UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI FARMACIA

TTC: THRESHOLD OF TOXICOLOGICAL CONCERN

INTRODUCTION AND HISTORICAL DEVELOPMENT

ILSI EUROPE DECISION TREE - APPLICATION TO FOOD CONTAMINANTS

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ILSI Japan International Symposium
Usefulness of Threshold of Toxicological concern (TTC) Concept for Risk Assessmant
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ILSI Japan, ILSI Research Foundation
Japanese Society for Food Hygiene and Safety Communication, Center for Food and Health Sciences

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK CHARACTERISATION

Could not be that the data requirements for risk assessment would be in relationship to human intake or exposure ?

Is there a level of exposure so low

that "risk assessment" could be based on

structural considerations alone

and toxicological specific data are not required ?

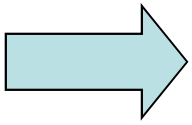
RISK CHARACTERIZATION

- **Hazard identification**
  - ❖ Inherent biological activity,

- **Hazard characterisation**
  - ❖ Dose-response analysis
  - ❖ Assessment of relevance for humans

EXPOSURE ASSESSMENT

- ❖ Levels of substance in food and diet
- ❖ Amounts of food consumed
- ❖ Intake in special population groups
- ❖ Intake in individuals
  - ❖Max/min, regularly/occasionally

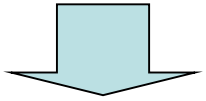


HAZARD IDENTIFICATION

❖ Identificatio… …erse… …effects
- ❖ Huma… …data
- ❖ Animal-b… …logical studies
- ❖ *In vitro* te… …data
- ❖ Structu… …sideration

HAZARD CHARACTERISATION

❖Quantification… …dverse… …lth effects
- ❖ Dose… …e… …cal effect
- ❖ Select… …data
- ❖ Mode/me… …f action
- ❖ Kinetic…
- ❖ Dyna…



RISK CHARACTERISATION

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK CHARACTERISATION

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.

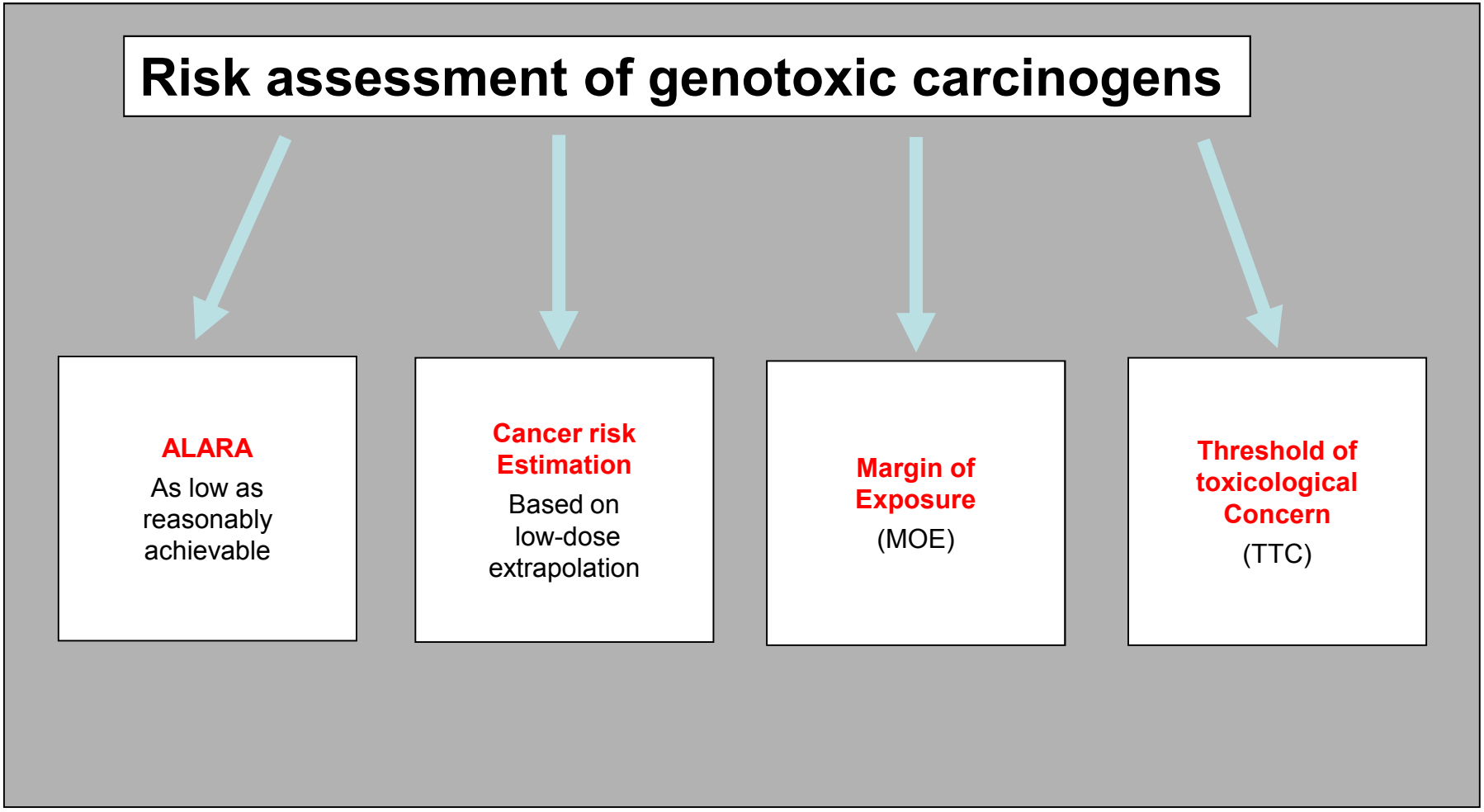
TTC APPLICATIONS

- **Migrant** substances from packaging materials (USFDA-TOR- 1993)
- **Flavourings** substances in food (WHO-JECFA 1993,1995,1999….)
- Endorsed for the risk assessment of chemicals (WHO-IPCS 1998)
- Non relevant **plant protection product metabolites** in ground water (EC-2002)
- **Genotoxic impurities** in pharmaceutical preparations (EMA 2003,2004)
- **Flavourings** substances in food (EFSA 2004)
- **Genotoxic constituents** in herbal preparations (EMA 2006)
- Suggested for **R**egistr, **E**valuat, **A**uthoriz and Restri of **Ch**emical substances (ECHA 2008)

- Suggested for application to **aquatic environmental** exposure (2005)
- Suggested for application to the **cosmetic ingredients** and their impurities (2007)
- Suggested for **prenatal developmental** toxicity (2010)
- Suggested for **mixture of substances** potentially detectable in surface water (2011)
- *Suggested for risk prioritization of **trace chemicals in food**. (2011?)*
- ……

RISK ASSESSMENT

AND FORMULATION OF ADVICE TO RISK MANAGERS



RISK ASSESSMENT

AND FORMULATION OF ADVICE TO RISK MANAGERS

Risk assessment for (genotoxic) carcinogens

Threshold of toxicological Concern

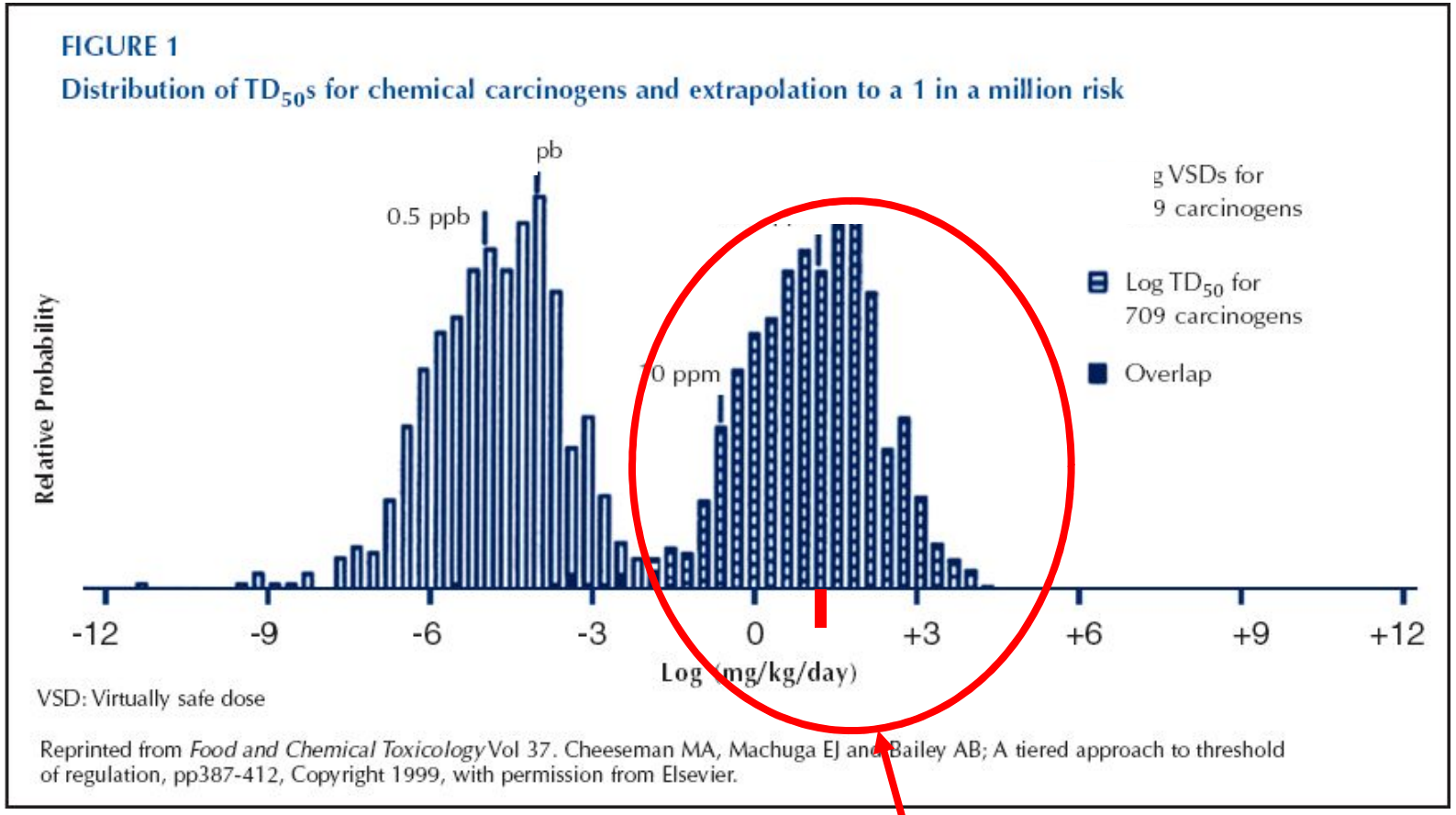
(TTC)

