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FEBRUARY 1976, VOLUME 15, No. 1

R&S 134622

INFORMATION BULLETIN B.I.B.R.A.

CURRENT DEVELOPMENTS IN
FOOD ADDITIVE LEGISLATION
AND TOXICOLOGY

BRITISH INDUSTRIAL
BIOLOGICAL RESEARCH
ASSOCIATION

the Committee, and in their turn, on behalf of all the members of RIRA for whose benefit the work has been carried out, I have great pleasure in expressing our deep thanks to all those RIRA staff who have been involved in the Safety Evaluation Studies which have culminated in the record issues of reports. Sincerely,

L.L. Katan,
Chairman, Research Policy
Co-ordinating Committee
27 January 1976

ARTICLES OF GENERAL INTEREST

VINYL CHLORIDE—PART I

Workers involved in the production of polyvinyl chloride (PVC) are exposed to differing levels of vinyl chloride monomer (VC), the greatest exposure being in the cleaning of polymerisation autoclaves. Such exposure can lead to acro-osteolysis (RIRA Bull. 1973, 12, 313), sometimes called 'VC disease', and to angiosarcoma (ibid 1974, 13, 353). Less severe exposure to VC can occur during subsequent processing of PVC and although clinical changes may not be manifest, pathological tests detect effects characteristic of clinically advanced cases (Lange *et al.* Ann. N.Y. Acad. Sci. 1975, 246, 18).

Acro-osteolysis

In an ill-defined survey of workers exposed to VC in Japan (Sakabe, *ibid* 1975, 246, 78), 49 out of 1597 complained of finger trouble, mostly paraesthesia (numbness and tingling) and pain. X-ray examination of the fingers of 1599 workers revealed abnormal findings in 104 cases, 80 of which could be attributed to causes unrelated to VC exposure and only two of which were clear cases of acro-osteolysis. More thorough examinations have been carried out on 70 patients who had been employed in a PVC-production plant for 0.5-21.7 years (average 7.7 years) in various processes including autoclave cleaning (Veltman *et al.* *ibid* 1975, 246, 6). Of the initial symptoms reported, upper abdominal complaints were the most common (in 42 out of 70), followed by tiredness, dizziness, increased perspiration and numbness, tingling and sensation of cold in fingers and/or toes. A survey by mailed questionnaire carried out on workers in a PVC-production plant (Spiras *et al.* Am. Ind. Hyg. Ass. J. 1975, 36, 779) revealed dose-response patterns for all these symptoms except abdominal complaints, which were not investigated.

Veltman *et al.* (loc.cit.) tabulated their pathological findings, the most frequent effects being thrombocytopenia (lack of platelets in the blood) in 87%, increased bromsulphthalein (BSP) retention (indicating hepatic dysfunction) in 67%, enlargement of the spleen in 57% and reticulo-

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Relationships between

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cytosis (indicative of active blood regeneration) in 47%. External changes consisted of club-like swelling and shortening around one or more of the terminal finger bones, accompanied by watch-glass-like nails and shortening of the nail plates, and of scleroderma-like changes of the skin of the knuckles and forearms. With some of these changes, complete regression could be expected provided that a certain degree of severity was not exceeded.

Histological findings showed hyperkeratosis, an increase in subepidermal capillaries and a lymphocytic infiltrate. The collagen bundles were swollen and the elastic fibres were thin, fissured and fragmented. This last finding distinguished the diagnosis from that of systemic sclerosis. In clinically changed skin, the histological findings were always present, but in six out of 28 cases they were found even in clinically unchanged skin, although this showed no direct correlation with the severity of internal findings.

Changes in the bones were noted as a band-like acro-osteolysis, particularly at the base of the finger nail. In most cases, complete restitution occurred after removal of the patient from VC exposure. Vascular changes were closely connected with the bone changes, and ranged from slight narrowing of the vascular lumina in the digital arteries to complete absence of filling of the arteries along the whole length of fingers affected by acro-osteolysis, the degree of severity being related to the severity of the bone changes.

