occurring in ichthyosiform clubbing of the fingers; alterations of nervous system, pains in the hands and vascular changes very similar to those of the Raynaud's phenomenon. The vinyl chloride was the only common substance used in

the 6 plants in the manufacturing process of polymerization. Therefore the concentration of this monomer in various technological phases of the work and in various places of the plants was controlled. At floor level and in the corridors it was between 10 and 150 p.p.m.; on the filters during the arrival of polymer it was about 2,000 p.p.m.; inside the autoclaves, before cleaning, the level was substantially higher. In the plants where the cases of osteolysis occurred, during cleaning, the concentration of vinyl chloride in the autoclaves was sometimes between 200 and 2,000 p.p.m. In the two plants where no cases were reported the concentration of monomer in the autoclaves did not rise above 150 p.p.m. In the first group of plants the workers remained inside the autoclaves for about 30 or 45 minutes. In the other two plants the cleaning period was no longer than 15 minutes.

Rats exposed to vinyl chloride vapours during the first months showed no modification. With the increase of the experimental time, a loss of weight and a decrease of the reactivity to external stimulation had been observed. Thirteen animals died of lesions of the lungs and 2 of abdominal hemorrhage. After the treatment one rat showed signs of swelling of both posterior paws. Roentgenographic examination revealed an osteolytic lesion on the right metatarsus. In addition to a fibrotic lesion, the histopathological findings were a degenerative alteration of connective tissue, alteration of the elastic fibres, blood vessels and teguments. In the metatarsus bone a large proliferation of the periosteum of a days-like appearance was noticed, in the coronal sections the bone revealed in the central part a condroid metaplasia and large areas had been substituted by cartilaginous tissue. Seven animals exhibited the same changes of the connective and bone tissue.

A diffused histopathological damage was noticed in the brain. The gray matter was affected at all levels. The neurons showed signs of atrophy, strong staining of cytoplasm, disappearance of the nucleoli and sometimes of the nuclei. Several cells presented vacuolar lesions around the nucleus.



Tenth
International Cancer Congress

TENTH INTERNATIONAL CANCER CONGRESS

Houston 22-29 May 1970

Session 3. Chemical Carcinogenesis: Various Chemicals

Carcinogenic Effect of Vinyl Chloride

P. L. VIOLA*
Regina Elena Institute for Cancer Research,
Rome, Italy

29

During the course of studies on the pathogenic action of vinyl chloride, it was observed that this compound is highly carcinogenic when applied to rats. Investigations were then carried out in order to establish the type (or types) of neoplasia that may arise. Male Wistar rats, weighing 150 g were exposed to vapors of vinyl chloride (3% total concentration in volume) for 4 hr a day, 5 days a week, for a total period of 12 months. After a period of 10 months, 70% of the animals developed squamous cell carcinoma of the external auditory meatus. In the lungs of some animals (32%), carcinomas and adenocarcinomas showing typical signs of squamous metaplasia were also found. Finally, 25% of the rats showed chondroid metaplasia of bone tissue with intense periostosis particularly located in the tarsal and metatarsal bones.

PROCEEDINGS

Istituto di Patologia Generale dell'Università di Perugia
Direttore: Prof. A. CAPUTO

PATHOLOGY OF VINYL CHLORIDE

P. L. VIOLA

During the last years a syndrome characterized by alterations of the skeleton, teguments, nervous system and hepatic function [1-5, 6] has been observed among the workmen associated with vinyl chloride polymerisation process. An experimental programme has been performed in order to evaluate the toxic effect of vinyl chloride on the animal organism, and in order to try to reproduce in rats the acroostolytic lesions observed in man.

MATERIALS AND METHODS

Twenty-five Wistar male albino rats, of average weight 150 gr., were exposed to vapours of vinyl chloride 4 hours a day for 5 days a week during 12 months. The animals were kept in a plastic air-tight container through which there was a constant flow of air containing 3 % in weight, equal to 30,000 p.p.m., of vinyl chloride. At the end of treatment the surviving animals were killed at twenty-day intervals, and the paws, brain, liver, kidneys and thyroid were examined histologically after fixation, inclusion and colouration by the enastoxylite-cosine, Van Gieson, P.A.S., Weigert, Relschowsky-Gomori methods. Twenty five rats of the same breed were set aside as a control.

RESULTS

During the period of exposure the animals were slightly soporific, but the first few months of treatment were well tolerated and the rats showed no change in body growth or behaviour and no organic alteration visible macroscopically or by radiological means. After ten months some of the animals began to show a decrease in weight, in aggressiveness, in their reaction to external stimuli, and often a disturbed equilibrium. Thirteen animals died from cardio-respiratory complications. Two animals died from hepatoperitonium. Most of the animals showed pathological involvement of the brain, liver, kidneys and thyroid. Six rats showed histopathological alterations of the skeleton.

