Exposure, effects, and public health challenges

An interview with Linda Birnbaum, Director of the US National Institute of Environmental Health Services

EMBO reports (ER): The mission of the National Institute of Environmental Health Services is investigating the health risks of environmental chemicals and pollutants. There’s a whole zoo of compounds such as DDT, lead, tobacco smoke and many other pollutants that have eventually been banned or regulated after research demonstrated their health hazards. What do you think is now the most important or the most controversial chemicals in terms of human and public health?

Linda Birnbaum (LB): It’s unequivocal that air pollution from mobile and stationary sources is a major long-term problem for human health. Much of the research of its effects was focused on the lungs and then included the cardiovascular system and it now expands into studying early-life effects in utero or early childhood. We’re beginning to understand that even very low levels of chemicals may have adverse effects during vulnerable stages, such as development.

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ER: What would be the direct effects of air pollution on human health on a population level?
LB: According to the World Health Organization, chronic, non-communicable diseases are now the largest health problem. That doesn’t mean infectious diseases aren’t important, but it’s clear that diabetes, cancer, cardiovascular diseases are growing problems, not only in the developed world but also in the developing world. The whole field of DOHAD—the developmental origin of health and disease—is extremely important. It may sound a little too deterministic, but I think what happens to you early in life sets your trajectory for the rest of your life. Much of the focus, for example, on obesity and diabetes has been on exercise and weight. I don’t disagree with either recommendation. However, there is growing evidence that exposure to environmental chemicals actually predisposes you to obesity or type 2 diabetes. So are we making it more difficult for people to control their weight because of the chemicals to which they had been exposed?

ER: Does this concept mean the baseline for your health or disease risk is already being set in utero or early in life?
LB: It’s not only the baseline, it may be your susceptibility or responsiveness to disease. We’ve moved beyond looking for specific effects, say, birth defects, to looking at functional decrements. Mercury, for example, gets methylated in the environment into methyl mercury, which is highly neurotoxic. At high levels of exposure it causes neurological damage with paralysis and mental retardation and very low levels are able to impact on your IQ. But you can’t look at Johnny individually and say “If your mother hadn’t had some methylmercury exposure, you would have three IQ points more.” You have to look at the whole population. I’m not saying that acute high-dose exposures aren’t important in the developing world—or in an occupational situation, or in an emergency, but many of our concerns are about chronic low-dose exposure that affects the whole population.

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ER: The original hypothesis about low-level exposure stems from the 1990s and the effects of endocrine disrupting chemicals, which are ubiquitous as plastic softeners, pesticides or flame retardants and, of course, as part of air pollution.
LB: When we talk about endocrine disruption, much of the focus has been on what we call EAT—estrogen, androgen and thyroid—but there are many other endocrine systems, which have been largely ignored until more recently. Much of the focus was also on reproduction, but our endocrine system does a lot in addition to reproduction. It is absolutely essential during development and to maintain homeostasis and normal physiology in...
adulthood, and it does it at incredibly low concentrations. If you add on to the activity of those hormones, or if you block their activity, you fall outside homeostatic state. If you think of a normal curve of distribution, there are people at the high and the low ends. So while a 10% decrease in testosterone might not be a problem for someone in the middle of the bell-shaped curve or at the high end, it could be a huge problem at the low end.

ER: How big is the health risk of these compounds?

LB: I’m talking about allergy, I’m talking about auto-immune disease, I’m talking about autism spectrum disorder, I’m talking about attention deficit hyperactivity disorder; many of these things are impacting the health and the well-being of populations and their prevalence is increasing too rapidly to be due to a genetic change.

Philip Grandjean [Harvard University, MA, USA] showed a decreased flu vaccine efficacy related to maternal exposure to chemicals like PCBs or perfluorinated compounds. There’s data from animal studies that exposure to different kinds of air pollutants can suppress the ability to respond to an influenza challenge. And there’s data now that air pollution is suppressing the T-lymphocyte response in children who live in areas of elevated air pollution. There’s evidence that a number of environmental exposures can be associated with an increase in auto-immunity. We are finding an association with elevated air pollution and an increase in autism-spectrum disorders.

ER: As you mentioned the data from animal studies, the question is how good are the animal models to investigate human disease? For instance, ADHD or autism-spectrum disorders are neurological disorders in higher primates, but a lot of the studies on environmental exposure are being done in rodents, which may not be the appropriate model organism.

