The TTC Concept - Application in the food area and possible applications to other sectors of health risk assessment

Prof. Em. Dr. Robert Kroes

Institute for Risk Assessment Sciences (IRAS) Utrecht University

The Netherlands

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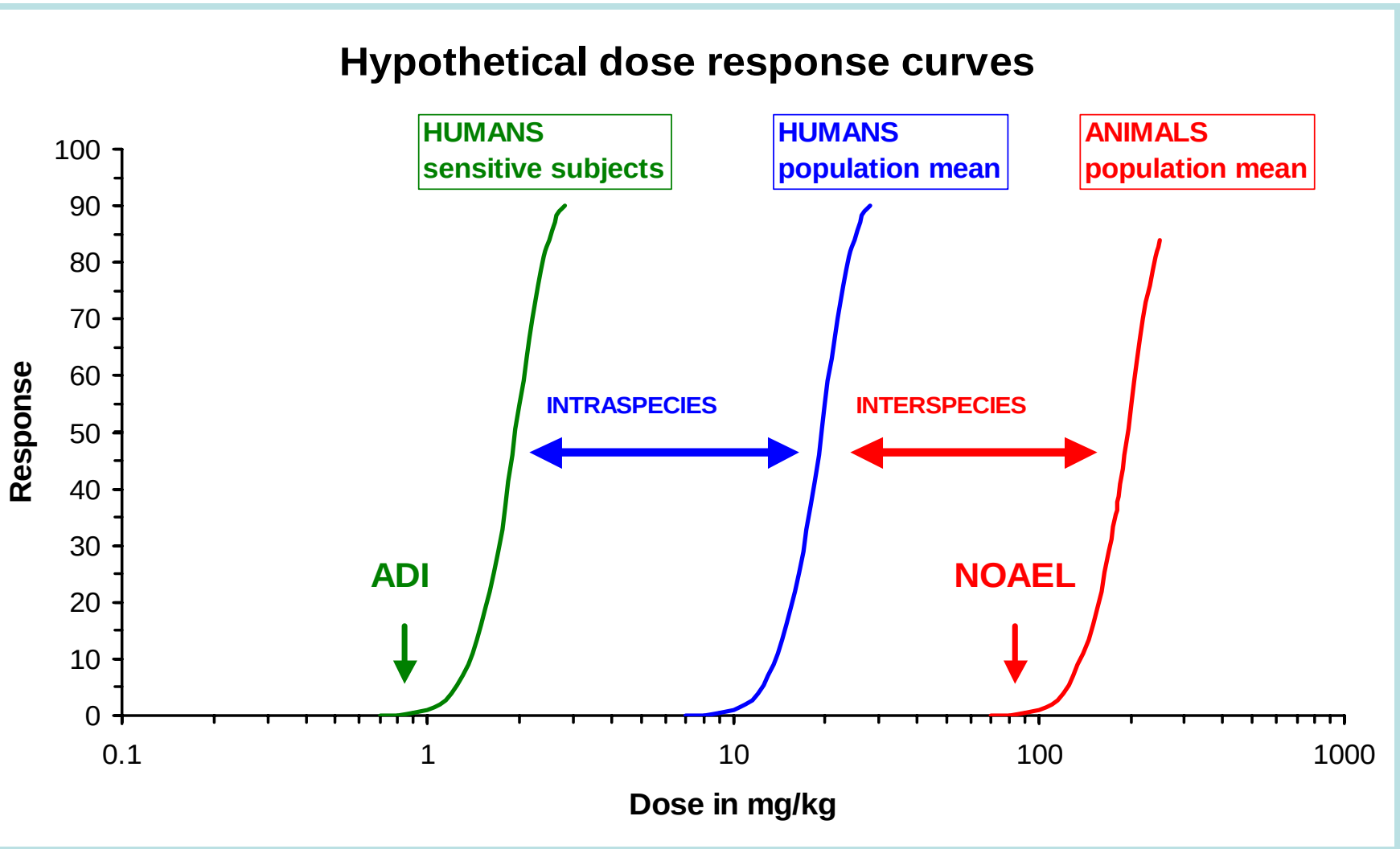
Threshold principles
Derivation TTC
Application TTC

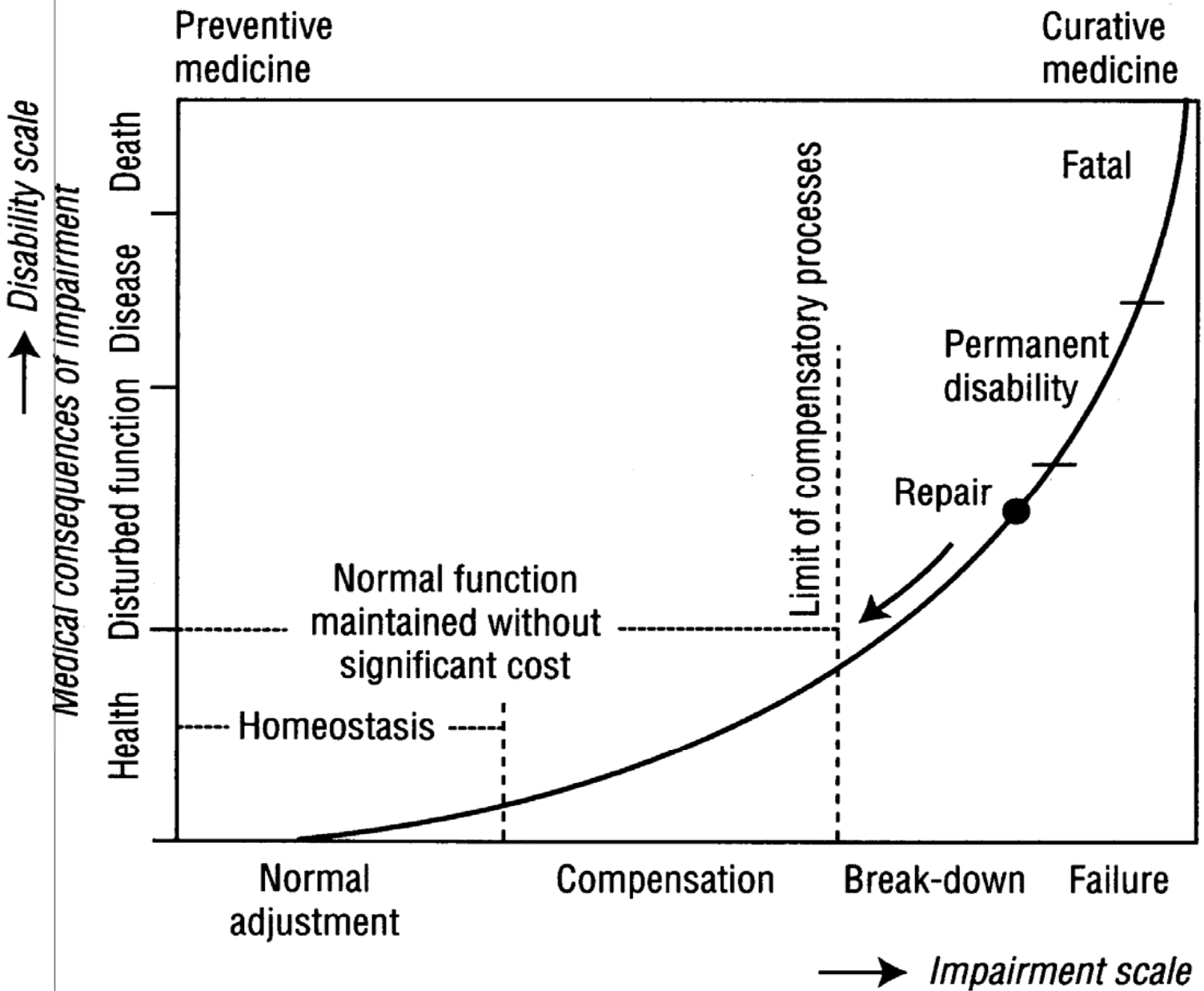
Chemical Risk Assessment Questions

What is the compound capable of doing?

What is the likelihood of such an effect at the levels to which humans are exposed?

What level of intake would be without appreciable health risk, if consumed daily over a lifetime?


Hypothetical dose response curves
HUMANS
sensitive subjects
HUMANS
population mean
ANIMALS
population mean
INTRASPECIES
INTERSPECIES
ADI
NOAEL
Response
100
90
80
70
60
50
40
30
20
10
0
0.1
1
10
100
1000
Dose in mg/kg


Preventive medicine
Curative medicine
Disability scale
Medical consequences of impairment
Death
Disease
Disturbed function
Health
Fatal
Permanent disability
Repair
Limit of compensatory processes
Normal function maintained without significant cost
Homeostasis
Normal adjustment
Compensation
Break-down
Failure
Impairment scale

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

ADVANTAGES

-an important pragmatic tool for risk assessors, risk managers and industry to allow the prioritisation of resources to compounds with high exposures and/or high toxicity.

-accelerates the evaluation process of substances to which humans are exposed to at low levels.

-allows resources used in food safety assessment to be focused on those chemicals of greatest public health importance

-reduces the number of animal toxicity studies considerably

-an important part of any chemical prioritisation procedure, or preliminary risk assessment, which is based on minimal chemical-specific data and which depends on the use of data on structural analogues.

-principle could also be used to indicate analytical data needs and to set priorities for levels of “inherent concern”.

