ChemicalWatch
GLOBAL RISK & REGULATION NEWS

The Regulatory Processes Involved in Acceptance of Non-Animal Tests Webinar

10 June 2015, 3:00pm BST

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Today's webinar aims

- **Karin Kilian** (European Commission) will discuss regulatory acceptance of non-animal tests – including the OECD process – REACH provisions, and updates to the test method Regulation;
- **Derek Knight** (Echa) will describe the purpose of testing and how data requirements can be met avoiding the use of animal (including weight of evidence approaches); and
- He will also provide information on the current state of play and various initiatives of the agency.

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Speakers

* **Karin Kilian,** European Commission, DG ENVIRONMENT

***Derek Knight,** ECHA

❖ Chair: **Emma Chynoweth,** Chemical Watch

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Questions

- **Please submit questions during the webinar using your chat box**

- Any unanswered questions can be raised on our Forum following the webinar: http://forum.chemicalwatch.com/

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The Test Method Regulation – a mechanism for regulatory acceptance of methods

The Regulatory Processes Involved in Acceptance of Non-Animal Tests

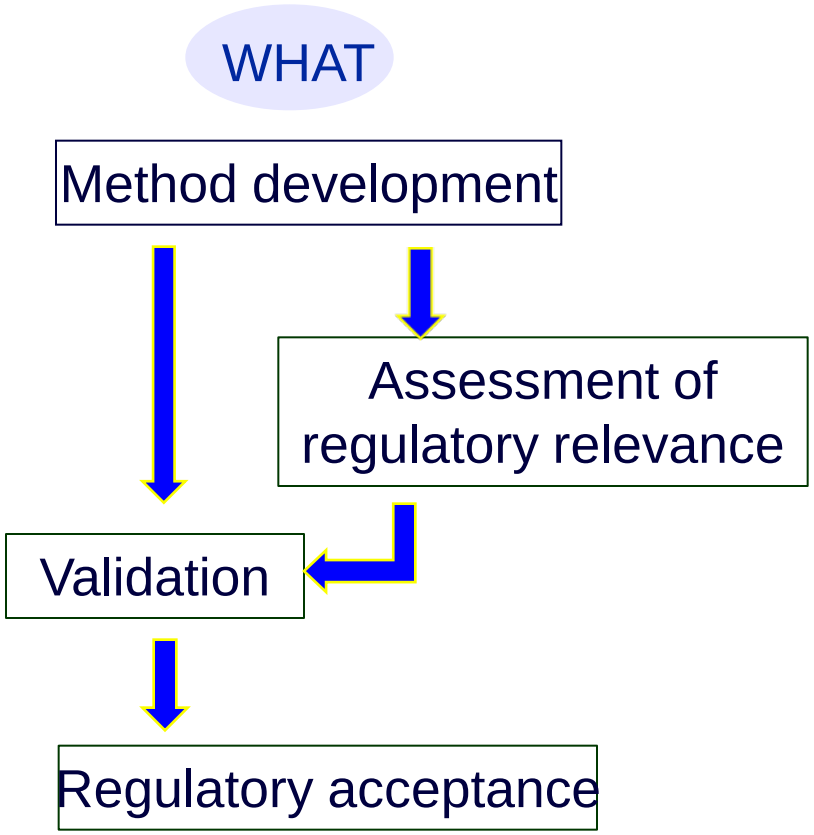
Chemical Watch Webinar
10 June 2015

Karin Kilian
European Commission, DG Environment

Outline

- **Regulatory acceptance processes – OECD, EU**
- **Chemical safety testing under REACH**
- **The Test Method Regulation**
- **Paradigm shift in toxicology – a challenge for regulatory acceptance**

Regulatory acceptance processes



WHO

Academia, Industry, Research institutes

ECVAM, PARERE

ECVAM, NETVAL, Method developers

International: OECD, ICH

EU: Regulation 440/2008, sectorial legislation, guidance

Regulatory acceptance - OECD

- Aim: international harmonisation of test methods for chemical safety through development of commonly agreed test guidelines (TGs)
- Framework: Mutual acceptance of data (MAD) - results from a chemical safety test conducted in OECD countries shall be accepted by other member countries if the test was carried out according to OECD Test Guidelines
- OECD TG cover the most relevant testing methods for general chemical safety testing and some methods specifically geared towards testing of pesticides/biocides for regulatory applications
- OECD TG cover methods to test for physicochemical properties, human health effects, the fate of chemicals in the environment and their effects on environmental systems

Regulatory acceptance - EU

- OECD TGs do not give information on the use a method under a specific regulatory framework
- Which/how much information needs to be generated?
- Depends on how chemicals are used and what are the specific risks arising from such applications

- Regulation (EC) 440/2008 (Test Method Regulation, TMR) provides inventory of methods having reached general regulatory acceptance
- Sectorial legislation (e.g. REACH, PPPR, BPR, CPR…) defines information requirements (general to very specific)

The EU chemical legislation REACH – Provisions on test methods

- Regulation (EC) 1907/2006 concerning the registration, authorisation and restriction of chemicals
- Gives prominent role to non-animal methods and approaches
- Contain explicit cross-reference to principles laid down in Directive 86/609/EEC (now replaced by 2010/63/EU on protection of animals used for scientific purposes)
- Implements 3R and "last resort" principle
- Establishes a "Regulation on test methods"
- REACH Annexes specify information requirements and applicable test methods

REACH promotes use of alternative methods

Concrete provisions:

