Experience & Needs from industry

Feedback from L'Oreal R&I

Workshop on Use of QSAR Toolbox
November 24th, 2011

L'ORÉAL

Content

- *Introduction & General feedback on the OECD Toolbox*
- *Case-studies highlighting several issues*
  - Coverage of databases & Profilers
  - Quality /Quantity (presence/absence) of information
  - Documentation of profilers & inventories
  - Multiple databases: human vs environmental safety
  - Multiple profilers : Info available to the end-user
  - Dealing with skin and liver metabolites
  - Risk of abusing of the tool
- *Concluding remarks*
- *Acknowledgements*

Introduction

- L'Oreal has been following the development of the OECD Toolbox since 2007 as part of its global efforts to develop/implement alternative methods to animal testing
  - *Input via both the sharing of expertise and regular feedback provided when new versions were released*
  - *Interest expressed in-house by different teams which are either using the Toolbox or interested in following its developement as potential future end-users :*
    - Developers of predictive computational approaches
    - Chemists
    - Eco(toxicologists)
    - Teams in charge of the REACh dossiers

General feedback

- OECD Toolbox Project: provides a public software co-developed by major stakeholders involved in the development of computational approaches to fill data gaps for regulatory use
  - ECHA
  - OECD Member States
  - Academics, institutions, experts
  - Industry
  - Etc.
- High level of complexity inherent to the process of read-across
  - Consideration of Physchem properties, chemical reactivity, metabolism, toxicology, etc.

Multiple expertise required to use the tool adequately. Adequate training is essential.

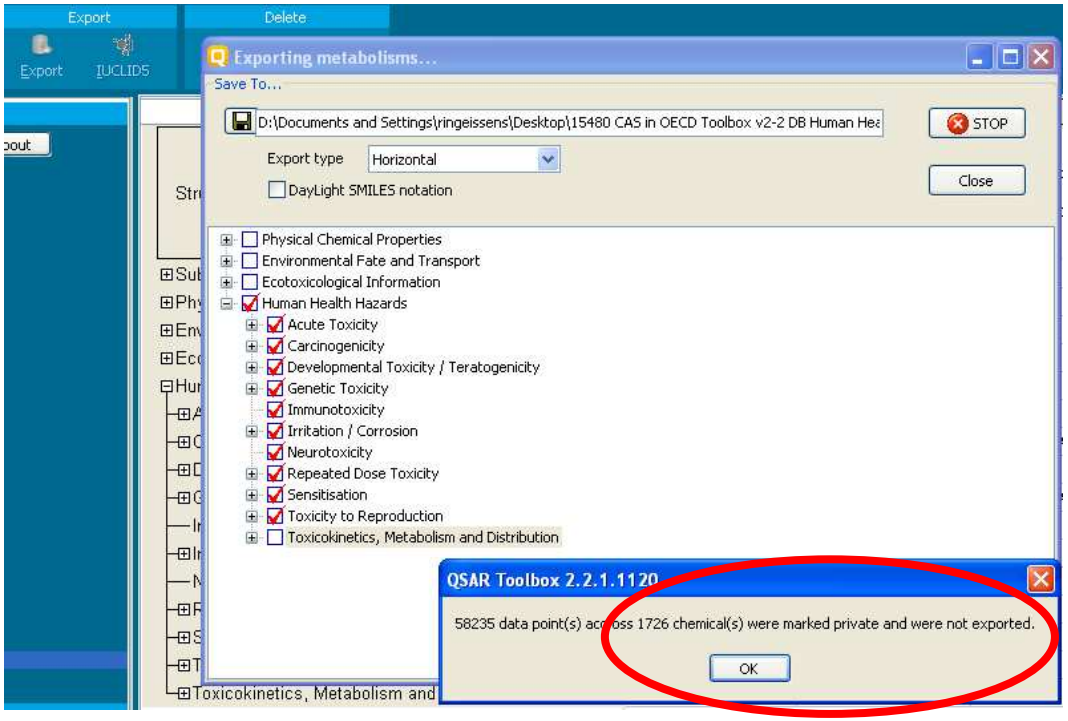
Coverage of Databases

- Some of the questions raised by chemists & safety assessors at L'Oreal regarding the ~ 50.000 chemicals present in the Toolbox & their associated safety data:
  - *What % of toxicological data being in the public domain is in the Toolbox?*
    - What public databases are not included in the current version of the Toolbox ? *Because of non authorization from institutions in charge of certain DBs, or because some data cannot at present be easily linked to adverse effects (eg HTS data)*
    - *Are there on-going DBs retrieval?*
  - *What is covered in terms of industrial use? agrochemicals (pesticides, etc), cosmetics, food ingredients, drugs, detergents, etc*
    - What do we know is missing? *Eg some chemicals used for a specific industrial application?*
    - *What % of the CAS registry is prsent in th toolbox?*
  - *How many chemicals have at least 1 data for human health endpoints? For Environmental endpoints?*

Need for more infos/statistics on inventories/DBs included in the Toolbox

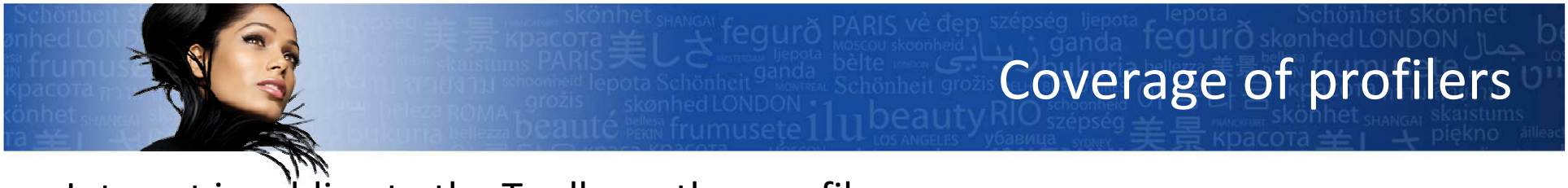
Coverage of Databases

- After selection of chemicals from DBs targeting human health endpoints, export of data was launched:



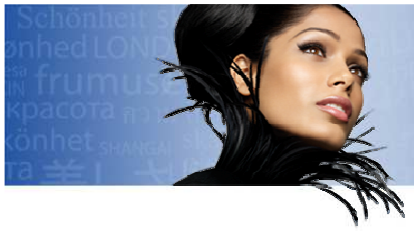
Eg DB REPDOSE Fraunhofer (615 chemicals): *"All copyright from the RepDose DB are owned in full by the Fraunhofer-Gesellschaft. Permission is granted to download or print material published from the RepDose DB for personal use only. This includes use of data for categorisation of chemicals via the read across or category approach. Its use for any other purpose, and in particular its commercial use or distribution, are strictly forbidden in the absence of prior written approval. "*

- Which data/quantity of data is downloadable?



