Message

From: Evans, Elizabeth [Evans.Elizabeth@epa.gov]
Sent: 10/15/2019 3:20:32 PM
To: Lowit, Anna [Lowit.Anna@epa.gov]
Subject: FW: OPP: Forbes Piece on Animal Testing and Pesticides

FYI only- here is a Forbes article – see the highlighted. Anna- please note that OPA responded to the Forbes inquiry.

From: Daguillard, Robert <Daguillard.Robert@epa.gov>
Sent: Tuesday, October 15, 2019 11:17 AM
To: OPP FEAD CSB <OPP_FEAD_CSB@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>
Cc: Dunton, Cheryl <Dunton.Cheryl@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>; Labbe, Ken <Labbe.Ken@epa.gov>
Subject: OPP: Forbes Piece on Animal Testing and Pesticides

Forbes: The EPA Is Changing How It Tests Agricultural Pesticides
https://www.forbes.com/sites/jennysplitter/2019/10/14/the-epa-is-changing-how-it-tests-agricultural-pesticides/#17173c432c14

If you ask most consumers whether they want to avoid pesticides in their food, they'll undoubtedly tell you yes, but few may understand how the government comes to approve these chemicals in the first place. On September 10, the U.S. Environmental Protection Agency announced a major change to its approval process, with an ambitious plan to eliminate the use of all mammalian testing by the year 2035.

It's a goal that some environmental groups say is too ambitious, potentially resulting in the unchecked approval of countless toxic chemicals. The scientists, regulators and advocates pursuing this change, however, disagree. They say the move will shift the agency towards a more accurate and humane approach to toxicity testing.

Chronic toxicity: beyond the poisonous dose

Pesticides are not a monolithic group. Some chemical formulations are made from synthetic ingredients, while others consist of only all-natural ingredients. Some persist or accumulate in the soil, water or in our bodies, while others break down relatively quickly. Still other chemicals are thought to have an endocrine-disrupting effect, even if they don't bioaccumulate.

Today In: Business

The risk of harm usually depends on the exposure. While consumers tend to take in only relatively harmless traces of chemicals from the fruits and vegetables they eat, the farmworkers who pick and pack these crops are exposed at much higher rates. Pesticide drift can also cause environmental harm, as has been the case with crop damage widely attributed to the pesticide dicamba.

One of the earliest methods of testing toxic substances on animals was developed in 1920 by the British pharmacologist J.W. Trevan. Trevan designed the test that measures a chemical's lethal dose—the point at which half of the animals in the test group have died due to chemical exposure.

Acute toxicity, that measurement of the lethal dose, is just one way of evaluating a chemical's toxic effects but, according to neuroscientist Alison Bernstein, PhD, it's not necessarily the most relevant, especially given the way most of us are exposed to chemicals in our daily lives.

"Most real human exposures are not acutely lethal," she writes in a blog post explaining the difference between acute and chronic toxicity, but have other, long-term or chronic effects that may or may not be toxic."

Farm workers pick strawberries at a farm on Telephone Road in Ventura. (Photo by Stephen Osman/Los Angeles Times via Getty Images)

LOS ANGELES TIMES VIA GETTY IMAGES

It's these chronic effects that first began to cause greater alarm in the 1960's, prompting a number of legislative attempts to create better regulatory oversight of agricultural toxicants. In 1970, President Nixon established the Environmental Protection Agency and, by 1972, all regulatory oversight of pesticides had shifted to the agency, where it remains to this day. While exact numbers aren't available, *Science* reports that toxicology tests of these chemicals submitted to the EPA use anywhere from 20,000 to over 100,000 animals annually.

Rodent tests are poor predictors for human health risks

Despite animal toxicity testing's long history, a growing coalition of scientists and animal rights advocates say these tests are both cruel and unreliable, a poor predictor for human disease. Human bodies aren't quite the same as mice or rats, explains Lena Smirnova, PhD, a neuroscientist at the Johns Hopkins Center for Alternatives to Animal Testing.

Johns Hopkins was one of five universities awarded an EPA grant for work developing alternative toxicity tests that could eventually replace animal testing. The Baltimore-based lab is working with microphysiological systems dubbed "mini brains" to observe neurotoxic effects.

"[Rodents] have a different metabolism," Smirnova explains. "They have different [types of] cells in the body. They react differently." According to one study comparing human and animal drug toxicities, for example, rodent models correctly predicted human toxicity in only 43% of the cases.