- Obligation for Commission to update REACH Annexes and Regulation on test methods in order to reduce animal testing
- Obligation for registrants to collect and examine existing data before performing new tests
- Far-reaching provision to waive testing by using non-testing approaches: grouping, read-across, QSAR
- Possibility to replace *in vivo* data by in vitro test results/weight of evidence assessment

Test Method Regulation – History and raison d'être

- Established in REACH as tool to "recognise" test methods as appropriate

  "Where test on substances are required to generate information on intrinsic properties of substances, they shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international methods recognised by the Commission or the Agency as being appropriate." (Article 13(3))

- Not a new concept: already the preceding chemical legislation contained a listing of applicable test methods (Annex V of Directive 67/548/EEC on dangerous substances)
- Provides full-text version of test methods in all EU languages
- Takes up OECD TG in EU law - necessary from legal point of view
- Constantly updated (6th and 7th Adaptations to technical progress (ATP) ongoing)

Test Method Regulation - ATP process

- Method prioritisation (in consultation with EU National coordinators for test methods (EU-NC)) – Priority for in vitro methods, methods with general relevance
- Adaptation of OECD TG to format and terminology of EU legislation, cross-check by EU-NC
- Consultation of EU services
- Translation
- Approval by Member State Committee
- Scrutiny period for EP and Council
- Final adoption by Commission and publication

Limitation of regulatory acceptance by means of TMR

- Rather slow process due to the necessary administrative steps connected to updating legal instruments
  > not well suited to bring new alternative methods into regulatory use
- Resource intensive
  > the number of new and updated methods that can be processed is limited

⇨ Backlog of OECD Test Guidelines not yet included

⇨ Only feasible for methods that have already reached widespread acceptance

Other means of regulatory acceptance for REACH

- REACH: "…recognised by [..] the agency as being appropriate" (= European Chemicals Agency, ECHA)
- Important mechanism to close temporal gap between OECD TG adoption and update of TMR + for methods with limited applicability
- Guidance: integration of new methods in ECHA guidance on information requirements for REACH provides detailed information on use (formalised process including several consultation steps)
- ECHA webpage on OECD and EU test guidelines – provides interim short information on possible application of new methods for REACH purposes, quick update possible after OECD adoption of new methods
- REACH even allows use of methods that have not (yet) reached regulatory acceptance on a case-by-case basis

"Information on intrinsic properties of substances may be generated in accordance with other test methods provided that the conditions set out in Annex XI are met."

Summary – REACH and Test methods

- REACH offers a very flexible approach to methods that can be used to generate data
- Standard information requirements can be adapted by using other methods/approaches
- Primary toolbox: TMR (*in vivo, in vitro, in chemico test* methods that have reached formal regulatory acceptance)
- But: possibility to use other methods (OECD approved, validated, "sufficiently well developed")
- Important role for *in silico* approaches
- ECHA Guidance and supplementary documents give detailed information on use of new (alternative) methods
- Depending on method status, detailed scientific reasoning/use in WoE approach may be needed

Paradigm shift in toxicology…

- Previously: tests for apical effects on whole organism or certain organ systems > "one endpoint-one test"
- Alternative testing methods typically more restricted in scope, often address individual mechanistic steps
- Result: approaches become more flexible, combination of several methods, case-by-case design depending of properties of test substance, existing information etc.
- AOP-based testing approaches, IATAs, ITS, WoE

…a challenge for setting regulatory requirements and formal regulatory acceptance of test methods

- Less problematic in areas with in-depth assessment of individual cases and close interaction with regulatory authority (e.g. pharmaceuticals)
- But challenge in areas based on more standardised approaches (e.g. general chemicals legislation)

? How can information requirements be set for such approaches? (what type/how much information is needed)

? How can regulatory authorities assess submissions based on such approaches? (resources, expertise needed)

⇨ toxicological paradigm change will also require re-thinking of approach to regulatory acceptance

Thank you for your attention!

Small print:
The views and interpretations expressed in this presentation are those of the author and cannot be taken to represent an official position of the European Commission

Regulatory & Scientific Acceptance of non-animal approaches

The Regulatory Processes Involved in Acceptance of non-Animal Tests

Chemical Watch webinar

10 June 2015

Dr Derek J Knight
Senior Scientific Advisor
ECHA

Contents

Introductory summary

- Different purposes for prediction; hence differing degree of tolerated uncertainty
- Complex endpoints cannot be predicted by a single test; instead use a WoE or IATA where information & evidence can be incorporated flexibly
- To decide on the acceptability of a replacement test consider the biology & the context in which the prediction is to be used; not only statistical correlation of the new test with the 'classical' test to be replaced.
- Role of OECD for international acceptance, perhaps with specific variations for particular regulators

REACH & CLP

- **Pre-registration**
- **Data sharing**
- **Registration**
- **Self-Classification**

Industry gathers information and ensures responsible and well-informed management of the risks

ECHA

MSs

- **Evaluation**
  - **Dossier evaluation**
  - **Substance evaluation**

ECHA and MSCAs control and request for further info

- **Authorisation**
- **Restriction**
- **Harmonised C&L**

COM, with support of ECHA and MSCAs, applies community wide risk management measures

