Endocrine disruptors: Learnings (recommendations) for grouping and read-across approaches

Eva Bay Wedebye and Marie Louise Holmer
Technical University of Denmark (DTU), National Food Institute

Environmental Endocrinology, 2026, **2**, wkaf004
https://doi.org/10.1093/enendo/wkaf004
Advance access publication 18 December 2025
Commentary

Endocrine disruptors: recommendations for grouping and read-across approaches

Marie Louise Holmer,[1,*] Rikke Donchil Holmberg,[1] Marta Axelstad,[1] Anna Opstrup Bindel,[1] Ana Caroline Vasconcelos Engedal Nissen,[1] Terje Svingen,[1] and Eva Bay Wedebye[1]

[1]National Food Institute, Technical University of Denmark, Kgs. Lyngby DK 2800, Denmark





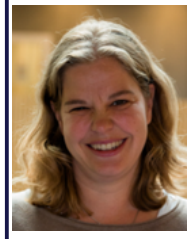
- Marie Louise Holmer



- Rikke Holmberg



- Anna Opstrup Bindel



- Marta Axelstad Petersen



- Ana CV Engedal Nissen



- Eva Bay Wedebye

Background

EU focus on grouping and read-across, examples from European COM documents:

- The EU Commission's Chemicals Strategy for Sustainability (2020) aims to implement a **generic risk management approach** to restrict the use of the most harmful substances, including endocrine disruptors (EDs), from use in consumer products
- Until in place, restrictions for all uses and **through grouping**, instead of regulating them one by one

- Several initiatives underway to identify ED groups, including the **Restrictions Roadmap** and ECHA's **Assessment of Regulatory Needs** (ARNs)

- **ED hazard classes in the EU CLP** regulation (2023)



Picture from Microsoft power point stock images

Nordic Council of Ministers project, purpose



Picture from Microsoft power point stock images

- **Competence building** on grouping of EDs in the (Nordic) chemicals authorities

➢ Ultimate goal to minimise negative effects on humans and the environment from exposure to EDs

➢ **Evaluation of 5 examples** of groupings to pursue **insights / learnings**

Methodology

Disclaimer

- The **5 examples analysed**:
  - Bisphenols
    - ECHA Assessment of Regulatory Needs (ARN) 2021
    - Restriction proposal (ENV) 2022
    - Comparative study (Kitamura et al. 2005)
  - Isobutyl paraben SVHC dossier 2022
  - Brominated Flame Retardants (not ED, learning example) 2016

- **Frameworks** used for systematic analyses:
  - OECD Guidance Document 194 on grouping (2017)
  - ECHA Read-across Assessment Framework (2017)

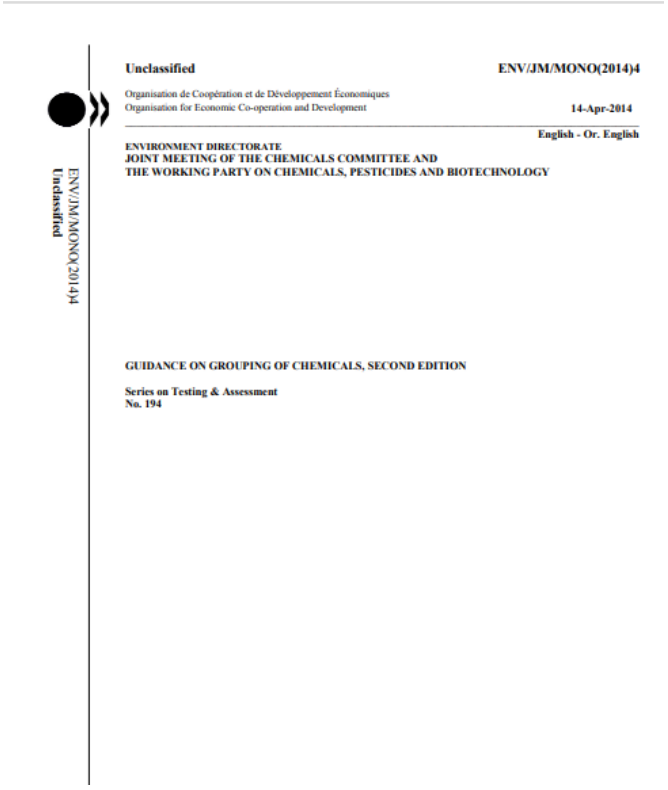
➢ **Discussion/learnings** of advantages, challenges, uncertanties, regulatory perspectives

➢ **NB** Not all examples were intended to fill data gaps using read-across but were analysed as if they were, and purpose not to evaluate/criticize but to learn



