Accelerated Testing of More Substances – Towards Better Chemicals Regulation

Every day, we are exposed to an increasing number of chemicals, many of which ultimately find their way into the environment.

Global production of chemicals is projected to triple by 2050 (EEA 2018, p. 10; Persson et al. 2022, p. 1512). As production volumes increase, so does the complexity of the substances and mixtures. These chemicals are now ubiquitous in products like toys and food packaging, eventually contaminating soil, water, air, and sediments through household and industrial waste. Once in circulation, these substances can reduce biodiversity and some of them (e.g., bisphenol A or perfluorinated compounds) are associated with the increase of non-communicable diseases, in particular cancer as well as cardiometabolic, respiratory and neurological disorders (Landrigan et al. 2018; UNEP 2019).[1]

1. The REACH regulation (Registration, Evaluation, Authorization, and Restriction of Chemicals) has governed all industrial chemicals in the European Union (EU) since 2007. As the central chemicals regulation, REACH defines the information required to place chemicals on the market or manufacture them within the EU.

Current methods for chemical assessment cannot handle these quantities.

The innovation of new substances and mixtures is progressing continuously. This means that the methods used to date for chemical assessment no longer fully meet the current regulatory requirements of the European Union's (EU) central chemicals regulation – REACH[1] (Wang et al. 2020; Fenner and Scheringer 2021; Escher et al. 2023). In the "chemical universe" of substances registered with the European Chemicals Agency (ECHA), 4,713 (64%) of a total of 7,358 substances (1-100 t per year[2]) were *"not yet assigned"* in June 2023. For 626 substances (9%), no further actions (*"currently no further actions proposed"*) such as assessing the need for regulation, collecting data, or risk management were planned at that time (ECHA 2024b). In 2023, ECHA also carried out 301 tests to meet the requirements of REACH registration dossiers. These concerned 274 individual substances and about 1,750 registrations. As a result, 251 decisions were sent to companies requesting additional data (ECHA 2024a). These examples show that, despite adjustments, the European evaluation and management processes for chemicals can only cover a fraction of the registered substances. Accordingly, many researchers identify significant gaps in these processes, especially given the growing number and structural diversity of substances placed on the market (Kosnik, Hauschild, and Fantke 2022).

2. Substances for which there is at least one active registration (Article 10, REACH) with a quantity of 1 to 100 tons per year and no active registration for quantities above 100 tons per year.

Science, industry, regulators, and NGOs are increasingly calling for New Approach Methodologies (NAMs) for chemical assessment.

The aspects of chemicals (assessment), environmental pollution, and health effects were discussed in five workshops (**see Box 2**). Several overlaps between all German stakeholder groups of EU chemicals policy were revealed, especially in identifying problems and solutions. All stakeholder groups confirmed that the existing risk assessment procedures in the EU are too slow and cumbersome, do not meet regulatory requirements, and in some cases need to be revised. At the same time, discussions were held on how the assessment could be accelerated while taking high quality standards into account.

A key consensus emerged between the different stakeholder groups as a possible solution: there is a need for increased use of *New Approach Methodologies* (NAMs); **see Box 1**.

The majority of stakeholders from different groups see two EU organizational strategies in this context that contribute to slow and cumbersome assessment procedures. First, in the current EU regulatory paradigm, animal testing is considered the "gold standard."

Criticisms of animal testing included their long duration, resource intensity, and the controversial transferability/variance of results due to species differences.

Second, obstacles were mentioned in the regulatory bodies responsible for the administration and management of the European chemicals policy. All stakeholders mentioned that EU agencies such as the European Chemicals Agency ECHA have insufficient financial and human resources to keep up with the speed of innovation of new substances and mixtures. Accordingly, there is also a lack of resources to promote regulatory acceptance of NAMs. Often, ECHA has no mandate to actively develop assessment concepts. In addition, participants noted differences in REACH implementation practices between EU authorities and EU member states.