REACH: Registration

- **Core of REACH**: EU/EEA manufacturers and importers of chemicals collectively obtain information per substance and use knowledge to ensure safe use
- Registration:
  - IUCLID format technical dossier for substances at 1 t.p.a. submitted using REACH-IT
  - Standard **information linked to tonnage**
  - **Testing Proposals for higher-tier studies** (i.e. at 100 & 1,000 t.p.a.)
  - **Chemical Safety Report** for substances at 10 t.p.a.
  - Transitional arrangements, i.e **'phase in' substances registered in 3 stages**

Purpose of properties assessment within REACH

- To assess a specific substance for a defined purpose to fill a REACH registration ‘information requirement’ for
  - Classification & labelling, i.e GHS/CLP Regulation
  - Hazard characterisation
  - Risk characterisation (which may lead to risk management measures)
- To screen a large set of substances to select groups with particular characteristics, such as low (or high) potential hazard (or risk)
- Hence different actors use the information for different purposes

Intelligent approach for properties assessment for REACH registration

- Registrants of the same substance have data sharing obligations to avoid duplicate testing.
- New animal studies: always as 'last resort'
  - First collect & assess all existing data, and identify data gaps
  - Consider whether data waivers apply
  - Consider if gaps can be filled by non-standard data
- Adaptation possibilities defined in REACH
  - Specific rules/ column 2 of endpoint
  - General rules / Annex XI 'adaptation' to use non-standard data: i.e. non-standard studies, *in vitro* tests, human epidemiology data 'read-across' & 'chemical categories/grouping', valid (Q)SARs & weight of evidence (WoE)
- Vertebral animal testing for higher-tier studies
  - Proposal to ECHA
  - Cannot be performed without ECHA's approval (after public consultation)

Conditions for non-standard data for REACH registration

- Results must be adequate for classification.
- Results must enable adequate risk assessment.
- Key parameters from the standard study are addressed, e.g. adequate exposure duration & route for toxicology data.
- Thoroughly-documented scientific explanation to justify the non-standard methods, e.g. a hypothesis for why the properties of a substance can be ‘read across’ with supporting evidence.

Legal basis for using WoE for REACH registration: Annex XI 1.2

- There may be sufficient WoE from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion.
- There may be sufficient WoE from the use of newly developed test methods ….. leading to the conclusion that a substance has or has not a particular dangerous property.

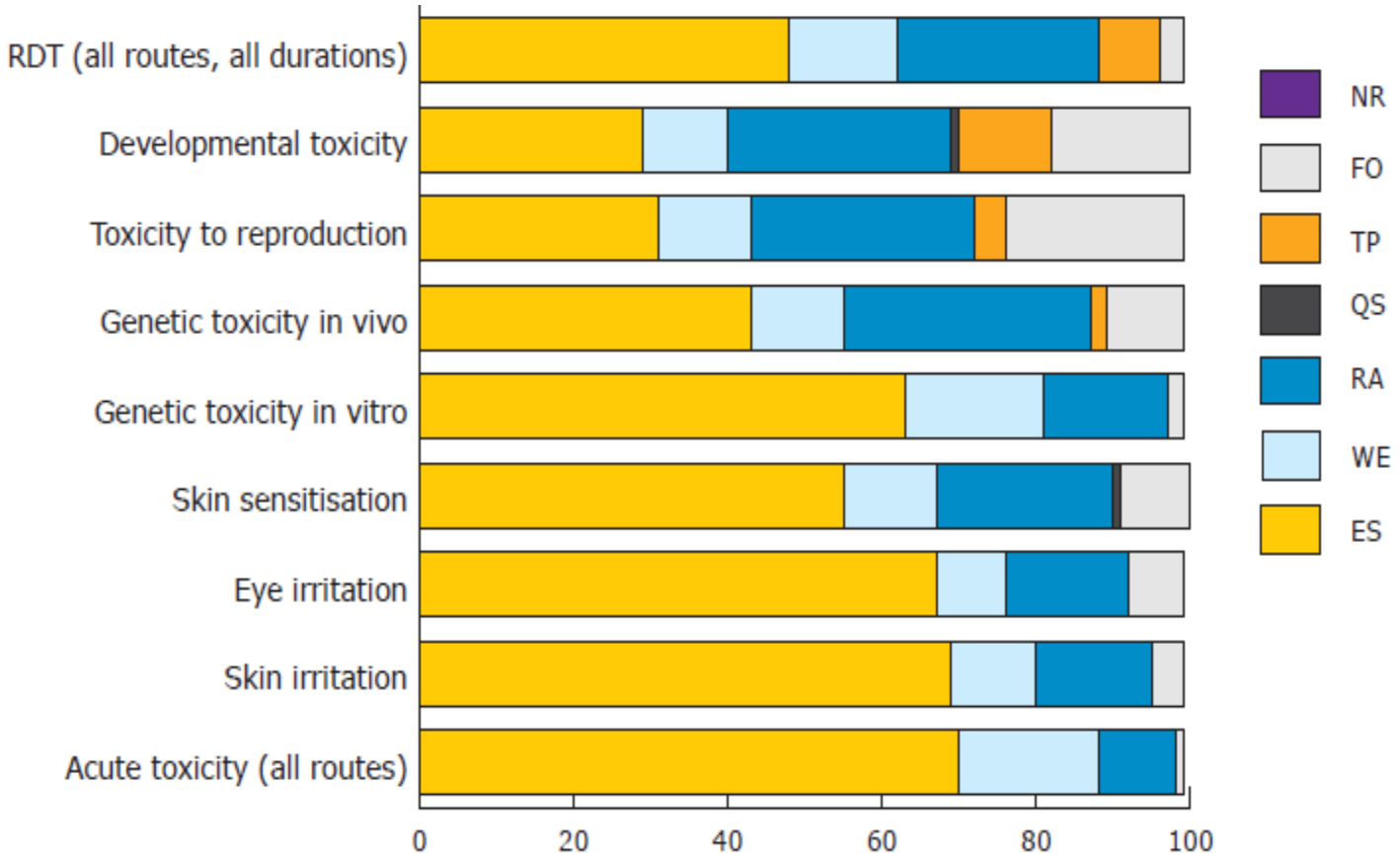
What is Weight of Evidence?

