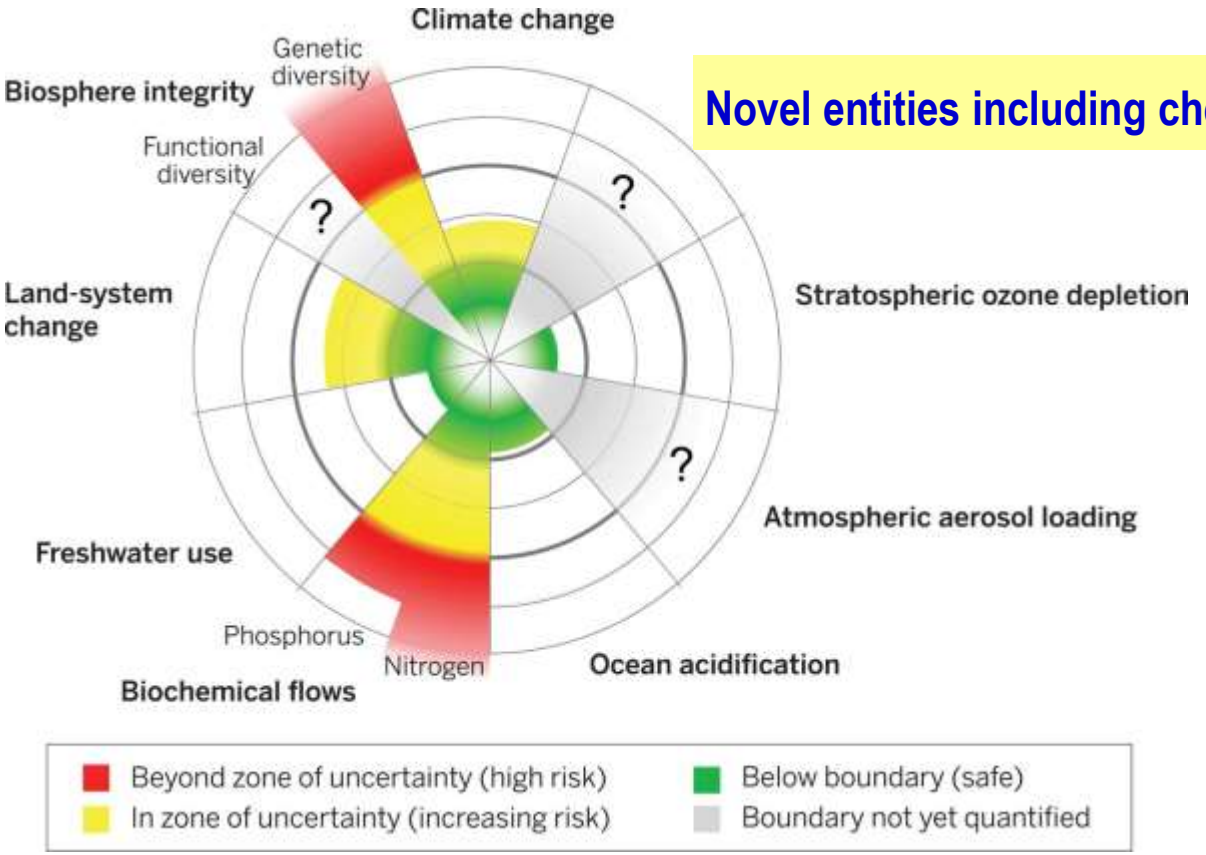
New approach methods for a non-toxic environment

Andrew Worth

Collaboration Workshop “Exploring the Regulatory Use of Alternative Approaches in Toxicology for the Safety Assessment of Chemicals”