THRESHOLD OF REGULATION (TOR)

APPROACH FOR FOOD CONTACT MATERIALS

- The Threshold of Regulation(TOR) value was based on a carcinogenicity database (FDA 1995)
- Analysis of carcinogenic potencies of 343 (updated to 709) substances from 3500 experiments of the Gold Carcinogenic Potency Database (CPDB) - Gold *et al.* (1984, 1989,1995) (Cheeseman *et al*., 1999);
- In the CPDB the potency of each chemical was expressed in terms of the dose producing 50% tumour incidence in test animals (**TD50's**) at the end of their lifespan (corrected for background tumours in controls) in the most sensitive species and sex.

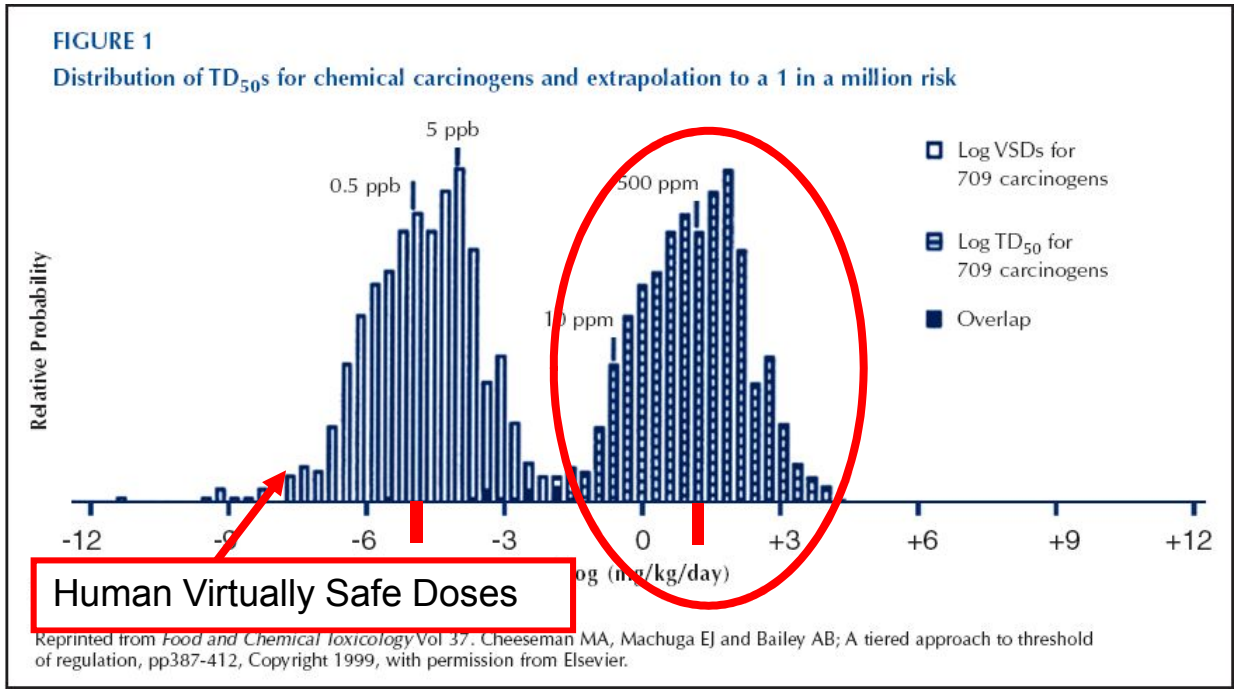
RODENT CARCINOGENICITY DATA BASE



Rodent TD_{50}

RODENT CARCINOGENICITY DATA BASE

The potencies plotted as a distribution of TD50s were transformed into a distribution of exposures calculated by linear extrapolation from TD50 values to represent an estimated lifetime risk of one in a million of developing cancer or "virtually safe dose" (VSD)



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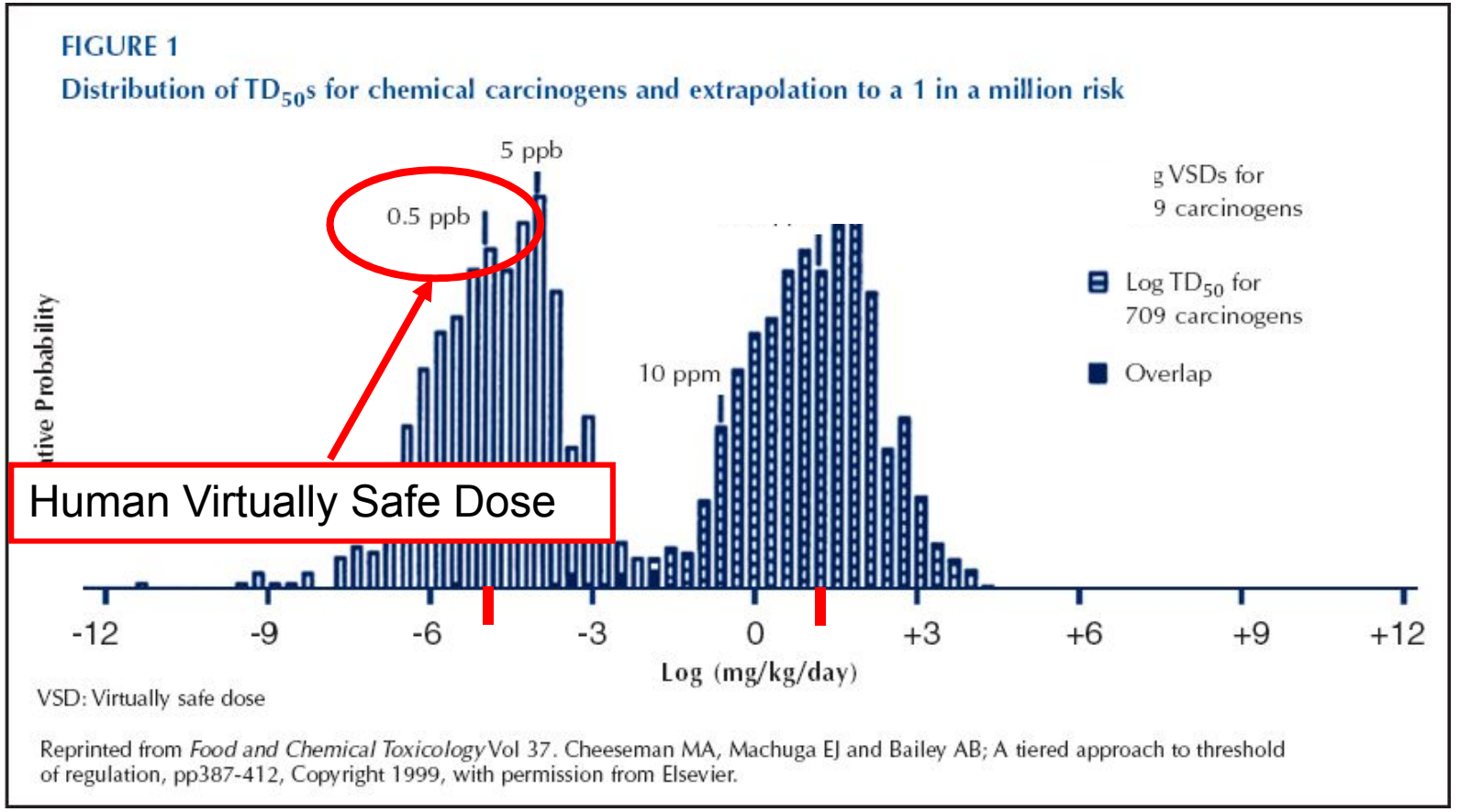

THRESHOLD OF REGULATION (TOR) APPROACH FOR FOOD CONTACT MATERIALS

- Dietary concentration of chemicals, without structural alerts for carcinogenicity, below 0.5 ppb (500 ng/kg or 500ng/L), is so negligible that it presents no public health concern:

  assuming that a person consumes 1500 g of food and 1500 g of fluids daily and the chemical is distributed evenly throughout the total diet

  a daily exposure level of 1.5 µg/person/day was derived

  Food contact materials with an exposure below this level are "Exempted from regulation".

- TTC principle is derived from FDA's Threshold of Regulation (TOR) approach for food contact materials.

