Meeting Report

EFSA – Johns Hopkins Food Safety Symposium 2019

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Assessing and managing risk when it comes to food safety involves a complex process that often places scientists in the uncomfortable position of having to defend their science against societal and political values that are at odds with scientific goals. When risk managers cannot trust science, we all are at risk. The only way to foster trust in the scientific process is a three-fold approach that includes engagement of the public, collaboration to solve issues that cross international, scientific and interdisciplinary boundaries, and support of new science that will improve our ability to draw conclusions that can be reproduced and validated.

These were the conclusions of the Food Safety Symposium, held on September 5, 2019 at the Johns Hopkins Bloomberg School of Public Health. The event, co-sponsored by the Center for Alternatives to Animal Testing (CAAT) and the Center for a Livable Future (CLF), focused on risk assessment and risk management in food. The symposium can be viewed on CAAT's YouTube Channel: <https://youtu.be/5QMM9uIRjN8>

The opening lecture, "Optimizing Scientific Value through Engagement with Society," was presented by **Bernhard Url**, executive director of the European Food Safety Authority (EFSA). He focused on the need for science and scientific agencies to be perceived as trustworthy by the public and by those who rely on scientific conclusions to make informed decisions about risk assessment and food safety.

In his presentation, Url asked, what defines quality in science and how do scientists create trust in the scientific process? He explained that EFSA's role in the process is limited to risk assessment and providing scientific advice to risk managers and regulators. They do not inspect or manage food safety, but instead provide scientific opinions on a wide range of issues to risk managers across Europe.

EFSA staff focus on plant and animal health, animal welfare as well as chemical contaminants, microorganisms and parasites. They also provide risk and safety assessments for what is known as "regulated products," such as genetically modified organisms (GMOs), pesticides, and food additives. They operate with a staff of 500 in Parma in northern Italy. In addition to the staff, most of whom are scientists, EFSA collaborates with scientists from EU member states. This allows EFSA the flexibility to bring in the top people on any issue, Url said. Since its creation in 2003, EFSA has used this approach to produce approximately 500 scientific outcomes per year.

Url emphasized that risk managers will not follow EFSA's recommendations if they do not trust the science upon which they are based. The issue is complicated by the fact that risk management involves the consideration of societal and political values that sometimes can run counter to the science. He cited a recent example involving the herbicide glyphosate, which has been re-

viled by activists as carcinogenic despite risk assessments having shown that glyphosate is safe when used according to authorized guidelines. With activists insisting that scientific opinions cannot be trusted, risk managers have been caught in the middle and found themselves questioning the scientific process, Url said.

Risk managers are under a lot of political pressure, and scientific assessments are not always easily managed because of this lack of public trust. In academia, Url pointed out, research is hypothesis-driven; either the results support the hypothesis or the hypothesis is discarded. Either way, there is a peer-reviewed publication in the end. But if there is a lack of trust in the regulatory community, it becomes a problem for everyone concerned with food safety, because the decision-making process breaks down. EFSA is not alone in this, Url said. In the United States, the Food and Drug Administration (FDA) also reports that communication and trust are pressing issues. He referred to this as the era of "Facebook science," in which decisions are based on how many "likes" an opinion receives, rather than on sound science.

A new approach to engagement with the public is necessary to move forward, Url explained. Transparency alone is not enough. The old, so-called "information deficit" model – "we know the truth, the people don't, but if we lob enough information at them, they will trust us" – no longer works, he said. EFSA strives to engage the public in their process at every step, because Url believes this is the only way trust can be created.

The process is critically important, because the questions facing scientists and risk managers are complex. Engagement is essential to persuade governments to invest in food safety research. For example, Url said, by 2050, we will need to feed 10 billion people while lowering greenhouse gases and restoring biodiversity. Scientists and policy makers will need to work hand in hand if they hope to find a solution to this dilemma. The goal, Url said, is for people to say, "I don't like your outcomes because they are counter to my values, but I trust your process."

The second presentation expanded upon the theme of stakeholder engagement. **Marta Hugas**, EFSA chief scientist, talked about efforts to use engagement to influence the scientific community's research agenda to meet the needs of risk assessment.

In doing risk assessment work, EFSA often encounters knowledge gaps. For example, how to model a way to measure the risk of exposure to multiple chemicals? How to assess the synergistic effect of pesticides on pollinators? How to prepare for the demands of global warming? How to replace animal testing with other models? How to include big data in risk assessments? What is the impact of microplastics in the environment on human health? How do we protect against vector-borne diseases and their impact on our food systems?