-the approach could be used in the assessment of impurities

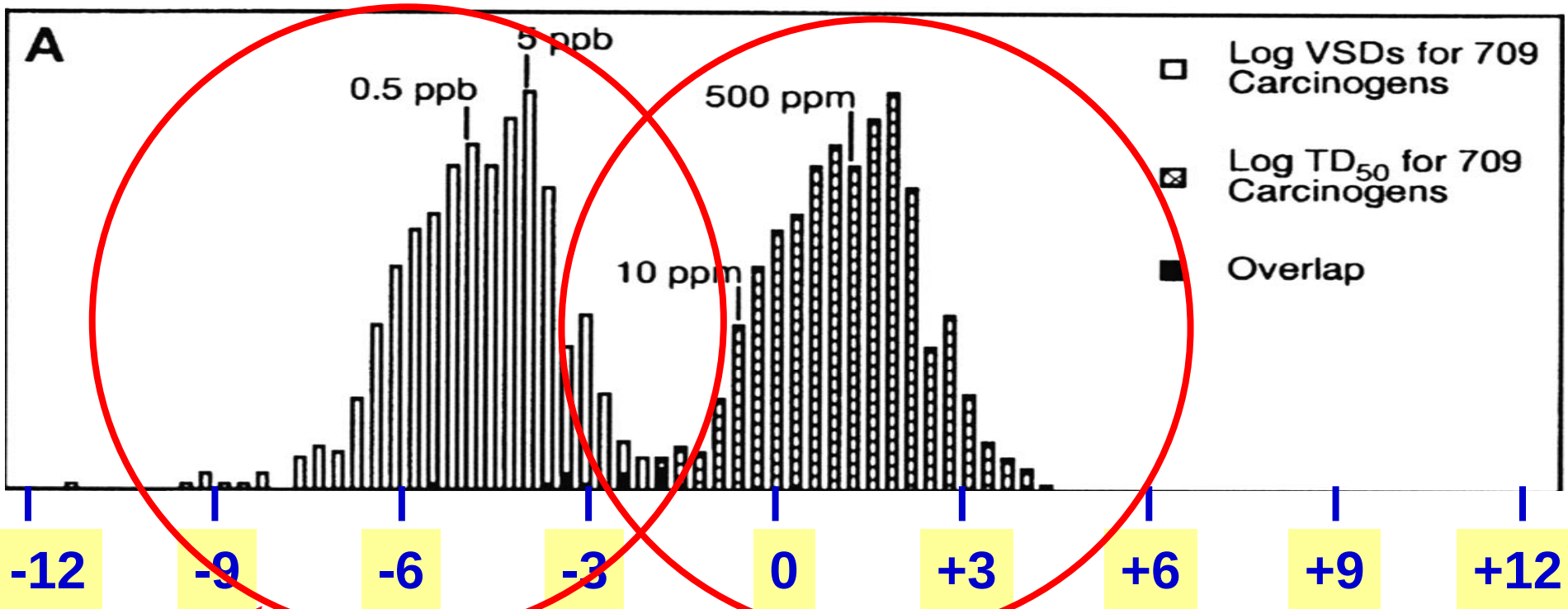
-is applicable to other sectors of health risk assessment such as in occupational and environmental settings and may also be further developed for environmental risk assessment

- **TTC principle is derived from FDA's Threshold of Regulation (TOR) approach for food contact materials**
  - **Dietary concentration below 0.5 ppb is so negligible that it presents no public health concern (assuming an average intake per day of 1500 g diet and 1500 g fluids this equals to: 1.5 μg/person/day)**
  - **Food contact materials with an exposure below this level are "Exempted from regulation"**

FDA' s TOR APPROACH

- Derivation of a threshold value based on carcinogenicity database
- Analysis of carcinogenic potencies of 500 substances from 3500 experiments of the Carcinogenic Potency Database (CPDB) - Gold *et al.* (1984, 1989)
- Distribution plot of the chronic dose rates [mg/kg bw/day] which would induce tumours in 50% of test animals at the end of their lifespan (corrected for background tumours in controls) in the most sensitive species and sex (TD50's)
- Extrapolation to a distribution of 10^{-6} risk to develop cancer with life-span exposure

