EPA's Proposal to Eliminate Animal Testing May Speed Up Pesticide Safety Reviews, but at What Cost?

Any new assessment protocols must consider alternatives to toxic pesticide use

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When U.S. Environmental Protection Agency (EPA) Administrator Andrew Wheeler announced that EPA will be phasing out testing of chemicals on animals[1] and replacing it with "computational toxicology (based on computer modeling)," the reaction was mixed. Environmentalists who work in the field of risk assessment pointed out the inadequacies of *in vitro* (in glass containers) and *in silico* (computer-based) methods of assessing risk. Meanwhile, animal rights organizations support the move. Could it be that both are wrong—or at least shortsighted—in their reactions?

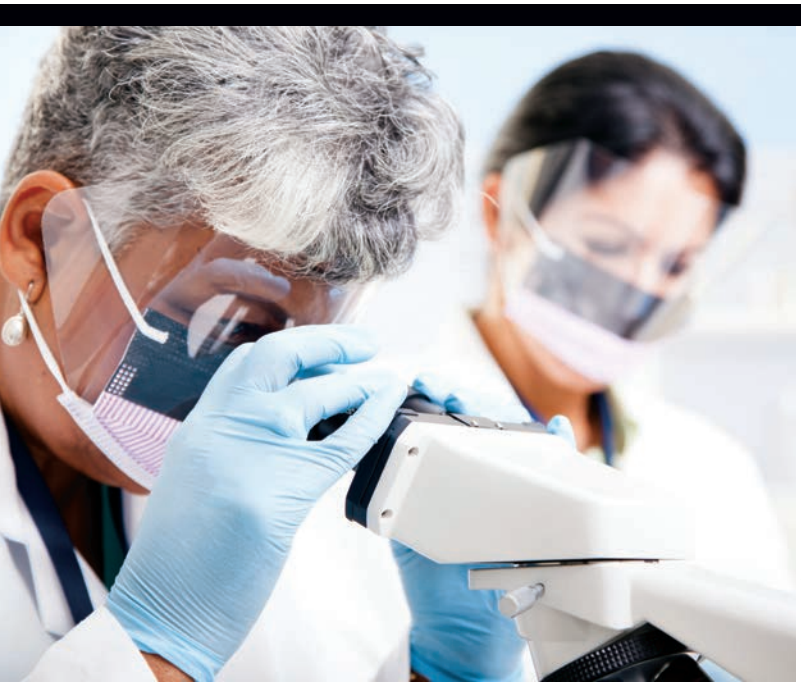
The announcement from EPA came in September, 2019: "Today's memo directs the agency to aggressively reduce animal testing, including reducing mammal study requests and funding 30% by 2025 and completely eliminating them by 2035," said Mr. Wheeler. "We are also awarding $4.25 million to advance the research and development of alternative test methods for evaluating the safety of chemicals that will minimize, and hopefully eliminate, the need for animal testing."

Jen Sass, PhD of the Natural Resources Defense Council (NRDC) says, "Phasing out foundational scientific testing methods can make it much harder to identify toxic chemicals—and protect human health."[2] Scientists Laura Vandenberg, PhD and Tom Zoeller, PhD, University of Massachusetts Amherst, agree, saying, "Cell- and computer-based approaches cannot reproduce effects that occur in the whole animal, especially during development."[3]

But Amy Clippinger, PhD, director of the regulatory testing department for People for the Ethical Treatment of Animals (PETA), says, "PETA is celebrating the EPA's decision to protect animals certainly—but also humans and the environment—by switching from cruel and scientifically flawed animal tests in favor of modern, non-animal testing methods."[4]

USING COMPUTATIONAL TOXICOLOGY

The computer-based methods encompassed by the term "computational toxicology" offer great promise for reducing toxic chemicals. In order to be protective, however, they must be used in concert with other methods and embedded in a regulatory system that requires chemicals to be removed from the market when hazards or safer alternatives are demonstrated. In other words, they must be part of an alternatives assessment process that questions their essentiality or necessity, given the availability of nontoxic methods or products. The methods should be used with a precautionary approach—in other words, if a chemical "fails" a computer model (or *in silico* test), it should not be allowed to be marketed. However, materials that "pass" such tests should move on to *in vivo* (in organisms) and *in vitro* tests to ensure that the complexity



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of endocrine and other physiological functions is fully considered. This approach takes on more urgency as part of a general national and worldwide emergency to eliminate fossil fuel-based pesticide production and use in an effort to confront the climate crisis and dramatic declines in biodiversity.

THE ARGUMENT FOR ELIMINATING ANIMAL TESTING

There are many reasons to avoid toxicological testing on animals. The primary argument against animal testing is that it inflicts pain and suffering on nonhumans without their consent, for purposes that do not benefit the experimental animal. This may be expressed in terms of rights—"Animals have a basic moral right to respectful treatment.... This inherent value is not respected when animals are reduced to being mere tools in a scientific experiment."[5]

EPA's concern for animals, however, is not the primary motivation for shifting away from testing toxic chemicals on animals. For several years, EPA has been researching efforts to estimate real world chemical interactions and exposure through computer models, known as "computational toxicology," in the belief that they offer some promise for identifying chemicals that adversely affect the endocrine system and have other toxic effects and speeding up reviews.

