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Studies on the Metabolism of Vinyl Chloride

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Vinyl chloride (VCM) is not carcinogenic by itself. it is bioactivated to the highly reactive alkylating oxirane chloroethylene oxide. Further metabolism, apparently, leads via an interaction of the primary alkylating metabolites with glutathion to *S*-(2-carboxymethyl)-cysteine and thiodiacetic acid which are eliminated with the urine. Up to now, it has not been ascertained whether the oxirane alone is the essential carcinogenic factor or whether other metabolites are also involved in carcinogenicity. Likewise, it is still unknown whether the metabolites excreted in the urine might be used as biological criteria for exposure to VCM, because these metabolites probably can originate from a series of substances other than VCM. This problem could stimulate investigations on the possible carcinogenic activity of these substances.

Studies on the pathway of the carcinogenic and mutagenic activity of vinyl chloride (VC) are not only of interest in relation to this special substance. Such studies also allow further insight into the possibly carcinogenic and mutagenic mechanism of chemically related substances which are suspected to be dangerous in occupational exposure. Furthermore, the knowledge of carcinogenic metabolites may furnish us with biochemical criteria to judge the dimension of risk in exposure to potentially carcinogenic and mutagenic substances.

Moreover, research into the carcinogenic activity of VC becomes more and more interesting when we just learn that also tobacco smoke contains about 30 ppb of VC, a concentration which may not be important *per se*, but which could assume increased importance in connection with the other carcinogenic substances contained in the smoke (*1*).

I want to report briefly some investigations which were performed in our country quite recently by Norpoth and co-workers in a working group in Munster in the Department of Occupational Medicine and the hypothesis derived from the results of these experiments.

In 1966 Grigorescu and Toba (*2*) had found chloroacetic acid as a metabolite of VC. This was confirmed in 1974 by Hefner and co-workers (*3*) and in 1975 by Radwan and Henschler (*4*).

Bartsch and colleagues (*5*) then supposed that the presumed intermediary metabolite, chloroethylene oxide, would be really the active alkylating substance because this substance proved to be a strong mutagen as well as VC in the presence of an oxygenating system. Its mutagenic activity in certain sensitive bacteria was superior to the activity of chloroacetaldehyde and chloroacetic acid.

About the same time Green and Hathway (*6*) as well as Norpoth and co-workers (*7*) identified thiodiacetic acid as a conjugated metabolite in the urine of rats which inhaled VC. This finding was in good agreement with the statement of Hefner and colleagues that free SH-groups in the liver, not bound to proteins, are strongly used by VC and its metabolites respectively. Reynolds et al. (*8*), however, were not able to confirm a loss of SH groups. On the contrary, they reported an increase of SH groups. It is not yet clear if this can be explained as a rebound effect.

Hefner et al. supposed *S*-(2-carboxymethyl) cystein to be a further metabolite. This compound has since been confirmed a metabolite of VC by Norpoth and co-workers. Since Yllner (*9, 10*) also found this substance and additionally also thiodiacetic acid to be the main metabolite of chloroacetic acid in experiments

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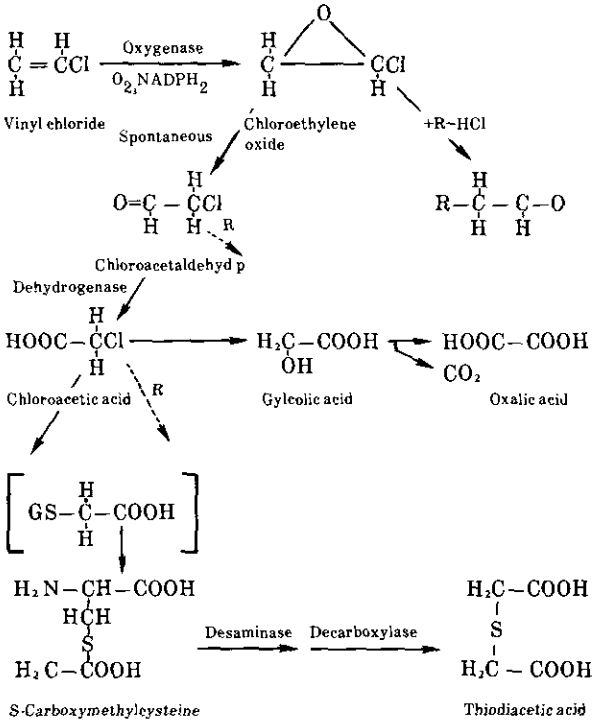
on mice, Norpoth and co-workers were interested in the problem of coincidence of metabolism in mice and men. They analyzed urine samples of patients who were given Ifosfamid, an analog of cyclophosphamide, and stated that a chloroethyl group is cleaved by side-chain oxidation so that choloroacetaldehyde can be produced Indeed, its metabolites could be identified as thiodiacetic acid and *S*-carboxymethyl cysteine. Estimation of the dechloroethylated products shows about 80% of the value related to these products to analyze as thiodiacetic acid and *S*-(2-carboxymethyl) cystein. Thus, the results in mice and men seem to be in agreement (*11*).