Coverage of profilers

- Interest in adding to the Toolbox other profilers
  - Eg groups of flavourings defined by EFSA (interest also in adding to the Toolbox safety data on chemicals that have been assessed as food additives and food flavourings by EFSA)
    - *Boundaries of these categories (more than 30) have to be defined*



Presence/Absence of information

- Read-across exercise on CAS 107-98-2
  - PGME: Propylene Glycol Monomethyl Ether

- Mutagenicity/Skin sensitization data from public sources are mentioned for the 3 analogs of PGME cited in Vink *et al.* (data captured from ECETOC and OECD reports)

Regulatory Toxicology and Pharmacology 58 (2010) 64–71

Contents lists available at ScienceDirect

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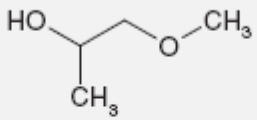
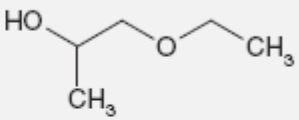
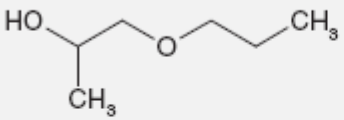
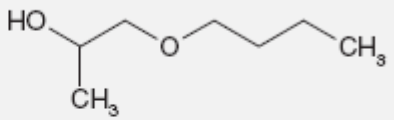
journal homepage: www.elsevier.com/locate/yrtph

Use of read-across and tiered exposure assessment in risk assessment under REACH – A case study on a phase-in substance

S.R. Vink [a,*], J. Mikkers [b], T. Bouwman [b], H. Marquart [b], E.D. Kroese [a]

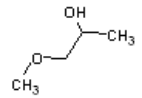
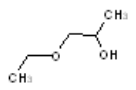
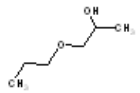
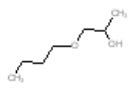
[a] TNO Quality of Life, Department of Research & Development, Zeist, The Netherlands
[b] TNO Quality of Life, Department of Food & Chemical Risk Analysis, Zeist, The Netherlands

Table 1
Molecular structure and physico-chemical properties of target substance PGME and its read-across candidates PGEE, PGPE and PnB.

Substance				
	1-methoxypropan-2-ol (Propylene Glycol Monomethyl Ether (PGME)) << Target chemical >>	2-propanol, 1-ethoxy- (Propylene Glycol Ethyl Ether (PGEE)) << Source chemical 1 >>	1-propoxy-2-propanol (Propylene Glycol Propyl Ether (PGPE)) << Source chemical 2 >>	1-butoxypropan-2-ol (Propylene Glycol n-Butyl ether (PnB)) << Source chemical 3 >>
CAS number	107-98-2	1569-02-4	1569-01-3	5131-66-8
Similarity		72.6% (Chem ID) 81.2% (DSSTox)	64.7% (Chem ID) 72.2% (DSSTox)	55.8% (Chem ID) 54.1% (DSSTox)

Presence/Absence of information

- The Muta/Skin sensitization data on analogs of PGME are missing in the Toolbox

		1 (Target)	2	3	4
Structure					
CAS Number		107-98-2	1569-02-4	1569-01-3	5131-66-8
Chemical Name		2-propylene glycol ... 1-methoxy-2-propanol 2-propanol, 1-meth... 1-methoxypropan-2-ol 1-methoxy-2-hydro... 1-methoxy-2-hydro...	1-ethoxy-2-propanol 2-propylene glycol (... 1-ethoxypropan-2-ol 2-propanol, 1-ethoxy-	propylene glycol n-... 1-propoxypropan-2-ol 2-propanol, 1-propoxy- 1-propoxy-2-propanol	1-butoxy-2-propanol propylene glycol m... 2-propanol, 1-butoxy- 1-butoxypropan-2-ol
Structural Formula		C(C)(O)COC	C(C)(O)COCC	C(C)(O)COCCC	C(C)(O)COCCCC
⊞Physical Chemical Properties	(4/10)	M: 119 °C, -95 °C, ...	M: 131 °C	M: 150 °C, -80 °C, ...	M: 172 °C
⊞Environmental Fate and Transport	(2/5)	M: 9.20E-7 atm-m3...			M: 3.76E-11 cm3/...
⊞Ecotoxicological Information	(3/5)	M: 5 parts per milli...	M: 5 parts per million		M: 5 parts per million
⊟Human Health Hazards					
Acute Toxicity					
⊞Carcinogenicity					
⊞Developmental Toxicity / Teratogenicity					
⊞Genetic Toxicity					
Immunotoxicity					
⊞Irritation / Corrosion	(3/3)	M: 0.09		M: 1.25	M: 1.12
Neurotoxicity					
⊞Repeated Dose Toxicity	(4/108)	M: 309 mg/kg/day, ...	M: 97.7 mg/kg/day	M: 111 mg/kg/day	M: 400 mg/kg/day
⊞Sensitisation	(1/1)	M: Negative			

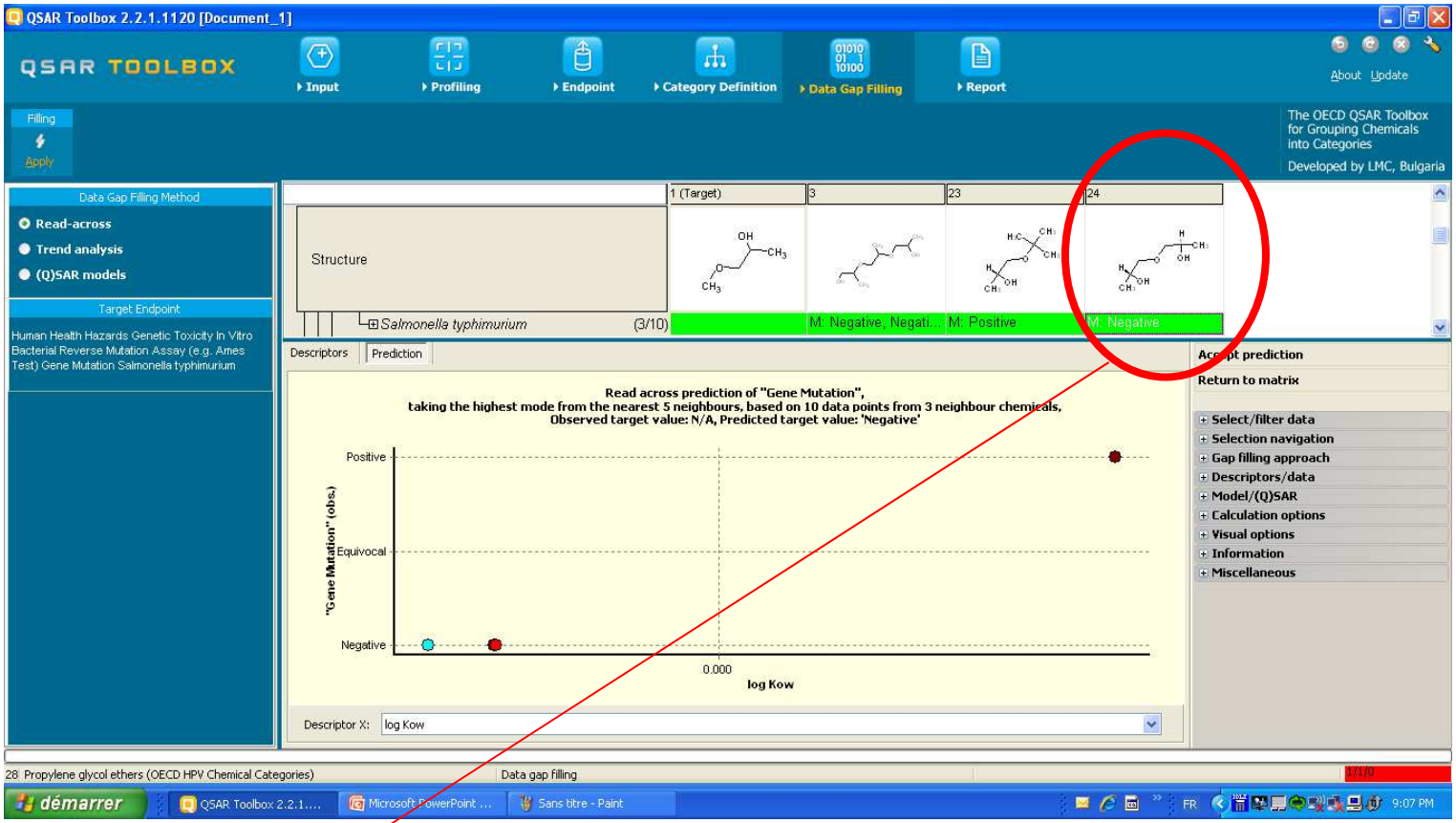
Vink et al.

