

CANCEROGENIC EFFECT OF VINYL CHLORIDE

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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.

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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.

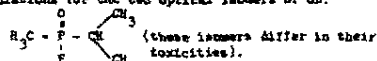
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ABSTRACTS

121 **A Four Week Inhalation Study in the Rat With 804-
Ave Dichlorodiphenyl Ether Dihydrochloride.** E. Cacioli and G. J.
Pietrangeli, 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 penetra-
tion 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 ob-
servable. 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); hemo-
crit (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. Roschier.
J. Juba*, American Cyanamid Company, Wayne, NJ; R. A. Foster*,
EAC Economics, Weymouth, MA; and R. V. Walworth, Pharmacokinetic
Research International, Beverly, MA (Intr. by S. Sperano).
The proper disposal of waste water treatment sludge has
been an important concern in environmental protection. En-
tensive 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 com-
post 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 follow-
ing 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 (Daphnia magna) LC50 (48 hr) >100,000 mg/L
Fresh Water Alga (Selenastrum
capricornutum) 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 com-
post: 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 Salmonella Microsome Assay non-mutagenic
The present results indicate that there were no biologi-
cally 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 Elec-
trostatic Molecular Potential Maps for Predicting Toxicity
of Organophosphorus Anticholinesterases.** E. C. Hershman*,
V. Lenchikova*, 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 in-
corporate a number of desirable options for ab-initio cal-
culations on large molecules. We carried out ab-initio cal-
culations for the two optical isomers of OB:



From the wave functions of the optical isomers of OB (calcu-
lated relative to internal body-fixed coordinates) we gener-
ated the electrostatic molecular potential contour maps
(relative to the same absolute space-fixed reference coordi-
nates) 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
O is related to the acidity of X and to the bond
strength of the P-X bond. For a series of com-
pounds, 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 dose and short-term exposure.** S. Serukli, Environ-
mental 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 con-
trol, 1, 10, 100, 300 and 600 ppm) and short-term exposure
(4 weeks) by inhalation have been studied by light and elec-
tron microscopy in 220 mice. Except for dead or seriously
sick animals, a large majority of the animals were sacrific-
ed 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 ex-
amine the effects of the chemical after a long-term recovery
period. Pulmonary tumors (alveolar tumors) and hepatic
and extrahepatic 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 rela-
tionship for incidence of alveolar tumors, and the
latency period was inversely related to dose. Two hemangio-
sarcomas (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).

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