- ECHA Practical Guide ‘How to report weight of evidence’
- Evidence-based approach involving an assessment of relative values/weights (strengths & weaknesses) of different pieces of information (individually each insufficient) in reaching & supporting a conclusion on a property of a substance
- Value of each piece of information is decided by expert judgement (or in principle using a formalised procedure)
- The weight given to the available evidence influenced by quality of the data, consistency of results, nature & severity of effects, relevance of the information for regulatory endpoint
- Case dependent
- WoE closely linked to integrated testing strategies (ITS) as available evidence can help decide on subsequent testing

How are alternatives to animal testing used for REACH registrations?

- 'The Use of Alternatives to Testing on Animals for the REACH Regulation': Reports June 2011 & 2014
  - First report of 24,560 registration dossiers covering 4,599 substances (to 28 February 2011)
  - Second report of 38,711 dossiers covering 8,729 substances (to 1 October 2013)
- Cover registrations at >100 t.p.a. (excludes SCC chemical intermediates & 'NONS' substances)
- Core data with Testing Proposals for higher-tier studies

2014 Reported use of non-test methods



Main findings from 2014 Report on non-standard data

- Registrants make use of alternative testing methods and strategies
- Categories & ‘read-across’ were the most commonly used to fill information requirements, consistent with the findings of the 2011 Report
- Combining information together from different sources (WoE) is the second most common method
- Computer modelling, i.e. (Q)SAR, was the third most common method
- Note that the findings are from what registrants have put in their dossiers, i.e. not checked to verify

First example: repeated-dose toxicity from 2014 Report

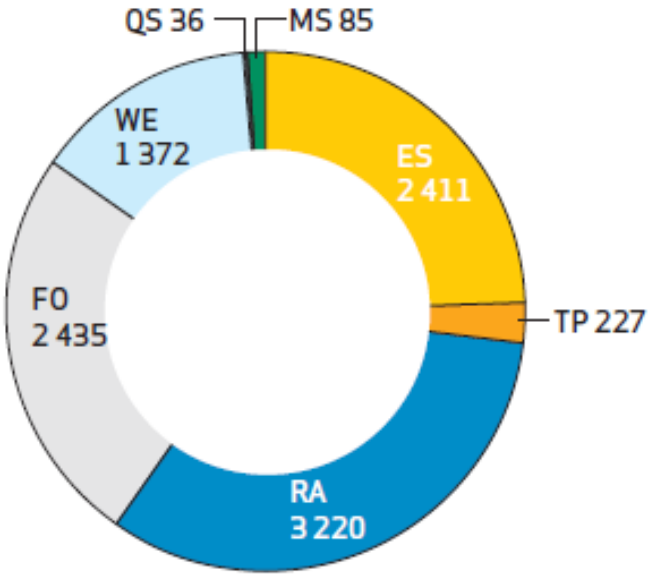


Figure 5.1: Repeated dose toxicity – all routes, all study durations (1 882 dossiers covering phase-in substances 100-1 000 tonnes per year, one or more ESRs may be present per dossier)

Second example: skin sensitisation from 2014 Report

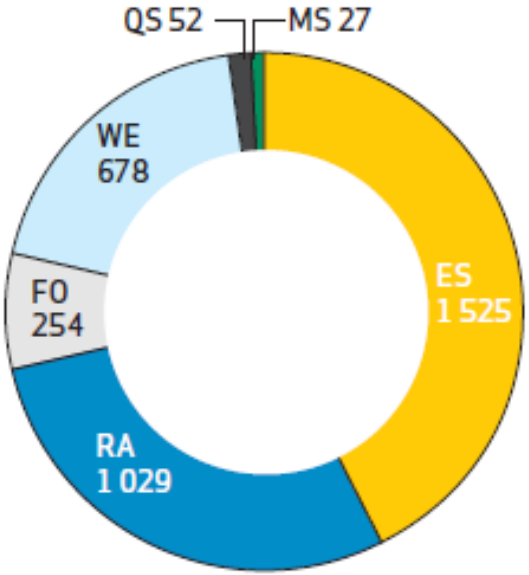


Figure 4.1: Skin sensitisation *in vivo* (1 870 dossiers covering phase-in substances 100 – 1 000 tpa, one or more ESRs may be present per dossier)

Read-across to predict properties

- Read-across: The results of (animal) toxicological study are ‘read-across’ from a ‘source’ substance to a ‘target’ substance of similar chemical structure.
- Chemical group or category: Read-across of toxicological study results within a set of similar substances.
- Similar chemical structures will have similar chemical & physical properties & hence (probably) similar biological (i.e. toxicological) properties.
- Scientific justification perhaps with supporting evidence (& test data), i.e. in effect WoE

Acceptability of read-across

- The ECHA Guidance & Practical Guide do not provide clear-cut (generic) criteria for the assessment of a read-across case:
  - They show how a case can be built, but do not show when it is acceptable to replace a study
  - That depends on the quality of the scientific explanation that forms the core of the case & any supporting evidence; i.e. these have to be credible & convincing.
- Acceptance depends on scientific judgments & regulatory considerations.