Picture from Microsoft power point stock images

OECD Guidance 194 on Grouping of Chemicals



Unclassified ENV/JM/MONO(2014)4

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

ENV/JM/MONO(2014)4
Unclassified

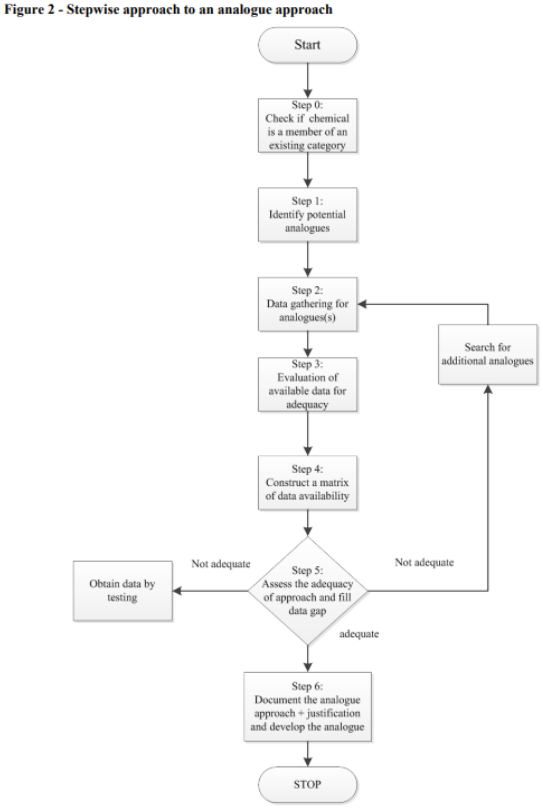
GUIDANCE ON GROUPING OF CHEMICALS, SECOND EDITION

Series on Testing & Assessment
No. 194

OECD (2017), Guidance on Grouping of Chemicals, Second Edition, OECD Series on Testing and Assessment, No. 194, OECD Publishing, Paris, https://doi.org/10.1787/9789264274679-en

- **Guidance, stepwise procedures and reporting formats** for different types of grouping approaches
- Aims to support development of grouping and read-across for use in hazard or risk assessment of substances
- Draws on approaches known to have been accepted by regulators or have been developed by regulators or registrants under voluntary programs

Analyses based on the OECD Guidance



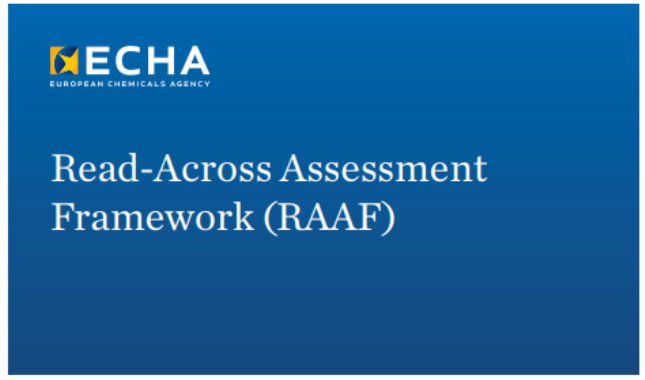
OECD (2017), Guidance on Grouping of Chemicals, Second Edition, OECD Series on Testing and Assessment, No. 194, OECD Publishing, Paris, https://doi.org/10.1787/9789264274679-en

Each case example evaluated against individual guidance steps:

- Was the step performed?
- If yes: Did the case example follow the recommendations for that step?

ECHA RAAF

- Framework and guidance for **consistent evaluation of the scientific aspects** of a proposed read-across case
- Read-across and grouping can be used to **adapt the standard testing regime** in REACH when the prediction is reliable, can be used for risk assessment and/or classification and labelling, and complies in general with the provisions
- 2026: Among the available adaptations for REACH-registered substances, read-across was the most commonly used (**24.4%**,https://echa.europa.eu/documents/d/guest/1173_report_use_of_alternatives_to_animal_testing_2026)



