European Food Safety Authority

Threshold of Toxicological Concern

Draft Opinion of the Scientific Committee

EFSA Stakeholder Consultative Platform
Brussels, 17-18 November 2011

Questions and concerns

- Is the TTC approach built on science or built on sand?
- Is it a useful risk assessment tool for public health or just a tool of convenience?
- Should it be used selectively or in any context?
- Is this the slippery slope towards no testing?

Outline

1. Why might EFSA need TTC as a risk assessment tool?
2. What is the TTC approach and does the underlying science support its use?
3. Where could TTC be applied in EFSA's work?
4. Comments and concerns raised in the public consultation

Does EFSA need TTC as one of its tools ?

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No risk assessor <u>wants</u> to work without chemical-specific data

BUT

- **Better analytical techniques reveal more and more chemicals at low concentrations in food and feed**
- **EFSA is asked for advice on exposure to substances for which there are no toxicological data**
- **Preliminary advice may be needed urgently**
- **Priorities for risk assessment may need to be set**

Does EFSA need TTC as one of its tools ?

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The view that every chemical needs to be tested

- **Ignores how accumulated knowledge in science can help reduce the need for testing**
- **Makes no recognition of strongly held views and regulations in Europe that we should strive to reduce animal testing wherever possible, whilst still ensuring that public health can be protected**

What is the TTC approach & is it based on science?

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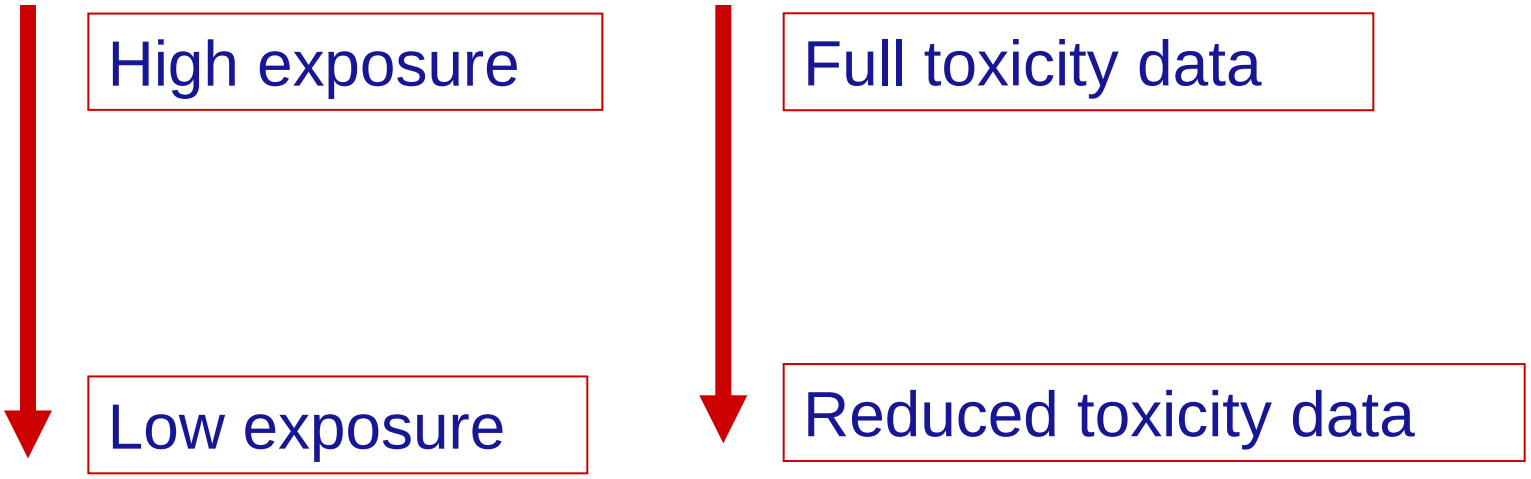
Background to the TTC approach

- Science uses observation and experiment to generalise knowledge that can be used to explain or **make predictions** about the world around us, including the behaviour of chemicals
- The TTC approach organises and applies a large body of existing toxicological data **to gauge the likely toxicity of an untested substance**
- It is based on a fundamental principle of toxicology — **toxicity is a function of dose and duration of exposure**
- It establishes generic human exposure threshold values (TTC values) **below which the probability of adverse effects on human health is considered to be very low**

Comparison to current EFSA approaches

The amount of toxicity testing EFSA requires on a substance is often related to the predicted human exposure



So is there a level of exposure that is so low that we can conclude there is unlikely to be a safety concern even in the absence of any toxicity data on that substance?

