FEDERCHIMICA
CONFINDUSTRIA

Vermeer Project for Safety evaluation: focus on international cosmetic regulatory framework

Regulatory approach on silico evaluation for chemicals

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Toxicity evaluation

Determining the toxicity of chemicals is necessary to identify their harmful effects on humans, animals, plants, or the environment.

Animal models have been used for a long time for toxicity testing. However, in vivo animal tests are constrained by time, ethical considerations, and financial burden.

Therefore, computational methods for estimating the toxicity of chemicals are considered useful.

In silico toxicology is one type of toxicity assessment that uses computational methods to analyze, simulate, visualize, or predict the toxicity of chemicals. In silico toxicology aims to complement existing toxicity tests to predict toxicity, prioritize chemicals, guide toxicity tests, and minimize late-stage failures in drugs design.

The relevance of in silico toxicology is now part of legislative acts but with some notations.

4 steps

Relevance

- Regulatory context, regulatory goal, regulatory endpoint

Reliability

- Traceability, reproducibility, repeatability...

Adequacy

- for the regulatory endpoint
- for classification/labelling and/or risk assessment (e.g. DNEL setting)
- in terms of covering the key parameters addressed by the corresponding standard information

Transparency: Adequate and reliable documentation

- Use standardised templates for communication (structuring the evaluation workflow, check list, easy access and database compatibility)

Some Definitions

Chemical Category, Read-Across, and Trend Analysis

A **chemical category** is a group of chemicals whose properties and toxicity effects are similar or follow a similar pattern. Chemicals in the category are also called source chemicals. The *OECD Guidance On Grouping Of Chemicals* lists several methods for grouping, such as chemical identity and composition, physicochemical and ADME properties, mechanism of action (MoA), and chemical/biological interactions. Structural similarity is described in the OECD guidelines as the starting point for grouping, but it is also criticized for lacking a 'scientifically supportable basis' for grouping, and it can be used if impurities or other constituents in the chemical composition would not change toxicity.

Read-across is a method of predicting unknown toxicity of a chemical using similar chemicals (called chemical analogs) with known toxicity from the same chemical category.

Trend analysis is a method of predicting toxicity of a chemical by analyzing toxicity trends (increase, decrease, or constant) of tested chemicals. A hypothetical example of trend analysis shows that when carbon chain length (CCL) increases, acute aquatic toxicity increases

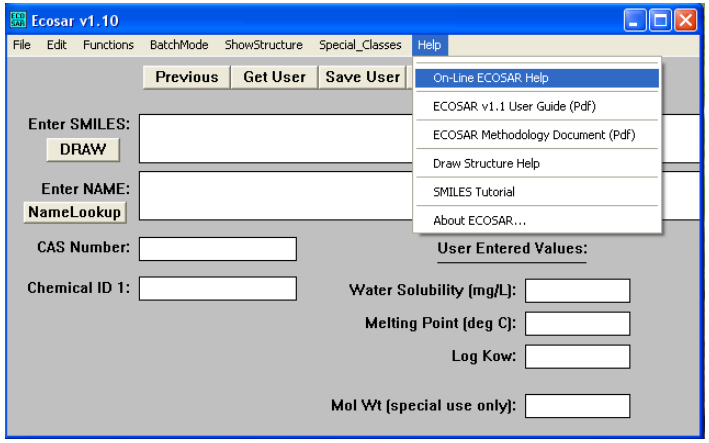
EPA and in silico

The application of methods for evaluating biological properties on the basis of chemical-physical characteristics for regulatory purposes was supported by U.S. EPA's Office of Pollution Prevention and Toxics (OPPT), which administers the Toxic Substances Control Act (TSCA), which since 1976 regulates all chemicals in the USA.

The reasons were the need arises to examine a large number of substances that had limited data not sufficient to ensure a proper assessment of risk during the 90’s

EPA and in silico

Example: ECOSAR for the following end points



Acute Effects:

Fish 96 hr LC50

Daphnid 48 hr LC50

Algae 72 or 96 hr EC50

Chronic Effects:

Fish ChV

Daphnid ChV

Algae ChV

The method used the SAR plus evaluation of chemical-physical end points (water solubility, log POW, vapour pressure ..). The SAR data were accepted by EPA since 2003.

