READ-ACROSS AS STRUCTURE ACTIVITY RELATIONSHIP IN RISK ASSESSMENT

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HUMAN HEALTH RISK ASSESSMENT

Risk ?

Exposure

X

Hazard

Historical safety data

Non-animal

- We **assess risk** to prevent adverse events in consumers
  - **What risk does ingredient X at conc. Y in product Z pose to the consumer?**
- To do so we require
  - **Exposure data – product relevant consumer exposure scenario**
  - **Hazard Characterisation data – dose response information on potency**

METHODS FOR HAZARD IDENTIFICATION & CHARACTERISATION

- Clinical data / human experience – the gold standard
- Historical *in vivo* non-human – species variability leading to question of transferability to human
- *In vivo* read-across – currently widely accepted alternative
- *In chemico & in vitro* – accepted in some cases – genotoxicity, HepG2, endocrine activity etc.

READ-ACROSS

- is a data gap filling technique within an analogue or category approach
- can be qualitative or quantitative
- forms part of the continuum of non testing approaches such as (Q)SAR
- is best used as part of weight-of-evidence approach

WHY READ-ACROSS?

- Endpoint information (from a study) for one or several substances (i.e. the source analogue) are used to predict the same endpoint for a "similar" untested substance (i.e. the target analogue)

- It potentially avoids the need for animal testing

- It is used as part of weight-of-evidence in a risk assessment

THE MOST CRITICAL ISSUE IN READ-ACROSS

- **is the justification of analogue(s) selection for the read-across (i.e., explaining the basis of chemical similarity on which the selection is based)**

- **is a recurring issue because similarity is typically assessed in a subjective manner**

SIMILARITY: COMMON CHEMICAL CONSIDERATIONS

1. Physico-chemical & molecular properties

2. Substituents, functional groups & structural fragments

3. Statistical similarity based on graph theory

SIMILARITY: COMMON BIOLOGICAL CONSIDERATIONS

1. **General considerations**
   - Bioavailability, Reaction chemistry, Metabolism
2. **Endpoint specific considerations. These will be informed by:**
   - **Structural alert for chemical-biological interaction**
   - ***In chemico* & *in vitro* data relevant to the read-across endpoint(s) both of which are anchored in the Adverse Outcome Pathway (AOP) construct**

EXPLAINING SIMILARITY

The aim:

is to explain the basis for similarity between the target chemical and potential source chemical(s) for an endpoint-specific read-across exercise in a robust and reliable manner

Answer:

How the chemicals are similar and why that similarity is important

FRAMEWORK FOR EXPLAINING SIMILARITY- I

needs to be:

1. **robust so it can be applied to any discrete organic substance,**
2. **flexible so it can be tailored to any toxicological endpoint, and**
3. **transparent enough to easily explain the outcome of the exercise to scientific and regulatory experts.**

FRAMEWORK FOR EXPLAINING SIMILARITY- II

needs to include:

1. **an evaluation of all types of chemical similarity,**
2. **where possible an evaluation of types of biological similarity, and**
3. **identify the seminal similarities to the read-across exercise.**

FRAMEWORK FOR EXPLAINING SIMILARITY- III

Many *in silico* systems (e.g., OECD QSAR Toolbox), provide helpful starting points for assessing similarity.

OECD, 2018. The OECD QSAR Toolbox, v.4.2 http://www.qsartoolbox.org/

UNCERTAINTY IN READ-ACROSS

may arise from several sources including:

1) **The quality of the study data for the source analogues,**
2) **The level of completeness of the data matrix for the source and target analogues,**
3) **The strength of the association between the chemistry and the biological endpoint,**
4) **The concordance and consistency in effects and potency of the endpoint under consideration and across other endpoints.**

It is key to explain the type(s) and degree of uncertainty for a read-across.

FRAMEWORK FOR ASSESSING UNCERTAINTY

needs to:

1. **Describe the rationale in a transparent manner.**
2. **Document the logic so it can be recreated.**
3. **Separate data uncertainty from read-across uncertainty.**
4. **Clarify the role of endpoint specific and endpoint non-specific factors in the assessment.**

READ-ACROSS FRAMEWORKS

- **Frameworks based on weight-of-evidence assessments in the context of "reproducible" and "transparent" are being developed**
- **RAAF (Read Across Assessment Framework)**
  - **a tiered systematic approach, developed by ECHA to facilitate its internal evaluation of read-across**

ECHA, 2016. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf

- **Framework developed by Wu, Blackburn and coworkers**
  - **Wu et al. (2010) Reg Tox Pharm 56: 67-81**
  - **Blackburn et al. (2011) Reg Tox Pharm 60: 120-135**
  - **Wu et al. (2013) Chem Res Toxicol 26: 1840-1861**
  - **Blackburn et al. (2014) Reg Tox Pharm 68: 353-362**

MUSTS & PREFERENCES FOR READ-ACROSS EXERCISES

Must have high quality data for read-across analogue(s).

