Grouping and read-across (human health) ECHA perspectives from REACH and CLP

EFSA Workshop on read-across: role and guidance in chemical risk assessment

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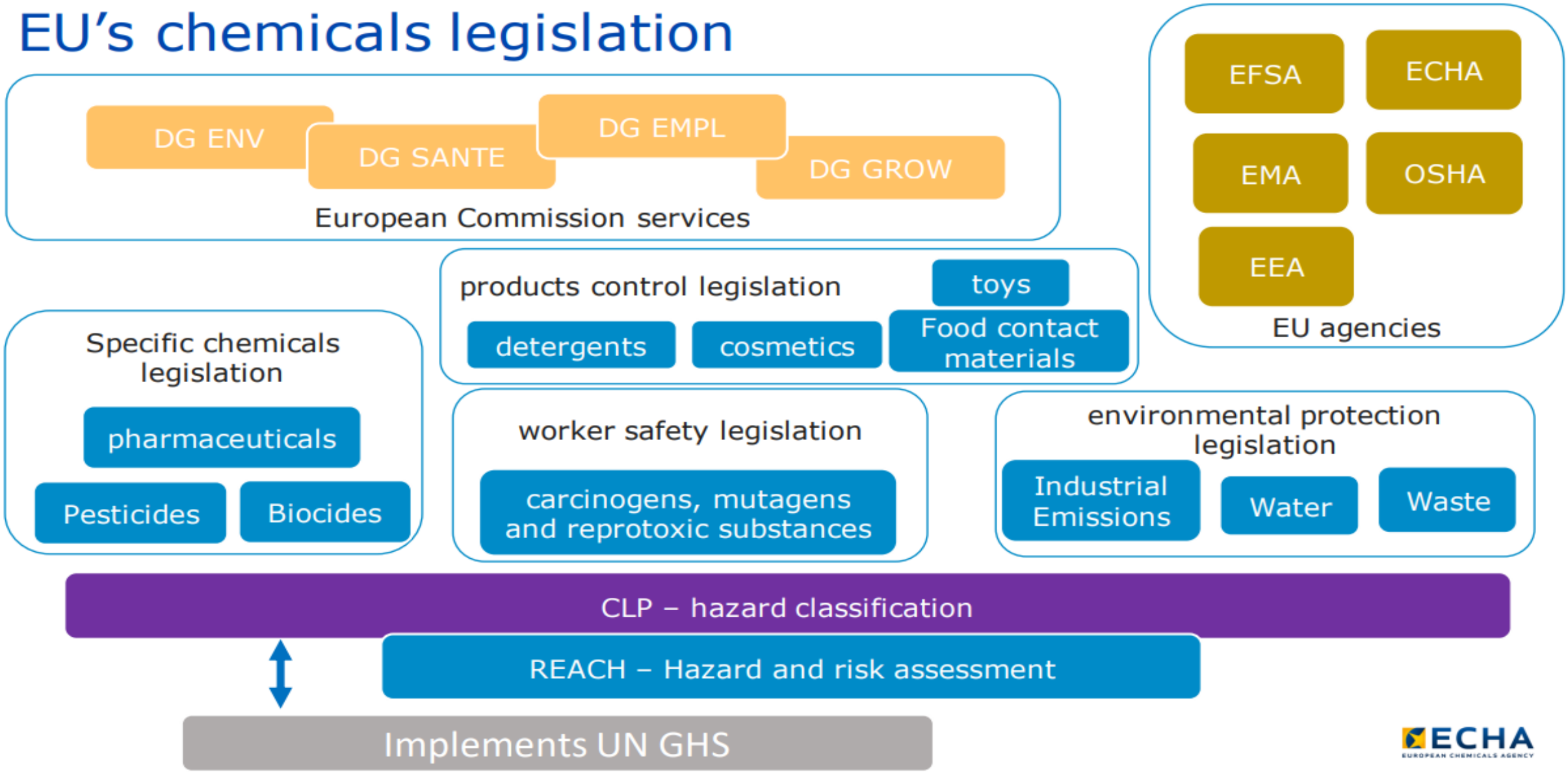
EU's chemicals legislation



Key elements of current system - REACH and Classification, Labelling and Packaging (CLP)

Substances of concern are identified based on their classification

- Defined hazard classes with clear corresponding criteria to allow consistent classification (implementing GHS)
- Based on adverse effects (e.g. effects on reproduction, endocrine disruption)
- Require derivation of safety levels / thresholds