9-10 November 2016, JRC Ispra

9 planetary boundaries – safe operating space for humanity



Novel entities including chemicals

Rockström *et al* (2009). Ecology & Society 14

Steffen *et al* (2015). Science 347

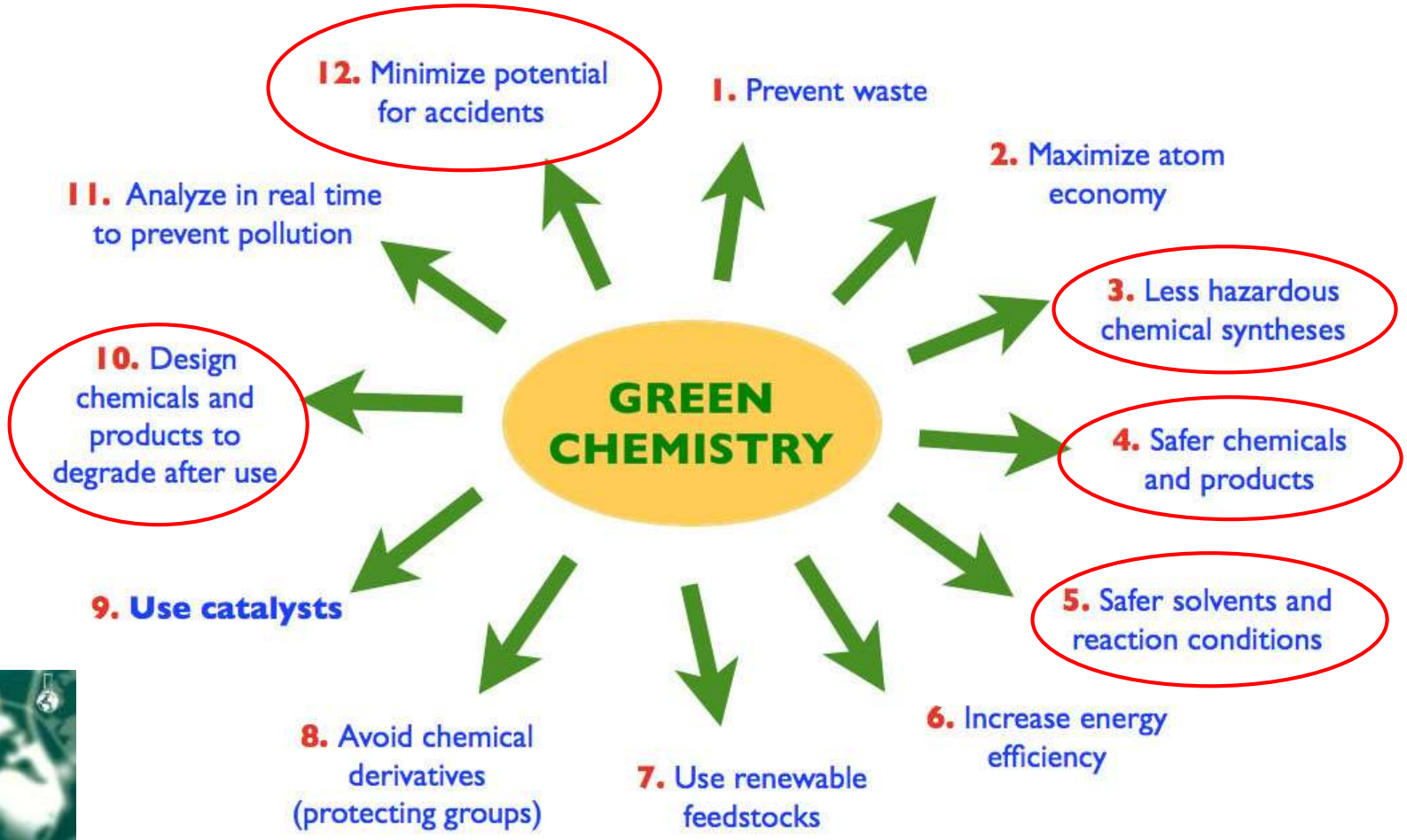
Towards a non-toxic environment

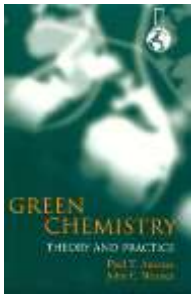
- 7th Environment Action Programme: *"Living well, within the limits of our planet"*
  - Long term vision for 2050
  - Actions up to 2020 and beyond
- Objective 3: *"To safeguard the Union's citizens from environment-related pressures and risks to health and well-being"*
- EC to develop, by 2018, a Union strategy for a non-toxic environment:
  - Nanomaterials
  - Endocrine disruptors
  - Combination effects of chemicals
  - Chemicals in products including non-toxic material cycles
- Competitiveness and innovation
- Sustainable substitutes for chemicals of concern

Commission-funded study

- DG ENV contract, December 2015- March 2017
- Analysis of policy gaps, opportunities, stakeholder views, best practices
- 7 focus areas:
  - Substitution and grouping
  - Chemicals in products and non-toxic material cycles
  - Safety of children and other vulnerable groups
  - Very persistent chemicals
  - Innovation and competitiveness
  - R&D on new, non-toxic substances
  - Monitoring and surveillance of chemical threats to health and the environment
- Commission workshop, 8-9 June 1016

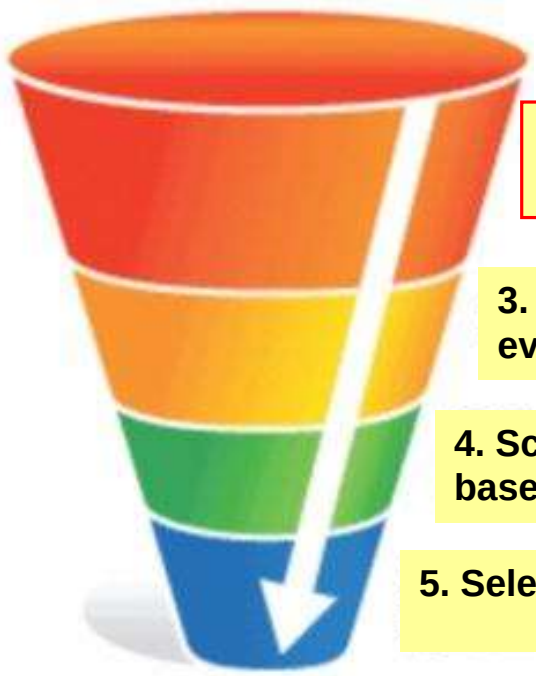
Sustainable chemicals: principles of green chemistry