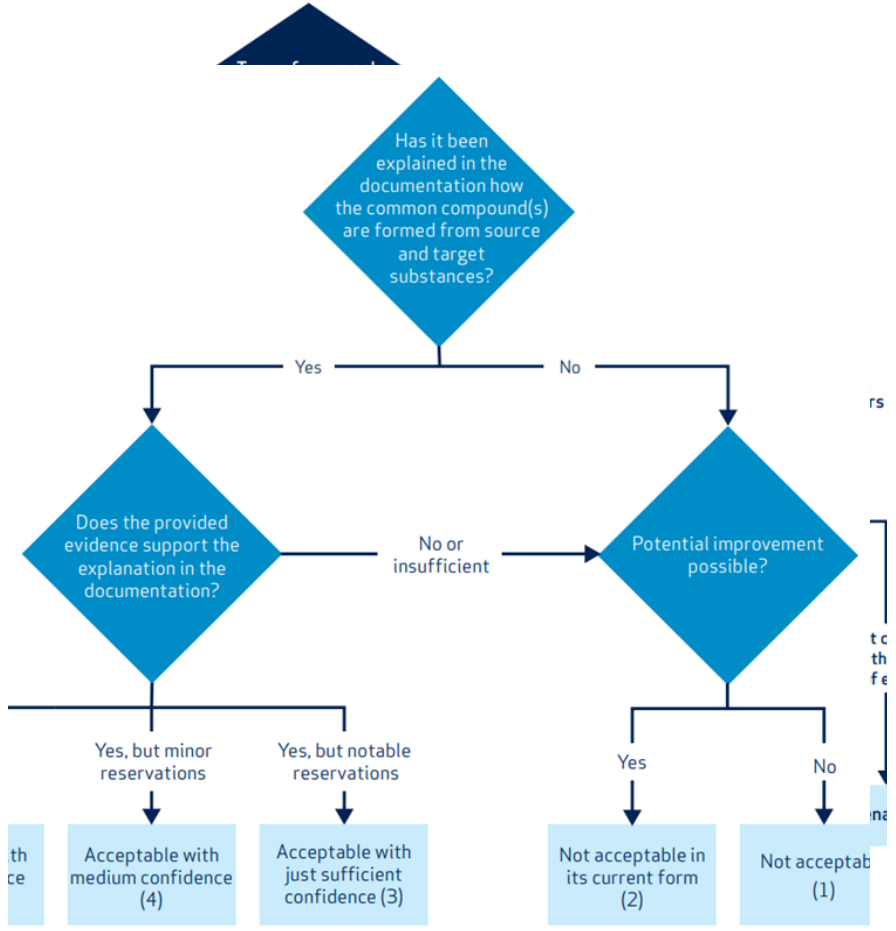


https://echa.europa.eu/documents/10162/17221/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a

Analyses based on the ECHA RAAF

Each case example evaluated against individual Assessment Elements (AEs):

- Was the task performed?
- If yes: Level of acceptability evaluated using flow diagram in RAAF



Overall learnings, general

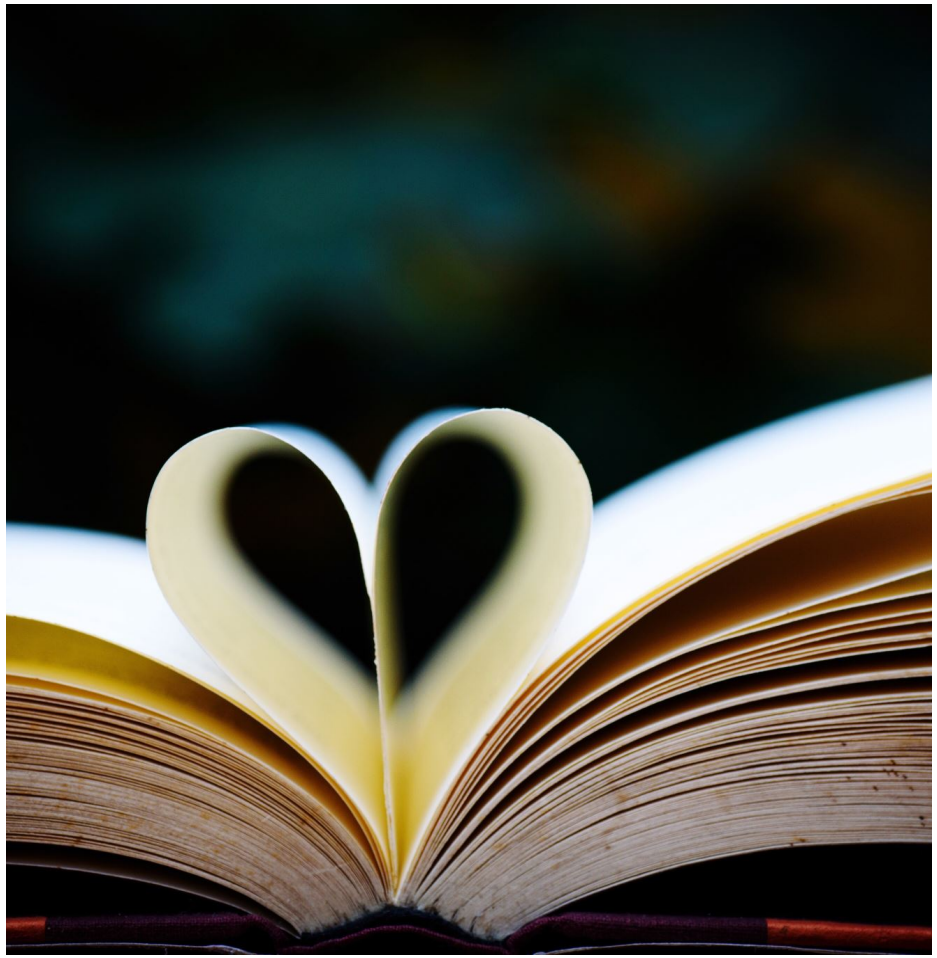
- The ECHA RAAF and OECD GD are **very useful** to guide grouping/read-across
- Category approach: Good to start with (too) **broad groups** to find boundaries, then make clear definition of boundaries / define all theoretical structures within the category, **irrespective of (current) regulatory domain and use profile**
- Data rich substances such as PPPs, BPs and REACH high-tonnage and SVHC ones are important **source substances**,
- If possible, obtain **regulatory assessment of potential source substances** if missing



