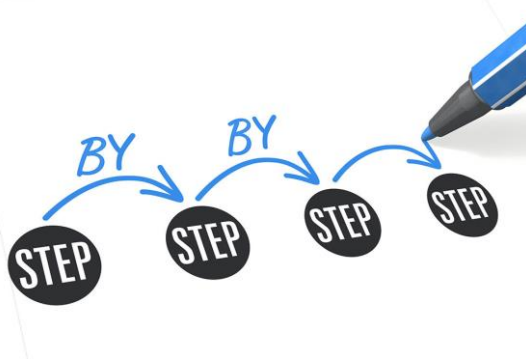
How to submit a CLH dossier part II

Online information session

9 December 2021

Welcome

Welcome



- Welcome to the second session: step 3
- 3 steps to support publication of practical guide:
  1. Organise information session to launch practical guide and survey 26 May 2021 ✓
  2. Survey to collect information completed in September ✓
  3. Organise follow up session to inform on survey and ……. TODAY

Programme

Moderator: Paul Ryan, Head of Unit, Hazard I, ECHA

Timing	Title	Speaker
14:00	Welcome and introduction	Stella Jones, ECHA Paul Ryan, ECHA Mike Rasenberg, ECHA
14:10	MS experience on dossier submission	Louise Conway, Health & Safety Authority, Ireland
14:30	Survey results	Chiara Perazzolo, ECHA
15:00	Break	
15:10	Alignment of EFSA pesticides peer review and ECHA CLH process – combined DAR/RAR-CLH dossier submission to EFSA/ECHA	Tunde Molnar, EFSA Dimitra Kardassi, EFSA Silvia Mazzega, EFSA
15:30	Biocide process and interlinks with CLH	Gesine Muller, ECHA
15:50	How to support grouping and read-across in CLP	Niklas Andersson, ECHA Jochen vom Brocke, ECHA
16:20—16:30	Conclusions and closing	Paul Ryan, ECHA

*Helsinki time

Introduction

How to submit a harmonised classification and labelling dossier - part II

9 December 2021

Paul Ryan
Head of Unit, Hazard I
European Chemicals Agency

Mike Rasenberg
Director, Hazard Assessment
European Chemicals Agency

Dossier submitter support

- Aim
  - Publish new practical guide to support dossier submitters
  - Help Member States prepare fit-for-purpose dossiers
- Dossier submission: first step of CLH process
  - Foundation of a good opinion from Risk Assessment Committee
  - Involvement and collaboration with dossier submitter builds better dossiers
- Today
  - What the survey has shown
  - First hand experience from a Member State
  - Pick up more on the PPP and Biocides dossiers
  - Look at challenging topic: read across

Member State experience on dossier submission

Louise Conway
Health and Safety Authority
Ireland

HEALTH AND SAFETY AUTHORITY

Health & Safety Authority

IE CA experience of submitting a CLH proposal

ECHA Webinar - How to submit a harmonised classification and labelling dossier

9 December 2021

Content

HEALTH AND SAFETY AUTHORITY

- Who we are
- Our experience so far with the CLH process
- CLH report template
- Accordance check process
- Interactions with ECHA
- Conclusions

Who we are

HEALTH AND SAFETY AUTHORITY

- Health and Safety Authority is the lead Irish Competent Authority for REACH and CLP

- Involved in the preparation of CLH proposals for REACH registered substances
  - Our focus is mainly on human health hazard classes although have an environmental proposal in the pipeline
  - We aim to prepare 1 new CLH proposal per year

PPP and biocides

HEALTH AND SAFETY AUTHORITY

- PPP and biocides fall under the remit of Department of Agriculture, Food and the Marine in Ireland
  - Responsible for preparation of CLH proposals for PPP & biocides
- Not covered as part of this presentation

HEALTH AND SAFETY AUTHORITY

Our experience so far

- Overall our experience is good
- The CLH guidance provides useful advice
- CLH template provides good structure for reporting the data
- ECHA colleagues are very willing to provide case specific technical advice – much appreciated!

- But….there is room for improvement!

CLH template – regulatory history

- CLH report template includes sections:
  - 3 - History of the previous classification and labelling
  - 4 - Justification that action is needed at community level
- Currently no section for regulatory history/activities (other than C&L)
  - Particularly relevant for REACH substances
  - For example, CLH proposal may be an identified follow up action from another REACH process, e.g. substance evaluation
- Suggest to update the template to indicate where such information should be included
  - This would ensure such information is reported in a consistent manner

CLH template – role of Annex I

- It is possible to prepare an Annex ("Annex I") to the CLH report
- In the Q&A following the CLH webinar in May 2021, it is stated *"the annex 1 was developed to facilitate using extracts from DARs, CARs and similar. If sufficient information is available in the report itself the annex is not needed."*
  - No mention of the role for REACH substances
- Preparation of Annex I is time consuming
- Not clear whether it is taken into account during the process, e.g. accordance check, RAC opinion forming
- Further guidance would be useful on when the preparation of Annex I adds value to the process e.g. useful for proposals with non-guideline studies

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Accordance check

- Before submitting for accordance check we:
  - Check the CLH report for consistency and accuracy
  - Compare our CLH proposal to other recent CLH proposals for REACH substances with similar hazard classes to ensure consistency
- Our proposals have not passed the accordance check for issues that were also present in other successful proposals
  - Our experience is that the outcome can be difficult to predict
- Difficult to “learn” from the process to improve our future proposals

Accordance check

- "Required " versus "recommended" revisions in accordance check outcome
  - Accept "required" revisions are necessary
  - Role of "recommended" revisions may need to be reviewed further
    - Some useful
    - Some appear to be the preferred wording/editorial style of the ECHA dossier manager rather than correcting an inaccuracy/omission
- Implementing these revisions takes time and resources by ECHA and the dossier submitter
  - Need to ensure they add value

Accordance check - suggestions

- Look for ways to improve the predictability of the accordance check process
- Ensure consistency between CLH proposals with similar hazard classes
- Look to harmonise the issues picked up in the “recommended” revisions
- Clarifying the role of Annex I to the CLH report may help
  - If something is reported in Annex I is this sufficient?

HEALTH AND SAFETY AUTHORITY

Interaction with ECHA

- Good interaction between ECHA and the dossier submitter:
  - Prior to submission of the CLH proposal
  - At the accordance check stage
  - During preparation of the response to comments following the consultation
- Limited interaction between ECHA and the dossier submitter after the response to comments are submitted
  - Dossier submitter no longer has an active role but still has an interest in following the case and seeing the outcome
  - Useful to provide update on where proposal is in the process e.g. which RAC meeting is it scheduled for

Conclusions

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- Overall our experience is good!
- ECHA colleagues are willing to provide support
- Some areas where further improvement may be needed to improve consistency and predictability
  - Reduce time and resources needed on both sides
- We need to work together to ensure process is as robust as possible

Thank you

HEALTH AND SAFETY AUTHORITY

Our Vision:

Healthy, safe and productive lives and enterprises

Survey results

How to submit a harmonised classification and labelling dossier - part II

9 December 2021

Chiara Perazzolo
Scientific Officer, Hazard I
European Chemicals Agency

Overview

43 questions:

