



The Threshold Of Toxicological Concern

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Thresholds in Risk Assessment

Most hazard endpoints are considered to be thresholded. A safe exposure threshold can be determined by applying uncertainty factors

↑
Effect

Safe dose
for target
population

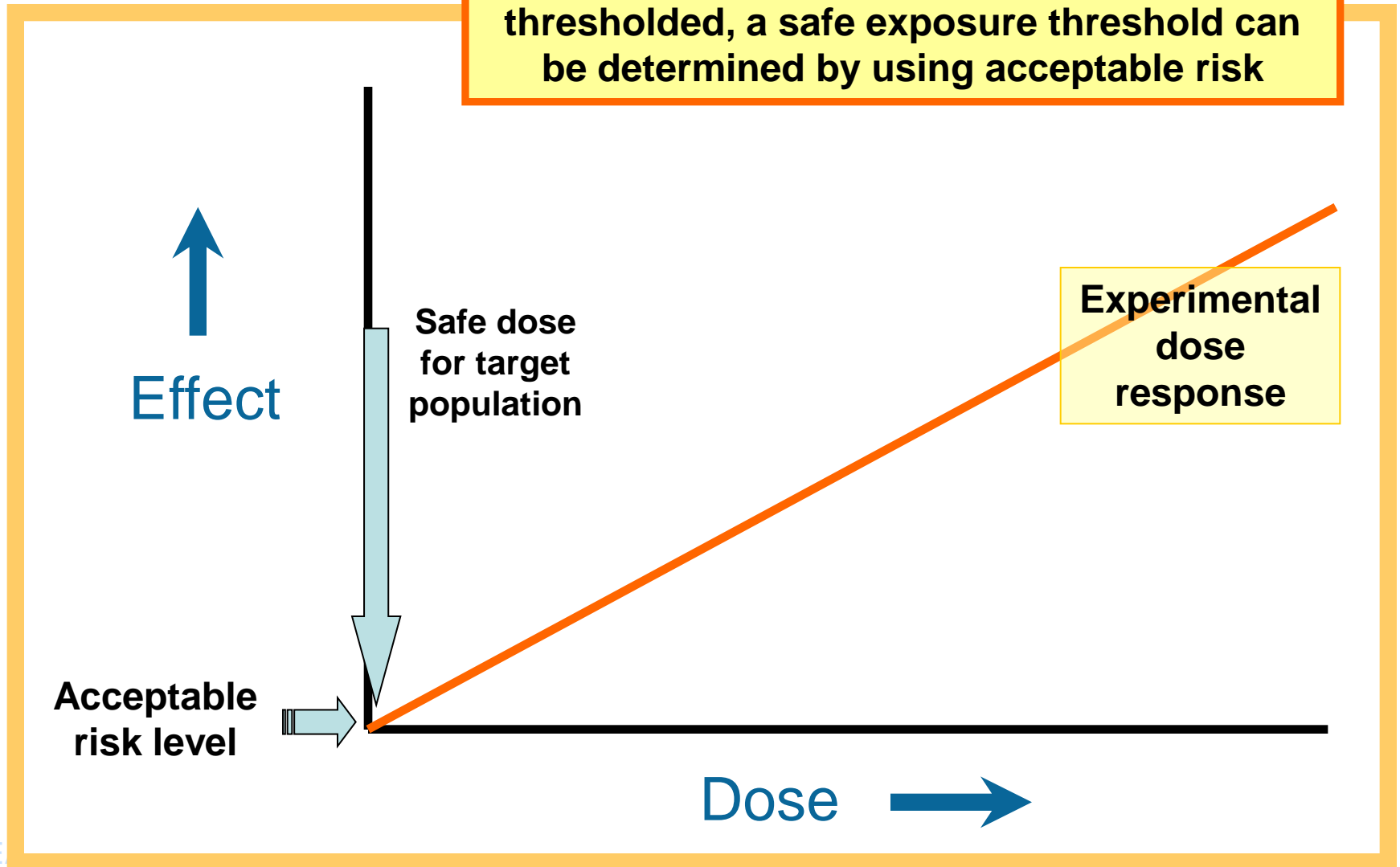
Experimental
dose
response

← Uncertainty
factor(s) →

Dose →

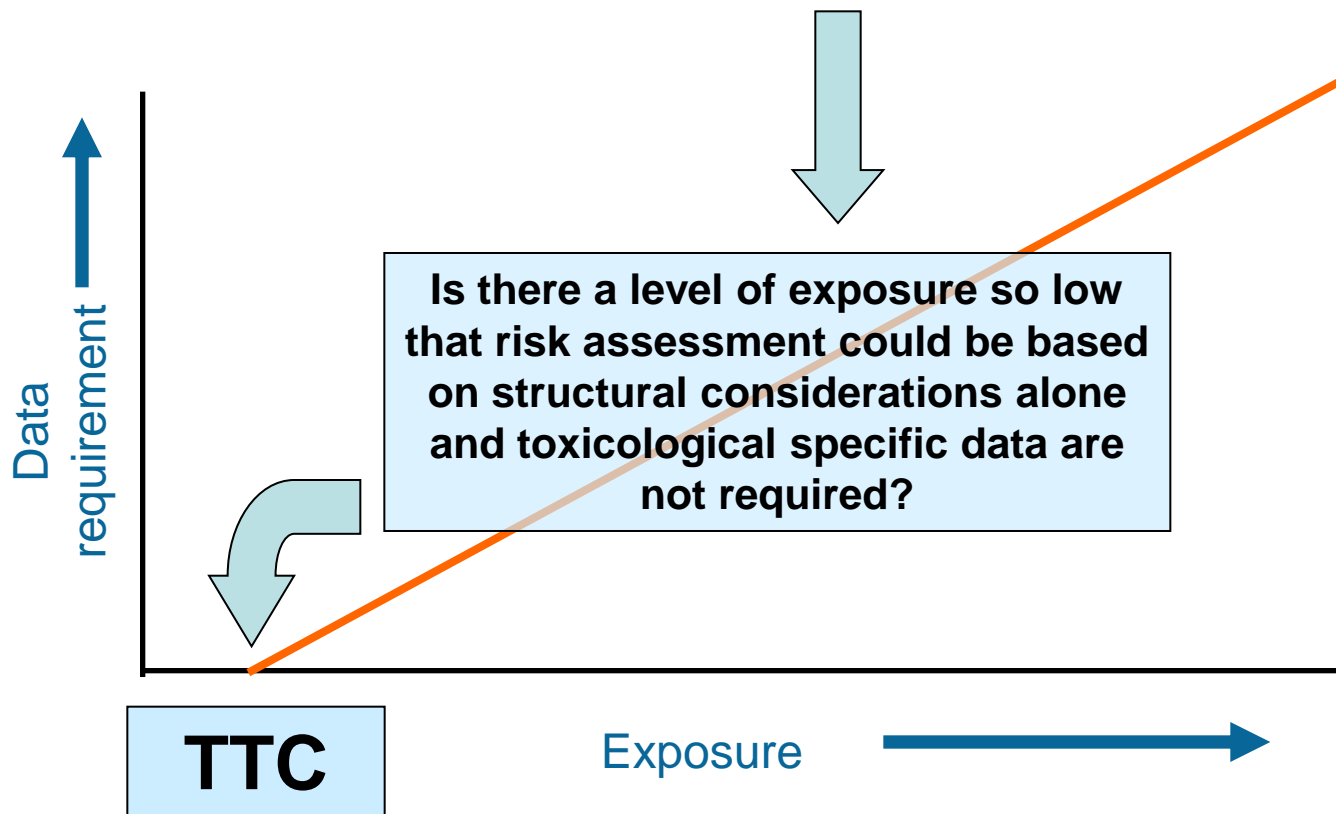
Thresholds in Risk Assessment

For hazard endpoints considered to be non-thresholded, a safe exposure threshold can be determined by using acceptable risk



Thresholds in Risk Assessment

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



What is the Threshold of Toxicological Concern (TTC)?



The TTC is a pragmatic risk assessment tool that is based on the principle that a human exposure threshold value can be established for all chemicals, below which there is a very low probability of an appreciable risk to human health.