Source: Microsoft power point stock images

Overall learnings, ED-specific

- **Data matrices** with detailed substance characterizations, *in silico, in vitro, in vivo* data for adversity, mechanistic and kinetic/ADME information, special focus to accurately capture:
  - Consideration of **complex hazard profiles** with possible non-monotonic dose–response curves, low-dose effects, mechanism-specific effect profiles that vary depending on the exposure timing, dose levels, and time point of effect assessment
  - Many EDs act through **more than one mode/mechanism of action** which may lead to the same adverse effect, analyse possible sub-groups for different MoA
  - Experimental *in vivo* adversity data may be available for fewer source substances but ***in vitro* MoA data** may be available for more substances to investigate trend
  - Integration of **data across relevant species**, such as mammals, birds, fish, and amphibians (increased focus in regulatory ED evaluations)

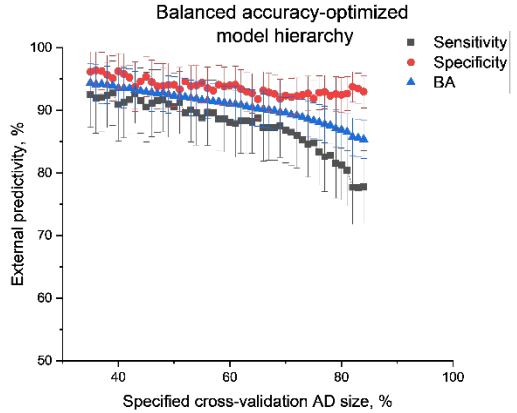


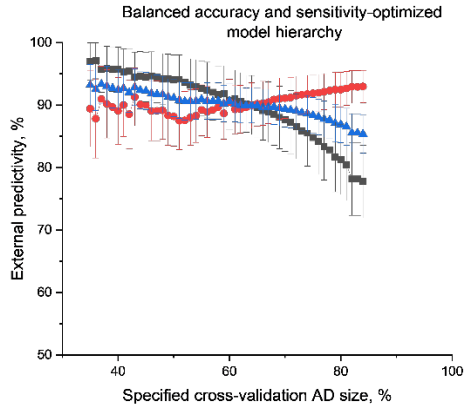
Source: Microsoft power point stock images

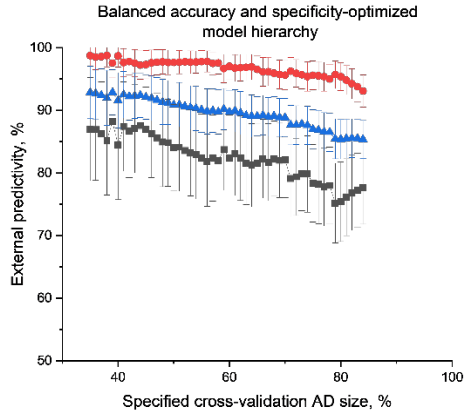
Overall learnings, (Q)SARs

- (Q)SARs can contribute e.g. regarding:
  - Develop read-across **hypothesis/justification**
  - Identifying molecular **sub-structures and other properties** of relevance for **MoA** in source and target substances, use complementary methods incl. docking
  - Investigating/defining **boundaries** of grouping, including for expanding / decreasing / sub-categorizing the group
  - Predicting **all theoretical members** within the structural domain spanned by source substances
  - In some cases, predicting not only AOP MIE and early KEs but also **late KE and AO**
  - Predicting KEs across an AOP and **compare alerts + other properties** predicted to be important
  - Predicting **impurities and metabolites/degradants**