In the EU, more than 30 agencies are responsible for providing scientific advice to policy-makers. Too often, Hugas said, they work separately instead of collaborating to identify the questions most in need of research. An integrated approach is necessary to address the complex questions facing policy-makers. Independent research often does not address the questions EFSA and other agencies need to answer. For example, recent research on the human microbiome has long-ranging implications for risk assessment. Studies indicate that the human microbiome could be affected by environmental chemicals. Scientists are accustomed to thinking of people, animals and the environment separately when they assess risk, but this research suggests that the health of all three is interrelated.

Hugas said EFSA is working to broker a new systems approach that brings policy makers in risk assessment together with members of the research community to make scientists aware of critical knowledge gaps and encourage targeted research.

In the third talk, **Martin W. Bloem**, director of the Center for a Livable Future (CLF) and the Robert S. Lawrence Professor of Environmental Health at the Johns Hopkins Bloomberg School of Public Health, reiterated the complexity of the food system in addition to stressing the challenges associated with food safety. Obesity, undernutrition, and climate change are significant global challenges that continue to negatively impact the world's population.

Bloem cited a 2019 study he co-authored with several colleagues from CLF. They developed a model to assess how alterations to dietary patterns across 140 countries would impact individual- and country-level greenhouse gas emissions and freshwater use. The model examined both per capita and whole country climate and water footprints of nine plant-forward diets. He suggested that in order to successfully counter climate impacts associated with food production and address diet-related morbidity and mortality, high-income countries should work to accelerate their adoption of plant-forward diets. However, he cautioned that there is no "one-size-fits-all" approach and that any recommendations should balance health, nutritional needs, cultural preferences, and planetary boundaries. The novel methodology used in the study allows for data-driven comparisons between countries and regions, Bloem suggested, and also takes into account different contexts and conditions in those countries. He believes this work will serve as the foundation for CLF's expanding role in addressing the food system, climate, and nutrition crises. He and colleagues have already begun connecting with partners at the global level to advance this work.

Keeve Nachman, Program Director for the Food Production & Public Health Program at the Johns Hopkins Center for a Livable Future, presented a talk entitled "Safe Urban Harvest." Because the research on which his presentation was based is currently unpublished, we have omitted a summary of its contents here, per his request.

Katya Tsaïoun, director of the Evidence-Based Toxicology Collaboration (EBTC) at the Johns Hopkins Bloomberg School of Public Health, underlined the importance of multi-stakeholder engagement and EBTC's relationship with regulatory agencies like EFSA. She emphasized the need for a rigorous, reproducible framework for risk assessment in food safety that is grounded in evidence-based methodologies and accepted by all international regulatory authorities.

Any new science will have to address three barriers, she noted: cognitive bias ("I use what I have always used because I always used it"), lack of trust, and resistance to change. She emphasized that progress in adapting systematic reviews and evidence-based approaches to risk management was made primarily in the last decade, starting with the pioneering application of systematic reviews in food safety by EFSA (2010). In the United States, the 2016 US EPA Toxic Substances Control Act (TSCA) mandates the use of systematic reviews in safety assessment.

However, she noted, there are still many challenges to applying systematic reviews to toxicology and risk assessment, which EBTC is working on with all stakeholders. For example, there is a lack of reporting standards in the primary scientific literature. In toxicology, there is currently no requirement for reporting key questions, hypothesis, models used, or findings in the abstract. This makes conducting systematic reviews very time-consuming. The structured abstract requirement, which is the standard for reporting clinical research, is a step that would begin to address this problem and would facilitate conducting systematic reviews not only by human researchers, but also by deployment of machine reading and AI-assistance in scientific literature reviews. There is also a lack of agreement among journals on the minimum standards for systematic reviews in the field of toxicology. EBTC is working with major toxicology journal editors-in-chief on a consensus statement for minimum standards.

EBTC, established by the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), strives to apply evidence-based medicine methods to toxicology. Their working groups conduct and supervise systematic reviews of published literature, work with all stakeholders on developing risk-of-bias and quality assessment tools for toxicological studies, and disseminate information about evidence-based methods to the toxicology community through participating in meetings, continued education sessions, and expert workshops and working groups. EFSA scientific staff are actively engaged in and are co-leading many of these EBTC projects.

Thomas Hartung, director of CAAT, said that Europe has become the leader in regulatory progress in risk assessment and food safety through the efforts of organizations like EFSA. In the United States, CAAT strives to build collaborations between academia, industry, and the federal government.