- General
- Practical guide
- Physical hazards
- Human Health
- Environment

Aggregated results published with updated practical guide

General

Practical guide

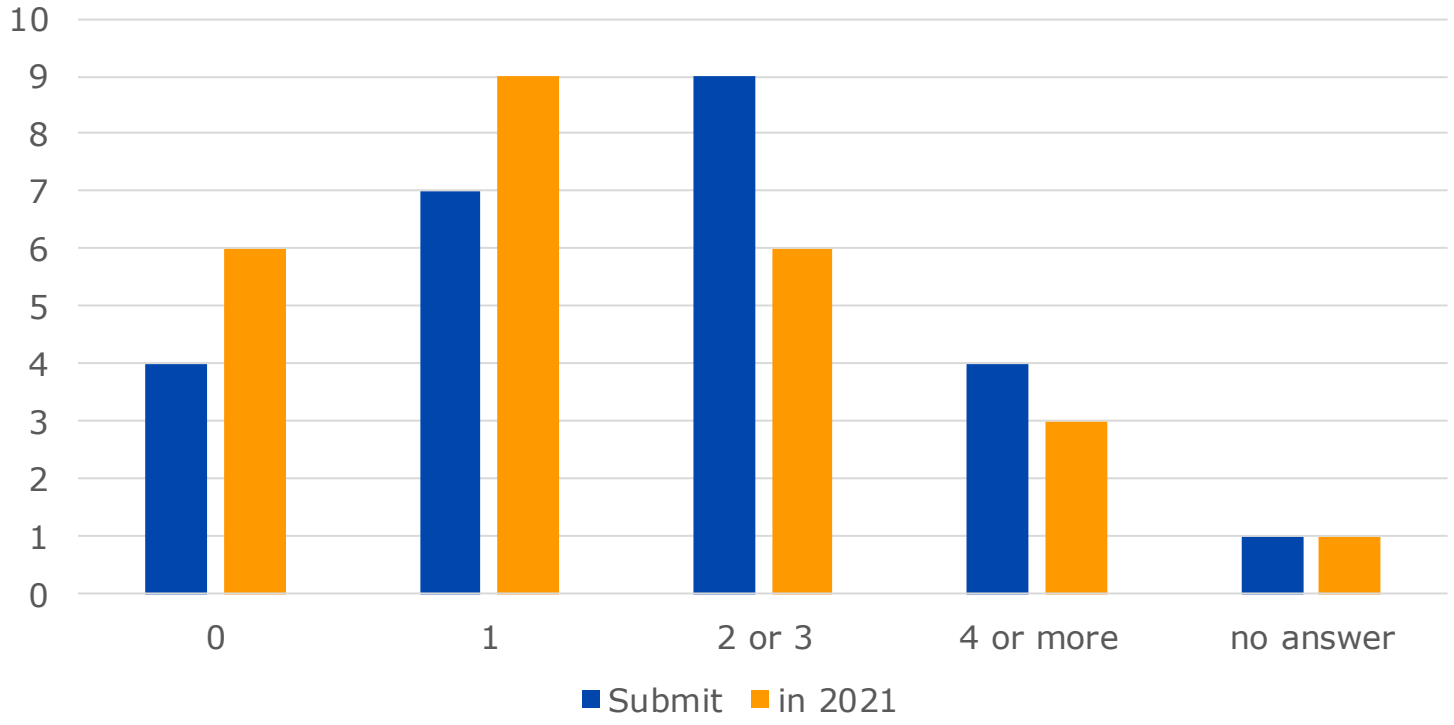
Physical hazards

Human Health

Environment

How many CLH dossiers do you/your organisation **submit** per year?

How many dossiers do you/your organisation plan to **submit in 2021**?



Are you aware of the importance of submitting a notification to the Registry of Intentions prior to submitting the CLH dossier?

21	Yes
0	No
4	No, but will in the future

General

Practical guide

Physical hazards

Human Health

Environment

Overall, did you find the practical guide:

20	Understandable and easy to apply
5	Somewhat understandable and applicable → specify
0	Difficult to understand and to apply → specify

- Information for PPP and CLH is not completed yet. Templates specific for PPP could not be identified
- In general, practical guide is understandable and applicable. However, …some topics well covered, others only briefly discussed and reader is referred to other guidance. Some points may have been better addressed in updated annotated CLP report template

Do you think the guide is missing important topics?

13	Yes, Please can you explain further and suggest topics to include?
12	No

- Plant protection products: Link with IUCLID
- Plant protection products: Sanitisation rules
- Biocidal products: To what extent a need to consider in-situ ingredients or reaction products when classifying substances?
- Grouping and read across

- Reliability evaluation of studies (registrants vs authority)
- Substance identity: ID in Annex VI, ID in registration dossiers vs. ID in AS dossiers
- Intellectual property regulations - potential conflicts with disclosure of information
- Section 2.7 (data availability)
  - more information on what extent data should be presented (not key data) in the report, in particular for data rich substances
  - should clearly state to what extent data apart from key data should be presented
  - information on what extent data should be presented (especially for non-key data) in the report in particular for data rich substances

Confidentiality

A CLH proposal is always published. Are the confidentiality rules sufficiently clear (REACH Article 119)?

12	Yes, the principles are clear, and drafting the CLH dossier in this respect is easy for me
9	No, I often have a problem to decide what information should be kept confidential
2	I did not know that REACH Article 119 applies to public access to data on a CLH dossier under GLP Regulation
2	Other, please specify

REACH Art. 119 is clear, however distinction to copyright is difficult

Confidentiality

Is it clear when authors' names of studies referred to in the CLH report need to be redacted?

20	Yes
5	No. Please, can you explain further and include examples if useful?

Authors name of unpublished studies are confidential

Read across, group entry

Have you used read across information from another substance than the substance for which the harmonised classification is proposed in your CLH dossier to justify if a harmonised classification is warranted?

11	Yes
8	No
6	Not yet, I'm preparing/planning one

If you have used read across assessment, did you develop the justification in CLH dossier using the ECHA RAAF guidance?

9 Yes
8 No

Read across, group entry

Are you aware of group entries already existing in Annex VI?

12	Yes
3	No
9	Yes, however it is difficult to understand which substances are part of these group entries

Read across, group entry

Challenges in applying read across and group entries?

- Experience missing
- Substance identity problems
- Read-across and group entries:
  - Which substances to include in the group
  - No TK information
  - Need for example (in the CLH report template)
  - Need for more training

Read across, group entry

Challenges in applying read across and group entries?

- Use of bioelution data: guidance on use of such data
- Substances which are only partly transformed / metabolised into the source substance: use % transformed
- Differences in physical/chemical properties potentially affecting the absorption especially if no data on TK are available
- It is not totally clear how detailed the studies for the source substances have to be presented when it is already harmonized classified (referring to the RAC opinion), keeping in mind that the CLH-Dossier should be a stand-alone document.
- A template as Annex to the CLH-Dossier would be helpful to develop a sound read-across.

General

Practical Guide

Physical hazards

Human Health

Environment

Physical Hazards (5 answers)

Is the section on the physical hazards in the PG clear?

5	Yes
0	Somewhat
0	No

Do you routinely use the screening procedures, if available, in the assessment of the physical hazard classes?

3	Yes, always
0	Yes, sometimes
2	No

General

Practical Guide

Physical hazards

Human Health

Environment

Human Health (12 answers)

Do you have any comments on the Human Health Hazards in the PG?

8	No, everything is clear
4	Yes → explain further, see below

- Use and presentation of toxicokinetic data
  - … especially for mutagenicity
- How to present data for data-poor and data-rich substances?

Human Health (12)

If substance has existing Acute Tox. min. classification […], do you routinely re-assess it, add ATE, even when *not your primary objective*?

6	Yes
2	Sometimes
4	No

When data available, do you assess eye damage/eye irritation even if classification for skin corrosion is present/proposed?

10	Yes, always
2	Sometimes
0	No

Human Health (12)

Are you aware of interlinkage between hazard classes, e.g. STOT SE is largely based on data from acute tox studies?

11	Yes
1	No

Do you consider assessing interlinked hazard classes to improve efficiency?

7	Yes, always
4	Sometimes, depending on priorities in my organisation
1	Sometimes, depending on the workload
0	No

Human Health (12)

There is a link between germ cell mutagenicity and carcinogenicity. Do you routinely assess/include data on germ cell mutagenicity when assessing carcinogenicity?

8	Yes, the proposal includes always assessment and proposal of both hazard classes
2	Yes, the dossier includes the data for mutagenicity., as supporting information, even if classification proposal is only for carcinogenicity
1	Sometimes
1	No

Human Health (12)
Historical Control Data

Have you included HCD in the evaluation of carcinogenicity?

9	Yes, always if available
2	Sometimes
1	No

If you used HCD, did you include reliability and relevance assessment as per CLP guidance?

6	Yes, always
4	Sometimes
2	No

Human Health (12)
Historical Control Data

If you used HCD, do you routinely include all information available to you, e.g. strain, breeder, years, individual study incidences, mean, quartiles, standard deviation…in the CLH report?

7	Yes, always if available
5	Sometimes
0	No

Human Health (12)
Additional information

Are there particular areas on human health assessment which you would appreciate having more in-depth guidance to help develop the CLH proposal?

- STOT SE and STOT RE
- Dermal/respiratory sensitization
- Reproductive toxicity
- Mode of action

General

Practical Guide

Physical hazards

Human Health

Environment

Environmental hazards (10 answers)

Do you have any comments on the section Environment hazards in the Practical Guide?

