

CANCEROGENIC EFFECT OF VINYL CHLORIDE

P. L. Viola

(Regina Elena Institute for Cancer Research)
Rome, Italy

Presented at the Tenth International Cancer Congress
Houston, Texas May 22-29, 1970

The demonstration of oncogenic activity of some chemical organic compounds employed for the preparation of "plastics" has been widely investigated and the limits and the effectiveness of their oncogenic power have been well defined. The present investigation demonstrates that it is possible to obtain for some experimental models a marked carcinogenic response to a monomeric precursor, i.e., vinyl chloride, of plastic polymers which follows a peculiar pattern for different tissues and organs of the rat.

Twenty-six Wistar (AR/IRE) male albino rats, of the average weight of 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 most important tissues and organs were histologically examined by conventional methods. Twenty-five rats of the same strain were kept aside as a control. 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 behavior and no organic alterations visible macroscopically or by radiological means. 65% of the animals developed tumors of the skin and 26% of these showed tumors of the respiratory tract exclusively localized in the lungs. Very few animals developed tumors in the bone and in this case the tumors were localized in the metaphysical region of the femurs, and it is worthy to mention that the femurs of both posterior limbs showed the carcinogenic transformation.

Tumors of the skin

The skin transformation which developed more frequently in the para-aural region, has been the epidermoid carcinoma, but we have seen also papillomas and rarely mucoepidermoid carcinomas.

RSV 0015993

Cancerogenic Effect of Vinyl Chloride
P. L. Viola

Tumors of the respiratory tract

Even if as far as the percentage is concerned these occur in a smaller number, their morphologic appearance is mainly of an adenocarcinoma; only in one rat it has been observed a tumor of the epidermoid type. Sometimes the tumor showed an early developmental stage and consisted predominantly of cubic or columnar cells arranged as regular or irregular tubular and papillary elements supported by poorly developed fibrous stroma.

Tumors of the bones

In the metaphysical region of the four limbs a large proliferation of cartilaginous tissue arises outwardly to the periosteum and seems to derive directly out of the osseous cortical by the growth of its cells. The cartilagenous growth is dishomogeneous as it is shown by the extension of finger-like prolongations into the boundary of neoformed tissue. Beside the chondroblastic, chondrocytic and angiomatous areas, manifestation of noticeable growth power, there are cartilaginous zones with regressive features, as fibrosis and hyalinosis.

The results reported above indicated that vinyl chloride is an effective carcinogenic agent for the rat. As for many carcinogenesis studies, where multiple tumors arise at different sites, in different tissues and organs, the data obtained need to be evaluated considering a more prompt positive response according to the ideal concentration of the carcinogenic. It is noteworthy to emphasize that the cutaneous system represents an impressive pattern of susceptibility to the vinyl chloride. Another point to be considered is that all the cutaneous tumors developed in the same site, i.e., the region including the area in which submaxillary and parotid gland are located.

No implications to human pathology can be extrapolated from the experimental model reported in this paper.

B150 QT743 P 244
SUZU NO XEROX
J AM COLL TOXICOL

ABSTRACTS

121

A Four Week Inhalation Study in the Rat With Sodium Dichloroisocyanurate Dihydrate. E. Cacioli and G. J. Pleschke, PNC Corp., Princeton, NJ.

A four week inhalation toxicity study (5 hrs./day; 5 days/week) was conducted by exposing groups of 10 male and 10 female rats to 3.22, 10.4 and 32.6 mg dust/m³. The test compound was sieved prior to use to generate a sample with lower particle size than normal to insure better penetration of dust deep into the respiratory tract. Since whole body exposure was used, poisoning by rats probably resulted in additional oral intake of dust remaining on fur after treatment. Typical mass median diameters for the dust particles were in the range 2.1 to 4.3 micrometers. All animals survived the study. When compared to untreated control animals, the 10.4 and 32.6 mg/m³ groups showed increased incidences of dry and moist rales, and nasal discharges. Results of gross necropsy were generally unremarkable. Results of microscopic examination of selected tissues from the high level and control rats did not reveal any definite evidence of exposure related effects. Clinical chemistry and urinalysis measurements for all groups fell within normal biological limits. A few hematologic parameters were elevated: hemoglobin (high level); hematocrit (high level females); erythrocyte count (mid and high level females). Depressed absolute and relative liver weights in the high level and elevated lung/body weight ratios observed in high level rats and mid level males appeared to be treatment related. The no-observed-effect level is considered to be 3.22 mg/m³ in the rat.

122

Toxicological Evaluation of A Compost From A Waste Water Treatment Plant Sludge. F. J. Roschke.

J. Juba*, American Cyanamid Company, Wayne, NJ; E. B. Foster*, GSC Economics, Weymouth, MA; and R. V. Walworth, Pharmacokinetic Research International, Waverly, MA (Invt. by S. Sperano).

