

Role of Cytochrome P450s in the Metabolism and Affects of Low Molecular Weight Alkenes

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CIIT staff evaluated the use of CYP2E1-null mice in toxicity and carcinogenicity studies with acrylamide (AM), acrylonitrile (AN), styrene, and butadiene. For these chemicals, adverse responses are believed to follow metabolic activation to epoxides, and cytochrome P4502E1 (CYP2E1) has been implicated to have a role in the conversion of the parent compound to the epoxide. Polymorphisms in CYP2E1 are considered important risk factors in the development of cancer and other diseases in humans. This effect may be related to the ability of CYP2E1 to increase or decrease the activation of a large number of known carcinogens which humans encounter in the environment. A major objective of this project included determining the role of CYP2E1 in the metabolism and short-term adverse effects of AM, AN, styrene, and butadiene. A second objective of this project is to determine if mice devoid of P4502E1 or mice pretreated with an inhibitor of cytochrome P450s have alternative pathways of metabolism that may lead to formation of additional toxic metabolites. The results of this study provide important data concerning the use of CYP2E1-null mice in toxicology testing, since an initial important first step in using these animals is to better understand the metabolism and dosimetry of compounds in both wild type and CYP2E1 null mice.

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Presentations(s):

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