

Threshold of Toxicological Concern (TTC): Environmental

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EU Scientific Steering Committee

Opinion adopted on 26-27 October 2000:

- An area where further work is needed is the introduction of a "thresholds of toxicological concern" approach as a means of reducing unnecessary testing and determining priorities for risk assessment



Outline

What is it

Which ones exist

How was the ETNC derived

Comparable to PNECs

Concluding remarks



TTC and Risk Characterisation

It is generally accepted that the data requirements for risk assessment should be related to the extent of exposure

↑
Data

Annex VII – more than 1 tpa

- short-term acute toxicity: daphnia and algae

Annex VIII – more than 10 tpa

- Short-term acute toxicity with fish

Annex IX – more than 100 tpa

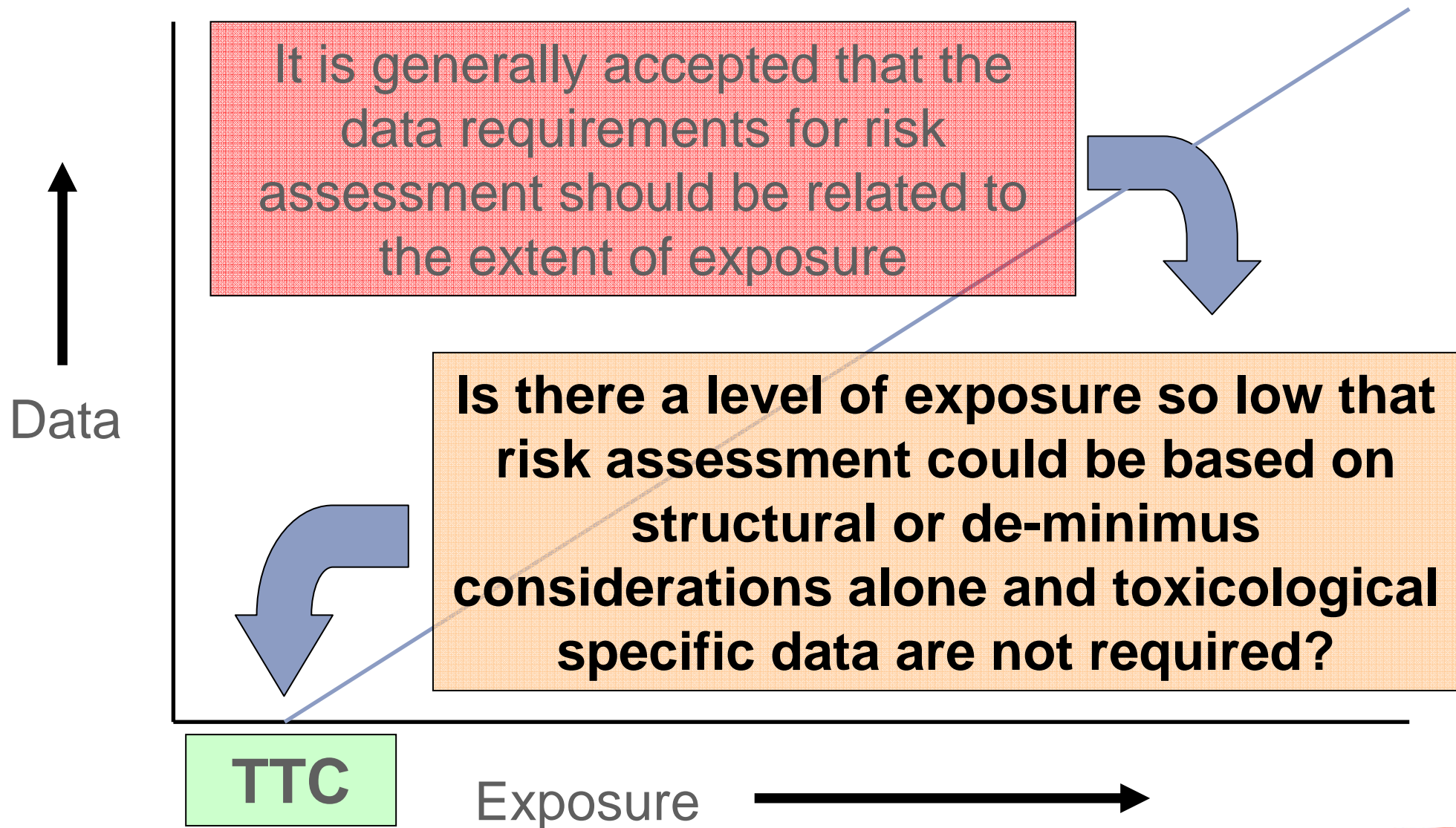
- Long-term toxicity with daphnia and fish
- Short-term studies on terrestrial organisms