1	Yes → which ones?
7	No
2	No answer

Please clarify in section 5.2 (bioaccumulation) whether conclusion can also be "inconclusive", e.g. based on results for different species

Environmental hazards (10)

What are the most commonly faced issues/problems you encounter when preparing your proposal for environmental hazards?

- Lack of full study reports or sufficient study summaries / data needed / lack of reliable info
- Degradability
- Level of detail required in CLH report

Environmental hazards (10)

Has the practical guide addressed these considerations?

5	Yes
1	No → specify
2	Partly → specify
2	No answer

No, or partly → specify:

… unclear type and/or level of reporting of available information in CLH report, especially for non-key/support data

Thank you!

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Alignment of EFSA pesticides peer review and ECHA CLH process

Combined DAR/RAR-CLH dossier submission to EFSA/ECHA

Tunde Molnar
Dimitra Kardassi
Silvia Mazzega

Information Session on ‚*How to submit CLH dossiers*‘
9 December 2021

Alignment of EFSA pesticides peer review and ECHA CLH process – combined DAR/RAR-CLH dossier submission to EFSA/ECHA

EFSA Pesticides Peer Review Unit

Applications Desk Unit

Tunde Molnar, Dimitra Kardassi, Silvia Mazzega

Trusted science for safe food

efsa
European Food Safety Authority

OUTLINE

- **Legal basis**
- **New Implementing act on renewals (impact on C&L)**
- **Combined AR/CLH template**
- **EFSA-ECHA collaboration**
- **Guidance/templates + IUCLID**

LEGAL BASIS

Article 36(2) of Regulation (EC) No 1272/2008:

=> active substances within the meaning of Regulation (EC) No 1107/2009 shall normally be subject to harmonised classification and labelling

New implementing act on renewals: (Regulation 2020/1740 of 20 November 2020)

- published on 23/11/2020, **repealing** previous Reg 844/2012 on renewals including **Regulation 2020/103** as regards the harmonised classification of a.s. **as of 27 March 2021**
- **Aim:** introducing the changes and **new requirements** arisen from the Transparency Regulation amending the General Food Law, pertinent for the renewal procedure (notification of intended studies+design, PC, pre-submission advice, disclosure and PC on valid application)
- the **content of Regulation 2020/103** on the **detailed rules of procedure** regarding the **submission of CLH proposals** in accordance with Article 37(1) of Reg No 1272/2008 during the **renewal** of approval of active substances has been **integrated** and **directly transferred** into the relevant parts of the new act.
- applicable for renewals for which the **approval** will **expire** on or after **27 March 2024**. Transitional measures apply (cf regulation).

NEW IMPLEMENTING ACT ON RENEWALS IMPACT ON C&L

- **New procedural elements impacting C&L**:
  - **submission of the application for renewal, consisting of the renewal dossier,** at the latest **3 years before the expiry of the approval period**.
  - electronic submission or the renewal dossier via a central submission system, using the **IUCLID** software package as **new dossier submission format**.
- **Elements taken over from Reg 2020/103**:

Obligation for Applicants:

- Content of dossier => Art 6(2j): A **proposal for classification** to be included where it is considered that the substance has to be classified or reclassified in accordance with **Regulation (EC) No 1272/2008**

NEW IMPLEMENTING ACT ON RENEWALS IMPACT ON C&L

- **Elements taken over from Reg 2020/103**:

Obligation for RMS:

- Art 11(9): the **RMS should submit the CLH report to ECHA at the latest at the same time when submitting the RAR to EFSA!**
- RMS has **13 months** after dossier submission to prepare the **RAR:**
  - Art 11(2e): mandatory inclusion of information on **classification** or its **confirmation** / **reclassification** in dRAR for at least the hazard classes specified in Art 11(9)
  - **Pending RAC proposal and ECHA assessment is ongoing**: limit the proposal to those hazard classes not covered by pending RAC proposal, unless new information available that was not part of the pending dossier
  - **Existing classification / RAC opinion**: for hazard classes already covered - due justification that the existing classification in Annex VI or the RAC opinion remains valid. The Agency (i.e. ECHA) may provide its views regarding the rapporteur Member State's submission.

NEW IMPLEMENTING ACT ON RENEWALS IMPACT ON C&L

Obligation for RMS:

Art 11(9): **hazard classes**

- **relevant to identify** whether an a.s. can be considered as a **low-risk** active substance according to Article 22 of Regulation 1107/2009 in conjunction with point 5.1.1 of Annex II to that Regulation, which also include the hazard classes relevant for the **cut-off criteria** set in points 3.6.2 to 3.6.4 and 3.7 of Annex II to Regulation (EC) No 1107/2009
  - — explosives,
  - — acute toxicity,
  - — skin corrosion/irritation,
  - — serious eye damage/eye irritation,
  - — respiratory or skin sensitisation,
  - — germ cell mutagenicity,
  - — carcinogenicity,
  - — reproductive toxicity,
  - — specific target organ toxicity – single exposure,
  - — specific target organ toxicity – repeated exposure;
  - — hazardous to the aquatic environment.

- The RMS should **duly justify why no harmonised classification and labelling is warranted** for hazard classes for which it considers that the criteria for harmonised classification and labelling set by Regulation (EC) No 1272/2008 are not fulfilled.

NEW IMPLEMENTING ACT ON RENEWALS IMPACT ON C&L

Elements taken over from Reg 2020/103:

Obligations for EFSA, ECHA, Commission:

- Art 13(1): **EFSA** to **take account of the RAC opinion** in the Conclusion which is established within 5 months + clock stop from end of the public consultation or **2 weeks after adoption of RAC opinion,** if any (whichever occurs later)
- Art 11(10): **ECHA**: '*The Committee for Risk Assessment 'shall endeavour' **to adopt the opinion**…within **13 months…'*** from submission of CLH report (indicative timeline defined to ensure that the RAC opinion is available to EFSA prior to the adoption of its conclusion)
- Art 14(1): **Commission** to **take account of the RAC opinion** for the Renewal report and the draft Regulation

=> RAC opinion should be available:

⇒to EFSA prior to EFSA's conclusion of the evaluation of the a.s.
⇒to the Commission/MSs prior to vote in the SCoPAFF for decision making

COMBINED AR/CLH TEMPLATE

Joint DAR/AR/CLH report template:

- For PPP active substances, as part of the **alignment** of EFSA pesticides peer review and ECHA CLH processes, **MSs are strongly advised to use the combined template** for preparation of **joint DAR/RAR and CLH reports**
- to be submitted in **parallel to both ECHA and EFSA**.
- the common template incorporating the CLH proposal and Volume 1 of the Assessment Report is available under EC website -> guidelines webpage (SANCO/12592/2012):

  - ✓ **same level of information** is made available to both EFSA and ECHA, ensuring **consolidated views, transparency and consistency** in the data set for the two processes
  - ✓ **avoid duplication of work** resulting from the need to present the same information based on the same hazard assessment in two different formats
  - ✓ joint format is aimed to **fit for both PPP and CLH processes,** i.e. the information needed for both processes to be in one document

=> facilitates the alignment of the active substance approval process undertaken by EFSA in the framework of Regulation (EC) No 1107/2009 with the CLH procedure undertaken by ECHA under Regulation (EC) No 1272/2008

COMBINED AR/CLH TEMPLATE

Please note:

- Joint format is a **compromise** in terms of structuring the information relevant for both the EFSA and ECHA processes
  - ⇒some **redundancy** may be accepted to facilitate reviewers of both processes to easily locate the information needed.
  - ⇒keep in mind the necessity of compromising between the format preferred by risk assessors in PPP and the format preferred by the members of RAC!
- **flexibility** is needed to permit the **inclusion of all information necessary for both processes** although may be relevant only for one of the processes
  - ⇒using the same report for both regulatory processes will increase transparency of the data assessment for classification purposes and facilitate preparation of assessments that allow for an independent review.
  - ⇒Even if there is no proposal for classification/no need to revise the current harmonised classification for a section, it is proposed that a comparison with CLP criteria should always be presented to allow a transparent conclusion to be drawn.

General principles of common template:

All information specific for classification is included in level 2 of **Vol 1**.

