Dear readers,

This *Special Issue* of ALTEX comprises the proceedings of the workshop on *Development of an Evidence-Based Risk Assessment Framework* held at the University of Ottawa in December, 2018[1]. The workshop was jointly organized by the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa and the Center for Alternatives to Animal Testing at Johns Hopkins University.

Although not motivated by animal welfare, the 2007 US National Research Council report on *Toxicity Testing in the 21st Century: A Vision and a Strategy* (NRC, 2007) provided scientific support for the use of alternatives to animal testing, proposing the use of cheaper and faster test methods to markedly increase the number of environmental agents that could be evaluated. Over the last decade, considerable progress in realizing this vision has been achieved (Krewski et al., 2020).

In parallel, the availability of an increasing number of new approach methodologies (NAMs), coupled with increasing regulatory acceptance of these alternative test methods, provides unprecedented opportunities for replacement, reduction, and refinement of animal use in toxicity testing. These are strongly supported by regulatory restrictions on the use of animals in toxicity testing (e.g., EU, 2010) and prioritization of national institutions to move away from vertebrate testing (e.g., US EPA, 2021), which are driving a continued decline in the use of animals for toxicity testing worldwide. Recent value-of-information analyses suggest that rapid, cost-effective alternative test methods can be advantageous in supporting earlier chemical risk decisions.

Evidence integration has emerged as a key theme in toxicological risk assessment. Recognizing and integrating NAMs as an equally important evidence stream, alongside human findings and animal studies, is the first step towards leveraging these new toxicity testing approaches for risk assessment. The challenge of evidence integration can be viewed in two directions, i.e., retrospectively, where different types of existing evidence need to be integrated, or prospectively, where different methods of evidence generation are combined in an integrated testing strategy often referred to as an integrated approach to testing and assessment (IATA). The integration of data from multiple lines of evidence affords an opportunity for expanded use of animal alternatives, in that if adequate information to support evidence-based risk assessment can be derived from NAMs, the requirements for animal test data can be reduced. This requires the development and implementation of frameworks to ensure the available evidence is collated, integrated, and assessed in a way that ensures the protection of human health and the environment. This *Special Issue* includes contributions from the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA) presenting their new approaches to evidence integration including mechanistic information from NAMs, as well as articles dealing with systematic review methodology and approaches to evidence integration and categorization, which each consider the integration of multiple evidence streams. The issue is rounded off with a detailed report on the first workshop.

The second of the series of these workshops – held at the University of Ottawa in December 2019 – explored the implementation of evidence integration approaches in health risk assessment in more depth. The proceedings of this second workshop will report on the following themes: 1) sources of evidence; 2) systematic review; 3) assessing data quality; 4) integration across multiple evidence streams; and 5) meta-analysis and other approaches for pooling data from multiple sources. The third and final workshop, currently being planned for December 2022, will focus on a series of case studies designed to illustrate the application of evidence integration in evidence-based health risk assessment in practice. Collectively, the proceedings of these three workshops will provide a foundation for expanded use of alternative test methods in evidence integration.

Thomas Hartung[1,2] and Daniel Krewski[3,4]

[1]Johns Hopkins University, Bloomberg School of Public Health, Center for Alternatives to Animal Testing (CAAT), Baltimore, MD, USA; [2]CAAT-Europe, University of Konstanz, Konstanz, Germany; [3]McLaughlin Centre for Population Health Risk Assessment, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada; [4]Risk Sciences International, Ottawa, ON, Canada

References

EU – European Union (2010). Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. *OJ L 276*, 33-79.

Krewski, D., Andersen, M. E., Tyshenko, M. G. et al. (2020). Toxicity testing in the 21st century: Progress in the past decade and future perspectives. *Arch Toxicol 94*, 1-58. doi:10.1007/s00204-019-02613-4

NRC – National Research Council (2007). *Toxicity Testing in the 21st Century: A Vision and a Strategy*. Washington, DC, USA: National Academies Press.

US EPA (2021). New Approach Methods Work Plan (v2). U.S. Environmental Protection Agency, Washington, DC. EPA/600/X-21/209. https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf

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