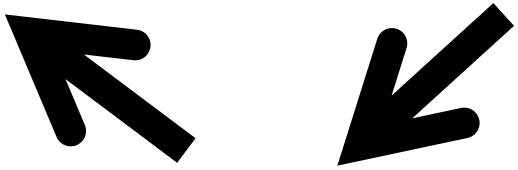
HPV Programme

Index of Robust Summaries for
ACC FND HPV Nitriles

Page

2.1 MELTING POINT

In a Council Decision in 1987, member countries decided to establish or strengthen national programmes to systematically investigate existing chemicals. By another OECD Council Decision in 1991, member countries agreed to investigate existing chemicals in a co-operative way, and to focus on high production volume (HPV) chemicals based on the assumption that production volume is a surrogate for data on occupational, consumer and environmental exposure (Council Acts 1987, 1991). Each country agreed to share the burden of assessing HPV chemicals by sponsoring a proportion of the HPV chemicals in the Programme. By sharing the work, countries and industry have benefitted from the assessments conducted by other member countries and industries.



Example of read acroos approach accepted by EPA for HPV pr.

Europe

In Europe the Directives EEC/67/548 and subsequent amendments did not mentioned the possible use of alternative methods based on structure, nor the use of data of similar substances but…..

- ✓ **exceptions were accepted for the execution of chemical-physical tests on the basis of the structures;**
- ✓ **the calculation data for the bioaccumulation potential were accepted**
- ✓ **evaluations based on chemical group analysis have been accepted in some cases to reduce animal tests**

REACH

The change with the Regulation 1907/2006 - REACH which indicates for the first time, at the level of European legislation, the possibility of using alternative methods and in particular of structure-activity models

Article 1

Aim and scope

1. The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation.

REACH

Whereas……

(38) The generation of information by alternative means offering equivalence to prescribed tests and test methods should also be allowed, for example when this information comes from valid qualitative or quantitative structure activity models or from structurally related substances. To this end the Agency, in cooperation with Member States and interested parties, should develop appropriate guidance. It should also be possible not to submit certain information if appropriate justification can be provided. Based on experience gained through RIPs, criteria should be developed defining what constitutes such justification.

REACH

Article 13

General requirements for generation of information on intrinsic properties of substances

1. Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, *in vitro* methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across). Testing in accordance with Annex VIII, Sections 8.6 and 8.7, Annex IX and Annex X may be omitted where justified by information on exposure and implemented risk management measures as specified in Annex XI, section 3.

Article 25

Objectives and general rules

1. In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. It is also necessary to take measures limiting duplication of other tests.

ANNEX VII

STANDARD INFORMATION REQUIREMENTS FOR SUBSTANCES MANUFACTURED OR IMPORTED IN QUANTITIES OF ONE TONNE OR MORE ([1])

Before new tests are carried out to determine the properties listed in this Annex, all available *in vitro* data, *in vivo* data, historical human data, data from valid (Q)SARs and data from structurally related substances (read-across approach) shall be assessed first. *In vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided. Prior to testing, further guidance on testing strategies should be consulted in addition to this Annex.

REACH

In the annexes

1.3. **Qualitative or Quantitative structure-activity relationship ((Q)SAR)**

Results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence or absence of a certain dangerous property. Results of (Q)SARs may be used instead of testing when the following conditions are met:

— results are derived from a (Q)SAR model whose scientific validity has been established,

— the substance falls within the applicability domain of the (Q)SAR model,

— results are adequate for the purpose of classification and labelling and/or risk assessment, and

— adequate and reliable documentation of the applied method is provided.

The Agency in collaboration with the Commission, Member States and interested parties shall develop and provide guidance in assessing which (Q)SARs will meet these conditions and provide examples.