Different approaches to increase the use of NAMs were discussed. For many stakeholders, increasing the regulatory acceptance of NAMs is particularly important. In this context, participants spoke of "a certain conservatism among authorities" or of authorities "that are relatively cautious" in the use of NAMs.[4] They attributed this in part to existing "regulatory traditions of how we test hazards". The authorities added that industry should also be willing to accept NAMs, even if it meant that dangerous substances and mixtures could be identified more quickly. Industry representatives declared their willingness to use NAMs wherever possible and feasible. Overall, all stakeholders emphasized the great importance of faster identification of dangerous substances and mixtures.

Based on these solutions, we ask you to support the increased use of NAMs and the expansion of further regulatory capacities. The development of resources and new technologies is crucial to strengthen the collaboration of stakeholders in the development of NAMs, adapting them to the challenges posed by the diversity of the chemical universe and validating them for regulation (**see Box 3**). Promoting collaboration and resource development can improve and accelerate the implementation of NAMs in chemicals regulation.

Since the collective term NAMs covers a wide range of methods, the various NAMs have different advantages and disadvantages. Participants identified a number of advantages that NAMs can offer over current methods: **i)** using better methods to test relevant properties of chemicals, **ii)** closing data gaps, **iii)** applying the latest scientific knowledge in decision-making, **iv)** increasing efficiency (e.g., saving time and money) and thus generally **v)** improving the hazard and risk assessment of chemicals in the EU through faster screening methods.

4. Direct quotes translated directly from the original German.

How can alternative methods be used in chemical assessment? Box 1

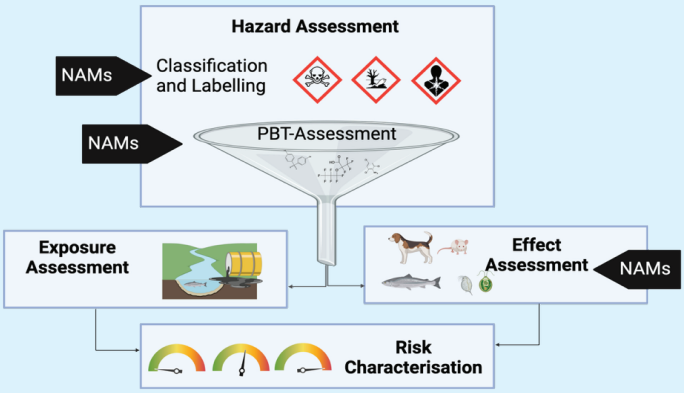

Figure 1: Simplified scheme for chemical assessment in the EU under the CLP Regulation on classification, labeling, and packaging of chemical substances and mixtures and the REACH Regulation on the Registration, Evaluation, Authorization, and Restriction of Chemicals and possible starting points for NAMs (graphic created in BioRender by Escher, B. (2024)).

The chemical assessment consists of several components. The hazard assessment, following the CLP regulation, is used to classify and label all chemicals on the market.[3] In addition to identifying possible toxicity, classification according to endocrine disruption, PBT (persistence, bioaccumulation, and toxicity), and PMT (persistence, mobility, and toxicity) have also been required since 2023. The REACH regulation determines the risk of harmful effects on human health and the environment. The information requirements increase as quantities increase. For quantities of 10 tons or more per year, a PBT assessment and risk characterization are also required for substances classified under CLP. A full assessment of exposure, toxicity, and risk characterization is only required for substances identified as problematic or those with high production volumes. In principle, NAMs could directly replace animal testing, but this requires complex *in vitro* to *in vivo* extrapolation models, which are still in development. NAMs are already suitable for use in classification and labeling as well as in PBT assessment, since only the hazard potential needs to be demonstrated (**see Figure 1**). According to industry stakeholders, the regulatory basis for this under CLP and REACH is currently lacking.

3. The EU regulation on classification, labeling, and packaging (CLP) of substances and mixtures is based on the United Nations Global Harmonized System (UN GHS). A substance or mixture can be classified as dangerous to humans or the environment due to its intrinsic properties. The result of the classification is the categorization into so-called hazard classes (including certain subcategories) with corresponding labeling.

How did we come to this conclusion? Box 2

A cooperation of various Helmholtz Centers is currently working on the further development of assessment indicators for EU chemicals policy in a SynCom Project. The **Modernizing Hazard Indicators (ModHaz)** project initially brought together a total of 55 representatives from four stakeholder groups from German-speaking countries – NGOs, authorities, industry, and science. The interaction took place in one online workshop per group in November and December 2023. The participants' statements were then evaluated using a discourse analytical approach (Leipold and Winkel 2017). In addition, as a next step, a synthesis workshop in March 2024 brought all stakeholder groups (24 participants) together in person to deepen the dialogue and further develop the results.