Computational toxicology uses computer models to combine data generated by a variety of real world tests, both *in vivo* and *in vitro*, with theoretical knowledge based on factors like structural relationships to chemicals with known toxicological properties. These models replace risk assessments based on testing of actual organisms with "toxicity-pathway-based risk assessments" based on virtual organisms having virtual tissues composed of virtual cells that interact with virtual chemicals. Exposure estimates are also based on computer models of how toxic chemicals and their metabolites reach cells in the body where they can affect physiological processes. The assessment of virtual risk produced by this process is anticipated to replace conventional risk assessment over the next decade or two.

The failure of EPA to test pesticides for their potential endocrine disrupting effects,[6] required by Congress more than 20 years ago by the Food Quality Protection Act (FQPA) of 1996, has driven the movement within the agency to adopt nonanimal testing procedures. To help meet the requirements of the act, EPA sponsored a National Research Council (NRC)/National Academy of Sciences report, *Toxicity Testing in the 21st Century—A Vision and a Strategy* (2007), which recommended the use of "computational toxicology."[7] With this approach, some in the agency suggest that they would be more successful in implementing the Tiered Protocol for Endocrine Disruption (TiPED), a five-tier testing protocol—ranging from broad in silico (computer simulation) evaluation through specific cell- and whole organism-based assays—developed by a multi-disciplinary group of independent scientists.

ANY OVERHAUL MUST INCORPORATE A PRECAUTIONARY APPROACH

While computational toxicology promises to eliminate the logjam in screening a large number of pesticides for their endocrine disrupting properties, and also presents a way to screen industrial chemicals coming on to the market—and could be used in overhauling the *Toxic Substances Control Act* (TSCA) review process—new models do not inherently address the need for a precautionary regulatory approach to toxic chemical approval. In fact, a precautionary approach makes the maximum use of existing data and minimizes the extensive animal testing conducted under current toxic chemical regulatory testing protocols.

It should be kept in mind that the need for testing toxic or potentially toxic chemicals only arises because the release of such chemicals in a way that exposes humans and others is under consideration. If we were committed to living without toxic chemicals, or at least a significant number, then we would not need to test chemicals to determine how toxic they are.

THE ARGUMENT AGAINST ELIMINATING ANIMAL TESTING

Those who argue against eliminating animal testing point out the shortcomings of other types of tests. The comparison of the different ways in which computational toxicology could be used by EPA under the *Federal Insecticide, Fungicide, and Rodenticide Act* (FIFRA), TSCA, and TiPED protocol for endocrine disruptors, and by European Chemicals Agency (ECHA) under the EU's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation illustrates some of the problems that might arise in EPA's proposed use for screening pesticides for endocrine disrupting chemicals (EDCs). Potential problems include:

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- **Reduced transparency for the public.** First of all, reliance on computer models can reduce transparency in regulation. Animal testing looks for actual effects on actual animals. Computational toxicology extrapolates estimates of actual effects from study results on related chemicals or effects inferred from results on cells in *in vitro* testing. This may not be transparent to the general lay public. Only those few with training in these methods will be able to understand and comment on their use. The chemical industry has always challenged the extrapolation of toxicological testing on laboratory animals to the human population, so it is expected that EPA will be challenged by industry when it proposes to restrict, cancel, or suspend the use of a pesticide based on the results of comprehensive computational models.

- **Lack of attention to complexities.** The extreme reductionist approach, depending on computer models with an unknown range of applicability, poses a problem for dependence on computational toxicology as the sole source of toxicity information. Particularly concerning is EPA's view that it could "eliminate currently used uncertainty factors." In fact, dependence on computational toxicology can increase uncertainty. Whenever relying on computer models, caution is essential to avoid the phenomenon of "garbage in, garbage out" (GIGO). Computer models must be based on sound science and have solid data as inputs. The creators of TiPED point out that, although computational methods have a place, reliance on them alone would create many false negatives. The committee found, "The complex biology of endocrine disruption means that **no single assay nor single approach** [emphasis in original] can be used to identify chemicals with EDC characteristics. Instead, a combination of approaches is necessary, including computational methods as well as both *in vitro* and *in vivo* testing.... Today's *in vitro* and computer models do not incorporate the complexity that this involves. For this reason, *in vivo* assays will also be necessary."[8]

- **Sacrificing precaution for a simpler testing scheme.** Under REACH, chemical manufacturers are required to both avoid animal testing and justify the need for the chemical based on the availability of safer alternatives. This adds an additional layer of protection that is not present in EPA's proposed methodology.

Much of the emphasis in proposals for using computational toxicology is focused on evaluating new chemicals—probably because taking existing chemicals off the market is such a daunting task. However, the current situation allows humans and all other organisms to be exposed daily to many chemicals that should not be present in the environment. Any methods of evaluating chemicals that are used must be embedded in a regulatory system that allows for the removal of EDCs and other problematic chemicals.