As mentioned above, these authors noted a high incidence of thrombocytopenia, presenting what was apparently the first report of this occurrence in connexion with VC exposure. Slight to severe cases were found in 87% of all persons examined and values ranged from 17,000 to 143,000 platelets/ μ l (lower norm, 150,000/ μ l). There was, however, no clear-cut correlation between the platelet count and either the period of exposure or enlargement of the spleen. The authors suggest that a platelet count should be an obligatory test in PVC workers. Improvement of platelet counts occurred in only six of 29 patients who had been removed from VC exposure for 1-1.5 years.

Two specific cases of acro-osteolysis have been reported in workers exposed to VC for 2 years, only the second year being at a high level of exposure (Walker, Proc. R. Soc. Med. 1975, 68, 343). Both men developed acute attacks of Raynaud's phenomenon (spasm of digital arteries, blanching and numbness of fingers), together with lytic bone lesions and thickening of the skin. After removal of these workers from exposure, the skin lesions appeared to regress and the lytic lesions to heal, but the vascular disorders seemed more permanent. In a subsequent discussion it was stated that there was no evidence that any catalysts or additives used in the VC polymerisation process were capable of producing this syndrome.

Investigations have also been carried out in PVC-processing industries (Lange *et al.* 199, 211), and although clinical manifestations such as scleroderma-like skin changes or Raynaud's syndrome were not observed, pathological findings in laboratory tests were similar to those in workers in PVC-production industries, where exposure to VC is generally considered to be greater.

Relationship between VC exposure and angiosarcoma

An association of PVC manufacture with the incidence of haemangio-sarcoma was first suspected as a result of several deaths in the industry from this otherwise very rare type of liver tumour, but criticisms have

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been levelled at a subsequent analysis of 161 deaths in two VC-PVC plants showing that the number of deaths due to all cancers was 50% higher than that in a comparable but unexposed population group (NIEHA Bull. 1974, 11, 354). Because up to threefold regional variations in cancer incidence are known to occur, it was suggested that the data from VC plant workers should have been compared with local and not national mortality data (Parekh & Williamson, Lancet 1974, II, 591). It was also pointed out (Falk *et al.* *ibid* 1974, II, 784) that 135 out of the 161 deaths stemmed from a plant in Louisville, Kentucky, concerned additionally with synthetic rubber production, and that a large proportion of the workers were not directly exposed to VC, thus raising problems of interpretation of the results.

Further support for these criticisms has been offered by a study of age-standardized mortality rates for a population of 2100 male workers in Penarth, Glamorgan, exposed to VC for periods of up to 27 years (Duck *et al.* *ibid* 1975, II, 1197). In the 136 deaths in men under 75 years of age, no cases of angiosarcoma were identified within the study period, although one has occurred since then. Observed and expected frequencies of death from various causes in the whole population of workers corresponded closely, and the frequency of neoplastic disease was similar in all subgroups of the population. A subsequent report disclosed that eight of the 27 angiosarcomas diagnosed in Holland since 1950 were of the liver, but none of the 27 patients had had any traceable contact with VC (Daldorff *et al.* *ibid* 1976, I, 246).

Conclusive epidemiological studies are not possible at present owing to difficulties in tracing all individuals exposed to VC, to the long latent periods of occupationally induced cancers combined with the relatively recent use of VC, and to a lack of information on levels of exposure. However, the urgency of the situation has prompted several other cohort studies of VC-PVC workers, and their results indicate support for the results of the Louisville study (NIEHA Bull. 1974, 11, 354).

A study of relatively long-term effects (Nicholson *et al.* Ann. N.Y. Acad. Sci. 1975, 246, 225) involved 257 individuals, each of whom had been exposed to VC for at least 5 years between 1946 and 1968. Of the 255 individuals traced, 24 had died (compared with 19 expected) and of the nine deaths due to cancer (3.9 expected) three were due to angiosarcomas of the liver. The angiosarcomas all occurred in individuals who had worked since before 1951 in PVC production, suggesting that as the time from exposure increases in cohort members with similar exposures, additional cases may occur.