REACH

In the annexes

1.5. **Grouping of substances and read-across approach**

Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint. The Agency, after consulting with relevant stakeholders and other interested parties, shall issue guidance on technically and scientifically justified methodology for the grouping of substances sufficiently in advance of the first registration deadline for phase-in substances.

The similarities may be based on:

(1) a common functional group;

(2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or

(3) a constant pattern in the changing of the potency of the properties across the category.

If the group concept is applied, substances shall be classified and labelled on this basis.

In all cases results should:

— be adequate for the purpose of classification and labelling and/or risk assessment,

— have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),

— cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and

— adequate and reliable documentation of the applied method shall be provided.

Other Countries

China: very conservative approach – the law permits the use of in silico data but it is preferrred the uso of animal data

Japan: few chemical –physical data accepted for new substances

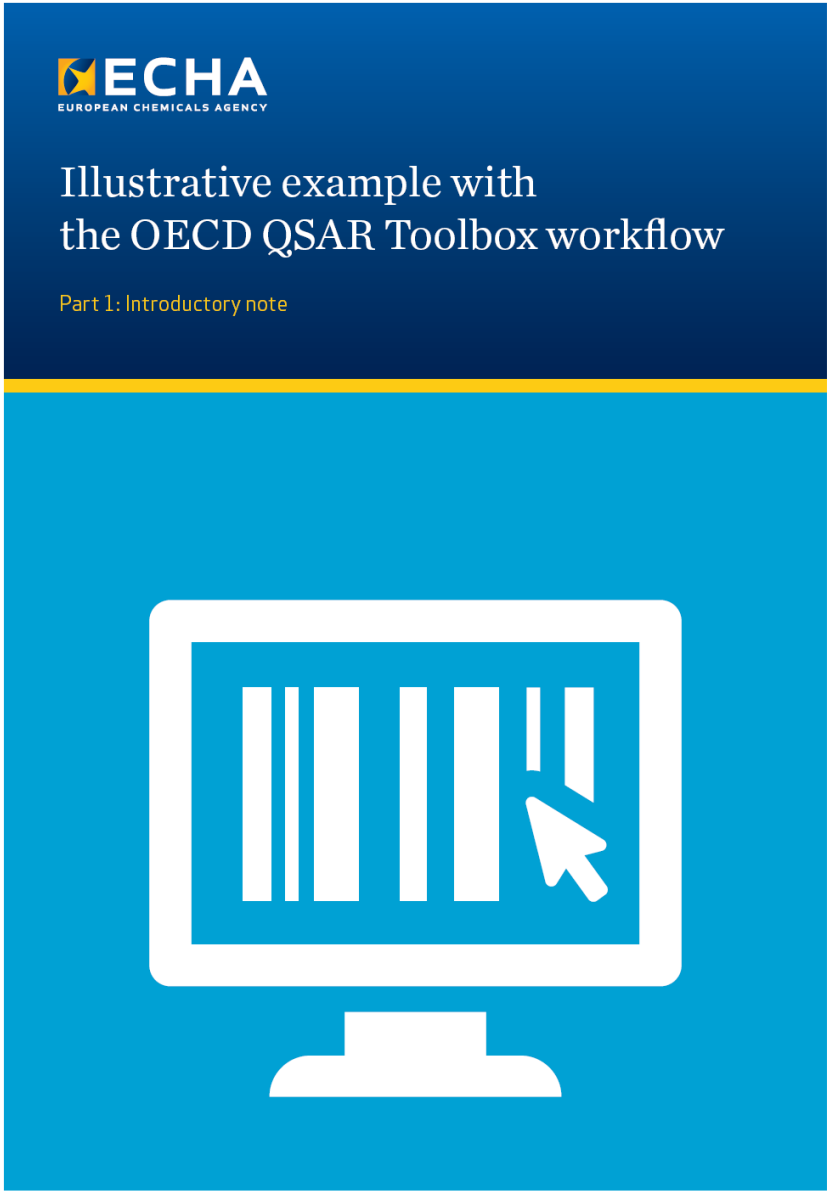
Australia: OK (Q)SAR and Read Approach with expert judgement

Canada – (Q)SAR tox accepted but only when "positive"

Korea - K-REACH permits in silico with Authority check

REACH

REACH support the use of in silico toxicology but suggesting the use of OECD tool box



REACH

REACH support the use of in silico toxicology but ….

