# Toxicity Forecast, with Robert Kavlock

Ashley Ahearn

Every year about 2,000 new chemicals are submitted to the U.S. Environmental Protection Agency (EPA) for safety approval. Figuring out how a chemical might affect human health involves lab studies that can cost millions of dollars and take years to complete. Now a team of researchers at the EPA is working on a way to make the safety testing process more efficient and less expensive. In this podcast, Robert Kavlock describes the EPA ToxCast™ project, which uses existing toxicity knowledge as a blueprint for broad-scale chemical assessment. Kavlock is director of the EPA National Center for Computational Toxicology and coauthor of "*In vitro* screening of environmental chemicals for targeted testing prioritization: the ToxCast project"

**AHEARN:** It's *The Researcher's Perspective*.  I'm Ashley Ahearn.

Tens of thousands of chemicals are currently on the market in this country, and many of them haven't undergone the testing needed to judge their safety when it comes to human exposure.

Every year the Environmental Protection Agency gets about 2,000 new chemicals submitted for safety approval.

Figuring out how a chemical might affect human health involves lab studies, usually on animals, which can cost millions of dollars and take years to complete.

But a team of researchers at the Environmental Protection Agency is working on a way to make the safety testing process more efficient and less expensive.  It's called the ToxCast™ project, and some research from the project was recently published in *Environmental Health Perspectives*.

Joining me to talk about it is Dr. Robert Kavlock. He's the head of the National Center for Computational Toxicology with the Environmental Protection Agency.

Dr. Kavlock, thanks for being here.

**KAVLOCK:** And thank you for having me.

**AHEARN:** So, why is it called ToxCast?

**KAVLOCK:** Ah, well the name really has two meanings. The first is we're trying to forecast the toxicity of a chemical, much like you'd try to forecast the weather, and give predictions about the kind of effects that might happen in animals, without using animals. The other part of the word, "cast," actually means we're trying to cast a real broad net as we're doing this. And so we're looking at hundreds of assays right now and using computers to try to understand the patterns that those chemicals are having across all those assays.

**AHEARN:** So tell me a little more about how these assays work.

**KAVLOCK:** Ok, so a lot of these assays that we're using in ToxCast were actually developed in the pharmaceutical industry to find new drugs. And what a pharmaceutical company will do when it's looking for a new drug is it will have what they call a library of chemicals and what they will do, using robots, is they'll test 10,000, 100,000, a million chemicals across one of these particular assays, and they'll try to find what they call a lead candidate for drug development. And then through a process of talking to chemists they'll try to make that a better and better and better drug. And what we've done is taken them and not looked for what good these chemicals might do in the environment but to take those same assays and see, well, maybe they could be causing biological effects—those are the mechanisms by which chemicals would be causing toxicity. And so we've collected a large array of these assays in this paper we published in *Environmental Health Perspectives*, 467 different assays, and then we've taken 300 chemicals that we pretty

much know a lot about, and we've tested them in these 467 assays and then used computers to help find these signals about what patterns the chemicals were causing and how those related to the toxicities that we knew would happen if we treated an animal.

**AHEARN:** So let's take one chemical for example. How about bisphenol A? It's already on the market. It's a known estrogen imitator. How would ToxCast treat bisphenol A?

**KAVLOCK:** Well we actually put bisphenol A into our first phase of experiments, one of the 300 chemicals, because we knew a lot about what it did. We know that it binds to the estrogen receptor, and we know at certain exposures that interaction with the estrogen receptor can cause some toxicities in experimental animals. And so as part of the proof of concept we would want to see in our data, could we see that same signal? And indeed when we look at our data, we have five assays that look at various aspects of whether a chemical acts like an estrogen or not. Bisphenol A is active in every single one of those assays that we've looked at. So, if we didn't see that, we would be really worried that the approach that we're using isn't going to work for chemicals we know nothing about. So bisphenol A being a very well-studied chemical helped us establish the proof of concept that our approach is actually going to be worthwhile looking at other chemicals.

**AHEARN:** But will your findings change the way we regulate bisphenol A, for example?

**KAVLOCK:** Not in the foreseeable future I don't think, because one of the things that we're trying to do with our assay system is find information on those chemicals for which we don't know anything and help guide the design of animal studies that will give information that will be important for risk assessment. So hopefully in the future this is going to lead to a much more intelligent way that we test chemicals for effects in animals and use that information to assess whether they're going to be harmful to humans or not.

**AHEARN:** The human body is such a complex system. How can you say that your findings in a test tube in a lab are going to be replicable or applicable to an entire human organism?

