食品安全委員会
内閣府 Food Safety Commission of Japan

NIHS

Future Challenges in Developing Assessment Methodologies
for Human Health Effects
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Category-based Read-across Approach, Considering Human Relevance

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The views expressed are those of the speaker and not an official position of NIHS.

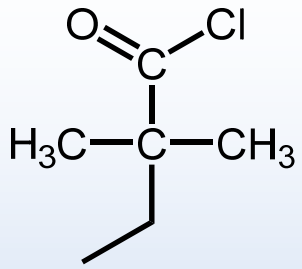
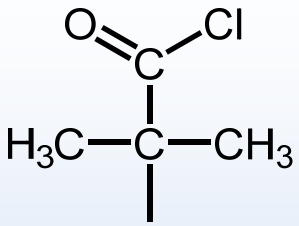
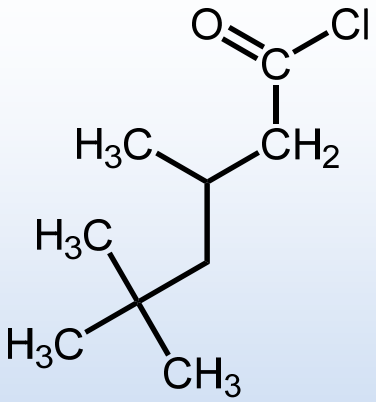
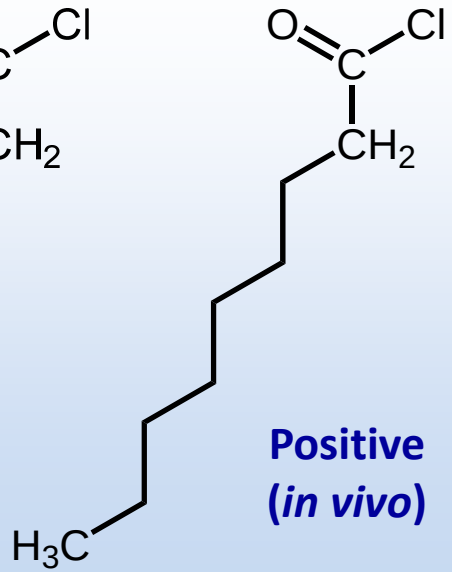
Topics of This Talk

- Databases and computational tools to support read-across approach

- Our recent read-across experiences in OECD IATA Case Studies Project

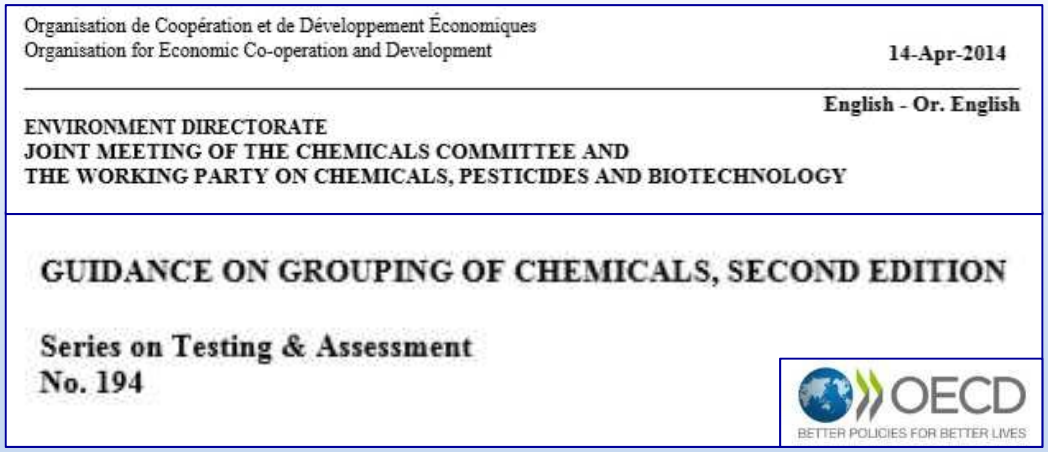
Read-across

Read-across is regarded as a technique for predicting endpoint information for one substance (target substance), by using data from the same endpoint from (an)other substance(s) (source substance(s)).

	Target substance	Source substances		
Structure				
Endpoint (Skin Sensitization)	**Positive (read-across)**	**Positive (*in vivo*)**	**Positive (*in vivo*)**	**Positive (*in vivo*)**

Benefits

- Read-across saves resources and animals
- Not a new concept, but gains importance
  - -as the number of assessed chemicals increase
  - -animal welfare gains importance
- OECD Guidance, strongly emphasized in REACH Guidance


Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

14-Apr-2014

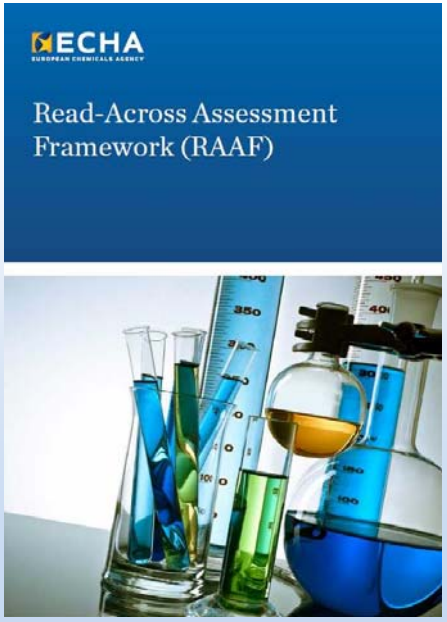
English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

GUIDANCE ON GROUPING OF CHEMICALS, SECOND EDITION

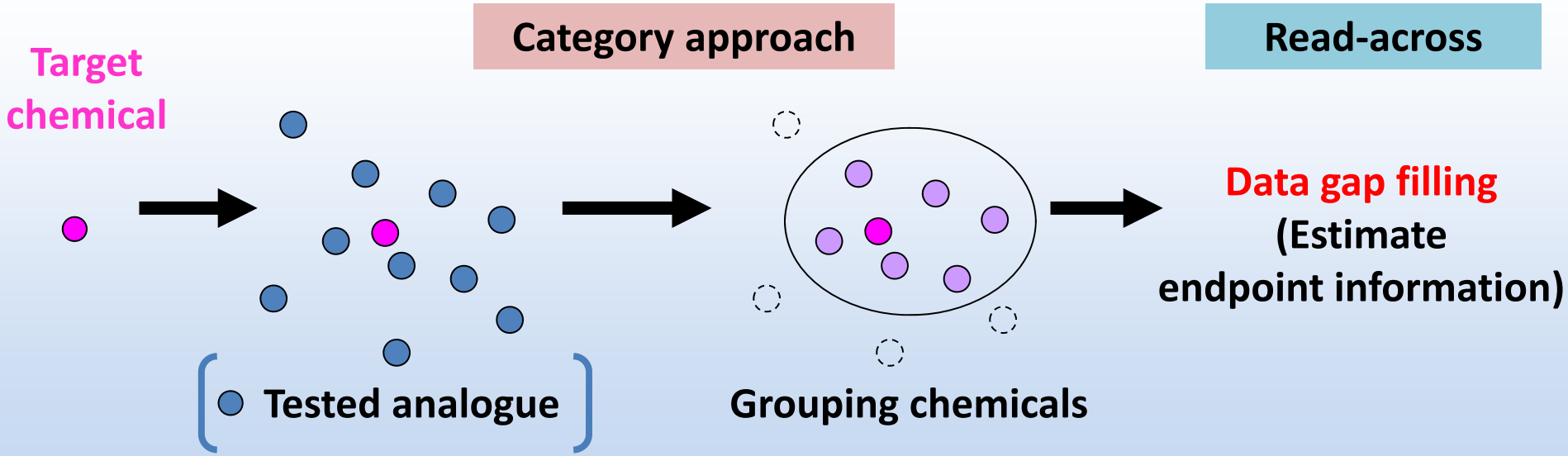
Series on Testing & Assessment
No. 194

OECD
BETTER POLICIES FOR BETTER LIVES



Terminology

- Category approach and analogue approach
  - Techniques for grouping chemicals
- Read-across
  - Technique of filling data gap in either approach