- **overall summaries** and **overview of the conclusions** reached in relation to the risk posed by the a.s. / representative product and uses and the proposal for CLH
  - In level 2 the standard summaries with the effects data should be presented, as required for the exposure and risk assessment in the approval/renewal process, with the C&L sections to be added additionally.
  - For the CLH process, Vol 1 is equivalent to the CLH dossier and as such it should be as much as possible a stand-alone document => all information for the assessment of the studies should be included in Vol 1 => Vol 3 includes additional data to allow in dept assessment or clarification
  - **Tabular overviews** for each section

- robust summary of studies on the hazard class in question (including overall relevance, uncertainty or controversy of the provided data, significance of any deviations from the guideline);=> all effects should be discussed
- comparison of results with the CLP classification criteria
- conclusion on C&L for the hazard class in question according to the CLP criteria

COMBINED AR/CLH TEMPLATE

European Food Safety Authority

➢ Additional recommendations

- Information should cover effects observed **at all dose levels** to address both **setting of NOAEL/LOAEL** and **need for classification**
- study summaries should contain enough information to assess their **acceptability** and the **reliability** of results
- It is recommended to indicate **magnitude and direction of change, statistical significance**
- cross references can be applied to Volume 3,
- More detailed (extended) results and study summaries are presented in **Vol 3**

=> all the endpoints should be described with a sufficient level of details to allow a proper and **transparent assessment** both by peer review and by RAC

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference

Results **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**
NOAEL: 1000 ppm (104.6 in males and 103.4 mg/kg bw in females) **2000 ppm (males 200.1 mg/kg bw/day, females 212.2 mg/kg bw/day)**: *Body weight*: ↓ 28% males, 14% females at end of study *Food consumption*: ↓ 23% males over course of study *Haematology:* ↑ red cell count: 6.9% males, 5.7% females; ↓ MCV: 6.2% males, 7.8% females; ↓ MCH: 5.9% males, 7.2% females *Clinical chemistry:* ↑ urea: 29.5% males, 25.6% females; ↓ globulin: 6.7% males, 9.7% females; ↑ A/G ratio: 10.1% males, 11.3% females; ↑ ASAT: 55.5% males, 27.1% females; ↑ ALAT: 122.6% males, 131.4% females; ↓ cholesterol: 11.4% males, 24.8% females

Practicalities after submission of joint template:

- **Accordance/completeness check** by both EFSA and ECHA in a timely aligned manner, serving the same general purpose
- Once the documents are in accordance, a **joint consultation** will be conducted in parallel on both websites, for a common duration of 60 days.
  - NB: only when the complete accordance check / completeness check (including re-evaluation of the updated documents following resubmission) has been finalised.

=> MS compliance in timely resubmission of the reports is crucial!

- **Sanitization** of the **common AR/CLH report** are submitted by the applicant(s) and verified **by EFSA** on the amended final document **following completion of the accordance check / completeness check on the resubmitted report**, before the public consultation starts
  - Article 63 of Regulation (EC) No 1107/2009 and Regulation (EU) 2018/1725

=> no need for further check by ECHA or MSCAs

- Close collaboration between EFSA-ECHA also during onwards steps

Guidance/templates for applicants submitting PPP dossiers and presentation of the CLH data in the dossier / ARs

- ECHA Guidance: "Guidance on the Application on CLP criteria" (July 2017) should be considered in drafting Volume 1 of DAR/RAR including all required information and comparison with classification criteria
- Practical Guide '***How to submit CLH dossiers***' published in **May 2021** on ECHA website: cf **chapter 6: PPP: common AR and CLH dossiers**
- Guidance for the PPP process + combined AR/CLH report (Word Version) template is available on the **EU Commission guideline website**: https://ec.europa.eu/food/plants/pesticides/approval-active-substances/guidelines-active-substances-and-plant-protection_en
- EFSA Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances and on the maximum residue level (MRL) application procedure (March 2021) - section 3.15: Assessment and presentation of studies, section 3.16: Guidance on presentation of results
- pre-submission support offered by ECHA to discuss the CLH report prior to submission - for PPP presubmission advice via EFSA/RMS (cf section 2.3 of EFSA's Administrative guidance)

IUCLID: for data preparation, electronic submission and management of pesticides dossiers, by means of the central submission system (ECHA Cloud Services)

=> **applications** submitted **after 27 March 2021** must be submitted using the IUCLID format via the EFSA submission portal

- **IUCLID 6.6** released in **October 2021:** details about enhancements/new features: https://www.efsa.europa.eu/sites/default/files/2021-10/iuclid-release-6.6.pdf
- **IUCLID PPP active substance User Manual:** https://doi.org/10.5281/zenodo.5091464
- **IUCLID crosswalks:** EU PPP Active substance application (product) to KCA&KCP Data set: https://doi.org/10.5281/zenodo.4946663
- IUCLID training for regulators + range of supporting materials such as animated tutorials, recorded webinars and training sessions can be found on the EFSA website.
- Detailed instructions and **pertinent templates** for **presentation of results** in tabular format are available in the IUCLID user manual
  - IUCLID templates for PPP Risk Assessment - Template 5.1 - Template for presentation of results in tabular format for mammalian toxicology studies

IUCLID - developments:

- **IUCLID PSN subgroup**: ToR and membership published on EFSA website
  - further development of features and tools which could automate pesticide dossier processing
  - Meeting minutes + ppts available on EFSA website
  - pesticides.mrl@efsa.europa.eu (+ dedicated Teams space of IUCLID PSN subgroup to which nominated PSN IUCLID members have access)
- in the medium/long term, with further IUCLID developments, the **Report Generator** is aimed to be used to create the AR/CLH, i.e. the **combined EU AR-CLH report aimed to cover both processes to be generated directly from IUCLID dossier** once the report generator could fit with the lay-out of the template
  - work is ongoing in collaboration with ECHA, with the goal of adopting the report generator format for the CLH report, for use for both EFSA and ECHA regulatory purposes.
- In case of questions, e.g. on **report generator =>** Contact: *IUCLID.servicemanager@efsa.europa.eu*

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Biocide process and interlinks with CLH

How to submit a harmonised classification and labelling dossier - part II

9 December 2021

Gesine Muller
Scientific Officer, Biocidal Active Substances
European Chemicals Agency

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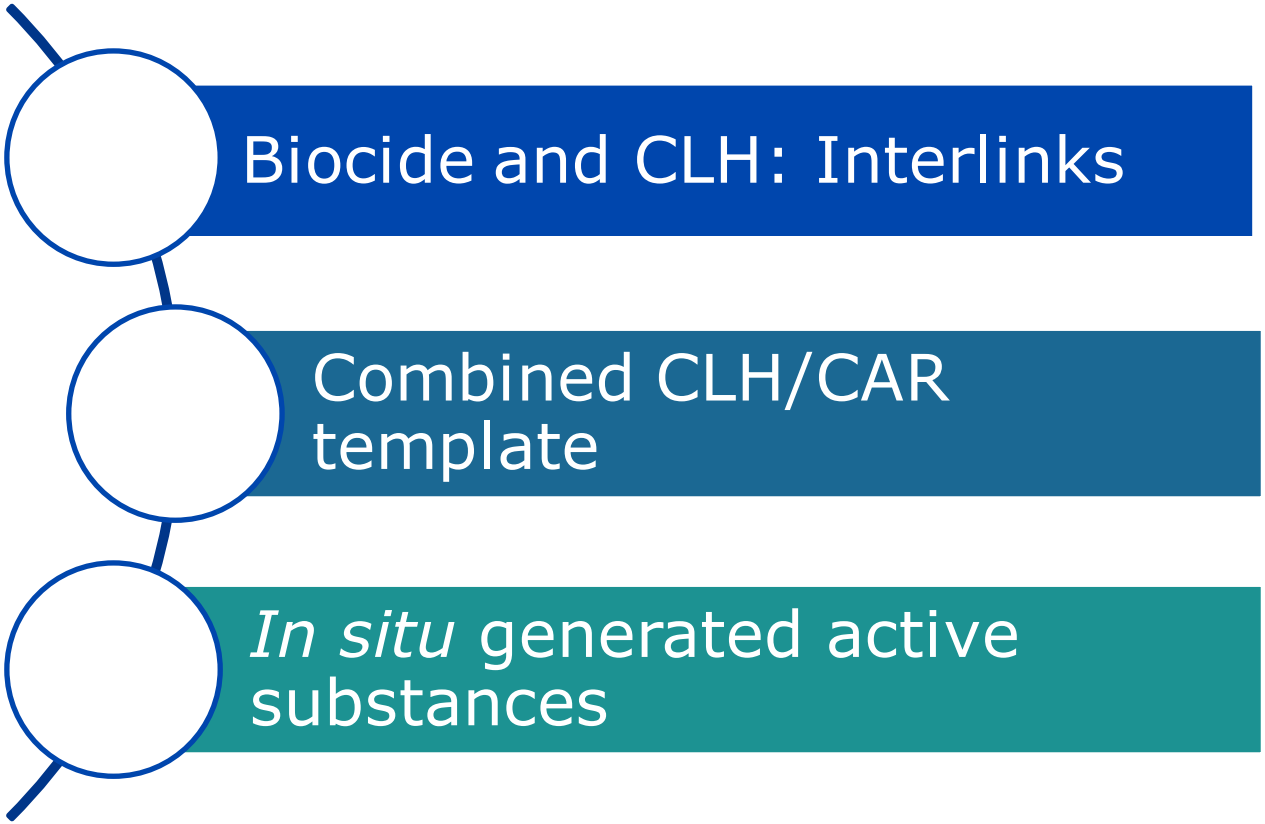
Biocide and CLH: Interlinks
Combined CLH/CAR template
In situ generated active substances

