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Formation and Inactivation of a Chemically Reactive Metabolite of Vinyl Chloride[1]

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Formation and Inactivation of a Chemically Reactive Metabolite of Vinyl Chloride. PESSAYRE, D., WANDSCHEER, J. C., DESCATOIRE, V., ARTIGOU, J. Y., AND BENHAMOU, J. P. (1979). *Toxicol. Appl. Pharmacol.* 49, 505–515. The mechanisms responsible for, and protecting against, metabolic activation of vinyl chloride were investigated in the rat. When [^{14}C]vinyl chloride was incubated with hepatic microsomes, a ^{14}C-labeled material became irreversibly bound to microsomal proteins; binding required NADPH, was decreased by CO, SKF 525-A, or glutathione, and was increased by 1,1,1-trichloropropene-2,3-oxide (TCPO). Inhalation of a 5% vinyl chloride atmosphere decreased hepatic cytochrome *P*-450 and glutathione. Pretreatment of the animals with DDT or phenobarbital (I) increased *in vitro* irreversible binding to microsomal proteins measured in the presence, but not in the absence, of TCPO and increased the *in vivo* loss of cytochrome *P*-450 during inhalation of vinyl chloride, but (2) decreased the *in vitro* irreversible binding to 10,000*g* supernatant proteins and the *In vivo* loss of glutathione during inhalation of vinyl chloride. These results are consistent with the views that (1) vinyl chloride is activated by cytochrome *P*-450 into its chemically reactive epoxide, (2) the epoxide may be inactivated by epoxide hydrase or by binding to glutathione, (3) pretreatment with DDT or phenobarbital increases both the formation rate of the epoxide and its inactivation rate by epoxide hydrase, and (4) cytochrome *P*-450 destruction is related to the formation rate of the epoxide, whereas glutathione depletion seems related to only that fraction of the formed epoxide which has escaped inactivation by microsomal epoxide hydrase and has diffused in the cytosol.

Vinyl chloride (chloroethylene) is massively used in the manufacture of plastics: Polymerization of this monomer leads to polyvinyl chloride, the most widely used synthetic plastic (Berk *et al.*, 1976). In workers exposed to vinyl chloride, angiosarcomas of the liver and/or hepatic fibrosis have been observed (Berk *et al.*, 1976). Hepatic angiosarcomas and liver lesions have been reproduced in experimental animals chronically exposed to vinyl chloride (Torkelson *et al.*, 1961; Lester *et al.*, 1963; Viola *et al.*, 1971; Maltoni and Lefemine, 1975; Prodan *et al.*, 1975).

Several carcinogenic and/or hepatotoxic compounds are transformed by the hepatic microsomal mixed-function oxidase system (MFOS) into chemically reactive metabolites that (1) covalently bind *in vitro* to microsomal proteins, (2) covalently bind *in vivo*

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Letters continued

A situation in which such a family with a latent, inherited disorder has suffered unexpected toxicity from an exposure, and in which the relationship of the affected individuals has initially escaped notice, remains to be reported. This family demonstrates the potential for such a circumstance.

Wynder[7] has used the term "metabolic epidemiology" in proposing integrated, interdisciplinary studies to define the extremes of risk for disease. The identification of subpopulations within the community at elevated risk for exposure related illness is one aspect of this approach.

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References

1. Clayton DG: A model for association in bivariate life tables and its application in epidemiological studies of family tendency in chronic disease incidence. *Biometrika* 65:141, 1978.
2. Calabrese EJ: Will elevated levels of lead exposure precipitate clinical symptoms of porphyria in individuals with the latent condition? *Med Hypotheses* 4:282, 1978.
3. Magnussen CR, Levine JB, Doherty JM, et al: A red cell enzyme method for the diagnosis of acute intermittent porphyria. *Blood* 44:857, 1974.
4. Fagius J and Grönqvist B: Function of peripheral nerves and signs of polyneuropathy in solvent-exposed workers at a Swedish steelworks. *Acta Neurol Scand* 57:305, 1978.
5. Tschudy DP, Valsamis M, and Magnussen CR: Acute intermittent porphyria: Clinical and selected research aspects. *Ann Intern Med* 83:851, 1975.
6. Anderson DE: Familial susceptibility, in Persons at High Risk of Cancer, J. F. Fraumeni, Jr. (Ed.). New York: Academic Press, 1975. pp 39-54.
7. Wynder EL: Metabolic epidemiology. *Lancet* 1:260, 1978.

Log Normal Distribution of the Incubation Period of Liver Angiosarcoma in Vinyl Chloride Polymerization Workers

To-the-Editor. — In the June 1978 issue of the *Journal of Occupational Medicine* (9:427-429), NIOSH presented data on 64 cases of liver angiosarcoma among vinyl chloride polymerization workers.

Fig 1 is a log-probit representation of the cumulative percent of the incubation periods of the vinyl chloride induced liver angiosarcomas. The incubation period is defined as the number of years from first exposure to diagnosis. A straight line was fitted to the data. The median of the incubation period for occupational angiosarcoma is 19.3 years with a dispersion factor of 1.40. The dispersion factor is defined as the anti-logarithm of the logarithmic standard deviation.