Quality data for decision making

- reliable, comparable and re-usable, allowing mutual acceptance of data (MAD) between different EU legislations and at international level

Reverse of burden of proof

- Authorities are not required to intervene by default
- Separation of duties (avoid duplication of work by authorities and industry)

Standard information requirements

- Predictability and legal certainty for both industry and authorities
- Feasibility from workload and enforcement perspective

Read-across workflows commonly start with the problem formulation

- Need to identify the target substance data gap
- Takes account of the regulatory context (e.g. prioritisation for further actions, grouping, filling regulatory data gaps, hazard identification, classification, risk assessment).
- The level of tolerable uncertainty may differ according to context.
  - e.g. Regulatory requirements may indicate conditions for assessing uncertainties

REACH

REACH Information Requirements

- Substance identity and composition information
- The minimum "Standard information requirements (SIR)"
  - tiered according to supply tonnage 1-10, 10-100, 100-1000 & >1000 (the standard testing regime)
- Use of relevant and internationally recognised Test Methods/GLP
- Animal testing as last resort - obligation to consider alternative methods
- Non-animal methods e.g. Skin/Eye irritation, Skin sens., in vitro muta.
- Acute and repeated dose toxicity, Reproductive Toxicity,
- If triggered - Carcinogenicity, Mutagenicity (in vivo), other

! Level of required information set by reference to Test Methods (and guidance)

!! Set of reliable information – adequate to serve different purposes

Note: "Specific rules" may allow adaptation (e.g. to take account of existing information, exposure, triggering of further requirements).

REACH Adaptations

- "General rules" allow adaptation of SIR
- In vitro/QSAR
  - For higher tier information requirements (e.g. RDT) no in vitro or QSAR methods currently accepted to fully replace the standard animal test
  - Can contribute to weight of evidence or support read-across
- Weight of Evidence approaches from different lines of information
- Grouping and read-across
  - Registrants responsible for read-across hypothesis and generating supporting data (whether standard TG data or non-standard data)
  - e.g. Registrants to provide TK data if needed to support the hypothesis - even if not a standard information requirement

! REACH Registrants are responsible for the grouping and read-across hypothesis and generating any needed supporting information

REACH Annex XI – Grouping and read-across

Group or category:
substances whose physico-chemical and (eco)toxicological properties **are likely to be similar** or follow a regular pattern **as a result of structural similarity**

→ **Read-across:** properties or effects of substances in the group may be **predicted from data for reference substance(s) within the group**

→ Similarities may be based on:

- Common functional group*
- Common precursors/breakdown products resulting in structurally similar chemicals*
- Constant pattern in changing of potency

! Under REACH Read-across of positive and negative results possible

!! Under BPR Annex VI […]* "indicating the presence of dangerous properties"

REACH Annex XI, Grouping and read-across

Requirements on the results:

→ Adequacy for the purpose of classification and labelling and/or risk assessment

→ Adequate and reliable coverage of the key parameters of

→ Exposure duration comparable to/longer than

} corresponding study that is normally done for a particular information requirement