Rodent Carcinogenicity Database – from Cheeseman et al 1999



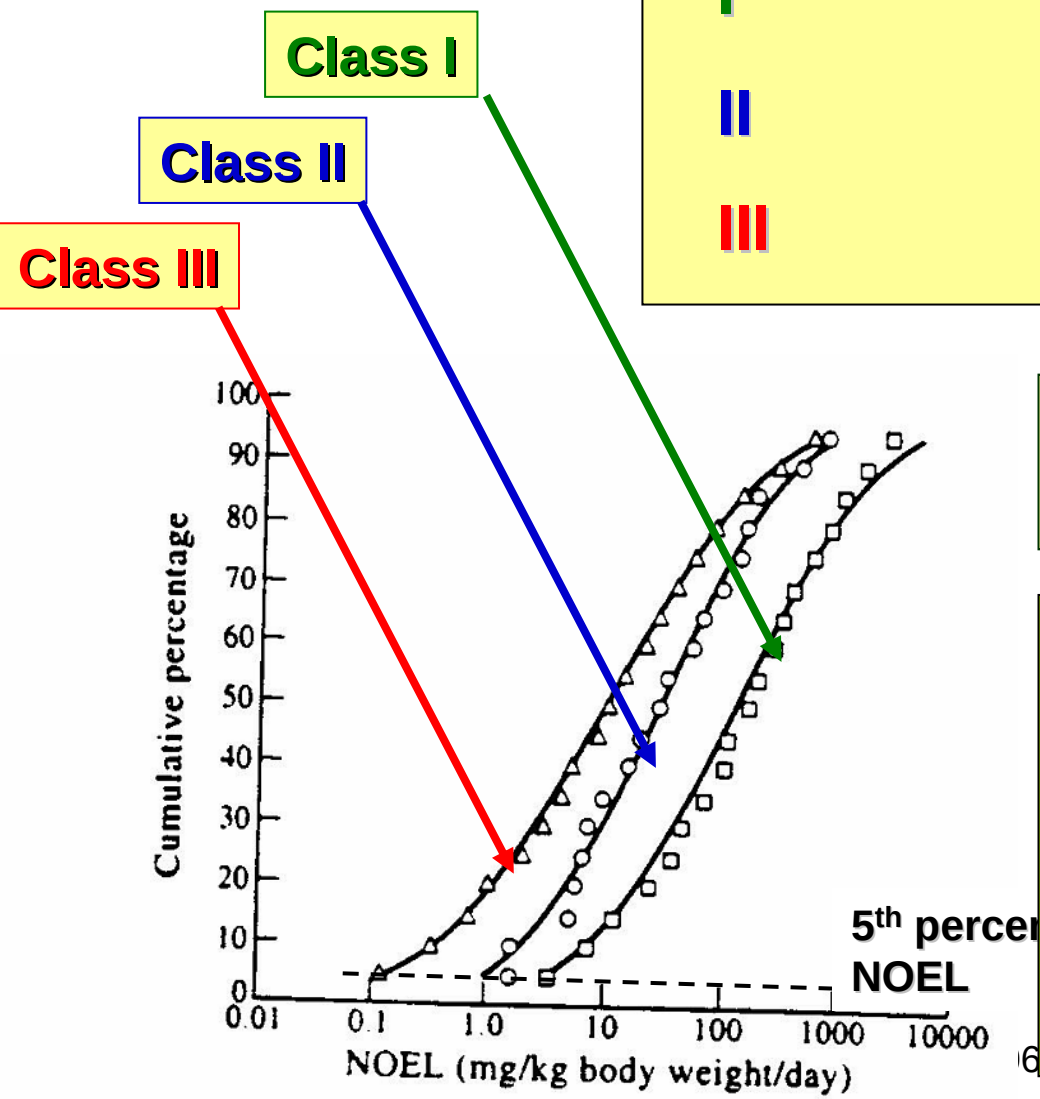
uman Virtually Safe Dose

Rodent TD_{50}

THRESHOLD IN RELATION TO STRUCTURAL CLASSES

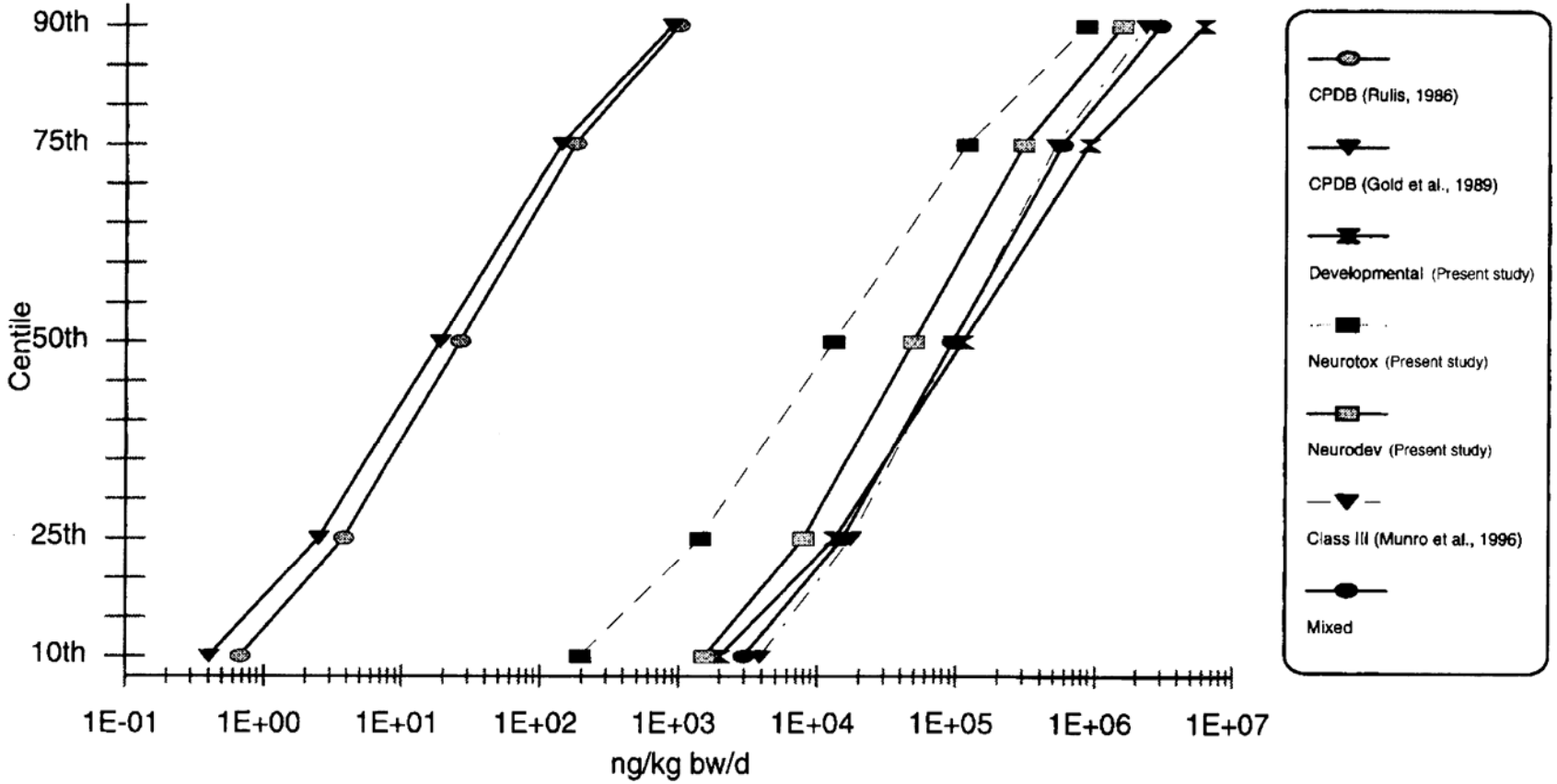
- Refinement by Munro *et al.* (1996)
- Non-genotoxic and non carcinogenic organic chemicals (over 900)
- Classification into 3 structural classes according to Cramer *et al.* (1978) Class I simple, Class II less complex than III and Class III complex structures
- Most sensitive species, sex, and toxicological endpoint recorded for each substance
- Plot of distributions of NOELs for chemicals by structural class
- Applying a 100-fold uncertainty factor to the 5th percentile per class

Class	5%ile NOEL (mg/kg/day)	Human threshold (μg per day) *
I	3.0	1800
II	0.91	540
III	0.15	90



* - calculated as NOEL/100 times 60kg body weight

Therefore converting the NOEL into a TTC uses the normal 100-fold uncertainty factor and provides the normal reassurance


90th
75th
50th
25th
10th
Centile
1E-01
1E+00
1E+01
1E+02
1E+03
1E+04
1E+05
1E+06
1E+07
ng/kg bw/d
CPDB (Rulis, 1986)
CPDB (Gold et al., 1989)
Developmental (Present study)
Neurotox (Present study)
Neurodev (Present study)
Class III (Munro et al., 1996)
Mixed

Conclusions on Munro's work

- **Level of toxicity is clearly influenced by structural class. It is indicated by the distinct separation of the distributions**
- **Results show options to integrate structural knowledge into the threshold approach**
- **Higher threshold values for compounds without structural alerts for genotoxicity or carcinogenicity may be appropriate**
- **Principles of this approach are partly applied by JECFA (evaluations of flavours)**

Other questions…

SPECIFIC ENDPOINTS

- Neurotoxicity / Developmental Neurotoxicity
- Developmental Toxicity
- Teratogenicity
- Immunotoxicity
- Endocrine Activity
- Allergenicity

- **Are these endpoints more sensitive than the TOR ? Would a generic threshold according to structural classes also cover these toxicity endpoints ?**

NEURODEVELOPMENTAL TOXICITY

DEVELOPMENTAL TOXICITY

have a similar cumulative distribution as structural class III chemicals

NEUROTOXICITY

has a different cumulative distribution as structural class III chemicals

Mean levels are however orders of magnitude (100-1000) higher as compared to the mean level of carcinogens (Gold's database)

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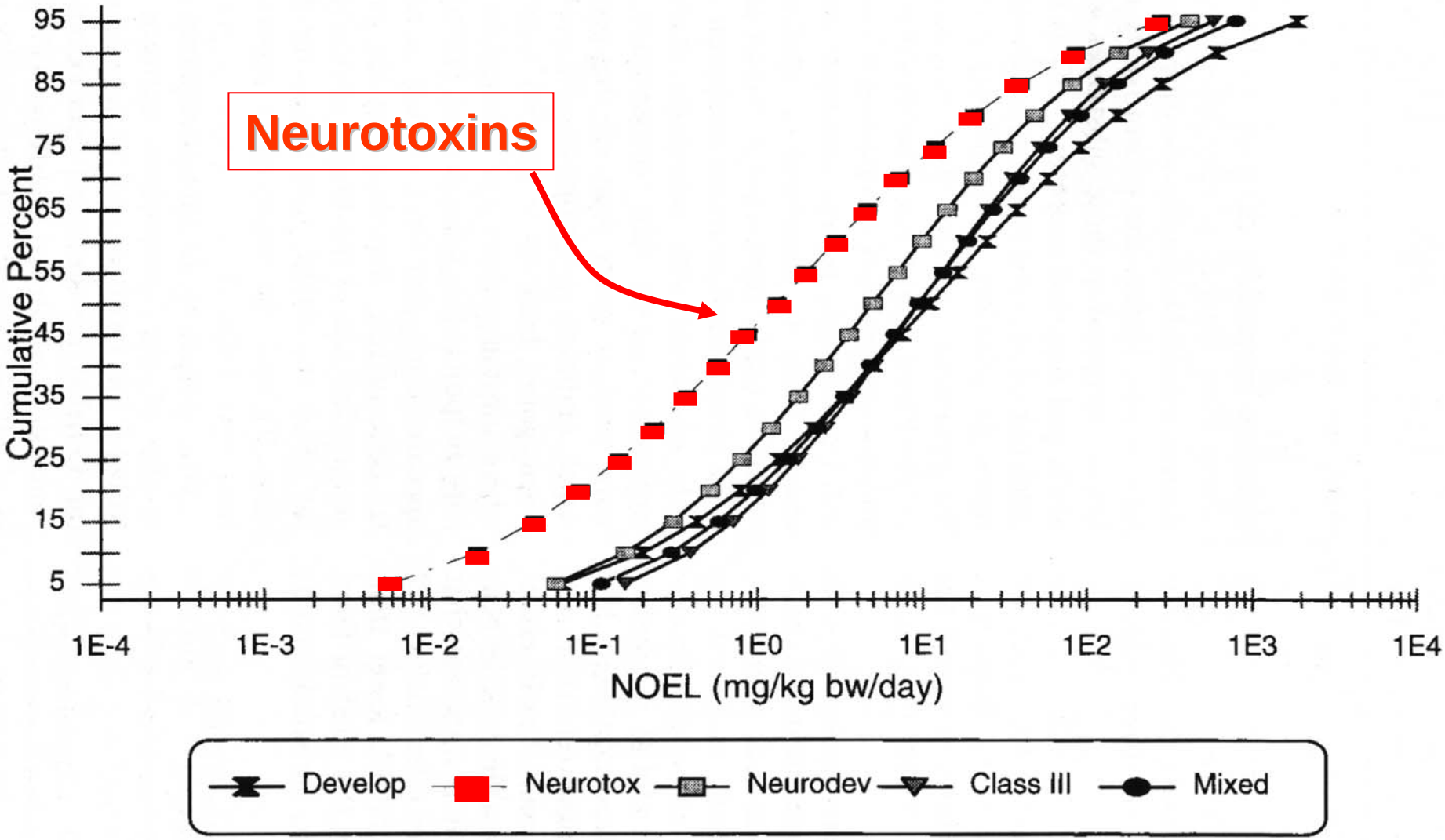
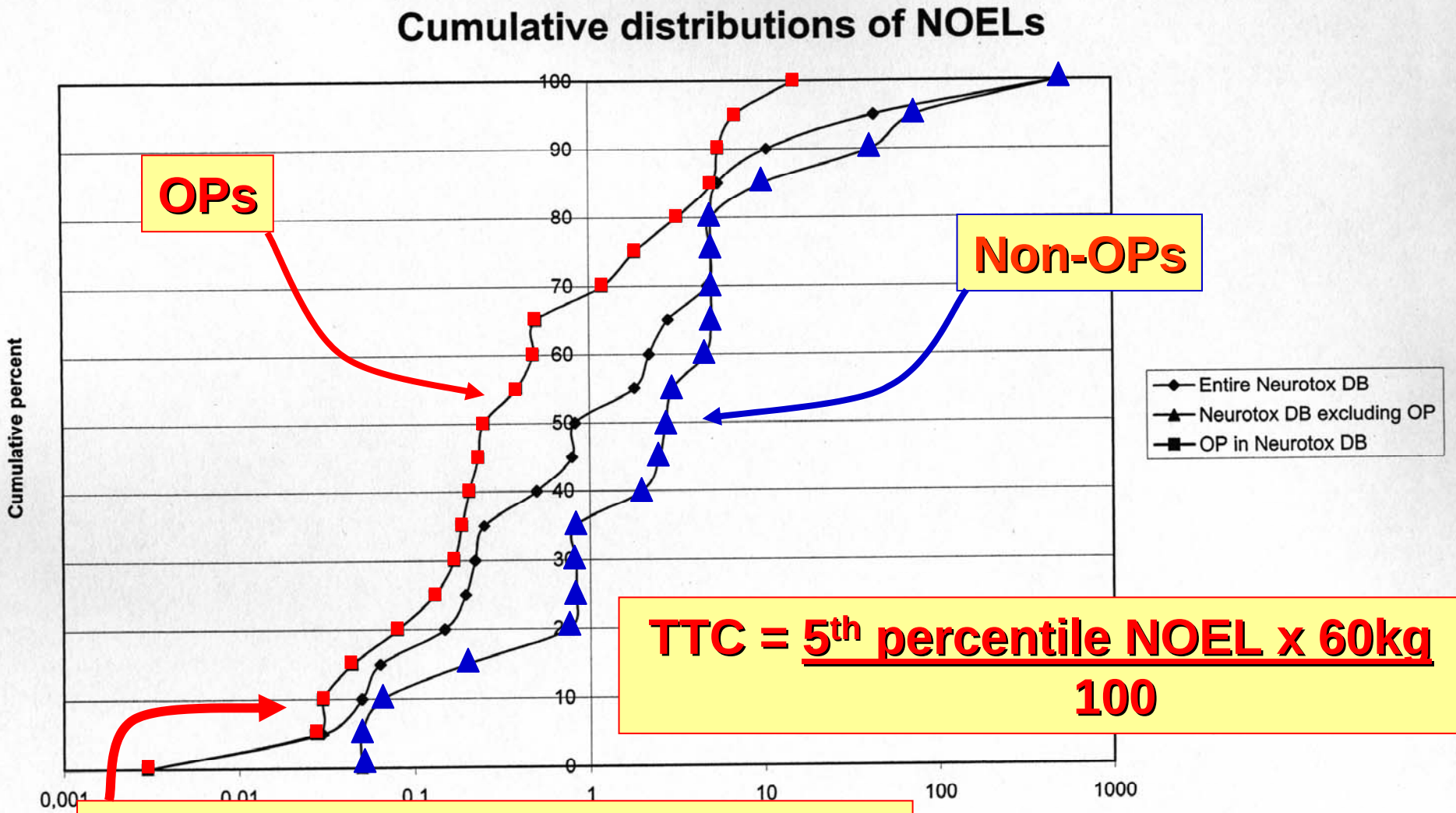
Neurotoxins a separate class?