Annex X – more than 1000 tpa

- Long-term toxicity studies on terrestrial organisms
- Long-term toxicity studies on sediment organism
- Long-term or reproductive toxicity to birds

Exposure →

TTC and Risk Characterisation



Thresholds of Concern

Threshold concepts of toxicological concern are based on the possibility of establishing an exposure threshold value for (groups of) chemicals below which no significant risk is to be expected

- Summary parameter of the existing, available data on the toxicity of chemicals
- Can be used when experimental data is lacking

Related concepts

Threshold of Toxicological Concern

- based on the possibility of establishing an exposure threshold value for chemicals, below which there is no significant risk

Threshold of No Further Toxicological Concern

- based on the identification of a dominant concern, e.g. carcinogenicity
- the evaluation of other toxicological end-point is considered not to influence the outcome of the hazard assessment.

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Environmental Concepts

EMEA paper on Environmental Risk Assessment for non-GMO-containing drugs (2001)

- describes a step-wise, tiered procedure for the ERA
- first tier consists of deriving a crude predicted environmental concentration (PEC) in the aquatic compartment for the pharmaceutical ingredient or its major metabolites
- if this crude PEC is < 0.01 ug/L, and no environmental concerns are apparent, no further assessment is deemed necessary

CSTEE opinion (2001)

- did not consider that the proposed number is scientifically valid
- examples of pharmaceuticals are available that show higher aquatic toxicities

Environmental Concepts

ECETOC Taskforce: Environmental Exposure Threshold of No Ecotoxicological Concern (ETNC) (2003)

- Derivation of a toxicity-data-based environmental exposure threshold
 - subscript function to indicate the environmental compartment for which the concept is considered applicable
- $ETNC_{\text{aquatic}}$
 - Aquatic Exposure Threshold of No Ecotoxicological Concern
- de Wolf W, Siebel-Sauer A, Lecloux A, Koch V, Holt M, Feijtel T, Comber M, and Boeije G (2005). Mode of Action and Aquatic Exposure Thresholds of No Concern (ETNC_{aq}). *Environmental Toxicology and Chemistry* **24**:479-485

Environmental Concepts

TTC concept for estrogen agonist in the aquatic environment

- CEFIC LRI workshop of regulatory, industry and academic scientists held to discuss the use of the TTC in aquatic environmental risk assessment.
- Examined the use of the TTC concept for endocrine active substances with an estrogenic mode of action.
- The feasibility and acceptability, general advantages and disadvantages, and the specific issues that need to be considered when applying the TTC concept for endocrine active substances in risk assessment were addressed.
- Issues surrounding the statistical approaches used to derive TTCs were also discussed.

Environmental Concepts

Internal thresholds or residues

- Critical or Lethal Body Burden for narcosis-type substances by **McCarty LS (1986)**
 - Link between bioaccumulation and ecotoxicity
 - Applicable to MOA 1 and 2 substances according to the Verhaar categorisation scheme
 - **$LBB = LC50 * BCF$**

