

ICPEMC

INTERNATIONAL COMMISSION FOR PROTECTION AGAINST
ENVIRONMENTAL MUTAGENS AND CARCINOGENS

ICPEMC Working Paper TG1/2*/79

Mutagenicity and teratogenicity of vinyl chloride monomer
(VCM)

Epidemiological evidence

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(Received 16 September 1981)

(Accepted 21 September 1981)

The rarity and special character of angiosarcoma hepatis and its association with exposure to vinyl chloride monomer (VCM) has occasionally led to the error that a case of this tumor is tantamount to such exposure. Apart from the possibility that a number of such cases may in the past have been taken for cholangiocarcinomas, the experience of a British team of histopathologists going over cases from Britain during 1963-1973 has revealed some over-estimate of the frequency of this lesion, with the additional experience that only 1 of the agreed 14 cases could be confidently associated with exposure to vinyl chloride (Baxter et al., 1977). It follows that exception must be taken to the conclusion that single cases of angiosarcoma hepatis from the surroundings of poly-vinyl factories may be taken as evidence of an escape directly from the plants or otherwise.

It would, however, be important if mutagenic or teratogenic effects of VCM be demonstrable either in the surroundings of factories or in the domestic environment of workers employed in PVC-producing facilities, and this possibility is the subject of the following review.

* It has been agreed to publish this document as a working paper for Task Group 1 of the International Commission for Protection against Environmental Mutagens and Carcinogens (ICPEMC). The views expressed are those of the author and do not necessarily represent those of the Commission. They are published to stimulate discussion and comments, which will be welcomed by the author. All correspondence and reprint requests should be addressed to the secretary of ICPEMC: Paul H.M. Lohman, Ph. D., Medical Biological Laboratory TNO, P.O. Box 45, 2280 AA Rijswijk (The Netherlands). Tel. 15-138777, telex 38034 pmtno nl (ICPEMC document 158-1981-15.5).

An investigation of a possible increased occurrence of birth defects in the surroundings of PVC plants or among the children of workers has been attempted by Infante (1976) and Infante et al. (1976). The studies were based on data from 4 Ohio communities, of which 3, Ashtabula, Painesville and Avon Lake, had at least 1 polymerization facility in operation, Ashtabula since 1954, Avon Lake since 1946, and Painesville since 1946, with a 2nd plant opened in 1967. The 4th community, North Ridgeville, was near to Avon Lake and was without PVC production. Population numbers ranged from 24000 in Ashtabula to 12000 in Avon Lake. Between the census years 1960 and 1970 the population of Avon Lake increased by 30%, whereas the populations of Ashtabula and Painesville remained about the same.

According to birth-certificate data for 1970-1973, it appeared that while the rate of malformations for the entire State per 1000 live births was 10.14, the rates in the index communities were: Ashtabula, 17.37; Painesville, 18.10; and Avon Lake, 30.33. For these 3 cities with PVC production facilities the differences between observed and expected numbers of malformations in each city were significant at the $P < 0.01$ level according to the χ^2 test. Nevertheless, the highest rates for malformations were found in North Ridgeville, 27.26; and in Geneva, 12 miles from Ashtabula, 25.40, both cities without PVC plants (Infante, 1976.)

Infante, furthermore, found an excess of CNS defects among still-births and live births from the index cities, with the exception of Avon Lake. Most of the excess, however, was attributable primarily to Painesville and secondarily to North Ridgeville. It was therefore obvious that the findings did not link PVC production with the said anomalies.

Edmonds et al. (1975), observing that the increase reported was not uniform and appeared more prominent in the Painesville area, analyzed data collected through the Center for Disease Control's hospital-based Birth Defects Monitoring Programme (BDMP). For 2 hospitals located in cities with polymerization plants, Pottstown in Pennsylvania and Painesville in Ohio, they compared CNS-malformation rates for white infants born during 1970-1974 with the rates for white infants in each State. No increase was seen in the Pennsylvania hospital, but an increase, primarily in anencephaly and spina bifida, was noted in the Painesville hospital amounting to 22 cases, or twice the expected.

After inspection of the birth-defect registry for Ohio, 1 more case could be included in the study, bringing the total to 15. Interviews with parents revealed that none of them had worked at either of the 2 PVC plants in Painesville. However, 2 of the fathers of controls had worked at 1 of the plants. A significantly larger proportion of control mothers than case mothers worked (including housewives) within a 10-mile radius of the PVC plant, which was probably a chance occurrence (95% confidence level).