The small metatarsal bones showed an extensive periosteal proliferation of cartilage-like material apparently originating by metaplasia directly from the bone. All around the newly formed cartilage the cellular components were compressed and arranged tangentially to the cartilage itself, forming a perichondral layer. The isogenous cartilaginous groups were irregularly arranged and their nuclei were of varying size and often number per cell. The edges of the cartilage were irregular, showing digital extroflexions resulting from a varying growth potential. There was also evidence of chondroid metaplasia in areas of mature compact bone, in which the cartilaginous elements were

Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride¹

P. L. VIOLA, A. Bigotti, and A. Caputo

Regina Elena Institute for Cancer Research, Rome, Italy

SUMMARY

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

INTRODUCTION

The oncogenic properties of some chemical organic compounds used for the preparation of "plastic" have been widely investigated, and their mutagenic effects have been well documented. Detailed information on this subject may be found in the literature [2-6, 8]; however, all information and references are exclusively related to highly polymerized compounds of roughly the same size as used in various industries.

Oncogenic polymers produce sarcomatous tumors, with the exception of polyurethanes which, as reported by Hurley [6], also induce adenocarcinomas. Recently, it has been demonstrated that sarcomatous tumors [1-4, 7] are transplantable, and it has been suggested that they may originate from the tissues of the capsule that gradually cover the plastic film. Thus, Brand et al. [1-4] have observed preinvasive areas made of poorly differentiated fibroblasts which were firmly attached to the plastic film up to the moment of malignant transformation.

This investigation demonstrates that even the monomer vinyl chloride possesses oncogenic properties which were with an appropriate model different from the model previously reported by several authors [9-12]. The carcinogenic response

to vinyl chloride follows a singular pattern for the different tissues and organs of the rat.

MATERIALS AND METHODS

The experiments were performed with vinyl chloride ($\text{CH}_2=\text{CHCl}$), the monohalogenated derivative of ethylene of commercial grade (99% purity) assumed to contain insignificant amounts of various nononcogenic contaminants.

Three-month-old Wistar (A/IRRE) male albino rats (about 150 g body weight) were exposed to vinyl chloride vapors for 4 hr a day, 5 days a week, for 12 months. The animals were kept in metal or plastic, airtight cages in which a constant flow of air, containing 3% v/v (equal to 30,000 ppm) of vinyl chloride, was introduced. Twenty-five rats of the same strain were the control group. At the end of the treatment, the surviving animals were killed at 20-day intervals, and the most important tissues and organs were examined histologically by standard methods. During the period of exposure, the animals were slightly soporific; however, the first few months of treatment were well tolerated and no changes in growth or behavior were noted. After 10 months of treatment, some animals began to show a hard swelling of the paracardiac region which became progressively larger until it reached the size of a walnut or slightly larger. In most cases, the swelling was unilateral; it was bilateral in only a few animals. After 1 or 2 months, the growing tissues became ulcerated and discharged necrotic debris, while a certain amount of tumorous tissue began to form on their surfaces. In addition, we observed that the masses were an integral part of the paracardiac region and could not be distinguished from the local tissues. Cases of necrosis were found. Pleura and pericardium often cases, the lungs were covered with a number of white nodules as large as grains of rice or even larger and harder than the lungs themselves. In 2 cases, the lungs were hemorrhagic with milky, thick fluid in the pleural cavity. The liver was sometimes increased in size and very fragile. The animals were subjected to X-ray studies at different intervals from the beginning of treatment in order to control the state of the skeletal bones.

All the animals that inhaled vinyl chloride showed a series of paracardiac lesions. Among these, most prominent were the disappearance of granular and Purkinje cells, degeneration

¹ A preliminary report of the results reported here was given at the Tenth International Cancer Congress, Houston, Texas, May 22-24, 1970.

Received July 31, 1970; accepted January 12, 1971.

MEDICINA DEL LAVORO

Istituto di Medicina del Lavoro dell'Università di Pisa
Direttore: Prof. L. BASCHIERI

LA MALATTIA DA CLORURO DI VINILE

Relazione tenuta il 2 novembre 1972 presso l'Università di Pisa
in occasione del XXXV Congresso Nazionale della Società Italiana
di Medicina del Lavoro

