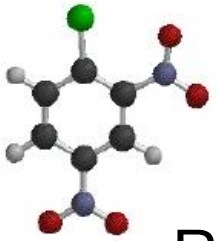
READ-ACROSS: MOVING FROM INTELLECTUAL ACCEPTANCE TOWARDS PRACTICAL APPLICATION

NORA APTULA

HUMAN HEALTH RISK ASSESSMENT

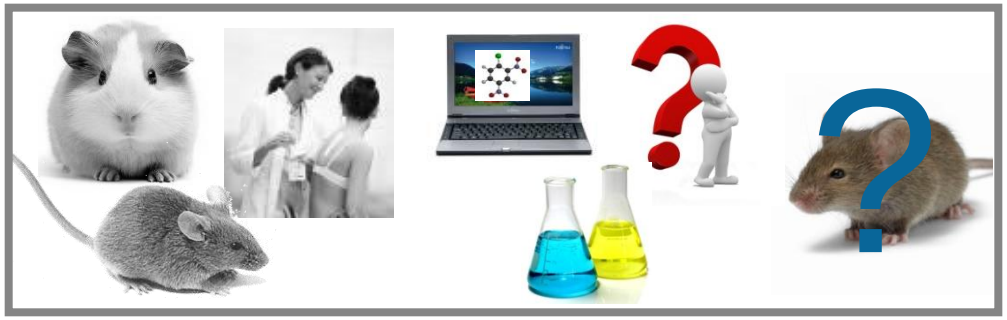


Risk ?

Exposure

&

Hazard



Historical Non-animal *In Vivo*

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**

RISK ASSESSMENT TODAY: AVAILABLE METHODS FOR HAZARD IDENTIFICATION & CHARACTERISATION

Clinical data / human experience – the gold standard

In vivo – variability, error, human validity (transferability)

Basketter *et al.* "Nothing is perfect, not even the local lymph node assay: a commentary and the implications for REACH" *Contact Dermatitis.* 2009, **60**, 65-69

Gottmann et al. "Rat and mouse bioassays don't always provide the same results in terms of carcinogenicity (i.e. low reproducibility)" *Environ Health Perspect. 2001,**109**, 509-514*

In vitro – accepted alternative…..how good is it?

In chemico & in silico (Read-across) – not yet widely accepted…why?

IN SILICO BASED ASSESSMENTS – LESS CERTAIN?

- **Often hazard characterization of a chemical is based on a single test study.**

- **Many factors affect the *in vivo* test outcome. Time consuming, expensive, animal welfare etc.**

- **Quantitative mechanistic models and read-across estimates can provide greater confidence than a single animal study.**

DRIVING FORCES FOR PRACTICAL APPLICATION OF READ-ACROSS

REACH Annex XI - Section 1.5 “Grouping of substances and read-across approach”

“Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or ‘category’ of substances. Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint.”

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**

Framework developed by P&G

- **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**

- **Framework in development by CEFIC LRI's read-across team (LERAT)**
  - **characterising scientific confidence for all REACH endpoints**