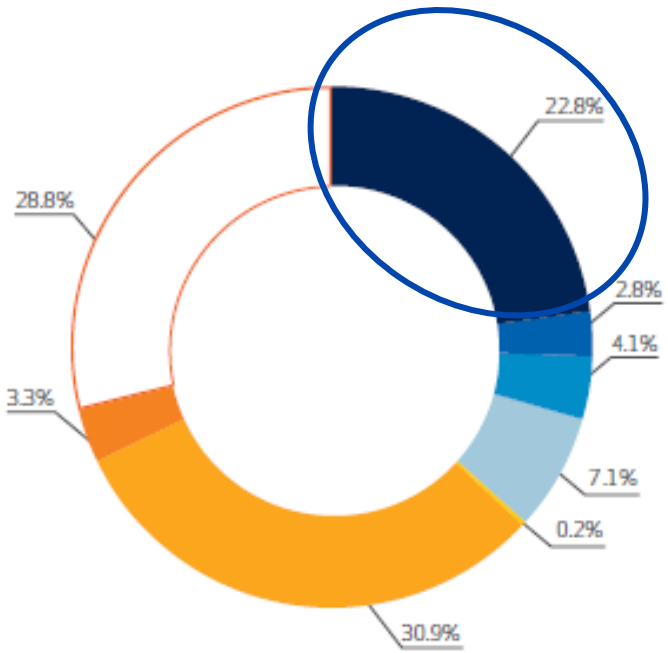
→ Adequate & reliable documentation

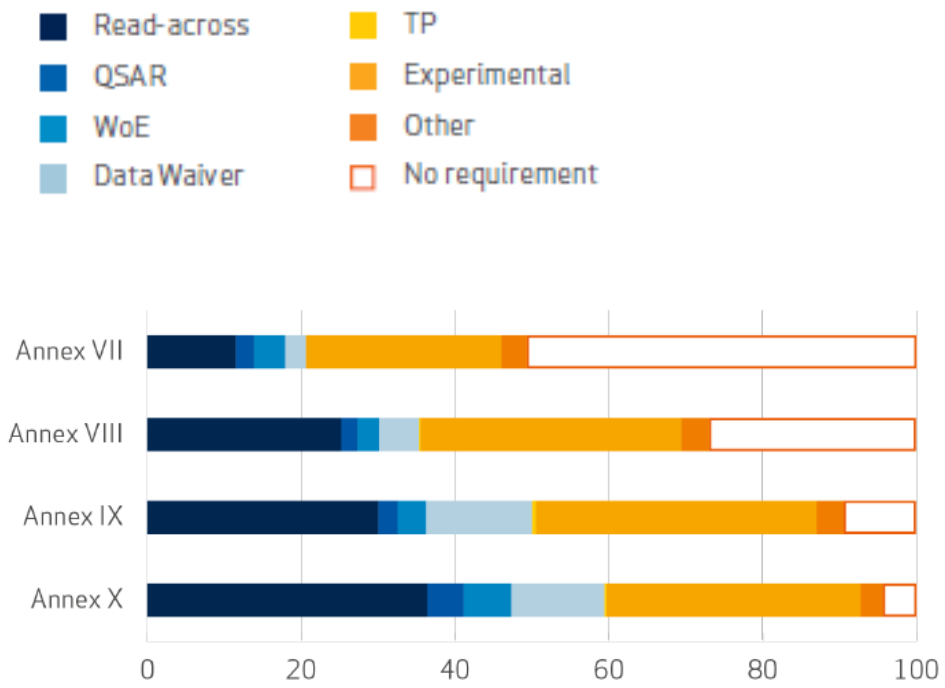
- robust study summary for each source study
- explanation why properties of registered substance may be predicted from other substances
- supporting information to scientifically justify

! In principle, the result of read-across should be adequate to be used in the same way as the result of the standard test.

Read-across: most commonly used adaptation

~75% of dossiers contain read-across for at least one endpoint





- **Read-across is the most frequently used option of alternatives to fulfil a standard information requirement: used in about 25% of cases**

Source: The use of alternatives to testing on animals for the REACH Regulation, Fifth report under Article 117(3) of the REACH Regulation, June 2023
https://echa.europa.eu/documents/10162/23919267/230530_117_3_alternatives_test_animals_2023_en.pdf/9cfc291e-9baf-ffa2-466c-2bc2c6f06b8e?t=1685428213290

Issues with regulatory acceptance

→ Read-across adaptations often fail to comply with legal requirements when examined under REACH compliance check procedure and are inadequate to ensure the safe use of chemicals

→ Issues include:

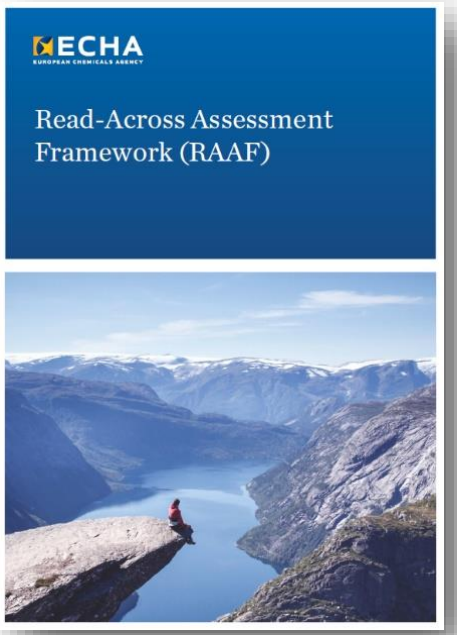
- poor documentation
- insufficient substance identification (source and target)
- shortcomings in hypothesis / justification of the prediction
- lack of or low quality of supporting data
- lack of data to support predictions based on toxicokinetics
- insufficient quality of the source studies