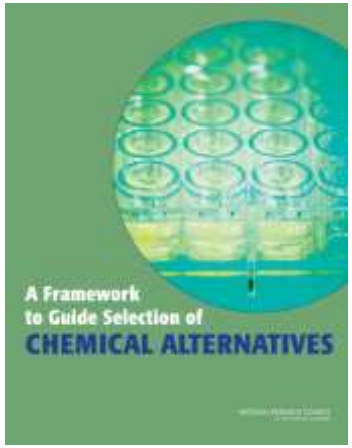


Anastas & Warner, 1998

Selection of sustainable substitutes / alternatives



1. Identify list of potential alternatives
2. Screen out chemicals of concern by evaluating hazard, exposure or risk
3. Screen out non-viable alternatives by evaluating technical performance and costs
4. Screen out alternatives with other impacts, based on life cycle considerations
5. Select and implement sustainable alternatives



NAS, 2014

Need to avoid “regrettable substitutions”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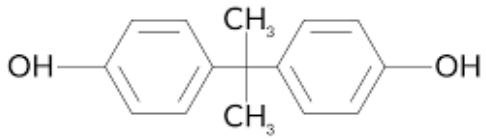
Environ Health Perspect; DOI:10.1289/ehp.1408989

Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes

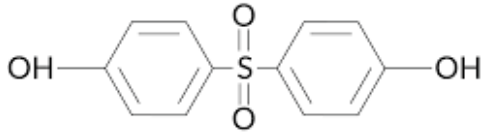
Johanna R. Rochester and Ashley L. Bolden

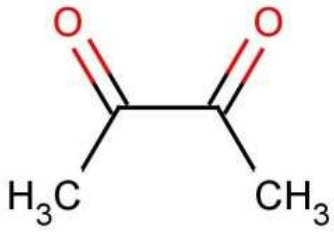
Author Affiliations open

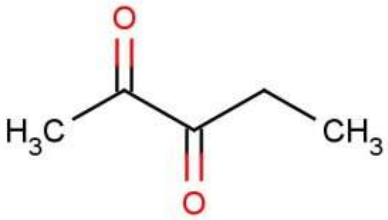
Bisphenol A



Bisphenol S







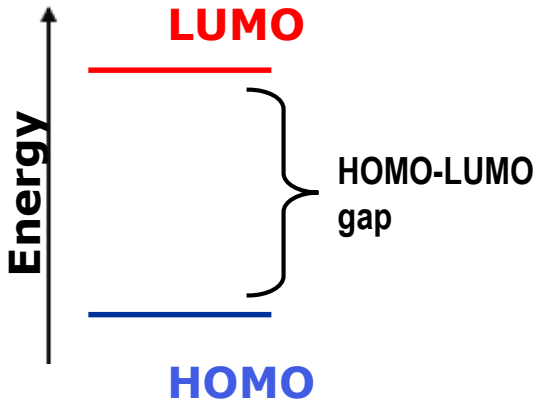
2,3-butandione “diacetyl” **2,3-pentanedione**

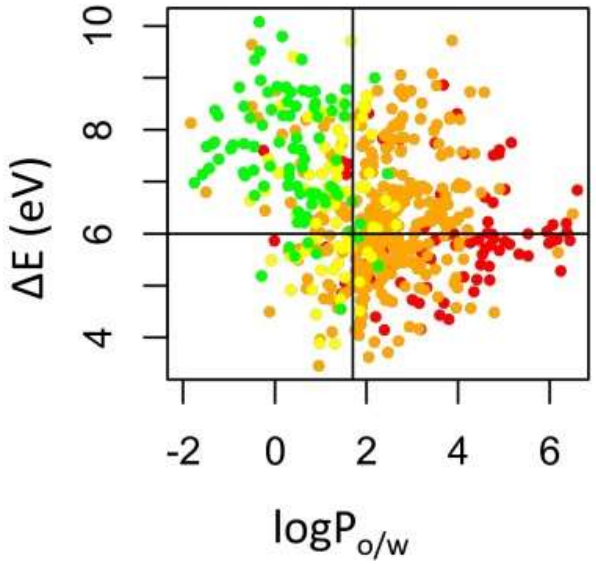
"Popcorn lung"

Grouping of chemicals for informed substitution

Grouping by	New approach methods
Use category / function	
Chemical class / structural features	Chemoinformatics
Physicochemical properties	QSPR, *in chemico* methods
Mode of action / mechanistic properties	QSAR, *in vitro* methods, PBD models
Hazardous properties	
Potential for exposure	PBK / fate models