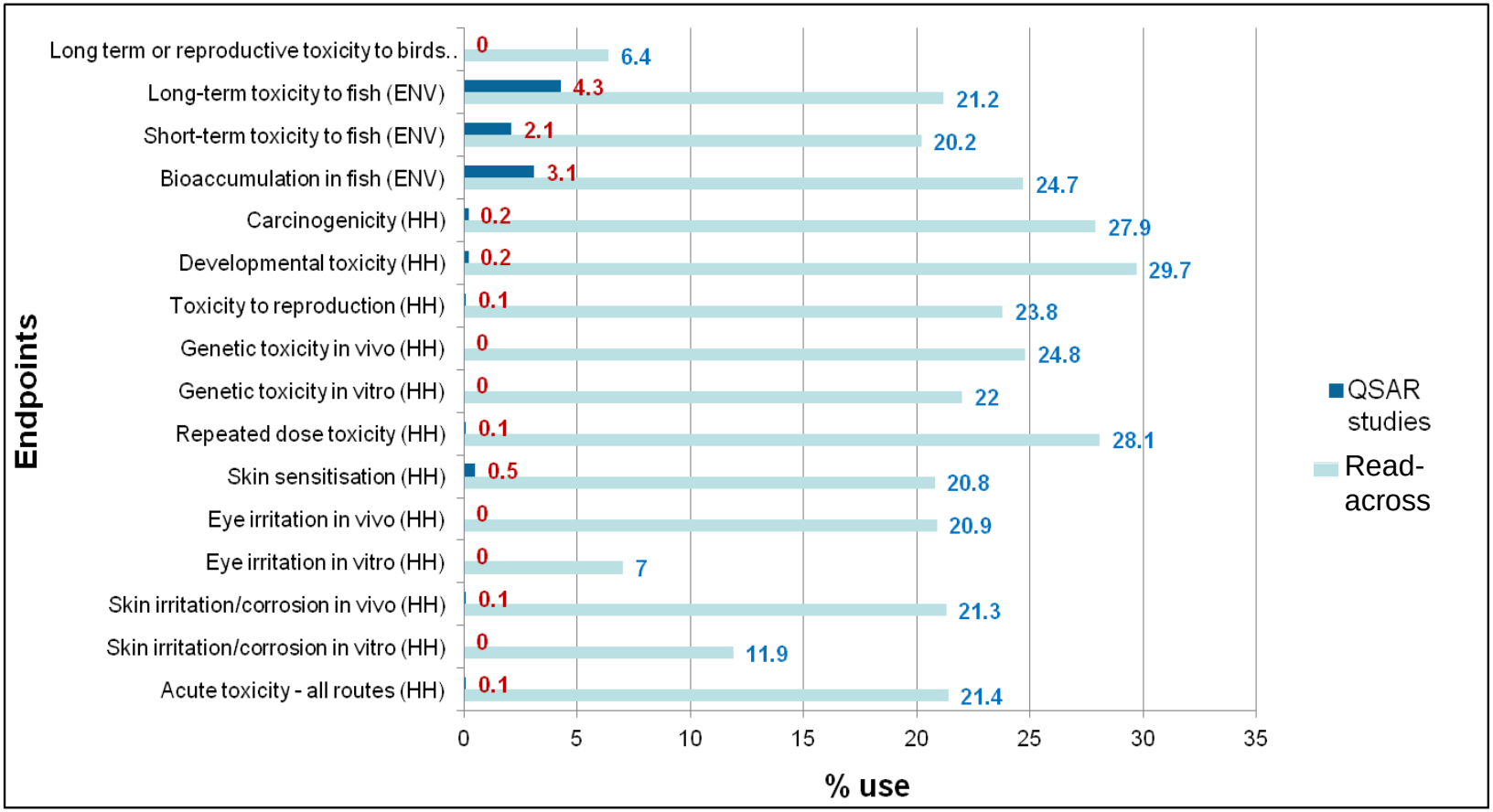
WHY DISCUSS READ-ACROSS?

- **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 reduces animal testing**

- **It is the primary non-testing approach to fill data gaps needed to meet the information requirements under REACH**

QSAR AND READ-ACROSS METHODS USED FOR REACH PHASE-IN SUBSTANCES ≤ 1000 TPA



WORKING DEFINITIONS

- **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**

WORKING DEFINITIONS

Techniques for grouping chemicals:

1. Analogue approach

- based on a limited number of chemicals

- too few chemicals to study trends in properties

2. Category approach

- based on more chemicals

- enough chemicals to study trends in properties

WORKING DEFINITIONS

- **A chemical category is a group of similar chemicals.**

- **Similarity means “likeness”.**

  No accepted means of defining chemical similarity.