Derivation of generic TTC values for the endpoint of cancer

Work of the US FDA (1986-1995) and Kroes et al. (2004)

- Analysed all available oral carcinogenicity potency data in rodents (Carcinogenic Potency Data Base-CPDB) ~ 730 substances by 2004
- Used linear extrapolation to low doses to estimate exposures that might increase the risk of cancer to no more than 1 in a million
- Derived thresholds of 0.15 and 1.5 µg/person per day below which consumers would be protected "with reasonable certainty of no harm" (FDA) even if an untested substance turned out to be a carcinogen
- Since 1995 FDA has used 1.5 µg/person per day as 'Threshold of Regulation' for food contact materials
- Excluded use of TTC for groups of substances known to be high potency carcinogens

EFSA conclusion on a TTC value for the endpoint of cancer

The Scientific Committee concludes in the draft opinion

- The TTC value of 0.15 µg/person per day is sufficiently robust and conservative to be used in EFSA's work, provided structures related to high potency carcinogens are excluded

This TTC value has been derived by linear extrapolation of rodent bioassay results, widely considered to be a very conservative approach

Derivation of generic TTC values for non-cancer endpoints

Work of Munro et al. (1996)

- Compiled existing toxicity data on 613 substances (industrial, food, consumer, environmental & agricultural chemicals, pharmaceuticals) and determined their no-observed-effect levels (NOELs)

- Allocated each substance to one of three broad structural classes (Cramer classes)

  Class I – simple structures, low likelihood of toxicity

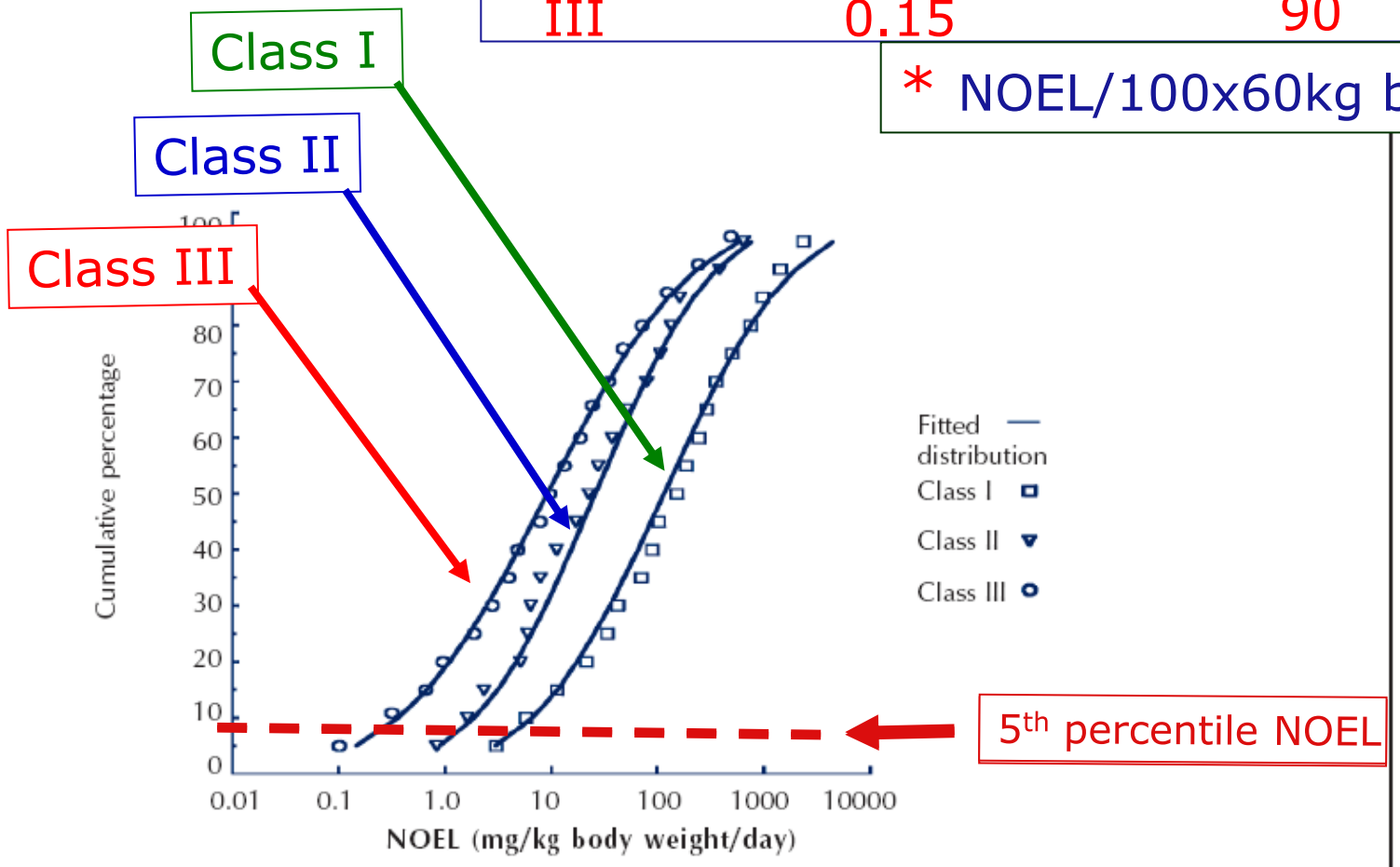
  Class III – more complex structures suggesting significant toxicity