Information on physico-chemical and toxicological properties of the selected source substances was obtained from publicly available review documents, *i.e.* for PGEE and PGPE, a dataset from ECETOC (ECETOC, 2005), and for PGME and PnB the SIDS Initial Assessment Report on Propylene Glycol Ethers was used (OECD, 2003).

➡ Read-across inconclusive due to lack of data

Quality of information (1)

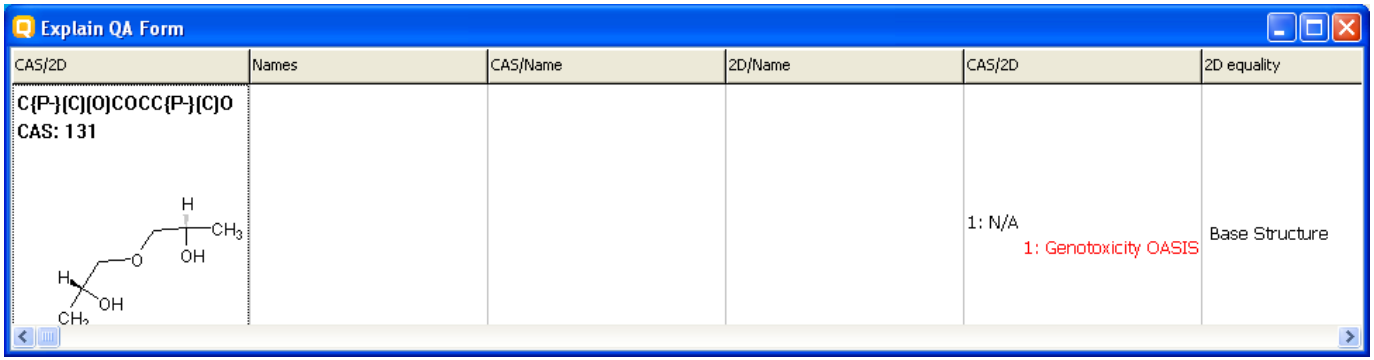
- Read-across applied to PGME for the AMES test
  - Categorization: No DNA binding >> OECD HPV « Propylene glycol ethers »
  - 3/28 analogs have a data (AMES test)



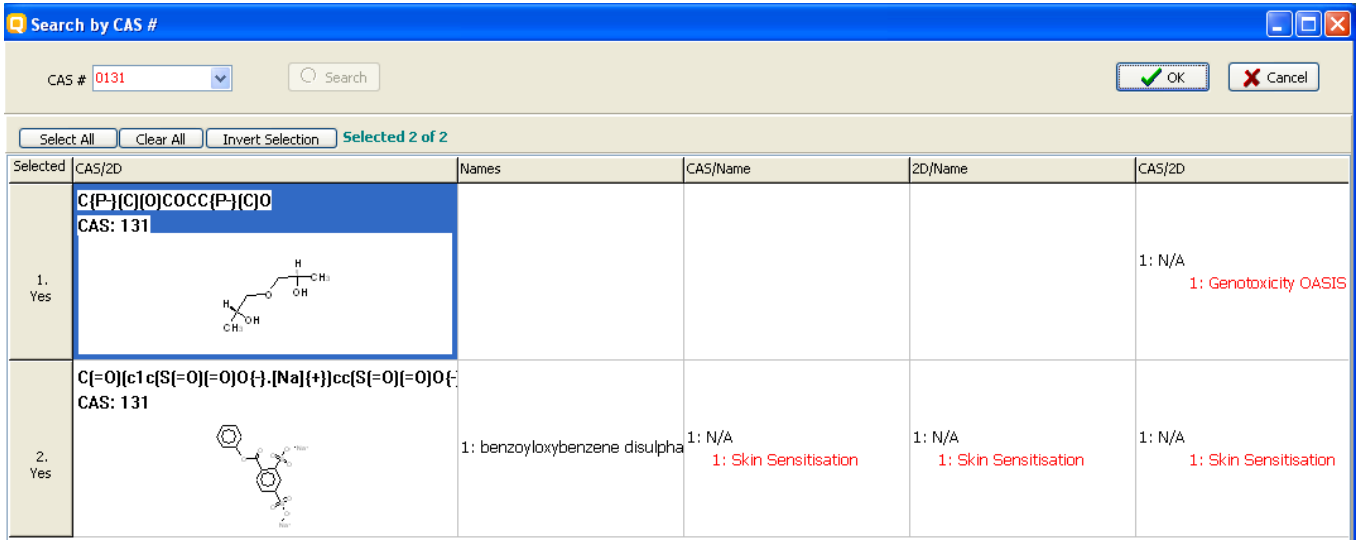
- CAS # *0-13-1

Quality of information (2)

- Info Gathered from the Data Gap filling window on « CAS # *0-13-1 »



- Info. Gathered in the INPUT window > « CAS # *0-13-1 »



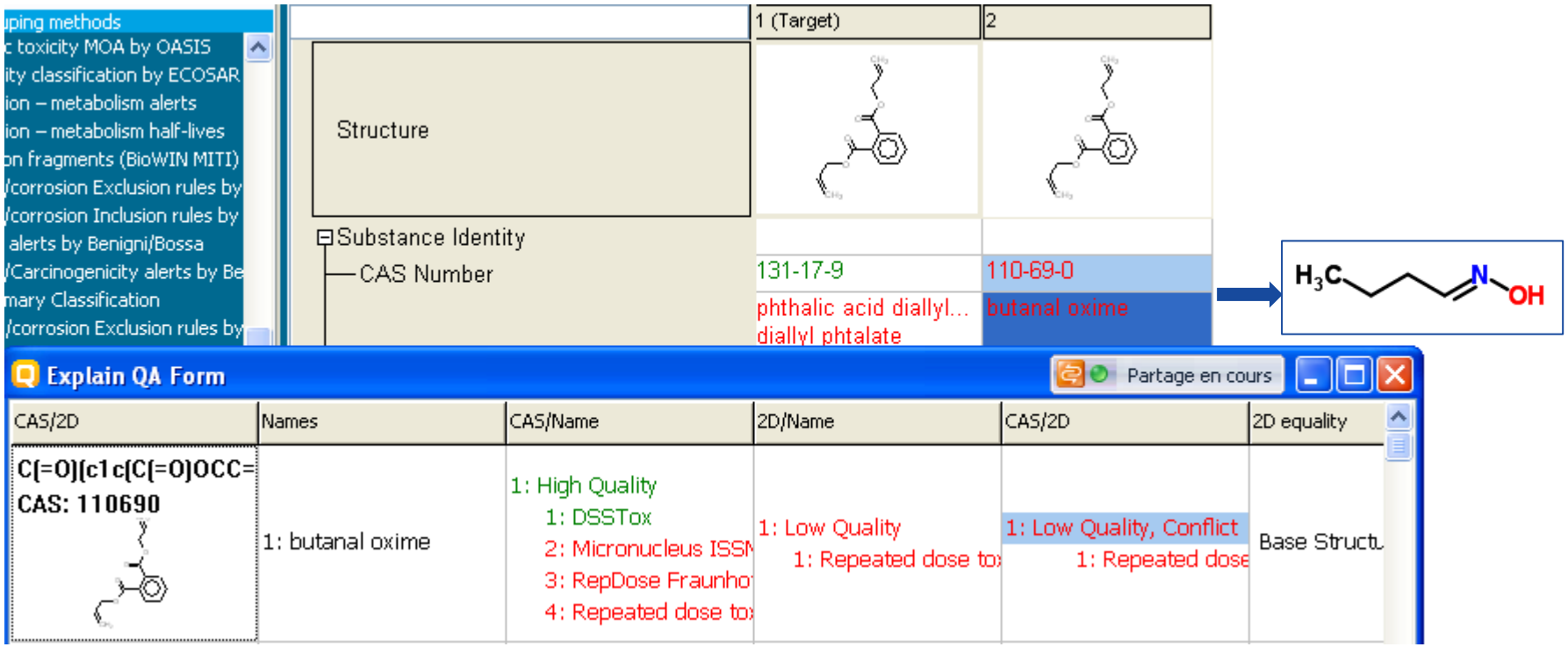
« QA (CAS/2D) »