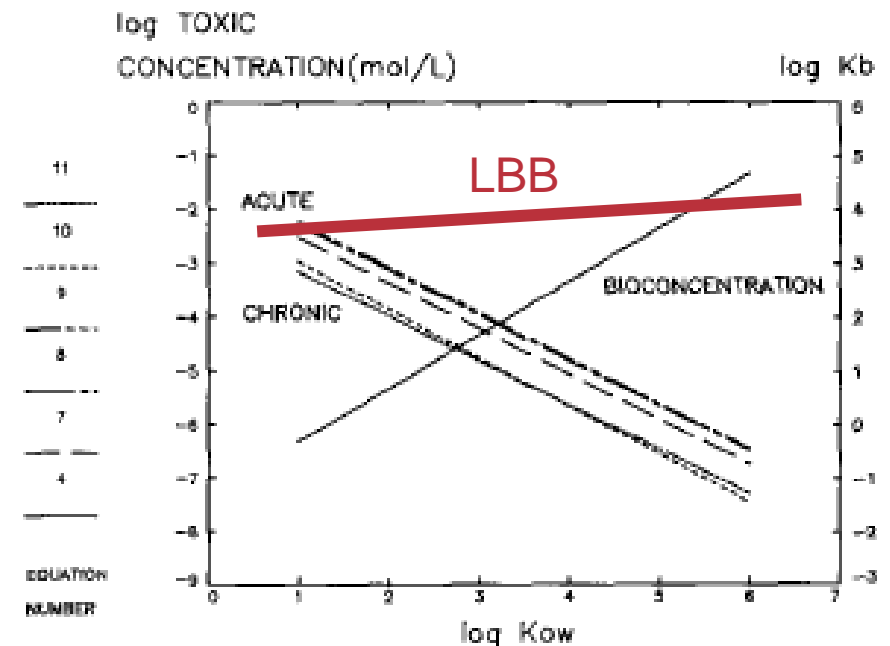


Fig. 1. Relationship between toxicity, bioconcentration and octanol-water partition coefficient for some narcotic organic chemicals.

McCarty LS (1986) The relationship between aquatic toxicity QSARs and bioconcentration for some organic chemicals. *Environ. Toxicol. Chem.* 5:1071-1080

Environmental Concepts

Internal thresholds or residues

- Critical Body Residue at death for reactive type substances by Verhaar et al (1999)
 - Is a surrogate dose metric for the amount of toxicant that has interacted with the target
 - Integrates exposure over time
 - Applicable to MOA 3 substances according to the Verhaar categorisation scheme
 - **Critical Area Under the Curve (CAUC)**

Verhaar, H.J.M, de Wolf, W., Dyer, S.D., Legierse, K., Seinen, W., and J.L.M. Hermens (1999) An LC50 vs time model for the aquatic toxicity of reactive and receptor-mediated compounds. Consequences for bioconcentration kinetics and risk assessment. *Env.Sci. Technol.* 33:758-763

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Environmental Threshold of No Ecotoxicological Concern (ETNC)

Data used:

- PNECs derived as part of the EU ESR (Priority List Chemicals)
- NOECs in the ECETOC Aquatic Toxicity database
- EU New Chemical Substances database
- EU HEDSET analysis
- US EPA Duluth Fathead Minnow database
- IRAS, the Netherlands, Guppy database
- QSAR prediction realistic worst case toxicity
- US EPA Freshwater Criterion Continuous Concentrations (CCC) for metals

EU Risk Assessments for Priority List Chemicals

PNECs derived for the aquatic environment in draft or completed EU Risk Assessments for EU Priority Lists chemicals

- EURATS-Online (status June 2002)
- The lowest number for each of 3 different Modes of Action (Verhaar categorisation)

Name	CASRN	PNEC (ug/L)	MOA ^a
Alkanes, C10-13, Chloro	85535-84-8	0.5	1
4,4'-isopropylidenephenol	80-05-7	1.6	2
Acrolein (Acrylaldehyde)	107-02-8	0.1	3

^a 1 = non-polar narcosis; 2 = polar-narcosis; 3 = electrophiles or pro-electrophiles

ECETOC database – lowest values

Data taken from the ECETOC Aquatic Hazard Assessment database.

