Hexachlorobenzene Exposure

Widespread Toxicant Produces Pervasive Effects

Toxicogenomics work in a rat model system has given new insight into how chemical toxicants can effect large-scale stress responses in the immune system [***EHP* 112:782–791**]. This month, Janine Ezendam and colleagues at Utrecht University, the Netherlands National Institute for Public Health and the Environment, and Novartis Pharma in Basel, Switzerland, use gene expression analysis to examine the impact of subchronic exposure to an important environmental toxicant, hexachlorobenzene (HCB), on multiple organ systems. They find that previously noted effects and newly discovered ones come together in a dramatic inflammatory response that touches multiple systems in exposed animals.

Primarily an antifungal pesticide, HCB has been out of commercial use in the United States since 1965 and is banned in many countries. Yet new HCB still enters the environment as a by-product of several activities, including the manufacture of other chemicals, wood preservation, and the burning of municipal garbage. It can build up in wheat, grasses, and some vegetables. With a half-life in soil of up to six years, the once widely used chemical is still found concentrated in fish, marine mammals, birds, and lichens, as well as in grazing animals that eat lichens or grass, and in animals that eat fish. It turns up in the human food supply in contaminated dairy products, meat, and fish. Low levels have been identified in the fatty tissue of almost all people tested, according to the Agency for Toxic Substances and Disease Registry.

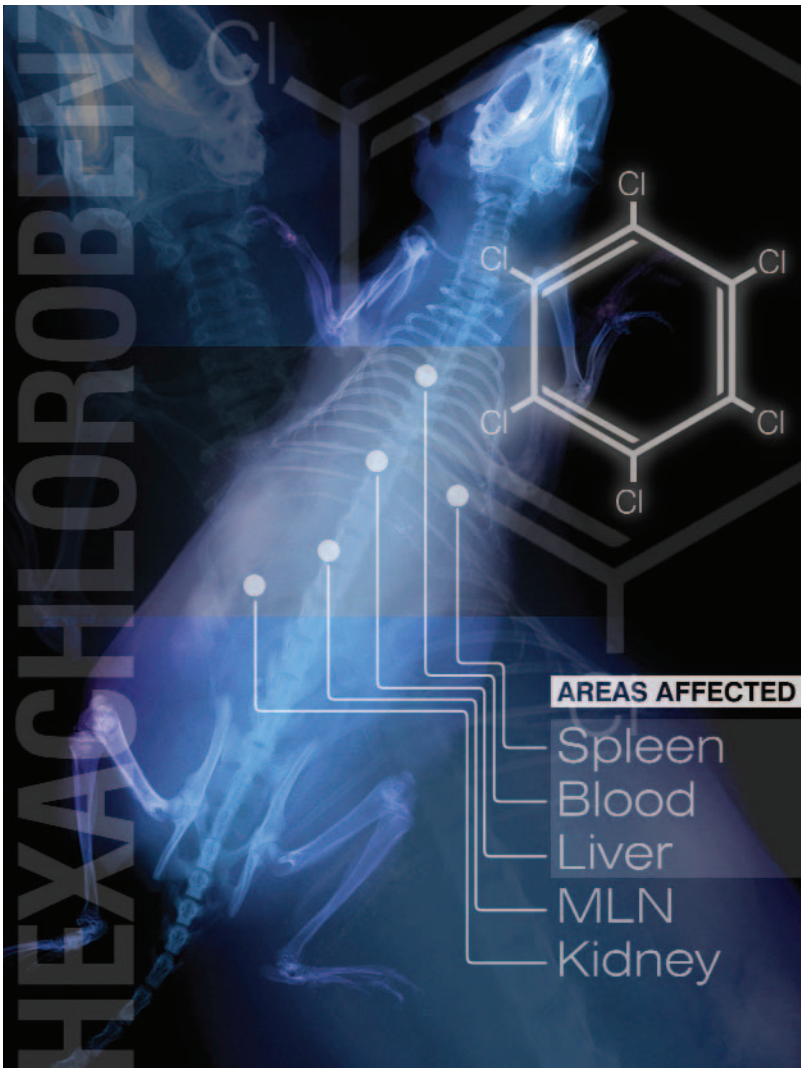
The accidental exposure of 3,000–5,000 people in Turkey between 1955 and 1959 provided a deeper, albeit tragic, understanding of HCB's effects in exposed individuals and in children born following maternal exposure. Humans and rats have been found to share many responses to HCB exposure, including porphyria (a buildup of porphyrins, the ring-shaped building blocks of heme, that results in skin lesions), neurotoxic effects, reproductive effects, and immune effects. Single small doses are relatively nontoxic, but continued exposure, even to small amounts, leads to breakdowns in health.

Brown Norway rats are especially susceptible to the immune effects of HCB. Ezendam and colleagues exposed Brown Norway rats for four weeks to ingested HCB at concentrations up to 450 milligrams per kilogram. Using DNA microarray analysis, the team demonstrated the impact of HCB on gene expression in the spleen, mesenteric lymph node (MLN), thymus, blood, liver, and kidney. Probing microarrays revealed substantial changes in gene expression in the spleen, blood, liver, kidney, and MLN. Overall, gene expression in the spleen, blood, and liver responded in a dose-dependent way to changes in HCB exposure. Changes in the kidney and MLN were less dose-dependent, and the thymus, an organ not believed to be an HCB target, showed few changes.

Genes related to the inflammatory response were among the strongest responders. Expression of genes related to macrophages were noted in the spleen, MLN, and liver. All of these organs house macrophages, phagocyte immune cells that secrete chemokines and cytokines, the signaling molecules that coordinate the overall immune response. These changes were in line with the known significance of macrophages in rats' response to HCB.

Several inflammation-promoting elements, including interleukin-6 (a cytokine that works across the immune system, promoting B cell and macrophage differentiation as well as T cell growth) were induced in different tissues by the exposure. Members of the mitogen-activated protein kinase family of signal transduction molecules were induced in the kidney, and a transcription factor known as signal transducer and activator of transcription 1 was induced in the liver. This suggests that the response to HCB exposure includes both up- and downregulation of cytokine signaling. Further expression in the liver and kidney, as well as in the spleen and MLN, included genes related to oxidative stress and antioxidants, to components of the complement pathway, to chemokines and their receptors, and to cell adhesion molecules.

Taken together, the data provide a big-picture view with considerable detail: the pattern of gene expression indicates that exposure to HCB triggers an inflammatory response that touches all of the organ systems studied except the thymus, as well as other effects not related to the immune system. The gene expression profiles confirm known elements of the pathology induced by HCB and extend them with insights about the involvement of other factors, including cytokines, chemokines, antioxidants, and other factors. A complete list of significant changes in gene expression, including many genes not discussed directly in the paper, can be found at ArrayExpress, the European Bioinformatics Institute's public repository for array data, at **http://www.ebi.ac.uk/arrayexpress/**. **–Victoria McGovern**



Multiple wounds. The toxicant hexachlorobenzene inflicts multisystemic damage through initiation of an inflammatory response.

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