Acute aquatic toxicity – reactivity and bioavailability





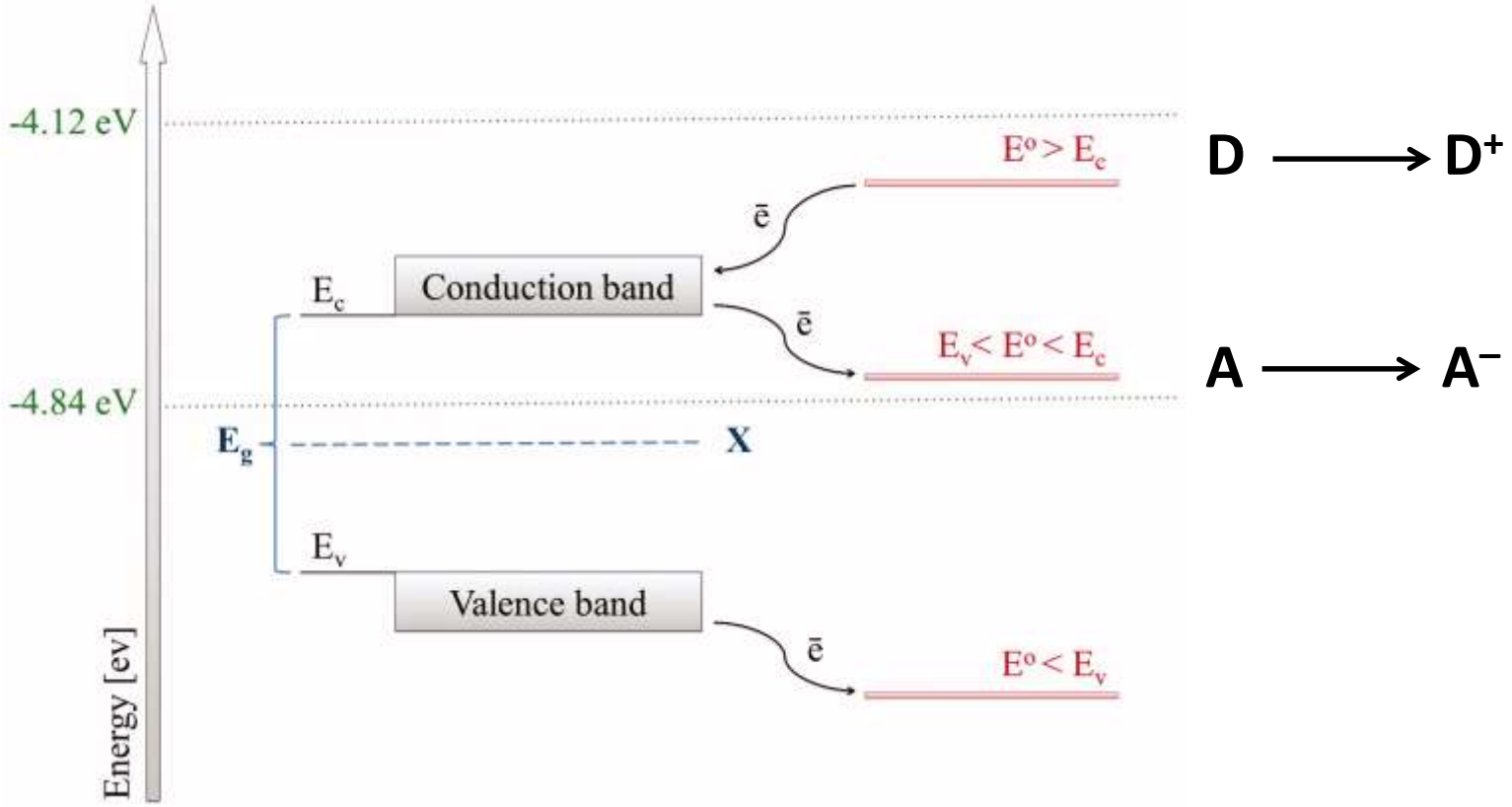
555 chemicals. Concern based on LC50, 96h fathead minnow

Red – HIGH **Orange – MEDIUM** **Yellow – LOW** **Green – NONE**

Kostala et al (2015). Identifying and designing chemicals with minimal acute aquatic toxicity. PNAS 112, 6289-6294.

