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International expert workshop on nextgeneration risk assessment

Integrated application of novel, animal-free methods in the health risk assessment of chemicals

How can different animal-free test methods be combined to enable meaningful and robust risk assessment of chemicals? This was just one of the questions discussed by international experts at a two-day workshop hosted by the German Federal Institute for Risk Assessment (BfR) on 27 and 28 May 2025.

The workshop focused on new approach methodologies such as computer models (*in silico* methods) or cell cultures (*in vitro* methods) which should, in the long term, be used to replace animal experiments in as many domains of chemical assessment as possible. The potential as well as the limits of applying such methods in the field are currently the topic of much discussion in order to provide viable animal-free testing and assessment strategies that offer a high level of protection for human health. This requires workflows that offer orientation in regard to which methods should be combined in what way in order to address certain regulatory (or scientific) problem formulations, such as the derivation of health-based guidance values, with a high degree of certainty. This approach is also termed next-generation risk assessment (NGRA).

The BfR is contributing its expertise to the EU project RISK-HUNT3R, which itself is a part of the ASPIS project cluster (Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies). A part of the RISK-HUNT3R project develops a workflow for assessing systemic toxicity based on animal-free *in silico* and *in vitro* methods, the (ASPIS-initiated) Alternative Safety Profiling Algorithm (ASPA). This workflow is intended to cover all relevant regulatory problem formulations and to provide corresponding modular testing, evaluation, and decision strategies. In addition to ASPA, the software tool NAMASTOX is being developed, which guides users through the workflow step by step and depending on the problem formulation. Workflows of this kind are a vital prerequisite for

the long-term shift from the current, animal-based assessment system towards animal-free NGRA.

The workshop brought together international experts from authoritaties and other stakeholder groups to pursue the goal of evaluating the functionality as well as the robustness of ASPA and NAMASTOX based on case studies. The results help to further improve the two concepts in order to create a first tested and functional version by the end of the RISK-HUNT3R project in 2026.

Currently, the assessment of health risks posed by food and feed, chemicals, and consumer products still requires results from animal studies in many areas. However, scientists around the world have been working according to the 3R principle to entirely replace animal experiments where possible, to reduce the number of animals used, where they are still needed, and to refine their living conditions to minimise suffering as far as possible.

The approaches used include *in silico*, *in chemico*, *in vitro*, and *ex vivo* methods. *In silico* methods use computer models in order to, for example, predict the effect or the distribution of certain substances within an organism.

In chemico methods study chemical reactions in order to examine aspects such as the reaction or interaction behaviour of a substance. *In vitro* methods use cell cultures, meaning cells which are cultivated outside of an organism using a growth medium. *Ex vivo* methods use tissue extracted directly from a living organism which is then analysed for certain chemical effects outside of the organism. By contrast, studies in live animals are termed *in vivo* methods.

Compared to animal experiments, these methods are in many cases implemented far simpler and also more flexibly. They generate larger amounts of data within less time. For instance, different cell models or different parameters can be studied in parallel or in combination with each other. Furthermore, they allow for important insights into fundamental mechanisms of toxicity and thus offer great potential to improve and innovate standard practices of risk assessment, an aspect captured by the term next-generation risk assessment (NGRA).

RISK-HUNT3R is a European research project dedicated to developing a new modular framework for animal experiment-free, next generation risk assessment (NGRA). The scope of the project includes the creation of integrated applications and innovative mechanism-based new *in vitro* and *in silico* methods which are relevant to human health. As a project partner, the BfR is involved as a partner in the work packages covering regulation, modelling, novel model systems, high-throughput technologies, and quality management in addition to being active in the project's Scientific and Regulatory Advisory Board.

Further information on the BfR website

Third-party funded projects of the German Centre for the Protection of Laboratory Animals (Bf3R) <u>https://www.bf3r.de/en/research/third-party-funded-projects/</u>

RISK-HUNT3R project website <u>https://www.risk-hunt3r.eu/</u>

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Agriculture, Food and Regional Identity (BMLEH) in Germany. The BfR advises the Federal Government and the States ('Laender') on questions of food, chemicals and product safety. The BfR conducts independent research on topics that are closely linked to its assessment tasks.

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