A SOLUTION

Certainly, environmentalists and animal rights activists should be able to find common ground. Use of *in vitro* and *in silico* methods will endanger many animals—wild and domesticated—if they lead to allowing the release of dangerous chemicals into the environment. But neither has animal testing protocol prevented the use and dispersal into the environment of dangerous chemicals. In fact, in arguing the need for animal testing, Drs. Vandenberg and Zoeller give evidence that current animal-based testing is inadequate:

> First, chronic diseases are at a record high in the U.S. and elsewhere. Today, nearly 20 percent (one in six) of America's children are diagnosed with a developmental disorder including ADHD, autism, and other learning disabilities....

> Second, many experimental studies show that chemicals approved as safe have harmful effects in human and animal studies. A failure to recognize the fact that chemical exposures are contributing to chronic diseases, with an accompanying increase in health care expenditures, is a failure to recognize the role that EPA must play in today's society.[9]

In addition to the need to evaluate and eliminate hazardous chemicals, the framework in which chemicals are evaluated must change. The *Organic Foods Production Act* (OFPA) provides us with a good model, since the law creates a default bias against synthetic chemical use—natural materials are acceptable unless shown to be hazardous, and synthetic materials are unacceptable unless it is determined that there is an absence of harm (in chemical life cycle analysis)—and the material is essential to and compatible with an organic management system, as defined by law and certified by a third party. As in the TiPED protocol, harm is evaluated regardless of exposure. Synthetic chemicals should not be allowed to be used unless they are essential, and unless their use is sustainable. The law incentivizes investment in nonsynthetic materials for agricultural and processing aids through a petition process that forces the synthetics they are replacing off the allowed list of substances.

We could both reduce the number of animals harmed in testing *and* protect the environment, including *all* animals, if we reverse the priorities in our policies. Instead of a default allowance of toxic chemicals (unless we have overwhelming proof of harm), we should insist on a default prohibition of the dispersal of synthetic chemicals unless they can meet a high standard of essentiality and absence of harm.

If such a standard seems impossible, consider the fact that the $52-plus billion (and still growing) organic industry is regulated by a law that requires such a standard—and more. The standard in OFPA is applied by a board of stakeholders—including farmers, environmentalists, consumers, retailers, scientists, and organic certifiers—who must find (by a two-thirds majority) that the manufacture, use, misuse, and disposal of the chemical is necessary for organic production because of the unavailability of wholly natural substitute products, is not harmful to human health or the environment, and is consistent with organic farming and handling. In addition, those decisions are required to be revisited every five years under a sunset provision. While the vested economic interests of industrial agriculture and major food processors are trying to chip away at these rigorous standards, which have served as the foundation of organic market growth, federal organic law provides a framework for assessing whether there is harm and justification for toxic chemical use in light of alternative practices and materials.

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Despite the constant barrage of petitions by manufacturers of inputs used in nonorganic production, the list of synthetic materials allowed in organic production remains small.[10] And organic production is growing faster than any other form of agriculture. Current retail sales in the U.S. in 2018 is up 6.3% from 2017.[11]

Jay Feldman is a contributor to this piece.

ENDNOTES

1 *https://www.epa.gov/newsreleases/administrator-wheeler-signs-memo-reduce-animal-testing-awards-425-million-advance.*

2 *https://www.huffpost.com/entry/epa-to-reduce-animal-testing_n_5d78e5e4e4b0432f81759073?guccounter=1.*

3 *https://www.ehn.org/epa-lab-animals-chemical-testing-2640450647.html.*

4 *https://www.cnbc.com/2019/09/10/reuters-america-update-1-u-s-epa-chief-to-reduce-agency-funded-animal-testing.html.*

5 Tom Regan, an American philosopher who specialized in animal rights theory, quoted in *http://www.lonestar.edu/stopanimaltesting.htm.*

6 See "Pesticides That Disrupt Endocrine System Still Unregulated by EPA," Spring 2008, "While France Bans a Common Endocrine Disrupting Pesticide, EPA Goes Silent," Spring 2019, *Pesticides and You*.

7 For more information, see the article "The Promise and Challenges of 21st Century Toxicology," *Pesticides and You*, 36:1, Spring 2016.

8 T. T. Schug, R. Abagyan, B. Blumberg, T. J. Collins, D. Crews, P. L. DeFur, S.M. Dickerson, T. M. Edwards, A. C. Gore, L. J. Guillette, T. Hayes, J. J. Heindel, A. Moores, H. B. Patisaul, T. L. Tal, K. A. Thayer, L. N. Vandenberg, J. C. Warner, C. S. Watson, F. S. vom Saal, R. T. Zoeller, K. P. O'Brien and J. P. Myers, 2013. Designing endocrine disruption out of the next generation of chemicals. Green Chem., 2013, 15, 181–198.

9 *https://www.ehn.org/epa-lab-animals-chemical-testing-2640450647.html?rebelltitem=1#rebelltitem1.*

10 *https://ota.com/advocacy/organic-standards/national-list-allowed-and-prohibited-substances.*

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