OECD PROJECT ON THE DEVELOPMENT OF IATA

CONSIDERATIONS FROM READ-ACROSS CASE STUDIES

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"Good Read-Across Practices: Making it work for you!"

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Background

- Member countries have been making efforts to expand the use of alternative methods in assessing chemicals
- The OECD has been developing guidance documents and tools for the use of alternative methods such as (Q)SAR, chemical categories and Integrated Approaches to Testing and Assessment (IATA).
- There is an on-going need for the investigation of the practical applicability of these methods/tools and for real case studies/assessments.
- In 2014, the Task Force on Hazard Assessment (TFHA) proposed an IATA Case Studies Project as a one of the high priority projects of the revised Cooperative Chemicals Assessment Programme (CoCAP) to increase experience with the use of IATA by developing case studies.
- The proposed project was endorsed at the 52th Joint Meeting in November 2014.

OECD IATA Case Studies Project

Objective:

To increase experience with the use of IATA by developing case studies, which constitute examples of predictions that are fit for regulatory use. The aim is to create common understanding of using novel methodologies and the generation of considerations/guidance stemming from these case studies.

Organization:

Project team consisting of representatives from Australia, Canada, Denmark, Japan, Netherlands, Sweden, United States, EU(EC), EU(JRC), EU(ECHA), BIAC and ICAPO.

Deliverables:

Deliverables will be in the form of guidance documents on methodologies with associated case studies.

Case Studies Reviewed in 2015

No.	Title	Lead Country	Purpose of Use
1	In Vitro Mutagenicity of 3,3' Dimethoxybenzidine (DMOB) Based Direct Dyes	Canada United States	Hazard characterization for a screening level risk assessment under Canada's Chemicals Management Plan
2	Repeat Dose Toxicity of Substituted Diphenylamines (SDPA)	Canada	Hazard characterization for a screening level risk assessment under Canada's Chemicals Management Plan
3	Hepatotoxicity of Allyl Ester Category	Japan	Hazard identification for a risk assessment under Japan's Chemical Substances Control Law
4	Bioaccumulation Potential of Biodegradation Products of 4,4'-Bis (chloromethyl)-1,1'-biphenyl	Japan	Assessment of bioaccumulation of new chemical substances under Japan's Chemical Substances Control Law

All of these case studies focus on application of IATA to grouping methods (read-across) and were developed based on actual cases of the regulatory use of IATA in the lead counties.

Template Used for the Case Studies

A template used for the case study was developed based on the reporting format in the OECD Guidance on Grouping of Chemicals [ENV/JM/MONO(2014)4].

1. Purpose
    1. Purpose of use
    2. Target chemical(s)/category definition
    3. Endpoint(s)
2. Hypothesis for the analogue approach/category
3. Source chemicals/Category members
    1. Identification and selection of source chemicals/category members
    2. List of source chemicals/ category members
4. Justification of data gap filling
    1. Data gathering
    2. Data matrix
    3. Justification
5. Strategy for and integrated conclusion of data gap filling
    1. Uncertainty
    2. Integrated conclusion

Case Study 2 (Summary)

Repeat Dose Toxicity of Substituted Diphenylamines (SDPA) [Canada]

Purpose of use: Hazard characterization for a screening level risk assessment under Canada's Chemicals Management Plan.

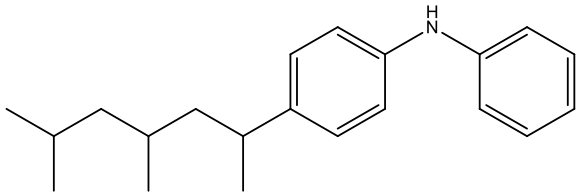
Hypothesis: Subgroups of SDPAs can be formed based on structural similarity and as a result, the substances exhibit a similar trend in physicochemical properties, oral bioavailability, and observed toxicological effects.

Justification: Similarity in structure, physicochemical properties and toxicokinetic parameters and metabolism; and trend in empirical toxicological data.

Data gap filling: A category for oral repeat dose toxicity consisting of 14 members of SDPA including UVCBs was formed. The category was subcategorized into 4 subcategories. The effect levels for six category members without test data were predicted by read–across within each subcategory.

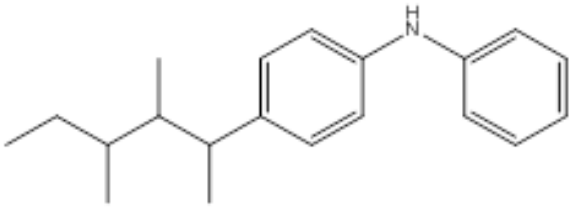
Case Study 2 (Example of Subcategory)

Monoalkylated SDPAs



(mixture of isomers)

With RDT Data



Without RDT Data

Case Study 2 (Examples of Review Comments)

Strongest aspect:

- Provides an example of application of read-across for UVCB chemicals
- Multiple justification considerations were demonstrated using the available information.