Overall: justification and provided evidence not adequate

An analysis of reasons for rejections of read-across in ECHA decisions was performed by

Ball et al. (2016) Toward Good Read-Across Practice (GRAP) Guidance, ALTEX 33: 149-166 10.14573/altex.1601251

ECHA Read-Across Assessment Framework



- Assessment of a read-across cannot currently be standardized and automatized in every detail
- Sets out different types of read-across - derived from general principles of structural-similarity based read-across
- Structures the scientific analysis of read-across commonly observed REACH in registration dossiers;
- Characterises confidence of the assessor;
- Does not replace expert judgement; has to be applied flexibly

- Not designed to assess Weight of Evidence or explain how the outcome translates into regulatory (legal) processes
- Other Guidance and advice for building and reporting read-across is available

Available at https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

ECHA Read-Across Assessment Framework

Type and amount of information needed depends on the read-across hypothesis and the information requirement to be read across

The RAAF defines two general read-across hypotheses:

1. (Bio)transformation into a common toxicant
   - Toxicokinetic information may support the approach
2. Different compounds have the same type of effects
   - Toxicodynamic information may support the approach

ECHA RAAF Assessment Elements

Examples (human health)

→ Common AE's

Analogue approach

AE A.1	Identity and characterisation of the source substance
AE A.2	Link of structural similarities and differences with the proposed prediction
AE A.3	Reliability and adequacy of the source study
AE A.4	Bias that influences the prediction

Category approach

AE C.1	Substance characterisation
AE C.2	Structural similarity and differences within the category
AE C.3	Link of structural similarities and structural differences with the proposed regular pattern
AE C.4	Consistency of effects in the data matrix
AE C.5	Reliability and adequacy of the source study(ies)
AE C.6	Bias that influences the prediction

→ Scenario-specific AE's (e.g.category scenarios 3/5 and 4/6)

SCENARIO 3	SCENARIO 5	ASSESSMENT ELEMENT TITLE
AE 3.1	AE 5.1	Formation of common (identical) compound(s)
AE 3.2	AE 5.2	The biological target(s) for the common compound(s)
AE 3.3	AE 5.3	Exposure of the biological target(s) to the common compound(s)
AE 3.4	AE 5.4	The impact of parent compounds
AE 3.5	AE 5.5	Formation and impact of non-common compounds

SCENARIO 4	SCENARIO 6	ASSESSMENT ELEMENT TITLE
AE 4.1	AE 6.1	Compounds the test organism is exposed to
AE 4.2	AE 6.2	Common underlying mechanism, qualitative aspects
AE 4.3	AE 6.3	Common underlying mechanism, quantitative aspects
AE 4.4	AE 6.4	Exposure to other compounds than those linked to the prediction
AE 4.5	AE 6.5	Occurrence of other effects than covered by the hypothesis and justification

ECHA RAAF assessment – What's the problem?

Assessment element	Examples of typical issues identified
Formation common compound	No information provided, not rapid/complete metabolism
Common underlying mechanisms	Cannot assess – no data on target, different effects in different types of studies
Consistency effects in matrix	Cannot assess – no data on target, different effects in different types of studies, clear different effects
Impact parent compound	Not complete/rapid metabolism, no data on parent compound
Formation/impact non-common compounds (NCC)	No info identity of NCC., no tox data on NCC
Occurrence of other effects than predicted	Cannot assess – no data on target, different effects in different types of studies, clear different effects
Structural similarity/differences in category	No info on applicability domain of the category, missing info on ID and composition of substances
Substance characterisation (source/category members)	Missing information on identification and composition

Testing strategies under REACH

- Registrants may have a promising read-across but lack reliable higher tier source data (e.g. OECD 414); proposals are needed to generate such higher tier studies
- They may propose to test another substance to use as source for read-across to their substance; ECHA may accept the future read-across as ***plausible*** subject to later assessment after data generation.
- Some selected highlights of a recent systematic analysis:
  - About 50% of TP relying on read-across were accepted
  - Bridging data increased odds of success
  - Apparent success rate was higher for group versus analogue approaches – so might be encouraged (where grouping possible)
  - Reading across from UVCBs to a mono-constituent substance might be discouraged

*A Systematic Analysis of Read-Across Adaptations in Testing Proposal Evaluations by the European Chemicals Agency.