LB: The problem is we’re sometimes asking the wrong question. The animal studies have been done with highly inbred, often transgenic strains. If you want to do a study with a rat, which will get breast cancer, I’ve got a rat for you. If you want to do a study with a rat, which will never get breast cancer, I’ve got another rat for you. Which rat does represent the human population? The answer is both. Many of our animal models are not modeling the...
genetic diversity or variability in humans. That being said, when I look at studies where a given chemical causes a multiplicity of effects in multiple animals including wildlife, it would be tremendous hubris to assume that humans are not susceptible. We are currently supporting the development in collaboration with others, of what are basically strains of mice that represent the diversity in mousedom. And I am optimistic that the use of these strains for testing will help us better understand the variability in humans.

ER: So do you think the mouse is still a good model if you take into account genetic variability?

LB: I think the problem is that a lot of people have tunnel vision. I can remember listening to a talk by a cardiologist about hormone-replacement therapy. And he said, if you dichotomize the population into those who have early heart disease versus those who don’t have early heart disease, then HRT is good for the heart for one population but not for the other. I wanted to raise my hand and ask him, “Wait a second, the heart and the cardiovascular system are just one part of a woman’s body. What about her breasts, what about her uterus, what about her brain?” All too often we’re quick to say, the effect that we see in this tissue is not relevant to humans, but we’re not looking at the whole mouse. I have been a little bit frustrated by some of the over-focus on specific mechanisms of action in understanding the risk of chemicals. I think the mechanism is very insightful and useful, but almost no chemical has a single mode of action. Different effects occur via different modes of action, and the modes of action may also not only be tissue or organ-specific but they also will be developmental stage-specific. We need a broader view and not assume that because someone didn’t see something that there is nothing wrong.

ER: The gold standard is both epidemiological evidence and mechanistic studies that give you correlation and causation respectively. If there’s an over-focus on the mechanism as you said, wouldn’t we need better epidemiology?

LB: Epidemiology, as you say, is usually association not causation but if the epidemiologists see an association, it certainly gives me confidence if I have laboratory data, animal data, mechanistic data, wildlife data, which support the epidemiological data. In many cases the epidemiological data has pointed to the problem before we have the experimental data, but in other cases it goes the other way.

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ER: How good would the evidence have to be to consider or support regulation or banning certain chemicals?

LB: I was always supportive of how the EU used to define the precautionary principle. You act in the presence of concern but in the absence of certainty. There is essentially never certainty in science. The tobacco industry prevented regulation of cigarettes for fifty years because only 11% of smokers ever get lung cancer, so smoking doesn’t cause lung cancer. Well that’s not true. Smoking does cause lung cancer. It’s a function of dose and timing and susceptibility. When you have large numbers of mechanistic studies in human cells and animals, and if you have epidemiological data that shows associations, you still don’t have certainty, but you have enough to say that there is concern.

ER: So this would be a case to involve the precautionary principle?

LB: If it is used appropriately. Some people say that means that you act in the absence of any information, and that’s not true. You ban or you regulate something, if you have exposure and if there’s lots of credible evidence that exposure may be associated with adversity.

ER: It seems that in the case of endocrine disrupting chemicals, the USA was actually ahead of the Europeans in terms of regulation. It was only during the discussions about the REACH legislation that endocrine disruptors became a concern in the EU.

LB: Well maybe, but there are many scientists in the EU now taking a leadership role. We can’t go crazy about these things. But we have to ask questions about some of these chemicals: are they needed, are there alternatives? The alternatives is a big issue, because—now I’m going to use a trite phrase, especially with all my work on flame retardants—you’re jumping from the frying pan into the fire. We have a tendency to substitute a chemical of concern with an untested chemical, which may turn out to be worse. I would very much like us to assess the safety of chemicals before we put them into the marketplace. But in our country, unfortunately I would say, regulations are based on an assumption that chemicals are safe until proven not so.

ER: Would this also mean that the regulation itself would have to adapt? Just by way of example, the EU has banned various neonicotinoids that are being used in agriculture because they affect honeybees. They got market authorization in the late 1990s because the tests didn’t show any effect on bees, but now EFSA said the tests are not realistic enough.

LB: Something that we’re starting to work with is how can regulators use the newer approaches to make decisions. I get very frustrated when I see people wanting to run the same assays that they ran 30 or 40 or 50 years ago. Science has moved on. Yes we want to know if there is high-dose acute toxicity, but we also want to know about what’s happening during development. In the 80s I was looking at teratogens where you expose mice or rats during organogenesis and you look for defects in the fetus. That’s never going to pick up altered behavior, it’s never going to pick up the inability to reproduce. We need to be sure that regulations are based on robust and well-conducted studies.

ER: There is a growing awareness on the role of the bacterial and viral gut flora in human health and disease. How far are we into understanding their role in susceptibility to exposure and disease?

LB: The key role of gut bacteria in terms of environmental toxicants is something that’s been ignored. Your microbiome is driven by your diet and that might alter your response to an environmental exposure. Vice versa, how does your response to an environmental exposure lead to perturbations of the microbiome? There’s clear data from animal studies that animals respond very differently to a range of different toxicants depending upon whether they’re on a high-fat or low-fat diet.