- High Quality
- High Quality, Conflict ?
- Low Quality
- Low Quality, Conflict
- Moderate Quality
- Moderate Quality, Conflict
- N/A ?
- (Vides) ?

- Understanding of what is not OK for such CAS numbers is not straight forward

Quality of information (3)

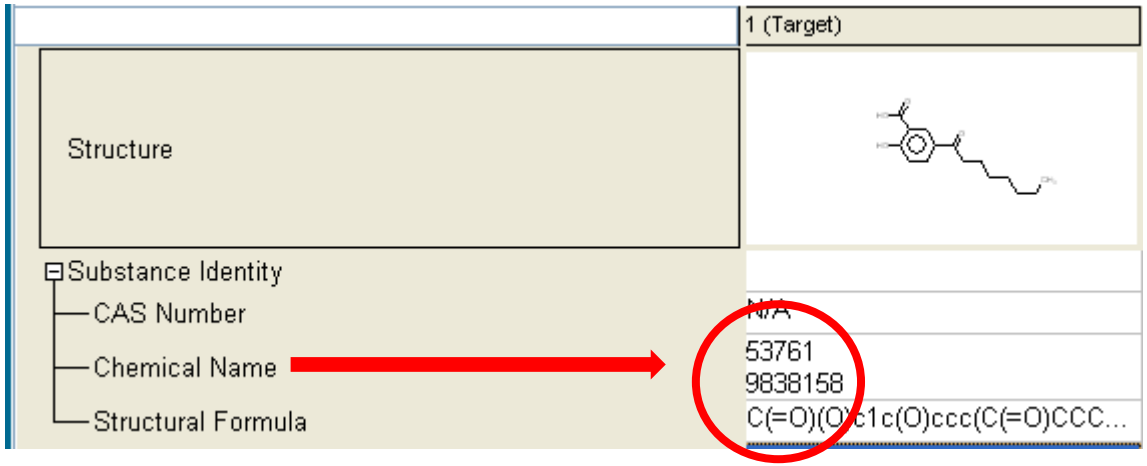
- Searching analogs of a phthalate derivative (CAS 131-17-9) by structure similarity (Tanimoto @ 95%): retrieving « CAS 110-69-0 » whith the same structure assigned and a wrong chemical name/CAS given (cf oxime)



- This CAS is in red meaning a concern with the quality of the information provided: is there a possibility to exclude such chemicals from the read-across?

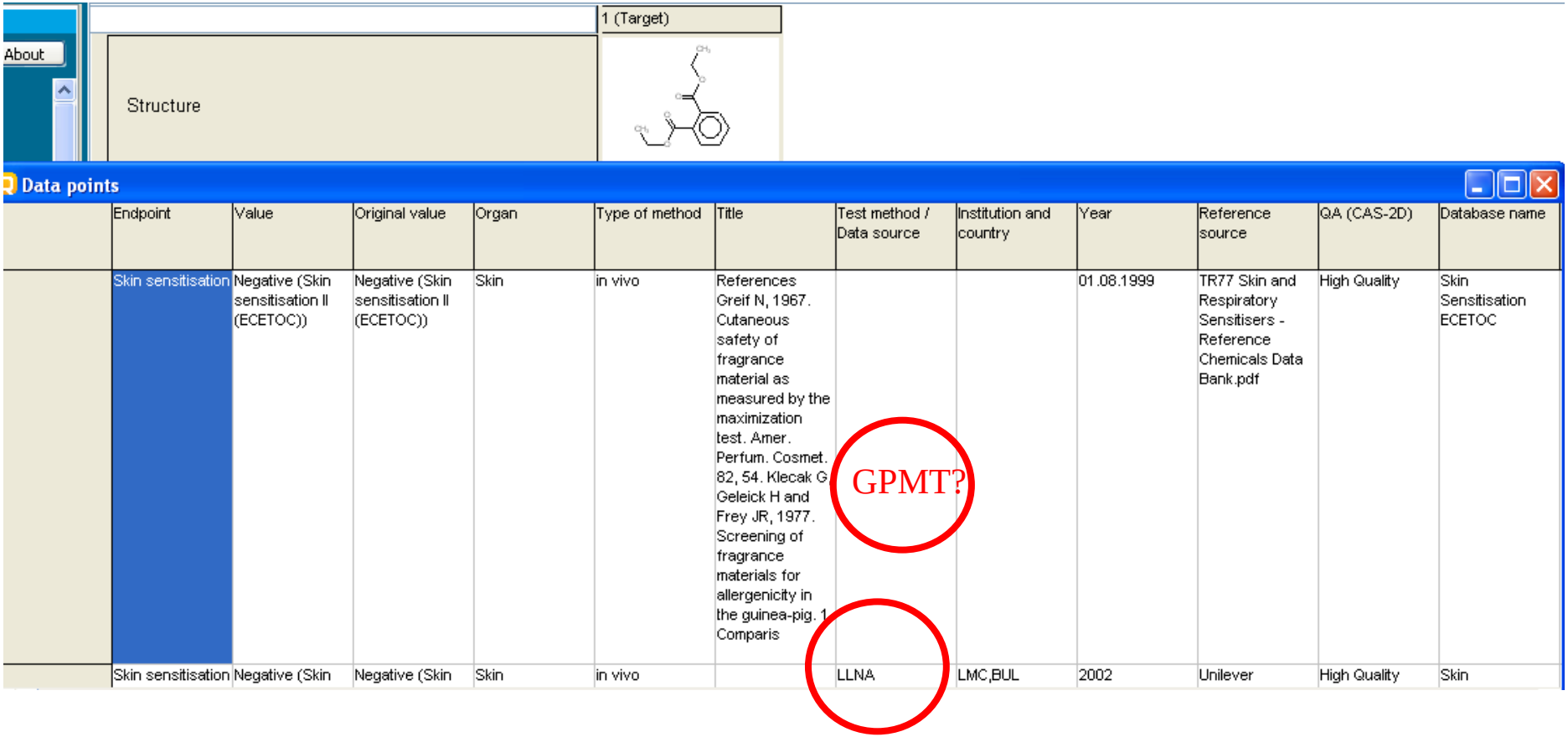
Quality of information (4)