In vitro preferred
In silico as screening

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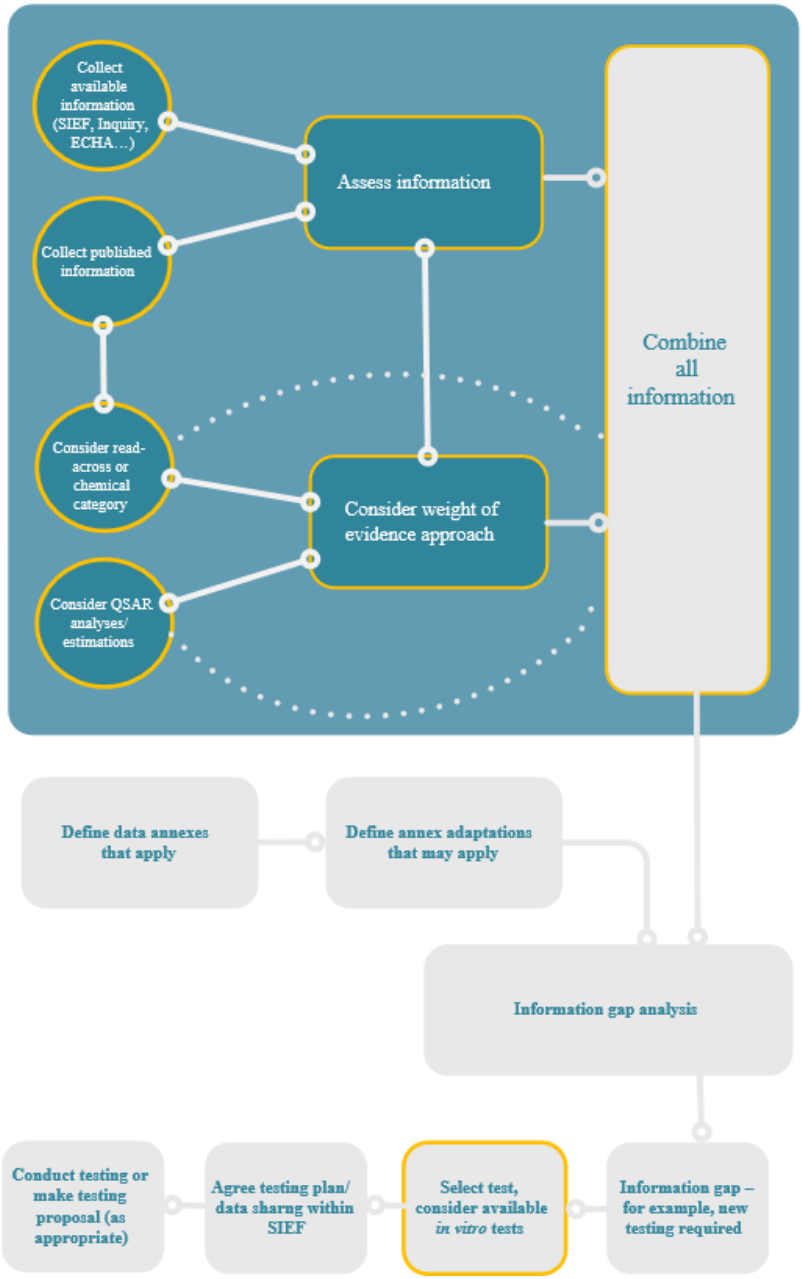

Cosmetic Ingredients

Substances - Polymers

Natural – Synthetic

Single structures - UVCB

Acute - Chronic

The assessors accept in principle validated *in-vitro* data and toxicological review for chemical groups

Proposals

In silico data is still not completely accepted by regulators

***In vivo* or *in vitro* data are preferred, but they have an intrinsic uncertainty**

It would also be useful to have validation / auditing systems GLP-type for in silico data, both on the validity of the system and the operators

Thanks for your attention