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

THRESHOLD IN RELATION TO STRUCTURAL CLASSES
Refinement by Munro *et al.* (1996)

- Munro and coworkers (1996) evaluated the use of TTC related to other endpoints than carcinogenicity (612 compounds)
- They used structural information based on an algorithm developed in 1978 by Cramer *et al*.
- The chemicals were grouped into three structural classes based on a "decision tree" approach.
- Most sensitive species, sex, and toxicological endpoints recorded for each substance

CRAMER CLASSIFICATION TREE

NUMBER OF CHEMICALS

Class I- Substances with simple chemical structure and efficient modes of metabolism that would suggest a lower order of oral toxicity	447
Class II – Substances that are in structural class in which there is less knowledge of the metabolism, pharmacology and toxicology, but for which there is no clear indication of toxicity	28
Class III – Substances of chemical structure that permit no strong initial presumption of safety, or that may even suggest significant toxicity.	137

Refinement by Munro *et al.* (1996)

Munro et al., 1996

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK CHARACTERISATION

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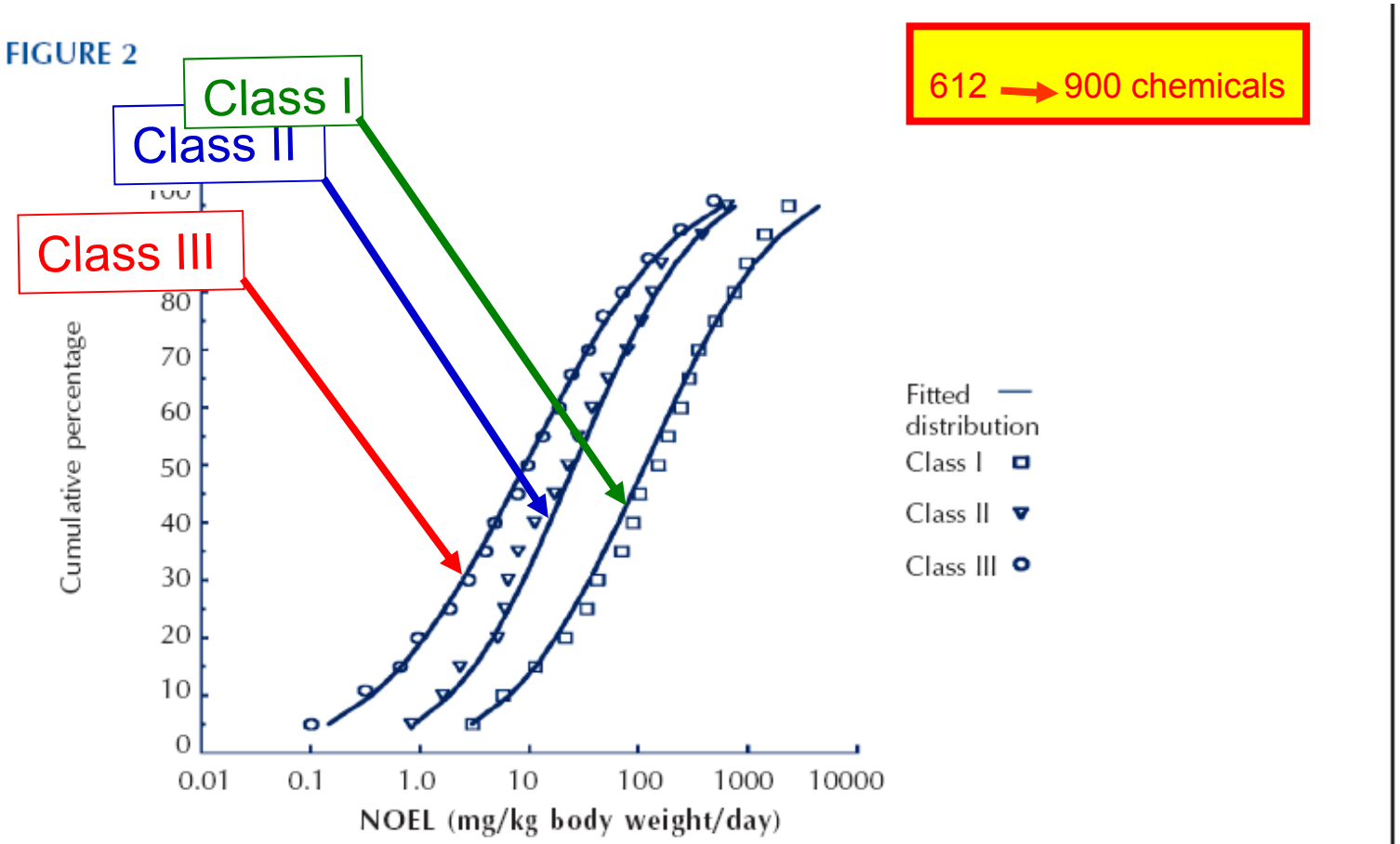
Plot of distributions of NOELs for chemicals by structural class

Refinement by Munro *et al.* (1996)

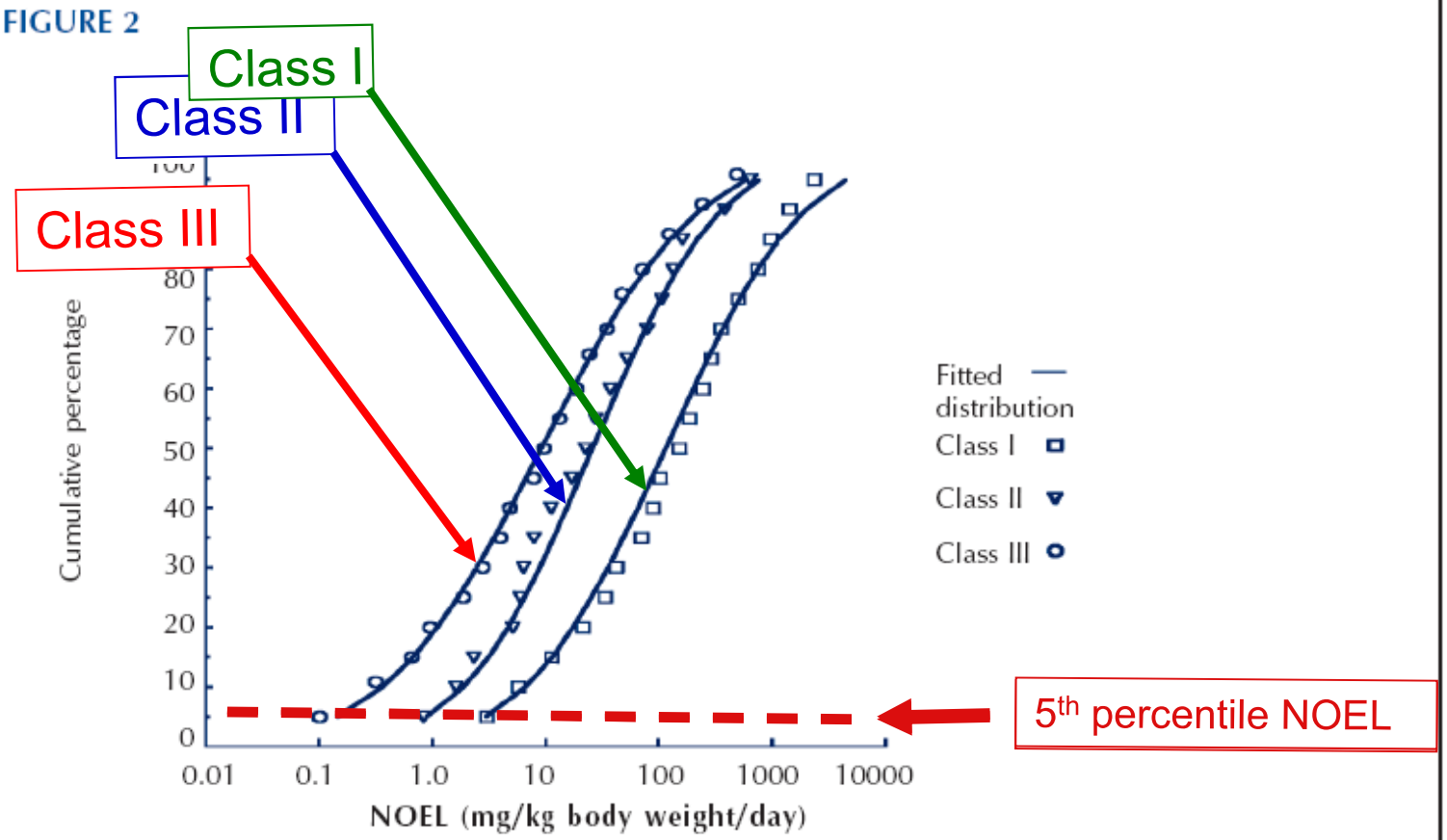
PLOT OF CUMULATIVE DISTRIBUTIONS OF NOELs FOR CHEMICALS BY STRUCTURAL CLASS



Reprinted from *Food and Chemical Toxicology* Vol 34. Munro IC, Ford RA, Kennepohl E and Sprenger JG; Correlation of a structural class with no-observed-effect levels: a proposal for establishing a threshold of concern, pp 829-867, Copyright 1996, with permission from Elsevier.