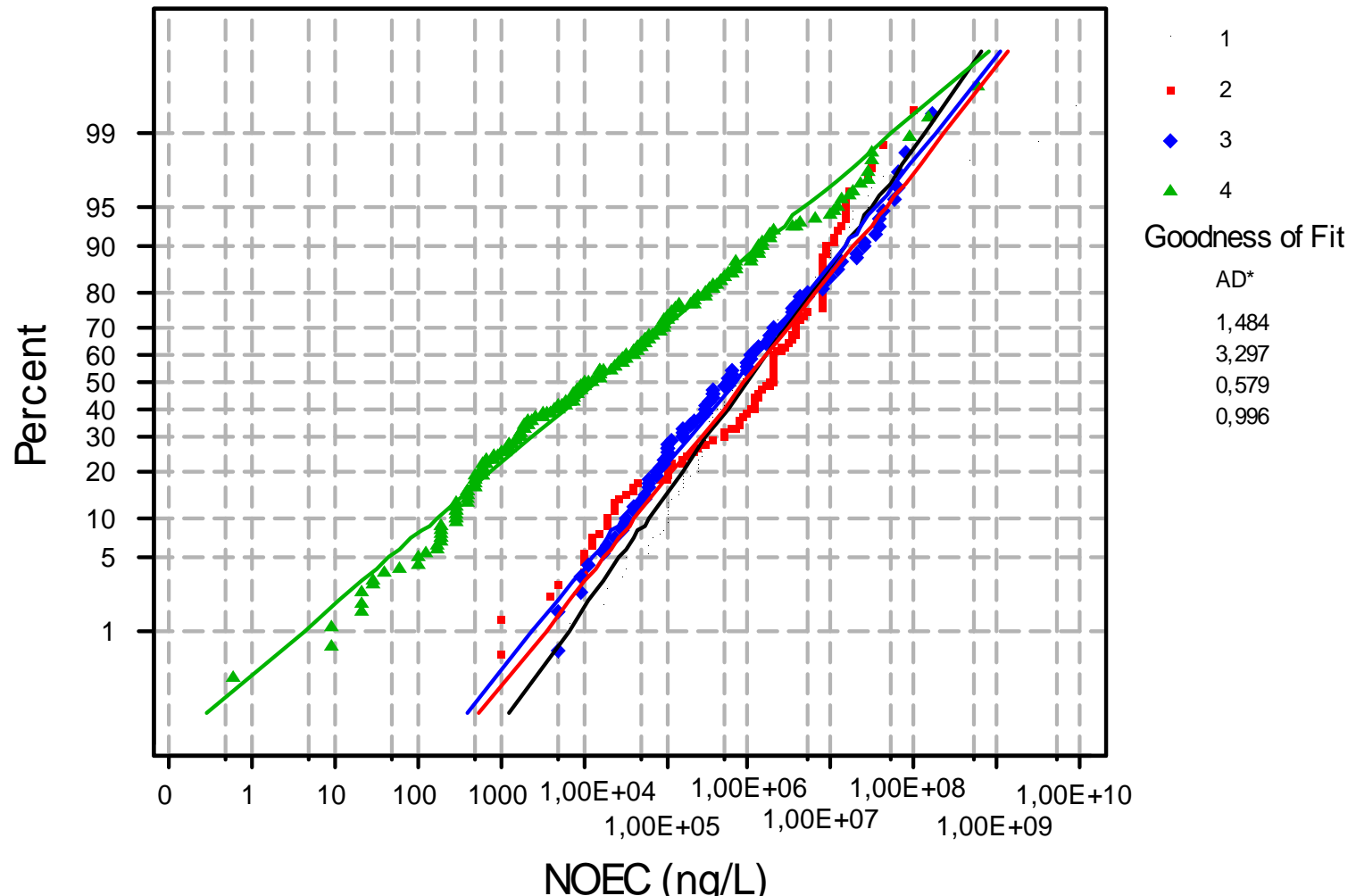
- Lowest NOEC values

Name	CASRN	NOEC (ug/L)	MOA
Pentachlorobenzene	608-93-5	5 ^a	1
3,4-dichloroaniline	95-76-1	1 ^b	2
2,4-dinitro-6-sec-butylphenol	88-85-7	4.9 ^c	3
fenthion	98-82-8	0,0006 ^d	4

