

Computational Approaches to Toxicity Prediction: Introduction to Grouping, Category Formation and Read-Across

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Content

- Brief introduction to computational approaches to predict toxicity including their history, motivation for use and development
- Description of concept of chemical grouping (or category formation) and main methods to define chemical similarity
- Exercise to find analogues for a chemical and perform read-across
- Documenting a read-across and assigning confidence

Learning Objectives

- To understand the role of read-across in predicting toxicity relevant to regulatory submissions
- To appreciate the meaning of grouping, category formation and read-across
- To undertake a simple read-across from publicly available resources
- To evaluate a read-across prediction of toxicity to assign confidence with a view to regulatory submission

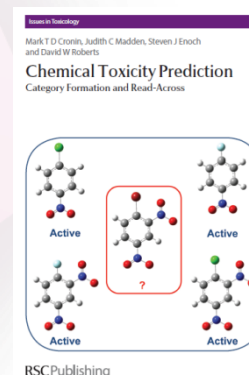
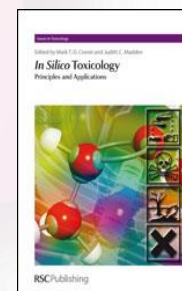
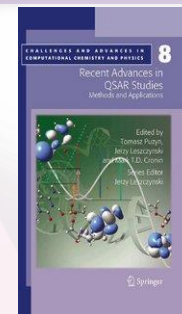
In Silico and Computational Toxicology Include

- Databases of existing information
- Structure-Activity Relationships (SAR)
- Category formation (grouping) read-across
- Quantitative Structure-Activity Relationships (QSAR)
- Expert Systems

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- Bioinformatics
 - Chemoinformatics
 - Biokinetics (PBPK)

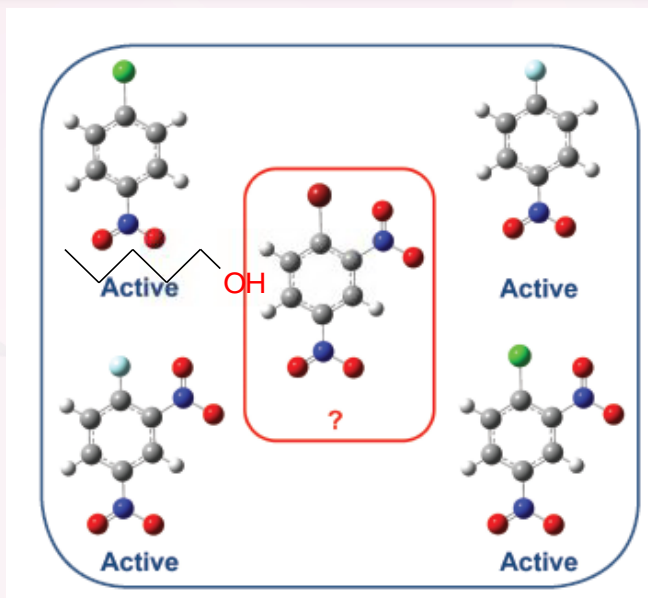
Further Information

- ECHA Guidance
 - <http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment> e.g. Chapter R6.
- OECD Guidance
 - <http://www.oecd.org/env/hazard/qsar>
- Puzyn T et al (2010) *Recent Advances in QSAR Studies: Methods and Applications*. Springer.
- Cronin MTD and Madden JC (2010) *In Silico Toxicology. Principles and Applications*. Royal Society of Chemistry.
- Cronin MTD et al (2013) *Chemical Toxicity Prediction: Category Formation and Read-Across*. Royal Society of Chemistry.
- <http://www.antares-life.eu/>
 - <http://www.antares-life.eu/index.php?sec=modellist>



Many other information sources are available

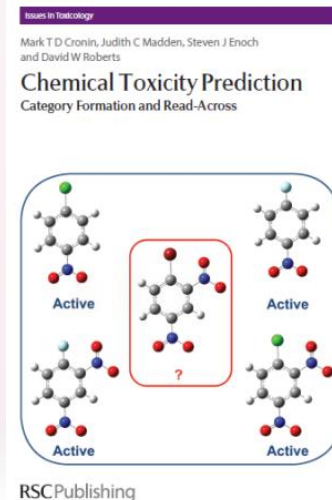
Grouping and Read-Across



Freely Available Tools: OECD QSAR Toolbox; ToxMatch

More information from:

- www.qsartoolbox.org
- OECD and ECHA Guidance (including RAAF)
- Cronin MTD et al (2013) *Chemical Toxicity Prediction*
- *Category Formation and Read-Across*. Royal Society of Chemistry, Cambridge, p. 184.