PLOT OF CUMULATIVE DISTRIBUTIONS OF NOELs FOR CHEMICALS BY STRUCTURAL CLASS

FIGURE 2



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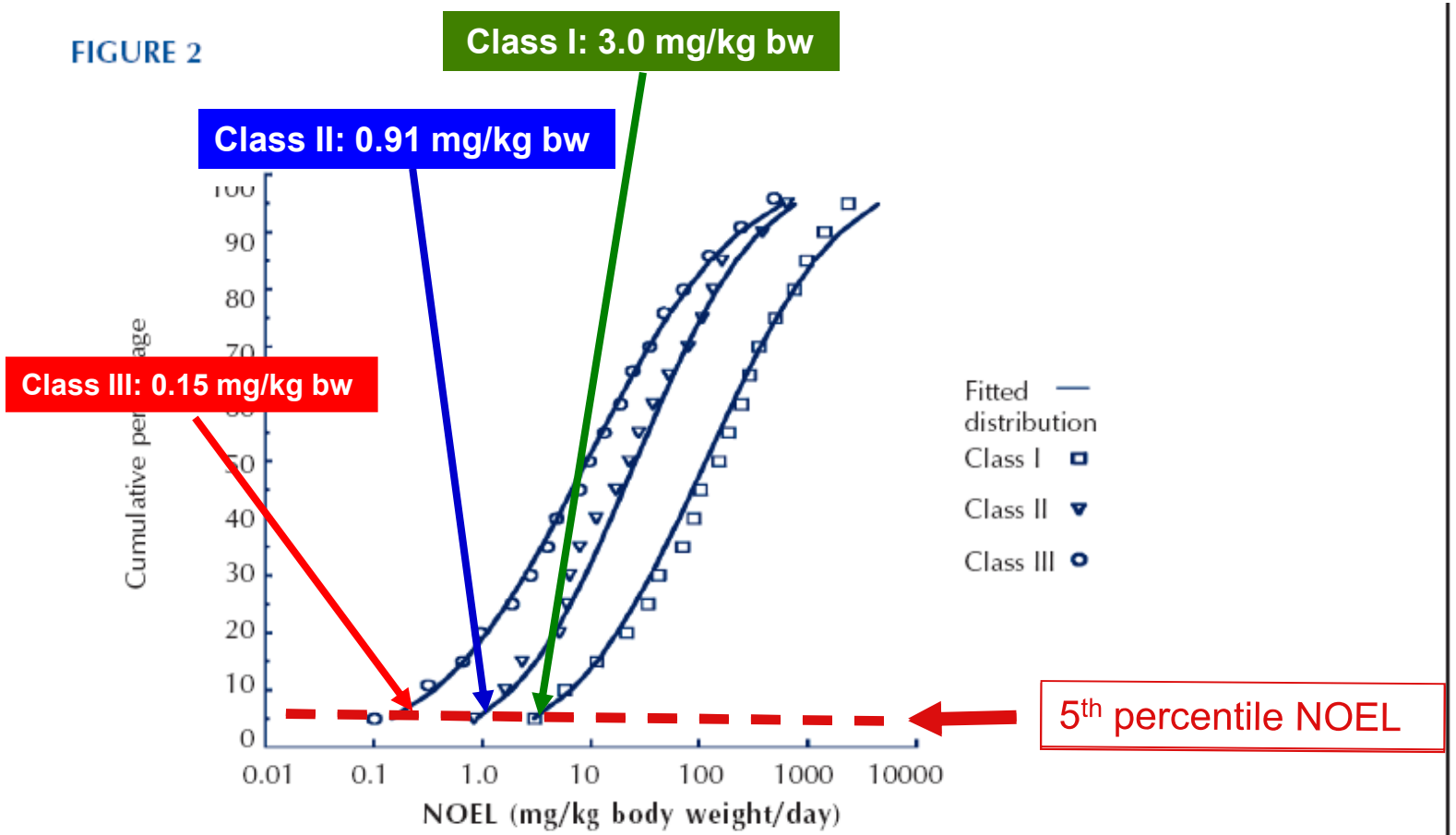

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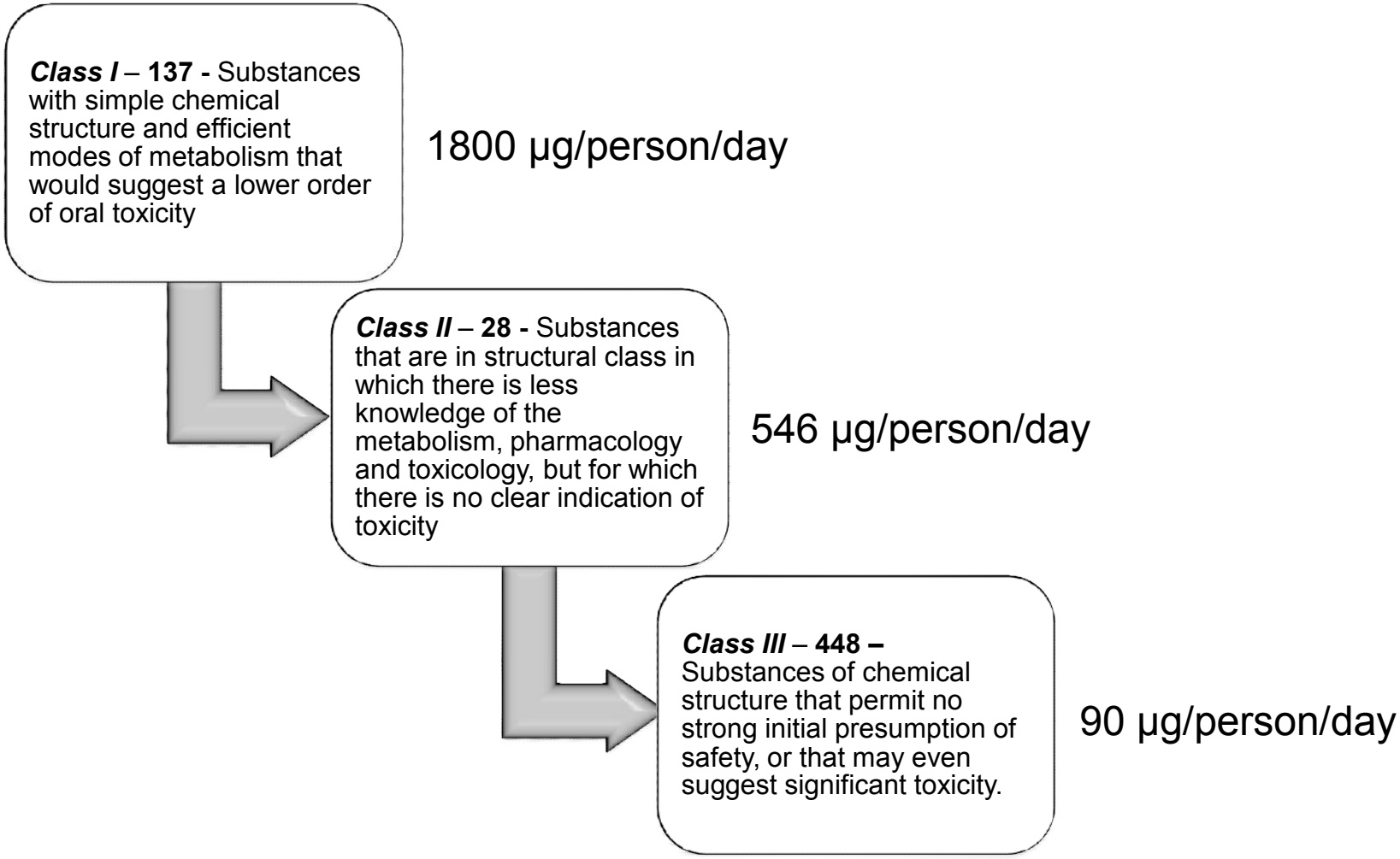
$$TTC = \frac{5^{th} \text{ percentile NOEL}}{U.F. = 100} \times 60 \text{ kg}$$

Refinement by Munro *et al.* (1996)

