Cefic calls upon robust evidence and coherence when grouping substances

Regardless of how grouping is used, Cefic believes it needs to be based on the following key principles:

- The grouping process should be transparent for all stakeholders;
- Grouping should consider risk and hazard profiles in addition to structural similarity;
- Similar family name or backbone should not be confused with similar hazard profile;
- Identification of substances in a group should be based on a unique substance ID to facilitate digitalisation;
- A proposed regulatory measure should be enforceable.

It is critical that grouping is based on solid scientific standards and applied coherently across REACH independently of its purpose.

Background

Grouping of substances can be a useful tool in chemical hazard assessment. It allows to predict properties of substances without having to test them all for each endpoint ('read-across'). As a result, one gains efficiency and avoids animal testing. Grouping is used to fill in chemicals safety data in REACH registration dossiers and it has become the new norm for regulatory action on chemicals. The hypothesis and underlying data supporting grouping for read-across purposes needs to be documented according to strict standards and is subject to compliance check by ECHA.

In recent years, authorities have started to apply grouping in the context of regulatory risk management.[1] By regulating multiple substances in one go, authorities aim to speed up regulatory action, drive uniformity in regulatory standards and approaches, avoid regrettable substitutions and save time and resources. The Chemical Strategy for Sustainability (CSS) seeks to strengthen this practice.

Both approaches are referred to as grouping, but they serve different purposes and use different practices: filling data requirements versus screening and prioritisation for further evaluation and regulatory control. The applied grouping practice and standard of proof will vary depending on the purpose (ref. Annex I "Inventory of different types of grouping applied today in registration and regulatory action with examples"). Nonetheless, **all grouping practices must be scientifically robust and transparent. Where similar grouping practices are applied, it must be done in a consistent and coherent way**.

[1] For example, restrictions on certain substances in tattoo ink, skin sensitisers in textiles, microplastics, etc. In ECHA Integrated Regulatory Strategy, the authorities have developed a computational methodology based on structural similarities selecting groups of substances from the chemical universe followed by a manual refinement into smaller groups.

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EU Transparency Register n° 64879142323-90

The following principles of applying grouping should be respected to create regulatory predictability and facilitate investment into chemicals[2]:

1. Grouping process should be transparent

In the context of regulatory action, being transparent on how and why substances are grouped together is critical.

Consultation with stakeholders should be included in the process when regulatory action involving grouping is proposed. Such consultation can be envisaged in early stages of dossier preparation, for example under the Call for Evidence. Comments provided at this stage would help refine grouping based on the expert/sector knowledge. This will make grouping evidence-based, manageable and enforceable.

2. Regulatory action should be achievable and enforceable

Enforcement can be challenging as market surveillance authorities are often expected to perform checks on a high number of substances, sometimes even without appropriate test methods. In general, restrictions on groups of substances will be more difficult to enforce than restrictions on single substances.

> *A case in point is the ongoing restriction process for skin sensitisers in textiles which might potentially include nearly 1000 substances. In this particular case, the ECHA Forum has stated that enforcement is difficult because of the extent of substances covered and lack of harmonised analytical test methods for certain substances.[3] Considering that almost 28 billion of clothing pieces circulate in the EU[4], enforcing such a broad group restriction, without available test methods, is challenging if not impossible.*

Therefore, regulatory measures based on grouping should consider further parameters for refinement that would make the measure work in practice. This becomes even more important when data generated under the Rapid Alert System (RAPEX) of the General Product Safety Directive show that even for restrictions on single substances, the level of non-compliance from imported consumer products in high. It is likely that more complex restrictions will be more difficult to enforce (skin sensitisers, microplastics, CMR in tattoo inks etc).