ECHA's read-across assessment framework (RAAF): to examine evidence

- For ECHA use in examining read-across cases in dossier evaluation, published 26/5/15 http://echa.europa.eu/documents/10162/13628/raaf_en.pdf
- RAAF initially for toxicology studies for mono-constituent substances
- Provides an internal tool for ECHA to use for a structured approach for scientific evaluation of read-across justifications made by registrants
- Registrants can use the RAAF to see the aspects of read-across justifications that ECHA considers to be crucial
- Preparatory assessment followed by a detailed scientific assessment

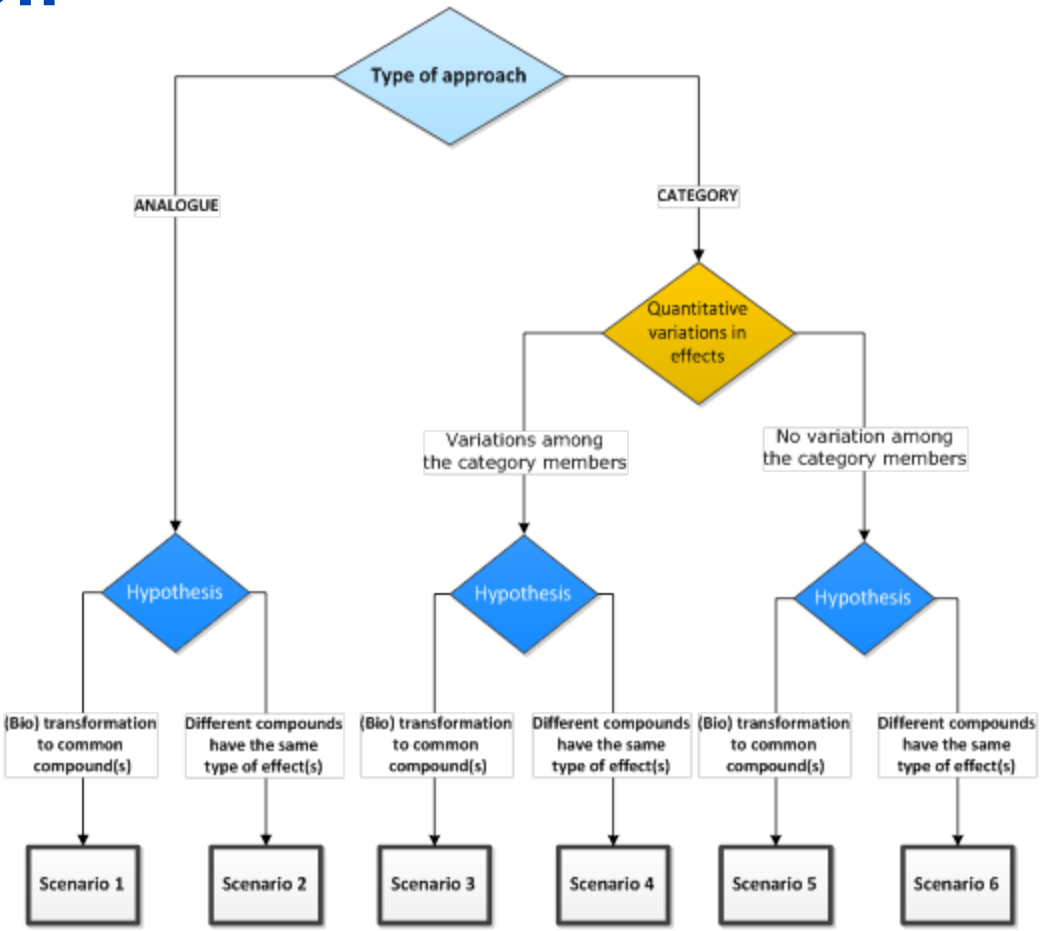
Basic concept of the RAAF

- Assessment conducted by using scenarios, assessment elements (AEs) & assessment options (AOs)
- Scenarios to account for the common read-across scientific justifications when used in the analogue & category approach
- Each scenario comprises a series of dedicated AEs addressing the crucial scientific aspects
- The expert's conclusion on the adequacy & scientific robustness for each AE is codified by selecting one of the predefined set of AOs for the AE

RAAF scenarios

Table 1 - Overview for scenario selection			
Scenario	**Approach**	**Read-across hypothesis based on**	**Quantitative variations**
1	Analogue	(Bio) transformation to common compound(s)	Effect(s) of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on worst-case approach.
2	Analogue	Different compounds have the same type of effect(s)	Effect(s) of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on worst-case approach.
3	Category	(Bio) transformation to common compound(s)	Variations in the strength of effect(s) observed among source substances. Prediction based on a regular pattern or on worst case approach.
4	Category	Different compounds have the same type of effect(s)	Variations in the strength of effect(s) observed among source substances. Prediction based on a regular pattern or on worst case approach.
5	Category	(Bio) transformation to common compound(s)	No relevant variations in strength of effects observed among source substances and the same strength predicted for the target substance.
6	Category	Different compounds have the same type of effect(s)	No relevant variations in strength of effects observed among source substances and the same strength predicted for the target substance

