VCI-POSITION ZU

New Approach Methodologies (NAMs)

New Approach Methodologies (NAMs) is the collective term for a wide range of non-animal test approaches and methods. A definition is given at the European Chemicals Agency (ECHA)[i].

The chemical industry is clearly committed to the goal of reducing animal testing and supports the 3R principle[ii], according to which animal tests should be avoided or reduced and alternative methods used wherever this is scientifically possible and feasible.

Already today, NAMs are applied for certain toxicological and ecotoxicological assessments of substances, e. g. for some “lower tier” endpoints such as testing for skin irritation (OECD TG 431, TG 439), skin sensitisation (OECD TG 497) or eye irritation (OECD TG 467).

A stronger implementation of NAMs is currently being discussed intensively in various sectors, for example, the revision of the CLP guidance documents or the upcoming revision of the REACH Regulation (e. g. introduction of test procedures for endocrine disruptors, adaptation of provisions on information (standard information requirements / SIRs)). Additionally, various projects and initiatives (such as ASPIS[iii], PARC[iv] and EPAA[v]) are focusing on the topics of NAM and NGRA (Next Generation Risk Assessment).

The VCI supports the ongoing activities on the implementation/use of NAMs, however, the association still sees limitations and challenges that call for further expert/technical exchange at national, European, and international levels. In the following, a description of the existing challenges and concrete starting points for solutions are given.

Background/Challenges

Diversity in regulation inside Europe

Within Europe there are no consistent rules for applying NAMs under different sector regulation. In fact, they are put into practice in many areas, ranging from REACH, cosmetics, and pharmaceuticals to food contact materials – while the relevant legal information requirements vary considerably.

Firstly, the legal requirements to animal studies (SIRs) – especially under REACH and the Biocidal Products Regulation – are still frequently common practice and might further increase in number with the forthcoming changes such as the REACH revision. Secondly, e. g. the Cosmetics Regulation bans animal tests for the testing of ingredients and end products.

The resulting conflict leads to a situation where, for example, downstream users in the cosmetics sector cannot or do not want to resort to results from animal tests for their purchased raw materials or intermediates in order to carry out risk estimates or to obtain certificates on the absence of animal testing.

Diversity in global registrations

The registration and evaluation process for chemicals is not harmonised at the global level, either. Quite often, results from alternative methods already accepted in the EU (for which e. g. OECD guidelines are available) are not accepted in countries outside the European Union. Depending on the circumstances, this might mean that animal tests are necessary to be able to comply with the regulatory requirements of the respective country.

For example, at present OECD TG 497 (combination of “in vitro” and “in silico” tests) to cover the endpoint of skin sensitisation for a standard registration > 10 t/a is not accepted in China under MEE12 (“China REACH”). Instead, a guinea pig maximisation test (OECD TG 406) is demanded which is no longer permitted under the European REACH Regulation. The lowest common denominator is then a local lymph node assay (LLNA) in mice (OECD TG 429) – even though the combination of “in vitro” and “in silico” methods according to OECD TG 497 ensures better predictability for humans than the LLNA.

Limitations in the use of NAMs for complex endpoints

NAMs are already used to assess simple endpoints (e. g. skin irritation, skin sensitisation, eye irritation). For complex endpoints (e. g. systemic toxicity, reproduction, or developmental toxicity), it is more difficult to transfer the requirements/information from animal testing to NAMs.

At the moment, there is still a lack of reliable and regulatory accepted NAMs for the assessment of complex endpoints. Furthermore, guidance on study outline and interpretation as well as cross-sectoral acceptance are needed so that NAMs can be applied for more complex legal information requirements and thus the conclusions from these test methods become acceptable also in regulatory terms.

For example, for the assessment of endocrine properties with NAMs it is currently only possible to make a predictive statement on biological activity – whereas it is not yet sufficiently possible to derive statements on classification and labelling from them.

Appraisal/Proposals for solutions/Necessary measures

Validate NAMs soon and clearly define the scope of application

- The individual NAMs need to be validated. Ideally, this should be done at OECD level.
- Further NAMs need to be developed and established, e. g. for complex endpoints or combinations of NAMs.
- During validation – and, where necessary, also after validation – the applicability domain of the different NAMs must be taken into account more strongly. For example, practical problems arising from certain substance properties (e. g. poor solubility) need to be considered. This can lead to technical solutions becoming necessary to be able to test the substances.

- The validation of NAMs should be accelerated or the process revised, respectively. Prioritisation would be needed for the aspect of acceleration. For example, NAMs for the determination of endocrine disruptors or toxicokinetic properties are a very high-priority area.
- Irrespective of ambitious timelines (e. g. within the EU Chemicals Strategy), the expert/technical discourse must not be neglected. All stakeholders should be involved for this purpose.

Develop and update guidance documents

- Technical guidance documents and defined approaches for applying NAMs and for the assessment of (eco-) toxicological endpoints need to be developed for users (industry, test institutes etc).
- Existing guidance documents on the regulatory assessment of chemicals under global regulatory legislations need to be adapted, for example, together with the introduction of new hazard classes under CLP and new information requirements.
- There are cases for which non-validated but “fit for purpose” NAMs are available. In these cases, too, guidance is needed for the use and assessment of (eco-) toxicological endpoints and the regulatory acceptance of results at a later stage.

Improve regulatory acceptance

- Regulatory acceptance should be independent of the result, i. e. both inculpatory and exculpatory evidence must be accepted for the assessment without demanding further data or animal studies.
- The integration of results in an assessment is decisive for already validated non-animal test methods. As quite often a battery of tests has to be carried out, the assessment of results is complex. Due to current regulatory requirements and a potentially higher acceptance of animal testing, it is observed that the use of animal studies is still resorted to, or animal tests continue to be demanded now as in the past.
- The lack of guidance on harmonised interpretation and its use in practice renders the application and acceptance of NAMs more difficult in the chemical industry and at authorities. In order to strengthen confidence in NAMs, an exchange on case studies between industry, public authorities, academia and NGOs could make a possible building block.
- With a view to avoiding/reducing animal studies for complex endpoints already now, the application of NAMs in the forms of “read across”, “grouping” and “waiver” approaches should gain in importance as well as better acceptance by public authorities.
- Regulatory acceptance for the use of NAMs is also needed for “Integrated Approaches to Testing and Assessment” (IATAs).
- The MAD (Mutual Acceptance of Data) concept should be applied for reliable planning.

Ansprechpartner: Dr. Claudia Drucker
Referentin, Wissenschaft, Technik und Umwelt
Produktsicherheit
T +49 (69) 2556-1462| **E** claudia.drucker@vci.de

Verband der Chemischen Industrie e.V. – VCI
Mainzer Landstraße 55
60329 Frankfurt

www.vci.de | www.ihre-chemie.de | www.chemiehoch3.de

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[i] Definition: ECHA 2016: NAMs were taken in a broad context to include in silico approaches, in chemico and in vitro assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard assessment. They also include a variety of new testing tools, such as “high-throughput screening” and “high-content methods” e.g. genomics, proteomics, metabolomics; as well as some “conventional” methods that aim to improve understanding of toxic effects, either through improving toxicokinetic or toxicodynamic knowledge for substances. (https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf/a2087434-0407-4705-9057-95d9c2c2cc57)

[ii] “3R“: Replace, Reduce and Refine animal testing

[iii] https://aspis-cluster.eu

[iv] https://www.eu-parc.eu

[v] European Partnership for Alternative Approaches