The authors of another study (Ott *et al.* Archs envir. Hlth 1975, 30, 333) were able to relate tumour incidence to levels of VC exposure. Of 594 cohort members, 72 were exposed to arsenic (which is known to produce an increased cancer risk) as well as to VC, and seven of the ten deaths in this group were due to malignant neoplasms (1.9 expected). Of the 522 individuals exposed to VC alone, 79 had died (89.1 expected), 13 as a result of malignant neoplasms (16 expected). No deaths due to angiosarcoma were observed. Although the number of deaths from malignant neoplasms was small, nine out of 13 were observed in individuals exposed to high levels of VC (4.6 expected) while only five (9.4 expected) were observed in all other groups.

These authors recognized that an increase in the time from initial exposure and in the number of individuals involved would improve the reliability of the epidemiological data, but in the interim their results are supported by four specific cases of angiosarcoma. In Sweden, Rydin &

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Holmberg (Ann. N.Y. Acad. Sci. 1975, 246, 249) diagnosed angiosarcomas in two VC-PVC plant workers exposed to VC for 18 and 23-27 years respectively. Since both these cases were initially classified as primary liver cancers, the real number of angiosarcomas associated with VC-PVC production may be larger than has hitherto been observed. Two further cases were reported among autoclave cleaners in Germany by Lange *et al.* (199, 911.) who noted that the case histories contained no information on 'VC disease'. Although evidence shows that the incidences of both acro-osteolysis and angiosarcoma are related to VC exposure, there is no correlation between the two diseases. Of seven cases of acro-osteolysis tested, none showed abnormal liver functions attributable to VC exposure (Creech & Makk, Ann. N.Y. Acad. Sci. 1975, 246, 86).

Diagnosis of VC-induced liver disease

Systematic tests carried out in an attempt to relate liver abnormality to VC exposure levels revealed two cases of angiosarcoma and nine cases of portal fibrosis in 274 PVC production workers and two cases of portal fibrosis in 909 workers not associated with PVC production in the Louisville plant mentioned above (Creech & Makk, 199, 911.). Blood samples were subjected to the standard sequential multiple analysis known as SMA-12, involving determination of calcium, total bilirubin, albumin, cholesterol, total protein, alkaline phosphatase, lactic dehydrogenase, glutamic-oxaloacetic transaminase, glucose, urea nitrogen, uric acid and inorganic phosphorus. Abnormalities in SMA-12 tests were followed up by a battery of liver-function tests. Those cases in which the battery showed some major abnormality were subjected to special procedures and treatment. No positive correlation was found between abnormal SMA-12 examinations and workers involved in PVC production, but the incidence of abnormal batteries amongst PVC production workers (10%) was significantly higher than that in workers in other areas of production (4.7%).

The efficiency of the normal SMA-12 in locating liver abnormality has still to be determined, particularly in the light of evidence from a patient who was investigated 2-5 years after being removed from VC exposure because of persistent liver dysfunction (Berk *et al.* Ann. N.Y. Acad. Sci. 1975, 246, 70). At the follow-up investigations, routine tests gave normal values, but histology showed the persistence and possible progression of hepatic fibrosis. Clearance studies using bilirubin, BFP, indocyanine green and chylol glycol showed only the disappearance of chylol glycol to be abnormal. The lack of response in many tests of hepatocellular function was attributed to the relative sparing of hepatocytes in VC-associated fibrosis.

[H.R. Potter]

[Part II of this review, to be published in the next issue of the Bulletin, will be concerned principally with the clinical and histological characteristics of vinyl chloride-induced angiosarcoma, with studies in animals exposed to vinyl chloride and with evidence relating to the mechanism of action and the metabolism of the compound.]

MORE LIGHT ON HEXACHLOROBENZENE

The increased occurrence of hexachlorobenzene (HCB) in the environment has given rise to some concern. It is used as a fungicide to control rust of wheat and can also occur as a waste by-product of chlorinated hydrocarbons

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