Must be able to define the chemical similarity.

Must have some indication of biological similarity.

Prefer chemical category rather than single analogue.

Prefer a hypothesis-based prediction.

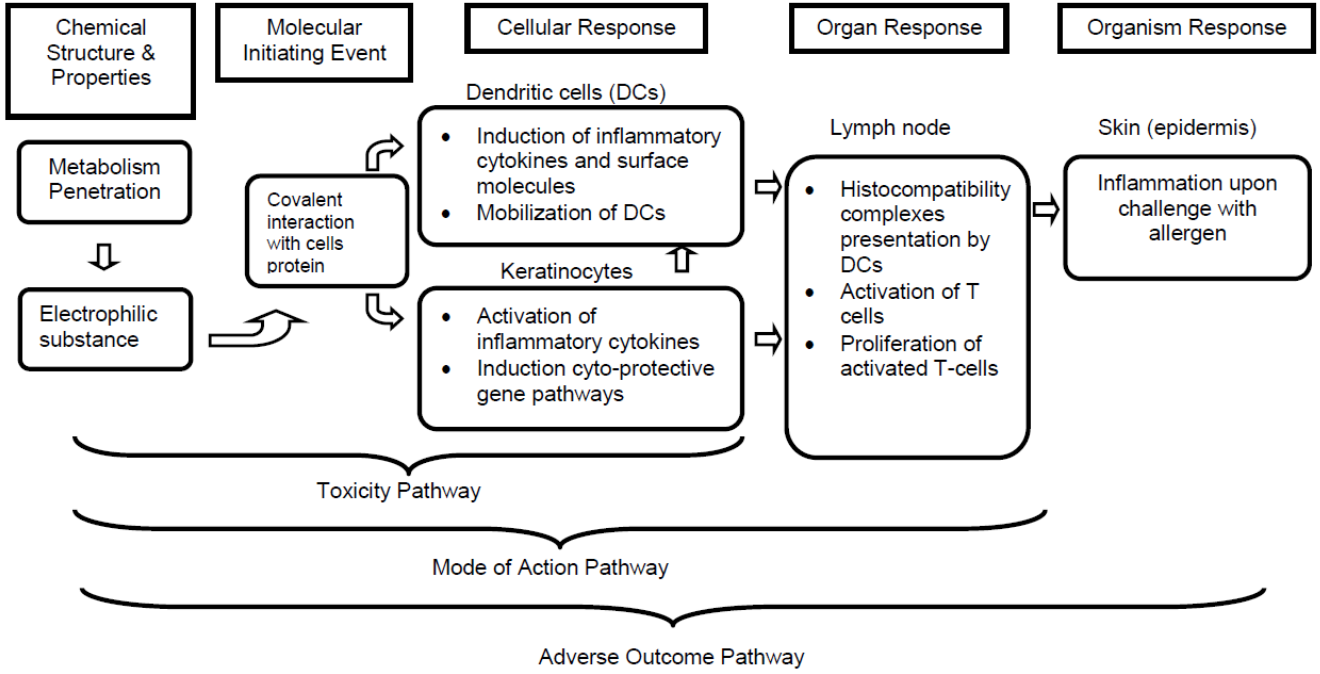
DOCUMENTATION OF A READ-ACROSS SHOULD INCLUDE

1. read-across hypothesis;
2. justification for the read-across hypothesis;
3. list of all the substances included in the approach;
4. list of identity information of all substances included in the approach (including the impurities);
5. list of the endpoint(s) that are to be read-across;
6. data matrix;
7. conclusion on the applicability of the proposed read-across approach on an endpoint basis.

READ-ACROSS FOR SKIN SENSITISATION – ACCEPTED?

