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New Leader Takes Over At NIEHS

Toxicologist Linda Birnbaum charts course for NIH institute

Cheryl Hogue

AS THE NEW ADMINISTRATION settles in, agencies across the federal government are undergoing transitions. But for one leadership change that took place two days before President Barack Obama took the oath of office, the timing was coincidental.

Cheryl Hogue/C&EN
Linda Birnbaum

Hear Linda Birnbaum talk about dioxins, regulation, and science

If you cannot play the audio file, download the free Quicktime Player.

Linda S. Birnbaum, the new director of the National Institute of Environmental Health Sciences (NIEHS), officially assumed her post on Jan. 18 and now oversees an institute with a $730 million annual budget. Located in Research Triangle Park, N.C., and part of the National Institutes of Health, NIEHS is home to the National Toxicology Program, which tests chemicals of concern to public health.

Birnbaum, the first toxicologist to head NIEHS, came to the institute from the Environmental Protection Agency. For 16 years, she served as director of EPA's Experimental Toxicology Division. During her last year at EPA, she coordinated efforts across the agency probing the contamination of Libby, Mont., with asbestos from a vermiculite mine.

Raynard S. Kington, acting director of NIH, says Birnbaum "has a long and distinguished career conducting research into the health effects of environmental pollutants." She is an expert in the toxicology of dioxins, brominated flame retardants, and endocrine-disrupting chemicals in general, and she has authored more than 600 peer-reviewed publications, book chapters, abstracts, and reports. She is a former president of the Society of Toxicology.

Birnbaum comes to an institute that was wracked by political turmoil during the tenure of David A. Schwartz, who was NIEHS director from 2005 to 2007. Schwartz was the target of several congressional investigations, including some involving conflict-of-interest allegations about testifying in lawsuits after he took the job at the institute.

In addition, Schwartz slashed the budget for NIEHS's open-access journal, *Environmental Health Perspectives*, by 85% and attempted to privatize it. (In response to this, the American Chemical Society, publisher of C&EN, at one time expressed interest in taking over *Environmental Health Perspectives*.) Schwartz also shifted the institute's funding to emphasize patient care at the expense of NIEHS's traditional focus on preventive programs. The morale of the staff is reported to have fallen significantly during Schwartz's controversial tenure.

DESPITE ALL that has happened in the recent past, Birnbaum sees great opportunity at NIEHS. "The institute has a marvelous scientific portfolio. It has a lot of excellent people working very hard doing a lot of important things," she tells C&EN.

Although she diplomatically skirts the question of whether she will flat-out reverse Schwartz's policies, Birnbaum has several changes in mind as she sets an agenda for NIEHS.

> **"We have a tendency in science to become experts about something very narrow. We're so focused on minutiae that we miss the big picture."**

"Some of my first challenges are to restore morale and develop a culture of openness and trust at the institute," she says.

Besides making efforts within NIEHS, Birnbaum has her eye on reaching out beyond the institute. For instance, although she's left EPA, Birnbaum is by no means severing ties with the agency. NIEHS is situated across a small lake from a major EPA laboratory where Birnbaum worked for 16 years. Pedestrians can easily walk between the facilities via a scenic footpath. But Birnbaum is keenly aware that scientists at these two government research facilities have had little interaction, even though the work of both programs is connected to the effects from chemicals in the environment. She's intent on building virtual bridges between the two.

In addition, Birnbaum wants NIEHS to strengthen its relationships with those outside the government, including scientific organizations and citizen groups. "I'm very excited and optimistic about opportunities to interact," she says.

One avenue of interacting with those outside NIEHS is *Environmental Health Perspectives*. In contrast to Schwartz, Birnbaum is a strong supporter of the publication.

"I am thrilled to see that *Environmental Health Perspectives* has the highest impact factor of any environmental journal," Birnbaum says. "It has a very wide readership," especially in the U.S., Europe, and China (there is an edition in Chinese). "It attracts people from the basic sciences to the most applied sciences, people doing basic chemistry to people doing epidemiology and clinical medicine as well," she says.

Meanwhile, Birnbaum also wants to strengthen NIEHS's connections with other parts of NIH. She says, "I need to work hard to reestablish close working relationships with our sister institutes in Bethesda," the Maryland town where NIH headquarters is located.