What is the Threshold of Toxicological Concern (TTC)?

The TTC is a “Threshold of Thresholds”

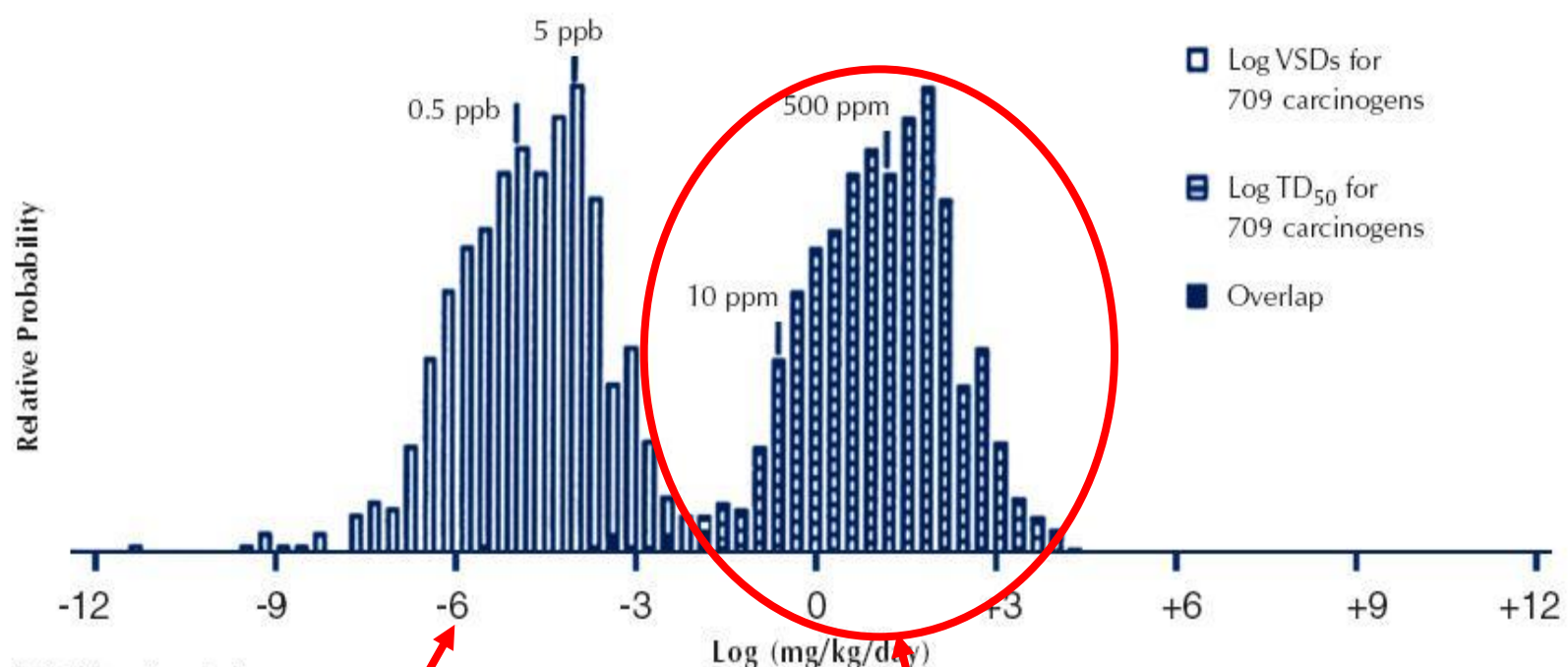
- The TTC is defined by examining the distribution of threshold values of chemicals for which we have experimental data
- From the distribution we can determine a threshold exposure at, or below which, the vast majority of chemicals would be determined as having an acceptable risk using standard risk assessment techniques

TTC for carcinogenicity

- The TTC approach was first applied to the human carcinogenicity hazard endpoint by Rulis (1986)
- The FDA's 0.5 ppb Threshold of Regulation (1995) was based on an evaluation of the distribution of carcinogenicity potencies of 477 substances included in the Gold database
- From this they concluded that *“a substance present in the daily diet for a lifetime at 0.5ppb would pose only negligible risk even if it were later shown to be a carcinogen”*
- A generic TTC value of 1.5ug/person has subsequently been established based on the assumption a chemical is present in all food and water consumed (1.5kg of each)