Computational Toxicology 3 (2017) 1–18

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

Navigating through the minefield of read-across tools: A review of in silico tools for grouping

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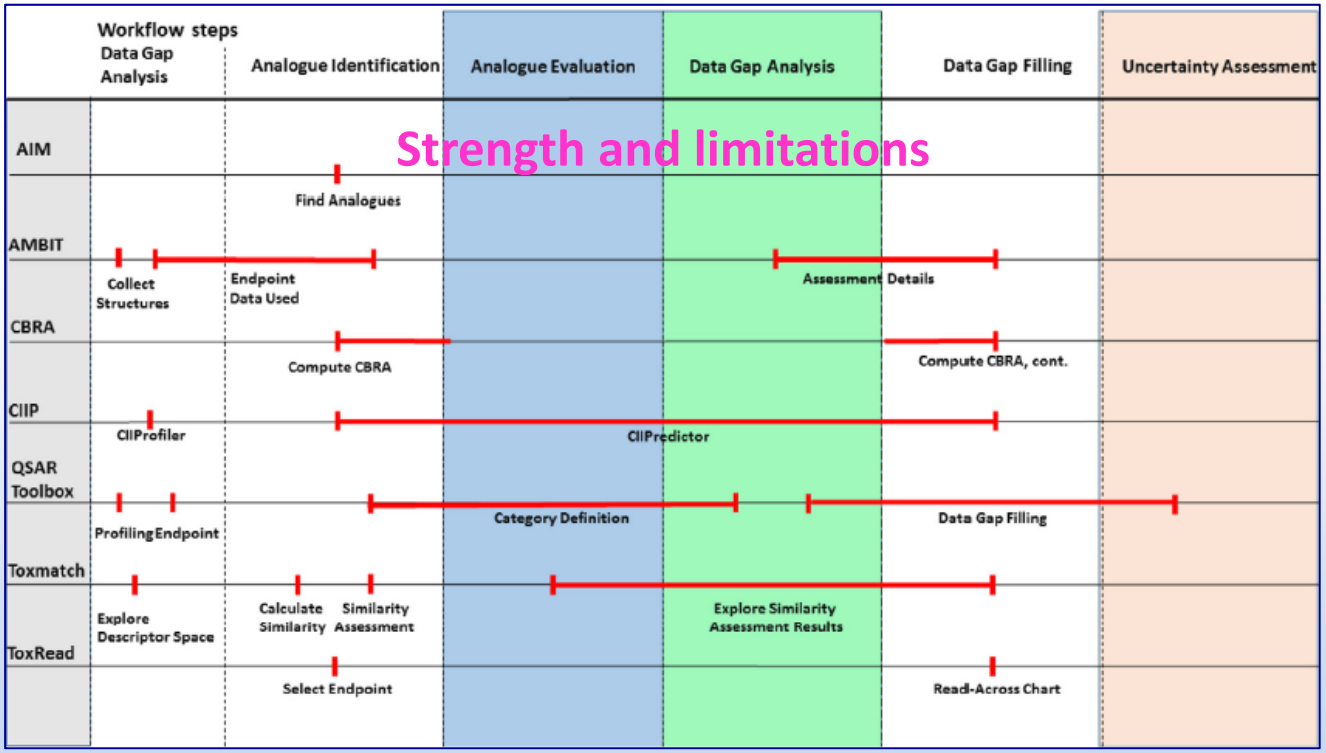
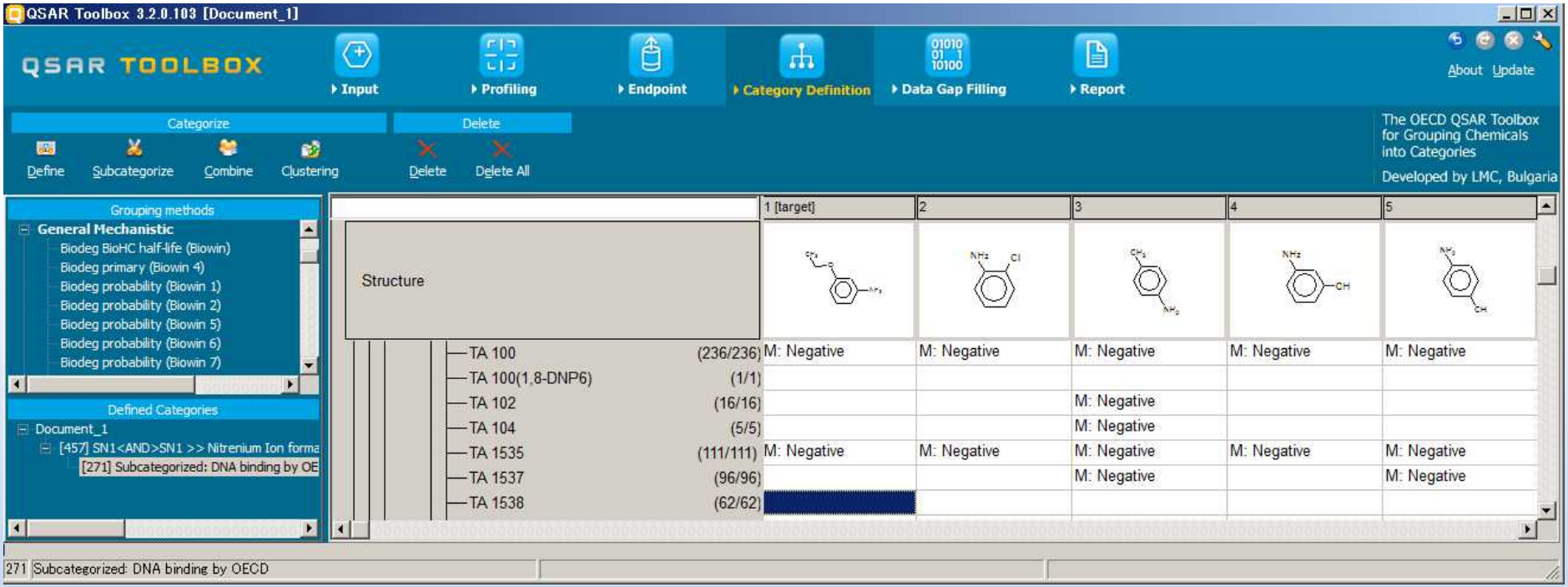
Publicly available tools