Although she has yet to oversee her first budget at NIEHS, Birnbaum indicates that the types of research that the institute funds may change. Specifically, she says the institute should return to its traditional focus on preventive programs.

"There's clearly a role for clinical medicine at NIEHS," Birnbaum says. "However, I think when we're talking about environmental health, it's not only 'bench to bedside,' it is also 'bench to public health.' We have a major role to play in the betterment of public health in this country."

ONE CRITICISM that Birnbaum expects to face involves regulatory decisions on chemicals. The decisions, such as those made by EPA and the Food & Drug Administration, rely on studies like those conducted by the National Toxicology Program in which laboratory animals are given high doses of a substance. Critics say these experiments inappropriately include exposures to chemicals that are far higher than what the public experiences.

"They are missing the point," Birnbaum says of these critics. The amount of a chemical given to a laboratory animal isn't what's relevant in these tests, she explains. "It's what's in the body or in the specific tissue at a specific point in time." In animal studies, she says, "if you actually look at the internal dose, frequently, it's not high."

The key, according to Birnbaum, is finding more sophisticated methods to determine how much of a compound is not just getting into the body but how much is getting into the tissue, where it can adversely affect health.

"I'm willing initially, for incremental improvement, to take what's in the blood" as a surrogate measure of tissue load, Birnbaum says. She notes that for some chemicals, such as dioxins, the concentration of the substance in blood may not be the best measure of tissue exposure inside the body. "At high levels of exposure, it isn't just in blood lipids, there's a heck of a lot of it that's bound up in the liver. So you may underestimate the total amount that's in the body, but it's a lot better than saying how much you were exposed to on a daily basis," she says.

Estimates of how much of a chemical gets to nerves, organs, or other tissue inside a person might also be made using other easily accessible bodily fluids, such as urine. But Birnbaum knows that this line of study—whether involving blood, urine, or other fluids—has limitations.

NIH

Home base Birnbaum now directs NIEHS, which is situated on a small lake in Research Triangle Park, N.C.

"Not everybody's eager to give you blood," she says. Plus, some chemicals or their metabolites aren't eliminated in urine. And a single metabolite may have more than one source; the body may transform any of several chemicals into the same end product.

Nonetheless, Birnbaum has hope that new tests based on proteomic or metabonomic technologies will allow researchers to easily study accessible bodily fluids for early signs of toxic responses due to exposure to chemicals. She cautions scientists to keep practicality in mind as they invent this sort of assay, known as an "omic" test. She expresses frustration about new techniques for identifying early signs of toxic response in brain, kidney, and liver cells that fail to heed this caution.

"I don't know too many people who are eager to give you a brain biopsy or a kidney biopsy so you can measure what is going on in that tissue specifically," Birnbaum says. "We have to be able to use easily accessible tissue."

In addition, the omic tests are expensive to carry out, she says, expressing hope that researchers will also develop less costly methods to detect early signs of disease.

High-throughput omic tests for initial toxicity screening of chemicals have captured the attention of the federal government in recent years. The National Toxicology Program is involved in this work, as is EPA through the agency's ToxCast program. While endorsing these new technologies, Birnbaum notes their limitation.

These screening efforts may link some chemicals with health hazards they weren't previously associated with, Birnbaum says. But she worries that results of high-throughput testing may incorrectly indicate that some compounds aren't hazardous when in fact they are.

"I am always concerned about the false negatives," Birnbaum says of the rapid screening. In environmental health, giving a clean bill of health to a substance that came up negative in a rapid screening test could cause public health headaches in the future, she says.

THOSE CONCERNED about public health, however, have moved beyond the question about the classic toxicity of a chemical: Will this substance make someone sick and, if so, at what dose? They are increasingly focused on substances that may disturb the body's endocrine functions.

Studies of chemicals suspected of being endocrine disrupters raise complex issues, Birnbaum explains.

"When you're dealing with hormonal activity, context is everything and interaction is everything. A given hormone in a given tissue at a given

Chemicals

Birnbaum On Dioxins' Toxicity, Regulation

Linda S. Birnbaum, the new director of the National Institute of Environmental Health Sciences, has spent a sizable chunk of her scientific career focused on dioxins, furans, and polychlorinated biphenyls. This family of chlorinated or brominated chemicals is commonly lumped together under the moniker "dioxins."