Distribution of potencies from the Carcinogenic Potency Database (Gold Database)

FIGURE 1
Distribution of TD₅₀s for chemical carcinogens and extrapolation to a 1 in a million risk



VSD: Virtually safe dose

Reprinted from *Food and Chemical Toxicology* Vol 37. Cheeseman MA, Machuga EJ and Bailey AB; A tiered approach to threshold of regulation, pp387-412, Copyright 1999, with permission from Elsevier.

Human Virtually Safe Dose

Rodent TD₅₀

TTC for carcinogenicity



A number of conservatisms are built into the process:

- **Linear extrapolation of carcinogenic risk from experimental TD50s is conservative**
- **No threshold for effect is assumed**
- **Incidence of carcinogens in the world of chemicals was taken to be 20%**
- **Threshold of Regulation assumes chemical to be present in *all* food and drink consumed**

Derivation of TTC for non-genotoxic chemicals based on structural class

- **For non-genotoxic and non-carcinogenic organic chemicals TTCs for systemic toxicity were developed by Munro *et al.* (1996)**
- **613 substances used**
 - **data from repeat dose toxicity studies**
 - **most sensitive species, sex, and toxicological endpoint recorded for each substance**
- **Classification of chemicals into 3 structural classes according to Cramer *et al.* (1978)**
- **Plotted distribution of NOAELs for each structural class**

Cramer classification scheme

Class I

Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity.