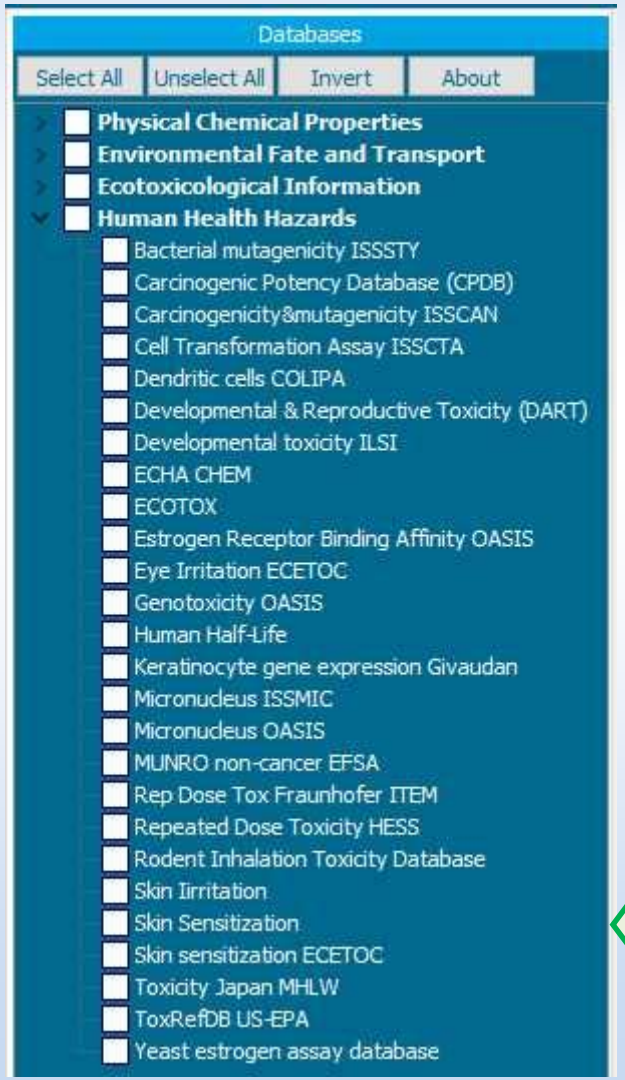
OECD QSAR Toolbox

- Free software to support data gap filling by category approach（http://www.qsartoolbox.org/）
- Functionality of finding analogues and the test data for regulatory endpoints are equipped.



QSAR Toolbox :
Databases and Profilers for Human Health Hazard

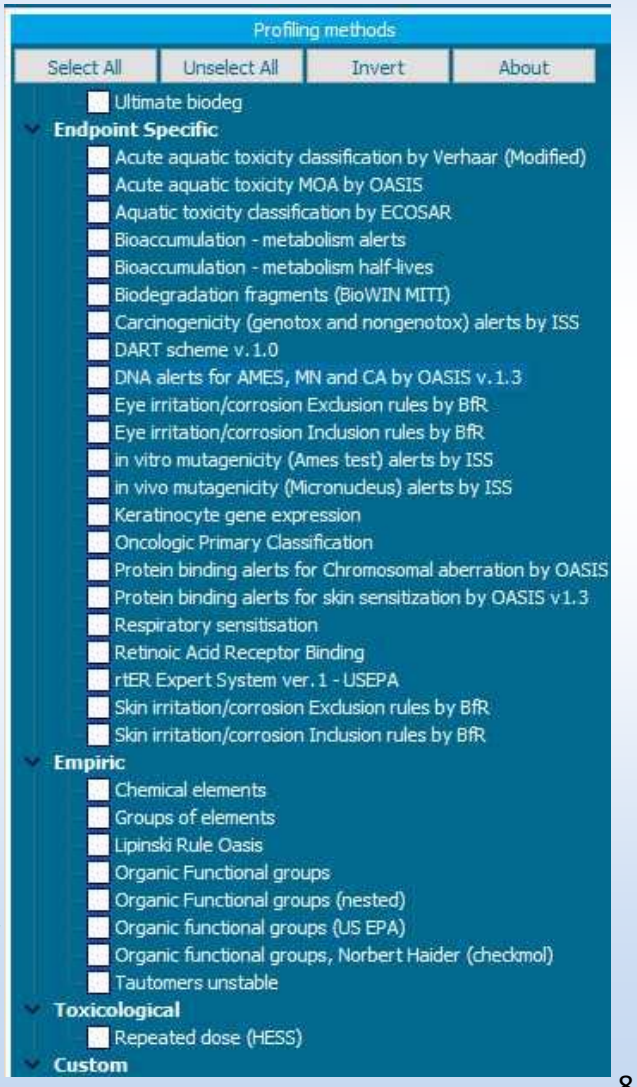
Databases



Bacterial mutagenicity,
Carcinogenic potency,
Cell transformation,
Developmental and reproductive toxicity,
Genotoxicity
etc.