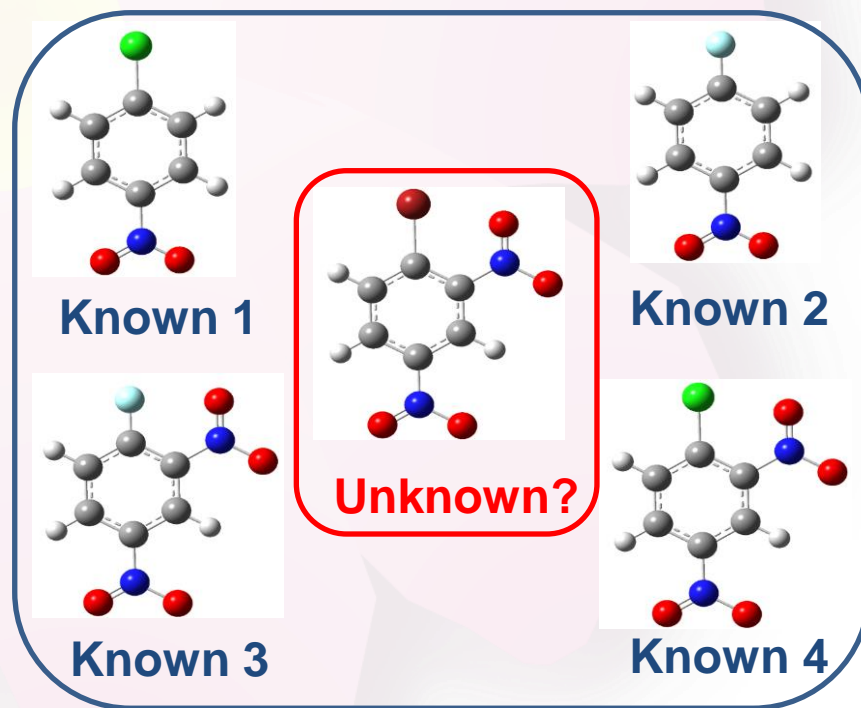


Category Formation (**Grouping**) for Read Across

- ***What is category formation?***



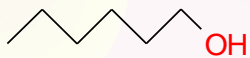
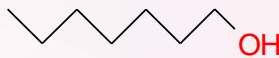
- The grouping together of chemicals that share a common property to form a category of related compounds

The common property may be mechanism of action; a specific functional group; ability to elicit same molecular initiating event, structural similarity etc



Category Formation (Grouping) for Read Across

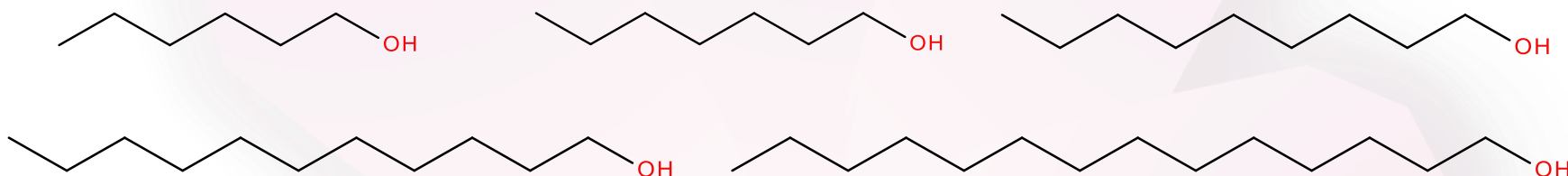
- ***What is read across and how can it be used?***
 - Read-across uses information from members of a group with known activity to predict activity of unknown(s)

					
Toxicity	● → ○		● → ○		SAR / Read-Across
Toxicity	● → ○		○ ← ●		Interpolation

Analogue or Category

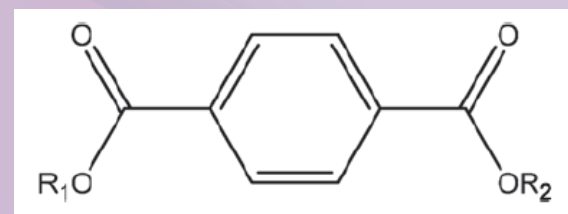
- An analogue is one, or a small number, of similar compounds
- A category contains more compounds and there may be an apparent trend in property
- Analogues or category members must be “similar”