Biocide and CLH – Interlinks

Legal basis:

Article 36(2) CLP Regulation (EC) No 1272/2008:
'a substance that is an active substance in the meaning of Directive 98/8/EC shall normally be subject to harmonised classification and labelling.'

Review Programme Regulation (EU) No 1062/2014:
'For substances meeting the exclusion or substitution criteria, the evaluating ***Competent Authority should submit to the Agency a proposal for harmonised classification and labelling*** *[…] for the endpoints of concern, while preserving the right of the Member State to submit a proposal on other or all endpoints.'*

Biocide and CLH – Interlinks

The substance meets the exclusion and substitution criteria according to the BPR (EU) No 528/2012 if

endpoints of concern

- Carcinogen category 1A or 1B;
- Mutagen category 1A or 1B;
- Toxic for reproduction category 1A or 1B
- Respiratory sensitiser (only substitution)

=> Article 5 and 10 BPR (EU) No 528/2012

Biocide and CLH – Interlinks

Consequences of classification:

Article 5, Exclusion criteria, Biocidal Products Regulation (EU) No 528/2012:

The **active substance shall not be approved** as the exclusion criteria are met unless one of the derogations in Article 5(2) of BPR applies:

(a) the risk […] from exposure […] is negligible

(b) the active substance is essential to prevent or control a serious danger […]

(c) not approving the active substance would have a disproportionate negative impact on society

Biocide and CLH – Interlinks

Further consequences of classification:

Article 10, Substitution criteria, Biocidal Products Regulation (EU) No 528/2012:

The **active substance shall be considered a candidate for substitution if**:

(a) it meets at least one of the exclusion criteria (CMR 1A, 1B) but one of the derogations apply

(b) it meets the criteria to be classified as a respiratory sensitiser;

(c) …

=> Agency shall examine whether the active substance fulfils substitution criteria when preparing its BPC opinion on the approval

Biocide and CLH – Interlinks

Further consequences of classification:

- Criterion for eligibility for simplified authorisation procedure (Annex I BPR)
- Article 19 BPR, Conditions for granting an authorisation:

4. A biocidal product shall not be authorised for making available on the market for use by the general public where:

(b) it meets the criteria according to Regulation (EC) No 1272/2008 for classification as:

— acute oral toxicity category 1, 2 or 3,

— acute dermal toxicity category 1, 2 or 3,

— acute inhalation toxicity (gases and dust/mist) category 1, 2 or 3,

— acute inhalation toxicity (vapours) category 1 or 2,

— specific target organ toxicity by single or repeated exposure category 1,

— a category 1A or 1B carcinogen,

— a category 1A or 1B mutagen, or

— toxic for reproduction category 1A or 1B;

Harmonised classification has implications on product authorisation

Biocide and CLH – Interlinks

Implementation in the biocide substance approval process

Substances considered to meet the substitution criteria:

"If the substitution criteria are met because of CMR properties, it is highly preferable and therefore strongly recommended that the RAC opinion on harmonised C&L is available at the time of submitting the CAR.

In any case a CLH dossier needs to have been submitted by the time of submitting the CAR "

Timing is critical:

BPC opinion development phase is 270 days

RAC opinion development phase is 18 months

(Link to Working procedure: 3a35e75d-7c08-4c87-b501-8c24f0081dde (europa.eu))

Biocide and CLH – Interlinks

Substances not considered to meet exclusion/substitution criteria:

*"If **changes are proposed** to an already existing harmonised classification, or*
***no harmonised classification is available** for the active substance, a **CLH dossier needs to have been submitted by the time of submitting the CAR**."*

*"If the eCA proposes **Muta. 2** classification, **the RAC opinion on CLH needs to be available at the time of submitting the CAR**, because the risk characterisation may be very restrictive as exposure would need to be minimised without an identifiable threshold of safety."*

Combined template

A combined CAR-CLH report template is available

- To facilitate the alignment of the two processes, CLP and BPR
- To facilitate the work for the evaluating Competent Authority and the CLH dossier submitter
- To avoiding duplication of work, to save time and resources and
- To ensure transparency and consistency between the two processes

The common template incorporates the CLH proposal and Competent Authority Report (CAR) or Renewal Authority Report (RAR), meaning from one template, two separate reports can be created, a biocides draft assessment report/CAR and a CLH report

- It is strongly recommended to use the combined CAR-CLH template for CAR/RAR preparation

Available on ECHA website under CLP templates and BPR templates

Combined template

Specific instructions for the common template are available, which should be considered when preparing a common CAR and a CLH dossier

*The **CAR** consists of the following parts (all parts should be included):*

- *Summary*
- *Part A*
- *Part B*
- *Part C*
- *Part D (Appendices)*

*The **CLH report** consists of the following parts:*

- *Summary*
- *Part A*
- *Appendix V of Part D (which includes References)*
- *Appendix VII of Part D (which includes study summaries)*

Combined template

- The parts used for CLH should be made non-confidential
  - fit for consultation on ECHA website
- Legal requirement to include additional information in the CLH report
  - All available relevant data from REACH registration dossier(s),
  - The assessment report(s) of active substances used in plant protection products (DAR) and,
  - Relevant and reliable key data from public sources,
  - Since based on the CLP regulation, a weight of evidence approach should be used

Combined template

Collaboration between the MSCA authorities for biocides and CLP is encouraged

- One CLH report per substance
- To enable an independent assessment of the data, it may be necessary to add important/detailed information from robust study summaries or full study reports of key endpoints, such as CMR (e.g. historical control data of tumour incidences, individual animal data if differences are seen between animals in same study and dose group)
- For reporting certain data e.g. results from studies, further guidance can be found in ECHA Practical Guide 3 How to report robust study summaries

In situ generated a.s.

In situ generated active substances can be defined as substances, which are **generated at the place of use** from one or more precursors

Obligation to classify active substances applies also to *in situ* generated active substances !!!

Because:

=> the classification is a criterion for concluding whether or not

- an active substance meets the exclusion or substitution criteria
- whether it is eligible to be listed into Annex I to the BPR
- the biocidal products can be made available on the market for use by the general public

In situ generated a.s.

'Harmonised classification of in situ generated active substances'
(*CA-Nov15-Doc.5.5 – Final)*

Problem:

- Many in situ generated active substances are reactive and unstable, some of them can be more stable and therefore placed on the market in a stable form
- Precursors are considered as biocidal product

- When is a harmonised classification on the in situ generated active substance needed?
  - 'A harmonised classification needs to be proposed on the in situ generated active substance for all the endpoints for which it is possible to perform the related phys/chem, tox and ecotox tests.'

  - 'The related CLH dossier to establish or amend the harmonised classification must be submitted in due time as for any other active substance.'

In situ generated a.s.

Is a harmonised classification on the precursor(s) needed?