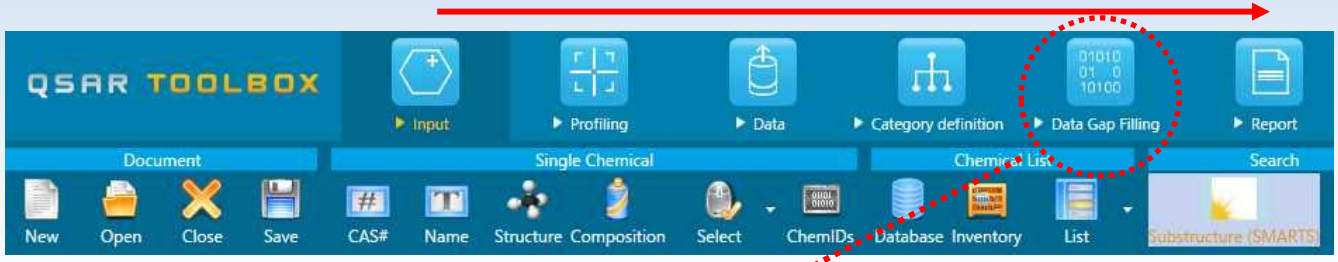
Repeated dose toxicity

Profilers

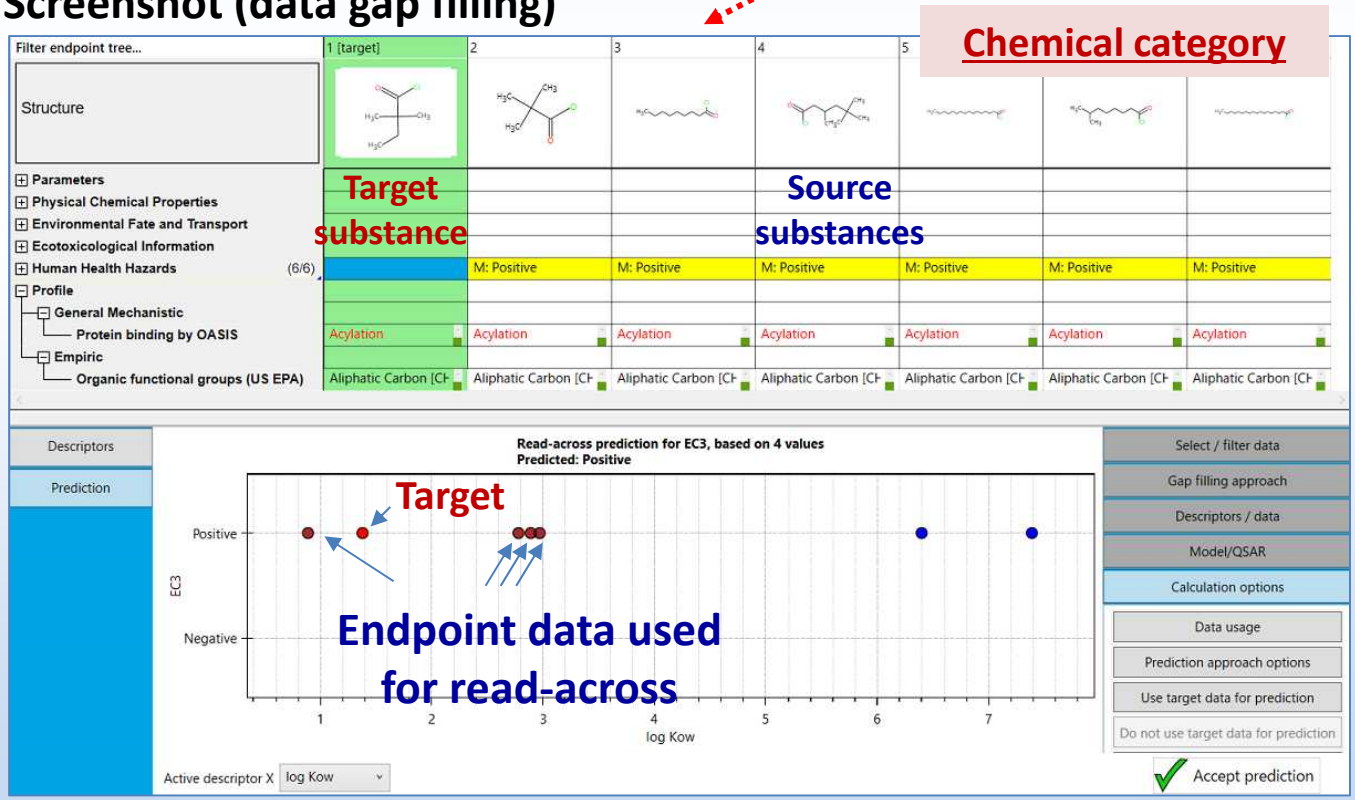


Chemical Category and Read-across

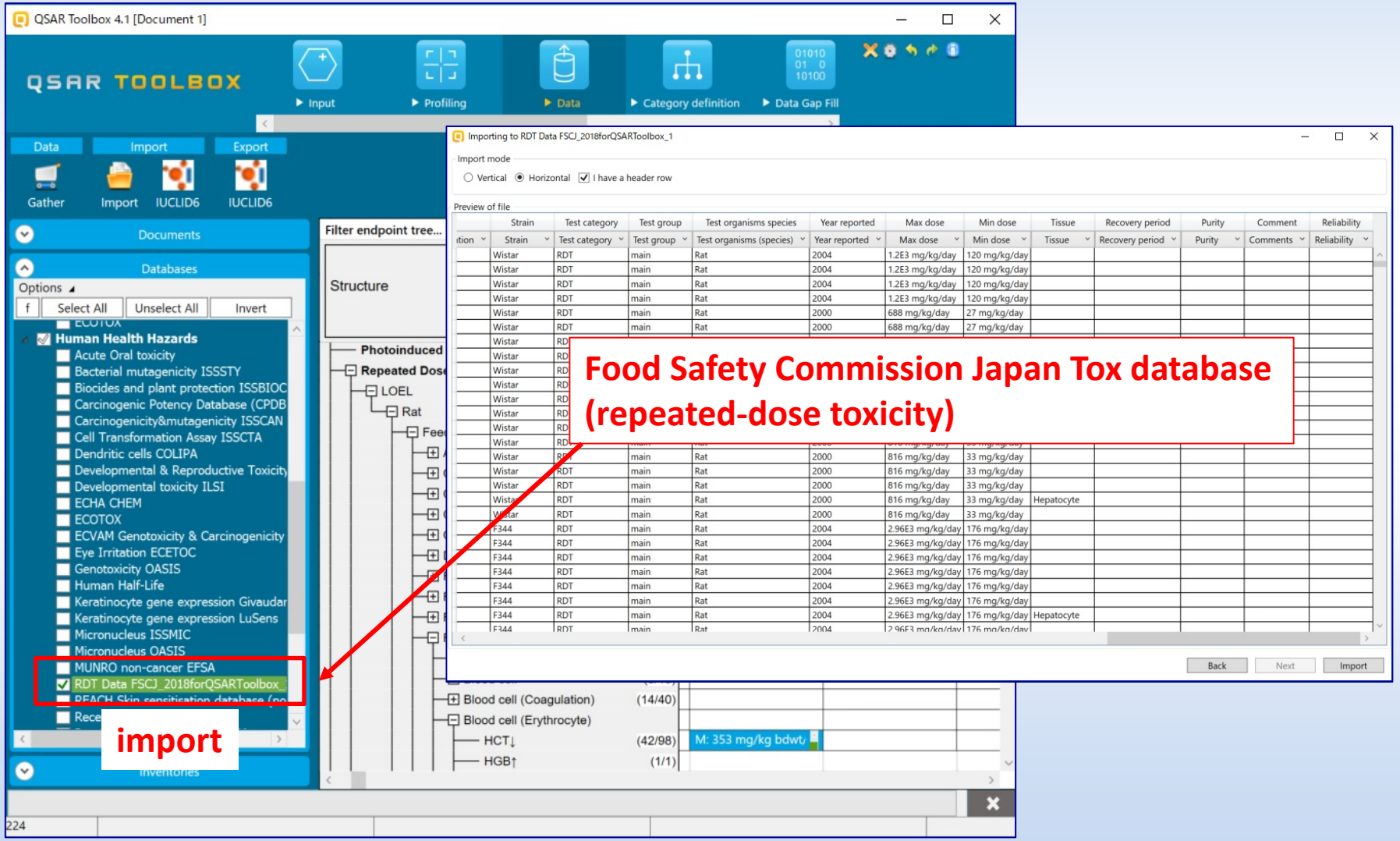
(A) Workflow



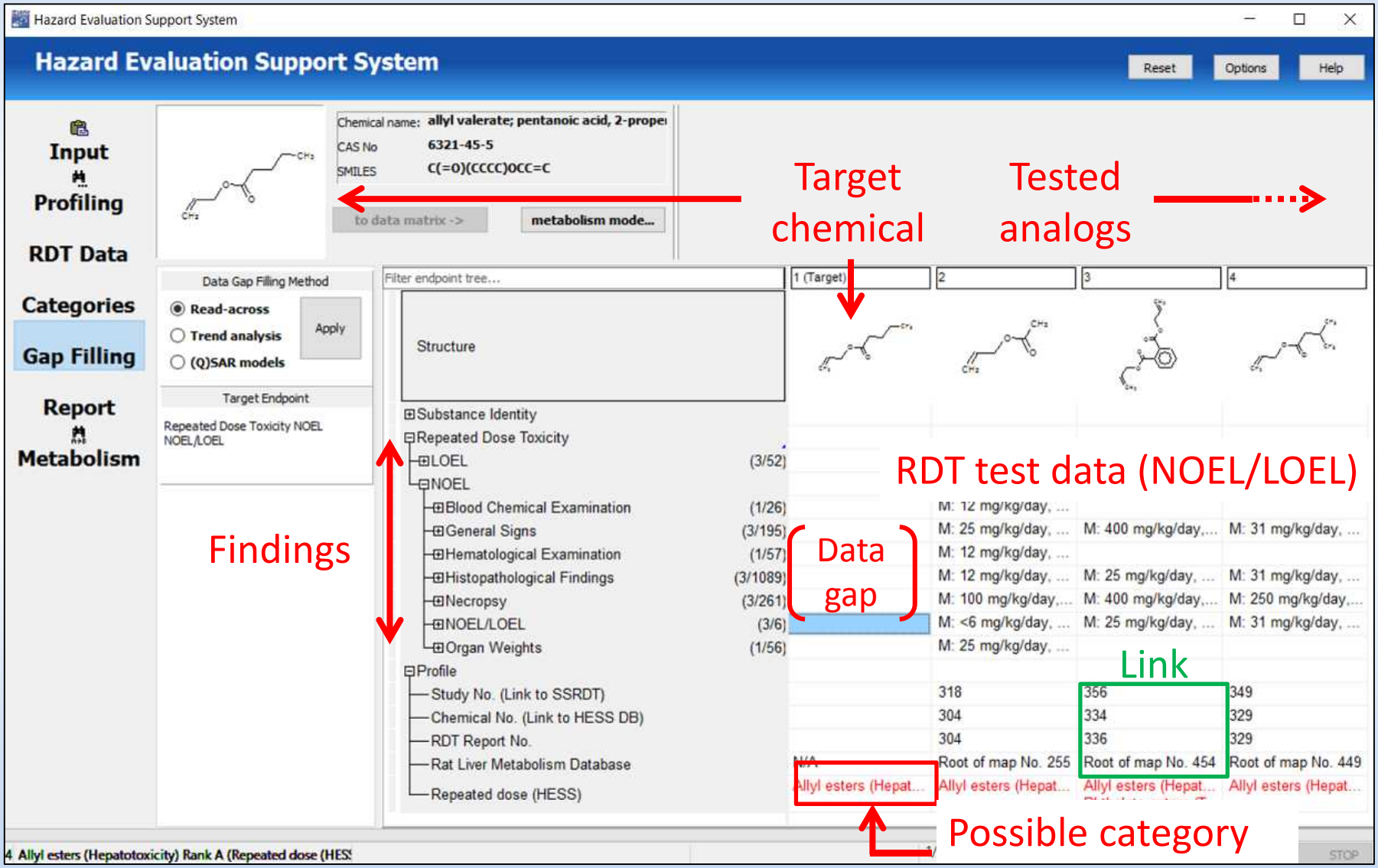
(B) Screenshot (data gap filling)