Nanoparticle cytotoxicity – reactivity

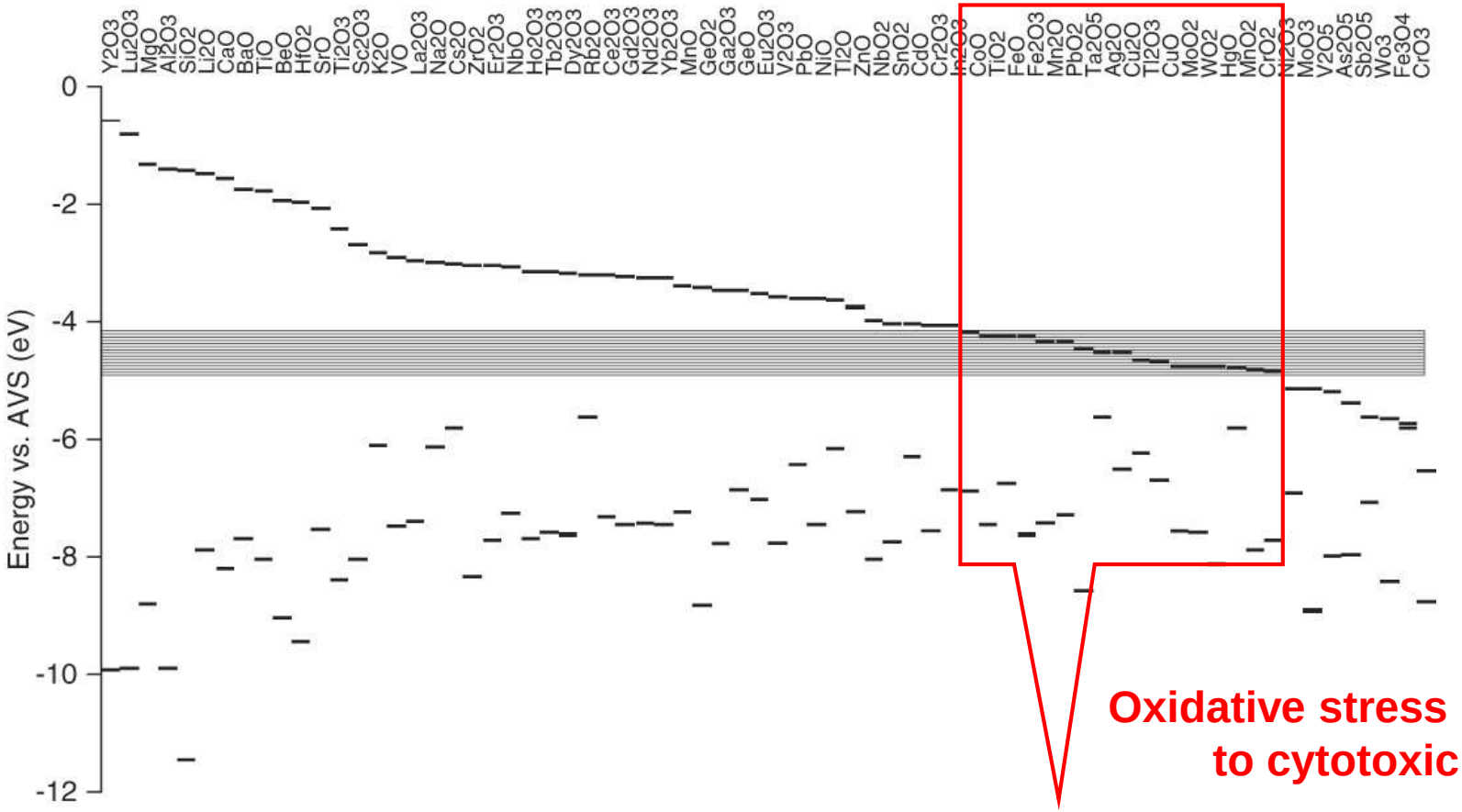
Cell redox couples



Burello hypothesis, 2011

Figure adapted from Gajewicz et al, *Nanotoxicology* 9, 2015

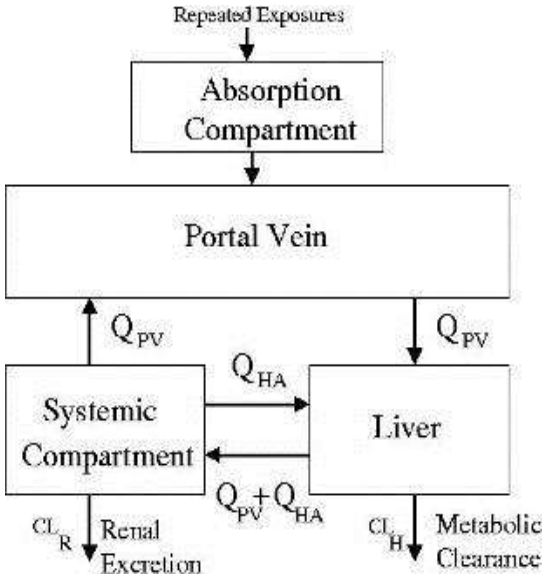
Predictions for 70 metal oxide nanoparticles



