Probing the Mechanisms of Toxicity and Cellular Repair in Carcinogenesis

“The balance between cellular damage and repair ultimately determines the potential risk to humans who are exposed to toxic chemicals. It is therefore crucial to understand the mechanisms of damage and repair in order to accurately assess the risk associated with a given level of exposure.”

—Dr. David Dorman, CIIT Centers for Health Research

When a person is exposed to a toxic chemical, the outcome depends on the dose received, the damage caused, and the body’s ability to repair damage. Each of these factors is governed by a range of biochemical and physical mechanisms. Understanding those mechanisms, and the interplay among them, is key to any effort to accurately predict the risk associated with a given exposure.

Recent advances in science and technology have made it possible for researchers to explore and test these mechanisms to a degree never before possible. In this LRI-supported research, scientists from CIIT Centers for Health Research (CIIT) used benzene as a model to probe the mechanisms of damage and repair related to carcinogenesis and to identify approaches that could be used for testing a broad range of toxic chemicals. Their findings and the tools they developed may help improve the accuracy of risk assessments, particularly for low exposure concentrations typically encountered in the environment.

Benzene is a common industrial chemical used to manufacture products such as certain plastics, resins, synthetic fibers, pesticides, over-the-counter and prescription pharmaceuticals, detergents, lubricants, and dyes. It is emitted to the atmosphere through the burning of coal, oil, gasoline, and tobacco, and the evaporation of gasoline and industrial solvents. Tobacco smoke accounts for about half of all exposure to benzene in the United States.

The U.S. Environmental Protection Agency (EPA) has classified benzene as a known human carcinogen. Long-term exposure to high levels of benzene in the air can lead to leukemia, lymphoma, anemia, and other disorders. In response to these risks, EPA regulates benzene emissions through the Clean Air Act, and restricts the level of benzene in drinking water through the Safe Drinking Water Act. The U.S. Occupational Safety and Health Administration (OSHA) has set a workplace exposure limit of 1 part of benzene per million parts of air per work day, and the Food and Drug Administration (FDA) prohibits the use of benzene in foods.

Once inhaled, benzene is absorbed rapidly by the body. However, the effects of long-term exposure depend crucially on what happens next. When it reaches the liver, benzene is metabolized by enzymes into more reactive metabolites. These metabolites are transported to the bone marrow, where they can affect the production of blood cells and the functioning of the immune system.

At various steps along the way, other enzymes may detoxify the metabolites of benzene to less-reactive ones. Damage to cells in the bone marrow may be fixed through the action of DNA repair enzymes, or the damaged cells may undergo programmed cell death to prevent the proliferation of mutated cells that would otherwise lead to cancer. The extent to which these repair processes succeed or fail to function properly determines how a person is affected by long-term exposure to benzene.

Little is known about the effects of long-term exposure to lower concentrations of benzene in non-occupational settings. Furthermore, not all individuals respond to benzene exposure in the same way, which suggests that genetic factors may play a role in susceptibility.

Paths to Toxicity and Repair

This simplified diagram shows various biological processes and events that can happen in response to exposure to benzene.

The Long-Range Research Initiative (LRI), a program of the American Chemistry Council, sponsors research that increases scientific knowledge of the potential impacts that chemicals may have on human health, wildlife, and the environment. Results are publicly available. This LRI Perspective is one in a series of documents that summarize LRI-sponsored research. See www.USLRI.org.
In order to develop reliable dose-response models for benzene, researchers need to understand the metabolic pathways and molecular mechanisms that lead to benzene toxicity. In this research, studies were designed to evaluate the effects of benzene metabolites on target cells in the bone marrow, to identify the mechanisms through which benzene metabolites lead to DNA damage, and to understand how metabolites and enzymes affect the body's repair systems. Studies also were designed to investigate possible genetic reasons behind individual differences in response to exposure to benzene.

To help define the roles of specific enzymes in the toxicity of inhaled benzene, the researchers ran experiments with mice specially bred to lack the ability to produce these enzymes. The investigators exposed these genetically modified mice and a control group to benzene, and then analyzed them for genetic damage and other responses.

Another study examined genetic effects on bone marrow and blood-cell-forming stem cells of mice that were exposed to benzene.

Researchers also investigated the toxicity of one of benzene's reactive metabolites, 1,4-benzoquinone, in human bone marrow precursor (progenitor) cells. This study was designed to examine the molecular mechanisms associated with DNA damage and repair in target cells.

The LRI-sponsored research has defined the role of key enzymes in benzene toxicity and the repair of cellular damage resulting from exposure to benzene. Specially bred (transgenic) mice that lacked one of these enzymes failed to produce toxic metabolites from benzene and were thus protected from its toxic effects. This observation demonstrated that the breakdown of benzene by enzymes is required for toxicity. These results will help researchers understand and predict how individuals may vary in their susceptibility to toxic effects from exposure because the amount of this enzyme varies significantly across individuals, and people with higher levels of the enzyme may be at greater risk.

Male and female mice respond differently to benzene exposure. These gender differences likely relate to the amount of benzene absorbed by inhalation and differences in the activity of key enzymes involved in benzene metabolism. It is not clear if humans exhibit similar gender differences in response to benzene exposure. The investigators studied benzene toxicity in human blood cells that had been produced from human stem cells. The toxic response of these cells to a key benzene metabolite was similar for cells from both genders, suggesting that risk assessments based on current approaches are likely to be adequate to protect men and women.

Exposure to reactive metabolites of benzene can lead to DNA damage in the bone marrow and in other organs. If left unrepaired, this damage could result in abnormalities in blood cell formation. The research showed that expression of the DNA repair genes in human bone marrow stem cells is likely to repair efficiently the damage caused by low levels of benzene and its metabolites.

In a separate project, LRI-sponsored researchers are exploring the role of individual susceptibility to carcinogens, using benzene as a model chemical. This study measures biomarkers of benzene metabolism and individual genetic profiles in a large number of individuals who have been exposed to benzene. For more information, visit http://www.uslri.com/documents/cat_4/doc_410.doc.

Ultimately, this research will help improve the accuracy of assessments of risks posed by benzene and other chemicals for realistic exposure levels in the environment and for occupational settings. EPA currently uses low-dose linear extrapolation in its cancer risk assessment model for benzene and many other chemicals, primarily due to uncertainties about the biological mechanisms of toxicity. As scientists learn more about these mechanisms, risk assessors will be able to develop a better understanding of the shape of the dose-response curve and more accurately predict risk at low doses.