The proper disposal of waste water treatment sludge has been an important concern in environmental protection. Extensive interest has centered on the composting of waste activated sludge which has the potential of transforming sludge into a useful material. Before such compost can gain widespread applications, the environmental safety and safe handling characteristics must be detailed. The present studies address a number of these considerations for a compost from American Cyanamid's Wallingford, CT, Plant. The compost was prepared by the mixing of sludge generated from the secondary waste activated treatment system with wood chips in aerated piles to produce a compost material following ca. 21 days of organic matter decomposition. In order to determine the acute toxicological effects of the compost on the environment, the following studies were performed and their respective results are indicated:

Rainbow Trout LC50 (96 hr)	>7,700 mg/L
Bluegill Sunfish LC50 (96 hr)	>7,700 mg/L
Water Flea (<i>Daphnia magna</i>) LC50 (48 hr)	>100,000 mg/L
Fresh Water Alga (<i>Salmonella</i>)	
<i>Capricornium</i> LC50 (96 hr)	>4,000 mg/L

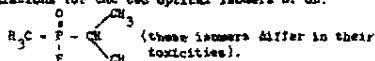
The following studies and their results were used to make a health assessment for the safe handling of the compost:

Acute Oral LD50 (rat)	>5,000 mg/kg
Acute Dermal LD50 (rabbit)	>1,000 mg/kg
Primary Skin Irritation (rabbit)	minimal erythema
Primary Eye Irritation (rabbit)	no significant effect
Dermal Sensitization	none
Ames <i>Salmonella</i> Microsome Assay	non-mutagenic

The present results indicate that there were no biologically meaningful effects in the acute environmental studies or the health assessment tests. The conclusion from these studies, therefore, was that the Wallingford Compost caused no significant toxicological effects.

123 **Ab-Initio Quantum Chemical Calculations and Electrostatic Molecular Potential Maps for Predicting Toxicity of Organophosphorus Anticholinesterases.** E. C. Hershberger*, V. Lenchuk*, V. S. Korik*, and Joyce J. Kaufman, Department of Chemistry, The Johns Hopkins University, Baltimore, Md. 21218 (Intr. by Joyce J. Kaufman).

Ab-initio calculations were carried out on a number of organophosphorus compounds using our own programs which incorporate a number of desirable options for ab-initio calculations on large molecules. We carried out ab-initio calculations for the two optical isomers of OB:



From the wave functions of the optical isomers of OB (calculated relative to internal body-fixed coordinates) we generated the electrostatic molecular potential contour maps (relative to the same absolute space-fixed reference coordinates) in three dimensions around each molecule. These maps indicate vividly the differing stereoelectronic requisites for the different optical isomers to form complexes with acetylcholinesterase (AChE) and suggest the basis for the difference in their in-vivo toxicities. These maps form three dimensional stereoelectronic holograms and can even be used for reverse image holography to ascertain if new, even hypothetical, molecules fulfill the requisites. The second phosphorylation step of the inhibition of AChE by organophosphorus anticholinesterases of the general formula $\text{R}_2\text{P}(\text{OR})_2$ is related to the acidity of X and to the bond strength of the P-X bond. For a series of compounds, aryl N-ethyl methyl phosphoramidates, in which the P-X bond is constant, the quantum chemically calculated P-O total overlap populations (TOP's) correlate the experimental log I₅₀'s for inhibition of AChE over four orders of magnitude with correlation coefficients of 0.96 (4th: TOP 0.9581; TOP² 0.9614). This research was sponsored by the Office of Naval Research, Biophysics, under Contract N00014-81-X-0007.

124

Neoplastic effects of vinyl chloride in mouse - lower doses and short-term exposure. S. Suroki, Environmental Sciences Laboratory, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029

Neoplastic effects of lower doses of vinyl chloride (0 control, 1, 10, 100, 300 and 600 ppm) and short-term exposure (4 weeks) by inhalation have been studied by light and electron microscopy in 220 mice. Except for dead or seriously sick animals, a large majority of the animals were sacrificed at three different stages: immediately after exposure, 12 weeks later, and 40 or 41 weeks after exposure. Six mice (4:600 ppm, 2: Oppa) were kept longer than 41 weeks to examine the effects of the chemical after a long-term recovery period. Pulmonary tumors (alveolar tumors) and hepatic and extrapulmonary hemangiosarcomas were induced in these animals. Alveolar tumors were first observed 10 weeks after exposure to 600 ppm. In the subgroups exposed to higher concentrations (600 ppm and 100 ppm) the incidence of tumors was higher and their appearance was earlier than in the subgroups exposed to lower concentrations (100 ppm, 10 and 1 ppm). These findings indicated a dose-response relationship for incidence of alveolar tumors, and the latency period was inversely related to dose. Two hemangiosarcomas (1 subcutaneous and 1 hepatic) were also induced in either a mouse's ear 29 weeks after exposure to the 10 ppm vinyl chloride and a mouse's liver 36 weeks after exposure to the 600 ppm vinyl chloride, respectively. (Supported by Research Grant ON 00681 from NIOSH).

AUG 23 1983

COPYRIGHT
MARY ANN LIEBERT IN
C PUBL NEW YORK NY

RSV 0015995