It was concluded that, although the follow-up confirmed a moderate increase in CNS malformations in Painesville, Ohio, no association had been found with vinyl chloride exposure.

A further study (Edmonds, 1976) of data from hospitals in Pottstown, Pennsylvania, and in Painesville, Ohio, revealed no difference between the cases and the

controls in possible exposure between the cases and plants.

In Kanawha County cases and controls showed no association with VCM.

In a personal communication among wives of workers without the use of controls, attempted a comparison before and after exposure number of rubber-factory. A total of 95 VCM-plant workers was interviewed.

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controls in possible exposure to VCM. Residential histories showed no difference between the cases and controls when compared at various distances from the PVC plants.

In Kanawha County the author found a difference in the pattern of residents for cases and controls living within 3 miles, but the available data suggested no association with VCM.

In a personal communication, Selikoff reported that he had estimated fetal deaths among wives of workers exposed to VCM at 7-14 per 100 pregnancies, although without the use of controls. Referring to this statement, Infante et al. (1976a) attempted a comparison of pregnancy outcome among wives of VCM workers before and after exposure, compared with wives of PVC workers and a similar number of rubber-factory workers matched as a group to the VCM workers by age. A total of 95 VCM-polymerization workers and 158 rubber and PVC-fabrication workers was interviewed in October 1974.

Interviews were conducted with workers, not with their wives. Questions about pregnancy outcome were contained in a much larger interview questionnaire, which was the initial item of a cross-sectional health survey including physical examination. No data were obtained on maternal age, but, on the basis of paternal age, fetal death rates for the primary VCM exposure group were age-adjusted to the control group separately before and after the husband's exposure.

It should be mentioned that Paddle (1976) asked for tabulation of the raw data before analysis finding that age adjustments appeared to have influenced figures misleadingly.

From these data published without delay by Infante et al., (1976b), in combination with those of the first publication, the following observations stand out. Before exposure, the mean paternal age at conception for study pregnancies was 26.4 years and for controls 23.0, with crude fetal death rates of 10.1 and 6.9%, respectively.

Because fetal loss is known to increase with increasing parental age, the fetal death rates for the primary VCM exposure group were age-adjusted to the control group. This reduced the rate for the study group, before exposure, from 10.1 to 6.1%.

Contrarily, the raw rate, after exposure, of 16.5% for the study group versus 8.8% for controls was only slightly influenced by age adjustment, showing 15.8% for the study group, so that Paddle's objection was fully justified.

The asymmetry in age, before exposure, between study group and controls, is paralleled with an asymmetry in numbers of families which, before the husband's exposure, numbered 70 for study families against 62 after exposure, versus 95 and 159, respectively, for control families.

Further objections were raised by Downs et al. (1977) in a critical review prepared for the plastics industry. They pointed out that matching by age should have been based on age prior before employment not on age at the interview, and that age adjustment to the controls' standard, made separately before and after exposure, does not justify comparison of these 2 values. The use of Mantel-Haenszel's test, which requires independence of the 2 rates being compared, is also found incorrect.

Therefore, when the evidence is weighted, it seems that there is no demonstration so far of an effect of VCM as alleged by Infante et al.

References

Baxter, P.J., P.P. Anthony, Mc. Sween et al. (1977) Angiosarcoma of the liver in Great Britain 1963-1973. Br. Med. J., 2, 919-921.

Downs, T.D., R.A. Stallones, R.F. Frankowski et al. (1977) Vinyl Chloride, Birth Defects and Fetal Wastage, The Society of Plastic Industries, 1977.

Edmonds, L. (1976) Birth defects and vinyl chloride. Proceed on Women and the Workplace, Conf., Jan 17-19th, Washington, DC, pp. 114-139.

Edmonds, L.D., H. Falk and J.F. Nissim (1975) Congenital malformations and vinyl chloride. Lancet, 2, 1098.

Infante, P.F. (1976) Oncogenic and mutagenic risks in communities with polyvinyl chloride production facilities. Ann. N.Y. Acad. Sci. 271, 49-57.

Infante, P.F., J.K. Wagoner, Mc. Michael et al. (1976a) Genetic risks of vinyl chloride. Lancet, 1, 734-735 and 1289-1290.

Infante, P.F., J.K. Wagoner and R.J. Waxweiler (1976b) Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride. Mutation Res., 41, 131-141.

Paddle, G.M. (1976) Genetic risks of vinyl chloride. Lancet, 1, 1079.

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