^a Chaisuksant ea 98; ^b Guilherme et al, 1999; ^c Woodward, 1976; ^d Roux, 1995

ECETOC database - Probability

Lognormal base 10 Probability Plot for NOEC (ng/L) By MOA
 ML Estimates



Data overview

All concentration values are expressed in ug/L

Database	Mode Of Action	Lowest Value	DCC(95%)	ETC-95		
US EPA Metals	not applicable	0,77				
Existing Substances RA	1	0,5		0,5		
Existing Substances RA	2	1,6		1,6		
Existing Substances RA	3	0,1		0,1		
Existing Substances RA	All (1-3)		1	0,202		
New Chemicals Database	1		10			
New Chemicals Database	2		10			
New Chemicals Database	3		100			
New Chemicals Database			100			
ECETOC AHA Database		5	22	10	0,5	2,2
ECETOC AHA Database		1	14	10	0,1	1,4
ECETOC AHA Database		4,9	9	100	0,049	0,09
ECETOC AHA Database		0,0006	0,036	100	0,000006	0,00036
Fathead Minnow	1	62	500	100	0,62	5
Fathead Minnow	2	14	1199	100	0,14	12
Fathead Minnow	3	3	71	1000	0,003	0,071
Fathead Minnow	4	0,2	6	1000	0,0002	0,006
	1			100		
	2			100		
	3			1000		
	4			1000		
QSARs -acute	1	12		100	0,12	
QSARs -chronic	1	1,4		10	0,14	

ETNC_{aq}, MOA1-3 = 0.1 ug/L

Environmental Concepts

Section 304(a)(1) of the Clean Water Act requires US EPA

- to develop criteria for water quality that accurately reflects the latest scientific knowledge.
- Freshwater Criteria Maximum Concentration (CMC) - acute limit
- **Freshwater Criterion Continuous Concentration (CCC) - chronic limit**

EPA has established such values for several metals and some pesticides.

- Numeric freshwater CCC criteria values for Cadmium, Chromium (III & VI), Copper, Cyanide, Lead, Mercury, Nickel, Selenium and Zinc
- Lowest number is for **mercury** with an EPA numeric criteria of **0.77 ug/L**

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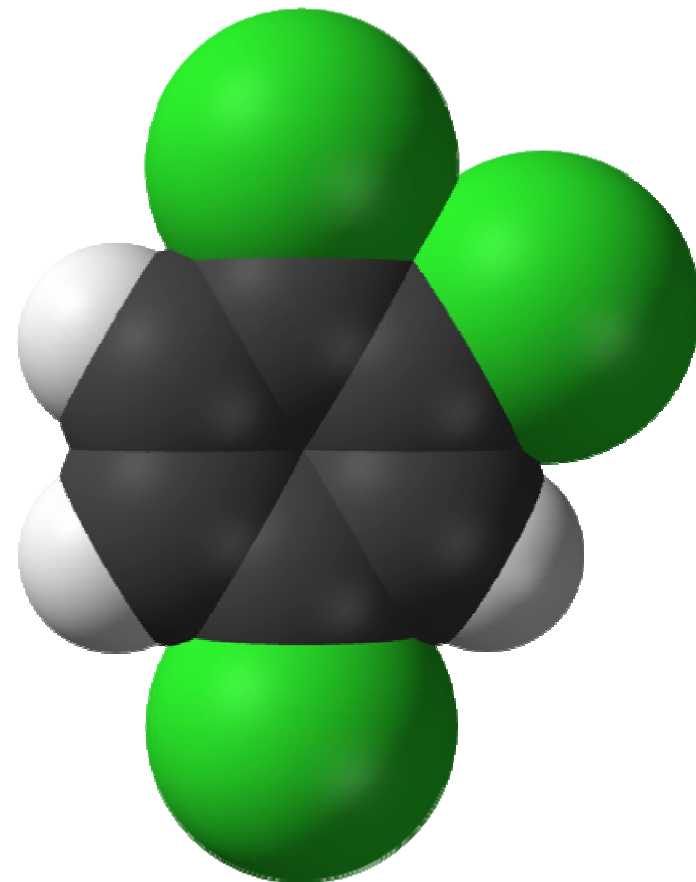
Comparable to PNECs

Concluding remarks

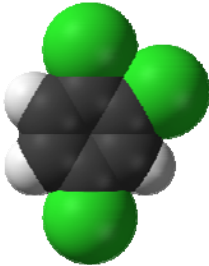


Substance identifiers

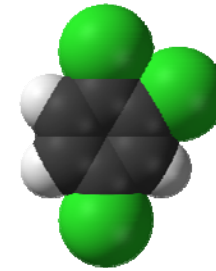
CASRN	120-82-1
Name	1,2,4-trichlorobenzene
Molecular Weight	181.46
Purity	>99%



