Conference on Comparative Metabolism and Toxicity of Vinyl Chloride-Related Compounds: Overview and Summary

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I suspect that there is little more that can be said about the metabolism and toxicity of halogenated olefins that has not been said at this meeting. Although I have faithfully attended and taken notes on all papers presented here, it would be foolhardy for me to attempt to make either complimentary or critical comments about each and every paper.

In the first session of this conference we learned of factors that influence the tumorogenicity, demonstrated experimentally, not only with the now-infamous vinyl chloride, but also with vinylidene chloride, hexachlorocyclobutadiene, trichloroethylene, and several other related compounds tested in the National Cancer Institute’s carcinogen screening program. Clearly, it would seem, the halogenated olefin class of compounds will be considered presumptive carcinogens. Are there ways to predict, short of long-term animal testing, whether or not a particular halogenated olefin represents a carcinogenic hazard? Papers by Drs. Henschler, Hathaway, Van Duuren, Leibman, and Van Dyke dealt with biological activity as a function of chemical and physical-chemical characteristics of compounds. Consideration of these relationships coupled with metabolic considerations may provide testable theoretical proposals for predicting the mutagenic and carcinogenic potential of halogenated aliphatic and olefinic compounds. Papers by Dr. Rosenkrantz and others suggest the usefulness of certain in vitro test systems for further evaluating mutagenic and carcinogenic potential.

Exciting as these possibilities are, several reports at this conference have raised the question as to whether some of the conventional indices of hepato- and nephrotoxicity produced by the halogenated olefins do not also have predictive value. That is, would detection of injury by these indices suffice to indicate the need to prevent exposures which might, at higher doses or longer times, be carcinogenic? Of course, this possibility is only practical if there is assurance that the surveillance of the health of workers or others who might be exposed to these compounds is adequate to detect the early and reversible indices of injury and that such detection leads to correction of the exposure conditions that resulted in early injury. I seriously doubt whether we have a sufficient data base on dose-response and time-response relationships for reversible chemical injury and irreversible events (as carcinogenesis) to adopt such an approach. However, the acquisition of data that may permit evaluation of such possibilities is an obvious area for research and should guide hypothesis formulations and experimental design.

We heard frequent mention of pharmacokinetic considerations as determinants of the toxic responses to halogenated olefins. Are the concepts of saturable metabolic pathways and rate-limiting activation and detoxication reactions sufficiently developed to allow us to decide whether or not effects seen in high-dose acute studies have implications for chronic low-dose exposures? Certainly there seems to be hope in this approach, an approach which may even allow monitoring of urinary excretion of metabolites in exposed workers as a means of determining their susceptibility to injury. However, the practical realization of such potential de-
mands that we know what metabolic pathways are important in producing either more or less toxic or carcinogenic metabolites. Indeed, we may be able to account for as much as 95% of a compound’s metabolism, but, if an unidentified metabolite which represents only 1% of the total is the active compound, it will be difficult to convincingly argue that we can evaluate hazard by pharmacokinetic considerations. Nevertheless, the coupling of distribution pharmacokinetics with enzymatic bio-transformation kinetics, or with specific target-molecule reaction kinetics, is the only logical means of attempting to move from empirical considerations in safety evaluation to scientific predictive models.

On the topic of multiple pathways of metabolism, the demonstration that the hepatotoxic action of halothane is enhanced under hypoxic conditions adds a new aspect to our considerations of the metabolism-toxicity relationship for this compound. The report and suggestion that a reductive pathway of metabolism may ultimately provide the toxic, reactive metabolite of halothane illustrates that we must not fall into the trap of thinking that microsomal oxidases are the only critical pathways for activation of these compounds. Indeed, four decades ago, it was the enzymatic reduction of prontosil that was one of the first demonstrations of metabolic formation of a more biologically active derivative of an otherwise inactive drug.

Some evidence was presented at this conference that indicates that the low-frequency occurrence of acute hepatotoxicity in humans exposed to halothane and related anesthetics is not, as once thought, a case of allergic response, but may instead be metabolically based. A logical question might be: What genetic or environmental factors contribute to this metabolic uniqueness?

The demonstration, by Dr. Rosenkrantz, of in vitro mutagenicity of urine samples from anesthesiology staff is, of course, a provocative observation in view of the apparent association of excess incidence of cancer in these hospital personnel. The possible application of in vitro screening methods to detection of presumptive carcinogens in human body fluids will most certainly force the issue of research to corroborate or refute the validity of these tests in the total hazard evaluation process. Perhaps the cytogenetic studies of the type described for vinyl chloride workers by Dr. Purchase will be a part of this evaluation.

We have heard much about covalent binding of halo-olefins and their metabolites. Indeed, non-specific covalent binding to proteins has served well as a means of detecting the formation of more reactive metabolites. However, we have really little information regarding what percentage of this binding, if any, is to critical biological macromolecules. Several papers pointed out the need to separate nonspecific and non-critical binding from critical target site binding, e.g., to nucleic acids or phospholipids. Similarly, it is obvious that glutathione is an important endogenous modulator of halo-olefin toxicity, at least in part because it provides a conjugating molecule for detoxification. It has been suggested that glutathione may act in other ways to protect reactive SH sites in membranes which may be critical target sites.

In short, we seem to have some ideas, but relatively little convincing demonstration of specific target sites, to explain the acute or chronic, non-tumorigenic, toxicity of the halo-olefins. Or does it have to be halo-olefins? Witness Rory Conolly’s observation of hepatotoxicity of ethylene in PCB-induced rats.

And what of interactions? Both the tumorigenicity and other cytotoxic or organ toxicity of halo-olefins have been reported at this conference to be modified by numerous factors: both endogenous, e.g. species, age, sex; and exogenous, e.g. diet, other chemicals, ethanol ingestion. How can these influences be predicted or how should they be taken into account in hazard evaluations? I suspect that the answer to that question will come only when we have a more thorough understanding of the mechanisms by which these interactions occur. Attempts to explain interactions have dealt previously with attempting to manipulate the epoxide hydrolase metabolism system and the glutathione transferase system. Certainly epoxide formation seems to be a central and critical intermediate in the biological activation of most (if not all) of the halo-olefins. Whether or not the use of inducers or inhibitors of epoxidation and of epoxide hydration will provide insight into mechanisms of toxic interactions of halo-olefins will likely be a subject of continuing investigation in a number of laboratories.

Finally, I think this conference demonstrates that in the last five years—since Dr. Viola’s and Dr. Maltoni’s first reports of tumorigenic action of vinyl chloride—we have come quite a distance in understanding the comparative toxicity and metabolism of halo-olefins. I think the conference also has illustrated that we have a lot yet to learn.

I want to thank Dr. Falk and the National Institute of Environmental Health Sciences for giving me, all of us, the opportunity to participate in this very comprehensive updating of the toxicology of this important class of chemical compounds. I think Dr. Falk deserves our highest praise and gratitude for identifying and bringing together all those who gave such excellent papers here.