Neurotoxins – Kroes et al 2000 FCT 38, 255-312.



Subdivision of neurotoxicity database into OPs and non-OPs



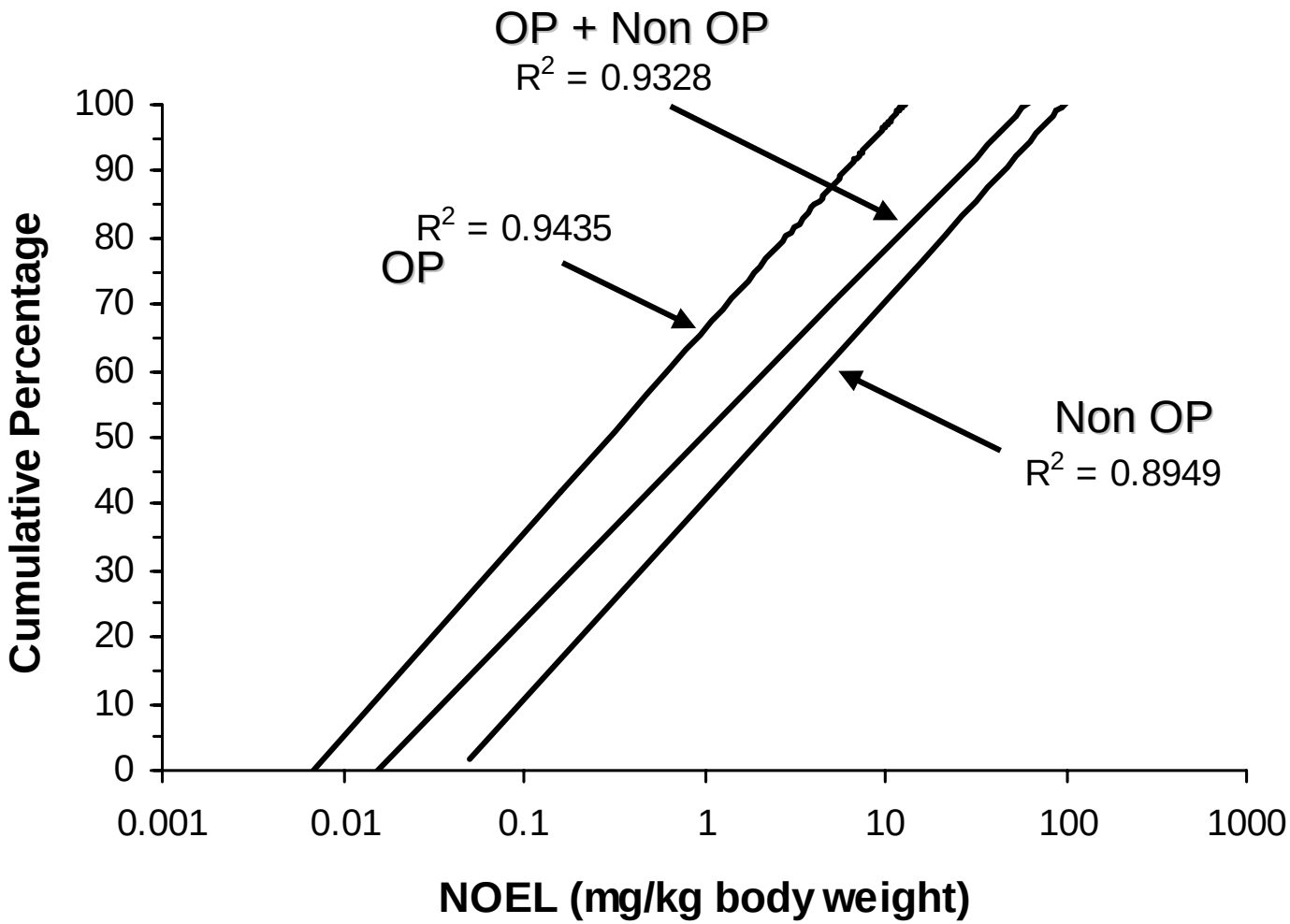
OPs

Non-OPs

TTC = $\frac{5^{th}\text{ percentile NOEL} \times 60kg}{100}$

5^{th} percentile NOEL = 30μg/kg/day

logarithmic regression



Neurotoxins a separate class?

- Only OP esters do have a different distribution
- Separate class for OP esters

  (18 µg/p/day)

- **IMMUNOTOXICITY**

  Immunotoxicity should not be considered as a more sensitive endpoint (comparison of NOEL with the distribution of non-immunotoxic NOEL's, n =37)
- **ENDOCRINE ACTIVITY**

  Endocrine effects at proposed threshold levels not to be expected in light of exposure to overall estrogens
- **ALLERGENICITY**

  Unlikely that small chemical molecules at proposed threshold levels would elicit such reactions (subsets of susceptible individuals, means to control by labelling)
- **TERATOGENICITY**

Teratogens a separate class?

A separate class may not be necessary

Methods

- **E/T ratio =** $\dfrac{\text{NOEL for Embryotoxicity}}{\text{NOEL for Teratogenicity}}$

- **E/T ratio >1 : Teratogenicity occurs at lower doses than general developmental toxicity**
- **N = 38**

E/T >1

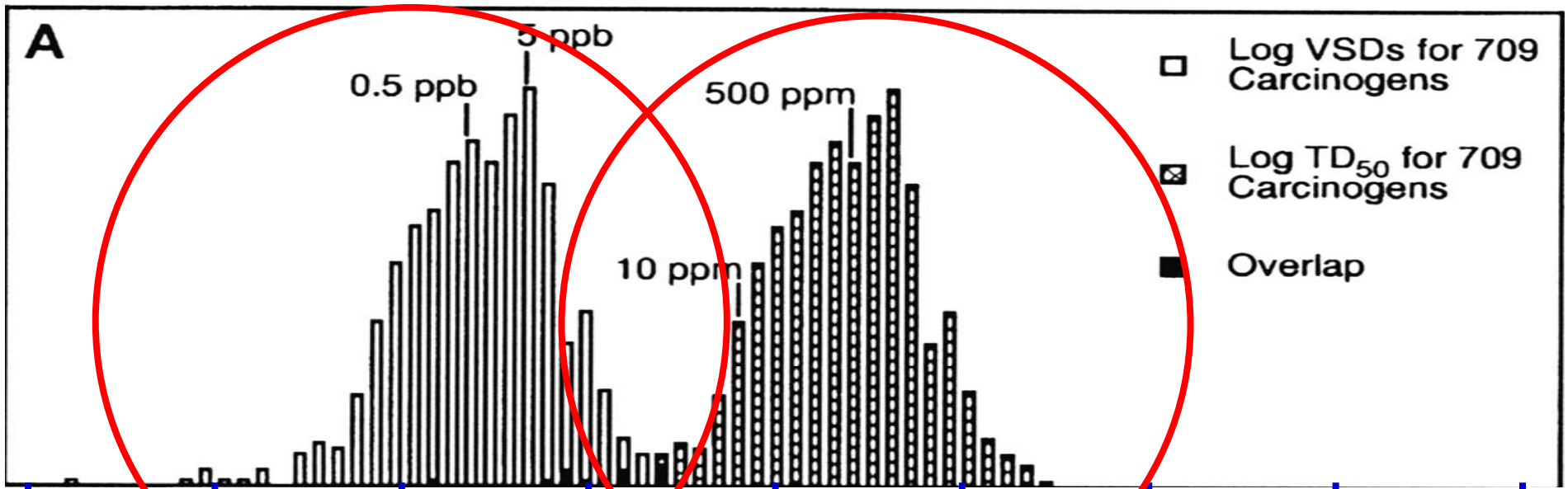
Chemical	E/T	general embryotoxicity	teratogenicity
sodium selenite	1.125	NOEL 15.57 mg/kg	NOEL 13.84 mg/kg
TBDF	5	NOEL 0.25 mg/kg	NOEL 0.05 mg/kg
ETU	8	NOEL 40 mg/kg	NOEL 5 mg/kg
BCAN	>1	NOEL 5 mg/kg	LOEL 5 mg/kg
1PeBDF	>2	NOEL (>) 4 mg/kg	NOEL 2 mg/kg
4PeBDF	>5	NOEL (>) 4 mg/kg	NOEL 0.8 mg/kg
TCDD	>30	NOEL (>) 0.003 mg/kg	NOEL 0.0001 mg/kg
TBDD	>32	NOEL (>) 0.192 mg/kg	NOEL 0.006 mg/kg