- This structure is not referenced in the Toolbox
  - Its CAS is 78418-01-6
  - Wrong information for « chemical name »



Quality of information (5)

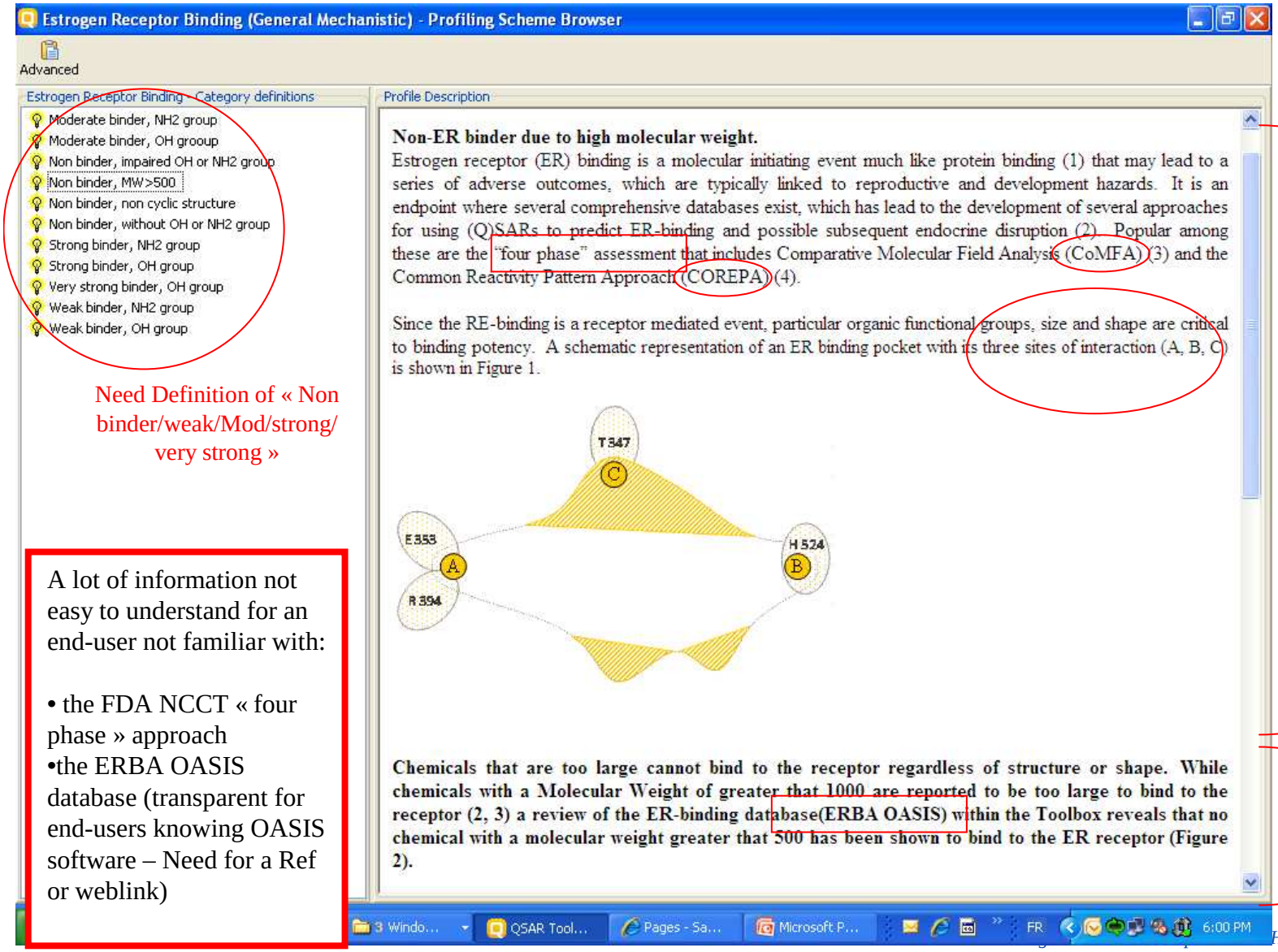
- GPMT assay not clearly indicated for CAS 84-66-2 (diethylphthalate)



	Endpoint	Value	Original value	Organ	Type of method	Title	Test method / Data source	Institution and country	Year	Reference source	QA (CAS-2D)	Database name
	Skin sensitisation	Negative (Skin sensitisation II (ECETOC))	Negative (Skin sensitisation II (ECETOC))	Skin	in vivo	References Greif N, 1967. Cutaneous safety of fragrance material as measured by the maximization test. Amer. Perfum. Cosmet. 82, 54. Klecak G Geleick H and Frey JR, 1977. Screening of fragrance materials for allergenicity in the guinea-pig. 1 Comparis			01.08.1999	TR77 Skin and Respiratory Sensitisers - Reference Chemicals Data Bank.pdf	High Quality	Skin Sensitisation ECETOC
	Skin sensitisation	Negative (Skin	Negative (Skin	Skin	in vivo		LLNA	LMC,BUL	2002	Unilever	High Quality	Skin

Documentation of profilers

- ER Binding Profiler



Need Definition of « Non binder/weak/Mod/strong/ very strong »

A lot of information not easy to understand for an end-user not familiar with:

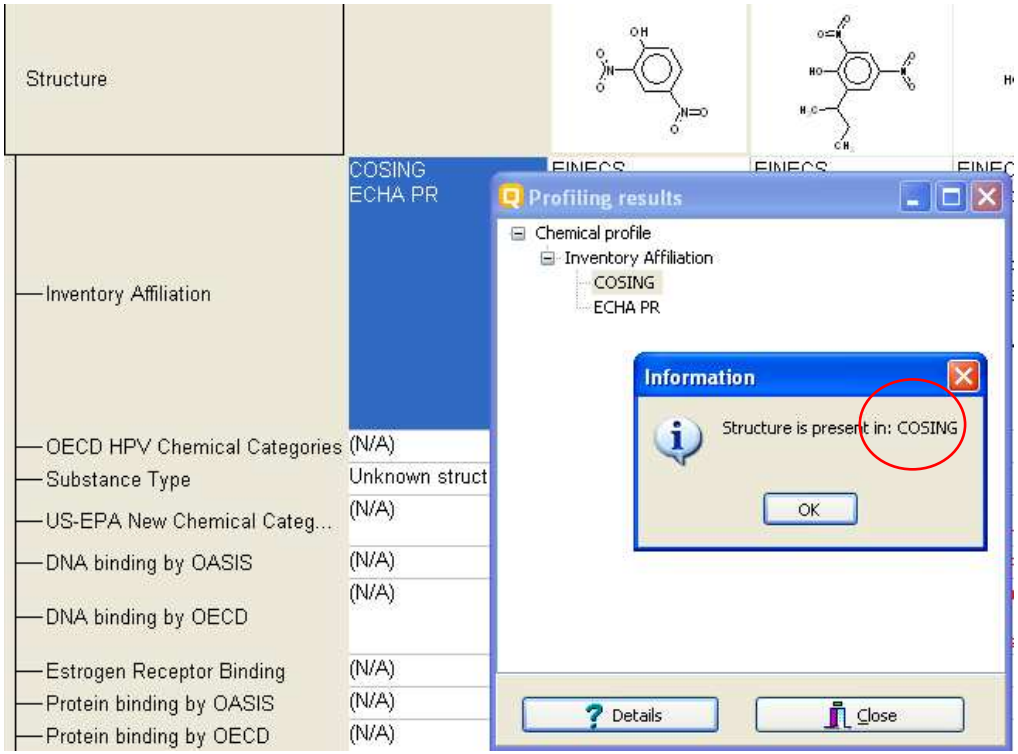
• the FDA NCCT « four phase » approach
•the ERBA OASIS database (transparent for end-users knowing OASIS software – Need for a Ref or weblink)

General intro on ER Binding: Should be moved to the « About » section.
Add a sentence explaining that the ER profiler of the Toolbox is based solely on structural motifs & MW ranges?