- 'The submission of a CLH dossier for the precursor(s) is not an element taken into account for the acceptability of the submission of the draft CAR to ECHA.'
- '… the eCA may also submit a CLH dossier for the precursor(s) to ECHA to establish or amend the harmonised C&L. This can later facilitate the product authorisation stage, and could be important for product authorisation:
  - Related classification could prevent the making available on the market for use by the general public,
  - It can help to manage the concerned substance(s) under REACH and other chemical legislations

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How to support grouping and read-across in CLP

How to submit a harmonised classification and labelling dossier - part II

9 December 2021

Jochen vom Brocke
Scientific Officer, Hazard II
European Chemicals Agency

Niklas Andersson
Senior Scientific Officer, Hazard IV
European Chemicals Agency

This talk in a nutshell*

Increasing confidence in using read-across:

- Read-across is one uncertainty among many
- Focus on driver of toxicity / mechanism
- Supporting data is key to success

Practical advice:

- Use the RAAF to make your case more robust
- Needs not be fulfilled strictly – see examples

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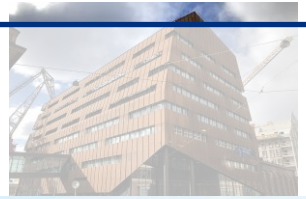
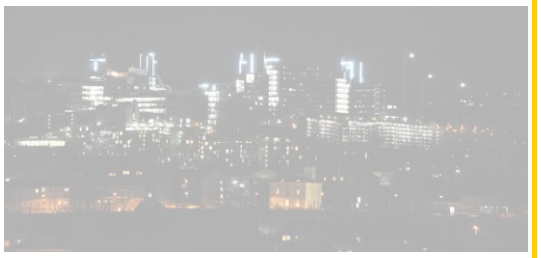


toxicology + **chemistry**

= most aspects of read-across

BfR
Bundesinstitut für Risikobewertung

BERGISCHE
UNIVERSITÄT
WUPPERTAL



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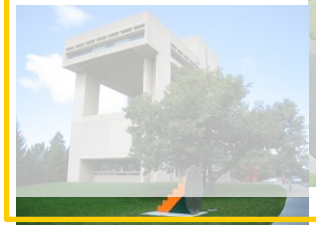


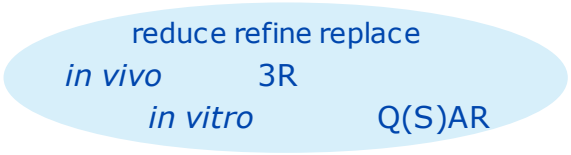
Overview

1. The problem (why not test everything?)
2. Uncertainties
3. The solution - how to build a case
4. Examples
5. Conclusion

Why safety testing?

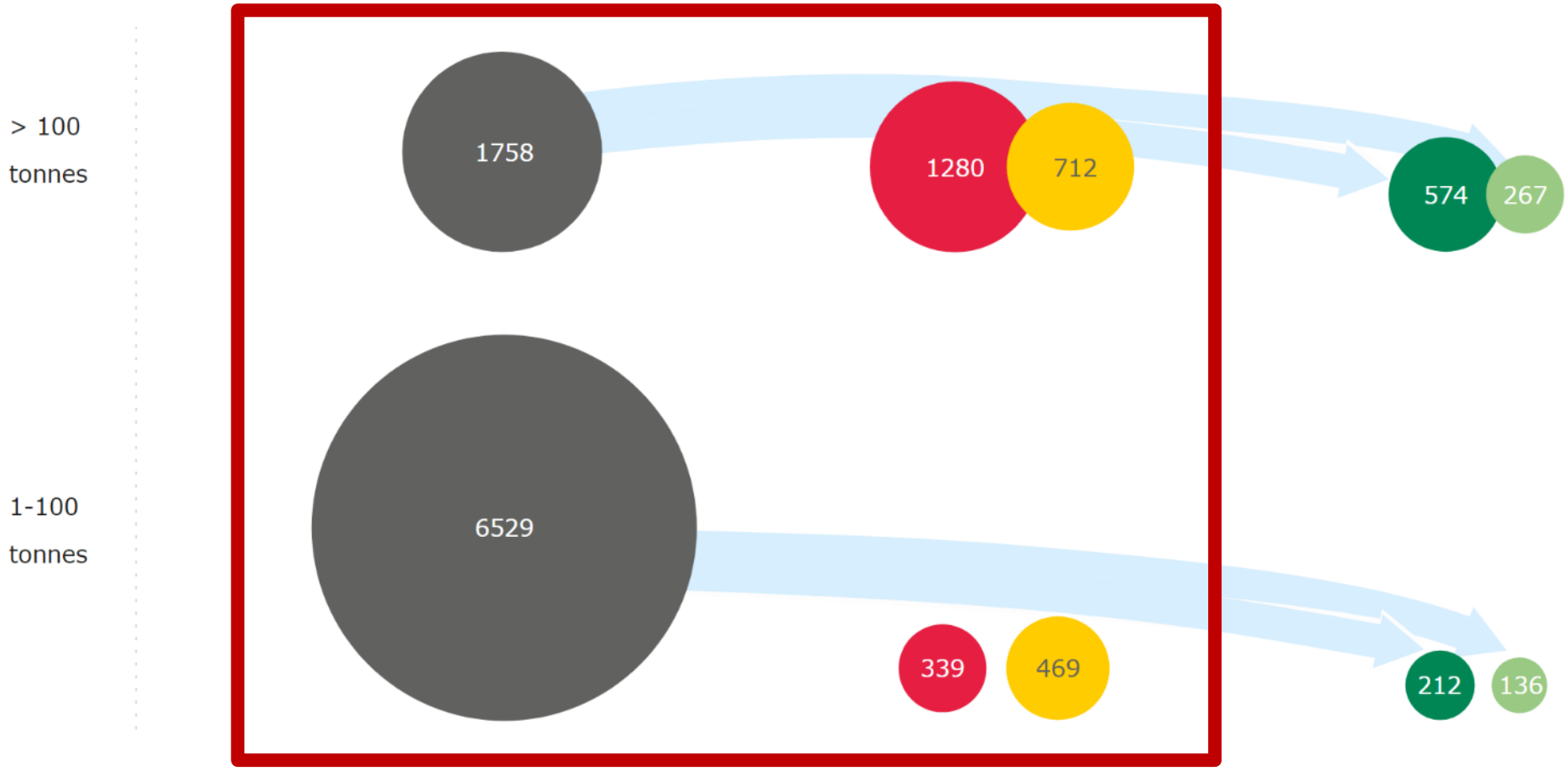
- Societal decision to protect human health and environment
  How?: (regulatory) risk management

- All tests are models
  no human testing



→ **Scientific basis** (educated estimations) for managing risks

Chemical universe 2021



Data as of 12/2020

Why use read-across?

- Societal decision to protect human health and environment
  How?: (regulatory) risk management

- All tests are models
  no human testing

reduce refine replace
in vivo 3R
in vitro Q(S)AR

→ **Scientific basis** (educated estimations) for managing risks

- **Optimise use of resources** (time) through "scientific method"
  Do we need to test every chemical with every test ?

KEY CONCEPT

KEY CONCEPT

→ (Just) One uncertainty more in the many uncertainties of models

Overview

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Uncertainties in hazard assessment

- Read-across (general cell-stress): 1,05 – 2,5x
- Read-across (receptor-based MoA): $10^{0 \text{ to } 6}$
- Biovariability: 1,3 – 3 fold
- Experimentation variability: 1,05 – 1,5
- Very limited statistical power of OECD TGs
- Limitations in extrapolation:
  - animal – human
  - Human – human
  - Animal – animal
- (Mixture toxicity, synergism/addition: 1 – 10 fold)

Biovariability

- "the toxicity profiles are different"
  (and so read-across fails)

- Are they true-ly?

  - Or is it natural biovariability?

KEY QUESTION

Richard Judson, … Russel S. Thomas*,
Toxicol Sci. 2016 Aug; 152(2): 323–339.
doi: 10.1093/toxsci/kfw092
*previously NTP, now director at US-EPA

Industrial chemicals vs. active substances

1060 substances (chem, pharm, PPP, BP) analyzed in 815 assays

Outcome 1: Activity can be divided into

1) specific biomolecular interaction: receptors, enzymes

2) cell stress: cytotoxicity from cell stress pathways, chemical reactivity, p/c-disruption of proteins+membranes

Outcome 2: Correlation!

- Active substances (Pharma, PPP, BP): type 1 toxicity
- Industrial chemicals: mainly type 2 toxicity, some type 1
- Concentration difference: factor 100+

Overview

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What is read-across?