New hazard indicators: the CTE/PTE concept.

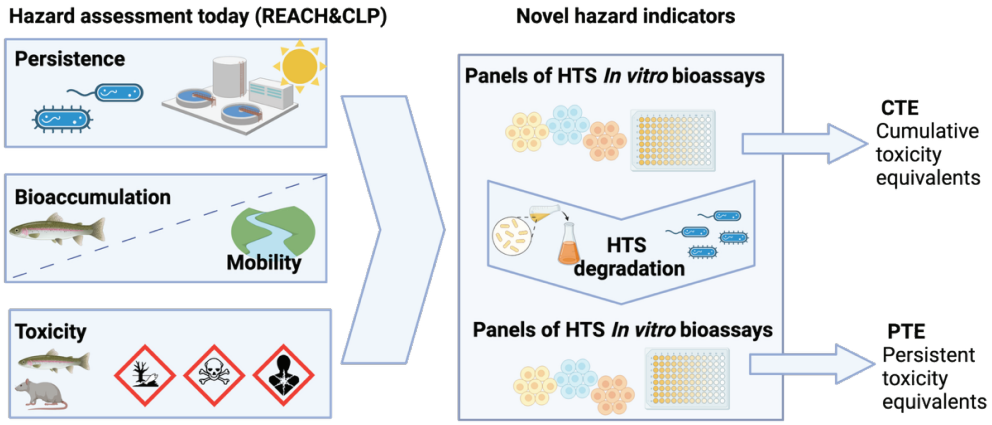

Figure 2: Proposed transition from the current PBT indicators in REACH to the vision of modern high-throughput screening indicators that integrate B (bioaccumulation) and M (mobility) into T (toxicity) and measure P (persistence) and T together. (Escher et al. (2023), graphic created in BioRender).

The acceleration of assessment procedures and the shift away from the regulatory focus on animal testing towards NAMs is considered desirable by all stakeholders.

In the workshops (**see Box 2**), a novel technical concept for the use of NAMs was discussed. The new indicators for hazardous substances (cumulative toxicity equivalents (CTE) and persistent toxicity equivalents (PTE), **see Figure 2**), proposed by a team of researchers from the Helmholtz Associations' Research Fields "Earth and Environment" and "Health", aim to increase the throughput of chemicals and enable their comparative evaluation, with an initial focus on hazard assessment under REACH, particularly in the PBT assessment (Escher et al. 2023). The main advantages of this new method are that it does not require animal testing, integrates persistence and toxicity assessment, and can be applied to single substances as well as groups of substances and mixtures such as UVCBs (substances of unknown or variable composition, complex reaction products, or biological materials).

The majority of participants welcomed the concept presented. All stakeholders mentioned the need to avoid **regrettable substitutions**.[5] This can be achieved, for example, by using grouping methods that are already anchored in REACH. High-throughput bioassays – as used in CTE/PTE – can help with meaningful grouping by answering two questions: **i)** Is a chemical or mixture of chemicals toxic?, and **ii)** How does the toxicity of substance(s) change with their degradation in the environment – does it decrease, stay the same, or increase? The Helmholtz Centre for Environmental Research (UFZ) is currently working with stakeholders from industry and authorities to apply and improve the CTE/PTE concept through case studies that tackle difficult to test compounds for which the classic PBT indicators are also inadequate and deficient (see *CoModHaz project, Co-Creation process for the modernization of chemical hazard indicators*).

The various stakeholder groups disagree on the extent to which NAMs should be used for chemical assessment on a legally binding basis or as a voluntary application (e.g., as a screening method for prioritizing substances), how to achieve a good balance between a high level of protection for people and the environment and the free movement of substances, and to what extent animal testing can and should be replaced. Incorrect conclusions, i.e., false positive and false negative results, must be avoided.

5. Substances or mixtures can be substituted to circumvent limits in REACH or to replace prohibited substances. These substitutes may have unfavorable or unknown properties for the environment and human health, so-called regrettable substitutions.

