Clarifying Dioxin's Cellular Invasion

Setting acceptable human exposure limits for TCDD – the most toxic member of the dioxin family – has spawned controversy since the 1970s, when animal research suggested that even trace quantities of this industrial byproduct might cause cancer. Two new studies now offer clues to the multi-step process whereby TCDD penetrates the nucleus of a cell and affects its genetic material.

The new findings support an emerging theory that the first step in TCDD's toxicity involves its binding to a protein, called a receptor, in the liquid interior of cells. If a certain minimum quantity of this chemical must accumulate before triggering the crucial binding of that receptor, as some scientists suspect, trace amounts of dioxin might have no adverse health effects. If so, identifying that no-effect threshold might allow regulatory agencies to establish a "safe" limit for the pollutant.

A research team led by Oliver Hankinson at the University of California, Los Angeles, has now isolated the biological substance, also a protein, that allows receptor-bound dioxin molecules to successfully invade a cell's nucleus, where its genetic material resides. In the May 17 SCIENCE, the group reports finding that even though the new protein does not bind to TCDD, it must accompany this dioxin or the toxicant will never penetrate the cell nucleus. "We showed that this factor [new protein] is necessary for the receptor-dioxin complex to move into the nucleus," says Hankinson.

His team also showed that without the new protein, TCDD could not turn on a gene for the production of a normally detoxifying enzyme. But with the protein, TCDD spurs the production of this enzyme, a member of the P450 family. P450 enzymes initiate a biochemical process that renders toxic chemicals more soluble in water, so that they can be excreted more readily by the body. But sometimes P450 makes contaminants more toxic instead. TCDD's stimulation of P450 production might therefore indirectly increase levels of other toxicants in the body. But the enzyme does not break down TCDD, leaving researchers uncertain about the direct mechanism through which TCDD causes its toxic effects.

In a second study, Thomas A. Gasiewicz of the University of Rochester (N.Y.) School of Medicine and his colleagues at the Stanford University School of Medicine showed that mixtures of TCDD and the receptor protein alone cannot bind to DNA. But when the researchers mixed TCDD and the receptor with fluid taken from ground-up cells, the complex indeed bound to DNA.

These results, reported in the March 19 BIOCHEMISTRY, suggest a second protein is involved in dioxin's action, Gasiewicz says. When his group measured the size of the complexes that did bind DNA, the researchers found they were larger than the receptor and dioxin combined – further supporting the theory that a second mystery protein was involved.

Gasiewicz and his co-workers have yet to isolate the second protein, but it appears similar to the one now reported by Hankinson's group. In fact, Gasiewicz told SCIENCE NEWS, "We think we could be looking at the same protein."

The two studies support an emerging TCDD-toxicity model, says Linda Birnbaum, director of environmental toxicology at the Environmental Protection Agency's (EPA) Health Effects Research Laboratory in Research Triangle Park, N.C. Earlier this year, dioxin researchers met at Cold Spring Harbor Laboratory on Long Island, N.Y., to iron out a model that might explain why TCDD sometimes appears nontoxic at low levels. The new work "is in support of that model," says Birnbaum.

What's "interesting and exciting" about the two new studies "is ... that they introduce more complexity" into the model for how TCDD works, Birnbaum observes. Each added level of complexity introduces a point that could require the buildup of certain minimum TCDD levels before triggering the next event in some chain of reactions that ultimately culminates in toxicity. If that is true, she says, TCDD might indeed prove nontoxic at levels below the threshold. Gasiewicz also points out that a need for the second protein may explain why TCDD's apparent toxicity varies so widely among different tissues and species.

In April, following the Cold Spring Harbor meeting, EPA Administrator William K. Reilly directed his agency to conduct a year-long reassessment of TCDD's health risks in light of the new model for this dioxin's actions.

"What EPA is going to do over the next year is work up a receptor-based model for dioxin," says Birnbaum. But, she cautions, "we don't yet know if those risk assessment models are going to be more, or less, restrictive" than current guidelines for dioxin exposure.

Ellen Silbergeld, an environmental toxicologist at the University of Maryland School of Medicine in Baltimore contends that "it would be extremely premature to make global regulatory decisions" based on the assumption that extra receptor-binding steps might mean there is a safe level of TCDD. Silbergeld, who is also an adjunct scientist to the Environmental Defense Fund, says there is no evidence that the dioxin receptor needs a specific accumulation of TCDD before it binds.

– C. Ezzell

New lead rules for water

The Environmental Protection Agency has issued new standards intended to dramatically reduce levels of lead in U.S. drinking water. The new rules "will reduce lead exposure for approximately 130 million people," especially children, said EPA Administrator William K. Reilly in announcing the move last week. "We estimate approximately 600,000 children will have their blood lead content brought below our level of concern because of these standards."

EPA ordered a phaseout of leaded gasoline in 1984 and banned leaded solder in 1986. Drinking water remains the largest lead source over which EPA maintains regulatory control.

The new rules, initially proposed almost three years ago (SN: 8/20/88, p.118), will force municipal water suppliers to monitor lead levels beginning in 1992 and 1993. In at least 90 percent of monitored households, tapwater lead values must not exceed 15 parts per billion, which "corresponds to an average level of approximately 5 ppb," according to EPA. The existing standards for drinking water allow an average lead level of 50 ppb.

When suppliers identify problem areas, they will have to lower the water's acidity with chemical treatment. Acidity increases water's ability to leach lead from the pipes through which it passes. Where residential water supplies flow through lead service pipes, such anticorrosive chemical treatment may not reduce lead leaching to acceptable levels; in these instances, the new rules give water suppliers 15 years to replace their lead plumbing.

Whereas EPA's previous standards permitted water providers to monitor lead levels anywhere in their distribution systems, the new standards require water utilities to measure lead where and when levels will be highest: at a customer's faucet, first thing in the morning. Suppliers must also focus their monitoring efforts on households at high risk: those whose water comes through lead service pipes or whose plumbing joints have been sealed with leaded solder since 1982. □