Example of a Category: Long-Chain Alcohols



Chain length branched alcohols	C ₆	C ₆ -C ₈	C ₇ -C ₉	C ₁₁ -C ₁₄
CAS no.	88230-35-7	90438-79-2	108419-32-5	108419-35-8
<i>In vitro</i> assay				
Gene mutation	Negative	Negative	Negative	Negative
Chromosomal aberration	Negative	Negative	Not performed	Not performed
<i>In vivo</i> assay				
Mouse micronucleus	Not performed	Not performed	Negative	Negative

Example of a Category: Terephthalic Acid and Esters



Chemical	CAS #	Molecular weight	Water solubility mg/L	Log P (octanol-water)
Terephthalic acid R_1 and R_2 : H	100-21-0	166.13	15 _{20, experimental}	2 _{experimental}
Monomethyl terephthalate R_1 : H R_2 : CH ₃	1679-64-7	180.17	1910 ₂₅	1.71
Dimethyl terephthalate R_1 and R_2 : CH ₃	120-61-6	194.19	19 _{25, experimental}	2.25 _{experimental}
Diethyl terephthalate R_1 and R_2 : CH ₃ CH ₂	636-09-9	222.24	184.3 ₂₅	2.65
Di-n-propyl terephthalate R_1 and R_2 : CH ₃ CH ₂ CH ₂	1962-74-9	250.29	18.8 ₂₅	3.63
Mono-n-butyl terephthalate R_1 : H R_2 : CH ₃ (CH ₂) ₃	1818-06-0	222.24	64.08 ₂₅	3.18
n-Butyl methyl terephthalate R_1 : CH ₃ R_2 : CH ₃ (CH ₂) ₃	52392-55-9	236.27	58.97 ₂₅	3.14
Di-n-butyl terephthalate R_1 and R_2 : CH ₃ (CH ₂) ₃	1962-75-0	278.34	0.95 _{25, experimental}	5.53 _{experimental}
Diisobutyl terephthalate R_1 and R_2 : (CH ₃) ₂ CHCH ₂	18699-48-4	278.34	2.528 ₂₅	4.46
2-Ethylhexyl methyl terephthalate R_1 : H R_2 : CH ₃ (CH ₂) ₃ CH(CH ₂ CH ₃)CH ₂	63468-13-3	292.37	0.69 ₂₅	5.03
Di-n-octyl terephthalate R_1 and R_2 : CH ₃ (CH ₂) ₇	4654-26-6	390.56	0.00018 ₂₅	8.54
Di-2-ethylhexyl terephthalate R_1 and R_2 : CH ₃ (CH ₂) ₃ CH(CH ₂ CH ₃)CH ₂	6422-86-2	390.56	4 _{20, experimental}	8.390

Ball GL et al (2012) *Crit Rev Toxicol* 42: 28-67.

Can We Fill These Data Gaps?

CAS #	Chemical name	ADME ¹	Acute	Repeated dose ²	Gene mutation	Chrom Ab ³	Genetox in vivo	Fertility	Devel ^{2,4}
100-21-0	Terephthalic acid	√	R ⁵ , M ⁶ √	R	√	√	√	R	R √
1679-64-7	Monomethyl terephthalate	-	-	-	-	-	-	-	-
120-61-6	Dimethyl terephthalate	√	R √	R, M √	√	√	√	√-	-
636-09-9	Diethyl terephthalate	-	-	-	-	-	-	-	-
1962-74-9	Di-n-propyl terephthalate	-	-	-	-	-	-	-	-
1818-06-0	Mono-n-butyl terephthalate	-	-	-	-	-	-	-	-
52392-55-9	Methyl n-butyl terephthalate	√-	-	-	-	-	-	-	-
1962-75-0	Di-n-butyl terephthalate	√-	R √	-	√	√	-	R √-	-
18699-48-4	Di-isobutyl Terephthalate	-	-	-	-	-	-	-	-
63468-13-3	2-Ethylhexyl methyl terephthalate	√-	-	-	√	√	-	-	-
6422-86-2	Di-2-ethylhexyl terephthalate	√	R, M √	R	√	√	-	R √	R, M √
4654-26-6	Dioctyl terephthalate	-	-	-	-	-	-	-	-

Can We Fill These Data Gaps?