To add:
•Reference/webling for the OASIS DB
•Species (Rat? Trout? Human?)
•Receptor subtype (Erα? Erβ?)

Documentation of Inventories

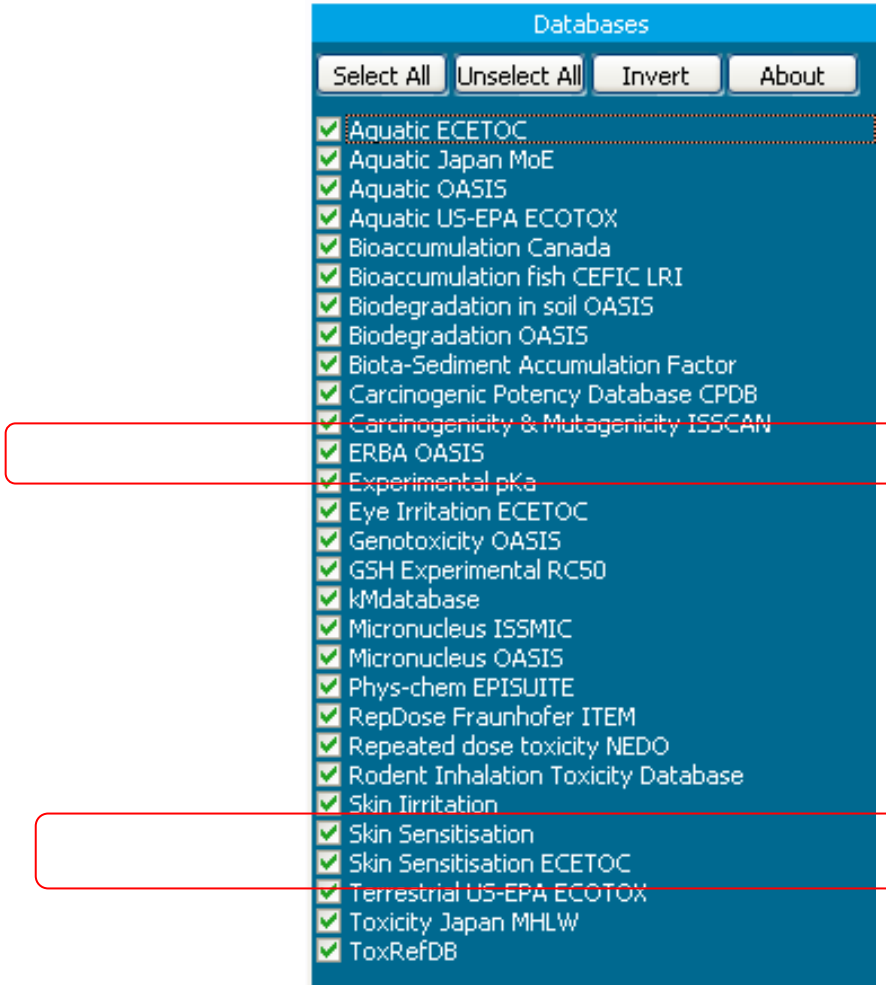
- Cannot find any information on the COSING inventory



- Add a « Help » functionality with searches by keywords (to complement the info available on the OECD Toolbox website)?
  - Cf need to retrieve information as quickly as possible

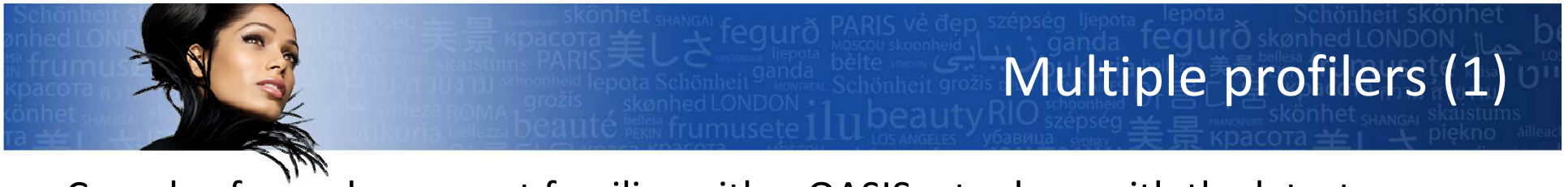
Multiple databases

- Very important to have multiple DB but would be easier to use if DB targeting human-health safety were separated from DB targeting environmental safety



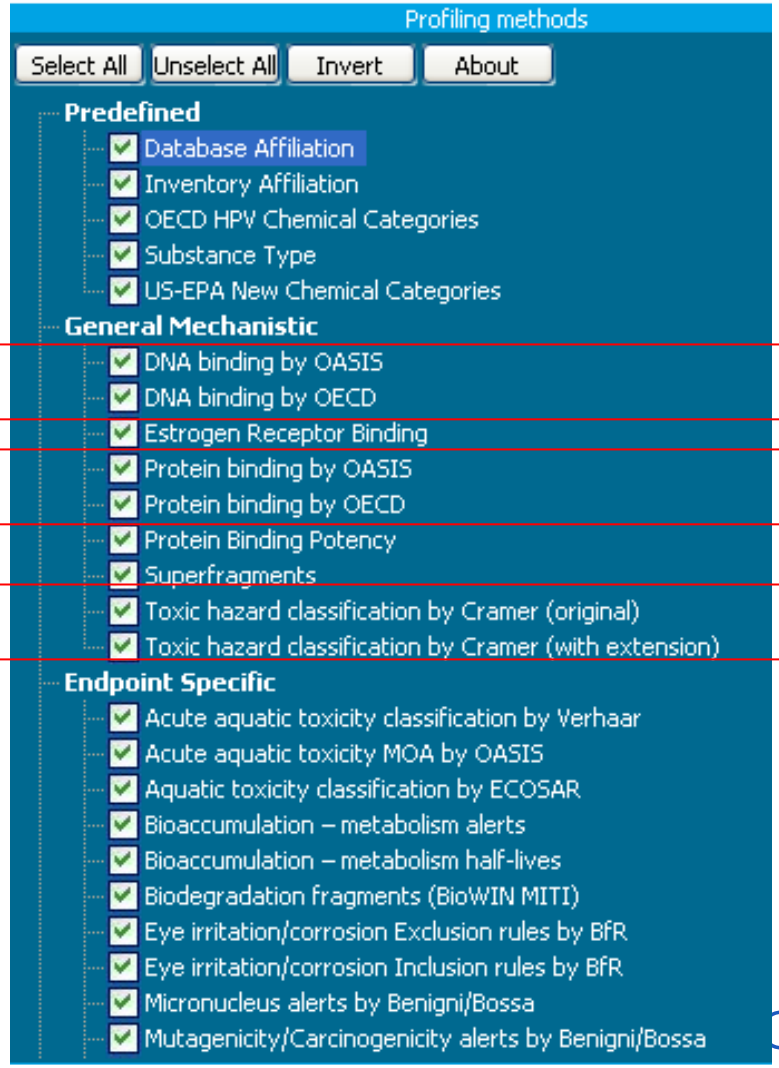
Name of DB: Not intuitive to an end-user not familiar with OASIS tools