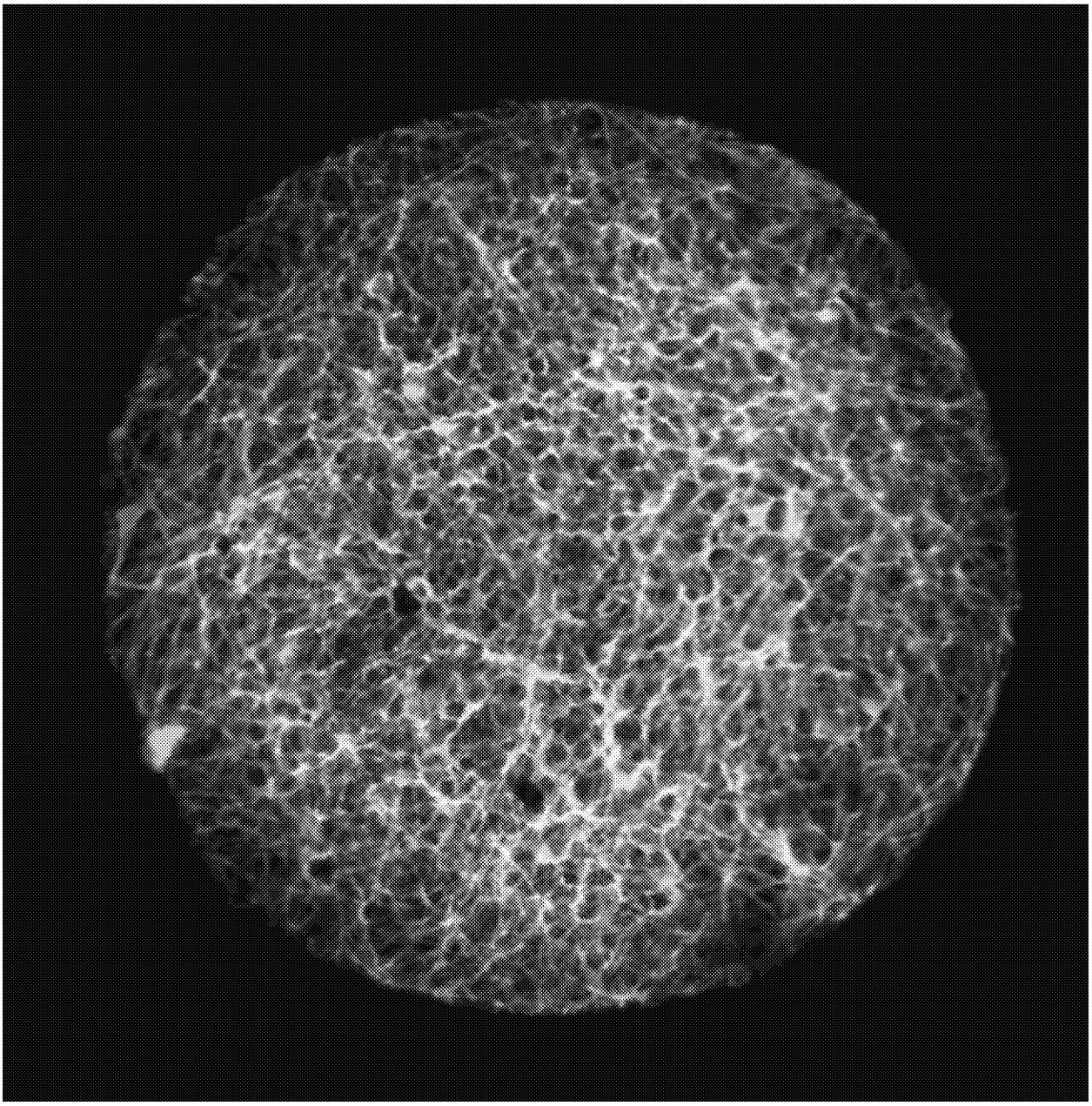
Rats and mice aren't even particularly predictive for each other, according to Smirnova. "If you look at something very complex, like reproductive toxicity or developmental toxicity or carcinogenicity, rats predict mice by around 60%. So why would we expect that it would be better in humans?"

Variations in people can make extrapolating from animal results even more challenging, Smirnova adds. "We have different ethnic groups. We have different backgrounds in terms of other diseases, [as well as] diverse environments."