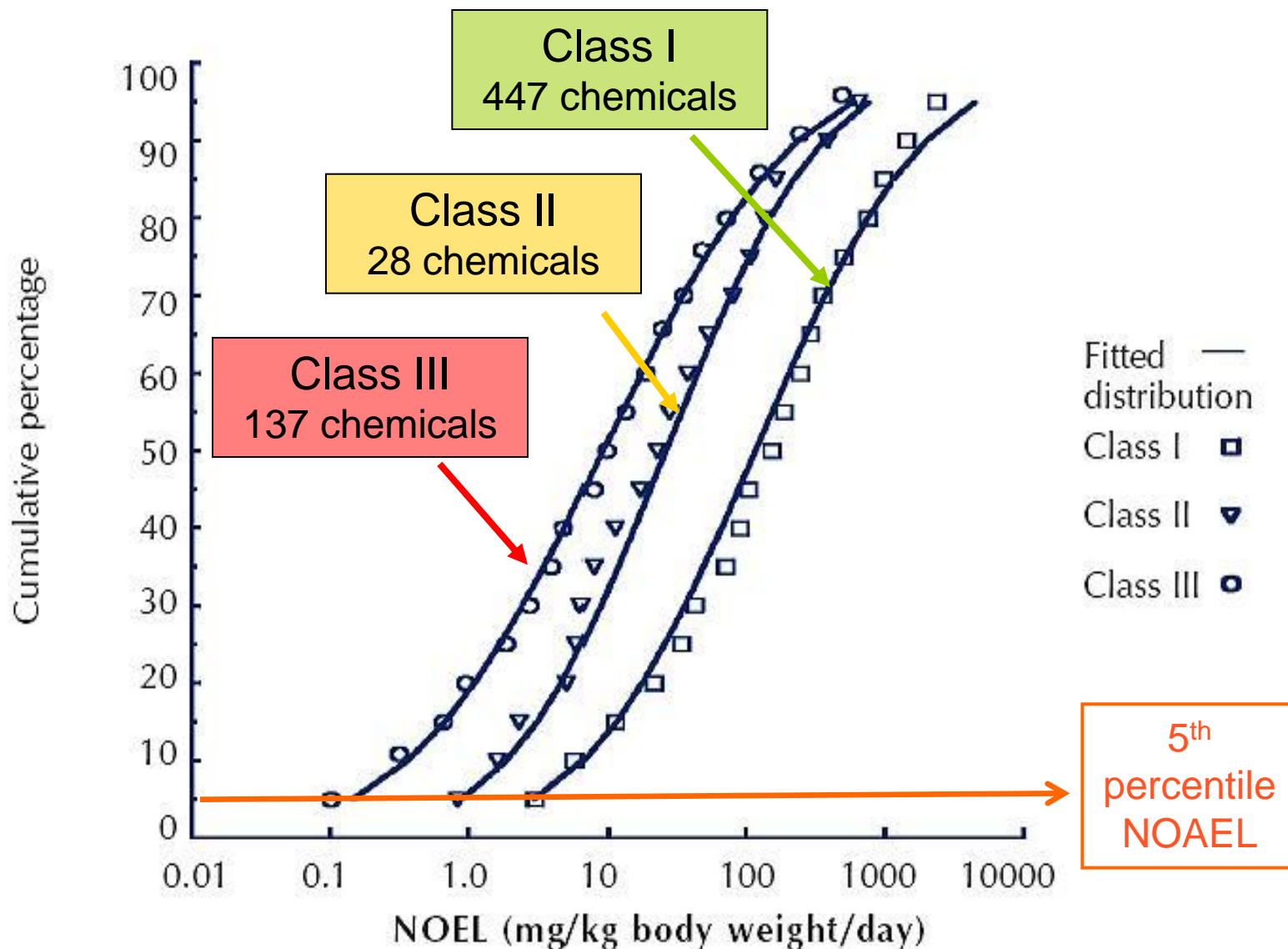
Class II

Substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III.

Class III

Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups.

Cumulative distributions of NOAELs for chemicals by structural class



Derivation of TTC based on the 5th percentile NOEL for each structural class

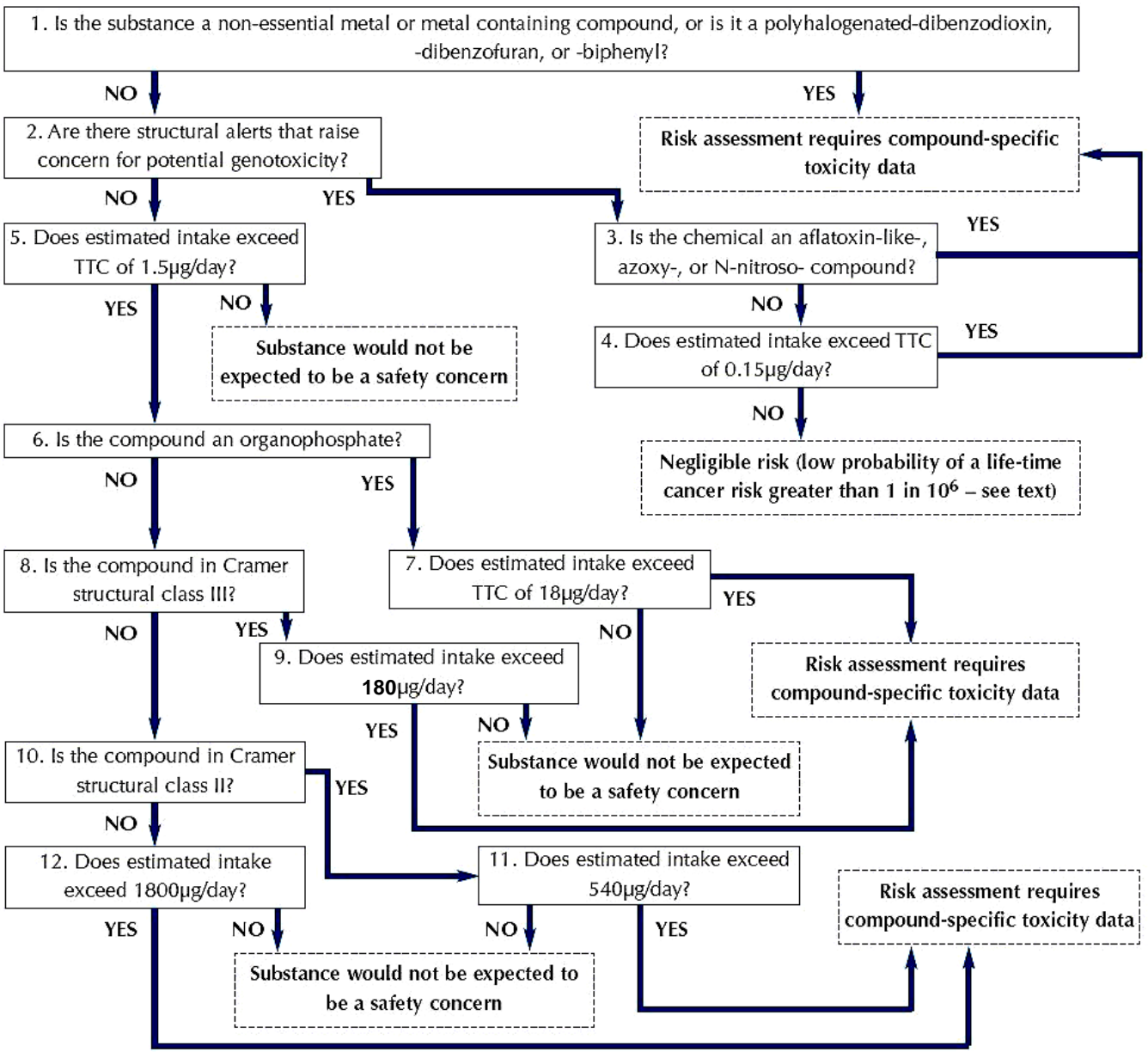
Structural class	5th percentile NOAEL (mg/kg bw/day)	TTC (mg/person/day)
I	3.0	1.8
II	0.91	0.54
III	0.15	0.09