1. **Mechanistic understanding of skin sensitisation – widely accepted**
2. **AOP for skin sensitisation – available and sufficient for different purposes**
3. **Chemical & Biological similarity – defined by mechanistic chemistry**
4. **Reducing uncertainty – possible by generating *in chemico* & *in vitro* data which characterise Key Events in the AOP**

AOP FOR SKIN SENSITISATION

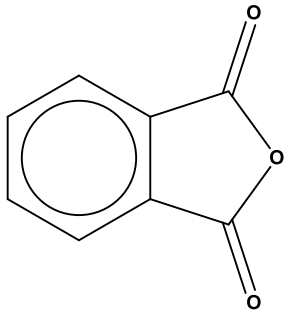


As cited in the OECD document ENV/JM/MONO(2012)/PART2.
More work is underway (Maxwell et al. (2014) Toxicology in Vitro 28(1))

SKIN SENSITISATION READ-ACROSS - REDUCING UNCERTAINTY

Criteria	No	Maybe	Yes
1. Is reaction mechanism known and understood?			
2. Are sufficient read-across analogue(s) within the same mechanistic domain and range of potencies available?			
3. Are the physicochemical properties of the read-across analogues(s) a good match for the target chemical?			
4. Are the skin sensitisation potency data for the read across analogue(s) of sufficient quality?			

READ-ACROSS CASE STUDY

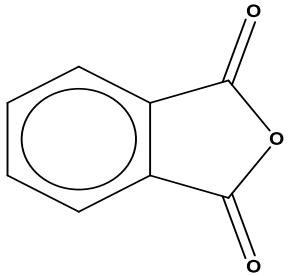


Phthalic Anhydride
Sensitisation Potency: ??
Log P = 1.6

Criteria	No	Maybe	Yes
1. Is reaction mechanism known and understood?			Acyl Transfer Agent (high confidence*)

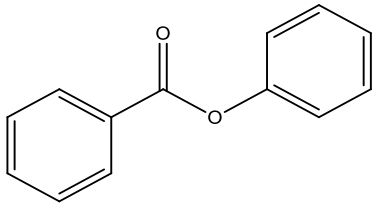
*if confidence is low – perform chemistry experiment to determine the reaction mechanism

READ-ACROSS CASE STUDY

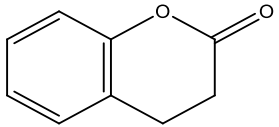


Phthalic Anhydride
Sensitisation Potency: ??
Log P = 1.6

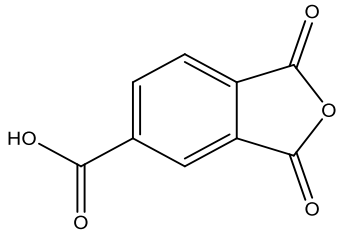
Criteria	No	Maybe	Yes
2. Are sufficient read-across analogue(s) within the same mechanistic domain and range of potencies available?			X



Phenyl benzoate
Potency: Weak

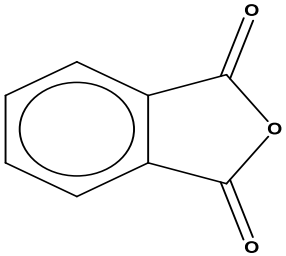


Dihydrocoumarin
Potency: Moderate



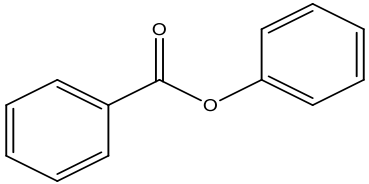
Trimellitic Anhydride
Potency: Moderate

READ-ACROSS CASE STUDY

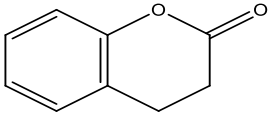


Phthalic Anhydride
Sensitisation Potency: ??
Log P = 1.6

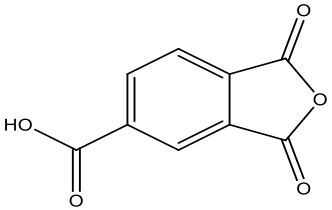
Criteria	No	Maybe	Yes
3. Are the physicochemical properties of the read-across analogue(s) a good match for the target chemical?		X Needs consideration	



Phenyl benzoate
Potency: Weak



Dihydrocoumarin
Potency: Moderate

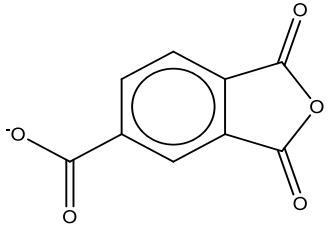


Trimellitic Anhydride
Potency: Moderate

REDUCING UNCERTAINTY

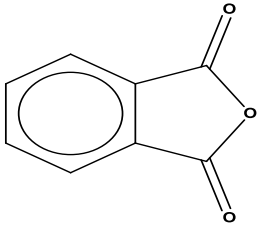
1. **Acyl transfer agents - the LLNA potency depends not only on reactivity, but also on log P - hard electrophiles (e.g., SB, SN2) show log P dependent potency explained by the argument that they react with membrane bound proteins.**
2. **Chemicals which have same reactivity but hugely different log P values, will have different LLNA potency.**
3. **Therefore for read-across purposes analogue(s) should be chosen based not only on EC3 and available human data, but also log P.**