Schematic presentation of RAAF scenario selection

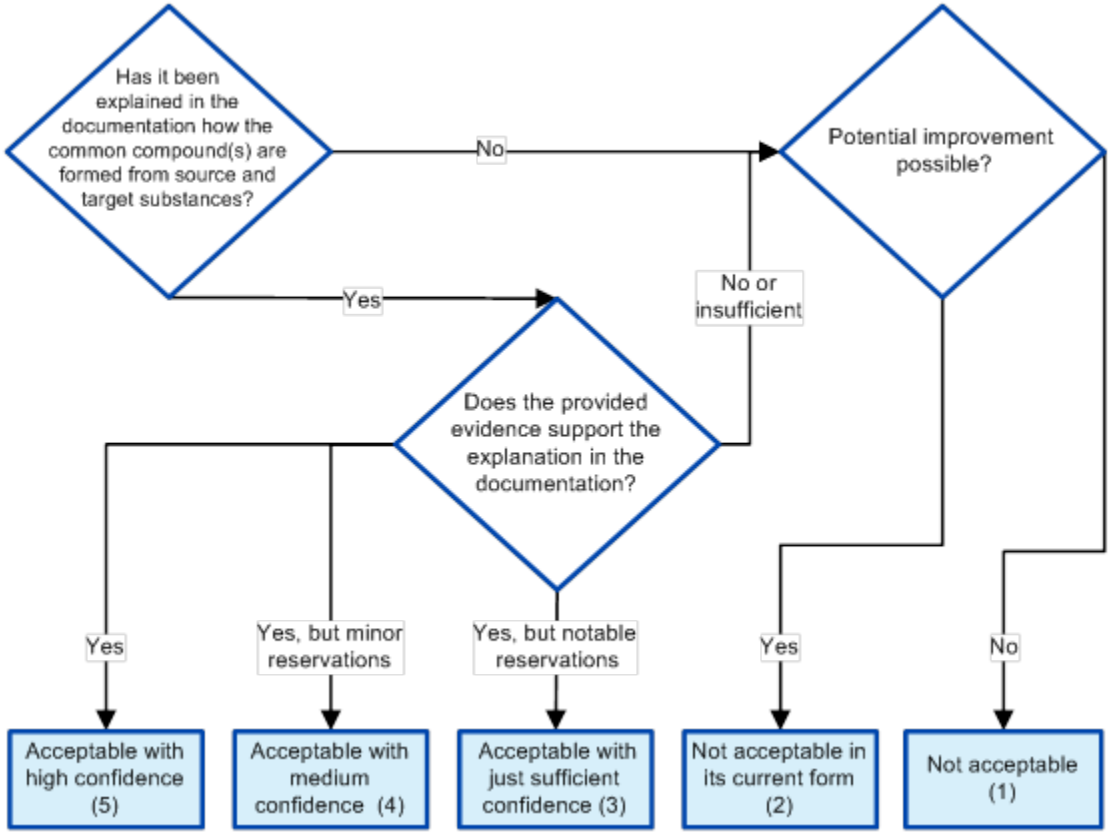


Overview of RAAF Assessment Options

Table 2 -Overview of the Assessment Options (AOs)

Scores	AOs	Meaning of the AOs
5	Acceptable with high confidence	Acceptance without reservations in the scientific explanation and documentation addressing the scientific aspects of the AE.
4	Acceptable with medium confidence	Acceptance with minor reservations about the scientific explanation and documentation addressing the scientific aspects of the AE.
3	Acceptable with just sufficient confidence	Acceptance with notable reservations. Minimum level of confidence in the scientific explanation provided in the documentation and addressing the scientific aspects of the AE.
2	Not acceptable in its current form	Acceptance for the AE under consideration may become possible if improved explanations and/or supporting evidence is made available by the registrant.
1	Not acceptable	A major flaw in the approach for the AE under consideration which is not expected to be resolved by the addition of supporting information.

Example of the decision logic within an AE



Overview of the analogue RAAF AEs

Table 3 - Overview of the analogue common AEs (scenarios 1 and 2)	
AE A.1	Identity and characterization 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

Table 4 - Overview of the scenario 1 specific AEs	
AE 1.1	Formation of common (identical) compound(s)
AE 1.2	The biological targets for the common compound(s)
AE 1.3	Exposure of the biological target(s) to the common compound(s)
AE 1.4	The impact of parent compounds
AE 1.5	Formation and impact of non-common compounds

Table 5 - Overview of the Scenario 2 specific AEs	
AE 2.1	Compounds the test organism is exposed to
AE 2.2	Common underlying mechanism, qualitative aspects
AE 2.3	Common underlying mechanism, quantitative aspects
AE 2.4	Exposure to other compounds than to those linked to the prediction
AE 2.5	Occurrence of other effects than covered by the hypothesis and justification

New-approach data to support read-across & categories: for better evidence

- Normally a mechanistic explanation is needed to justify why structural similarity is associated with similar biological properties. This may be supported by additional evidence/data
- Information from *in vitro* molecular screening & 'omics' assays & computational models can be used to improve the robustness of the read-across case:
  - Empirically as a common 'signature' for target & source substances
  - More robustly by making intelligent use of the known toxicological profile of the source substance to choose assays pertinent for the relevant biological pathways

Seurat-1 'Safety Evaluation Ultimately Replacing Animal Testing': rational combination of evidence

- First step in long-term goal towards replacement of *in vivo* repeated-dose systemic toxicity testing