…“data from structurally related substances”…

What is read-across?

Chemical Similarity in Toxicology (Abstract example)

Which two are most similar? And why?

Slide courtesy of Dr. Lennart Anger, Genentech/San Francisco

Read-across in a nutshell

Hypothesis

Justification

Experimental evidence

Predicted properties

Consequences

Composition

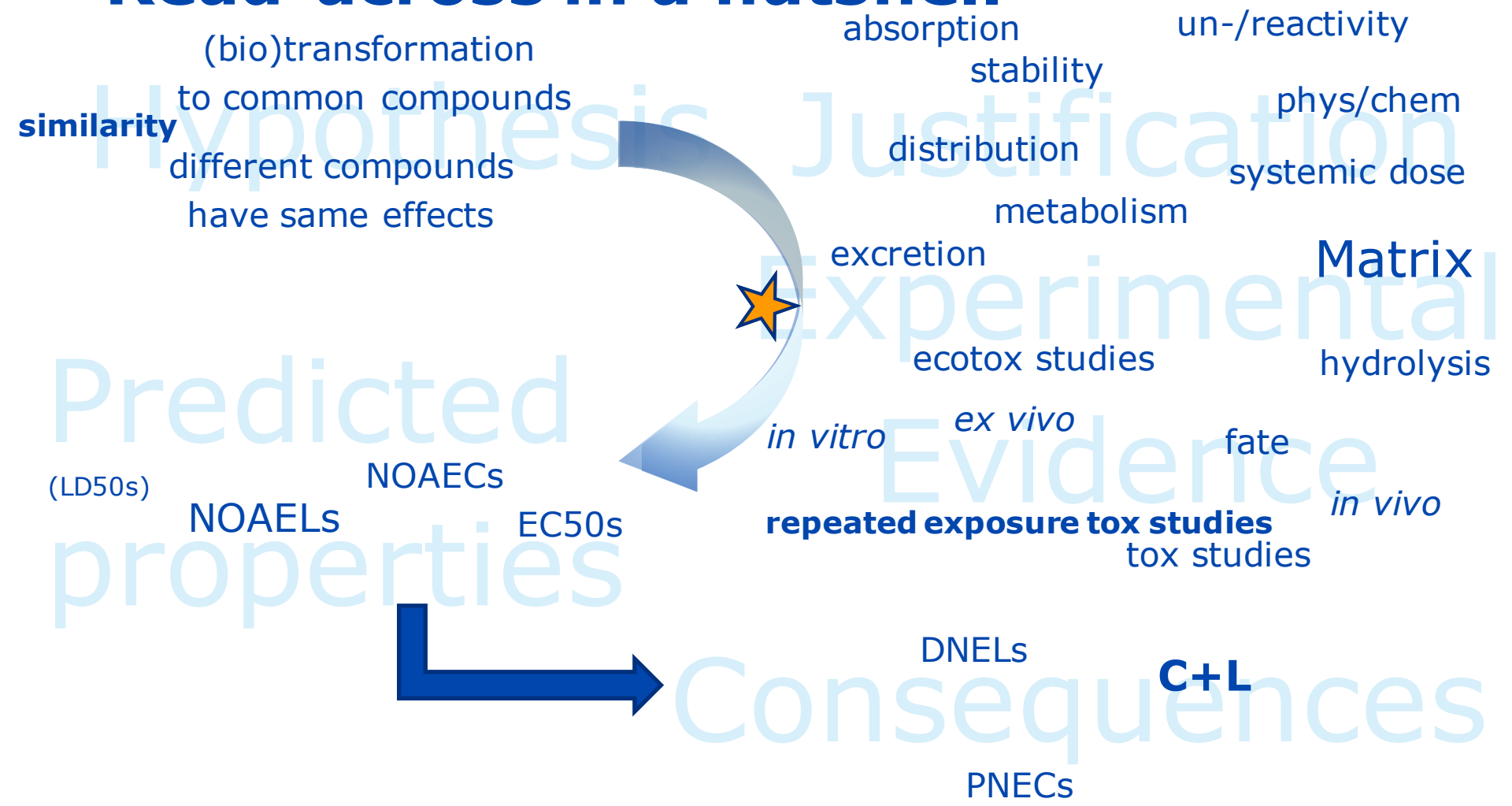
Substance concept - Art. 3(1)

Not limited to single structure

constituents

UVCBs

Read-across in a nutshell



How to build a read-across case

- Expertise: chemistry plus (eco)toxicology

1. Starting point here: "seed substance" with known hazard
2. Identify structural analogues
3. Hypothesize the mechanism
4. Identify information that supports the hypothesis
5. Predict the properties (qualitative/quantitative)

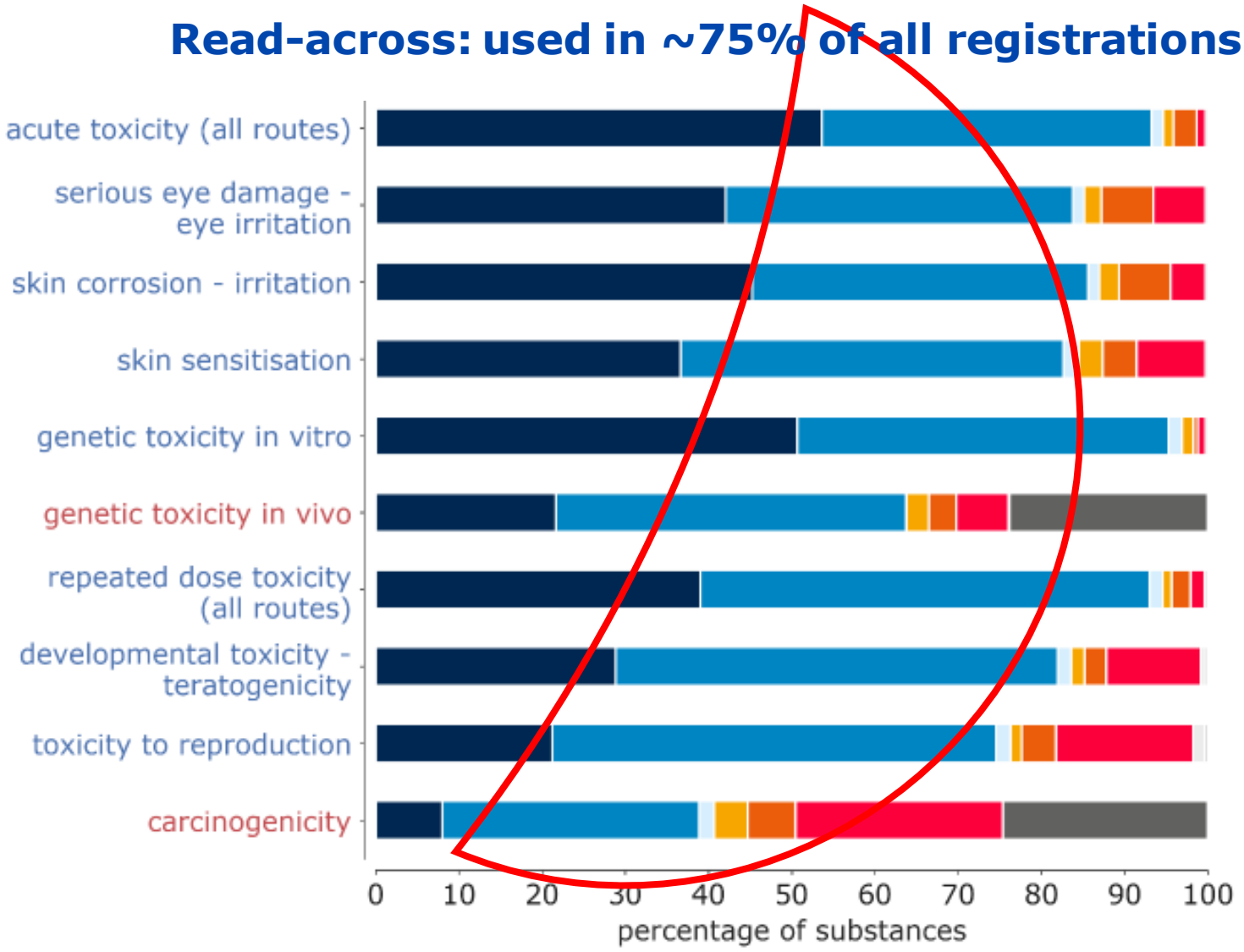
Practical tips (1)