Comment for revision:

- Subgroups should be used to better account for observed or potential differences in chemical structure, physicochemical properties, bioavailability and systemic effects.
- Descriptions of similarity in toxicological effects of the category members were insufficient.
- How to assign the qualitative labels (Low/Medium/High) of uncertainty was not clear. (→ Use of descriptive language instead of labels)

Uncertainty:

- Potential impacts of the structural differences of subcategory members on toxicity.
- Level of similarity in metabolism, physicochemical properties and toxicokinetics parameters, for which not much empirical data is available.

Case Study 4 (Summary)

Bioaccumulation Potential of Biodegradation Products of 4,4'-Bis (chloromethyl)-1,1'-biphenyl [Japan]

Purpose of use: Assessment of bioaccumulation potential of biodegradation products of new chemical substances under Japan's Chemical Substances Control Law (CSCL).

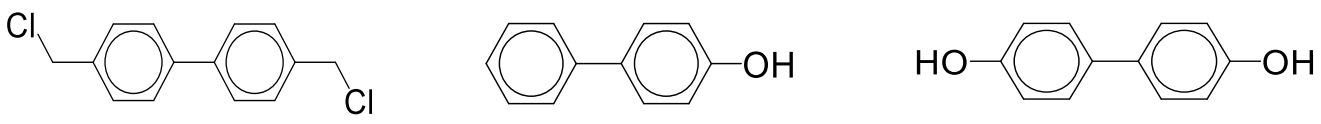
Hypothesis: Bioaccumulation potential of the specified analogues of substituted biphenyl compounds are similar.

Justification: Structural Similarity, QSAR prediction results, HPLC data, similarly.

Data gap filling: The bioaccumulation potentials of Targets 1-4 are qualitatively evaluated as “Low - Not highly bioaccumulative" in CSCL criteria.

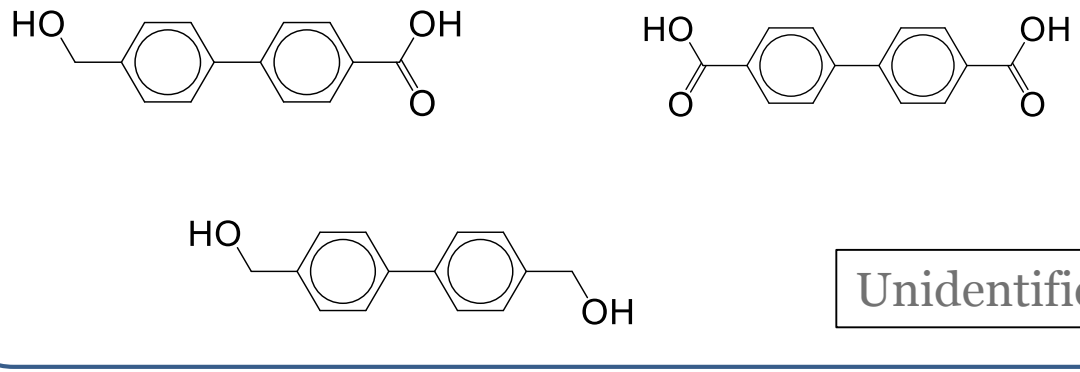
Case Study 4 (Source and Target Chemicals)

Source chemicals (with BCF data)



Metabolite

Target chemicals (without BCF data)



Unidentified

Case Study 4 (Examples of Review Comments)

Strongest Aspect:

- The link (via degradation) to the parent chemical including the effective way to use the HPLC data for estimating bioconcentration potential of metabolites.
- Good correlation between the experimental BCF values and the QSAR predicted values for the more structure similar source chemicals ensures the reliability of the prediction result of the target chemicals.

Comment for Revision:

- Reporting of QSAR prediction (e.g. Possible reason for why the (Q)SAR prediction BCF values of one of the source chemicals are much higher than the experimental value should be explained.)
- The bioaccumulation potential of one target chemical with unknown structure was assessed by read-across without any consideration of the chemical structure. (→ Use of metabolic simulator in QSAR Toolbox)

Uncertainty:

- Uncertainty related to the potential differences between bioaccumulation and bioconcentration that would result depending on the route of exposure.