Converting the NOEL into a TTC uses the normal 100-fold uncertainty factor and is based on a 60kg adult

Further refinements to the TTC

- **Over a number of years, refinements have been made to the original TTC process:**
 - **Examination of data sets to ensure that the TTC is protective for all toxicological endpoints - immunotoxicity, developmental neurotoxicity, developmental toxicity, and neurotoxicity, with the exception of organophosphates**
 - **Individual TTC developed for organophosphates**
 - **TTC for Class III chemicals re-evaluated after removal of organophosphates**
 - **Exclusion of chemical classes with high carcinogenic potency (Cohort of Concern)**
 - **Exclusion of other chemical classes not covered by the TTC - polyhalogenated dibenzodioxins, -dibenzofurans and -biphenyls, heavy metals, other non-essential metals and metal containing compounds, proteins, endocrine disruptors**

Kroes et al. (2004) decision tree for TTC



Current uses of TTC

Indirect food additives – USA FDA (1995)

- TTC of 1.5 μ g/person/day

Flavouring components – JECFA (1997), EFSA (2004)

- TTC defined using structural alerts/Cramer tree

Genotoxic impurities in pharmaceuticals – EMEA (2004)

- TTC of 1.5 μ g/person/day

Contaminants in foods – proposed by ILSI (1995)

- TTC defined using Kroes decision tree

TTC principle endorsed by the WHO IPCS (1998) and the SC on Toxicology, Ecotoxicology and Environment (2003)

SCCP, SCHER and SCENIHR draft opinion (2008) considers use of the TTC not applicable to cosmetic ingredients

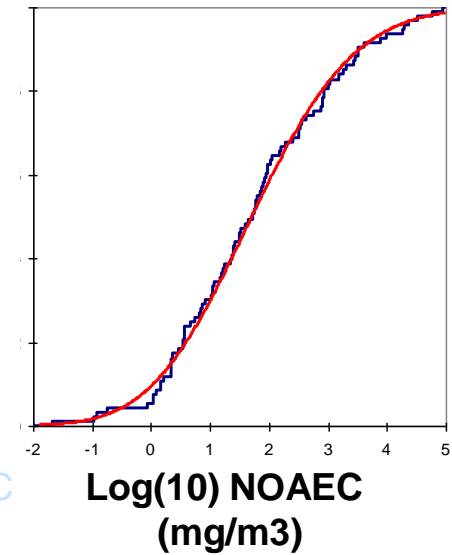
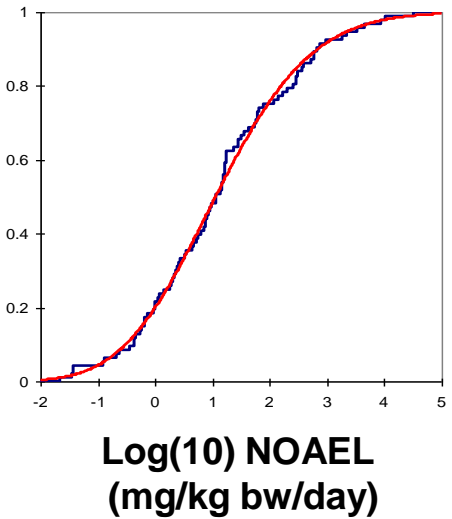
EFSA currently evaluating further the use of the TTC