Names of Skin sensitization DB: Confusing



Multiple profilers (1)

- Complex for end-users not familiar with « OASIS » tools or with the latest evolutions of the Cramer classification



41 Cat
115 Cat

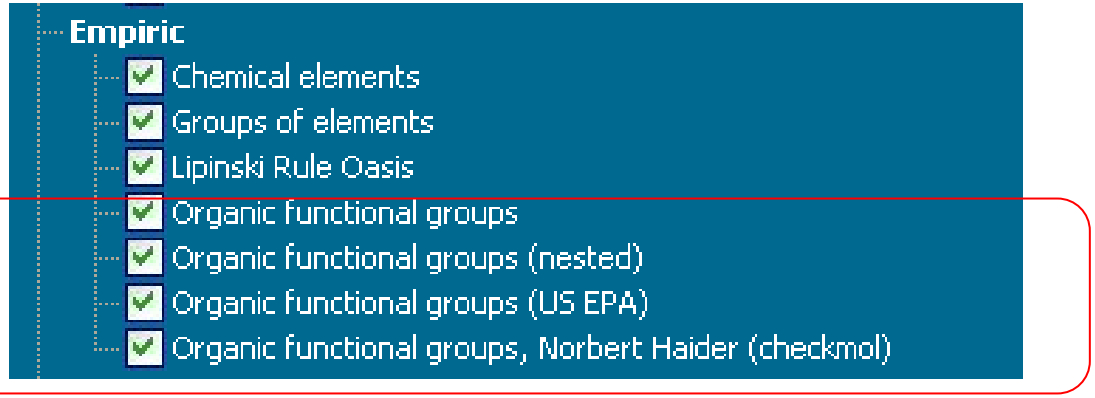
67 Cat
122 Cat

39 Nodes
44 Nodes

No additional explanation available to the end-user to know whether to use Cramer with extensions or not

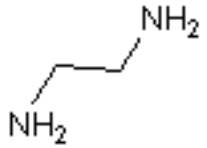
Multiple profilers (2)

- Too complex for end-users to have 4 different profilers built on organic functional groups ?



Importance of using the skin metabolism simulator

- Ethylene diamine (CAS 107-15-3)
  - Use of the skin metabolism simulator
    - 6 metabolites proposed for the target -> the dialdehyde glioxal is among predicted metabolites (cf Schiff base formation leading to skin sensitization)

	1
Structure	
Protein binding by OASIS	2 x No binding 4 x Schiff base formation with aldehydes
Protein binding by OECD	1 x 1-2-Dicarbonyls 4 x MA: Direct Acting Schiff Base For... 4 x Mechanistic Domain: Schiff Base ... 3 x Mono-carbonyls 2 x No binding

    - Primary amines undergoing oxidative deamination to aldehydes > Need infos on parent chemicals producing - via biotic metabolism - aldehydes (causing SS via Shiff Base formation) (currently missing in the simulator documentation)

Inherent complexity when dealing with metabolites (1)

- Dipropyl- (CAS 131-16-8) versus Diallylphthalate (CAS 131-17-9)

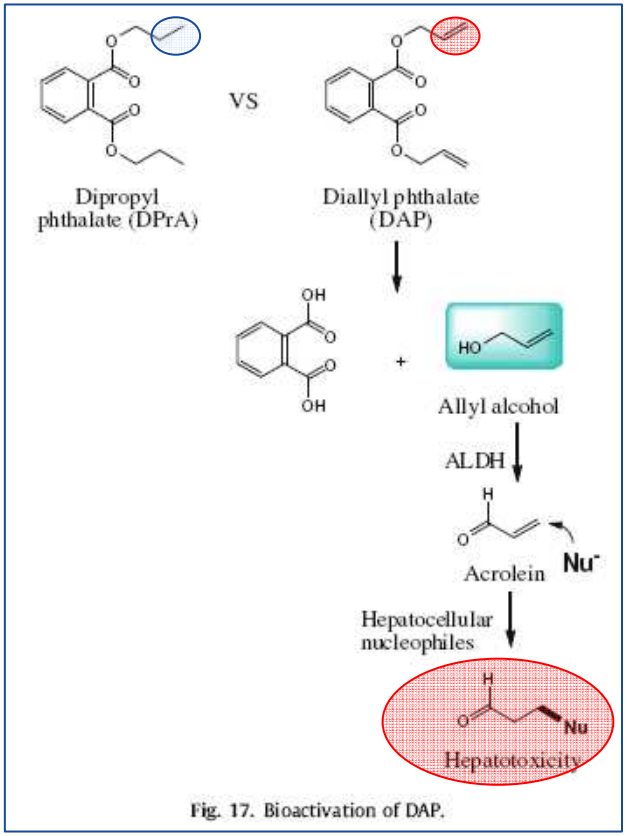
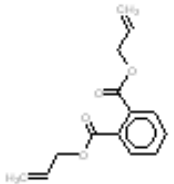
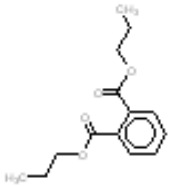


Fig. 17. Bioactivation of DAP.

S. Wu et al./ Regulatory Toxicology and Pharmacology 56 (2010) 67–81

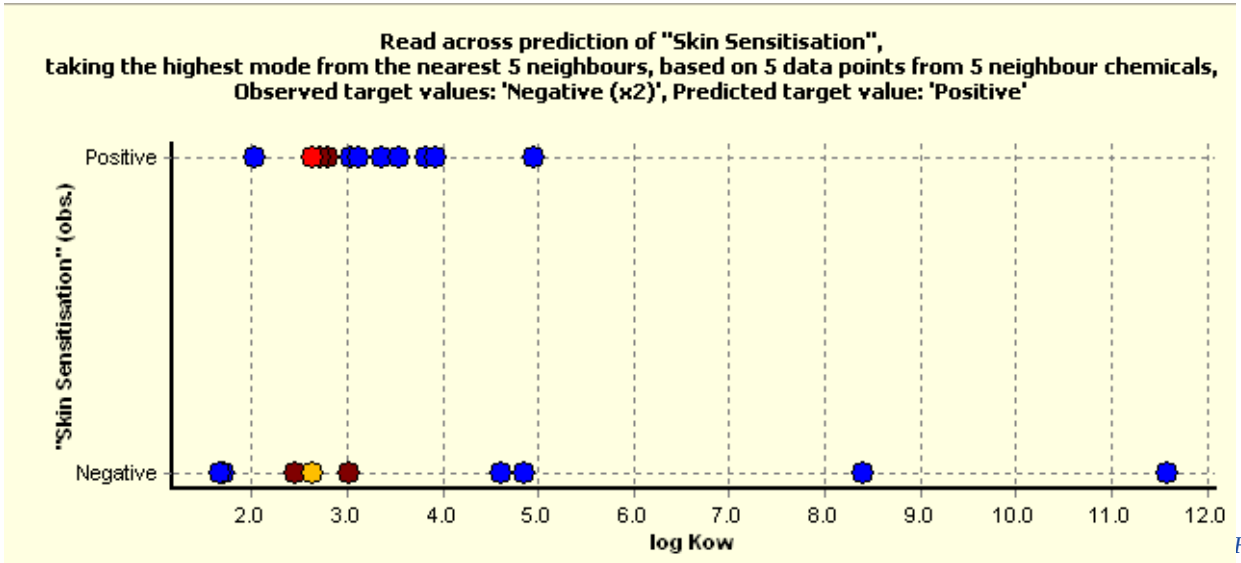
- Use of the liver metabolism simulator (cf no metabolites retrieved when using « observed liver metabolism »)
    - 12 metabolites proposed for diallylphthalate-> it becomes rapidly difficult to handle the multiple compounds (parent & metabolites) in the software