- More (Q)SARs needed for ***in vivo*** **ED-related hazard** endpoints (e.g. specific reproductive and organ toxicity endpoint – NB in some cases based on **human** clinical data)
- More QSARs – based on high-quality curated data - needed for AOP MIE/KE/AO **continuous endpoints** (potency, such as PoD)








SAR AND QSAR IN ENVIRONMENTAL RESEARCH
2025, VOL. 36, NO. 5, 365–391
https://doi.org/10.1080/1062936X.2025.2510964

Taylor & Francis

OPEN ACCESS

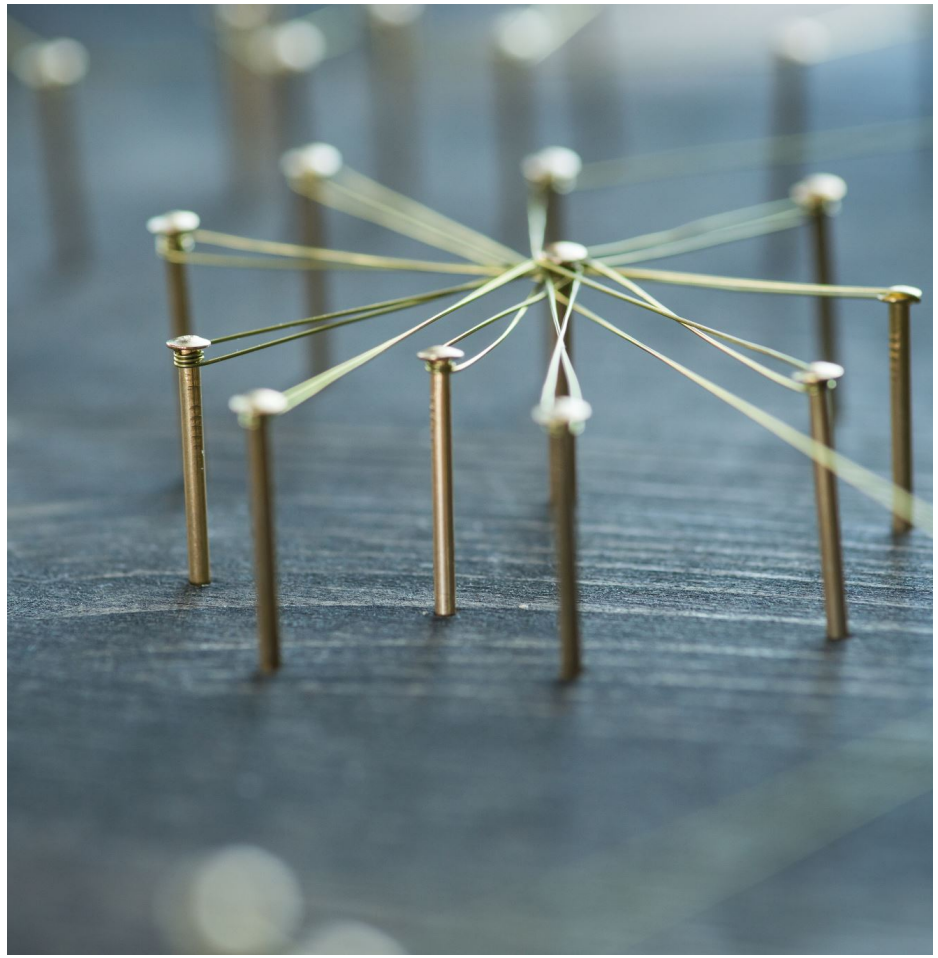
High performance, large chemical coverage or both: DanishQSAR and hierarchies of post-hoc ensemble models optimized for sensitivity, specificity or balanced accuracy

N.G. Nikolov and E.B. Wedebye

DanishQSAR mothod publication, DNT models manuscript in prep.

External 50*5-fold cross-validation results from RiskHunt3R DTU DanishQSAR models for DNT *in vivo*, N= 860 (302 positives and 558 negatives)

Thank you for your attention
Questions?



Source: Microsoft power point stock images

Acknowledgement of financial support:

Nordic project:

- Nordic Council of Ministers, NKE Nordic Working Groups for Chemicals, Environment and Health

Scientific paper:

- Danish EPA


DTU