Hannah M. Roe, Han-Hsaun D. Tsai, Nicholas Ball, Fred A. Wright, Weihsueh A. Chiu, Ivan Rusyn. ALTEX 41(1), 22-38 (2024)

REACH - Testing strategies - Sector approaches

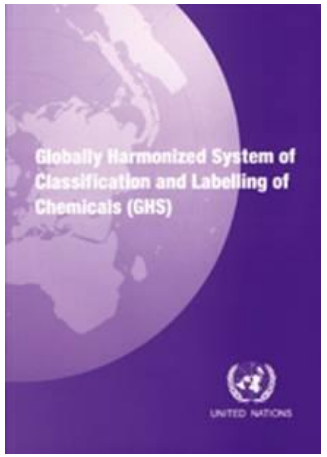
- Every grouping and read-across can have unique aspects
  - (e.g multiple registrants, data availability/data requirements, allowable compositional differences, chemistries and chemical classes, (de-)toxifying metabolisms, positive vs. negative read-across, many MoA, logistical issues, availability of expertise or CROs)
- Consortia management for groups can present business/logistical challenges
- As a general advice:
  - Be realistic in the data gap analysis – create a data matrix
  - ECHA would normally expect a complete set of Annex VII/VIII information
  - the (Annex VIII) OECD TG 422 provides screening level information on both reproductive and repeated dose toxicity and may provide useful supporting ('bridging') information
  - Generate TK data if needed to support hypothesis
- 'Rule of thumb' For a category of mainly Annex IX/X substances, experience shows that a proportion of 30-50% higher tier studies with data from the registered substances is needed to support the read across hypothesis
  - Deviations from these percentages possible with proper justification (e.g. taking account of adaptation possibilities, allowance for large groups, worst case, very similar compositions)

More information at: ECHA-CEFIC collaboration on dossier compliance and https://echa.europa.eu/adaptations-recommendations

CLP

The CLP* Regulation (EC) No 1272/2008

- EU Legal framework for classification & labelling of chemicals
- Hazard classes based on building blocks from United Nations' Globally Harmonised System (GHS).
- CLP is a cornerstone of chemicals management in Europe
  - Rules are clear, simple to apply, sufficiently protective
- CLP assesses the Hazard arising from intrinsic properties of a substance or mixture



! Core element for **one-substance-one-assessment**

* EUR-Lex - 02008R1272-20250201 - EN - EUR-Lex

Harmonised Classification and Labelling (CLH)

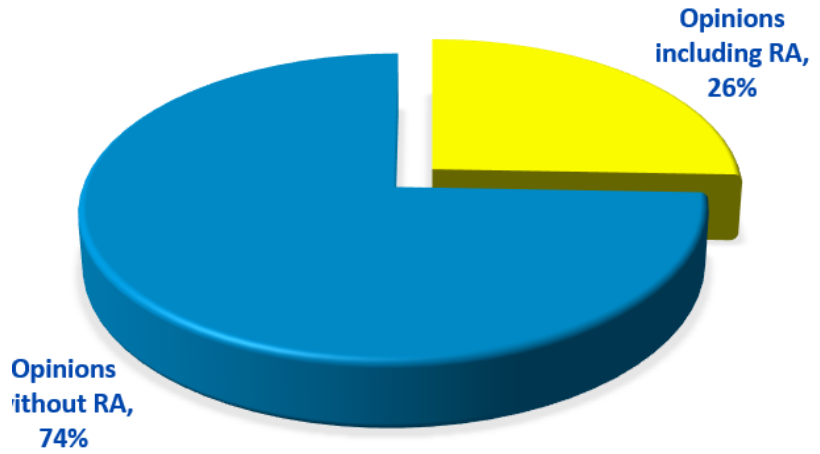
- Industry have to (self-)classify according to CLP criteria
- The CLH process leads to harmonised entries in Annex VI CLP
  - Industry cannot deviate from this entry
  - Usually, the read-across is of hazardous property from a source to a target substance
- There are already ’group entries’ in Annex VI to CLP
  - Risk Assessment Committee (RAC) has given opinions on groups using read-across
- Recently revised CLP further encourages the use of groups in the case of harmonising classifications (Article 37 (8))
  - ECHA is developing a Practical Guide on ’Grouping and read-across under CLP’