Development of a TTC for other toxicological endpoints

- **The TTC was originally developed to cover human carcinogenicity and systemic toxicity endpoints**
- **It is feasible to apply the same concept to other human toxicological endpoints, and to environmental toxicity endpoints**
- **Recent publications propose the use of the TTC concept for:**
 - **Inhalation toxicity**
 - **Skin sensitisation**
 - **Aquatic toxicity**
 - **Environmental oestrogens**

Development of TTC for inhalation

Cumulative probability



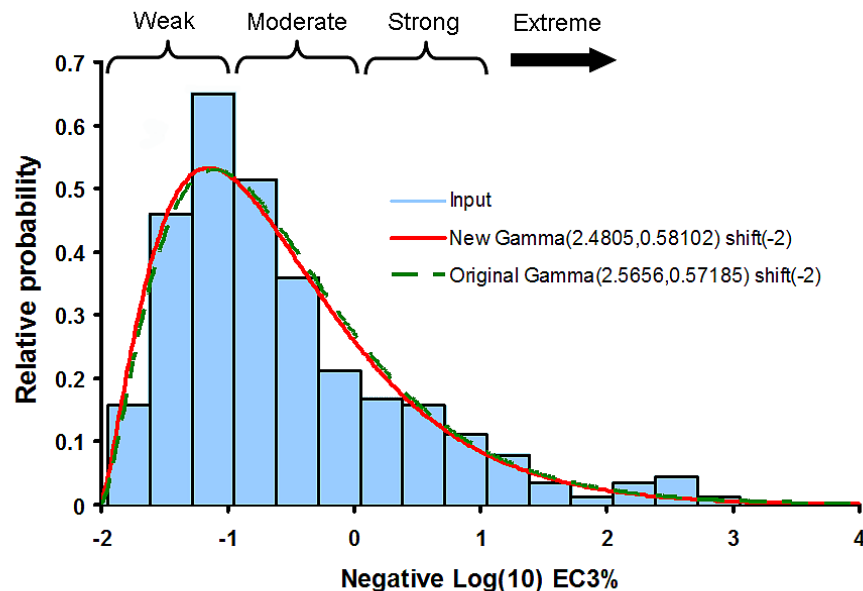
- 93 chemicals with inhalation toxicity data examined
- Systemic effects and local (lung) effects were investigated separately
- Distributions of NOAELs for systemic effects, and NOAECs for local effects were derived
- Using the 5th percentile NOAEL or NOAEC a TTC for humans was derived

	5th percentile NOAEL/C	TTC
Systemic effects (µg/kg bw/day)	130	5.1
Local effects (µg/g lung weight/day)	38	1.6