  Class II – structures in between I and III

- For each class, plotted the distributions of potencies expressed as NOELs

Class	5th percentile NOEL (mg/kg/day)	TTC (µg/day) *
I	3.0	1800
II	0.91	540
III	0.15	90

* NOEL/100x60kg bw



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.

EFSA conclusions on TTC values for non-cancer endpoints

Cramer classification scheme

- Advances in knowledge indicate revision and refinement of Cramer scheme for classification of chemical structures would be timely
  - *It was devised in the late 1970s*
- Nevertheless, the current Cramer classification scheme is fit-for-purpose in the regulatory context
  - *EFSA's analyses, together with those of an outside contractor, show it is conservative and therefore protective of human health*

EFSA conclusions on TTC values for non-cancer endpoints

TTC values

- TTC values should be expressed on a body weight basis
  - *To take account of lower body weight of children for comparison with age-specific exposure estimates*

- TTC value for Cramer **Class II** is not well supported

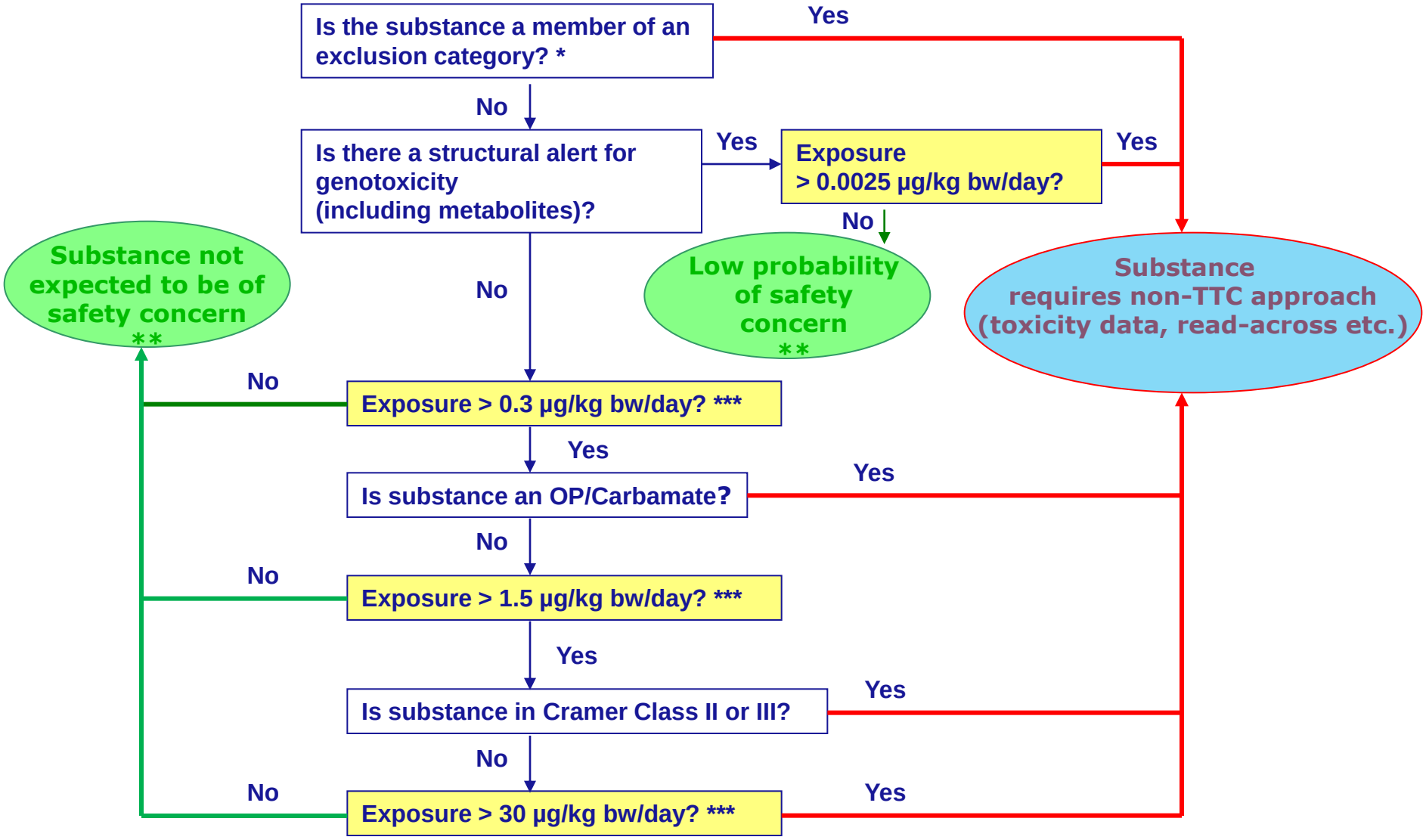
  consider treating Class II substances as if they were Class III
  - *Few substances are ever classified in Class II (except flavourings)*