ER: The One Health concept aims to create a more holistic view on human health, public health, animal health, and the environment with microbiome linking it all together. Do you think that this is slowly
changing the way you and others are looking at environmental exposure and public health?

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LB: I would hope so. I am actually a big proponent of the One Health concept. We have often ignored the signals we get from wildlife or domestic animals in terms of human health. We need to be more attuned to what they may be telling us. We need to realize that what we see in animals is also likely to happen in at least some people. The other thing I would like to mention is that we’re beginning to realize that many of the things we’re dealing with involve epigenetics and epigenomics. Epigenetic changes that happen in utero, or in early development, will probably not be reversible. But epigenetic changes that happen in adults may in fact potentially be reversible, and actually that is the basis for certain chemotherapeutic agents.

ER: How would the One Health concept practically affect your research? We still focus on the individual compound, the target molecule, the exposure and the physiological effect. So how would research have to adapt?

LB: We’re trying to move into an area of predictive toxicology. We partner with the EPA and with other parts of NIH and with the FDA in a program called TOX 21. This involves not only rapid screening but looking at a large number of different responses. We are using high-throughput approaches with cell-based systems, C. elegans or zebrafish to rapidly screen large numbers of compounds: I’m talking about thousands, if not tens of thousands of chemicals. We have run over ten thousand compounds within the last year or two through over seventy different assays focused on oxidative stress and nuclear receptor activity. You begin to build up what I would call patterns of bioactivity. You see that some chemicals are very bioactive; other chemicals are not. For my money, as I prioritize screening and testing, we’re going to put more effort onto those chemicals that show high bioactivity.

ER: Regardless of the effect?

LB: Regardless of the specific effect. And the use of these in vitro rapid-screening approaches also allows us to analyze combinatorial mixtures with large numbers of chemicals and different ratios and ask questions about mixtures that approach the situation in the real world.

ER: Would that allow you to untangle synergistic and antagonist effects?

LB: Yes. You only see synergism when you have very low levels of exposure; you only see antagonism if you have high levels of exposure. Using an assumption of additivity is not a bad starting point, but we do need to go beyond it. It’s going to be a while before we can move away from whole animal testing in many cases, but we will get a better idea of where we need to focus.

ER: One side of toxicology is the effect, and the other side is the exposure. What do you see currently in terms of improving the measurement of exposure? It’s easy to measure exposure in a lab animal, where you give them a defined concentration of a compound. But how hard it is to measure real exposure in a human population?

LB: One approach is biomonitoring, where you actually measure the levels of a compound or metabolite in readily accessible biological fluids. I get frustrated when people tell me “this is the concentration in the brain” in their experimental animals, but people don’t want to give you a piece of their brain. You need to understand the relationship between what’s in the brain and what’s in the blood or in the urine. The other approach is the exposome where you look at the totality of human exposure. The exposome is extremely complicated, because it is rapidly changing over time, potentially from day to day if not minute to minute. Many people are beginning to develop the high-resolution, analytical assays that are needed to look at the totality of human exposure. And there are statistical approaches to look for associations.

ER: Do you think that epigenomics as part of the exposome will have an impact in better understanding the link between exposure, susceptibility and effect?

LB: Absolutely. The genetics is the hardware and the epigenetics is the software controlling whether genes are turned on or off. For a long time we thought humans only have twenty thousand genes—only two percent of their total DNA—so what’s the other stuff doing? We’re beginning to understand that the other stuff is where a lot of the key epigenomic action is happening. There are already quite a number of studies looking at epigenetic changes in cells, in animals, and now in some human studies, in response to certain kinds of chemicals.

ER: How difficult do you find it talking to politicians and lawmakers about these issues when you try to convince them to change the regulation of market authorizations, or to invoke the precautionary principle?

LB: I stick to the science. I’m not in a regulatory agency, I head a large research organization, and our mission is to provide the best science that can be used by others in decision making. But I think at this point we have a conflict of interest among scientists, as well as among regulators and clearly among legislators.

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ER: One last question. Why is your campus the only one outside the NIH campus in Bethesda?

LB: The reason is that in 1960, the democratic governor of North Carolina, Terry Sanford, was able to deliver the state to Jack Kennedy. As a payback, Kennedy promised that some federal organizations would be located in North Carolina. Two years later, Sanford set aside almost 600 acres of land for a federal campus. We share our beautiful campus: The United States Environmental Protection Agency has some of their research labs on the other side of the lake.

ER: Dr Birnbaum, many thanks for the interview.

The interview was conducted by Holger Breithaupt.