All others: E/T either equal or <1 (N= 30)

- **Additional Questions:**
  - **Other TTC for specific structural alerts?**
  - **What about accumulative properties?**

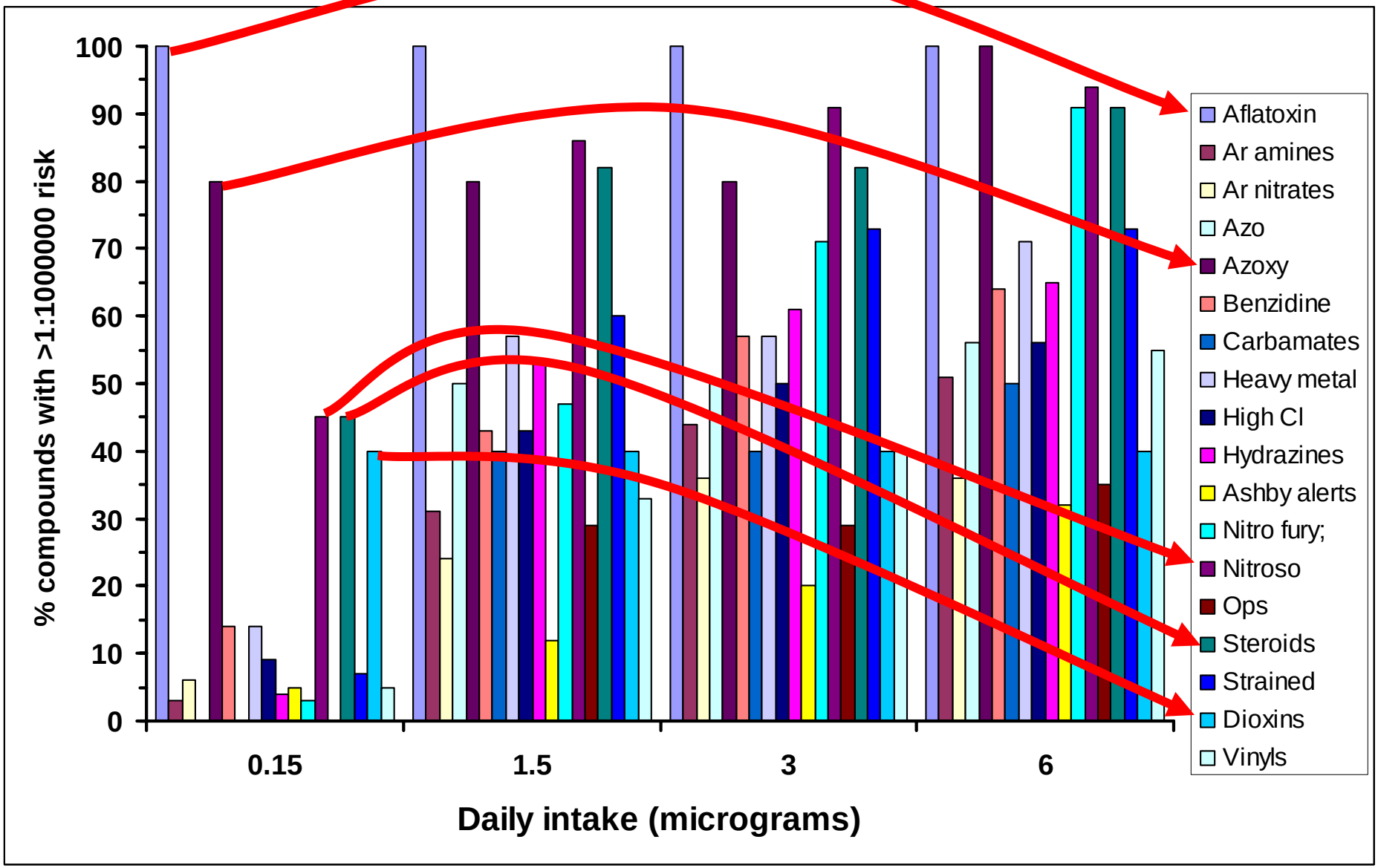
- **Establishment of the dose giving a 50% tumour incidence (TD50) using data for the most sensitive species and most sensitive site (Cheeseman *et a*l., 1999).**
- **Based on a selected subset of the database containing 730 carcinogenic substances which had adequate estimates of the TD50 following oral dosage.**
- **Simple linear extrapolation from the TD50 to a 1 in 10^6 incidence.**
- **The approach assumes that all biological processes involved in the generation of tumours at high dosages are linear over a 500,000-fold range of extrapolation.**
- **Simple linear low-dose extrapolation is conservative because the possible effects of cytoprotective and DNA repair processes on the shape of the dose- response relationship are not taken into account.**
- **All of the compounds were analysed assuming there is no threshold in the dose-response.**