Types of read-across assessed under CLH – some general examples

- Ion dissociation
- Common hydrolysis compounds
- Simple salts (e.g. Na. Ca, K etc.)
- Conjugated base and acid

- Different substances share same toxic metabolite
- From toxic metabolite of substance

- Chain length category
- Very similar structures
- Isomers



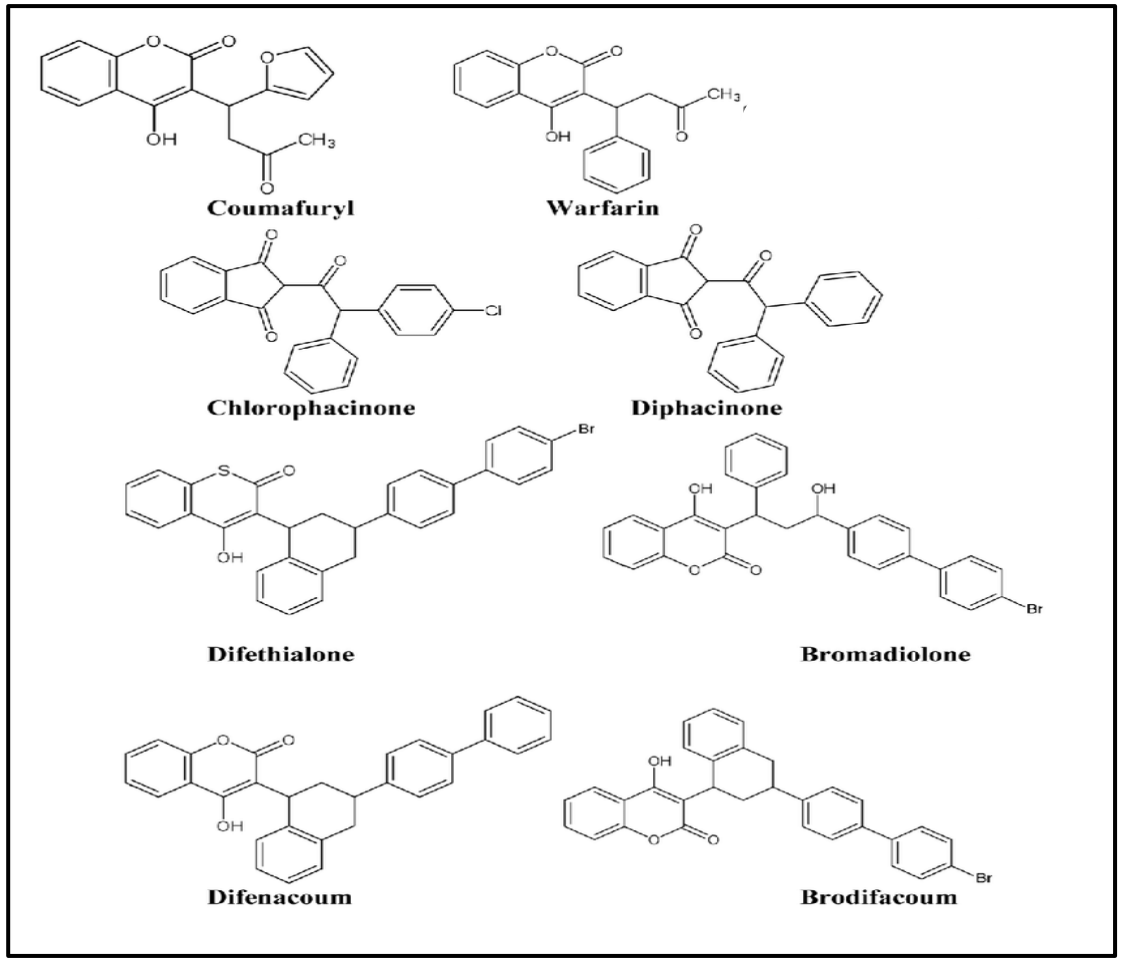
Read-across in RAC opinions 2017-2021

Grouping and read-across under CLP

- all available information bearing on the determination of hazard is considered – this includes application of the category approach (grouping, read-across)
- In principle, possibility to use NAM data
- However, with current methods and knowledge they cannot yet be used alone for prediction of the ”higher” hazard classes:
  - NAM results would need to be comparable with the classification criteria;
  - In addition to toxicodynamics, information on toxicokinetics and/or underlying mechanisms is very valuable – NAMS of sufficient reliability which support the basis of prediction may play a role here
  - Experience of assessing read-across based on some NAM methods/techniques (e.g. omics) is more limited as few are currently presented
  - There are new hazard classes to consider (e.g. ED HH)