Importing a Custom Database

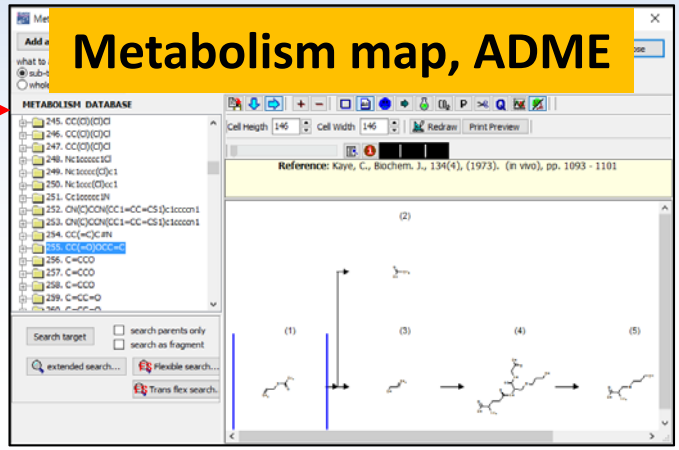


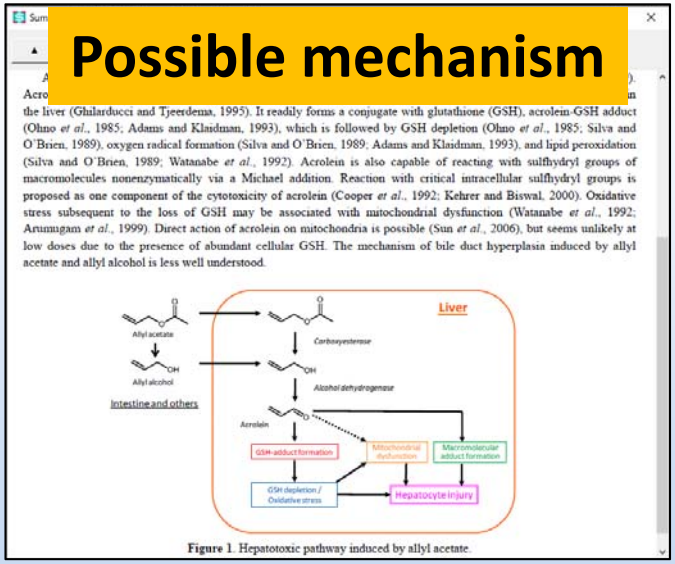
HESS: A tool to find analogues and the repeated-dose toxicity test data for read-across



Download free from http://www.nite.go.jp/en/chem/qsar/hess-e.html

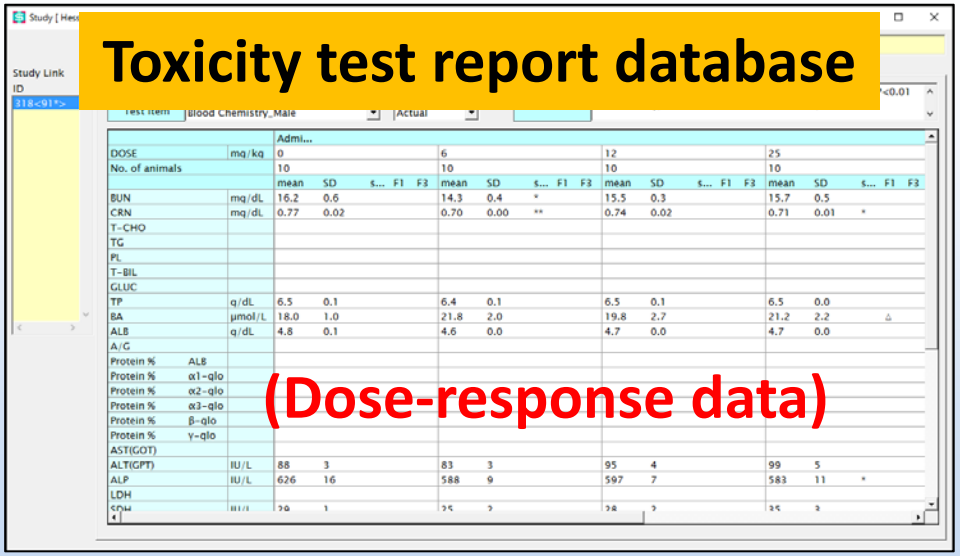
Link to Metabolism/Mechanistic Information and Toxicity Test Results of Analogues





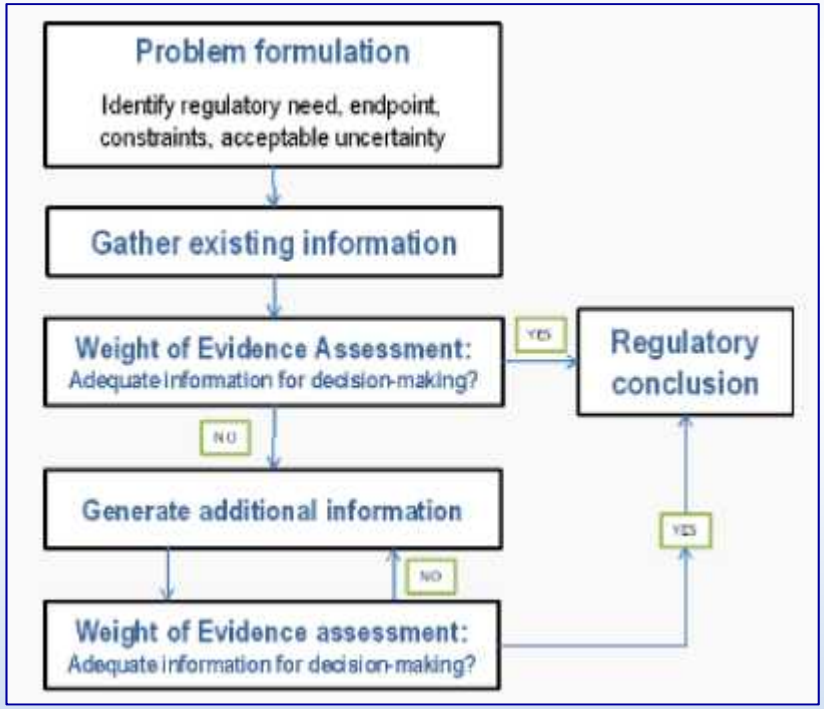
Form mechanism-based category

Confirm the test data of the nearest analogue for read-across



OECD IATA Case Studies Project (2015-)

- IATA (Integrated Approaches to Testing and Assessment)
- Combinations of in silico, in chemico, in vitro approaches. Read-across is a part of IATA.
- Provide a forum to increase experience with the use of IATA for regulatory purpose
- Develop guidance
- Project team: Australia, Canada, Denmark, Japan, Netherlands, Sweden, United States, EU (EC), EU (JRC), EU (ECHA), BIAC and ICAPO



http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

Development of Case Studies by Member Countries/Bodies

FY2015

- In Vitro Mutagenicity of 3,3’ Dimethoxybenzidine (DMOB) based Direct Dyes [Canada & US]
- Repeated Dose Toxicity of Substituted Diphenylamines (SDPA) [Canada]
- Hepatotoxicity of Allyl Ester Category [Japan]
- Bioaccumulation Potential of Biodegradation Products of 4,4’-Bis (chloromethyl)-1,1’-biphenyl [Japan]


ENVIRONMENT, HEALTH & SAFETY NEWS

OECD

October, 2016

Just released!