Rodent Carcinogenicity Database – from Cheeseman et al 1999



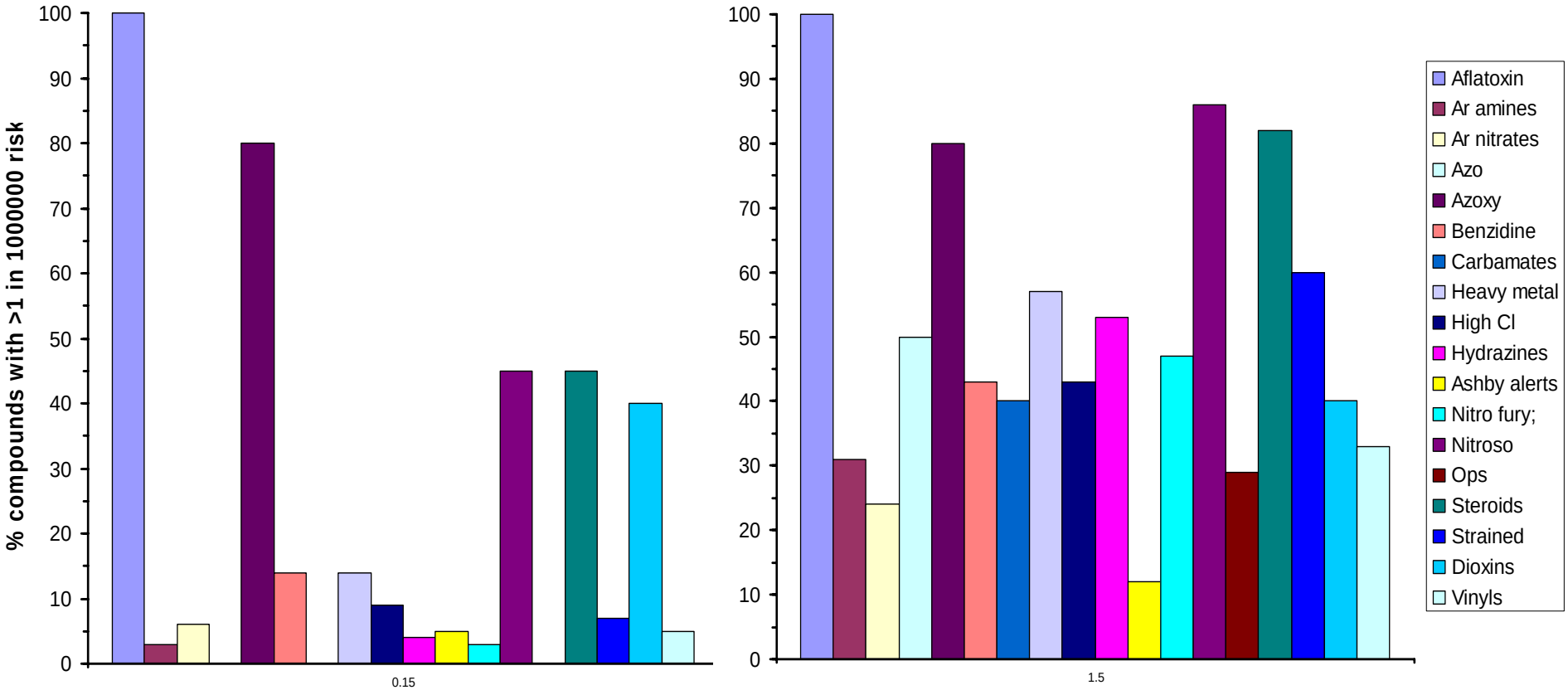
Human Virtually Safe Dose

Rodent TD_{50}



Cohort of Concern = aflatoxin, azoxy, nitroso, [steroids], dioxins

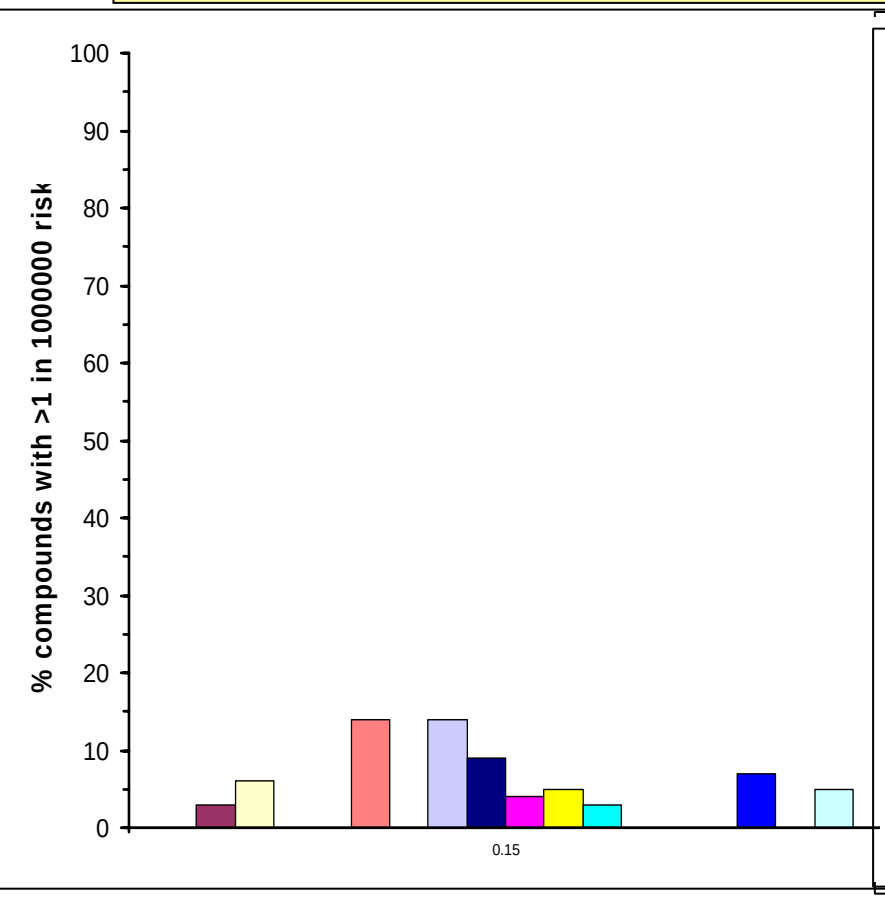
% Compounds with a calculated risk > 1 in 1000000

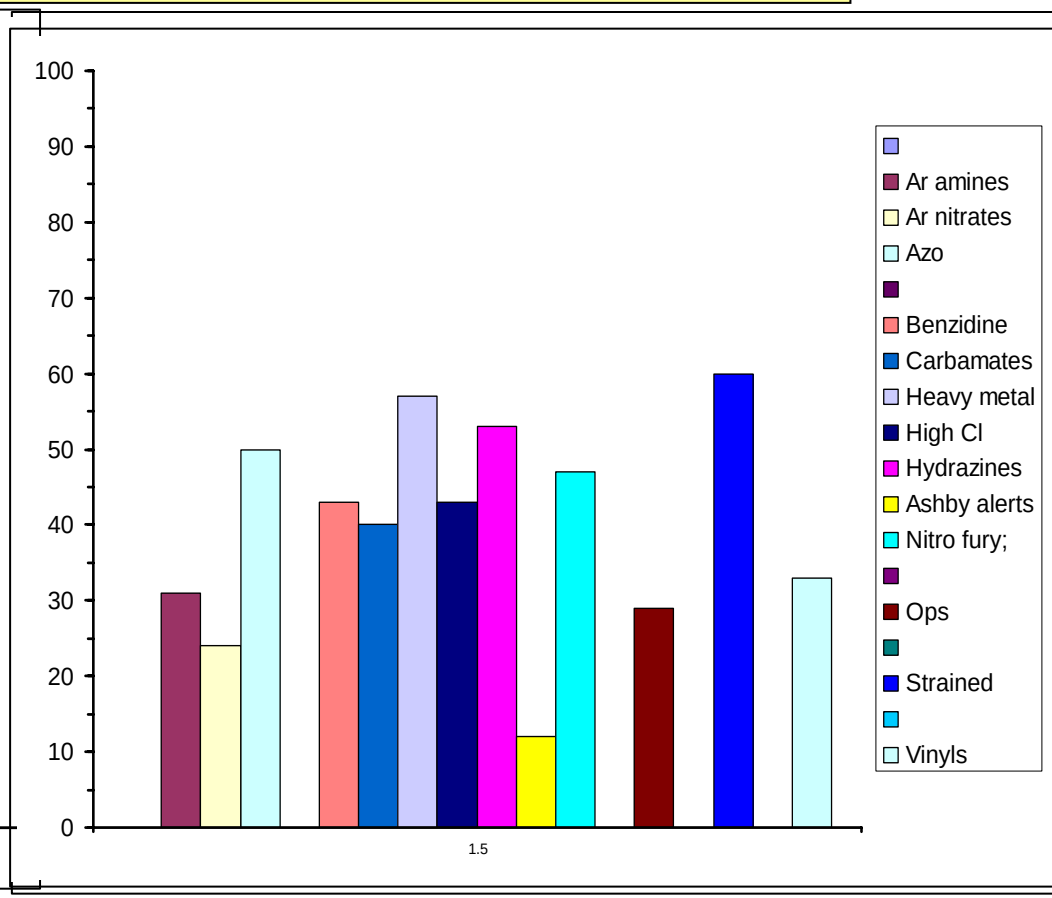


0.15µg/day

1.5µg/day

% Compounds with a calculated risk > 1 in 1000000





0.15µg/day

1.5µg/day

Other TTC for specific structural alerts?

- For specific structural alerts (i.e.aflatoxin-azoxy-, N-nitroso-, dibenzodioxin- and dibenzofuran-like structures) a TTC should NOT be considered.
- For all other structural alerts a TTC of **0.15µg/day** can be applied

What about metabolism and accumulative properties?

Clearance and bioavailability are the main pharmacokinetic parameters that determine species differences and inter-individual variability

Compounds that are extensively metabolised or excreted would be covered by the normal approaches

Compounds that are not eliminated rapidly by excretion or metabolism would show extensive accumulation

Such compounds might show larger than expected species differences related to the reason for accumulation, such as sequestration/reversible binding or absence of a site for metabolism

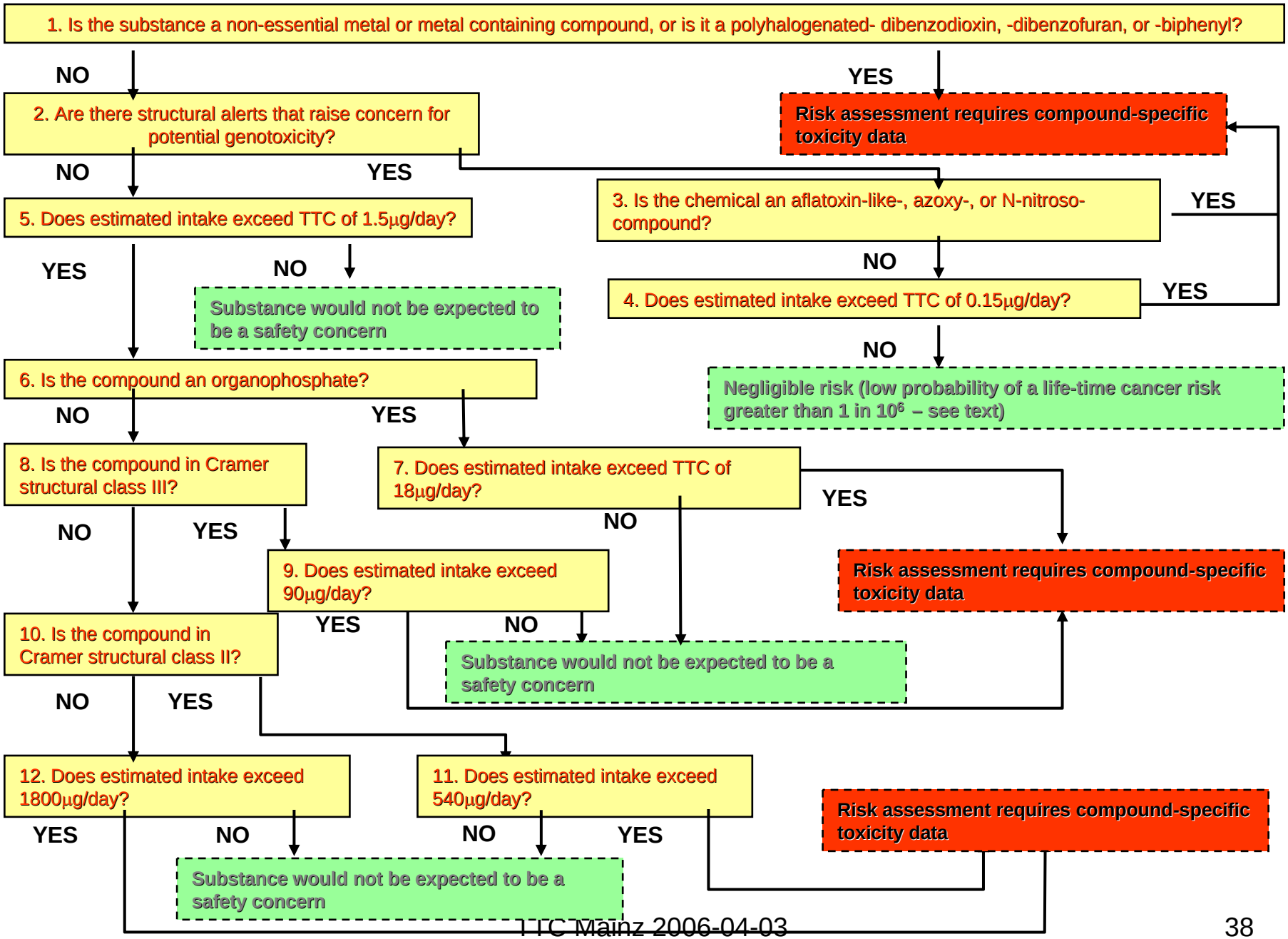
Known examples are heavy metals, such as cadmium, which are excluded, and polyhalogenated aromatics, which have their own well established risk characterisation