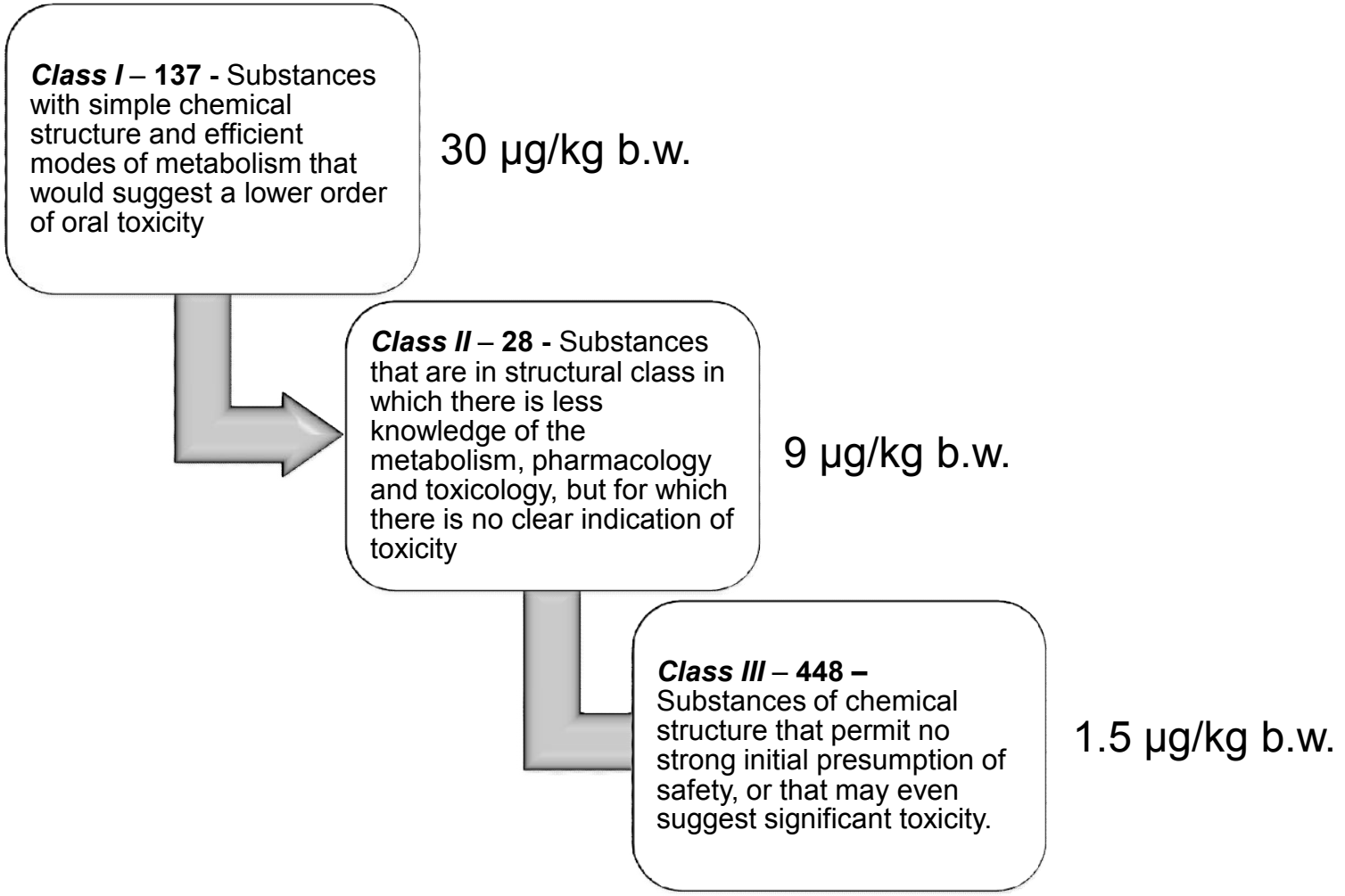
CRAMER CLASSIFICATION TREE

TTC EXPOSURE LIMITS

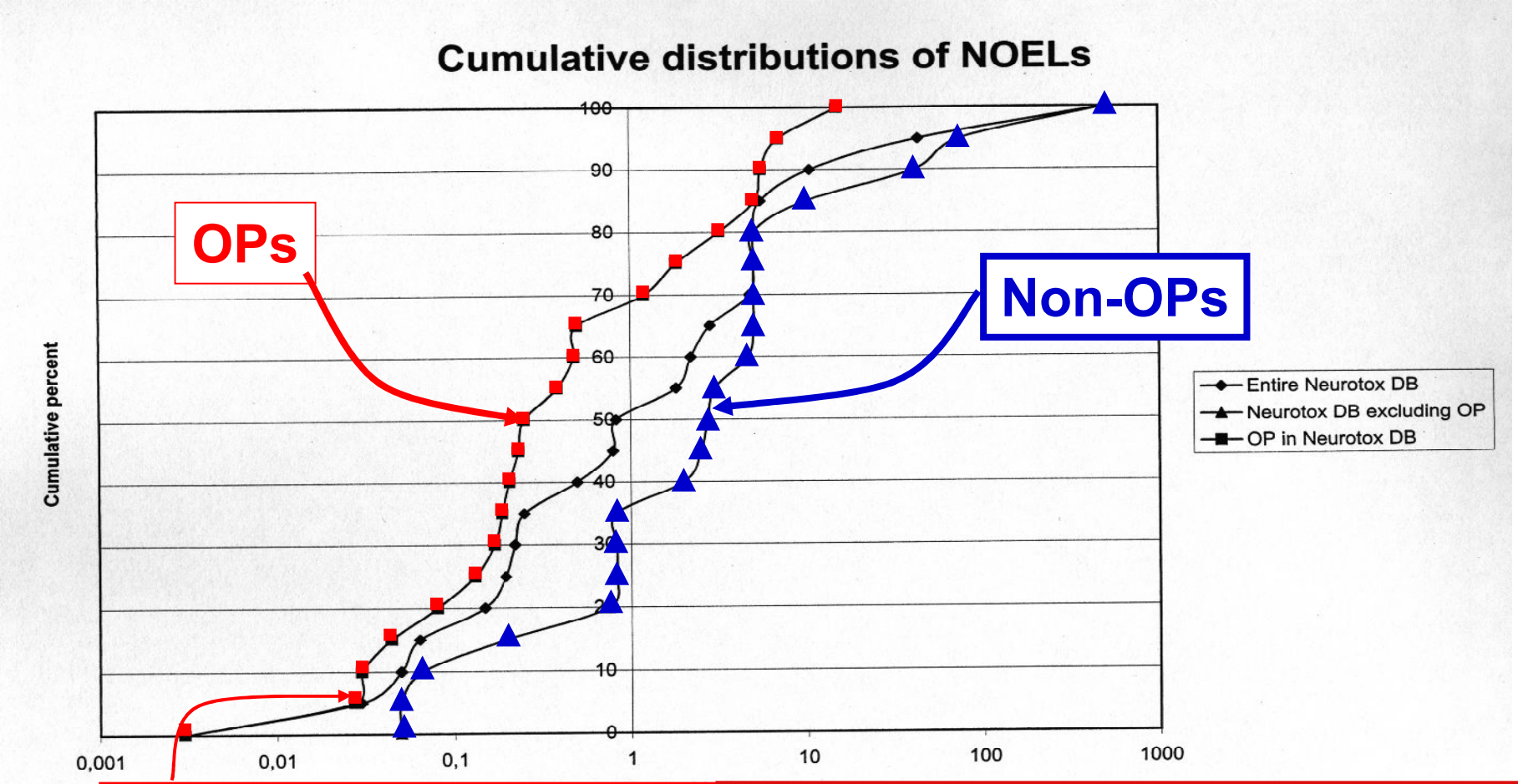


CRAMER CLASSIFICATION TREE

TTC EXPOSURE LIMITS



SUBDIVISION OF NEUROTOXICITY DATABASE INTO OPS AND NON-OPS



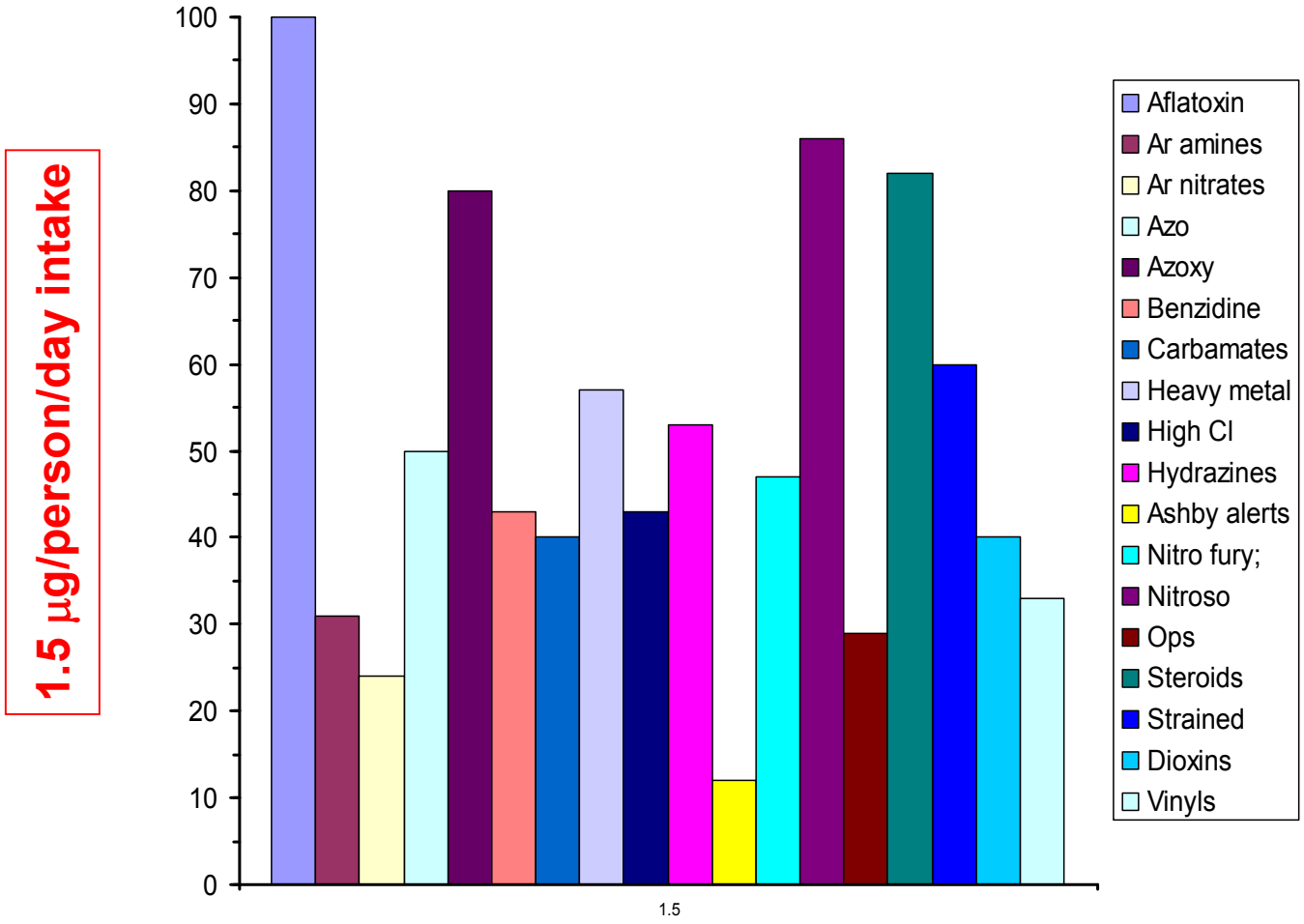
5th percentile NOEL = 30µg/kg/day

TTC = 30/100 x 60kg = 18 µg/person/day

GOLD DATA BASE CARCINOGENS

Upper bound risk for cancer lower than one in a million

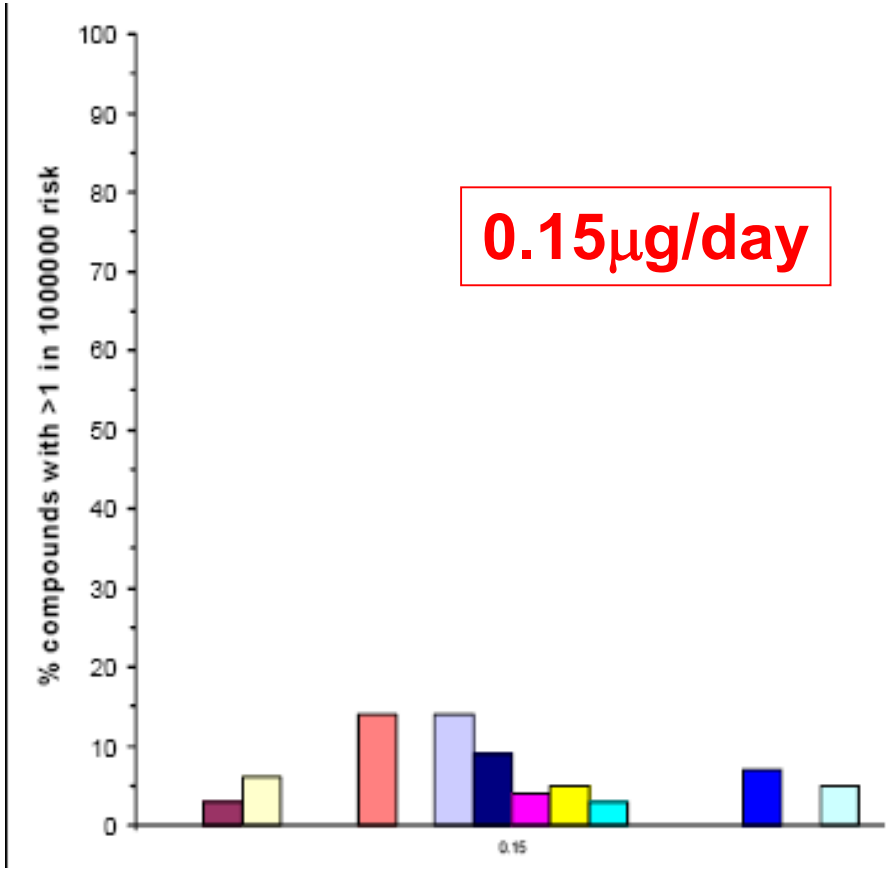
(calculated by linear extrapolation from the TD50)



CARCINOGENS WITH STRUCTURAL ALERT FOR GENOTOXICTY

Upper bound risk for cancer lower than one in a million?

(calculated by linear extrapolation from the TD50)



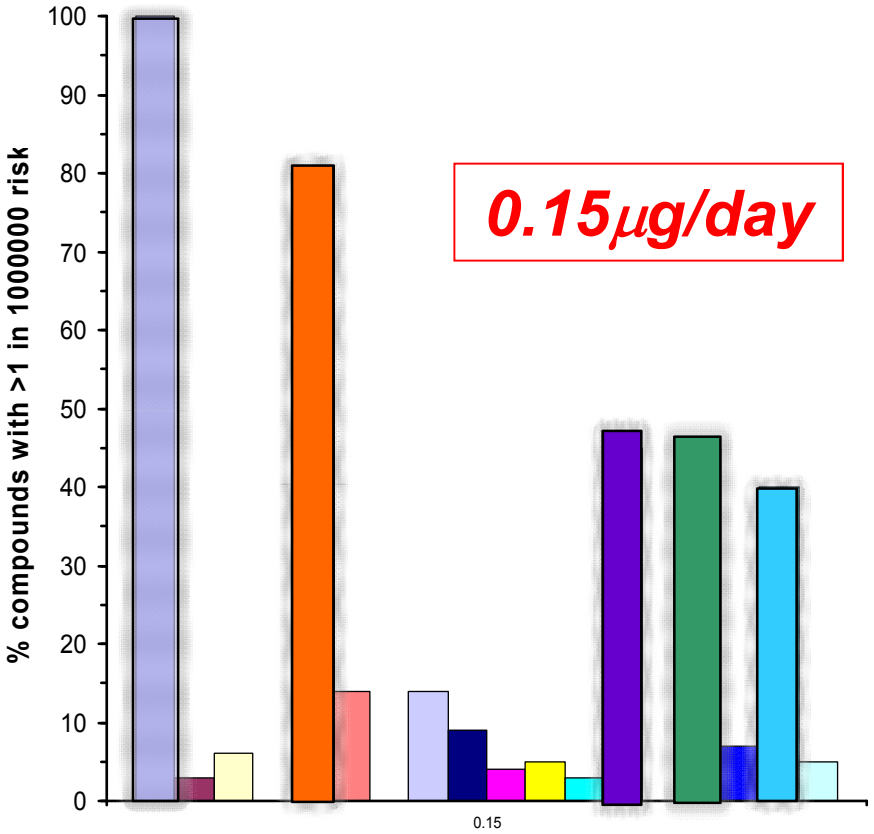
0.15µg/day

- Recommmendation of using a TTC of 0.15 µg/day for substances with structural alerts for genotoxicity

EXCLUSION OF HIGH POTENCY CARCINOGENS

Upper bound risk for cancer of greater than one in a million

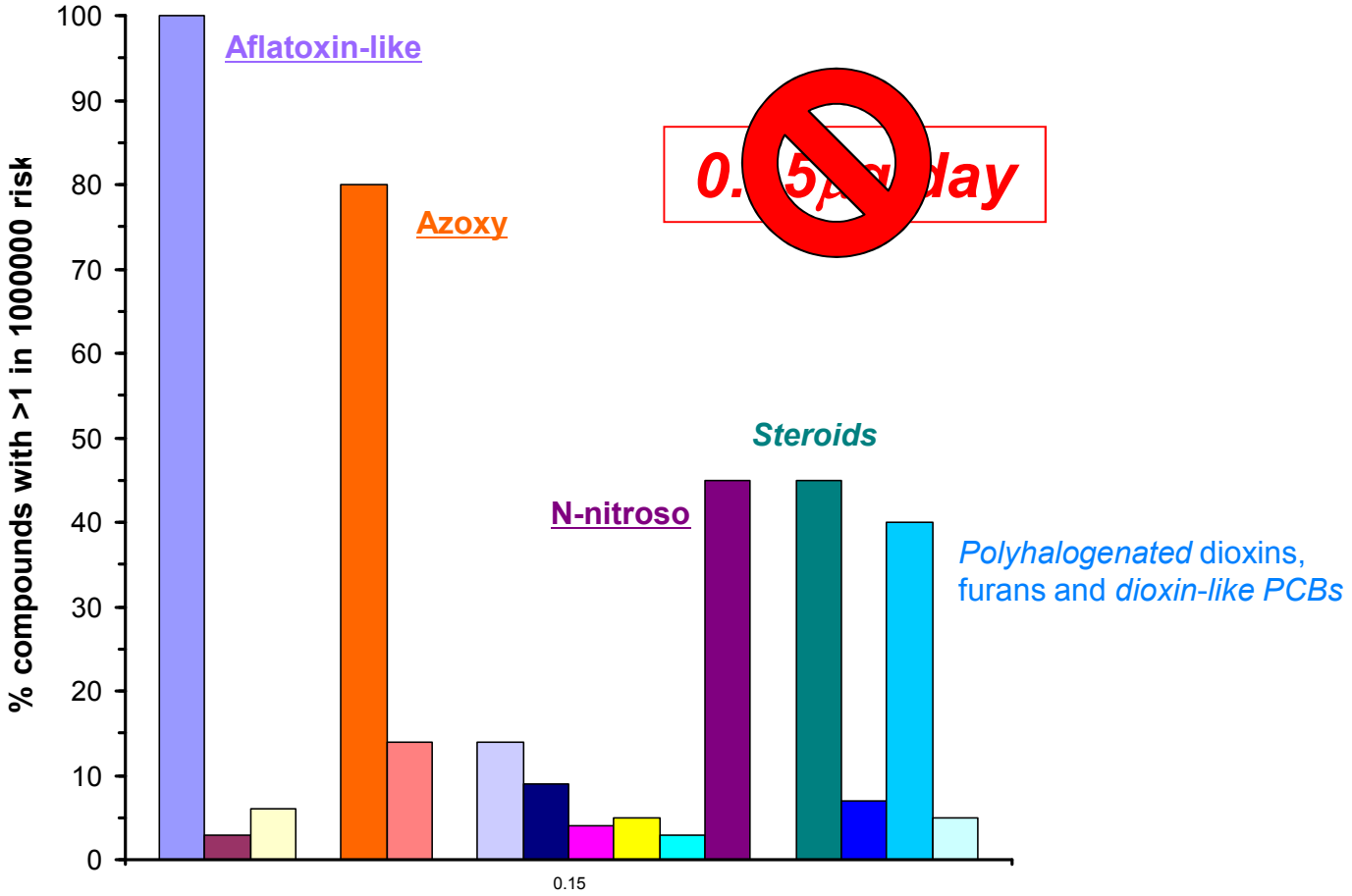
(calculated by linear extrapolation from the TD50)



- Recommmendation of using a TTC of 0.15 µg/day for all other substances with structural alerts for genotoxicity which are not part of the “cohort of concern)

COHORT OF CONCERN

Upper bound risk for cancer of greater than one in a million (calculated by linear extrapolation from the TD50)



THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

IN RISK CHARACTERISATION

a TTC should NOT be considered.