CLH - examples of MoA based read-across

- Coumarin derivatives like warfarin
- Different chemical structures;
  - some more 'similar' than others
- Similar Mode of Action to wafarin
  - inhibition of vitamin K epoxide reductase
  - Structural fragment (binds to enzyme)
  - Human data on warfarin and MoA shows adverse effects not readily detected in standard animal test
- Responsible for teratogenicity and classified accordingly



ECHA Report "Key Areas of Regulatory Challenge"

- Mapping of research needs to address urgent regulatory challenges on a range of endpoints and issues.
- In respect of read-across, further developments should consider at least the following elements:
  - the relevance of the biological model (NAM) used to generate NAM information to 'bridge' the information from the source to the target substance and vice versa;
  - the threshold of similarity for the target and source substance, in particular when aiming at grouping multiple substances (conditional to hazard mechanism);
  - the toxicological relevance of the NAM information in the context of regulatory endpoint of interest

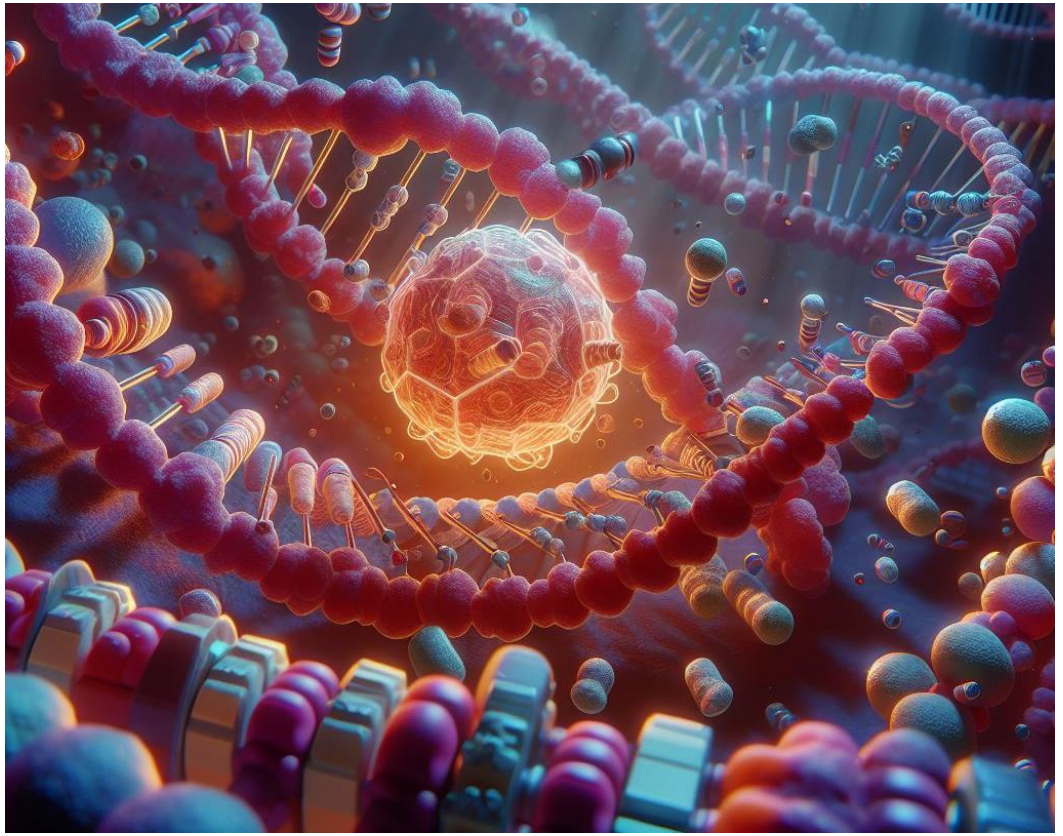
Available at https://echa.europa.eu/technical-scientific-reports

