Dioxin Risks Revisited

Armed with a new understanding of how dioxin works on the molecular level, a number of scientists are challenging EPA to change the way it does risk assessment

WHEN A DISPARATE GROUP OF 38 researchers and regulators from the United States and Europe got together at a recent meeting on dioxin, they reached an agreement that surprised almost everyone. At the Banbury Center at Cold Spring Harbor Laboratory, they agreed that before dioxin can cause any of its myriad toxic effects, be they cancer or birth defects, it must first bind to and activate a receptor. And this unlikely agreement on how dioxin works at the molecular level—and some hurried calculations scribbled on a blackboard—could force a dramatic change in how the federal government assesses the risk of this and similar carcinogens.

After the decades of scientific debate that have dogged this chemical, consensus on anything seems surprising. Scientists have been struggling to figure out just how dangerous dioxin really is ever since it was first detected in the late 1950s as a by-product of herbicide manufacture. Animal studies have shown this ubiquitous pollutant to be exquisitely lethal, the most potent carcinogen ever tested. But human effects have been notoriously difficult to pin down, as shown by the decades-long controversy over the dioxin-tainted defoliant Agent Orange. Even among highly exposed groups, like the people who lived near the chemical plant that exploded in Seveso, Italy, in 1976, the only undisputed effect until recently has been the skin disease chloracne. Just last month, however, a new epidemiologic study provided what may be the strongest link yet between high doses of dioxin and human cancer (see boxes on pp. 625 and 626).

In the absence of definitive human data, the Environmental Protection Agency has assumed the worst, adopting a linear risk assessment model that posits that there is no safe level of dioxin and that its toxic effects rise proportionately with dose. EPA then set a stringent acceptable intake level at 0.006 picograms per kilogram of body weight per day. By contrast, Canada and some European countries, which dismissed the linear model as unrealistic, have set their limits about 170 to 1700 times higher than EPA's, at 1 to 10 picograms per kilogram per day. Yet, sighs toxicologist Michael Gallo of the Robert Wood Johnson Medical School in New Jersey, "It's the same chemical on both sides of the Atlantic."

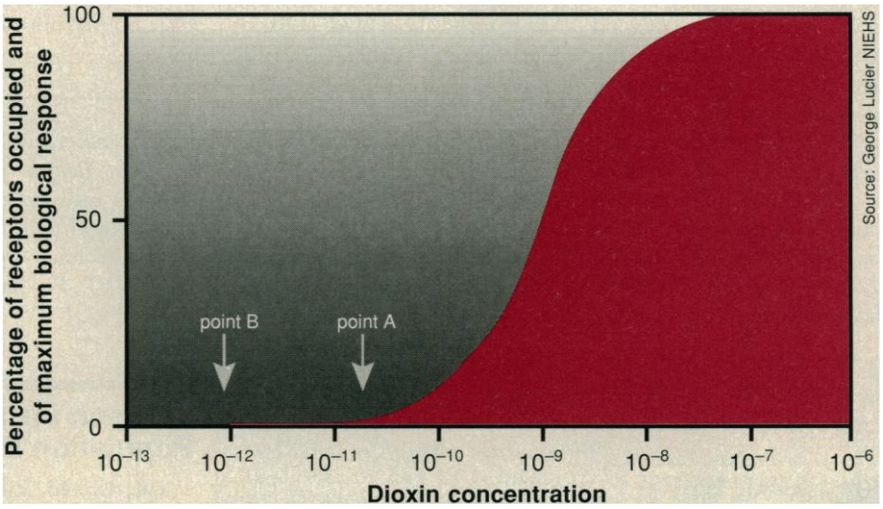
Now comes the Banbury Center meeting. Organized by Gallo, Robert Scheuplein of the Food and Drug Administration, and Cornelius van der Heijden of the National Institute for Public Health in the Netherlands, it suddenly offered a way out of the morass. If receptor binding is indeed the essential first step before any toxic effects can occur, as the meeting participants agreed, then that implies there is a "safe" dose or practical "threshold" below which no toxic effects occur. And that, in turn, means that the model EPA uses is wrong. "It topples the linear multistage model," exclaims Gallo.