**KAVLOCK:** Excellent question. Our approach is very, very reductionist in nature. So we're taking the protein or the cell that we think is the target of a chemical, we're isolating it, and we're exposing it to the chemical in a very artificial environment. And the question that you ask is, how do we know that that actually reflects what happens back in the biology that's happening in an individual? And no system is ever going to be perfect. Rats aren't perfect at predicting humans by any means, and *in vitro* systems are not going to be perfect for predicting all of human biology. The robots that we're using don't have livers, and so the fact that, you know, when a chemical comes into the human body, one of the first things it does is it winds up in the liver, and the liver takes a look at it and says, you know, "I want to get rid of this," so it starts to metabolize it and get it in a format that we can excrete it easier. Well, mimicking that in *in vitro* systems happens to be a real challenge, and we're now working through a number of different ways that we think might address that. But we're still not happy we've got a really good solution for that.

And then another lack that we have is we're looking at 467 assays right now. We may need to have 2,000 or 3,000 assays before we cover enough human biology to be comfortable that when we say something doesn't have an effect, that we've covered all the bases correctly.

**AHEARN:** Yeah, that's a big, big statement to make. I mean, you're basically ruling out—potentially at a very early stage—future testing on a chemical, it seems.

**KAVLOCK:** Well, and it's the issue of false negatives. You want to have as few false negatives as possible in the system, because if you put something low in a priority queue, we may never get to it, and so you really want to have confidence that when you say something is negative, it really does have a low potential.

**AHEARN:** So for some chemicals in the environment—I'm thinking again of bisphenol A that imitates estrogen—we've seen results in lab studies, anyway, at very low doses over long periods of time. Can you talk a little about how ToxCast could address that issue in terms of in-lab testing?

**KAVLOCK:** So let's presume we knew nothing about bisphenol A. Let's say it was found on the moon, and it was a new chemical. Nobody knew anything about it. You know, it would be given to us, we'd put it into the ToxCast program, and we would look at the kind of activity that was being displayed. And lo and behold, for this particular chemical that came from the moon that we knew nothing else about, we see that it's interacting with the five different estrogen receptor assays that we have in our battery. And in fact, of the 300 chemicals we've looked at, it's the most active one against that assay. So our results would tell us, if we knew nothing else about this chemical, that it looks like it's an estrogen, it's interacting with estrogen biology, and therefore if you're going to do animal studies, you would focus on animal studies that would inform you about what estrogens would do in the body.

**AHEARN:** But again, it wouldn't—I mean, your ToxCast would not itself—be able to give you that data, those long-term exposures.

**KAVLOCK:** No, no. Certainly not right now. Maybe five or ten years from now as this field develops and gets more mature.

**AHEARN:** The government just approved $30 million for more testing on bisphenol A, and I'm just curious, how much could ToxCast save taxpayers?

**KAVLOCK:** Well, that's a difficult number to come up with.

**AHEARN:** Right off the top of your head [LAUGHING].

**KAVLOCK:** Right now we're spending about $20,000 a chemical to do this fingerprinting that we're doing. You contrast that with about $10 million of toxicology that you would do on a food-use pesticide, which would be the Cadillac treatment for toxicology.

**AHEARN:** Yeah.

**KAVLOCK:** It's really hard to say how much we would save, but you have to think of it, what we would learn too, because the thousands of chemicals out there that we want to know something about, we're not going to spend $10 million a chemical on it. Our lives are too short, animal facilities are too limited, and frankly some of these chemicals don't make $10 million worth of profit for the chemical industry even. So I think it's really chipping away at this knowledge gap that we have that's the real strength, and I don't know what price you can put on that.

**AHEARN:** How will ToxCast change the way we regulate chemicals in this country? I mean, will people be more safe because of ToxCast?

**KAVLOCK:** Hopefully, that's why we're doing this, is to increase human health protection. And by having these technologies available we can look at a lot of different chemicals in a way that's never been able to be possible before. We're going to be able to identify a larger number of chemicals that have the highest potential for risk and that we can begin to then look at them from a regulatory agency and say, "Well, how do we manage that risk? How do we mitigate that risk? How do we reduce exposures to those chemicals that are going to cause the most potential for harm?" And right now we don't have a very efficient way of doing that for large numbers of chemicals, so this is the hope that as we go forward in the future we're really going to be able to do a much better job of finding the bad actors out there and doing something about them.

**AHEARN:** Well Dr. Kavlock, thank you very much.

**KAVLOCK:** And thank you.

**AHEARN:** Dr. Robert Kavlock is the head of the National Center for Computational Toxicology with the Environmental Protection Agency.

**AHEARN:** And that's *The Researcher's Perspective.* I'm Ashley Ahearn. Thanks for downloading!

**Ashley Ahearn**, host of *The Researcher's Perspective*, has been a producer and reporter for National Public Radio. She is an Annenberg Fellow at the University of Southern California specializing in science journalism.