For controversial pesticides like glyphosate or chlorpyrifos, more predictive testing of carcinogenicity and neurotoxicity could be able to provide some much-needed clarity. Chlorpyrifos, for example, is an organophosphate

insecticide that the EPA declined to ban for agricultural use in 2017. Former EPA administrator Scott Pruitt questioned the reliance on epidemiological studies showing increasing rates of disease in agricultural communities.

The decision was controversial and, as a result of increasing pressure and lawsuits brought by environmental and farmworker advocacy groups, the state of California recently reached an agreement with the pesticide's manufacturer to ban the chemical outright in the state. More toxicity evidence could shed new light on this controversy, potentially revealing more information about how these chemicals impact the human brain.



Fluorescent microscopic image of mini-brains. Neuronal markers are stained with green and red colors.

LENA SMIRNOVA, JOHNS HOPKINS

From inertia to a new way of thinking

In 2007, the National Academies of Sciences published a landmark report urging a reduction in animal testing and a move towards new methods for toxicity testing. But the report didn't spark an immediate response from EPA regulators, says Warren Casey, PhD, whose work at the National Toxicology Program helped drive the reduction in animal testing at agencies like EPA.

"It's certainly one of the most cited National Academies' reports," says Casey, but when he first started working on animal testing reduction in 2010, he says "it was pretty clear that there was a huge gap between something like what was being talked about in the National Academies report and what was actually happening in regulatory agencies."

"You've got this inertia," says Amy Clippinger, PhD, President of the International Science Consortium for People for the Ethical Treatment of Animals. Clippinger is also a member of the scientific advisory panel working towards reducing animal testing at the EPA and other government agencies. Overcoming inertia, she says, requires a real paradigm shift. "You have to stop and really think about things differently."

For Casey, the starting point was to involve the regulators themselves. "No one was really digging hard to try to make a connection between what's required now for regulators and then kind of work backwards to figure out what tests are already being used," he says. Just asking these very simple questions eliminated an enormous amount of testing, says Casey.

He first saw real traction at the EPA in 2013 (other agencies are making similar shifts on their own timelines), when a new working group was formed that included EPA scientist Anna Lowit, PhD, who Casey says has been instrumental in implementing change.

The EPA declined to grant an interview with Lowit, but provided a statement that reads, in part:

For more than four decades, EPA has invested in the research and development of NAMs for testing chemicals, and continues to develop methods for broader acceptance and implementation for use of NAMS in risk assessment. NAMs refers to any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment that avoids the use of intact animals. Two examples of NAMs are in vitro tests using cells in culture and computer-based prediction models.

FDA Spokesperson

Tools like data mining can reduce animal testing

While it might not be as sexy as the experimental mini-brains, Casey says organizing the agency's testing data into something searchable turned out to be a highly effective way to reduce unnecessary animal testing.

"Helping [the regulators] get the resources they need...was, I think, a real turning point," he says. "We think a lot of this information is somehow computerized and that it would be easy to get to," but, according to Casey, that's far from the case. "We had our staff go through thousands of scanned PDF documents to pull out a lot of information."

UNITED STATES - SEPTEMBER 24: Sara Amundson, president of the Humane Society Legislative Fund, holds Paxton, a 4-year-old rescue rabbit, during an event to note the importance of using cruelty-free products that are not tested on animals, in Rayburn

CQ-ROLL CALL, INC VIA GETTY IMAGES

With searchable systems in place, regulators can use data mining and other computational tools to locate previous testing results and determine whether the animal test is even needed. "There's actually a tremendous opportunity to save a lot of animals by using waivers [for certain toxicity tests] instead of alternative methods."

Both Clippinger and Smirnova say this is really a whole new framework for toxicity testing. The starting point, says Clippinger, is not to simply replace the test but to first carefully consider the evidence that the test was actually providing.

In some cases, regulators are reviewing new chemicals that are virtually identical to many existing chemicals that are already well-tested. In those cases, additional testing may not be needed. "When the chemical has properties that are similar enough to something they've already tested," says Casey, "they don't require [a repeat of the same] test."

Researchers outside of government agencies are using many of these computational methods too, in some cases to make more accurate assessments of the risk of disease.