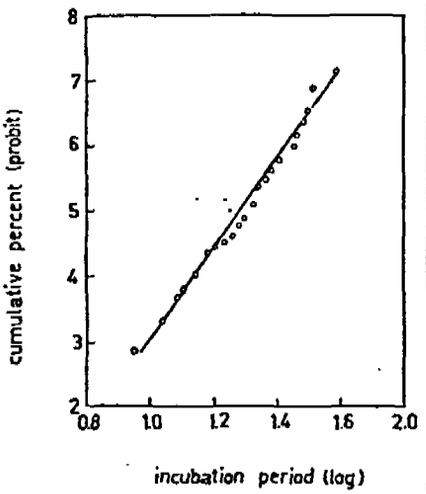

Fig 1. — Log normal distribution of incubation period of 63 liver angiosarcoma cases in vinyl chloride exposed workers. Estimated median (19.3 years) and dispersion factor (1.40) closely resemble those for occupational bladder tumors in the dyestuff industry.

Thus, Sartwell's model[1] of the distribution of incubation periods of infectious diseases applies equally to the distribution of incubation periods in occupational liver angiosarcoma. Armenian and Lilienfeld[2] demonstrated earlier that this was also true for the incubation periods of other neoplasms in humans. The median of the incubation period and the dispersion factor for vinyl chloride induced angiosarcoma of the liver strikingly resemble those calculated by these authors for occupational bladder tumors in the dyestuff industry.

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References

1. Sartwell PE. The distribution of incubation periods of infectious disease. *Am J Hyg* 51:310-318, 1950.
2. Armenian HK and Lilienfeld AM: The distribution of incubation periods of neoplastic diseases. *Am J Epidemiol* 99:92-110, 1074.

Book Review

Patricia Yarvote, M.D.
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Chloroform, Carbon Tetrachloride, and Other Halomethanes: An Environmental Assessment. Prepared by the Environmental Studies Board, Commission on Natural Resources of the National Research Council, 294 pp, $8.95 1978. Report available in paperback from the Printing and Publishing Office, National Academy of Science, 2101 Constitution Avenue, Washington, DC 20418.

The study assesses the scientific and technical information available on a class of potential multimedia environmental pollutants, the nonfluorinated halomethanes. This class of compounds includes the chlorinated, brominated and iodinated methanes. Chloroform and carbon tetrachloride have been considered in greatest detail because there is more extensive data available on these, and they have been demonstrated to be carcinogenic in high doses in test animals.

A quantitative assessment of human and ecosystem exposures and effects is explored in depth as well as sources, concentrations and global mass balances. Various control options are outlined such as changes in water disinfection practices which would reduce locally elevated concentrations of chloroform and other halomethanes at waste-water treatment plants. The economic analysis of benefits and costs associated with control practices is reviewed.

The participants conclude that further studies are needed to evaluate carcinogenesis, mutagenesis and teratogenesis dose-response effects from low-level environmental exposure to halomethanes. Better primary and secondary calibration standards are essential to assure valid and reproducible lab results. More information is also needed on the worldwide distribution of halomethanes in the environment, including the oceans and glaciers.

Although this is a highly technical document of limited interest, it is an important source of information for those involved with this class of compounds. — Patricia M. Yarvote, M.D.

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Cancer Research
Clinical Oncology

Vinyl Chloride and Trichloroethylene: Comparison of Alkylating Effects of Metabolites and Induction of Preneoplastic Enzyme Deficiencies in Rat Liver

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Summary. [1,2-^{14}C] Vinyl chloride and [1,2-^{14}C] trichloroethylene were incubated with rat liver microsomes, NADPH and RNA (from yeast). Whereas trichloroethylene metabolites were irreversibly bound to proteins in microsomal incubations to a higher extent than vinyl chloride metabolites, irreversible binding to RNA was lower for trichloroethylene metabolites. Hydrolysis of the RNA which was reisolated from microsomal incubations with ^{14}C-vinyl chloride or ^{14}C-trichloroethylene and separation of the nucleosides showed different alkylation products arising from vinyl chloride and from trichloroethylene, characteristic for vinyl chloride being formation of 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine. The different reactivities of metabolites of vinyl chloride and of trichloroethylene prompted a comparison of the oncogenic effects of both compounds against the rat liver cell. Newborn rats were exposed for 10 weeks to 2000 ppm vinyl chloride or trichloroethylene (8 h/day; 5 days/week). After this period livers of the animals were stained for nucleoside-5-triphosphatase. Whereas the vinyl chloride exposed rats showed focal hepatocellular deficiencies in this enzyme, which are supposed to represent an early sign of malignancy, no such changes were induced by trichloroethylene exposure. The data therefore suggest differences between the hepatocarcinogenic activity of vinyl chloride and possible effects of trichloroethylene on the liver.

Key words: Vinyl chloride – Trichloroethylene – Rat liver – Liver carcinogenesis – Alkylation

Possible carcinogenicity of trichloroethylene is subject of recent discussion. The close structural relation to the proven hepatocarcinogen vinyl chloride prompted the argument that trichloroethylene, via similar routes of metabolic activation as vinyl chloride, might be cancerogenic (Van Duuren, 1975). Mutagenicity of trichloroethylene metabolites in bacterial test systems (Greim et al., 1975) and cova-

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