READ-ACROSS – PRACTICAL APPLICATION

- **One way of moving read-across from intellectual acceptance towards practical application is to have some agreed upon guiding principles.**

- **As a first step, I will present what I view as the critical issues in read-across.**

FIRST ISSUE - IN VIVO DATA

- **Read-across requires experimental data.**

- **Different formats of sources of data/ information.**

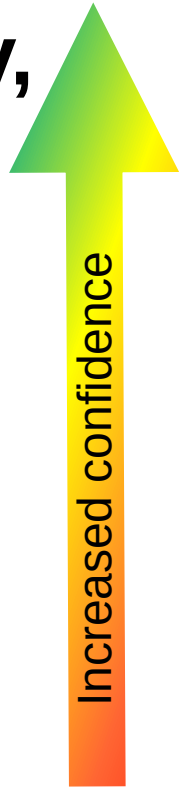
- **Finding chemicals with existing experimental data; assessing the quality of the data, sharing the proprietary data etc. will likely be a limiting factor to read-across in the near term.**

SECOND ISSUE - CHEMICAL SIMILARITY

- **What is chemical similarity?**
- **The identity of a chemical is defined by a variety of structural factors.**
- **No simple similarity scale.**
- **In the extreme each chemical is its own category.**

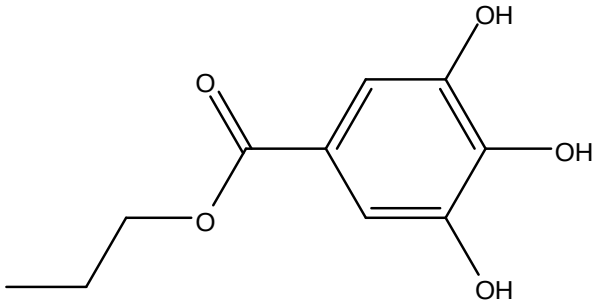
SIMILARITY IN FORMING CHEMICAL CATEGORIES FOR TOXICITY

- Common mechanism of toxicity,
- Common metabolism,
- Functional groups,
- 2D molecular similarity.



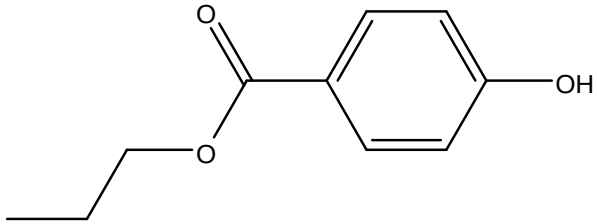
READ-ACROSS BASED ON STATISTICAL SIMILARITY (2D SIMILARITY)

- **Chemicals which are “similar” in molecule structure are often dissimilar in terms of toxicity, including both the ability to elicit a particular hazard, as well as potency within that hazard.**



propyl gallate

EC3 = 0.32%



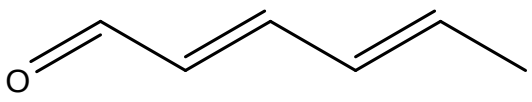
propyl paraben

non-sensitiser

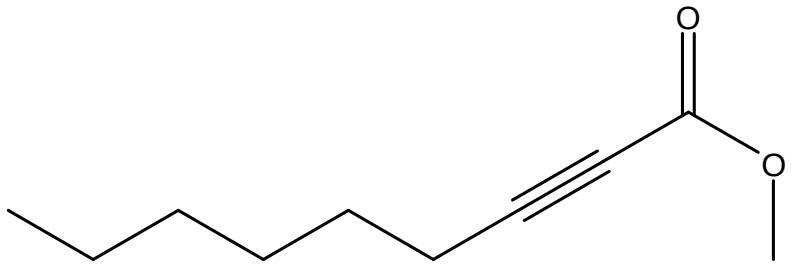
Tanimoto Similarity = 0.83%

READ-ACROSS BASED ON MECHANISTIC SIMILARITY (COMMON CHEMICAL REACTION)

- **If 2 (or more) chemicals in the same mechanistic domain are similar in their toxicity–determining parameters - they should be similar in their toxicity, irrespective of whether or not they are similar in structure.**



