EPA Moves to Reassess the Risk of Dioxin

Urged on by the scientific community, EPA is developing a new model for estimating dioxin's risk

GALVANIZED BY THE RESULTS OF A RECENT scientific meeting on dioxin's molecular actions, Environmental Protection Agency (EPA) administrator William K. Reilly has launched a major new effort to reassess the toxicity of this ubiquitous—and infamous—chemical.

Responding to criticism that the model EPA now uses to assess dioxin's risk is obsolete, Reilly has asked agency scientists to come up with a new "biologically based" model that will draw on an emerging understanding of the first steps that take place as dioxin enters a cell (for example, see pages 924 and 954). Reilly and others call the new effort "precedent-setting" not only for how the agency regulates carcinogens but also for EPA's quick response to new scientific developments—not its strong suit in the past.

Until now, EPA has gauged the risk of dioxin exposure by using the same model it applies to most carcinogens: the linear multistage model, which assumes that risk rises in proportion to dose. Agency officials have long viewed the model as a "default"—one adopted for lack of a real understanding of how carcinogens work—and their intent was always to replace it with something more realistic once mechanisms were understood. But so far, they say, such evidence has been lacking. Now it may at last be in hand, at least for dioxin and perhaps a handful of other chemicals that behave similarly.

The turning point came in an 8 March briefing for Reilly and his top deputies given by three agency scientists: William Farland and Peter Preuss, both at EPA headquarters in Washington, D.C., and Linda Birnbaum of EPA's Health Effects Research Laboratory in North Carolina. Part of the briefing was devoted to recent epidemiologic studies, including the new one by Marilyn Fingerhut of the National Institute for Occupational Safety and Health (NIOSH), which found perhaps the strongest link yet between high doses of dioxin and human cancer (see *Science*, 8 February, page 625). The EPA scientists also discussed a reanalysis of data from a 1976 study of cancer in dioxin-exposed rats that figured heavily in EPA's original risk assessment. After reexamining the original slides of liver tissue, investigators have concluded that the animals developed fewer tumors than was originally believed.

But it was Birnbaum and Farland's description of a meeting last November at the Banbury Center at Cold Spring Harbor Laboratory that Reilly says made the most compelling case for change. At that meeting a group of dioxin experts agreed that before dioxin can cause any of the ill effects it has been linked to—cancer, immune system suppression, chloracne, and birth defects—one "necessary but not sufficient" event must occur: the compound must bind to and activate a receptor, known as the aryl hydrocarbon or AH receptor (see *Science*, 8 February, p. 625). After that, the dioxin-receptor complex is transported to the nucleus, where it binds to specific sequences of DNA and turns genes on and off, thereby causing its myriad effects. It had long been known that dioxin binds to a receptor, but before the Banbury meeting it had been unclear whether all of dioxin's effects or just some were mediated this way.

Key mover. *Linda Birnbaum had been urging EPA to change how it does dioxin risk assessment.*

The Banbury group also agreed that dioxin has to occupy a certain number of AH receptors on a cell before any biological response can ensue. The result is a practical "threshold" for dioxin exposure, below which no toxic effects occur. That conclusion flies in the face of the linear model's underlying assumption: that the risk of harmful effects begins with exposure to a single molecule and increases from there. Faced with this new picture of dioxin's action, the Banbury participants urged EPA to develop a new, receptor-based model for dioxin risk assessment.

Reilly bit. He has now asked scientists in EPA's Office of Research and Development, in collaboration with academic researchers around the country, to come up with just such a model. The goal, explains Michael Gallo of the Robert Wood Johnson Medical School, one of the organizers of the Banbury meeting who is now working with EPA, is to pinpoint the threshold or "safe" dose below which none of dioxin's ill effects should occur.

In building the model, Gallo and his EPA colleagues hope to draw on work on the dioxin receptor now under way in a number of labs around the country. In this issue of *Science*, for example, a group headed by Oliver Hankinson of the University of California at Los Angeles reports on the cloning of a protein that is necessary for the receptor to function. Various roles have been proposed for the new protein; one intriguing possibility is that it is part of the receptor itself. The dioxin receptor thus might contain at least two proteins, one that binds to dioxin (and presumably whatever natural molecule dioxin mimics) and another that binds to DNA. "Boy, is that exciting," says Gallo, who adds that the new findings will feed directly into the model.

Until the model is complete, no one can say for sure whether it will show dioxin to be more or less risky than EPA now calculates, though Gallo and others speculate that it will turn out to be less risky. One of the major questions is how close the presumed "safe" dose is to the background levels of dioxin to which the general population is exposed. If background exposure is already near the "safe" dose, then there may not be much room for additional exposure.

Those background levels are largely unknown, so Reilly has added that question to the EPA scientists' assignment. Over the next year Birnbaum and other EPA scientists, in collaboration with researchers from NIOSH, the Centers for Disease Control, and the Air Force, hope to get a fix on blood levels of dioxin and the handful of polychlorinated biphenyls that behave similarly and thus could increase its risk. Meanwhile, other researchers will be studying the sources and routes of dioxin exposure—most of which are dietary—and how it is passed up the food chain.

Reilly wants the new model and related work complete within a year, at which time the results will go on to EPA's Scientific Advisory Board (SAB) for peer review. Three years ago, the SAB sent EPA scientists back to the drawing board when they tried to revise the dioxin standard, saying the science wasn't sound enough. Birnbaum and other EPA researchers predict a different outcome this time. ■ LESLIE ROBERTS