Spurred on by the Banbury meeting, Gallo and others are now urging EPA and the other federal agencies to abandon that model, which they use as a "default" model for lack of a better alternative, and try to predict dioxin's risk based on a molecular understanding of how the chemical works. When EPA regulators adopted the default model for carcinogens in the late 1970s, their intention was always to replace it with something more appropriate—once they knew enough to do so. But that has rarely happened. "If we can't do it for dioxin, for which we have so much information, then we probably can't do it for anything," says Gallo, who thinks that this new approach will also be applicable to other carcinogens that work through receptors. "This is bigger than dioxin."

EPA scientist Linda Birnbaum, director of the environmental toxicology division of EPA's Health Effects Research Laboratory in North Carolina, is no less enthusiastic. "It's a new way to do risk assessment. We can set a limit below which there cannot be an effect, on a mechanistic basis. Instead of saying we know nothing and have to extrapolate back to zero, we are saying we know a hell of a lot and can make predictions."

But everything about dioxin is contentious, and the Banbury meeting sparked its own share of dispute. Consensus broke down on just what such a receptor-based model would predict in terms of dioxin's danger. Gallo and Scheuplein contend that the new model will show dioxin to be far less risky than U.S. agencies now calculate. Others, like George Lucier of the National Institute for Environmental Health Sciences (NIEHS) in North Carolina, say such speculation is premature. And Ellen Silbergeld, a toxicologist formerly with the Environmental Defense Fund and now at the University of Maryland, thinks speculation that dioxin is less risky may be dead wrong.

And even if the new model does indicate that EPA's risk number is far too conservative, revising it would be horrendously dif-



A dioxin receptor model. *New findings suggest that responses to dioxin increase slowly at first but then shoot up after passing a critical concentration.*

ficult—especially for a molecule as politically charged as dioxin. Gallo calls the substance a powerful "litigen," referring to the scores of lawsuits that have been filed by people alleging health effects from environmental exposure to dioxin. Michael Gough of the Office of Technology Assessment and author of *Dioxin: Agent Orange* predicts "a tremendous uproar from environmental groups and Congress." Indeed, John Moore tried to revise both the dioxin risk number and the model during his tenure as assistant administrator for pesticides and toxic substances at EPA. He was foiled both times, essentially because the scientific rationale wasn't strong enough.

Now it may be, thanks largely to the Banbury meeting, says Moore, who now heads the Institute for Evaluating Health Risks in Irvine. What tipped the scale is not so much new experimental data as the accumulating weight of evidence. Indeed, awareness that dioxin binds to a specific receptor, known as the Ah, or aromatic hydrocarbon receptor, goes back to work done in the 1970s by Alan Poland of the University of Wisconsin. Since then, the nagging question has been whether all of dioxin's effects—including cancer—are mediated through the receptor.

That question was at last laid to rest at Banbury. When researchers pooled their data, they realized that for every effect studied so far, in every experimental system, binding to the receptor was the first and essential step. Indeed, no effect can occur until the receptor-dioxin complex is activated and transported to the cell nucleus, where it interacts with the DNA and sets off a cascade of events. Poland cautions, however, that someone may yet turn up an effect that is not mediated this way.

What's more, says Gallo, drawing on classic receptor-occupancy theory, several thousand of the receptors have to be occupied before any biological response is seen—though the exact number is a matter of considerable controversy. To Birnbaum of EPA, "The key point is that there is a dose of dioxin below which the receptor does not function, and if it is not activated, there can be no effect," though she and others shy away from saying there is a threshold in the strict sense. The upshot, most but not all of the Banbury participants agreed, is that the straight line predicted by the linear multistage model is wrong. Instead, the curve at its lower end looks like a hockey stick in which the response increases very slightly at low doses, along the blade, and then shoots up almost linearly at the bend in the stick.

The key question, then, is where the response shoots up in humans, which the group set out to determine in a flurry of

High Dioxin Dose Linked to Cancer

Dioxin sleuth. *Marilyn Fingerhut ran NIOSH study.*

For two decades now a debate has been raging about whether dioxin causes cancer in humans. Animal studies have shown one form of dioxin, TCDD, to be the most powerful carcinogen ever tested, earning it a reputation as a pariah, the Darth Vader of chemicals. But human epidemiologic studies, which have been hampered by insufficient exposure data or small numbers, have been equivocal. Over the past few years a "revisionist" school has emerged, asserting that, in the absence of any definitive cancer link in humans, dioxin must have been given a bum rap. Now, a new study by federal scientists presents what many consider the strongest evidence yet that dioxin is indeed a human carcinogen—but apparently only at exceedingly high doses. In an editorial accompanying the study, which was published in the 24 January issue of *The New England Journal of Medicine*, biostatistician John Bailar III of McGill University in Montreal calls it "a model of its kind. We are likely to wait a long time for appreciably better or broader evidence of the effects of TCDD on human health."