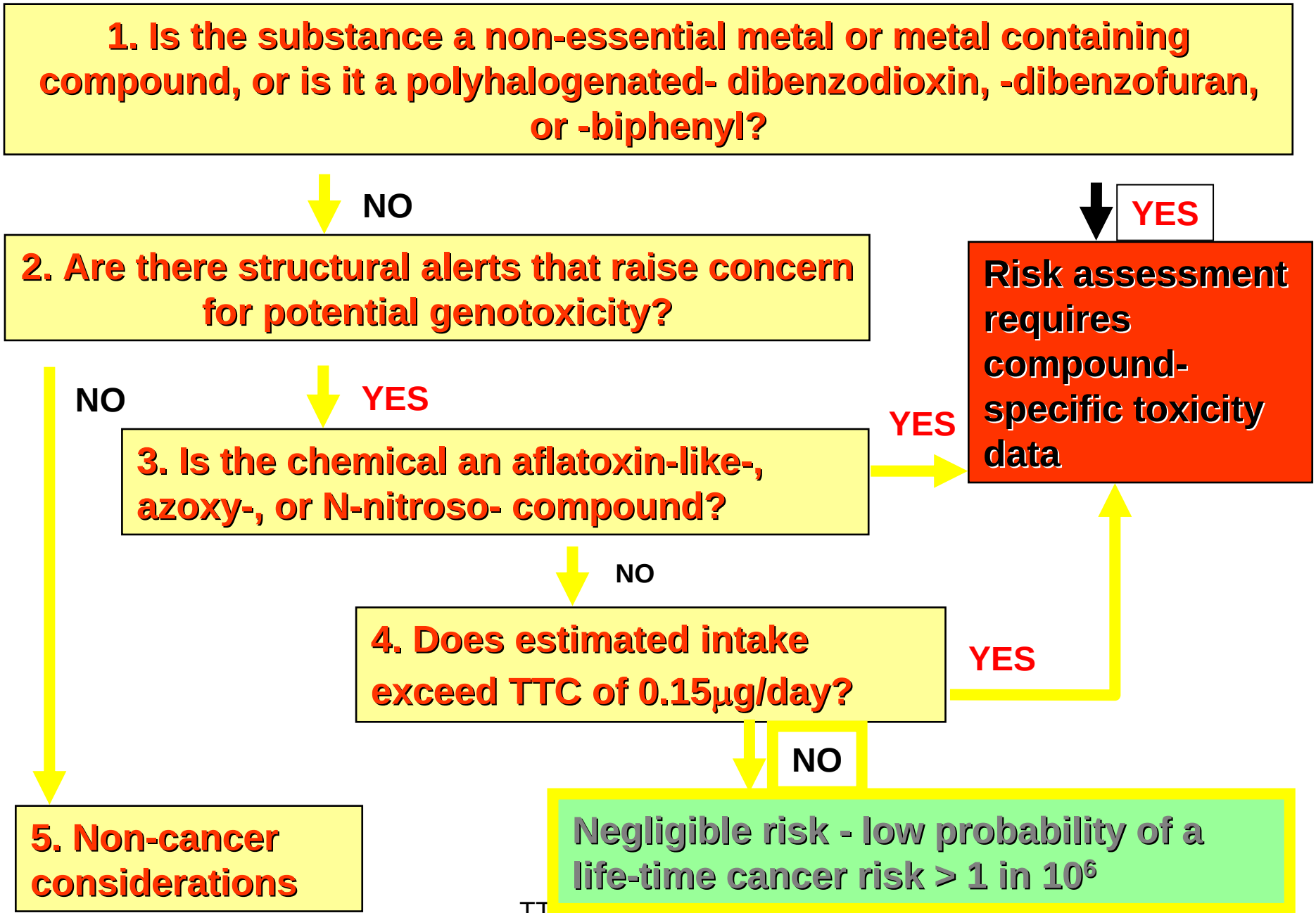
Application TTC

- In general TTC cannot be applied to:
  - Proteins
  - Heavy metals
  - Structural alerts of concern
  - Extreme accumulation potential

Application TTC

- How to apply the TTC?
- Stepwise approach on a case by case basis:
  - Specific structural alerts? → NO TTC
  - All other structural alerts → TTC 0.15 μg/person/day
  - Structural alerts excluded → OP ester? →
  - If OP ester → 18 μg/p/day
  - Class III chemical? → 90 μg/person/day
  - Class II chemical? → 540 μg/person/day
  - Class I chemical? → 1800 μg/person/day