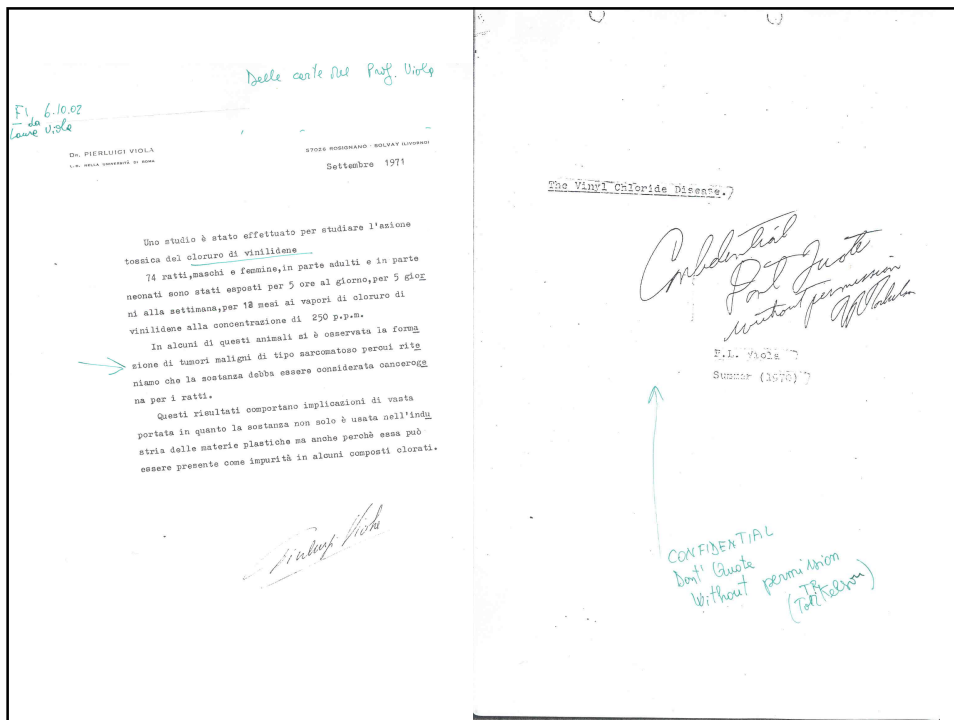
P. L. VIOLA

In questi ultimi anni si è avuto un rinnovato interesse degli studiosi per la tossicologia dei composti macromolecolari ed in particolare per il cloruro di vinile monomero (VCM). Questo composto è un derivato monoalogenato delle etilene a formula $\text{CH}_2=\text{CHCl}$ i cui sinonimi sono: cloroetilene, cloroetano, cloruro di etilene.

Esso è prodotto industrialmente per idroclorazione dell'acetilene o per sintesi mista a partire dall'etilene e acetilene oppure per clorazione e ossiclorazione dell'etilene. A temperatura e pressione normale è un gas incolore, di odore dolciastro, più pesante dell'aria 2,23 volte.

Principali caratteristiche fisiche del composto sono:

Peso molecolare	62,50
Peso specifico del liquido	0,99 ($-25^\circ\text{C}/4^\circ\text{C}$)
Punto di ebollizione	$-13,8^\circ\text{C}$ ($+7^\circ\text{F}$) (1 atm)
Punto di fusione a 1 atm	$-153,71^\circ\text{C}$ (-245°F)
mm Hg	10 100 692 2660
Tensione di vapore	$^\circ\text{C}$ $-87,5$ $-51,8$ $-15,8$ $+25,0$
densità = 2,55 gr/litro	
1 mg/litro = 391 p.p.m.	
1 p.p.m. = 0,00256 mg/litro	
Punto di infiammabilità	-78°C ($-108,4^\circ\text{F}$)
Limite esplosivo	472 $^\circ\text{C}$ (882 $^\circ\text{F}$)
Temperatura di autocombustione	tra 3,6 e 26,4 in volume di aria
Volume specifico	a 70°F 1 atm, 6,2 CUFT/LB
Densità del gas	16 $^\circ\text{C}$ (aria = 1) 2,15
Temperatura critica	158,4 $^\circ\text{C}$ (317 $^\circ\text{F}$)
Pressione critica	52,7 atm
Calore latente di ebollizione	(punto di ebollizione) 5,5 K cal/mole
Calore latente di fusione	(punto di fusione) 1,181 K cal/mole



Verbale della Riunione del 17.4.74 all'Istituto Superiore di Sanità sul cloruro di vinile (dattiloscritto, s. d.), partecipanti: Pocchiari, Gatti, Carere, Bartalini, Viola, Maltoni, Peretti, Spinazzola, Garattini, Santi, Montesano, Saracci, Loprieno, Ricciardi.