- For specific structural alerts: i.e. **aflatoxin-like**, **azoxy** and **N-nitroso**-compounds (potent genotoxic carcinogens)
- **Polyhalogenated dibenzo-p-dioxins, -dibenzofurans and dioxin like PCB's** (non-genotoxic carcinogens, bioaccumulative, with very large kinetic differences between animals and humans)
- **Steroids** (potent non-genotoxic carcinogens)
- **Non essentials metals and metal containing compounds** (not included in the data base)
- **Proteins** (risk of allergenicity, not included in database)
- **High molecular weight chemicals such as polymers** (not included in database)

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK CHARACTERISATION

➢ HOW TO APPLY THE TTC ?

- **Stepwise approach on a case by case basis:**
  - **Cohort of Concern ➔ NO TTC**
  - **Structural alerts for potential genotoxicity ➔ 0.15 μg/person/day**
  - **Carcinogens without structural alerts ➔ 1.5 μg/person/day**
  - **Structural alerts → OP ester? ➔ 18 μg/person/day**
  - **Class III chemical ➔ 90 μg/person/day**
  - **Class II chemical ➔ 540 μg/person/day**
  - **Class I chemical ➔ 1800 μg/person/day**

ILSI EUROPE EXPERT GROUP ON THE

APPLICATION OF THE THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) CONCEPT TO UNEXPECTED PEAKS IN FOOD

Alan Boobis, David Carlander, Richard Cubberly, Corrado Galli, Heli Hollnagel, Sander Koster, Elke Richling, Tanja Wildemann, Gunna Würtzen

APPLICATION OF THE TTC CONCEPT TO UNEXPECTED PEAKS FOUND IN ANALYSIS OF FOODS AT TRACE LEVELS.