Hartung said CAAT was established 38 years ago to focus on the "3Rs" of animal alternatives: replacement of animal experiments with non-animal models; reduction of the number of animals used in scientific research; and refinement of animal experiments to ensure that animals experience as little pain and discomfort as possible. Philanthropic support makes up more than 50% of their budget; about 30 corporations also contribute significant support. Their board includes representatives from industry, academia and both U.S. and international regulatory agencies including EFSA. CAAT has a European branch, CAAT-Europe, which was established in 2010. He emphasized that CAAT is focused on more than animal welfare; their focus is on science and on extending non-animal approaches to areas in which animal models are not a good fit.

Although there is a common misconception that integrating alternatives to animal testing is impossible, Hartung noted that in toxicology, in 2018, \$14.4 billion was spent on *in vitro* testing versus \$4.2 billion for *in vivo* tests (Meigs et al., 2018). Although this

testing primarily took place in the product development arena rather than the regulatory world, it is proof of progress, he said.

In vitro tests are the future for regulatory testing, Hartung said, if only because animal models are not reliable. A 2018 CAAT study found that the six most common *in vivo* toxicology tests used in Europe are only 81% reproducible and only 69% reproducible for toxic chemicals. “No regulator can sleep well with a tool that is only 69% reproducible”, he said. *In vivo* tests used to study the carcinogenicity or reproductive toxicity of chemicals have similar issues, he said.

One issue in food safety that Hartung identified is the fact that much of the U.S. data that has been collected is not in the public domain, limiting its usefulness. As an example, 80% of the data that would be required for food additives is inaccessible.

Hartung also discussed the need for more work in exposure science, which he said is as important as understanding the hazards of chemicals in risk assessment. He said work on the human exposome (Sillé et al., 2020) – the totality of human exposure to chemicals – is critical for the future of the field, because it will allow scientists to understand both the impact of exposure on phenotypes and thresholds of exposure; in other words, to focus their energy on areas of greatest exposure or greatest impact. CAAT has helped establish an exposome center, *The Exposome Collaborative* at Johns Hopkins University, to continue to explore the application of this approach to toxicology.

One focus of CAAT is metabolomics, which allows the study of how exposure to the vast array of chemicals in the world is changing human beings at the molecular level. He is interested in applying this science to toxicology and in assuring that the quality of the data produced is high enough to be trusted. Hartung said there is an opportunity to combine research on the exposome with a mechanistic understanding of chemical-induced adverse effects, or the “toxome.”

CAAT, in collaboration with the EPA and other partners, has embarked on studying the human toxome by applying systems toxicology. With this approach, he said, “we can make sense of all the stuff we are measuring in our omics technologies.” Individual omics approaches to studying chemical effects often have so much noise it is impossible to draw reliable conclusions. However, Hartung said, “if you see a change in the same pathways on a protein level, a metabolic level, and a gene level, you can actually say there is a meaningful change taking place here.” Their work has led to nearly 30 publications to date as well as new tools available to the community.

CAAT also is interested in using big data to address some of the complex questions presented by risk assessment. In 2016, through the use of natural language processing, they were able to mine 800,000 toxicology studies for information about 10,000 chemicals. Currently, the database allows CAAT to make predictions about new chemicals in a two-step process. Using the database, CAAT has developed a RASAR – read-across based, structure-activity relationship software (Luechtefeld et al., 2018). Read-across typically means evaluating unknown chemicals based on what is known about similar chemicals; structure-activity relationship studies evaluate chemicals based on their chemical description.

RASAR, which allows them to express conclusions based on their degree of certainty and which can be validated, has enabled CAAT to create a map of 10 million chemicals. On this map, chemicals that are similar in structure are close to one another and chemicals that are different in structure are further away from one another. Now, new chemicals can be added, allowing predictions about the chemical’s behavior based on the “neighborhood” in which it resides on the map. The database also allows data fusion. For example, Hartung said that when trying to determine whether certain chemicals may cause eye irritation, if data is lacking, the database can instead provide data on whether those chemicals cause skin irritation. Early tests of RASAR have found it to be more reliable at predicting toxicity than *in vivo* tests. The FDA is preparing to evaluate RASAR for toxicity of food additives and cosmetics. Ultimately, CAAT is hoping that financial support will allow them to make RASAR freely available to the scientific community worldwide.

In other work, Hartung said CAAT has a strong interest in improving *in vitro* systems through the use of stem cells and organotypic culture as well as high content analysis of cell cultures. He said that 21st century science starts with 21st century cell culture and its quality assurance. They are developing Good Cell Culture Practice (GCP) 2.0 to be disseminated widely among the toxicology research community. In-house, they have developed iPSC-derived human organotypic brain cultures. In terms of food safety, there is interest in using this model to study the impact of nutrition on the aging brain.

Finally, Hartung shared that CAAT offers free online toxicology classes through Coursera. Nearly 3,000 people have taken one of these courses.

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