Action 8: Introduce a new safety assessment scheme that supports an increased uptake of reliable animal-free safety assessment methods (New Approach Methodologies or "NAMs")

The Issue?

REACH requires companies that manufacture or import chemicals in the EU/EEA to register their substances with ECHA. Amongst other elements, they need to assess if their chemicals may cause adverse effects to human health and the environment. This is done based on standard information requirements outlined in REACH. These requirements depend on the quantity of the substance manufactured or imported into the EU/EEA and are explained in Annexes VI to X. Generating the required information means performing certain tests, either animal or animal free.

Under REACH, two mechanisms exist to adapt or waive mandatory data requirements, particular for animal testing:

- **Endpoint-specific adaptations in Column 2 (Annexes VII-X):** According to its Annexes, REACH allows companies to omit additional animal testing if sufficient data or studies are available, so called "adaptations". This also applies to the most complex data required under REACH, such as repeated dose, reproductive and developmental data. Despite this process, there have been cases where these adaptations were not accepted, leading to more animal testing.

- **General rules for adapting testing regime set out in Annex XI:** REACH allows some or all information requirements to be adapted in case testing is not technically possible or not scientifically required, i.e. by using information from other registration dossiers or "read-across", scientific literature and existing testing, etc. These adaptations can also include implementation of strictly-controlled conditions or risk-based exposure, if certain provisions are met. However, such adaptations are not often accepted, leading to additional resources and contradicting the legal obligation (REACH Art. 25) to perform animal testing only as "a last resort".

The EU REACH regulation requires industry to provide extensive data on its chemicals. Much of this data requirements relies on the use of animal studies, which creates a conflict with the REACH requirement to use animal testing as a last resort (Article 25). To address this, REACH attempts to strike a balance between several objectives: that sufficient information is available on the properties of registered substances; that practical and economic challenges of generating this data is taken into account; and that the use of animal testing is minimised. This balance is implemented in several ways within the REACH legal text, for example:

- the use of tonnage bands to set the minimum data requirements;
- the possibility to waive information requirements where appropriate;
- the possibility to adapt the standard information requirements.

However, experience to date shows that successfully adapting the standard information requirements by making use of the provisions in Annex XI and Column 2 of Annexes VII to X has been very challenging.

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There is a high bar for the acceptance of new approach methodologies or NAMs - including *in vitro*, *in chemico* or computational (*in silico*) methods) – when used as alternatives to the required animal study. As a result, these adaptations are underutilised, coupled with low acceptance where they are used. The inevitable result: requests to perform new studies using animals.

In addition to these existing challenges, the proposed REACH revision may introduce new information requirements. These changes could impact almost all substances registered, including the approximately 10,000 substances in the 1–10 t volume band.

While the new information requirements will require the use of NAMs, there is concern they may ultimately lead to **more** testing in animals, either due to unsuitability of the proposed test method for the substance or the triggered follow up of positive/negative/ambiguous findings. It is therefore crucial that any new assays clearly outline, i. the value the information brings to chemical safety assessments and ii. how the results will be interpreted and weighted against other data. This clarity will allow the design of clear, simple rules in legislative text. A reduction of burden for industry and agencies can only materialise when information is not being requested for *all* chemicals, but only for chemicals in uses where the information is likely to have an impact on risk management.

The Solution

Facilitate the transition to animal-free chemical safety assessment

We highly appreciate the willingness of the European Commission to accelerate the phase out of animal testing in chemical safety assessment, ultimately leading to full replacement of animal testing. At the same time, the European Commission has committed to a simplification of REACH. We also recognise that phasing out animal testing is a long-term journey, and so in the short term, we need to focus efforts on facilitating the transition.

As part of the transition, we propose four recommendations:

- **Promote validated alternatives as the default:** Identify Information requirements where there are suitable alternatives to the existing animal studies and formally implement these as the preferred approach to meeting the information requirement. These alternatives should be well structured and ideally aligned with a recognised Defined Approach[1] (or similar), capable of identifying the presence or absence of a hazard, and contribute the data needed to enable the derivation of point of Departure (PoD)[2] for safety assessment. To become a mandatory Information requirements under REACH, methods must be recognised internationally. Before becoming mandatory under regulations, further opportunities to use available and relevant animal-free methods should be explored. This will help to to build confidence, trust and capabilities.
- **Eliminate redundant or rarely necessary animal studies**: Identify information requirements which use animal studies but are considered redundant, or, only required in exceptional circumstances. These should be removed from the REACH Annexes or moved to column 2 with a clear explanation of when they may be needed/requested. The intention is to ensure these studies are exceptionally used instead of being a “default” information requirement.

[1] According to OECD, A defined approach (DA) consists of a selection of information sources (e.g. *in silico* predictions, *in chemico, in vitro* data) used in a specific combination, and resulting data are interpreted using a fixed data interpretation procedure (DIP) (e.g. a mathematical, rule-based model).

[2] Point of departure (POD) is a concept used in risk assessment to calculate the reference dose of exposure that is likely to have no appreciable risk on health.

- **Ensure new or revised requirements allow for NAMs:** Any new information requirement or revision of an existing requirement should support the use of NAMs. Where it is foreseen that the integrated approach to testing would involve the use of animal studies, clear triggers should be introduced in the legislative text that take into account not just the need to "verify" the presence/absence of a hazard, but also other triggers to improve understanding, i.e. the potential for exposure (internal and external). A clear and simple approach will only be compatible with the REACH simplification objective and the intent to enable innovation towards safer alternatives when the results are sufficiently specific to only raise concerns when truly appropriate.
- **Enhance guidance, training, and stakeholder engagement:** Improve the confidence of the use and acceptance of NAMs by offering improved guidance, training, and opportunities for engagement for *all* stakeholders. This includes creating "safe spaces" to discuss NAMs and how to use/apply them, particularly for "difficult" to test and more complex to asses substances (e.g. UVCBs, surfactants, etc).

Maintain the balance between the need to have information with the practical considerations and the impact on industry

With any new testing approach, there will inevitably be a learning curve - both for those generating the data and those charged with its interpretation. Early in this curve, the process will naturally be more uncertain, complex and resource intensive. In addition, not every assay will be relevant, suitable, or predictive for every chemical. It is also clear that many substances pose real challenges in the assessment of their toxicological properties. Equally, not every chemical/use will require all possible data to exclude concerns.

We therefore recommend that when introducing or amending information requirements, these should be proportionate and phased in. The focus should first be on substances for which the information will add most value to the risk assessment and management of chemicals and then assess whether the data are needed for all other substances. They should also take into consideration that not every substance can or should be assessed with every assay and allow for workable adaptations/waivers to avoid unnecessary testing.

This approach will enable registrants and authorities to build confidence in the new approaches, while easing the resource burden across the industry, testing facilities and authorities.