Physico-chemical properties

Physical state	liquid	
Melting point	17°C	
Boiling point	213.5°C at 1,013 hPa	
Relative density	1.456 g/cm ³ at 20°C	
Vapour pressure	21.5 Pa at 20°C	
Water solubility	36 mg/l at 20°C	
Octanol/water	log Kow = 4.2	
Henry's Law constant	181 Pa m ³ /mol at 20°C	

Toxicity data



ETNCaq

Mechanism of action

MOA1 (Non-polar narcosis)

$$\text{ETNC} = 0.1 \text{ ug/L}$$

(Q)SAR estimated with ECOSAR (US EPA)

Fish	96hLC50	1.6 mg/L
Daphnia	48hIC50	2.0 mg/L
Algae	72hErC50	1.37 mg/L

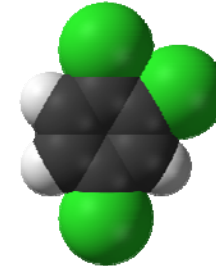
Assessment factor = 10,000

$$\text{PNEC} = 0.137 \text{ ug/L}$$

Assessment factor = 1,000 (US EPA)

$$\text{PNEC} = 1.37 \text{ ug/L}$$

Toxicity data



Measured data

Fish	96hLC50	1.0 mg/L
Daphnia	48hIC50	1.55 mg/L
Algae	72hErC50	1.4 mg/L

Assessment factor = 1000 (EU TGD)

PNEC = 1 ug/L

Assessment factor = 100 (US EPA)

PNEC = 10 ug/L

Fish	28dNOEC	0.04 mg/L
Daphnia	21dNOEC	0.06 mg/L
Algae	72hNOEC	0.37 mg/L

Assessment factor = 10 (EU & US)

PNEC = 4 ug/L

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Use of the TTC's

Strength

- Pragmatic approach to prioritising and assessing risks of very large number of substances
- Considers all available data
- Clear and simple to understand & communicate
- Refinements of analyses allows specific endpoints & effects to be considered

Weakness

- Potential loss of information
- Derivation requires careful consideration of assumption on data quantity, quality & confidence on the fitted distribution
- Derivation requires careful and transparent explanation to end user
- Use requires good & comprehensive exposure information

Application: isolated on-site stored and transported intermediates

REACH information requirements

- Available data
- Use under strictly control conditions
- No Chemical Safety Report



Product Stewardship: site-specific risk assessment

- Intermediates are most often reactive substances (MOA3)
- Perform emission and exposure assessment
- Risk Characterisation: Compare local PEC_{aq} to $ETNC_{aq,MOA1-3}$