Inherent complexity when dealing with metabolites (2)

	1 (Target)	2
Structure		
Liver metabolism simulator	12 metabolites	4 metabolites
Database Affiliation	12 x (N/A)	4 x (N/A)
Inventory Affiliation	12 x (N/A)	4 x (N/A)
OECD HPV Chemical Categories	12 x (N/A)	4 x (N/A)
Substance Type	12 x Discrete chemical	4 x Discrete chemical
US-EPA New Chemical Categories	2 x (N/A) 1 x Acrylates/Methacrylates (Acute to... 2 x Aldehydes (Acute toxicity) 2 x Anionic Surfactants 2 x Epoxides 5 x Esters (Acute toxicity)	1 x Aldehydes (Acute toxicity) 1 x Anionic Surfactants 1 x Esters (Acute toxicity) 1 x Neutral Organics
DNA binding by OASIS	1 x Alpha, beta unsaturated aldehydes 2 x Epoxides, Aziridines 3 x No binding	1 x Aldehydes 3 x No binding
DNA binding by OECD	1 x Alpha, beta- unsaturated aldehydes 2 x Epoxides 2 x MA: Direct Acting Epoxides and r... 1 x MA: Direct Acting Schiff Base For... 1 x MA: Polarised Alkenes_Michael a... 1 x Mechanistic Domain: Michael addi... 1 x Mechanistic Domain: Schiff base 2 x Mechanistic Domain: SN2 1 x Mono aldehydes	1 x MA: Direct Acting Schiff Base F... 1 x Mechanistic Domain: Schiff base 1 x Mono aldehydes 3 x No Binding

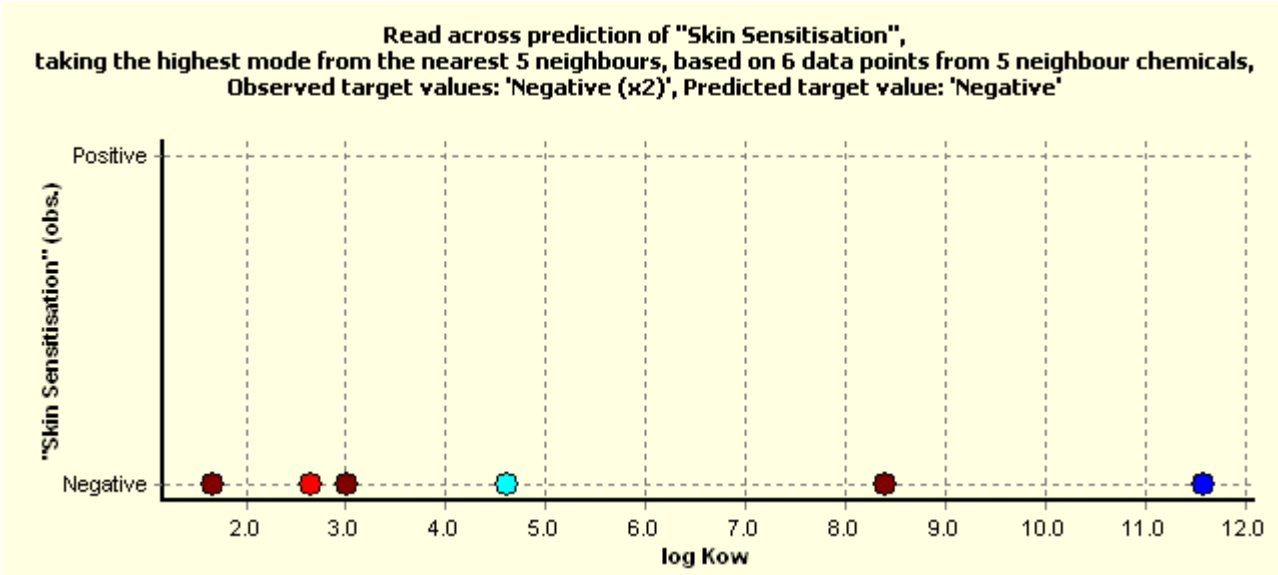
Risk of abusing of the tool (1)

- CAS 84-66-2 (diethylphthalate) : Read-across for Skin Sensitization
  - Profiling:
    - Rq: No category « Phthalates » available
    - No Protein-binding category
    - ECOSAR, US EPA : category « Esters »
    - Organic Functional groups (nested): « Arene, carboxylic acid ester »
      - 51/1353 analogs have a skin sensitization data
      - Sub-categorization with « chemical elements » >> 23/306 analogs have a SS data
        - *Dimethyl & Dipropylphthalate are missing since no SS data available*
        - *Dibutylphthalate is Neg in LLNA*

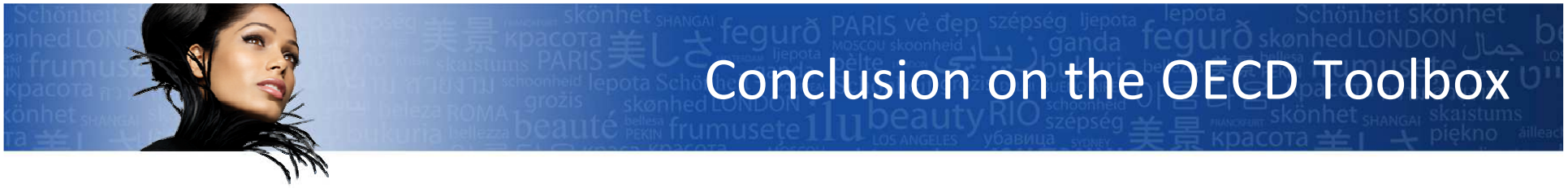


Risk of abusing of the tool (2)

- CAS 84-66-2 (diethylphthalate) : Read-across for Skin Sensitization
  - Further sub-categorization done with a focus on analogs of the category « No protein binding »
    - *Only 1/5 neighbours is a phthalate (Dibutylphthalate in blue below), other neighbours are di- or tri-carboxylates (meta or para substitutions, not ortho as it is for phthalates)*



- In the end: Read-across is conclusive? Inconclusive?



Conclusion on the OECD Toolbox

- A powerful tool made publicly available

- More development/refinement would make it more user-friendly and increase confidence in the data obtained
  - *include a reliability index to read-across outcomes?*

- Training is key to ensure as much as possible a proper use

- Appropriate use requires multiple expertise

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  - L Colombe (Ecotoxicologist)

Thanks for your attention!