Birnbaum has witnessed how regulation has virtually eliminated production of these toxic chemicals over the past three decades.

"The major sources that were present in the '60s and '70s are no longer significant sources at all. The processes that created them are no longer being used" commercially, she says. Plus, studies show that the levels of dioxins are dropping both in the environment and in people's bodies.

"That's the good news," Birnbaum says. "On the developmental stage may cause one thing to happen. The same hormone in another tissue or another development stage may cause exactly the opposite kind of thing to happen," Birnbaum says.

Scientific understanding of how the endocrine system works continues to evolve, she points out. "Twenty years ago, we knew that estrogen worked through a receptor. But now we know there isn't one estrogen receptor, there are multiple estrogen receptors," Birnbaum says. Plus, there are interactions. "We know that the estrogen receptor, for example, doesn't act in isolation but interacts with other hormones and receptors," she explains.

Then there's the issue of hormonal variations among individuals, Birnbaum adds. For instance, if a given exposure to an endocrine-disrupting chemical decreases a man's testosterone by 10%, plenty of men would experience no effects, and their levels of this hormone would remain in the normal range. But this would not be the case for men who, before exposure, have testosterone levels on the lower end of the normal range.

Such complexities feed into public health policy and science policy debates, such as the one over bisphenol A (BPA). This chemical, which is used in polycarbonate bottles and epoxy-based food can liners, is an estrogen mimic. FDA is in the midst of a debate over whether it should allow continued use of BPA in food and beverage containers (C&EN, Nov. 17, 2008, page 42). In September 2008, the National Toxicology Program deemed BPA of "some concern" for developmental and behavioral effects in fetuses, infants, and children (C&EN, Sept. 8, 2008, page 28).

"There is not enough around to make a difference at the current levels you see in the human population," Birnbaum says of BPA. Yet BPA is one of more than two dozen chemicals people are exposed to that act as weak estrogen mimics, she continues. "They're all weak, but if you even just use a simple dose addition method, all of a sudden the total estrogenic activity is not insignificant," she adds.

Birnbaum points out that the endocrine system goes beyond the heavily studied estrogens, androgens, and thyroid hormones. "There are many other endocrine systems in our body that we need to consider," she says.

"We have a tendency in science to become experts about something very narrow. We're so focused on minutiae that we miss the big picture," she says. "Our bodies and our integrated systems are not simple. There are all the interactions between the parts."

This sort of understanding about parts integrating into a whole offers insight into how Birnbaum is approaching her post at NIEHS.

"The mission of NIEHS is to reduce and prevent environmental impact on disease," Birnbaum says. "It's not only the disease of the individual." Effects may be subclinical or difficult to detect in a given person, but they may affect the overall health of the population, she explains.

"If we can understand how a certain environmental chemical or environmental stressor causes a disease process," she says, researchers can work to stop progression of health problems, as well as prevent them.

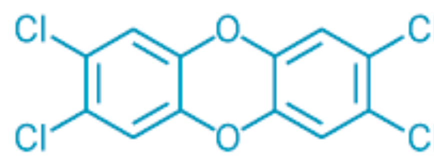
other hand, our continued scientific study of dioxins has revealed that they're much more toxic than we used to believe."

In the past, researchers were concerned about dioxins being lethal after short-term exposure. But nowadays, Birnbaum says, "we are concerned about their subtle developmental effects" and possible long-term cancer risks from exposure.

"For years, with dioxins, nobody really understood that they affected heart development. Well, we knew that it was true in fish, and we knew it was true in birds," she explains, "but nobody had ever really shown that it caused effects during mammalian development or in adults." That's because scientists weren't looking for these outcomes, she says. Now that researchers are probing the possibility of these effects, they are finding them.

In addition, dioxins are linked to an increase in type 2 diabetes. Age and obesity may be more important risk factors for this disease than dioxin exposure, Birnbaum says, but that doesn't make regulation of these substances irrelevant.

"You can't control your age. Many people are not very successful at controlling their weight," she says. "But we as a society can control our dioxin exposure."



INFAMOUS 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is the most hazardous member of the family of chlorinated and brominated dioxins

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