- During ***routine monitoring of a food*** in a quality control laboratory, an extra peak is detected using LC-fluorescence detection that had not been seen previously in the analysis of that food.
- In the evaluation of ***a new processing technology*** (irradiation, a new heat-process, etc) a series of new peaks was detected at trace level that were not present in the food being processed in traditional manner.
- A manufacturer intends to use a food contact material containing ***a novel raw material to package a food***. An unknown peak occurs in the food.
- A manufacturer of an approved food additive has ***changed the production process*** slightly. An LC-MS comparison of the existing additive and the new product shows some minor differences that are not described in the specifications. This includes few new peaks

Are the unexpected peaks a health concern?

TTC EXCLUDED CLASSES;

CLASSES OF SUBSTANCES NOT COVERED BY TTC

Class/Group	Reason for exclusion
Aflatoxin-like compounds[1]	Potent genotoxic carcinogens
N-nitroso-compounds[1]	Potent genotoxic carcinogens
Azoxy-compounds[1]	Potent genotoxic carcinogens
Steroids[1]	Potent non-genotoxic carcinogens
Polyhalogenated dibenzo-p-dioxins, - dibenzofurans and dioxin like PCB's[1]	Bioaccumulative, non-genotoxic carcinogens, with very large kinetic differences between animals and humans
Proteins[2]	Risk of allergenicity, not included in database
(Non)-essential metals[2]	Not included in database, some are bioaccumulative
High molecular weight substances such as polymers[2]	Not included in database

[1]Cohort of Concern

[2]other 'TTC excluded classes

TIERED APPROACH;

PROPOSAL TO DEAL WITH UNKNOWN PEAKS

	Proposed tier	Background
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
Tier 2	Exclusion by chromatographic technique, sample preparation and/or detection method used or partial identification	Analytical techniques are relatively specific, so that a peak detected can only stem from a certain range of substances. They may also indicate the type of substance without providing a full identification.
Tier 3	Exclusion by targeted analysis	Analyses designed to detect certain structural elements can be applied.
Tier 4	Dietary exposure to food sources containing the unknown peak	Due to nutritional habits, exposure depends heavily on the food type.
Tier 5	Quantification of unknown compounds	For risk assessment, the concentration of the unknown peak in the sample has to be estimated with sufficient accuracy.

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TIER 1

EXCLUSION DEPENDENT ON SAMPLE SOURCE

- Requires a thorough knowledge of the product with all potential contaminants that may be present.
- What is source? Packaging? Transport? Storage? Processing?
- Use expert judgment to exclude specific toxic classes. For example;
  - Polypropylene-FCM unlikely to contain dioxins, aflatoxins etc.
  - If unidentified peak is off-flavour, non-essential elements, dioxins etc can be excluded because they are not volatile.

Based on expert judgement

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TIER 2

EXCLUSION BY CHROMATOGRAPHIC TECHNIQUE, SAMPLE PREPARATION, DETECTION

- the chromatographic technique used
  - it can be excluded that an unidentified peak in a GC chromatogram is a protein,
- the sample preparation technique used
  - a peak was detected in an aqueous extract of a meat product. Dioxins can be excluded based on their solubility characteristics in water.
- the detection technique used.
  - a peak detected with a fluorescence detector will not be a steroid as these do not fluoresce

TIERED APPROACH;

PROPOSAL TO DEAL WITH UNKNOWN PEAKS

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TIER 3

EXCLUSION BY TARGETED ANALYSIS

- If expert judgment does not help out completely, targeted analysis may need to be performed.
  - specific GC methods for N-nitroso substances
  - ICP-MS for non-essential elements
  - immunoaffinity clean-up followed by HPLC with post column derivatisation and fluorescence detection for aflatoxins.

TIERED APPROACH;

PROPOSAL TO DEAL WITH UNKNOWN PEAKS

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TIER 4

DIETARY EXPOSURE TO FOOD SOURCES CONTAINING THE UNIDENTIFIED PEAK

- The magnitude, frequency and duration of exposure to a unknown substance. consumed in foods has to be taken into account
- What is exposure to foods containing unidentified peak?
- Such food is not consumed throughout a lifetime, but for shorter periods, a few days or weeks (presence in specific batches) or intermittently (appearing periodically).
- The TTC values in current use are based on the assumption of continuous, lifetime exposure.

TIERED APPROACH;

PROPOSAL TO DEAL WITH UNKNOWN PEAKS

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TIER 5

QUANTIFICATION OF UNKNOWN PEAKS AND RISK CHARACTERIZATION

- Use non-selective extraction/clean-up procedure to prepare unknown for detection.
- Use method suitable for quantification (if not already used).
- Change extraction and clean-up parameters to maximise recovery of the unknown.
- Quantify against a suitable range of standards added to the sample at target concentration derived from the TTC.

ILSI EUROPE EXPERT GROUP ON THE

APPLICATION OF THE THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) CONCEPT TO UNEXPECTED PEAKS IN FOOD

EXAMPLES

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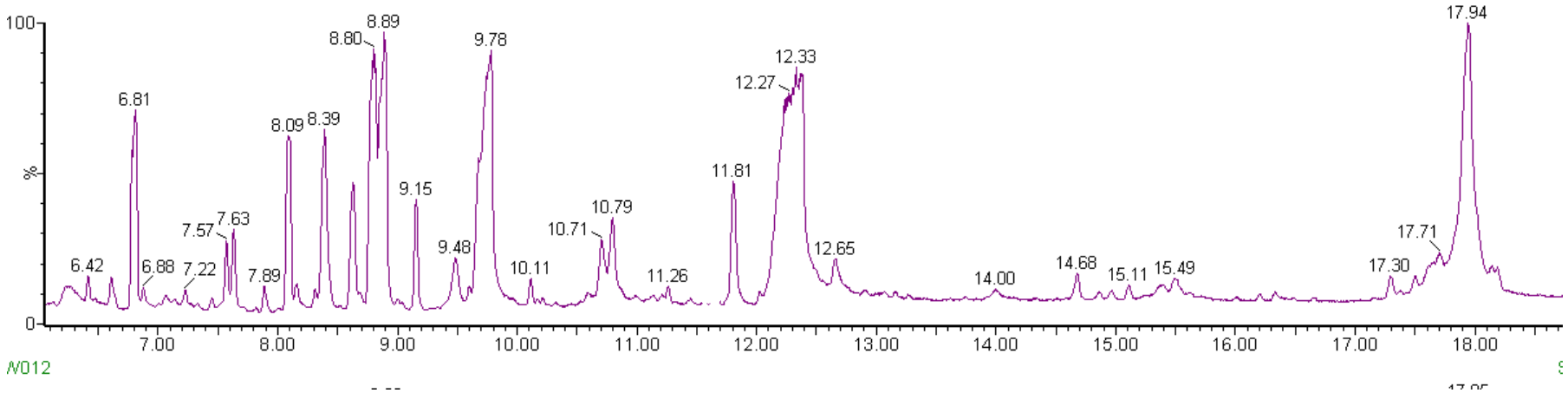
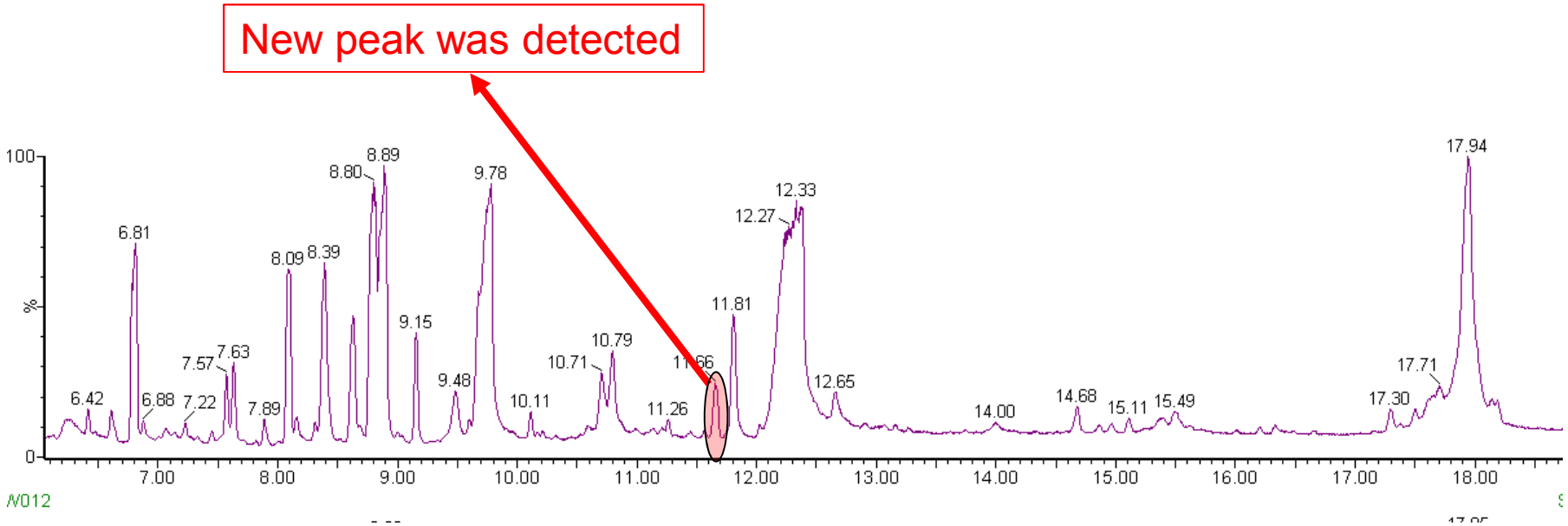
EXAMPLES: CUCUMBER



pesticide screen of cucumber extracts by GC-MS

EXAMPLES: CUCUMBER



pesticide screen of cucumber extracts by GC-MS

EXAMPLES: CUCUMBER

Tier 1 Exclusion by sample source

- Cucumber watery fruit. Negligible amounts of fat → **Dioxin like compounds** unlikely.
- **N-Nitroso compounds** are formed in the presence of nitrites and are more associated with processed foods than fresh fruit and vegetables and so are also excluded.
- **Azoxy compounds** are not typically associated with cucumber and therefore they were discounted at this stage

EXAMPLES: CUCUMBER

Tier 2 Analytical method (GPC and GC-MS)

- **Proteins and polymers** structure excluded by GPC
- **Steroids** require very high GC oven temperatures.
- **Aflatoxins** not volatile enough for GC analysis.
- MS library did not give (partial) identification.

