

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

"hockeystick" 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."

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 plaintiff'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.

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