In the exhaustive study, which took nearly 13 years to complete, Marilyn Fingerhut and her colleagues at the National Institute for Occupational Safety and Health examined the mortality records of essentially all U.S. chemical workers exposed to dioxin on the job from 1942 to 1984: a total of 5172 men at 12 different plants. What sets the study apart, other than its size, is that this is probably the most highly exposed population ever studied, says Fingerhut. What's more, their exposure was well characterized. The NIOSH team measured TCDD levels in the blood serum of 253 of the workers. The result: the levels correlated well with their surrogate measure, which was how long a worker was in a dioxin-contaminated job.

The workers overall had a 15% increase in mortality from all cancers. But that picture changed dramatically once the cohort was divided into a low-exposure and a high-exposure group. Low exposure was defined as working less than 1 year in a dioxin-contaminated job; high exposure as 1 year or more. The men in both groups had their first occupational exposure to dioxin at least 20 years earlier, allowing for a 20-year latency period for cancer. In the low-exposure group, there was no increased risk of cancer, even though those men were exposed to dioxin levels an estimated 90 times higher than the general population. By contrast, the high-exposure group, who received doses estimated to be 500 times higher than the general population's, had an almost 50% excess risk of dying of cancer. The increase was mostly in soft tissue sarcomas, a form of cancer linked to dioxin in other epidemiologic studies. But there was also an unexpected increase in cancers of the respiratory system. The study did not show a significant increase in the handful of other cancers that have been linked to dioxin in epidemiologic studies. "Even a study this large, with all the workers in the U.S., has limitations in size for looking at individual cancers," explains Fingerhut.

The study has other limitations as well. For one, workers were exposed to other occupational chemicals, often for 20 years, and the epidemiologists could not control for their effects. Nor could they control for smoking. Fingerhut thinks neither factor is likely to explain the excess cancer risk, but she cannot definitively rule out that possibility. Nevertheless, she sees the study's outcome as very clear, writing: "The increased mortality is consistent with the status of TCDD as a carcinogen." This study probably defines the upper end of human effects, adds Fingerhut, who leaves it to others to speculate about what it means for people exposed to lower doses of dioxin.

Will this study settle the dioxin controversy? Not likely, if newspaper headlines are any indication. "Extensive Study Finds Reduced Dioxin Danger," heralded *The Washington Post*. "High Dioxin Levels Linked to Cancer," warned *The New York Times*. And the study is already being cited as evidence in the flap over Monsanto's alleged falsification of its dioxin studies (see box on p. 626). Indeed, Bailar predicted that "parties on both sides of the continuing debate about the regulation of dioxin exposure will no doubt cite this work in support of their positions." ■ L.R.

excitement on the last day of the meeting. Instead of direct measures of receptor binding, they used a handy surrogate: the increased activity of the cytochrome P450 enzyme system, widely considered the most sensitive response to dioxin in all species. No toxic effects are known to occur at levels below those required for enzyme induction.

After reviewing data on the necessary dose for enzyme induction in all species, Gallo, Birnbaum, Scheuplein, and others took turns at the blackboard, trying to calculate what the "safe" level in humans might be. Their rough, back-of-the-envelope calculation: 1 to 3 picograms per kilogram per day—several hundred times higher than current U.S. standards and in the same ballpark as those set by some European countries, which arrived there by an entirely different method.

Not so fast, says Maryland's Silbergeld, who cautions against "replacing one stupid model with another." For one, a receptor-based model does not necessarily predict a "hockey stick" curve, nor does receptor binding necessarily imply a "safe" dose, says Silbergeld, who thinks her colleagues are underestimating the intricacies of receptor theory. Nor is she convinced "that the result [of the new model] will be that different from EPA's current figure. As a scientist, I object to the EPA model. But [its predictions] may be very, very close, for totally irrelevant reasons."

Working with EPA scientists, Gallo is now setting out to refine the risk number for dioxin. George Lucier and his colleagues at NIEHS are doing the same. The idea is to build a conceptual model of cellular responses to dioxin and then turn that over to mathematicians to develop a predictive tool to estimate dioxin's risks—not just for cancer but for any toxic endpoint. William Farland, who runs the dioxin risk assessment effort at EPA, expects a "straw man" model to be complete in about a year. The next step would be to see if it passes muster with the scientific community—and if it in fact offers an advantage over the status quo. "This is an improvement, not a cure-all," warns Lucier.