EXAMPLES: CUCUMBER

Tier 3 Exclusion by targeted analysis

- Presence organometallics could not be ruled out.
  - ICP-MS analysis showed normal levels of non-essential elements.

ALL 'EXCLUDED CLASSES' RULED OUT

EXAMPLES: CUCUMBER

Tier 4 Exposure to food item containing unidentified peak.

- Cucumber intake of 6.5 g/day (UK NDNS 2001) .
- As the unidentified peak could be potentially genotoxic, the TTC value of 0,15 ug/day would apply.
- → no safety concern when 23 µg/kg (23 ppb) cucumber.

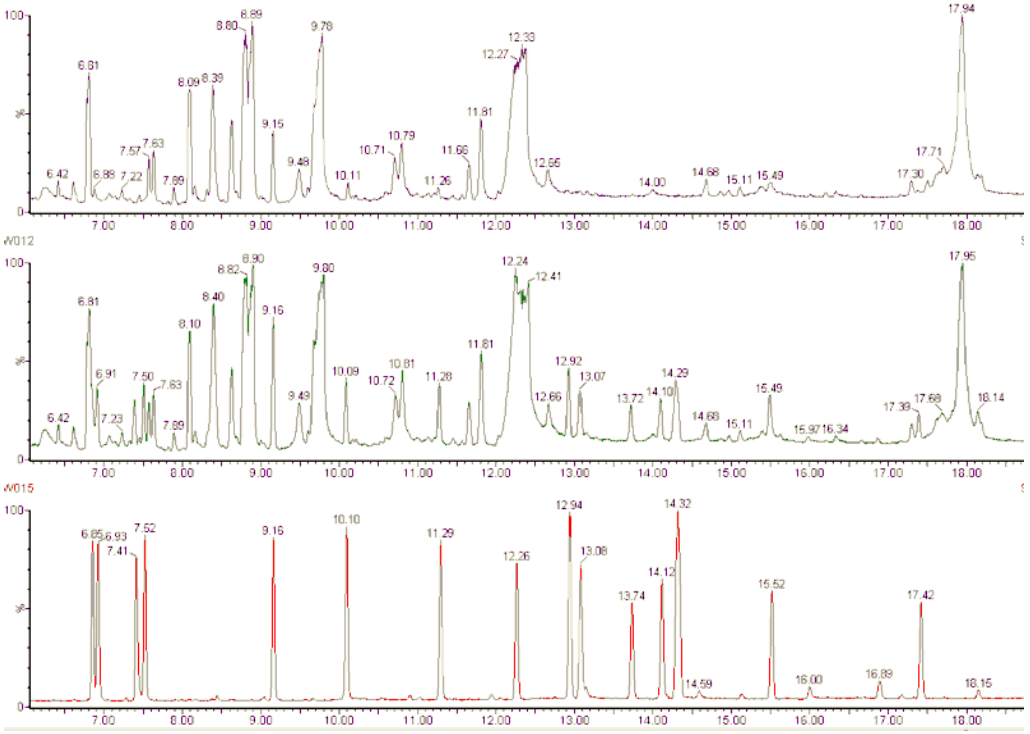
EXAMPLES: CUCUMBER

Tier 5 Quantification

Unspiked cucumber

Cucumber spiked with standards at 23 µg/kg (23 ppb)

Standard solution in solvent



EXAMPLES: CUCUMBER

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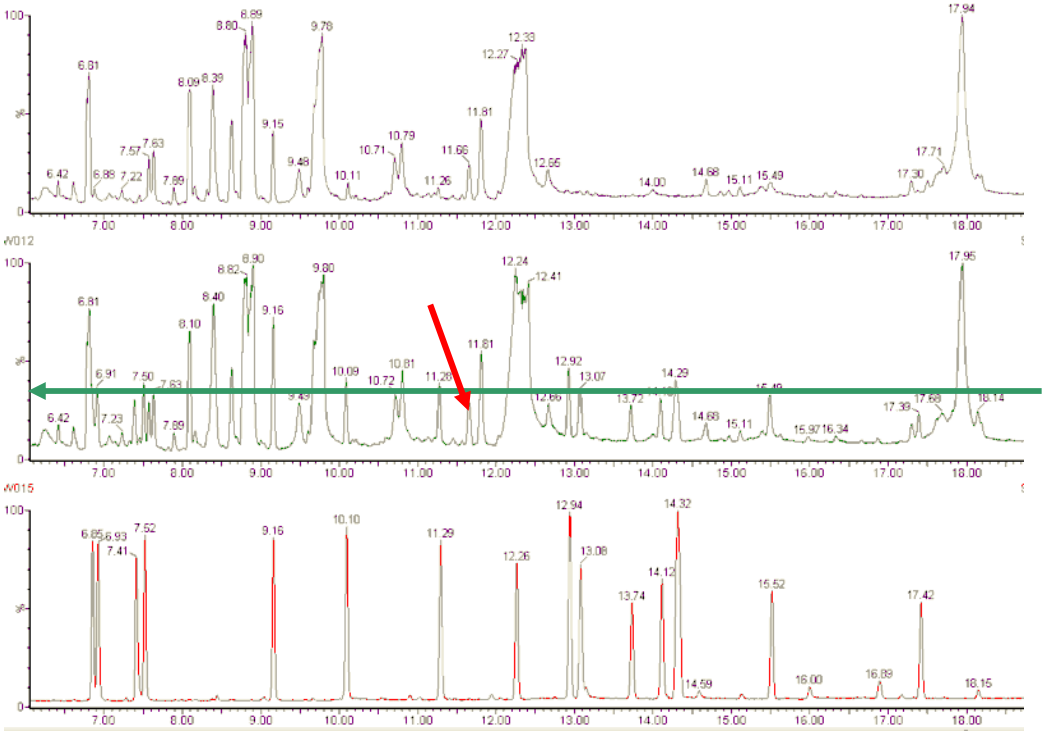

Mean response (peak height) of spiked substances is set as the level of concern at 23 µg/kg (23 ppb)

EXAMPLE: OFF-FLAVOR

- Consumers noticed a strange smell and taste on preparation of a dry ready meal. It was important to assess the risk to the consumer from consumption of this product.

- The distinctive odor was traced to a single ingredient (dried vegetable) and this was analysed for volatile contaminants by headspace-GC-MS.

EXAMPLE: OFF-FLAVOR

Tier 1 Exclusion by sample source

- Contamination was likely to have occurred during processing.
- **Aflatoxins, steroids, proteins, non-essential metals and high molecular weight compounds** are not sufficiently volatile to contribute to an off odour.
- Contamination of foods with **dioxins and PCBs** has been extensively reported but there are no accounts of an associated off flavour.
- **Azoxy compounds** are not typically associated with food and can therefore also be excluded
- It is reasonable to assume the unknown peak caused the off flavour described by consumers. None of the ‘TTC excluded classes’ are associated with off flavours or odours

EXAMPLE: OFF-FLAVOR

Tier 2 Analytical method

- headspace GC-MS → volatiles.
  - Exclusion of aflatoxins, proteins, steroids, dioxin like compounds, high molecular weight polymers and metals
- Partial identification mass spectrum

  → presence chlorine isotope pattern → trichlorinated aromatic compound (which is not genotoxic).

EXAMPLE: OFF-FLAVOR

Tier 3 Exclusion by targeted analysis

- All ‘TTC excluded classes’ excluded in tier 1 since they do not give rise to flavours or odours.
- Additionally, some structural information was deduced in tier 2 (trichlorinated aromatic compound)
- → no targeted analysis required

EXAMPLE: OFF-FLAVOR

Tier 4 Exposure to food item containing unidentified peak

- The risk assessment based on consumption of one ready meal per day containing 1g of the contaminated ingredient.
- Applying the TTC limit for non genotoxic substances of currently 90 µg/day (Cramer class III) for the contaminant means the maximum acceptable concentration in the ingredient would be 90 µg in 1 g of the contaminated ingredient or 90 mg/kg (90 ppm).

EXAMPLE: OFF-FLAVOR

Tier 5 Quantification

- Samples (1g) of the contaminated dried vegetable were spiked with trichlorophenol and trichloroanisole, compounds believed to be similar in properties to the contaminant based on the mass spectra, added at a concentration to give a response similar to that of the unknown peak.
- The unidentified peak was measured at a level significantly below 90 mg/kg and the risk to consumer safety was deemed acceptable.
- However, the product was considered unpalatable and was withdrawn from sale of quality grounds

CONCLUSIONS

- Tiered approach presented guides the risk assessor through the TTC. Worst case TTCs (than 0,15 ug exposure) should be appointed to unidentified peaks.
- TTC applied to unidentified peaks, not for safety assessment of whole food.
- Approach is no guarantee that toxic substances are absent.
- Uncertainties: exposure, genotoxicity
- Good communication analytical chemists, toxicologists and risk assessors

THANK YOU