CC/NUMBER 36
SEPTEMBER 5, 1983

This Week's Citation Classic

Jerina D M & Daly J W. Arene oxides: a new aspect of drug metabolism. *Science* **185**:573-82, 1974.
[Sect. on Oxidation Mechanisms and Sect. on Pharmacodynamics, Lab. Chemistry, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, Natl. Insts. Health, Bethesda, MD]

The monooxygenase-catalyzed formation of phenols from aromatic substrates is a well-recognized biochemical pathway in animals, plants, and higher microorganisms. Arene oxides have been demonstrated as precursors of these phenols as well as numerous other secondary metabolites. The 'arene oxide pathway' constitutes an important and requisite part of normal cellular function. But for certain compounds, the metabolic formation of arene oxides represents the onset of toxic and carcinogenic processes within the cell. [The *SCI*® indicates that this paper has been cited in over 775 publications since 1974.]

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May 31, 1983

"Prior to 1968, the pathway by which monooxygenase enzymes convert aromatic substrates into phenols was unknown but was generally thought to consist of an insertion of oxygen into the carbon-hydrogen bond. Our entry into this area stemmed from attempts to develop rapid, simple radiometric assays for the enzymatic formation of phenols. The principle of these assays was the anticipated release of tritium during insertion of oxygen into a specific carbon-tritium bond. This approach had worked admirably for tyrosine hydroxylase.[1] *But for other 'aryl hydroxylases,' including the cytochromes P450, a far from stoichiometric release of tritium was observed compared to product formed.* In an attempt to develop an assay for phenylalanine hydroxylase with purported 4-tritiated phenylalanine, Gordon Guroff had become suspicious of the specificity of labeling of the substrate, since the 4-hydroxylated product tyrosine contained considerable tritium. The problem was resolved through the use of specifically 4-deuterated phenylalanine, which the enzyme converted to 3-deuterotyrosine.[2] This discovery of migration and retention of aryl ring substituents on hydroxylation by monooxygenases led to a stimulating and rewarding team effort involving members of both Bernhard Witkop's and Sidney Udenfriend's laboratories at the National Institutes of Health (NIH), and Udenfriend coined the imaginative term, the 'NIH shift,' to describe the phenomenon.[3]

"Research was directed toward establishing the mechanism of this novel reaction. Although discrete ionic species could be invoked, arene oxides, which are epoxides of formal aromatic double bonds, represented mechanistically attractive intermediates. K-region arene oxides of polycyclic aromatic hydrocarbons had been known for several years and were quite stable, while benzene oxide and other non-K-region arene oxides had just been synthesized and were quite unstable (reviewed in references 4 and 5). Despite the failure of our initial attempts to demonstrate that benzene oxide was the initial liver microsomal metabolite of benzene, a new microsomal enzyme, epoxide hydrolase, was identified and shown to catalyze the trans addition of water to arene oxides to form dihydrodiols. Cytosolic glutathione transferases were found to catalyze the addition of glutathione to benzene oxide. Studies with the more stable naphthalene 1,2-oxide allowed its characterization as the initial metabolite of naphthalene and provided the proof that it was the requisite intermediate in the formation of naphthol, the trans 1,2-dihydrodiol and a glutathione conjugate.[6,7] Numerous studies from these and many other laboratories followed which established the germinal role of arene oxides in the metabolism of aromatic hydrocarbons by monooxygenase enzymes.

"We believe that the extensive citation of our article stems from its impact on concepts in drug metabolism. The article not only drew attention to a new and major pathway by which drugs and other xenobiotic compounds are metabolized and excreted, but also emphasized the fact that highly reactive arene oxides could be responsible for the toxic and carcinogenic effects of certain aromatic hydrocarbons. Since writing the article one of us (J.W.D.) has concentrated his efforts in the area of neurochemistry, while the other (D.M.J.) has continued research in the field and has been the recipient of the 1982 B.B. Brodie Award for research in drug metabolism. A new review on the chemistry and biochemistry of arene oxides will shortly be available."[8]

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3. **Guroff G, Daly J W, Jerina D M, Renson J, Witkop B & Udenfriend S.** Hydroxylation-induced migration: the NIH shift. *Science* **157**:1524-30, 1967.
4. **Vogel E & Gunter H.** Benzene oxide-oxepin valence tautomerism. *Angew. Chem. Int. Ed.* **6**:385-401, 1967.
5. **Jerina D, Yagi H & Daly J W.** Arene oxides-oxepins. *Heterocycles* **1**:267-326, 1973.
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7. ----------. The role of arene oxide-oxepin systems in the metabolism of aromatic substrates. III. Formation of 1,2-naphthalene oxide from naphthalene by liver microsomes. *J. Amer. Chem. Soc.* **90**:6525-7, 1968.
8. **Boyd D R & Jerina D M.** Arene oxides-oxepins. (Hassner A, ed.) *Small ring heterocycles.* New York: Wiley. Vol. 42. Part 3. In press, 1983.

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