2,4-hexadienal
EC3=3.5%



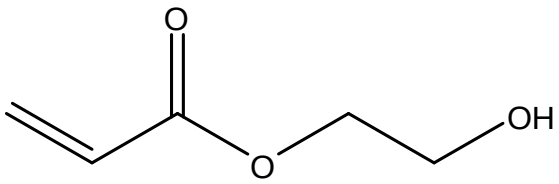
methyl 2-nonynoate
EC3=2.5%

Tanimoto similarity = 0.2%

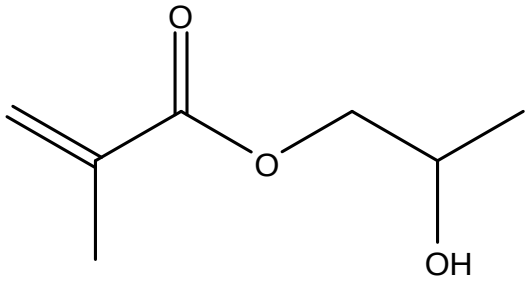
Michael acceptor similarity = 100%

READ-ACROSS BASED ON MECHANISTIC POTENCY SIMILARITY

- **If chemicals in the same mechanistic domain have different trends in phys-chem properties or reactivity then define different sub-groups for read-across.**



2-Hydroxyethyl acrylate
EC3=1.4%



2-Hydroxypropyl methacrylate
non-sensitiser

Michael acceptor similarity = 100%

Different reactivity potential clusters; Acrylates are moderately reactive, while methacrylates are weakly reactive.

THIRD ISSUE - CATEGORISATION SCHEME

- **Categorisation schemes used in read-across must group chemicals into a toxicologically meaningful category.**
- **Such categories to be truly useful in read-across must be endpoint specific.**
- **Examples**

- when grouping chemicals for acute inhalation toxicity from vapors, it is relevant to exclude chemicals with low vapor pressure.

- when grouping chemicals for acute aquatic toxicity, it is relevant to exclude chemicals with low water solubility.