CAS #	Chemical name	ADME ¹	Acute	Repeated dose ²	Gene mutation	Chrom Ab ³	Genetox in vivo	Fertility	Devel ^{2,4}
100-21-0	Terep								R √
1679-64-7	Monc								-
120-61-6	Dime								-
636-09-9	Dieth								-
1962-74-9	Di-n-								-
1818-06-0	Monc								-
52392-55-9	Methy								-
1962-75-0	Di-n-								-
18699-48-4	Di-iso								-
63468-13-3	2-Eth terepl								-
6422-86-2	Di-2-								R, M √
4654-26-6	Diocyl terephthalate								-

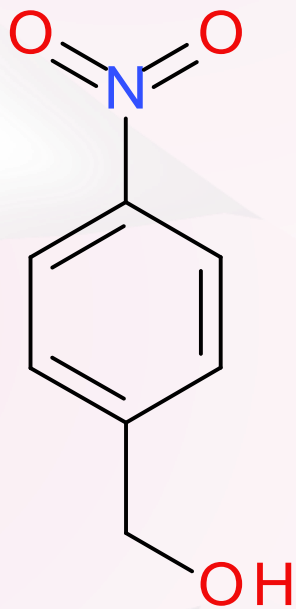
Probably.... If we have....

- High quality “source” data
- Consistency within the data for the category
- We are interpolating
- There is a good reason and justification for data gap filling

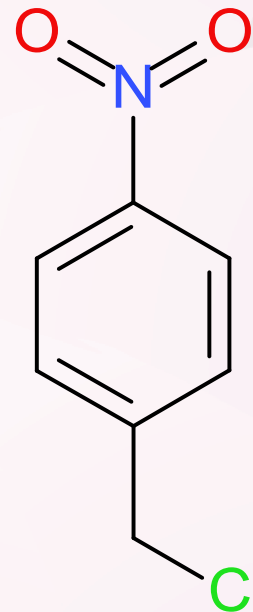
Why is Read-Across Used

- Its simple, cheap and transparent
- It has regulatory acceptance (if done correctly)
- Provides solutions to problems

If it Looks Similar, It is Similar?



Non Sensitiser



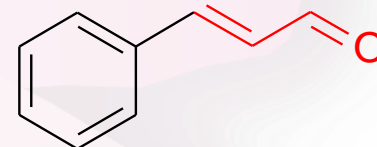
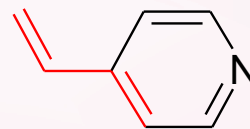
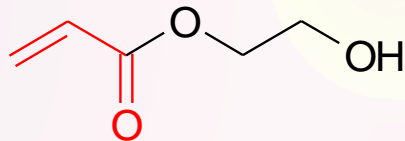
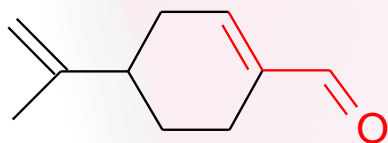
Strong Skin Sensitiser

Guide to Grouping Chemicals

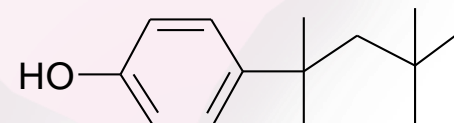
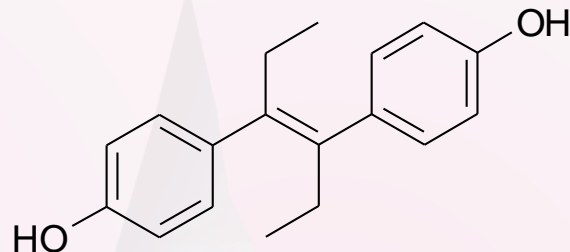
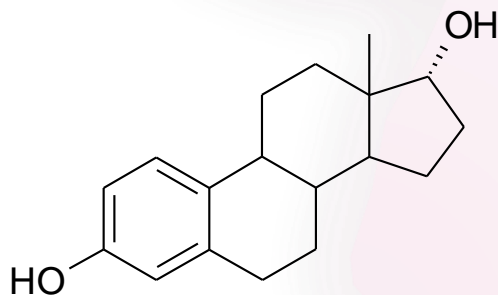
Structural Analogues



Mechanistic Analogues



Mode of Action Analogues

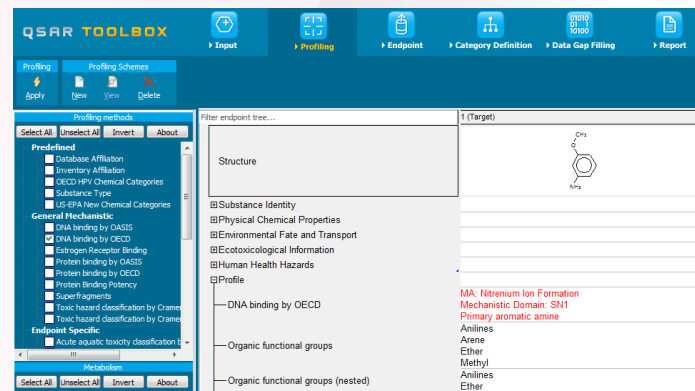


Other Options for Grouping Chemicals

- Compounds that are **metabolised** to a common molecule
- Compounds that are **degraded** rapidly to common products