SEAC

Development of TTC for skin sensitisation

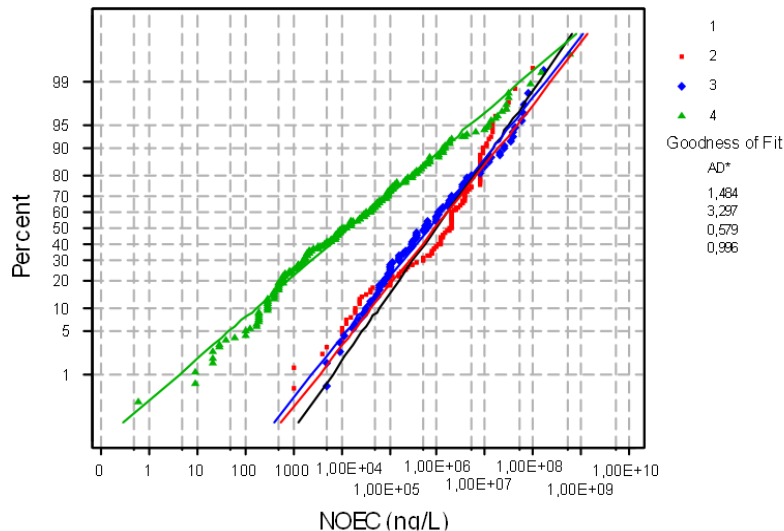
- Database of 271 chemicals tested in mouse Local Lymph Node Assay (LLNA)
- Incidence of sensitisers in the world of chemicals was defined as 20%
- Chemicals classified according to their reactive chemistry domain
- Dermal Sensitisation Threshold (DST) established for those chemicals which fall into the non-reactive domain



- **DST of $900\mu\text{g}/\text{cm}^2$ determined**
- **Because of the nature of the skin sensitisation QRA approach assessment factors need to be applied to the DST to obtain an Acceptable Exposure Level for humans**

Development of TTC for environmental (aquatic) exposure

- ECETOC task force derived a toxicity based Environmental Exposure Threshold of No Ecotoxicological Concern for freshwater systems ($ETNC_{aq}$)
- Analysed environmental toxicity databases (acute and chronic endpoints) and substance hazard assessments
- Stratified chemicals based on Mode of Action (Verhaar categorisation)

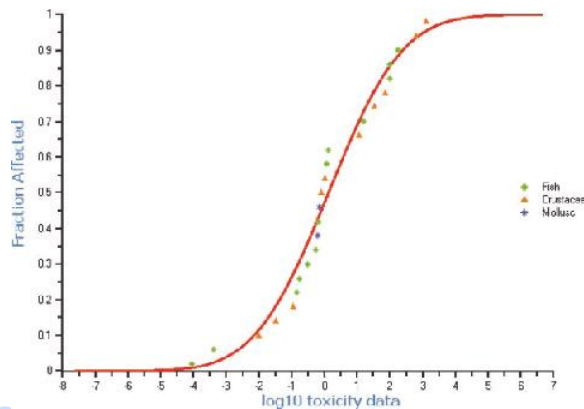


- Derived an $ETNC_{aq}$ for MOA1-3 chemicals as $0.1 \mu\text{g/litre}$ based on 95th percentile values from distribution with appropriate application factors

Development of TTC for environmental oestrogens

- 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
- Case study used the USFDA's Endocrine Disruptor Knowledge Base (EDKB) and the Institute of Environment and Health's REDIPED database to identify 69 substances that are oestrogenic in screening tests

• 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



TTC strengths



- **The TTC concept provides a scientifically valid and transparent method of defining a level of human exposure, for any chemical, at and below which the risk of adverse effects is very low**
- **The currently methodology has an established use in the evaluation of food contact chemicals, flavours and contaminants in foods, and is also used for genotoxic contaminants in pharmaceuticals**
- **The use the TTC concept benefits consumers, industry, and regulators, by avoiding unnecessary extensive testing and safety evaluations when exposure is below the relevant threshold value**
- **TTC methodology may also be useful for toxicological endpoints such as skin sensitisation and inhalation, and also for environmental toxicity endpoints**

TTC potential weaknesses

- **The TTC is a probabilistic tool – not protective of *all* chemicals**
- **Determination of the TTC relies on sufficient data, and on data quality**
- **TTC may ‘dilute’ data since databases used often encompass numerous toxicological endpoints for chemicals with differing mechanisms of action**
- **Consideration needs to be given to the chemicals on which the TTC is developed – new chemicals need to fall within the appropriate chemical space**
- **TTC values are small – will only supported very limited exposure scenarios**
- **Use of the TTC requires accurate exposure data**

The Threshold Of Toxicological Concern



Thank you for your attention