1. Start simple:
   - salt-based read-across
   - category (from registrant) / outcome of a GMT
   - "textbook-known" rapid & complete hydrolysis
2. Search the chemical neighbourhood
   - Manually/chemist, or using e.g. QSAR toolbox
   - sort-out only at a later stage (e.g. hypothesis)
3. Hypothesis – usually from one of two scenario types:
   - *"(bio)transformation to common compounds"*
   - *"different substances have the same type of effects"*

Practical tips (2)

4. Supporting information
   - Scrutinise all chemical neighbours
   - Reports from other (international) authorities
   - Build on registrant's efforts to avoid testing
     - Biotransformation scenario: hydrolysis or ADME data
     - Same-type of effects scenario: comparison of tox profiles, bridging studies
5. Predict qualitatively & quantitatively
   - Watch out for trend-breaks! (n-hexane)
   - Address when/why evidence might seem to contradict the hypothesis
   - Bonus: discuss the uncertainty added by the read-across, and whether it is proportionate to be on the cautious/ conservative side when accepting it

Read-across: used in ~75% of all registrations



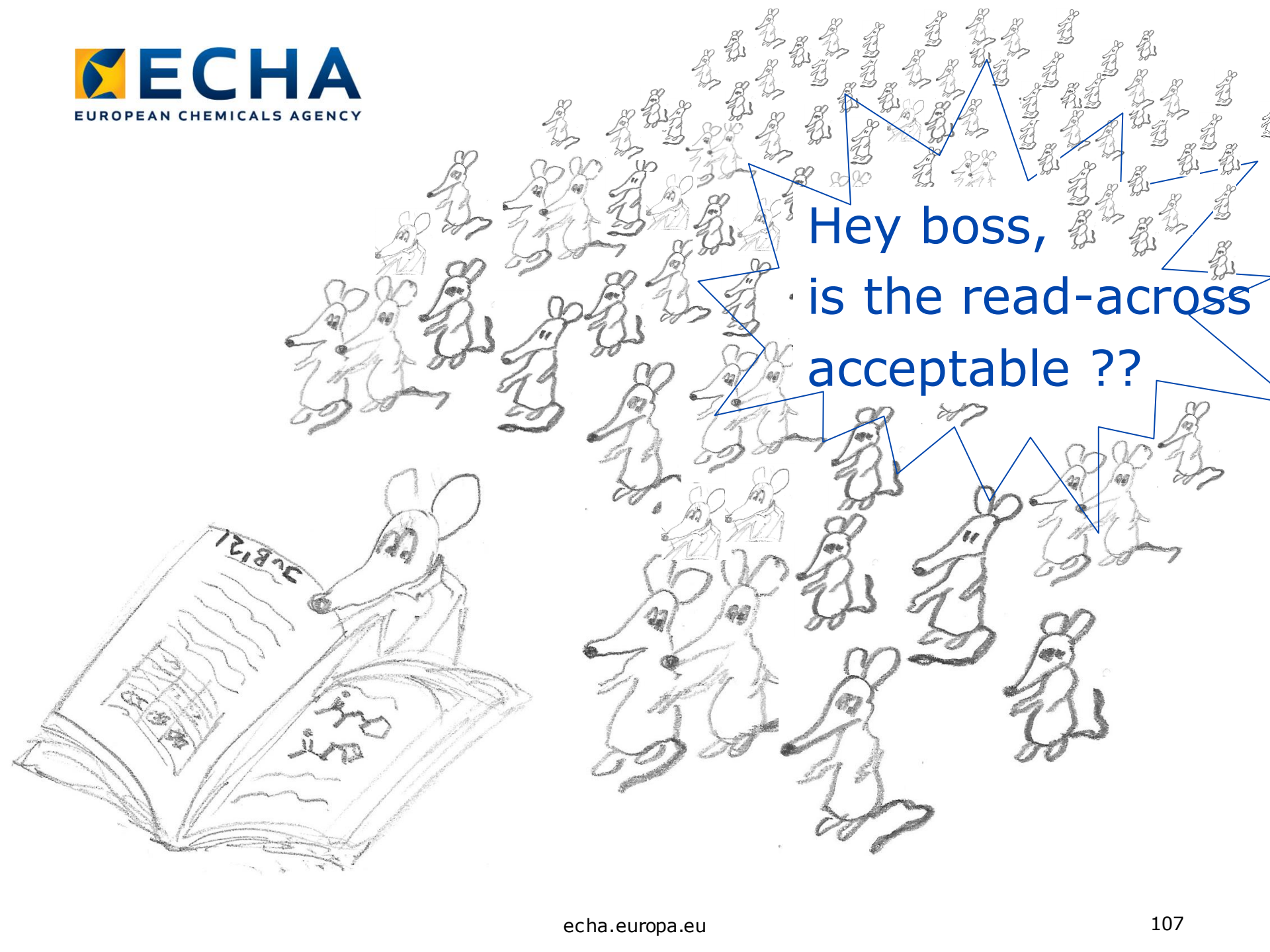
Source: *The use of alternatives to testing on animals for the REACH Regulation, June 2020*

Using RAAF for classification (CLP)

- Needs not be fulfilled strictly
- e.g. not all criteria fulfilled for existing entries
  - Vitamin K analogue anti-coagulants
  - Many entries in Annex VI to CLP (e.g. petroleum-based)

- Useful to increase robustness of the case

- (RAAF was designed to assess read-across adaptations under REACH; usually "absence of effects" cases, which then need to cover all aspects)


Hey boss,
is the read-across
acceptable ??

Overview

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Example – receptor mediated

- Anti-coagulants, vitamin-K analogues
- Mechanism: receptor antagonism

- **Dissimilar** structure with one common stereo-electronic feature: receptor-binding

- Similarities in ADME properties

Example – similar structure (1) salt-based read-across

- Cadmium salts
- Lead compounds
- Hypothesis: driver of toxicity is the cation (Cd^{2+}, Pb^{2+})
- Supporting evidence:
  - Toxicity *in vivo* with selected Cd or Pb compounds
  - All soluble
  - Extrapolation of effects to analogue compounds which solubilise the cation / based on p-c effects

Example – similar structure (2) DOTO/DOTCl

- Dioctyl-tin octanoate (DOTO) read-across from
- Dioctyl-tin dichloride (DOTCl)
  - Hypothesis: biotransformation of DOTO to DOTCl
  - Supported by *in vitro* hydrolysis data, demonstrating rapid conversion of DOTO to DOTCl in gastric acid
- read-across for filling information requirement accepted

- Repr. 1B classification → SVHC identification
- … *in vivo* testing to overrule read-across (2015)

Overview

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Alternatives to animal testing?

Does the alternative enable risk management, e.g. C+L, DNEL, target organ identification?

- *in silico* / QSAR– usually no
- *in vitro* / NAMs – usually no
- read-across, supported by *in silico/vitro/vivo* – usually yes

→ Single most powerful method, based on higher-tier studies as bridge pillars

Key messages: *Read across…*

- is one uncertainty among many
- requires data to support the hypothesis
- requires change of (RAAF) perspective when predicting from a known hazard
  - Focus on driver of toxicity / mechanism
- is resource-optimisation: to ensure safe use
  - of substances across the chemical universe
  - as quickly as possible.

My thanks to

- ECHA colleagues & mentors, especially:
  - Chiara Perazzolo
  - Jonas Nygren
  - Niklas Andersson
  - Read-across Network

- Lennart Anger, Genentech, San Francisco

Thank you!

jochen.vombrocke *(at)* echa.europa.eu

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References

- Read-Across Assessment Framework (2017)
- Read-Across Assessment Framework – considerations for multi-constituent and UVCB substances

- Guidance on information requirements and chemical safety assessment, R.6 QSAR and grouping of chemicals
- Practical guide on how to use and report (Q)SARs

- Read-across - illustrative example
- Practical guide on how to use alternatives to animal testing

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Conclusions and closing

How to submit a harmonised classification and labelling dossier - part II

9 December 2021

Paul Ryan
Head of Unit, Hazard I
European Chemicals Agency

Conclusions and closing

- Survey outcome
- Member State experience
- EFSA – PPP dossiers
- Biocides CLH dossiers
- Read-across

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