Norpoth and colleagues have found thiodiacetic acid also to be a metabolite of dichlorodiethyl ether. Thus, conversion to chloroacetaldehyde is very probable. Chloroacetaldehyde itself may be a carcinogenic substance. With VC certainly the additional formation of chloroethylene oxide is an important factor.

When we try to get a synopsis of the results in metabolic research of VC as presented in the reaction scheme (*1*), the first oxidation step is followed by a chain of detoxicating reactions, some of which occur spontaneously and some of which are enzyme-catalized. The first three



alkylating substances are of decreasing toxicity. They can have biologically alkylating activity, or they may be detoxicated stepwise. Chloroacetaldehyde and chloroacetic acid are known to be toxic substances. New animal experiments by van Duuren (*12*), however, did not prove chloroacetic acid to be a carcinogen.

The results of investigations of Henschler and co-workers (*13*) could be interpreted to indicate that all precursors of oxiranes which are not symmetrically halogen substituted, such as trichloroethylene, and also vinylidene chloride, vinyl bromide, vinylidene bromide, perhaps also vinyl iodide, may be carcinogenic.

Regarding the development of biological criteria for dangerous, carcinogenic, and mutagenic exposure, we have still the problem of the specificity of the criterion.

Thiodiacetic acid can probably originate from: 2-chloroethanol, 2-bromacetic acid, chloroacetic acid, chloroacetaldehyde, bromacetaldehyde, 1,2-dichloroethane, 1,2-dibromoethane, and 1,1,2-trichloroethane.

All drugs containing oxidatively cleavable chloroethyl side chains, such as cyclophosphamide, for instance, are supposed to cause development of thiodiacetic acid.

These hypotheses likewise might be discussed for *S*-(2-carboxymethyl) cysteine which has also been shown to be a naturally occurring substance in the intermediary metabolism.

Most of these investigations have been included *in vitro* tests in mutagenicity. As there exists a close correlation between carcinogenic and mutagenic effects of chemical substances I feel that at present there exists no better possibility to learn about the metabolic activation of carcinogenic substances in a reasonably short time. It should be considered also that there are some difficulties in the interpretation of such experiments, as, for example, in the case of English research workers who just recently were not able to find a mutagenic effect in mice with the dominant lethal test when they exposed the animals to concentrations up to 30,000 ppm of VC.

REFERENCES

1. Hoffmann, D., et al. Chromatographic determination of vinyl chloride in tobacco smoke. Anal. Chem. 48: 47 (1976).
2. Grigorescu, I., and Toba, G. H. Clorura di vinyl. Aspecte de toxicologie industriala. Rev. Chim. Rom. 17: 499 (1966).

3. Hefner, R. E., Jr., Watanabe, P. G., and Gehring, P. J. Preliminary studies of the fate of inhaled vinyl chloride monomer in rats. Ann. N.Y. Acad. Sci. 246: 143 (1975).
4. Radwan, Z., and Henschler, D. Uptake and metabolism of vinyl chloride in the isolated perfused rat liver preparation. Naunyn Schmiedebergs Arch. Exp. Path. Pharmak. Suppl. 287: 100 (1975).
5. Malaveille, C., et al. Mutagenicity of vinyl chloride, chloroethylenoxide, chloroacetaldehyde and chloroethanol. Biochem. Biophys. Res. Comm. 63; 363 (1975).
6. Green, T., and Hathway, D. E. The biological fate in rats of vinyl chloride in relation to its oncogenicity. Chem. Biol. Interactions 11: 545 (1975).
7. Müller, G., and Norpoth, K. Bestimmung zweier Urinmetabolite des Vinylchlorids. Naturwiss. 62: 541 (1975).
8. Reynolds, E. S., et al. Hepatotoxicity of vinyl chloride and 1,1-dichloroethylene. Am. J. Pathol. 81: 219 (1975).
9. Yllner, S. Metabolism of 1,2-dichloroethane-^{14}C in the mouse. Acta Pharmacol. Toxicol. 30: 257 (1971).
10. Yllner, S. Metabolism of chloroacetate-1-^{14}C in the mouse. Acta Pharmacol. Toxicol. 30: 69 (1971).
11. Norpoth, K.: Studies on the metabolism of Ifosfamide in man. Cancer Treatment Reports, 60: 437 (1976).
12. Van Duuren, B. L., Carcinogenic activity of alkylating agents. J. Nat. Cancer Inst. 53: 695 (1974).
13. Greim, H., et al. Mutagenicity *in vitro* and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem. Pharmacol. 24: 2013 (1975).