Once the model is complete, perhaps the biggest question, in terms of dioxin's danger, is the background exposure of the general population, which comes chiefly from diet but also from environmental sources. If background exposure is comfortably below the practical "threshold" needed for receptor activation (point B in the figure), then there may indeed be a safe dose. But if background exposure is higher, near the "threshold" (point A), "then there is no margin for additional exposure," says Moore. Background exposure is now estimated to be about 1 picogram per kilogram per day—slightly below the rough "safe" number the Banbury group came up with—which may not leave much room for additional exposure.

At this juncture, EPA officials are enthusiastically embracing the new scientific approach. Don Barnes, a dioxin expert and executive director of EPA's Scientific Advisory Board, talks of "a real breakthrough, a sea change in our view of dioxin." In fact, the topic is deemed important enough that a special briefing is planned for EPA administrator William Reilly and top agency officials.

But how far is EPA likely to go if the modeling exercise does reveal that dioxin is less risky than the agencies now calculate? Gough of OTA, for one, thinks that the answer is not very far: "Dioxin is the most potent carcinogen ever tested. If they back off this one, they will open the door to every chemical manufacturer in the world" whose chemical acts in the same way. "That is a door they will reluctantly open." Gallo contends that the door will open just a crack, as there are less than a dozen carcinogens known to work the way dioxin does. And he predicts that the new receptor-based risk model will cut both ways: some carcinogens will turn out to be far riskier than now predicted; others, like dioxin, less risky.

Moore agrees that change will not be easy. "For issues this emotional, you have to be purer than Caesar's wife anytime you propose to change the status quo. There would have to be a fair degree of support within the scientific community for it to come to pass, especially if the potential change is a 'relaxing' of the number."

Eric Bretthauer, EPA's assistant administrator for research and development, concedes that "the agency hasn't traditionally relaxed numbers." But, he says, "I think there is a willingness at the policy level to take it on. My view is we have to be open to changes in science, whatever their effect on regulatory policy." He adds, however, that "the science has to be very clear."

■ LESLIE ROBERTS

Monsanto Studies Under Fire

The Environmental Protection Agency has launched a criminal investigation to determine whether Monsanto Corp. of St. Louis falsified three epidemiologic studies of its workers, which showed no increased health risks from dioxin other than the skin disease chloracne. The investigation, which EPA is mandated to conduct in response to a petition requesting it from the activist group Greenpeace USA, should resolve, once and for all, the allegations that have been swirling around these studies for almost a year. EPA officials would not confirm or deny the existence of the investigation, but *Science* obtained internal agency memos discussing it.

The EPA has not notified Monsanto that it is under investigation, but says Dan Bishop, the company's director of communications, "We hope there is one, we welcome it. It is the only way to put this matter to rest." In fact, the company wrote to EPA twice over the past few months, begging the agency to perform a scientific audit of the studies. Bishop calls the fraud allegations "bald-faced lies."

The main charges are that Monsanto epidemiologists misclassified exposed workers as unexposed in their control group and that they omitted workers who had died of two cancers that have been linked to dioxin exposure in other epidemiologic studies. The charges first came to light last February when a plantiff's lawyer in *Kemner* v. *Monsanto*, a case involving a tank-car accident, reviewed the studies, decided they were fraudulent, and alerted the press to the alleged cover-up. That brought in Greenpeace, and also Cate Jenkins, a chemist in EPA's regulatory branch. She has since made the Monsanto studies something of a personal crusade, petitioning EPA's Science Advisory Board to audit these and other studies, and meanwhile sending numerous copies of her memos to various environmental groups, Vietnam veterans organizations, and her friends on Capitol Hill. Jenkins maintains that Monsanto's studies have directly affected how EPA regulates dioxin. Other agency officials deny that, saying that EPA's current—and very stringent—standard for dioxin exposure is based on animal studies.

Everyone *Science* spoke with who is familiar with the Monsanto studies agrees that they are flawed, but probably not as the result of criminal intent. The scientific questions about the studies may now be moot, however, as all but six of the Monsanto workers in the three studies have been carefully reexamined as part of a larger federal study just published, which suggests that high dioxin doses can cause human cancer (see box on page 625). The other questions may be tougher to resolve. When EPA completes its investigation, the agency will report to the Justice Department and recommend either that they prosecute or close the case. ■ L.R.