First Four Case Studies from the Integrated Approaches to Testing and Assessment (IATA) Case Studies Project

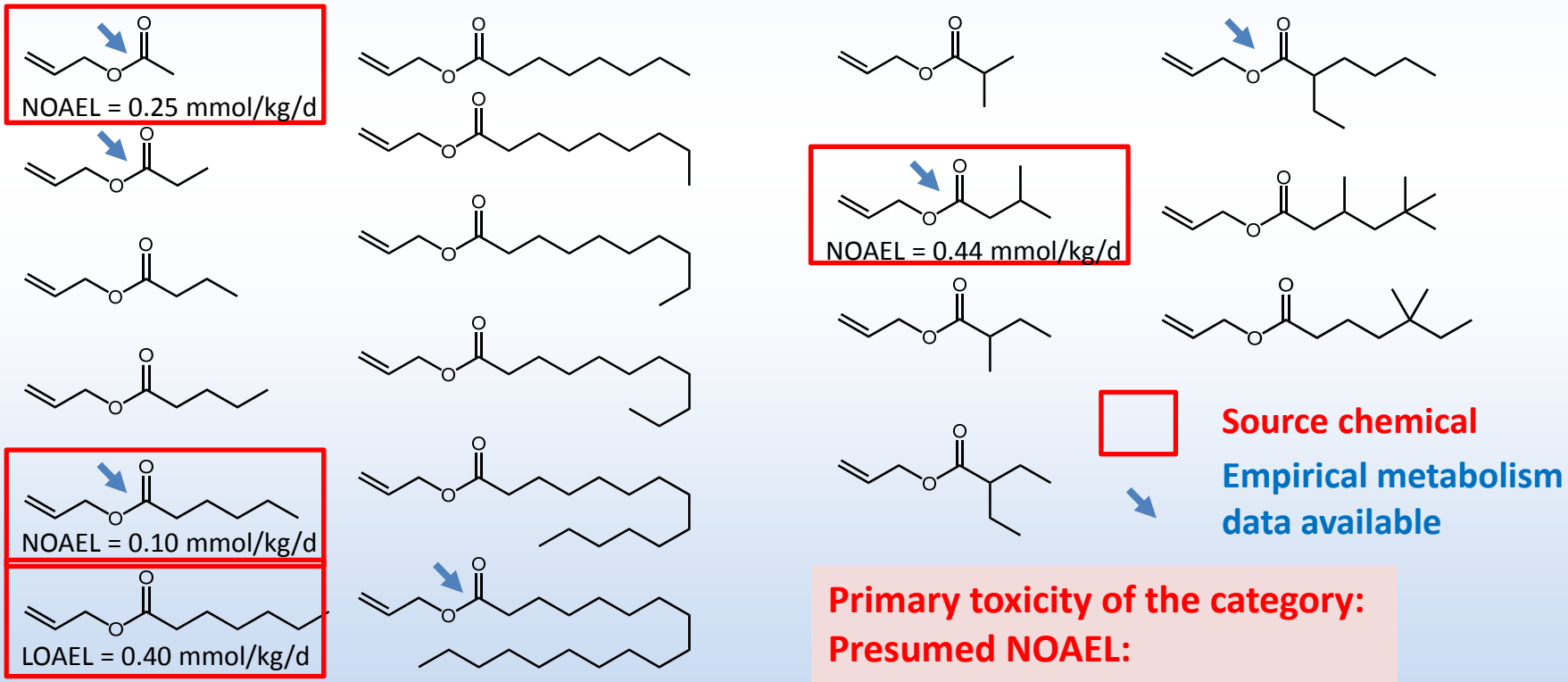
The first four case studies from the IATA Case Studies Project were published along with a reporting template and considerations document highlighting the learnings from the first review cycle.

The IATA Case Studies Project was launched in 2015 to increase experience with the use of IATA by developing case studies, which constitute examples of predictions that are fit for regulatory use.

From 2015 to 2018 cycles, 15 case studies were developed by the member countries/bodies and reviewed by the project team.

Case Study 1 Developed by JP

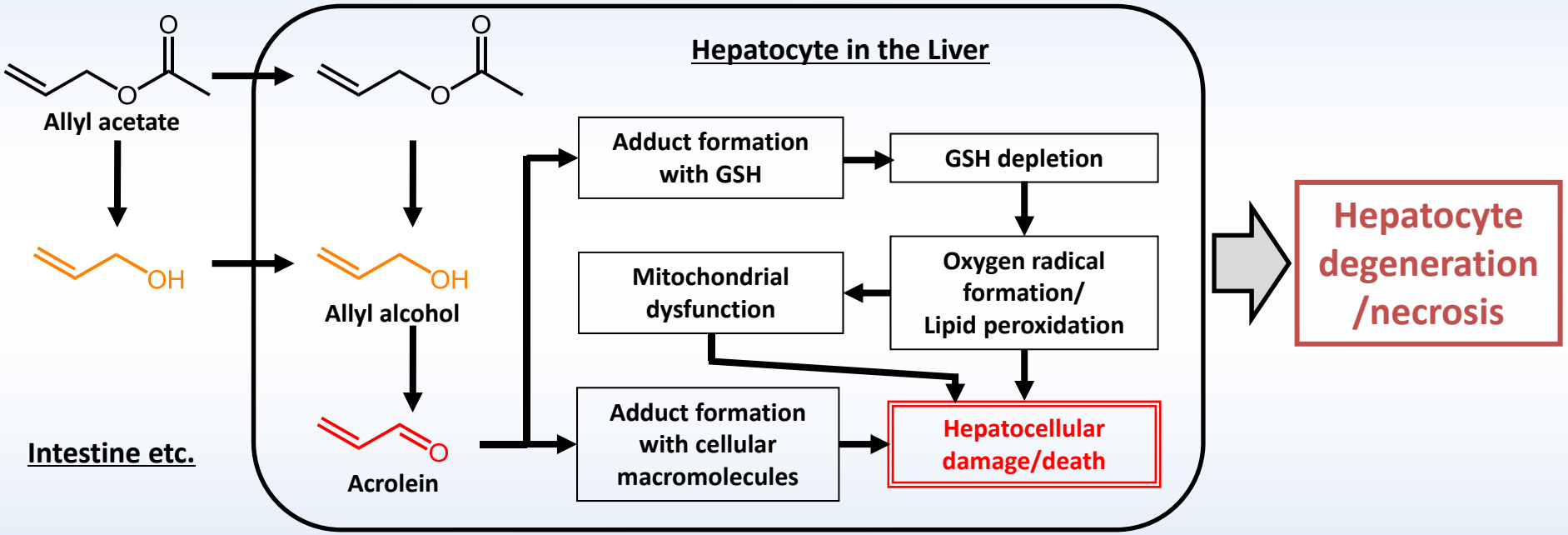
Purpose: to assess repeated-dose toxicity of allyl ester category using toxicity data of the tested analogues. NO(A)EL values are derived for the hazard classification under the Chemical Substances of Control Law (CSCL).



