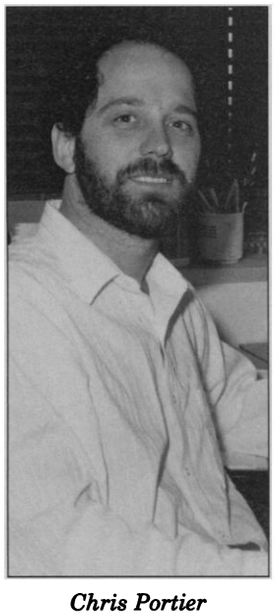
More Pieces in the Dioxin Puzzle

Ten months ago it seemed there might be a "threshold" for dioxin's effects; now comes evidence to the contrary

ALMOST HALFWAY THROUGH A MAJOR REassessment of dioxin's toxicity, the infamous chemical is proving to be even more slippery than many scientists initially suspected.

Less than a year ago, some of the nation's leading dioxin experts, including Michael Gallo, associate dean for research at the Robert Wood Johnson Medical School in New Jersey, and Linda Birnbaum of the Environmental Protection Agency's (EPA) Health Effects Research Laboratory in North Carolina, urged EPA to reassess dioxin's risk. The scientists were spurred on by new evidence about how the chemical acts at the molecular level, which suggested there might be a practical "threshold" or "safe" dose below which no toxic effects would occur (*Science,* 8 February 1991, p. 624). If so, they said, then the linear model EPA uses to predict risk is probably off, perhaps by a large margin.

In response, last May EPA administrator William K. Reilly launched an effort to build a new, biologically based model for assessing dioxin's risk. Once complete, this will be one of the first times EPA has replaced its generic cancer risk model—which assumes that risk increases linearly, starting with the slightest exposure—with a mechanistic one. But now, just 5 months into this reevaluation, comes new evidence from George Lucier and Chris Portier of the National Institute of Environmental Health Sciences in North Carolina suggesting that there is no threshold, at least for some of dioxin's effects. The old linear model might not be that far off after all. They emphasize, however, that the final verdict is not in yet.



Chris Portier

The linear model was first called into question by evidence from a number of labs that dioxin, unlike many carcinogens, must first bind to and activate a receptor before it can cause cancer or any of its other effects. The notion of a practical "threshold" came in, explains Gallo, because it appeared that a minimum number of receptors must be occupied by dioxin before the receptor complex is "activated."

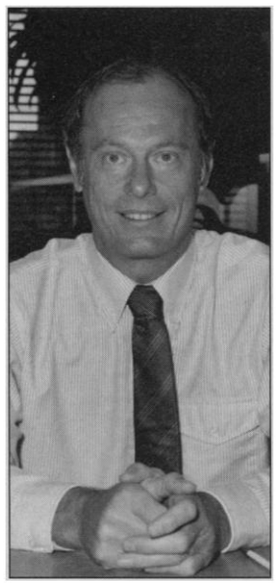
Not so, say Lucier and Portier, who about a year ago set out to answer the dioxin threshold question once and for all. Their strategy, which they described in late September at the Dioxin '91 meeting in Research Triangle Park, was to focus on specific biochemical changes believed to occur along the pathway to carcinogenesis and see how each one responds to dioxin dose. Lucier concentrated on the biology; Portier on the modeling.

Lucier's group began by feeding rats varying but extremely low doses of dioxin every 2 weeks. (The lowest was 100 picograms per kilogram per day.) At the end of 30 weeks, the researchers measured several simple, dioxin-induced changes, such as the activity of the cytochrome p450 enzyme system, which goes up in response to dioxin, as well as alterations in the binding capacity of several receptors, including the epidermal growth factor receptor, which signals cells to divide. They also looked at more complex responses, such as cell proliferation and the number and size of precancerous lesions in the animals' livers.

The result? Contrary to the predictions of just 10 months ago, there was "absolutely no deviation from linearity" for the simple responses they measured, says Lucier. In other words, the effects increased in proportion to the dioxin doses measured in the rats' livers.

But this simple linear relationship may not hold for more complicated responses like cell proliferation or cancer, Lucier and Portier caution. Indeed, they are still analyzing their data for cell proliferation, but so far it appears to have not a linear response but a sublinear one—in other words, it is less sensitive to dioxin at low doses. That observation, Lucier concedes, is "not inconsistent" with a threshold. But the bottom line, he and Portier argue, is that they found "lots of different dose-response curves for receptor-mediated events"—which should put an end to the notion that just because dioxin binds to a receptor, there is ipso facto a threshold.

"That is their interpretation," retorts Gallo, who has taken the lead in developing EPA's new receptor-based model. Though he calls Lucier and Portier's new study "super," he thinks they go too far in their interpretation. At even lower doses, he suspects, they would have seen a threshold. Says Gallo: "I am still convinced that a fixed number of receptors have to be occupied before we see a response in animals." But Lucier and Portier's new data have made a convert out of EPA's Birnbaum, who is playing a key role in the dioxin reevaluation. "We are not sure a certain number of receptors have to be activated anymore," she concedes, adding that the issue "is turning out to be even more complicated than people thought earlier."



George Lucier

The key task now, say Lucier and Portier, is to determine which of the effects they have analyzed is the most representative of cancer—and thus most useful in reevaluating dioxin's cancer risk. In the end, says Lucier, "Mike and I may wind up in full agreement. It may be that the receptor-mediated events important to cancer do exhibit a threshold."

Portier is now incorporating Lucier's animal findings, along with data from other groups studying dioxin's mechanisms, into a biologically based mathematical model similar to the one Gallo is working on with EPA scientists. The goal of both exercises is to reconstruct each step in the pathway that leads from dioxin exposure to cancer, using all existing data and filling in the holes with their best guesses. Right now the two groups are working independently but exchanging information. Birnbaum hopes to bring them together to see which model is best or whether a "fusion approach" is needed.

Once the new model is complete—Reilly has called for it in May 1992—it should be possible to get a more accurate fix on just how risky dioxin really is. At this stage, no one is placing any bets, not even Gallo, who just 10 months ago predicted that it would turn out to be far less risky than EPA now estimates. "I have no idea how it will come out," he says now. ■ LESLIE ROBERTS