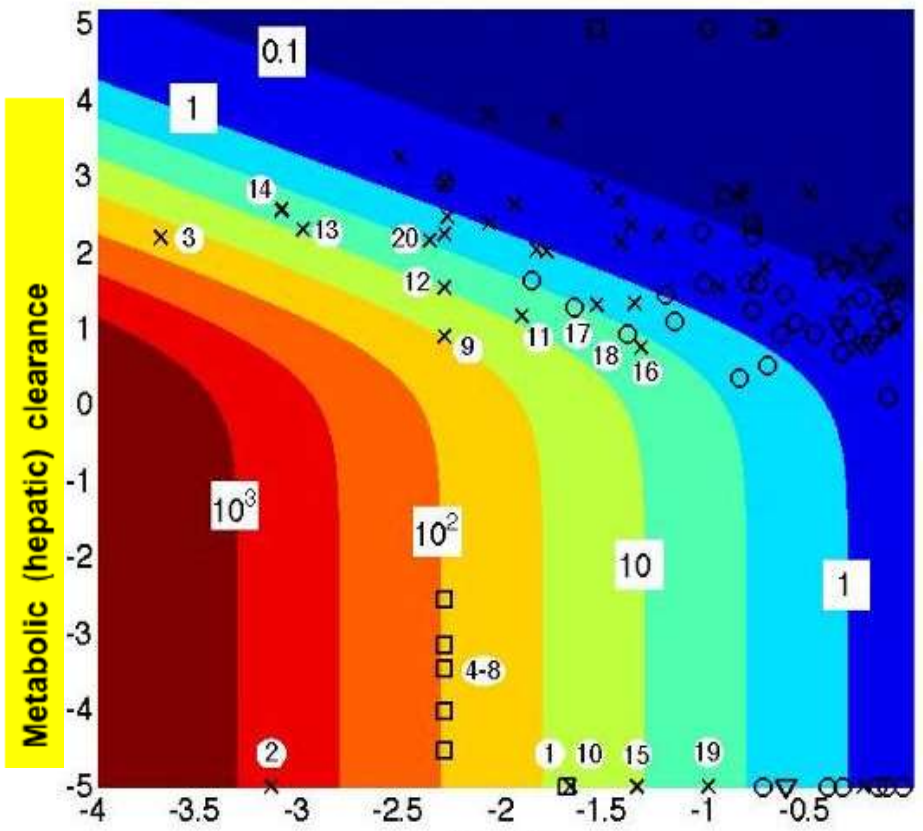
Oxidative stress leading to cytotoxicity

Burello & Worth, *Nanotoxicology* 5, 2011

Bioaccumulation in humans



Simple PBK model

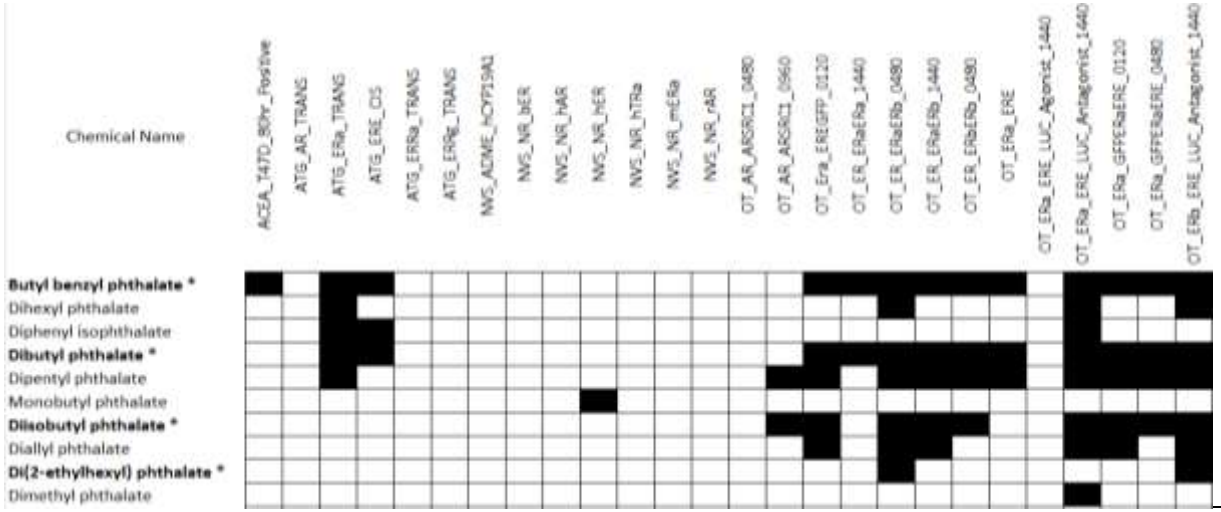


Unbound fraction – renal clearance

Tonnelier et al (2012). Screening of chemicals for human bioaccumulation potential with a physiologically based toxicokinetic model. Arch Toxicol 86, 393-403.

Endocrine activity – EATS pathway interactions

Biological fingerprints for 10 phthalates based on data from 26 endocrine-related Toxcast assays



Biological similarity matrix for 10 phthalates based on data from the 26 endocrine-related Toxcast assays

