12/12/75

Mr. F. F. Hoy:

This is the last page of the Dow study on metabolic pathways of VCM. Note the conclusion suggests that VCM may have a threshold and can be detoxified by the body at low concentrations per our recent tel phone conversation.

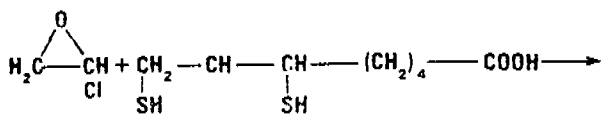
R. S. BROOKMAN

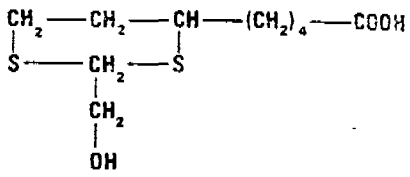
why SK&F-525-A causes a slight inhibition of metabolism in rats exposed to approximately 1000 but not 65 ppm VCM. Also it may explain why monochloroacetic acid may be excreted by rats exposed to 5000 ppm but not 50 ppm VCM. In the former case, chloroacetaldehyde is produced by each of the hypothesized pathways which may result in a greater amount being oxidized to monochloroacetic acid than being conjugated with glutathione and/or cysteine.

Inferences from the results of these studies about the toxicodynamics of VCM are preliminary, but worth mentioning. First, the saturation of a primary metabolic pathway for VCM degradation and redirection through other pathways provides some hope that a threshold concentration for the untoward effect of VCM may exist. Metabolites of VCM formed only via the alternate pathways may constitute the ultimate toxin and carcinogen.

It has been reported that the administration of cysteine or glutathione provides protection against the untoward effects of various aliphatic and aromatic mustards, triethylenemelamine, X-rays, and ionizing radiation[1,2,5,11,15]. Conceivably, cysteine and glutathione may provide a natural defense against tumor-producing free radicals generated within the body, as well as synthetic or naturally occurring alkylating agents which are absorbed into the body. Therefore, reduction of the nonprotein sulfhydryl content of the liver in animals exposed to VCM may constitute predisposition to toxicity and carcinogenicity mediated via other materials.

Finally, the speculated formation of chloroethylene oxide seems particularly pertinent insofar as postulation of the mechanism of carcinogenesis. This compound is undoubtedly a very active difunctional alkylating agent. It is most interesting that inorganic arsenicals have been reported to cause untoward hepatic effects, portal cirrhosis and angiosarcoma, like those reported for VCM[12]. The mechanism of toxicity for arsenic has been shown to occur via its reaction with 6, 8-dithiooctanoic acid (α-lipoic acid)[6]. In this reaction arsenic forms a stable bridge between the two sulfhydryl groups. If chloroethylene oxide were formed, it would readily react with α-lipoic acid, bridging the sulfhydryl groups like arsenic.





Although this postulated mechanism is highly speculative, the rarity of materials known to produce untoward hepatic effects like those of VCM must be given some weight.

ACKNOWLEDGMENTS

These studies were supported in part by a grant from The Manufacturing Chemists Association. The technical advice of Dr. B. K. J. Leong in designing the inhalation apparatus and the critical review of the manuscript by Dr. V. K. Rowe are gratefully acknowledged.

REFERENCES

1. Ball, C. R. 1966. Biochem. Pharmacol. 15:809-816.
2. Calcutt, G., T. A. Connors, L. A. Elson and W. C. J. Ross. 1963. Biochem. Pharmacol. 12:833-837.
3. Carter, E. A. and K. J. Isselbacher. 1972. Lab. Invest. 27:283-286.
4. Dow Chemical Co.—Unpublished data.
5. Goldenthal, E. I., M. U. Nadkarni and P. K. Smith. 1959. Rad. Res. 5:571-583.
6. Gonsalus, I. C. 1953. J. Cell. Comp. Physiol. 41 (suppl. 1):133.
7. Heim, W. G., D. Appleman and H. T. Pyfrom. 1955. Science 122:693-694.
8. Johnson, M. K. 1965. Biochem. Pharmacol. 14:1383.
9. Johnson, M. K. 1967. Biochem. Pharmacol. 16:185-199.
10. Maltoni, C.—to be published in Ann. N.Y. Acad. Sci.
11. Patt, H. M. 1953. Physiol. Rev. 33:35-76.
12. Popper, H. National Institute of Health, Bethesda, MD. Personal Communication.
13. Sedlak, J. and R. H. Lindsay. 1968. Anal. Biochem. 25:192-205
14. Soliman, M. R. I., H. D. Johnson and A. E. Wade. 1974. Drug Metab. and Disposition. 2:87-96.
15. Stacey, K. A., M. Cobb, S. E. Consens and P. Alexander. 1958. Ann. N.Y. Acad. Sci. 68:657.
16. Wagner, E. R. and Muelder, W. W. in press. Ann. N.Y. Acad. Sci. (1974).
17. Zief, M. and C. H. Schramm. April 18, 1964. Chem. Ind. 660-661.

OCC 0714