- Joint funding by the European Commission & Cosmetics Europe: € 25 million + € 25 million

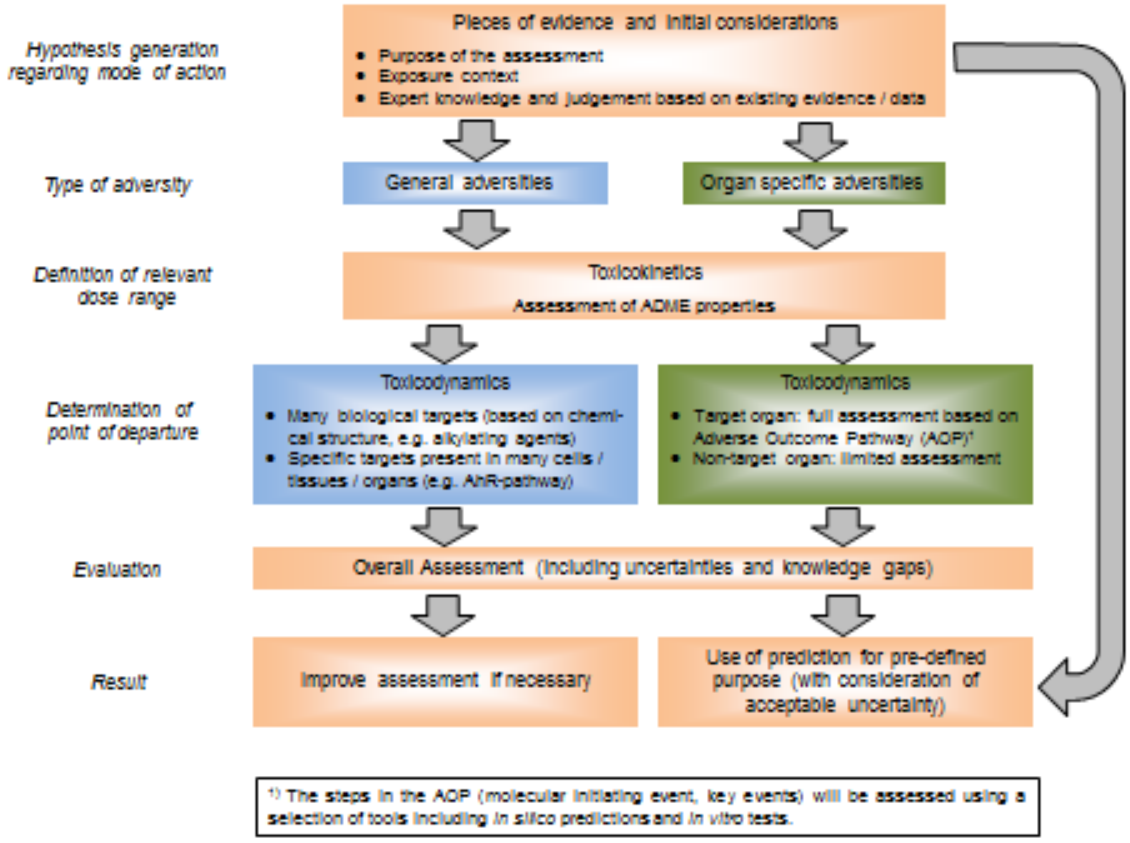
OBJECTIVES

- Development of an **innovative concept for repeated dose systemic toxicity testing**.

- **Proof of concept** for a future full implementation of a **mode-of-action** strategy.

- Development of **innovative testing methods** more predictive than existing testing procedures.

SEURAT-1 'Conceptual Framework': a 'generic IATA' to combine evidence



SEURAT-1 read-across Case Study

- Read-across case study to illustrate how ‘new approach’ data can be used to improve the quality of read-across arguments; i.e. to increase the ‘confidence’ in the case or to extend the scope of read-across or to expand categories
- This is an achievable target within SEURAT-1 & is important to demonstrate the usefulness of the project
- ‘Conceptual framework’ enables rational integration of evidence, notably existing animal studies & ‘read-across’ predictions