Primary toxicity of the category:
Presumed NOAEL:

Similarity Hypothesis (Case Study 1)

Possible Mode of Action/Adverse Outcome Pathway



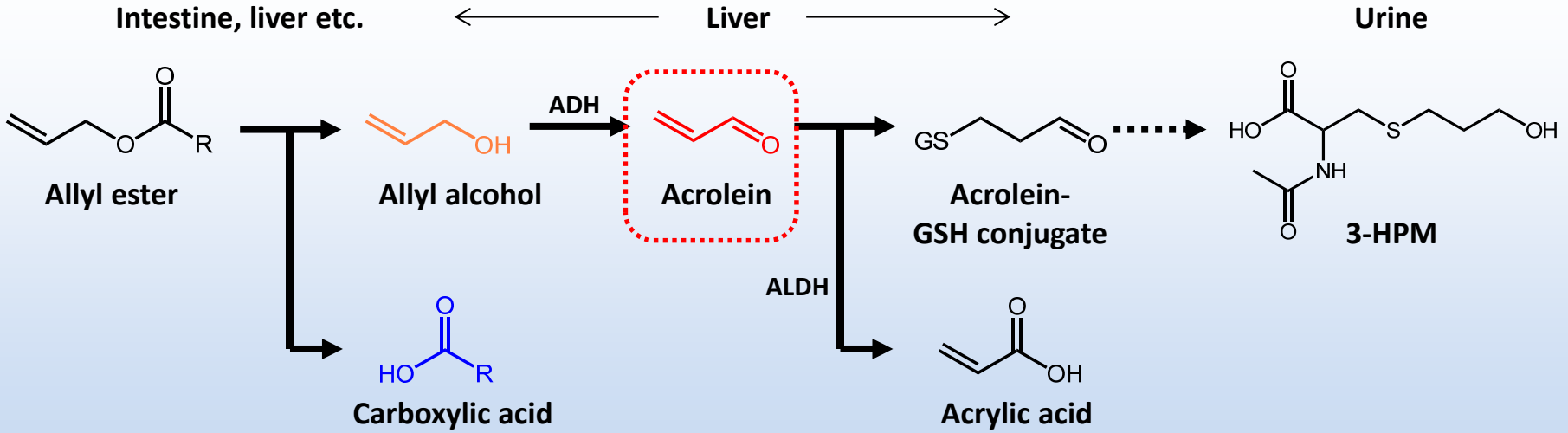
The mechanism of bile duct hyperplasia is not understood, although allyl alcohol formation is apparently linked to the toxic response.

Similarity hypothesis: Allyl esters that can be predictably metabolized to allyl alcohol are likely to produce hepatotoxicity.

Category Justification (Case Study 1)

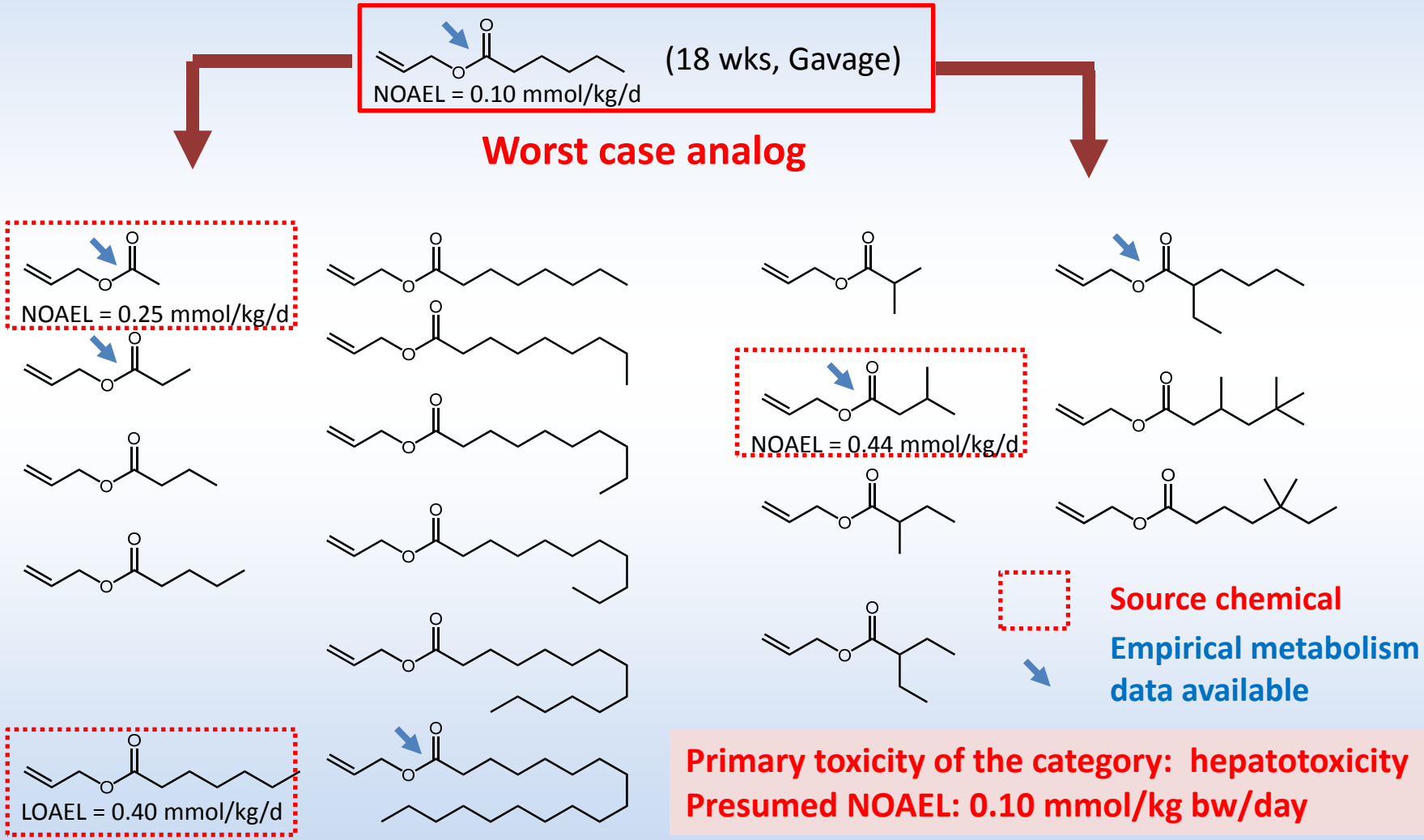
- Toxicity
  - ✓ Primary toxicity: hepatotoxicity
- ADME
  - ✓ In vitro: hydrolysis in intestine
  - ✓ In vivo: 3-HPM in urine
  - ✓ Hydrolytic rate (linear vs branched)

- Why and how is structural similarity associated with similar biological properties?
- Why read-across for the property under consideration is acceptable despite of the structural dissimilarities?



(Data is gathered and is used to connect category members.)

Read-across (Case Study 1)



Primary toxicity of the category: hepatotoxicity
Presumed NOAEL: 0.10 mmol/kg bw/day

Reviewers' Comments (Case Study 1)