REDUCING UNCERTAINTY



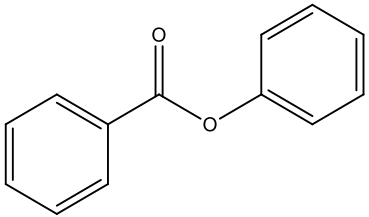
- pKa for trimellitic anhydride is 3.49
- At skin pH = 5.5, amount ionized will be >99%
- Therefore, the log P for this form is -4.03

READ-ACROSS CASE STUDY



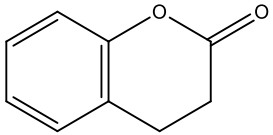
Phthalic Anhydride
Sensitisation Potency: ??
Log P = 1.6

Criteria	No	Maybe	Yes
3. Are the physicochemical properties of the read-across analogue(s) a good match for the target chemical?	Trimellitic Anhydride – not a good analogue		



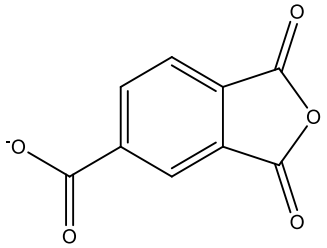
Phenyl benzoate

Potency: Weak
ClogP = 3.6



Dihydrocoumarin

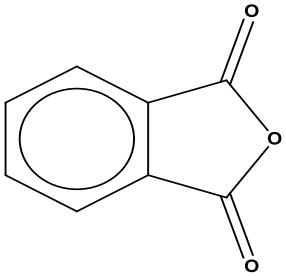
Potency: Moderate
ClogP = 1.6



Trimellitic Anhydride

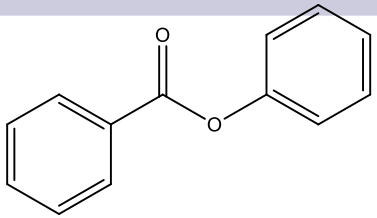
Potency: Moderate
ClogP = -4.03

READ-ACROSS CASE STUDY

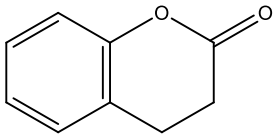


Phthalic Anhydride
Sensitisation Potency: ??
Log P = 1.6

Criteria	No	Maybe	Yes
4. Are the skin sensitisation potency data for the read-across analogue(s) of sufficient quality?			X LLNA & HRIPT data

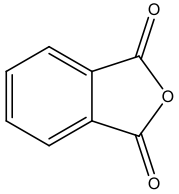


Phenyl benzoate
Potency: Weak



Dihydrocoumarin
Potency: Moderate

READ-ACROSS CASE STUDY -CONCLUSION

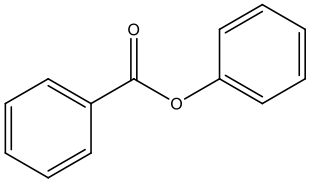


Phthalic anhydride

Historical data
Sensitisation potency (human) - no data
Potency (LLNA): Strong

$k = 1.5\ E\text{-}3\ [mM^{-1}s^{-1}]$

Read-Across Potency: Strong/Extreme

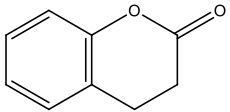


Phenyl benzoate

Sensitisation potency (human) - "class 3"*

Potency (LLNA): Weak

k - too slow to measure



Dihydrocoumarin

Sensitisation potency (human) - no data

Potency (LLNA): Moderate

$k = 9\ E\text{-}6\ [mM^{-1}s^{-1}]$

* Basketter et al. (2014). Dermatitis, 25(1)

SUMMARY

1. **In the near-term, read-across is the primary means of filling data gaps without additional *in vivo* testing.**
2. **Outcome used for many purposes – human health risk assessment, REACH etc.**
3. **Frameworks for assessing 'similarity' and 'uncertainty' will aid in providing consistency, efficiency and transparency to read-across exercises.**
4. **Integration of additional empirical data (*in vitro, in silico*, omics) should strengthen confidence in read-across assessments and ultimately allow us to expand actionable chemical domains.**