1. Is the substance a non-essential metal or metal containing compound, or is it a polyhalogenated- dibenzodioxin, -dibenzofuran, or -biphenyl?
NO
YES
2. Are there structural alerts that raise concern for potential genotoxicity?
Risk assessment requires compound-specific toxicity data
NO
YES
3. Is the chemical an aflatoxin-like-, azoxy-, or N-nitroso-compound?
YES
5. Does estimated intake exceed TTC of 1.5μg/day?
NO
YES
NO
4. Does estimated intake exceed TTC of 0.15μg/day?
YES
Substance would not be expected to be a safety concern
NO
6. Is the compound an organophosphate?
Negligible risk (low probability of a life-time cancer risk greater than 1 in 10⁶ – see text)
NO
YES
8. Is the compound in Cramer structural class III?
7. Does estimated intake exceed TTC of 18μg/day?
YES
NO
YES
9. Does estimated intake exceed 90μg/day?
Risk assessment requires compound-specific toxicity data
10. Is the compound in Cramer structural class II?
YES
NO
Substance would not be expected to be a safety concern
NO
YES
12. Does estimated intake exceed 1800μg/day?
11. Does estimated intake exceed 540μg/day?
Risk assessment requires compound-specific toxicity data
YES
NO
NO
YES
Substance would not be expected to be a safety concern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YES
2. Are there structural alerts that raise concern for potential genotoxicity?
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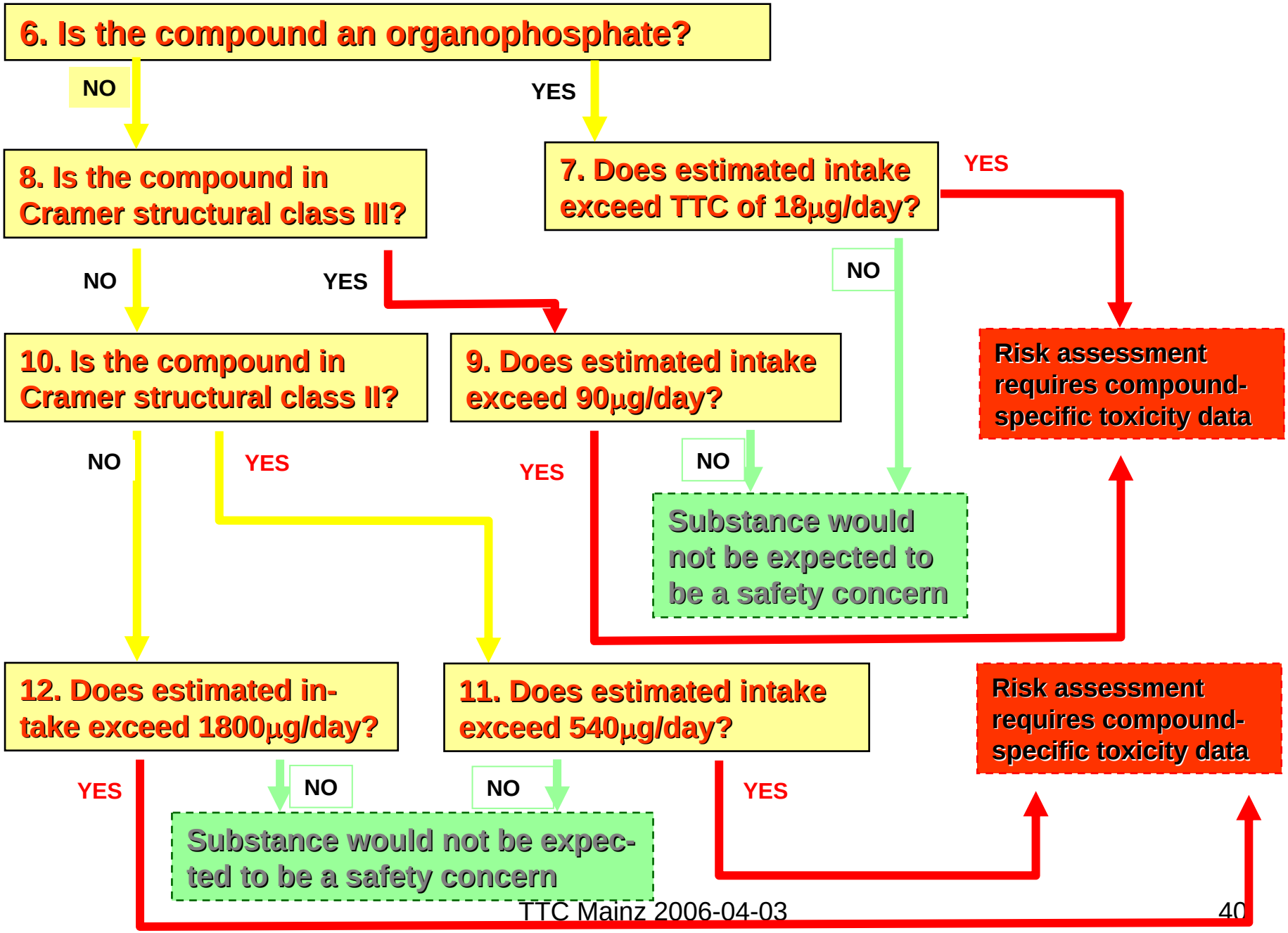
NO
YES
YES
3. Is the chemical an aflatoxin-like-, azoxy-, or N-nitroso- compound?
NO
4. Does estimated intake exceed TTC of 0.15µg/day?
YES
NO
5. Non-cancer considerations
Negligible risk - low probability of a life-time cancer risk > 1 in 10^6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Substance would not be expected to be a safety concern
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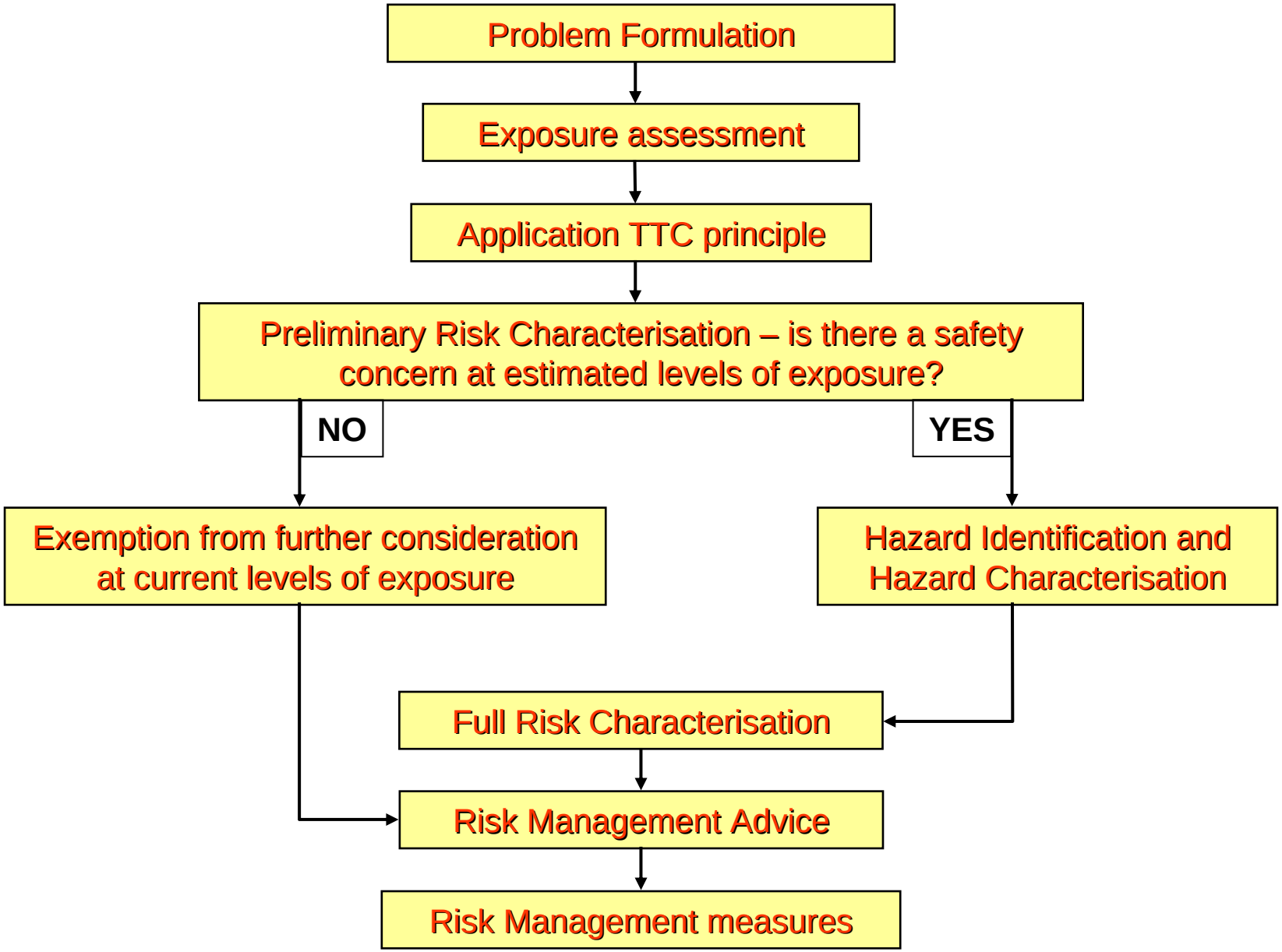
Substance would not be expec-ted to be a safety concern



Kroes et al 2005

Applications (Health)

Food:

- **Flavours**
- **Contaminants**
- **Packaging materials**
- **Additives**
- **Can also be used to indicate analytical data needs and to set “analytical evaluation thresholds“ above which toxicological assessment may be indicated.**

- **BUT: accurate exposure assessment is a necessity!**

Applications (Health)

Non Food:

- **Cosmetics**
- **EMEA applies TTC for contaminants in drugs**
- **Leachables OINDP**
- **Consumer products (see Blackburn et al, Reg. Tox Pharm. In press)**
- **Environmental contaminants**

- **BUT: accurate exposure assessment extremely important !!!**
- **For topical effects relevant data bases have to be set up for analysis**

Applications (Environment)

- **The TTC principle could also be applied in environmental risk assessment (but to day only limited toxicity data are available to establish generic thresholds)**
- **For fresh water systems an environmental threshold of no toxicological concern has been proposed (de Wolf et al, Env. Tox and Chem. 24, 479-485, 2005)**

Application TTC for cosmetic ingredients and end products

- TTC is based on oral data
- Cosmetics are used topically and have the potential to lead to local effects and to systemic effects
- In first instance focus on systemic exposure via topical application
- NOT (yet) local topical effects

Application TTC for cosmetic ingredients and end products

- Since TTC is derived from oral toxicity data the main question is:
  - Are chemicals used in cosmetics sufficiently comparable to the chemicals used to derive the TTC for food chemicals.
  - Answer: Yes! Except for: Inorganic salts and various metals and pharmaceutical type compounds

Is systemic exposure via the percutaneous route sufficiently comparable to systemic exposure via the oral route?

- Is first pass metabolism qualitatively and quantitatively comparable or not?
- The 5th percentile oral NOAEL values used to derive the TTC values for class III compounds would overestimate the potential toxicity of the same compounds following topical exposure, even if 100% of the topical dose entered the general circulation as the parent compound.

Is systemic exposure via the percutaneous route sufficiently comparable to systemic exposure via the oral route?

- Is first pass metabolism qualitatively and quantitatively comparable or not?
- Although fewer compounds were used to derive the 5th percentile oral NOAEL values for class II and class I, the available data indicated that these values and the resulting TTC values would also be relevant to topical exposures.

Classification of chemicals (on the basis of their physicochemical properties) in terms of their potential to be absorbed across the skin

Jmax (µg/cm2/hr)	*MW(Daltons)*	*Log P*	*Category*
Jmax = 0	Non-reactive chemicals > 1000 Dalton	any	Negligible
Jmax < 0.1	> 300	< -1 or > 5	Low
0.1 < *Jmax* < 1.0	~ 200-300	> 2.0, 2.5	Medium low
1.0 < *Jmax* < 10	~ 150-250	~ 1.0 -2.0	Medium high
10 < *Jmax* < 100	~60-200	~ 0.5 – 3.0 (3.5)	High
Jmax > 100	< 150	-0.5 – 1.5 (2.0)	High

Development of a generic approach to set default values for percutaneous penetration based on chemical (behavi-oral) parameters such as maximal flux, MW and log Pow

Jmax (µg/cm2/hr)	*Default % DA(24 h)*
Non-reactive chemicals with MW > 1000	Negligible
Jmax < 0.1	10
0.1 < *Jmax* < 10	40
Jmax > 10	80

Additional exposure defaults

- default retention factor of 0.01 or 0.1 (1 or 10%) for rinse-off products (SCCNFP, 2003, p. 77).
- default adjustment factors of 3-fold for ingredients used only once per week and 10-fold for ingredients used less frequently.
- Consideration of potential simultaneous exposure- mixtures and/or combined exposure
- Consideration of potential aggregate (total) exposure

The following steps in internal (systemic) exposure assessment are suggested:

- Define product type, its intended use and related skin surface area involved.
- Define concentration of ingredient in the product
- Estimate external exposure per day (SCCNFP 2003, EPA 1997)
- Establish use pattern: daily or intermittent use, if the latter is the case apply the default factor related to the use interval
- Estimate skin absorption of ingredient based on its physical and chemical characteristics (maximal flux, POW and MW)
- If rinse off product apply retention factor
- Calculate internal (systemic) exposure per person per day (Internal Exposure Dosage for a 60 kg person)
- Where relevant calculate total exposure when several cosmetic products contain this target ingredient
- Use this Internal Exposure Dosage in the TTC decision tree

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK ASSESSMENT

THANK YOU!