Application: data poor substances

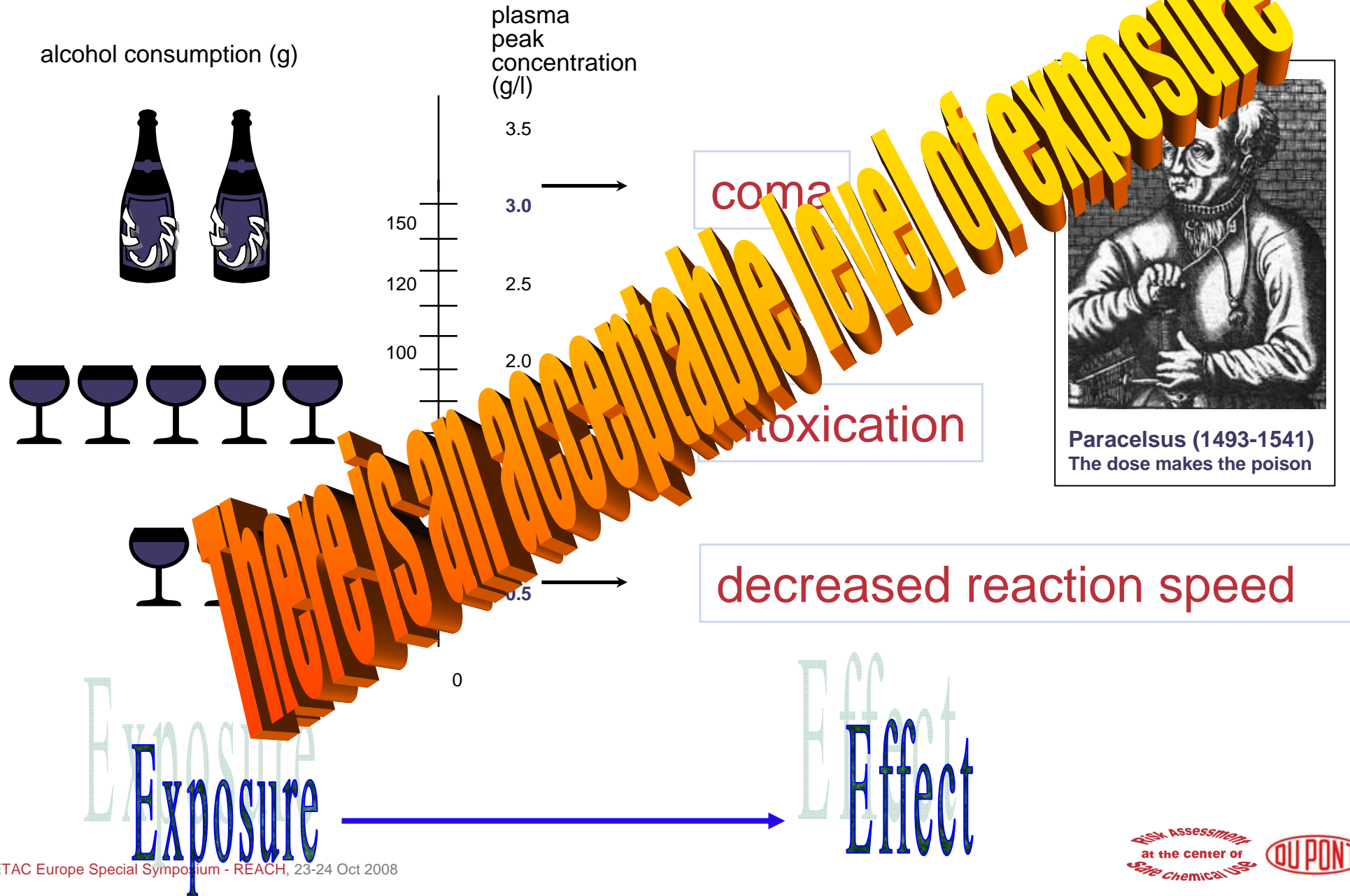
REACH - Extrapolation from *in-vitro* data on mechanism of action to an *in-vivo* toxicological reference value

- Endpoints or mechanisms of dominant (public) concern

In absence of further information to the end-user

- To put environmental monitoring data in perspective
 - If a measured/estimated concentration of an (unknown) substance lies below any of the relevant environmental TTCs the substance is of no immediate concern

Application: Communication





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US EPA Duluth Fathead Minnow database

MODE OF ACTION AND AQUATIC EXPOSURE THRESHOLDS OF NO CONCERN

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TOM FEITEL,†† MIKE COMBER,‡‡ and GEERT BOEIJE††

Data taken from the US EPA Duluth Fathead Minnow database.