ECHA activities to support NAM

- ***Lower tier endpoints***
  - OECD QSAR Assessment Framework (QAF) implementation project
  - Further development of the OECD QSAR Toolbox
  - Assessment of the prediction's reliability for selected endpoints (acute oral toxicity, aquatic toxicity, bioaccumulation)
- ***Higher tier endpoints***
  - Better utilisation of omics to support read-across and grouping
  - Inclusion of omics in Test Guidelines studies to generate molecular/ mechanistic data
  - Introduction of in vitro toxicokinetic measurements
- ***Sharing data and knowledge***
  - IUCLID
  - Making data available for research and development purposes
  - Assessment of REACH data for regulatory purposes, through Scientific publications
  - Framework Contracts to develop knowledge

Framework contract on the development of NAM based tools and data for hazard identification and characterisation

- → ***3 specific contracts are running***
  - → *OECD guidance on Sampling for omics measurements*
  - → *Use of omics data to substantiate grouping and read across*
  - → *Use of toxicokinetics information in a regulatory context*
- → ***1 specific contract just initiated***
  - → *omics to enhance fish toxicity testing*



Concluding remarks

- Grouping and read-across is a well-established technique to assess hazards and use fewer animals than testing substances individually.
- Regulatory requirements set the conditions for acceptable use of non-standard information. The regulatory requirements may differ but the fundamental scientific principles of assessing read-across and associated uncertainties are broadly similar;
- NAMs show promise to reduce uncertainties; a need for examples to explore different techniques, and to develop criteria and more detailed advice is recognised
- Further research needs to support regulatory read-across with NAM have been identified to guide research undertaken in collaboration with a range of stakeholders (regulators, academia, industry). ECHA is also supporting NAM developments.
- In dialogue with stakeholders, many activities aim at further developing criteria for use of NAMs which also informs how they might be applied at regulatory and policy levels.
- NB. Third workshop to discuss the roadmap to phase out animal testing for chemical safety assessments at ECHA June 2025 (see https://echa.europa.eu/events/2025)

Thank you

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Credits to my ECHA colleagues: Andrea Richarz, Jonas Nygren, Virve Sihvola

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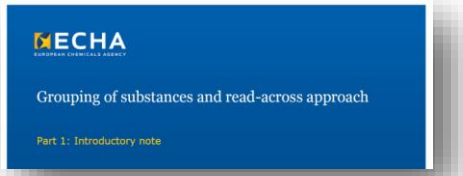
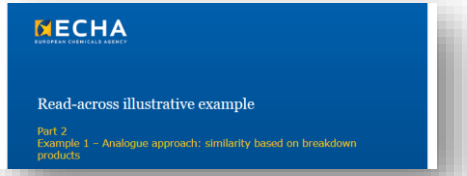
Information slides

Guidance on grouping and read-across

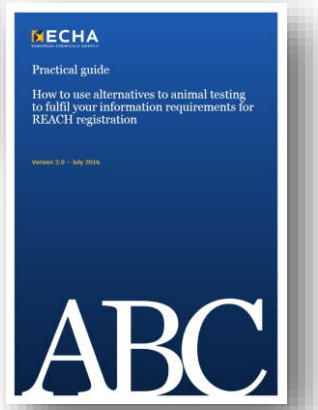
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals

→ Illustrative example of a grouping of substances and read-across approach
- Part 1: An Introductory Note
- Part 2: An illustrative example





→ Practical guide on how to use alternatives to animal testing to fulfil the information requirements for REACH registration

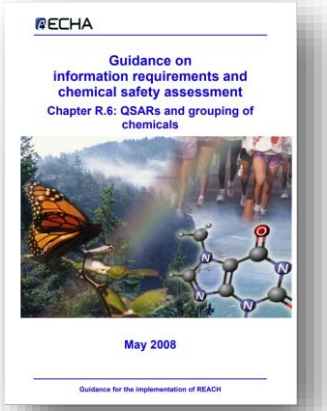


https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Guidance on Information Requirements and Chemical Safety Assessment

→ Chapter R.6 - QSARs and grouping of chemicals
- including: Appendix R.6-1 for nanoforms

→ Endpoint specific guidance (Chapters R.7a, b, c)



New approach methodologies workshop: Towards an animal-free regulatory system for industrial chemicals

→ held on 31 May - 1 June 2023 | ECHA, Helsinki

→ on ECHA website:

- recorded presentations
- video interviews
- workshop report

https://echa.europa.eu/-/new-approach-methodologies-workshop-towards-an-animal-free-regulatory-system-for-industrial-chemicals