(Viola) **"...nel primo lavoro presentato a Tokio da Viola, non furono menzionate le lesioni cancerogene osservate sugli animali per necessità di ulteriori accertamenti e per titubanze di ordine soggettivo, in quanto non si riteneva la sperimentazione sugli animali capace di dimostrare una cancerogenicità anche per l'uomo"...**

"Dal 1966 ha tenuto in osservazione 2 gruppi di operai (300 + 200) sui quali ho effettuato due visite annue ed un completo check up con radiografia; nel periodo di 10 anni (1961-1971) ha osservato su 271 operai due casi di cancro al fegato, 1 tumore al cervello ed 1 neoplasia polmonare. Almeno 3 casi di tumore sono stati osservati su gruppi di operai addetti ad altre lavorazioni.

Nel 1970 fu interessato dall'Associazione chimica americana a svolgere delle ricerche più estese sul VC, ma il progetto non ebbe alcun seguito."

Marroni, M. (a cura di) Iniziative della F.U.L.C. contro il pericolo di cancro nella produzione del cloruro di vinile e del cloruro di polivinile, Rassegna di Medicina dei Lavoratori, giugno 1975, pp. 339-346. "Il 3 settembre 1974 si riuniva a Firenze l'annunciato incontro di rappresentanti della Regione Toscana, dei Sindacati di categoria e dei C.d.F. dell'industria chimica, sui pericoli del CV e PCV"

*"Viola ricorda che già nel 1969 parlò con la **Commissione interna** spiegando che il CV <<entra fra quelle 1.200 sostanze che sperimentalmente sappiamo danno i tumori negli animali, ma ancora non sappiamo se questa azione può presentarsi negli uomini. **Ma io prometto sulla mia parola di uomo che vi terrò informati di qualsiasi cosa avvenga**>>.*

*<<Quando ho saputo che la Goodrich aveva denunciato nei primi di questo anno (1974) la morte di due operai per CV, una settimana dopo ho chiamato quei tali ed ho detto: Guardate, io 4 anni fa vi avevo promesso di tenervi al corrente. Oggi io so questo. **Mi pare che maggior collaborazione, maggior rapporto fra medico e quelli che sono interessati non si può**>>.*

Maltoni, C. Cloruro di vinile: la ricerca sperimentale e suoi risultati (estratto della relazione presentata al Convegno della FULC di Firenze del 3 settembre 1974), in: Sapere, novembre 1974, pp. 41-45.

"... Negli anni tra il 1962 e il 1965 casi di acroosteolisi vennero osservati tra operai di sei delle otto fabbriche di VCN-PVC della Solvay stessa. Nello stesso periodo la Solvay rese noto questo rischio ad altre industrie del settore, che ebbero modo di rilevare la stessa lesione tra loro dipendenti. Fu in base a quelle rilevazioni che nel 1967 il prof. Viola iniziò, a Rosignano Solvay le sue ricerche" ...

*"**Immediatamente dopo il resoconto di Houston entrammo in contatto con il professor Viola, che gentilmente mise a nostra disposizione le sezioni istologiche dei suoi tumori**" ..*

"raggiungemmo le seguenti conclusioni: 1) nelle condizioni sperimentali del professor Viola il CVM mostrava chiaramente un effetto cancerogeno sul ratto; 2) 30.000 ppm di CVM erano una dose estremamente alta; 3) i tumori descritti come cutanei originavano dalle ghiandole di Zymbal" ... "4) i tumori descritti come polmonari, da noi esaminati, erano nella nostra opinione metastasi da carcinomi delle ghiandole di Zymbal."

"Allo scienziato incombe l'obbligo di approfondire le sue conoscenze e di fare la fotografia più esatta possibile della pericolosità dei prodotti.

Spetta, poi, ad altri sostenere e promuovere quei provvedimenti legislativi che se, da una parte, debbono tutelare quel bene irrinunciabile che è la salute dell'uomo, dall'altra debbono preoccuparsi di non distruggere le fonti della sua ricchezza.

E' in questa occasione che ognuno deve assumersi le proprie responsabilità, che non è consentito tirarsi indietro per paura di compromettersi".

P.L. VIOLA

Assemblea dei medici degli stabilimenti Solvay
(2-3-4 novembre 1977)

minuto in un quaderno
di circa 50 pagine contenenti
sperimenti di carcinologia sperimentale (per
occupazionale) (per
pubblica-
zione
in
rivista
pubblicata
da A.
Reggiani)

Epidemiologia dei Tumori da lavoro di Viola

1928 ha inizio in USA la produzione di EVM
1933 " " " Europa " " CVM
1957-1961 in numerosi distretti anglosassoni alti tumori
1956 - Corina diventa il primo caso di ammalato
1968 - ~~malattia~~ ~~causata~~ ~~dal~~ ~~farmaco~~ ~~epitossico~~ ~~perossido~~
1970 - Viola dimostra che il CVM è
un potente cancerogeno nei ratti
1973 - Si trovano i primi casi di angiosarcoma
del fegato da CVM nell'uomo in USA

"Storia di un ricercatore di campagna dalle mani pulite"