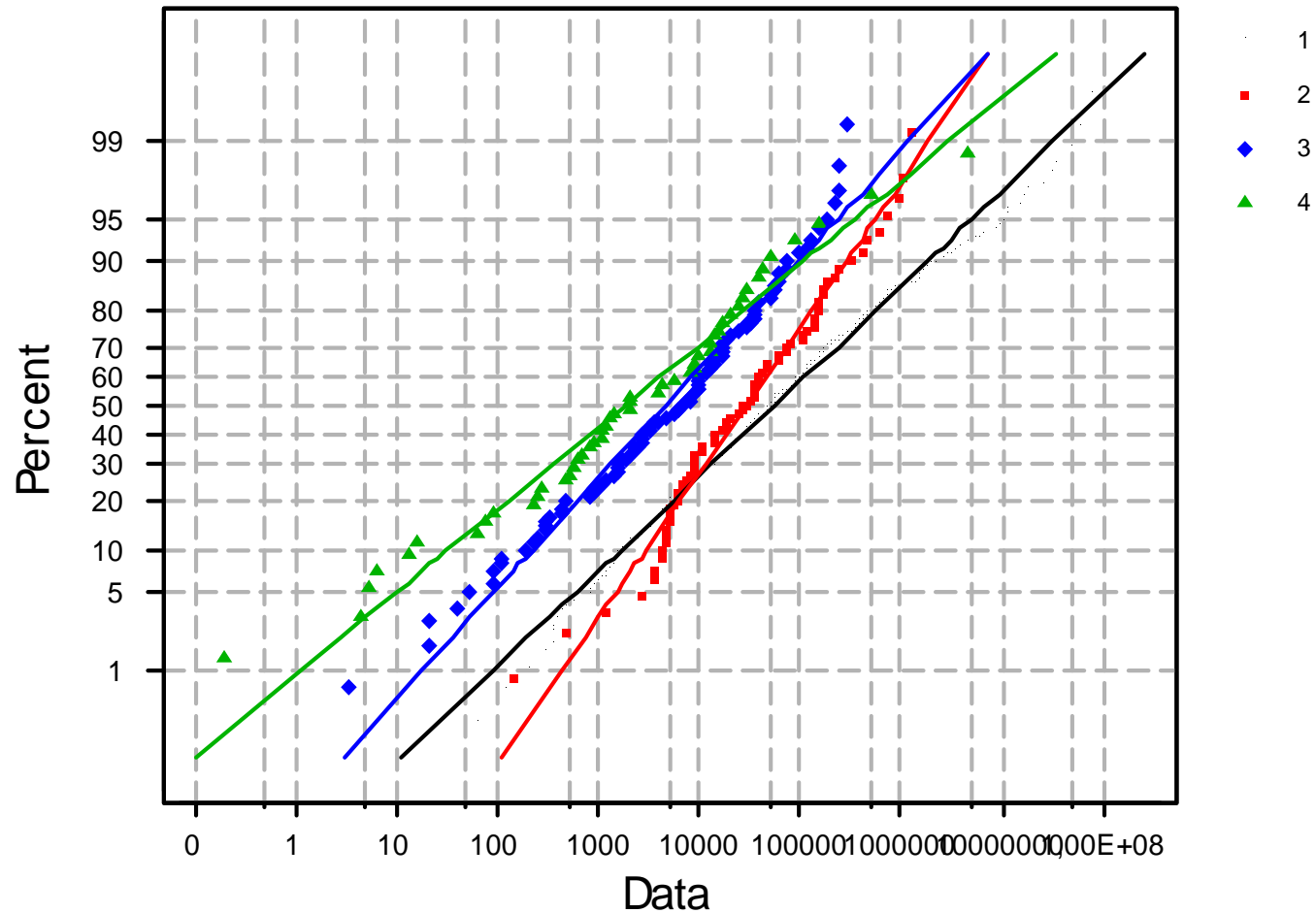
- Lowest LC50 values

Name	CASRN	LC50 (ug/L)	MOA
4-Decylaniline	37529-30-9	62	1
Nonylphenol	104-40-5	14	2
N-vinylcarbazole	1484-13-5	3	3
Flucythrinate	70124-77-5	0,2	4

^a Chaisuksant ea 98; ^b Guilherme et al, 1999; ^c Woodward, 1976; ^d Roux, 1995

US EPA Duluth Fathead Probability assessment

Lognormal base 10 Probability Plot for LC50 (ug/L) By MOA_
 ML Estimates



EU-TGD QSARs

Prediction for a 'reasonable worst case' chemical with QSARs from the EU-TGD (1996/2003)

- At high log Kow a convergence of acute aquatic toxicity based on non-polar and polar narcosis MOA occurs
- Validity range of these QSARs is till approximately log Kow = 6
- For a chemical to have a **log Kow = 6** it should at least have a **MW of 200**

<u>Organism</u>	<u>L(E)C50 (ug/L)</u>	<u>NOEC (ug/L)</u>
Fish	64	40
Daphnia	19	1.4
Algae	12	-