Computational Tools for Grouping Chemicals

- OECD (Q)SAR Application Toolbox
- ToxMatch
- Toxtree
- ChemProp
- Leadscope
- Analogue Identification Method



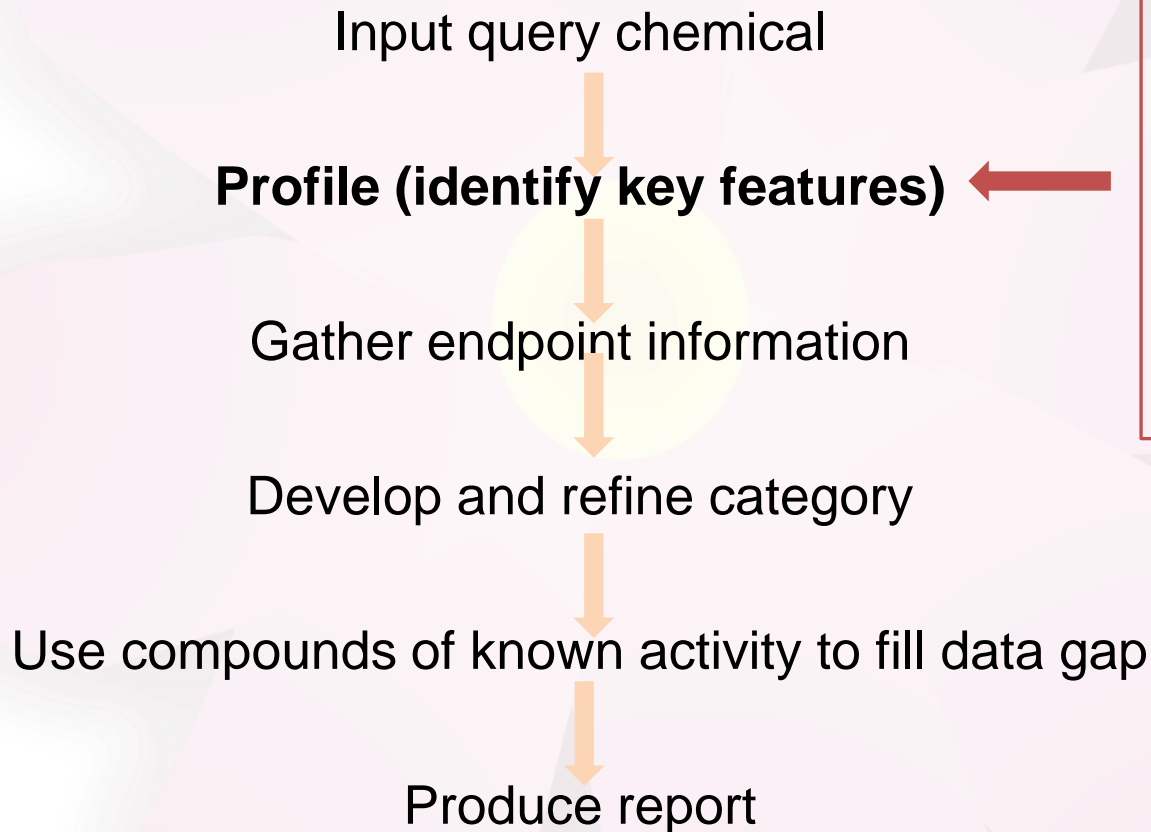
- AMBIT
- VITIC
- Databases



Software for Grouping: OECD QSAR Toolbox

- OECD Expert Group on QSAR established 2003
- Recognised need for transparent, properly evaluated QSARs
 - 2004 OECD Principles for Validation of (Q)SARs established
- Toolbox 1st released 2008 (version 3.2 April 2013; ver 4 late 2014)
 - Software for grouping chemicals into categories and filling gaps in (eco)toxicity data needed for assessing hazard
- Uses **category formation and read across** to infer activity of query chemicals from known compounds
- Freely available (with detailed use guidance documents) from <http://www.qsartoolbox.org/>

Workflow of Toolbox



Profilers:
Mechanistic
Empiric
Toxicological
Endpoint
specific
or by affiliation

You Must Demonstrate Confidence in Read-Across Prediction

- Support the read-across with other information
- Refer to AOP lecture....

Conclusions

- Read-Across is being increasingly used to solve problems
- Relies on “similar” chemicals being found and good toxicity data
 - Both of these issues are complex
- For regulatory acceptance, justification must be given
 - OECD Guidance on Grouping and ECHA’s Read-Across Assessment Framework

Acknowledgements



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