Examples of the Topics in the OECD Guidance on Grouping of Chemicals Illustrated by the Case Studies

Topics in the Grouping Guidance	Case Study
2.3.2. Category and subcategory membership and applicability domain 2. Subcategories	2, 3
2.4. The mechanistic basis of using analogues or chemical categories	1, 3
3.4. Computational methods based on external models	1, 2, 4
6.2. Metabolic or degradation pathways and toxicokinetics	1, 2, 3, 4
6.6.1 General guidance on developing categories for organic UVCBs	2
7.1. Reporting Format for analogue approach	4

Identified Areas for Further Developing Guidance

1. Building hypotheses based on MOA/AOP
2. Definition of analogues/category boundaries
3. Justification of data Gap filling
4. Uncertainty Analysis
5. Integrated Conclusion

Area 1: Building Hypotheses Based on MOA/AOP

- More elaborated hypotheses would strengthen the similarities (and potential differences) with respect to target endpoints of the category members
- Uncertainties regarding human or environmental relevance identified in the case studies could be clarified with MOA/AOP
- Strengthening the mechanistic basis of the case studies will lead to extend the use of the case studies.
- OECD has published guidance for developing AOPs [ENV/JM/MONO(2013)6] and a number of AOPs are under development.
    - expected that AOPs can be applied to support grouping methods, however there is a need to continue to demonstrate how to incorporate AOP information in IATA

Area 2: Definition of Analogues/Category Boundaries

- There is a need to have more detailed description on the definition of the structural boundaries and physicochemical properties of the analogues.
- How to describe clear category boundaries is common issue for all endpoints.
- Most case studies lacked a discussion on the structural differences in the chemical structures of analogues whereas their structural similarities were well discussed.
- Several useful tools such as OECD QSAR Toolbox to identify substructures leading to a variation in toxicological effect.
    - However, acceptable structural differences for analogues are typically defined by expert judgement and should be documented.

Area 3: Justification of Data Gap Filling

From the review results of the four case studies the following specific issues were identified in this area.

- How to describe the similarity/trend of the observed effect of the target endpoint (e.g. repeated dose toxicity endpoints).
- The extent of data related to the target endpoint to be used in the data-gap filling justification (e.g. other endpoint/species data)
- How to incorporate new types of in vitro data
- How to report QSAR prediction results
- How to integrate data derived from different methods or models

Area 4: Uncertainty Analysis

- Each case study contains different uncertainties since the data or the resources to be used for the case studies are limited under each regulatory context.
- Uncertainty analysis helped the reviewers to consider the impacts of uncertainty with respect to the purpose of use of the case studies and to consider the acceptable degree of uncertainty to the specified purposes.
- The importance of uncertainty communications is recognized and identified as a high priority area for gaining further experience in the IATA case studies context and then further developing guidance.

Area 5: Integrated Conclusion

- The case studies were developed based on use in certain regulatory contexts of the lead countries.
- Possible challenges in applying the results in other regulatory contexts.
- From the experience, it was recommended that if the purpose of the case study is very specific, general conclusion for other purposes could be separately described.
- In addition, it would be helpful to develop guidance on how the methodology could be combined with other approaches in order to apply it in different regulatory frameworks.

Summary (1)

- Case studies based on actual use in the lead countries provided concrete examples of how to use the grouping methods in a regulatory context.
- This experience provided insight into the importance of considering the difference between pragmatic approaches for a specified purpose and perfect read-across.
- Understanding of the background of the regulatory framework and purpose of the case study helped the reviewers to explore the issues in practical use of the methods.
- Comparison between case studies with different purposes and target endpoints helped to identify common challenges with grouping methods, which were shared between the member countries.

Summary (2)

- The experience gained and shared through these case studies demonstrates the value of working collaboratively through case studies as a promising way for expanding the use of alternative methods in the member countries.
- Recognized that more case studies are needed for developing guidance.

The four case studies reviewed in 2015 and a considerations document with the case studies are expected to be published within a few months after getting approval of member countries
http://www.oecd.org/chemicalsafety/

Nominated Case Studies for Second Review Cycle [2016]

1. Structure Related Repeated-Dose Toxicity Profiles Assessment, by Using Toxico-Genomics Data [Japan]

2. Pesticide Cumulative Risk Documents [United States]

3. An Endocrine IATA Example for Estrogenicity [BIAC]

4. 90-Day Rat Oral Repeated-Dose Toxicity for Selected n-Alkanols: Read-Across [ICAPO] (SEURAT-1)

5. 90-Day Rat Oral Repeated-Dose Toxicity for Selected 2-Alkyl-1-alkanols: Read-Across [ICAPO] (SEURAT-1)

Further Information

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