In cases where a restriction is solely based on hazard (e.g. restriction on skin sensitisers in textiles, leather, fur and hide), it should only include those substances where the hazard has been confirmed by authorities (for example harmonised classification in CLP Annex VI or Candidate List under REACH). For instance, during the restriction process on skin sensitising substances in textiles, leather, fur and hide, the initial idea of including self-classified substances was rejected by ECHA Committees due to possible contradictions in self-classifications which is not manageable for industry and impossible for the authorities to implement.

3. Structural similarity should be complemented by hazard and risk profiles

A clear hypothesis for grouping has to be provided. Afterwards, during assessment several aspects of similarity have to be addressed in such a way that they provide evidence to justify the hypothesis. Chemical structure[5] is clearly the appropriate starting point to consider when grouping substances. How to group according to structural similarity is extensively described in existing ECHA Read Across Assessment Framework (RAAF) and

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[2] Robust grouping will ensure that structurally similar alternatives that are safe are not suddenly subject to group restriction.

[3] European Chemicals Agency: RAC and SEAC opinion on draft restriction for skin sensitisers in textiles, leather, fur and hide, pg 56: https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e182446136

[4] Data source EUROSTAT

[5] For example, presence of common functional groups.

OECD guidance.[6] These guidance documents also describe how to "read-across" available hazard data to identify structurally related substances. Grouping of structurally related substances must be done according to these frameworks, where the purpose is registration or regulatory management.

It is important to note that structural similarity on its own cannot be conclusive. Structurally similar chemicals may have very different toxicological, ecotoxicological and physico-chemical and toxico-kinetic properties. The next step is to assess the hazard properties of the various members of the group and to identify similarities and differences within the group of structurally similar substances.

When looking into hazard profiles, priority should be given to actual robust experimental data on the substances over predicted data. In cases where there is a lack of experimental data or data of poor quality on specific substances, structure activity relationships (SAR and Quantitative SAR) can help to understand toxicological properties including, for example, acute and chronic fish toxicity. Overall, the assessment of hazard profiles should be carried out in a Weight of Evidence manner including the identification and weighting of evidence and uncertainties.

> *For instance, grouping on PFAS is based on their strong and stable carbon-fluorine bond. This very broad PFAS grouping, gathering close to 4700 chemicals with quite different structural, physical and chemical properties and with a wide variety of uses, shows the complexity and questionable nature of such a broad approach.* [7, 8]

4. Similar family name should not be confused with similar hazard profile

Substances with a similar family name or similar chemical backbone may not necessarily present the same concern.

> *For example, a recent restriction on phthalates has grouped DEHP, DBP, DIBP and BBP, which are so called "low molecular weight phthalates/LMW", based on their chemical structure and molecular weight, the same reproductive hazard (Cat 1B CLP) and a presumed common mode of action. Another phthalate, DINP is not comparable with LMW phthalates as it does not show adverse reproductive effects.*[9] *DINP is used as a substitute to DEHP because of its demonstrated performance and durability (flexible vinyl articles) and known evidence of safety.*[10] *In fact, DINP like other high molecular weight HMW phthalates does not show the same reproductive effects as LMW phthalates.*

This example demonstrates that grouping of all phthalates for a regulatory action is not justified.

5. Identification of substances in a group should be clear

Regulatory actions targeting a group of substances need to clearly specify each substance with the relevant identifier (CAS or EC number) and other substance identity information as appropriate. This is needed for legal certainty and for enforcement purposes. In addition, a precise substance ID can support digitalisation and

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[6] OECD: Grouping of chemicals: Chemical Categories and Read-Across: https://www.oecd.org/env/ehs/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm; ECHA RAAF Guidance: https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a

[7] European Environment Agency: Emerging chemical risks in Europe-PFAS: https://www.eea.europa.eu/themes/human/chemicals/emerging-chemical-risks-in-europe

[8] European Chemicals Agency: Hot topics-PFAS: https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas

[9] RAC opinion proposing harmonised classification and labelling DINP (page 20): https://echa.europa.eu/documents/10162/56980740-fcb6-6755-d7bb-bfe797c36ee7

[10] Overall, this substitution process has taken over 25 years with an estimated investment by the plasticiser industry of over 6 billion Euros, with the EU regulatory processes conducted in parallel with this transition, involving relevant stakeholders.

definitions of safe and sustainable by design substances planned in the EU as part of the Chemicals Strategy for Sustainability (CSS).

