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Introduction: Session on Metabolism

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Benzene, discovered by Faraday in 1825, and isolated from coal-tar by Hofmann in 1845, was not obtained pure until 1952 when it was synthesized labeled with ^{14}C. Although at that time exposure to benzene was associated with aplastic anemia, its toxicity was not generally considered to be a serious problem and was loosely associated with probable impurities. The material was used freely as an industrial and laboratory solvent and in several household products, and process workers often used benzene in preference of water to clean up at the end of a shift. The synthesis of [1-^{14}C] benzene, its partial purification as the nickel ammonium cyanide clathrate complex, and ultimate chemical purification to constant specific radioactivity revealed that many simple derivatives of benzene described by Beilstein and in the chemical literature were impure and even since have not been adequately characterized. The use of ^{14}C-benzene in metabolism studies over 30 years ago established unequivocally that 1,2,4-trihydroxybenzene, L-phenylmercapturic acid, and *trans-trans*-muconic acid were minor metabolites, a quantitative account was made of the major pathways of metabolism to phenol, catechol and quinol and their conjugates, and its oxidative metabolism to $^{14}CO_2$ and to 2-carbon fragments, which resulted in the incorporation of ^{14}C into tissue proteins and fatty acids, was established.

Benzene is radiomimetic, a property probably associated with its causation of aplastic anemia and possibly also with its carcinogenicity as, similar to radiation-induced malignancy, benzene-induced malignancy is characterized by a multiplicity of tissue sites. This contrasts with the monohalobenzenes that are not radiomimetic, probably not carcinogenic, and are metabolized mostly by epoxidation to give the corresponding catechols and phenylmercapturic acids, which are only minor metabolites of benzene. Hence, the unique toxicity of benzene may well be associated with unique aspects of its metabolism such as the ring scission product mucondialdehyde, or one or more of the polymeric polyphenols formed from the primary phenolic metabolites. However, there is no doubt that multiple mechanisms are involved in benzene toxicity and carcinogenicity, and these may include synergism between different metabolites, such as benzoquinone and mucondialdehyde as suggested by Snyder (*1*), or synergism between glutathione-depleting metabolites of benzene and hydroxyl radicals, generated by futile cycling of cytochrome P-450 or possibly by redox cycling of quinonoid metabolites. Indeed, the formation of DNA adducts from metabolites of benzene may be of minor importance, as the indications are that benzene and its metabolites are only weakly genotoxic, at least in man.

Recent studies on the cytochrome P-450 superfamily of mixed-function oxidase enzymes have indicated that one major family, namely, the cytochromes P-448 (P450 I), are primarily responsible for the activation of carcinogens and toxic chemicals, while most other families of the cytochromes P-450 result in their detoxication. Determination of the conformations of the active sites of these different cytochromes P-450 has enabled chemicals to be characterized by computer graphic calculation of their spatial conformations and electronic structures, as substrates of the cytochromes P-448 (P450 I) or cytochromes P-450, and thus to be identified as potential carcinogens, mutagens, co-carcinogens, or promoters. By these procedures, benzene is classified as a weak carcinogen and as a substrate of both the cytochromes P-448 and P-450. Indeed benzene is a preferential substrate of one particular family of cytochromes P-450, namely cytochrome $P\text{-}450_{ALC}$ (P450 II E), which metabolizes alcohol, benzene, and aniline, is known to be induced by these substrates and is associated with the generation of hydroxyl radicals, probably formed by futile cycling of the cytochrome. The toxicity of alcohol, particularly in necrosis of the gastrointestinal tract, is known to be associated with oxygen radical production. The possibility, therefore exists of a synergism between alcohol and benzene, and of the role of reactive oxygen and the formation of circulating lipid peroxides in the hemopoietic toxicity and carcinogenicity of benzene. It would be valuable to know if the reconstituted cytochromes P450 I, P450 II B, and P450 II E, metabolize benzene to different products.

It should be remembered that the microsomal

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cytochromes P-450 are not confined to the liver but are ubiquitous to all tissues and that they are also found in the endoplasmic reticulum of leukocytes. Hence, the known activation of bone marrow macrophages by benzene (*2*) may involve induction of cytochrome P450 II E with subsequent generation of reactive oxygen radicals.

These and many other new developments in the metabolism, toxicity, and carcinogenicity of benzene were presented and discussed by leading researchers in the field at the recent symposium organized by Drs. Lucier and Snyder and their committee. Nevertheless, many problems remain, including the pathways of metabolism in man, the chemical nature of the ultimate toxic metabolites, the mechanism of benzene carcinogenesis and, in particular, the risk assessment of exposure to benzene present in automobile fuels and exhaust emissions.

REFERENCES

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