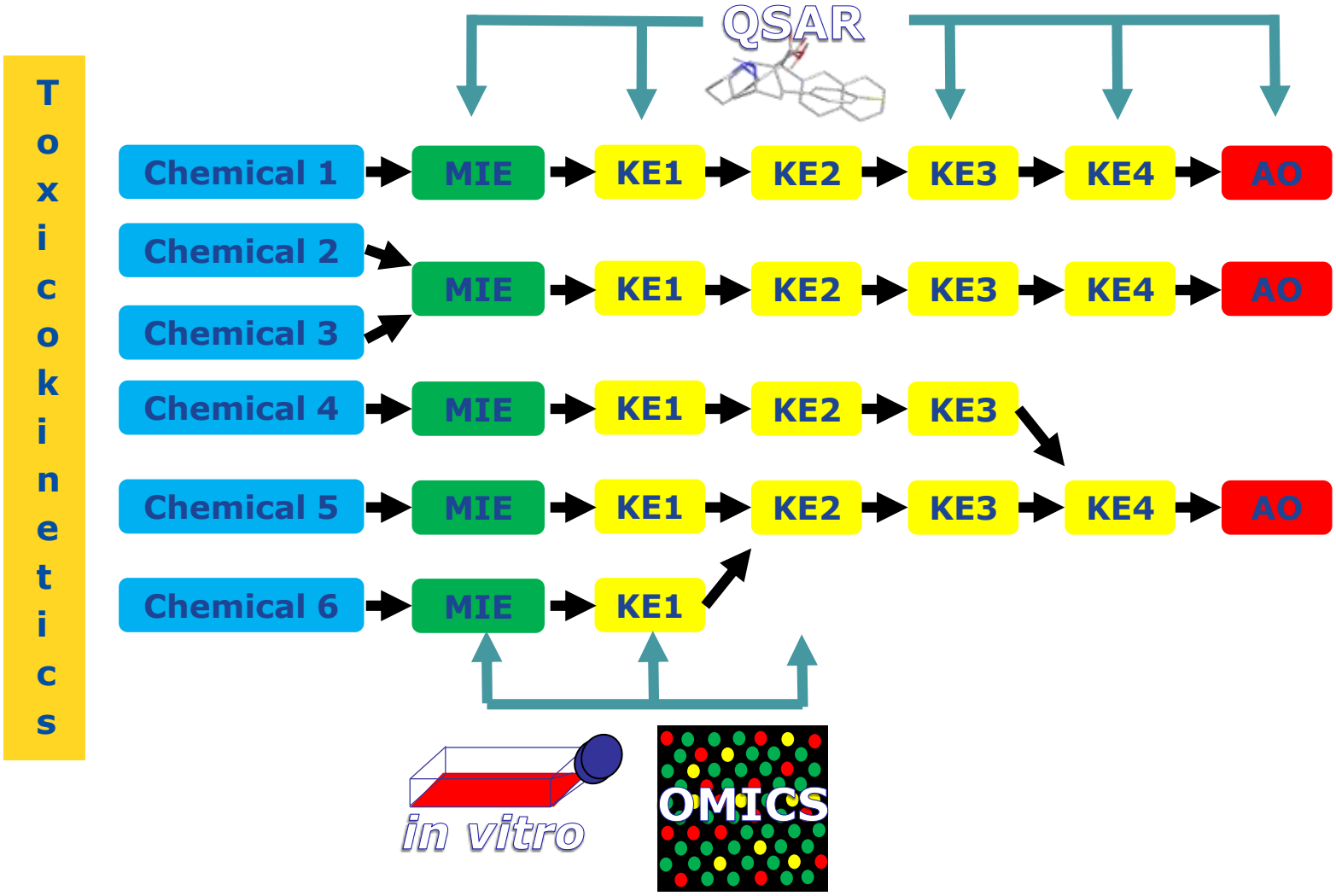
	Butyl benzyl phthalate	Dihexyl phthalate	Diphenyl isophthalate	Dibutyl phthalate	Dipentyl phthalate	Monobutyl phthalate	Diisobutyl phthalate	Diallyl phthalate	Di(2-ethylhexyl) phthalate	Dimethyl phthalate
Butyl benzyl phthalate	100	31	23	92	71	0	57	46	15	8
Dihexyl phthalate	31	100	40	33	36	0	30	43	50	25
Diphenyl isophthalate	23	40	100	25	17	0	9	13	0	33
Dibutyl phthalate	92	33	25	100	77	0	62	50	17	8
Dipentyl phthalate	71	36	17	77	100	0	82	55	18	9
Monobutyl phthalate	0	0	0	0	0	100	0	0	0	0
Diisobutyl phthalate	57	30	9	62	82	0	100	67	22	11
Diallyl phthalate	46	43	13	50	55	0	67	100	33	17
Di(2-ethylhexyl) phthalate	15	50	0	17	18	0	22	33	100	0
Dimethyl phthalate	8	25	33	8	9	0	11	17	0	100

Mixtures: component-based prediction approaches

	Independent Action (IA)	*Concentration Addition (CA)*
When to use	***Dissimilar MoA / different target organs***	***Similar MoA / common target organ***
Mathematical definition	$E_{Mix} = 1 - \prod_{i=1}^{n}(1 - E_i)$	$ECx_{(Mix)} = \left(\sum_{i=1}^{n} \frac{p_i}{ECx_i}\right)^{-1}$
Something from nothing?	***If individual chemicals elicit no effect, also no mixture effect***	***Combined effects can occur even if individual components are below threshold of effect***