Authorities make use of the ECHA RAAF guidance explaining how grouping should be justified and documented in registration dossiers, with clear identification of substance by CAS/EC numbers and other substance identity information. While similar guidance does not exist for other regulatory processes, it would be beneficial to apply the guidance (with appropriate modifications) to restriction and authorisation.

Referring to "related substances" or broad group names is not precise enough to identify substances in the scope.

> *For instance, the Call for Evidence on Bisphenol A and structurally related bisphenols of similar concern for the environment*[11] *is too ambiguous: in this case, the only defined structural element is the presence of two phenols that are connected to each other. This leads to the potential inclusion of a large number of chemicals (minimum 20 000), which apart from the presence of two phenol moieties, cannot be considered structurally related nor have similar hazards and impact on the environment. Many of these chemicals may not be produced in significant quantities to be registered under REACH.*

The absence of clear identifiers for single substances stalls digitalisation and development of innovative digital solutions. The aim of a green and digital transition as described in the CSS is only achievable if one can make use of large data sets clearly linked to the substance ID and put it in practice such as when tracking substances in the supply chain, ensuring compliance to restrictions both for the businesses and customs authorities, etc.

In conclusion, whether grouping for registration or regulatory action, one must ensure transparency, scientific robustness and coherence of application among all stakeholders, including regulators, across REACH processes.

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About Cefic
Cefic, the European Chemical Industry Council, founded in 1972, is the voice of large, medium and small chemical companies across Europe, which provide 1.1 million jobs and account for 15% of world chemicals production.

[11] European Chemicals Agency: Call for Evidence BPA and structurally related bisphenols of similar concern for the environment: https://echa.europa.eu/previous-calls-for-comments-and-evidence/-/substance-rev/26502/term

Annex I

Inventory of different types of grouping applied today in registration and regulatory action with examples

Grouping methods in registration may be based on:

- **Structural similarity**
- **Similar physiochemical property**
- **Similar toxicological property**
- **Similar ecotoxicological properties**
- **UVCB**

Grouping methods in regulatory action may be based on:

- **Similarities in hazard profiles and mode of action** where only substances with a harmonised classification in CLP Annex VI or substances identified on the Candidate List under REACH should be considered as subject to regulatory action (example proposed restriction on skin sensitisers in textiles, leather, fur and hide).
- **Similar physical properties** where the concern arises from mere presence of the substance and resistance to (bio)degradation (example restriction on microplastics).
- **Similar exposure route:** which may be linked to use, where concern arises from exposure to (a group of) substances (example restriction on substances in tattoo ink and permanent make-up).
- **"Arrow head approach"/Metabolites or degradation products** where concern arises from the degradation products or metabolites, hence the restriction applies to all substances related to the degradation products (example restriction on azo colourants and azodyes which by may be broken down to specific aromatic amines already restricted under REACH; restriction on Nonylphenol Ethoxylates NPE and its degradation product Nonylphenol NP).
- **Similar risk profiles** concluded from the assessment of exposure, hazard and use triggering a concern (example restriction on decaBDE due to its PBT/vPvB concerns and use as flame retardants in plastics and textiles).
- **Similar mode of action/mechanism** where similar substances contribute together to an identified toxicological concern (example proposed restriction on siloxanes (D4/D5/D6))**.**
- **Specific use** where concern arises from substances found in certain products (example restriction on CMR 1A/1B in textiles and clothing for consumer use).
- **Specific restriction conditions** based on limit value for safety of humans or the environment derived no-effect level (DNEL) (example restriction on aprotic solvents).