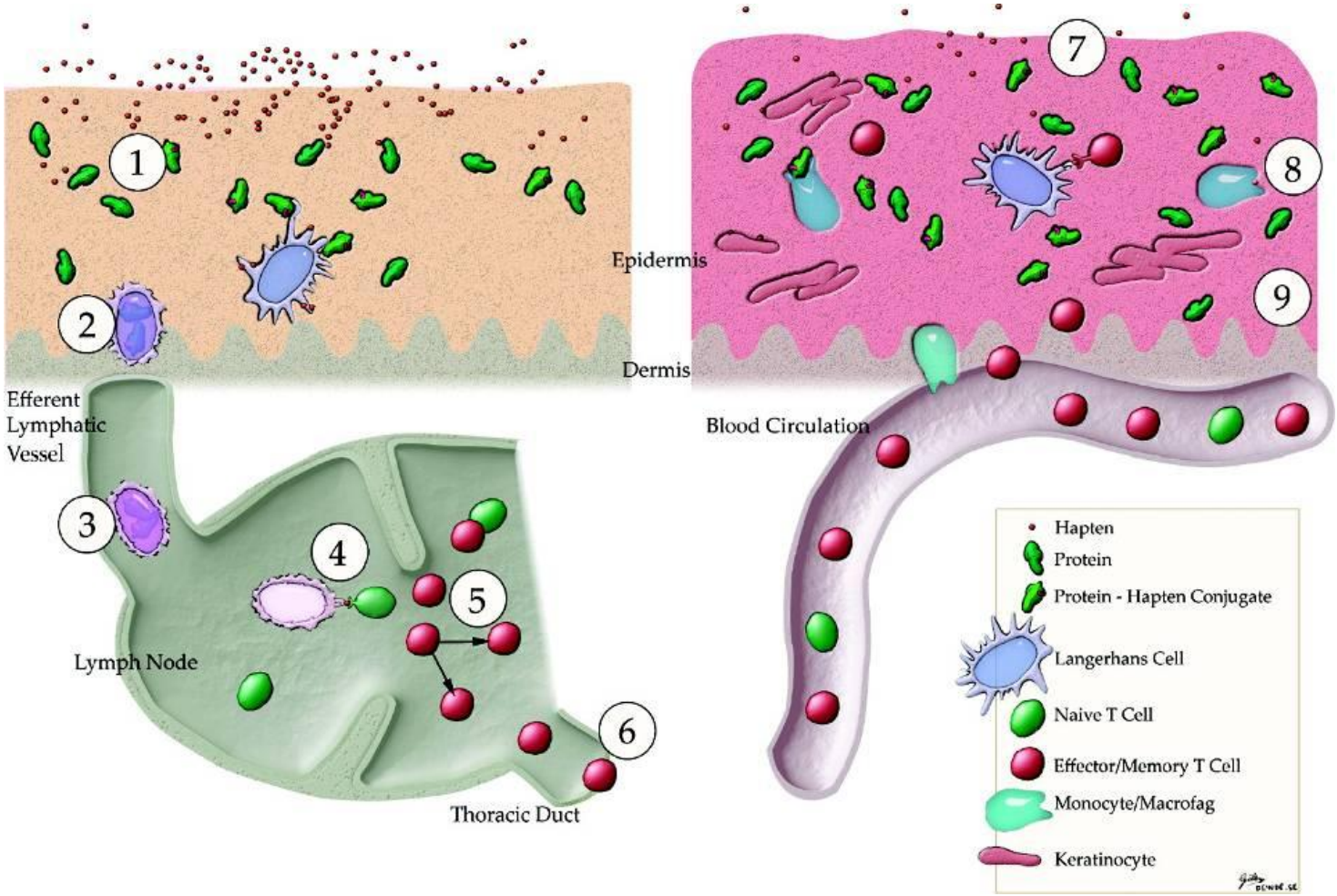
CHEMICAL CATEGORIES FOR TOXICITY

- **The most acceptable categories are based on integrating knowledge on how chemicals interact with biological systems with knowledge of the biological response once compensatory systems are overcome (i.e. mechanistic information).**

KEY ELEMENTS TO A HIGH QUALITY CHEMICAL CATEGORY

1. Shows in a scientifically convincing manner why the chemical category is a good one.
2. Provides the necessary information which underpins the explanation.
3. Mechanistic Transparency.

MECHANISTIC TRANSPARENCY: SKIN SENSITISATION



1. Haptenation; **2**. Epidermal inflammation & LC activation; **3**. LC migration; **4**. DC: T cell interaction; **5**. T cell proliferation; **6**. Increase in hapten-specific T cells; **7**. Hapten re-exposure; **8**. Acute inflammation; **9**. T cell-mediated inflammation

Karlberg *et al. Chem. Res. Toxicol.* 2008, **21**, 53-69.

IMPORTANCE OF MECHANISTIC TRANSPARENCY

“A regulatory decision based on a model estimate has to withstand a challenge in court.”

Vince Nabholz (US EPA)

In other words you have to be able to explain to a judge how you derived the read-across and why it is adequate for the intended purpose.

ISSUE FOUR - CONFIDENCE IN READ-ACROSS

- **Enhanced when experimental data for structural analogues bracket the predicted value for the target chemical (e.g., data for methyl acrylate and butyl acrylate is used to predict ethyl or propyl acrylate).**

- **Increased as the number of analogues within the chemical category increases (i.e. RA from many to one).**

- **Improved when supplemented by data from relevant *in vitro* and *in chemico* endpoints (i.e. increased weight-of-evidence).**

CONFIDENCE IN READ-ACROSS - UNCERTAINTY

may arise from several sources including:

- **The quality of the study data for the source analogues,**
- **The level of completeness of the data matrix for the source and target analogues,**
- **The strength of the association between the chemistry and the biological endpoint,**
- **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:

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

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;

data matrix;

6. conclusion on the applicability of the proposed read-across approach on an endpoint basis.

IN SUMMARY

- **Read-across is a Non-testing Method for filling data gaps based on a chemical category.**

- **Used in weight-of-evidence approach for assessments.**

- **Several critical issues discussed.**

- **Way to move read-across from intellectual acceptance towards practical application – agreed upon guiding principles.**

GUIDING PRINCIPLES FOR ACCEPTANCE OF READ-ACROSS

- **Mechanistic justification: Explanation why the read-across estimate has predictive value in regard to the endpoint under consideration.**

- **Statistical justification: Demonstration of the reliability of the data trend over the category members that justifies the read-across.**

- **Relevant *in vitro* and *in chemico* endpoints: Report data and trends for other endpoints relevant to the *in vivo* endpoint under consideration.**

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