Options for action.

Box 3

We welcome the announced revision of the REACH regulation and urge the European Commission to publish a proposal in 2025. Based on our analysis, we propose the following options for action.*

- **Shift the regulatory focus from animal testing to NAMs**
  (New Approach Methodologies) to accelerate assessment procedures, enabling faster identification of dangerous substances and mixtures.
- **Support the development and validation of NAMs for regulatory purposes**
  to address the challenges posed by the complexity and diversity of the chemical universe.
- **Foster cooperation among stakeholders**
  to increase the acceptance of NAMs.
- **Explore approaches to promote chemical simplification**
  (reducing substance complexity and production volumes) to decrease chemical pollution, testing complexity, and data gaps.
- **Adopt the Grouping of Chemical Substances approach**
  to prevent regrettable substitutions and improve grouping methods through the use of high-throughput screening methods.
- **Integrate a Mixture Assessment Factor**
  (MAF) that is derived from experimental evidence, such as effect-based monitoring data, into chemical safety assessments to better identify and represent chemical ubiquity.
- **Develop clear criteria for identifying endocrine-disrupting properties.**
- **Restrict the use of substances with high weight of evidence regarding adverse health and environmental effects,**
  such as PFAS, to minimize environmental and human health risks.

*Please note that these options are proposed by the authors and are not coordinated positions agreed upon with the stakeholders.

Authors and Advisory Board Policy Brief

Main author and contact: H. Hempel
Authors: P. Einhäupl, B. Escher, M. Heidenreich, S. Leipold, P.-J. Schweizer, K. Sielemann, V. Srebny
Advisory Board: R. Ebinghaus, M. Lange, S. Scholz, A. C. Zenclussen

Stakeholders involved in 5 workshops

Since in some cases more than one person per organization attended the workshops, the number of organizations listed does not correspond to the total number of participants.

NGOs and civil society

Doctors against animal experiments
German Federation for the Environment and Nature Conservation (BUND)
CHEM Trust Europe
ClientEarth
European Network for Environmental Medicine (EnvMed)
Food Packaging Forum
German Forum on Environment and Development
Greenpeace
Health and Environment Justice (HEJ) Support
International Collaboration on Cosmetics Safety (ICCS)
People for Animal Rights Germany – The Federal Association Against Vivisection (BVTVG)
Pesticide Action Network (PAN) Germany
PETA Science Consortium International (PSCI)
Women Engage for a Common Future (WECF)
WWF Germany

Research and science

German Society of Endocrinology
German Sport University Cologne
German Veterinary Medical Society – DVG e.V. | Section Laboratory Animal Science
Swiss Federal Institute of Aquatic Science and Technology (Eawag)
Freie Universität Berlin
Society for Laboratory Animal Science (GV-SOLAS)
Karlsruhe Institute of Technology (KIT)
Leibniz Research Institute for Environmental Medicine (IUF)
Ecotox Centre, Switzerland
Ökopol – Institute for Environmental Strategies
RWTH Aachen
Technical University of Munich

Companies and trade associations

Beiersdorf
German Association of the Fragrance Manufacturers (DVRH)
DyStar Colours, Germany
Evonik
Görg (Business law firm)
Henkel
Plastics Europe
Sasol
German Chemicals Industry Association (VCI)

Legislation and regulation

Bavarian State Office for the Environment
Federal Office for the Environment (FOEN), Switzerland
Federal Institute for Occupational Safety and Health (BAuA)
German Federal Institute for Risk Assessment (BfR)
Federal Ministry for Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV, Germany)
Hessian Agency for Nature Conservation, Environment and Geology
Hessian Department II 3 – Chemical Safety, Genetic Engineering, Accident Prevention
German Environment Agency (UBA)

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Contact workshops: Henry Hempel, Helmholtz Centre for Environmental Research – UFZ, henry.hempel@ufz.de
Contact CTE/PTE concept: Prof. Dr. Beate Escher, Helmholtz Centre for Environmental Research – UFZ, beate.escher@ufz.de

Project ModHaz: https://earthenvironment.helmholtz.de/changing-earth/syncom/projects/modernizing-hazard-indicators/
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RIFS POTSDAM

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