Mixtures

Adverse Outcome Pathway network

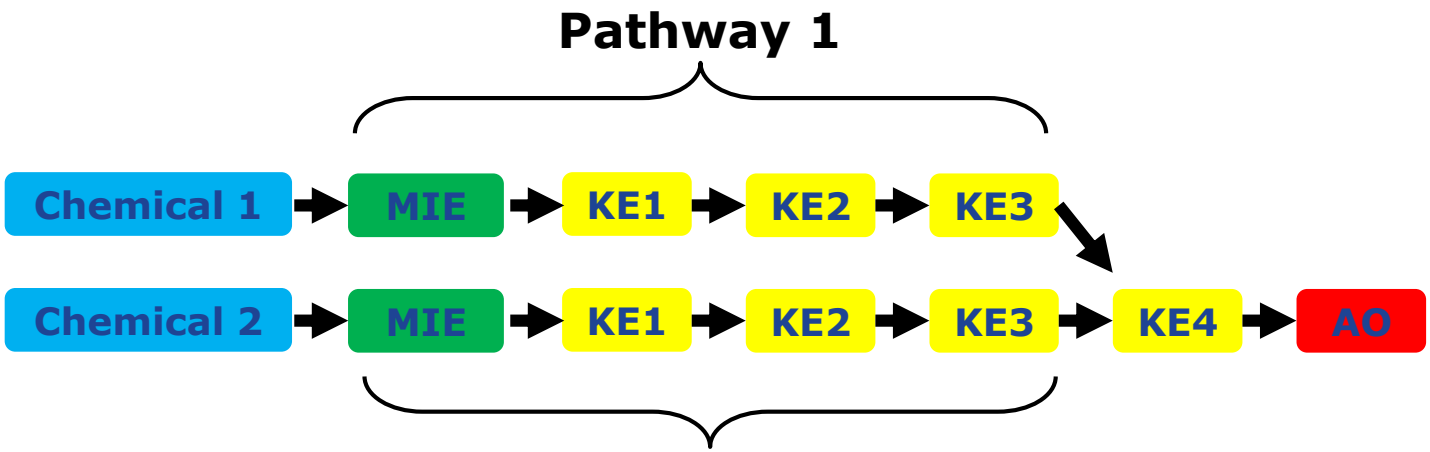


Bopp et al (2015) JRC Technical Report, EUR 27471 EN

AOP-based interpretation of IA and CA

Independent Action

$$E_{1,2} = E_1 + E_2 - (E_1 \cdot E_2)$$



Concentration Addition

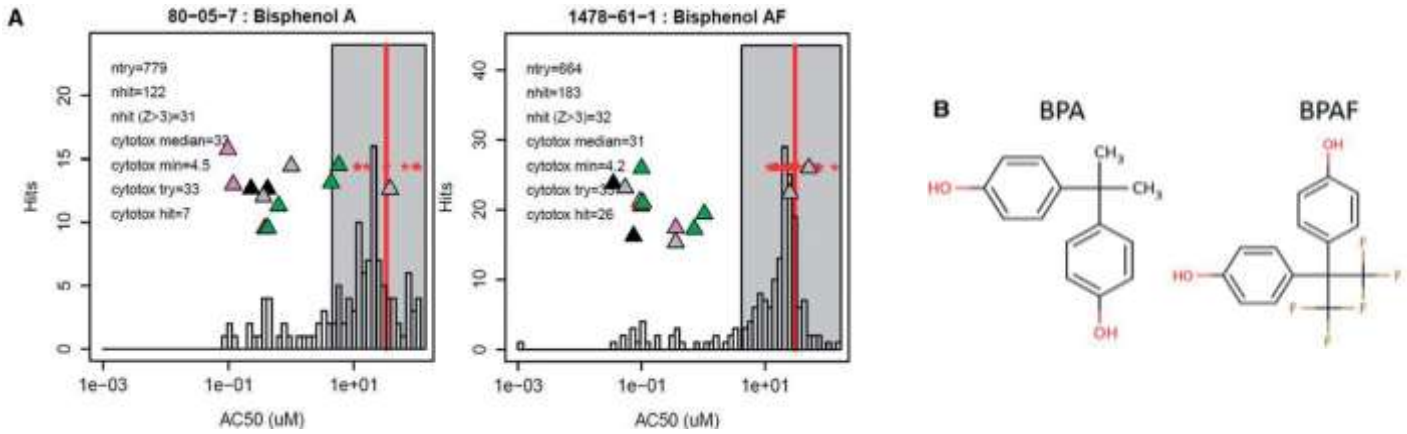
$$1/ECx_{1,2} = (C_1/ECx_1)+(C_2/ECx_2)$$

C_1 - Concentration of chemical 1

C_2 - Concentration of chemical 2

General criteria for low / no concern?

- Readily degraded / not persistent
- Not bioavailable
- Not bioaccumulative
- Not chemically reactive (e.g. by free radical formation, covalent bond formation)
- Non selective biological activity



Judson et al, 2016, *Tox Sci* 152

Conclusions

- Need for agreement on properties (and criteria) of (no / low) concern
- Opportunity to define properties in terms of chemistry and mechanistic biology
- Use of new approach methods:
  - Grouping and ranking based on levels of concern
  - Direct prediction of apical endpoints not necessary
- Protection rather than prediction!

Conclusions

"A clever person solves a problem. A wise person avoids it."

Albert Einstein