Uncertainty analysis

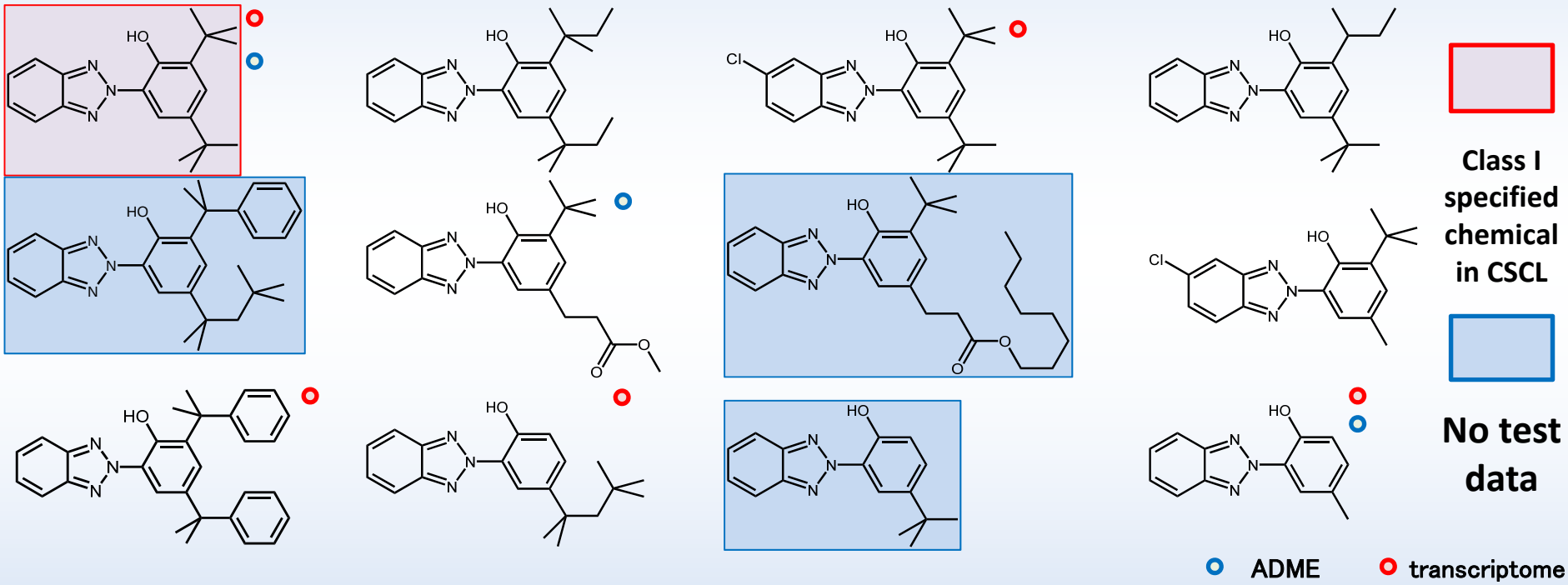
- Is the hepatotoxic effect the critical effect of these substances?
- How does the steric hindrance influence the toxicity?
- Not convinced that the other part of the metabolites, the carboxylic acids, do not have other toxic properties.
- More clarify category boundary (for branched subcategory)
- Ideally, the hypothesis should allow a quantitative estimation of the toxicity.
- Is this is also relevant for humans? A more in depth discussion of this would be valuable.

Discussion on Human Relevance

- Lack of toxicological information on allyl esters in humans
- Plausible to assume that hydrolytic enzymes in the intestine and other tissues, as well as ADHs in the liver, participate in metabolic activation in humans
- Acrolein was detected in the blood, bile and urine of man who had accidental oral ingestion of allyl alcohol (Toennes et al., 2002).
- Allyl alcohol and acrolein showed cytotoxic effects in human hepatocytes (Dvorák et al., 2003, Mohammad et al., 2012).

Case Study (2) Developed by JP

Screening assessment of phenolic benzotriazole category for repeated-dose toxicity



Primary toxicity: hepatotoxicity
NOEL: 0.1 – 100 mg/kg bw/day

Structural differences affect toxicity levels

→ **Use of ADME and liver transcriptomic data for subcategorization** → **Read-across**

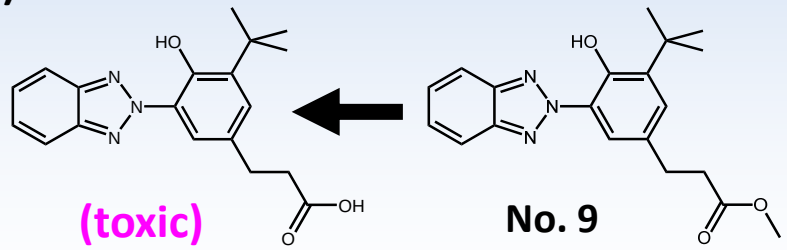
Reviewers' Comments (Case Study 2)

- A proper hypothesis should describe the basis on which it is considered that the members of the (sub)categories will share the same properties as far as the repeated-dose toxicity is concerned.
- Better explanation is needed on why only hepatotoxicity was considered and not nephrotoxicity. Are we sure that for the target substances the effects on kidney will be induced at higher doses than the hepatotoxic effects?
- The reason for conducting the transcriptome tests for this category should be stated relating to the hypothesis. A short discussion of the selected genes and how they relate to hepatotoxicity is needed.

Uncertainties in Selecting an Analogue and Performing Read-across (Case Study 2)

(A)

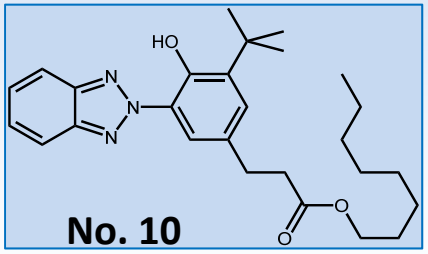
Source



(toxic)

No. 9

Target



No. 10

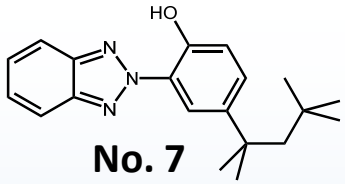
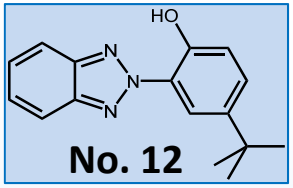
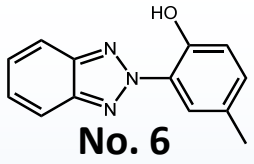
Read across from No.9

Uncertainty level: high

Higher Bioavailability

Toxicity underestimated

(B)

	Source	Target	Source
	 No. 7	 No. 12	 No. 6
Transcriptome	CAR: Cyp2, PPAR: Cyp4	Not available	Nrf2-Phase II
Hepatotoxicity	Higher NOAEL		Lower NOEL
Protocol/GLP	non-TG/non-GLP		OECD TG422/GLP

- Uncertainty level is high: Transcriptome and kinetics data not uniformly available
  - "high uncertainty" may be an obstacle to derive prediction.
  - No.6 recommended as a source: better quality study and more conservative for screening, and mention the branching difference as an uncertainty for the effect

Areas Identified for Guidance Development

- Definition of analogues/category boundaries
  - Lacked a discussion on the structural differences whereas their structural similarities were well documented
- Uncertainty analysis and reporting
  - Each case study contains different uncertainties because of limited data or resource
  - Uncertainty analysis helps reviewers to consider the acceptable degree of uncertainty to the specified purposes.
  - There are several studies on uncertainty of read-across, but no international guidance. (Blackburn, 2014; Schultz, 2015)

Lessons Learned from Our Case Studies

- Read-across is conceptually simple but practically difficult.
- It takes a lot of time to gather information for preparing read-across cases.
- Crucial factors for regulatory acceptance
  - Transparency and reproducibility
  - Increase in confidence: similarity hypothesis based on mechanism, and quality and quantity of test data used for read-across
  - Decrease in uncertainty: supporting data of TK, in vitro testing, omics or related information for bridging chemicals

Acknowledgement

- Akihiko Hirose, Mariko Matsumoto (NIHS): IATA case study
- Makoto Hayashi (BSRC, MIC): HESS platform
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- Jun Yamada (NITE): HESS platform
- Yasushi Yamazoe (FSCJ): ADME, Mechanism
- Masayuki Kurimoto, Tomoko Kawamura, Minoru Miura, Hideo Ohata, Shinji Tsujii, Natsuho Taira, Akiko Ohno (NIHS): Toxicity Database
- Ryuichi Hasegawa (NITE): Mechanism, read-across
- Jun Kanno, Satoshi Kitajima (NIHS): Percellome toxicogenomics
- Yuki Sakuratani, Masashi Horie (OECD): OECD IATA Project

BSRC; BioSafety Research Center, MIC; Makoto International Consulting, NITE; National Institute of Technology and Evaluation, FSCJ; Food Safety Commission of Japan

Thank you very much for your attentions!