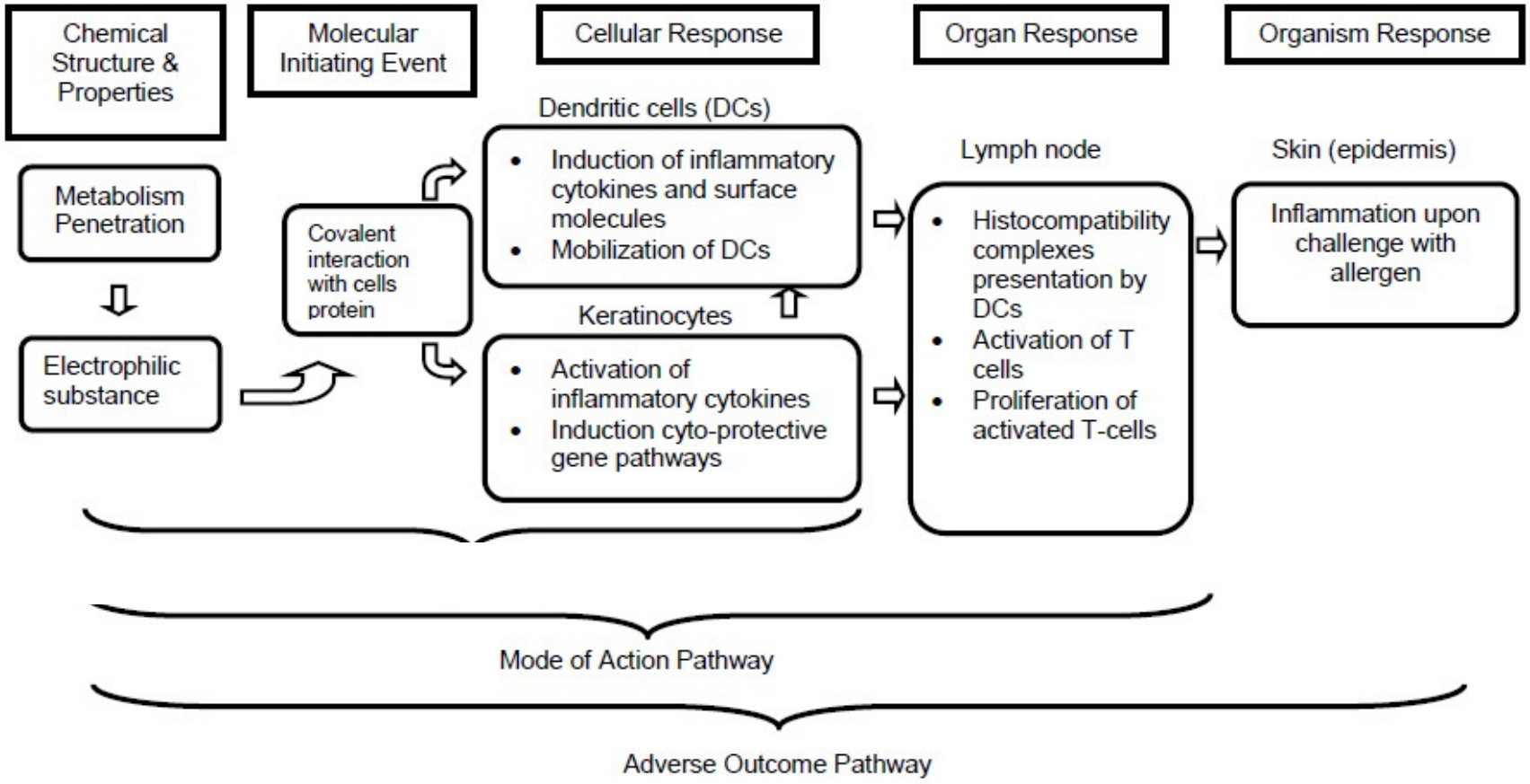
Workshop on New Approach Methodologies in Regulatory Science 19 to 20 April 2016

- ECHA's Topical Scientific Workshops foster discussions among academia, regulators, industry & other stakeholders on possible regulatory impacts
- Anticipated outcome is new or improved approaches to apply to REACH, CLP & Biocides Regulations
- The 2016 Workshop explores the regulatory application arising from fundamental change in scientific thinking.
- The drivers are a better understanding of the underlying biology behind how chemicals cause adverse effects to human health and new tools and techniques which provide a huge amount of data available from 'omics' and high-throughput screening methods.
- The Workshop draws inspiration from the EU research programme SEURAT-1 and the US Tox 21 initiative

Development of a Skin Sensitisation IATA: rational combination of evidence

- IHCP JRC leading OECD to develop an Integrated Assessment & Testing Approach (IATA) for skin sensitisation; ECHA contributes & steers the work towards a prediction scheme that can be used for REACH & CLP
- OECD skin sensitisation Adverse Outcome Pathway (AOP) incorporated into the IATA
- Assays used to assess molecular initiating event (MIE) & key events (KEs)
- Individual assays have limitations on chemical structures & physical properties; hence aim to use them within an integrated approach.
- Update ECHA Guidance for the 2018 REACH registrations

Basis of skin sensitisation AOP



WoE for low acute oral toxicity

- Update ECHA Guidance for the 2018 REACH registrations
- Key piece of evidence is from oral repeated-dose toxicity study (for registration > 10 t.p.a.): if NOAEL > 1000 mg/kg/day, acute oral toxicity is very likely > 2000 mg/kg
- NRU *in vitro* study for cytotoxicity (or equivalent)
- Other evidence: physico-chemical properties, TK forecast, QSARs etc

Themes for R&D

- Communicate regulatory needs to scientists
- Precise problem formulation to guide R&D to get concerted action
- Build on & incorporate current methods with targeted development
- Combined in WoE as a rational integration of tests/data/predictions into ITSs & IATAs & ‘test batteries’
- Underlying biological mechanisms support combined approaches, i.e. AOP/MoAs

Concluding remarks on the importance of WoE & rational combination of evidence

- No short cut to prediction of complex toxicological properties by statistical correlations with the ‘classical’ test to be replaced alone; should be based on biological mechanism, i.e. Adverse Outcome Pathway (AOP) & Mode of Action (MoA)
- Replacement test may need an explanation on how to be used for a particular regulatory purpose & how to use other evidence & take other considerations into account
- Regulatory acceptance requires discussion & agreement on scientific, philosophical, ethical & political issues; ‘emotional’ considerations & historical traditions

Disclaimer

The views expressed in this presentation are solely those of the author and the content does not represent an official position of the European Chemicals Agency.

Thank you for attending

What did you think about the webinar? Please take part in our email survey (in your inbox now)

A downloadable recording of this presentation (with slides) will be available in the next day or so.

If you have any questions, please contact Lorna (lorna@chemicalwatch.com)

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