Clippinger points to a PETA researcher working on a study evaluating how useful the two year rat assay has been for predicting cancer risk, for example. In a number of instances, animal tests were ordered even though the cancer risk was already abundantly clear. In those cases, says Clippinger, "you don't need an additional test to predict cancer."

researcher in Johns Hopkins lab

MICHAEL HUGHES, CAAT

Mini brains and other human cell-based testing alternatives

At Johns Hopkins, Smirnova is testing the pesticides chlorpyrifos and rotenone on her lab's "mini brains" to observe their neurotoxic impacts. These blob-like "organs-on-chip" may not look like much in their petri dishes, but scientists like Smirnova believe they're the future of animal testing alternatives.

To create these mini brains, scientists first take blood or skin cells and genetically reprogram them back into an embryonic stem cell state. The stem cells can then be grown to mimic the key brain functions that the scientists want to test. "It's really booming," says Smirnova, of the still fairly new research area. "Eventually you may even be able to do a human on a chip," she says, adding cautiously, "in the future," of course.

Smirnova's lab is continuing to develop these mini brains as an alternative testing method. "We want to make it as easy as possible [to] perform the screening," she says, of their future plans. "We want to...optimize our mini brains [so] we can test, let's say, six different assays in one test."

These human cell-based approaches have many different applications. Some researchers are working on animal testing alternatives in carcinogenicity, while others are working in the area of reproductive toxicity. There are also researchers developing computational models and data mining tools.

These days, the field of animal testing alternatives is exploding, says PETA's Clippinger. "I would say that for all of the different [disease] endpoints, someone is working in that space."

Animal rights advocates align with small government conservatives

The groups who favor reduced animal testing are a bit of an unlikely coalition, according to Justin Goodman, whose organization, White Coat Waste, has worked with both Republican and Democratic legislators to persuade agencies like EPA to reduce animal testing.

Goodman says these allies include "not only traditional animal rights types who are predominately liberal but...animal lovers across the political spectrum [and] people who favor things like small government." The common thread is their agreement that these tests aren't providing useful information. "There's no evidence to show that these studies predict what will happen in people," he argues.

Jennifer Sass, PhD, a senior scientist with the National Resources Defense Council, disagrees, at least as far as complex disease endpoints like cancer are concerned. "NRDC's position is that animal tests work," she says. The environmental advocacy group would like to see EPA take a more precautionary approach and prohibit chemicals that show any evidence of harm in animals.

Sass, who is also part of the scientific advisory panel to the National Toxicology Program, does support the replacement of acute toxicity tests. It makes sense to replace an animal skin test in cases where you can examine the toxic impacts to human skin cells themselves in a petri dish, for example. But she's concerned that the EPA is moving far too fast to replace tests in more complex areas like cancer or reproductive toxicology.

French farmer Nicolas Denieul sprays Roundup 720 glyphosate herbicide produced by US agrochemical giant Monsanto on May 11, 2018, on a field of no-till corn in Piace, northwestern France. - Using a 10-year old conservation farming practice, French

AFP/GETTY IMAGES

Scientists do need to be cautious, says Casey, especially when it comes to chemicals that could be linked to something like cancer risk. "There's a lot of sensitivity." New tests need to be properly validated. "People have to have confidence that it can actually predict what it's supposed to predict."

Casey points out that the more experimental approaches are a long way from adoption at the regulatory level, including the mini brains. Before that can happen, says Casey, these experimental methods will need to be thoroughly vetted, which means results that can be reproduced and replicated.

Sass says her concerns are driven more by policy than they are disagreements over data. "Usually we agree on the science," she says. "I can sit down with industry and EPA scientists and we can all agree on what the data is, but then what do you do with that," she asks. "If two cells die in a culture dish, do you ban a chemical? No, but what if it's two hundred?"

Clippinger, however, remains confident in the EPA's approach. "When new tests are accepted or previously required tests are waived, it's because EPA scientists have done a thorough scientific review." But not everyone shares her confidence, especially given the current presidential administration's history of ignoring its own scientists.

Still, Clippinger maintains "this is one area where it doesn't matter what sector you're from, there's a lot of agreement on the need to modernize toxicity testing." The way forward for many of these environmental advocacy groups, she says, is to become more involved in the process.

"We want all sides represented," she says firmly. It's been a long road for her own organization, PETA's science consortium. "It's really different than it was twenty years ago," Clippinger says, when "we had to really fight to get any meetings." Now, "we actually don't even have the bandwidth to keep up."

Cheers, R.

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