EFSA conclusions on TTC values for non-cancer endpoints

TTC values

- TTCs values for **Cramer Class I** and **Class III** are sufficiently robust and conservative to be used in EFSA's work, but lower TTC needed for structures related to OPs and carbamates
  - *EFSA's analysis of data on the substances in the lowest 10th percentiles of the Munro NOEL distributions for Class I and Class III confirmed the NOELs*
  - *Analysis of the EFSA database on pesticides (as an exercise), and NOELs for reproductive and developmental toxicity of EU classified industrial chemicals, showed TTC values are protective* (***BUT note there is no intention to use TTC for pesticide actives***)
  - *In the published literature, similar oral TTC values have been derived by others from different datasets*

GENERIC SCHEME FOR THE APPLICATION OF THE TTC APPROACH



* Exclusion categories – see next slide

** If exposure of infants < 6 months is in range of TTC → consider if TTC is applicable

*** If exposure only short duration → consider margin between human exposure & TTC value

Exclusion categories

- High potency carcinogens (e.g. aflatoxin-like, azoxy- or N-nitroso substances)
- Inorganic substances
- Metals
- Proteins
- Steroids
- Substances known/predicted to bioaccumulate (e.g. polyhalogenated-dibenzodioxins, -dibenzofurans, -biphenyls)
- Insoluble nanomaterials
- Radioactive substances

What information do we need to apply the TTC approach?

- The chemical structure
- Suitably conservative estimates of human exposure, which take account of high-exposure scenarios and include exposure from all sources and routes

Where could TTC be applied in EFSA's work?

- **In principle, TTC could be applied to any substance for which exposure is very low**

- **However, in the context of EU legislation, it is clear that TTC would not be used when there is a requirement to submit toxicity data**

  (e.g. not for technically active substances in pesticides, food additives, nutrient sources, feed additives, etc)

- **It should only be used with careful consideration of the context and any necessary modifications to the generic scheme (e.g. as currently used for flavourings)**

Where could TTC be applied in EFSA's work?

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The TTC approach could be a useful tool for evaluation of low-level exposures to:

- **Impurities, breakdown and reaction products in e.g. food additives, nutrient sources, feed additives, food contact materials, etc**
- **Trace contaminants in food and feed**
- **Plant metabolites and degradates of pesticide active substances (already used for pesticide metabolites in groundwater)**
- **Metabolites of feed additives formed in target species not otherwise covered by laboratory animal tests**

The public consultation: main issues raised

- **Would the TTC approach be used as only as a screening tool for prioritisation, or also to decide that a substance requires no further data/evaluation?**

  A. Both — but remembering it would not be used for substances for which there is a legal requirement to submit toxicity data

- **Lack of clarity on the potential uses of TTC within EFSA**

  A. There will be further clarification in the final opinion

- **Are TTC values sufficiently conservative to cover endocrine effects?**

  A. EFSA's analysis on industrial chemicals and the underpinning databases for TTC show that adverse effects on reproduction and development are covered

The public consultation: main issues raised

- **Are the non-cancer TTC values based on 5th percentile NOELs sufficiently conservative?**

  A. The TTC values are one hundred-fold lower than the 5th percentile NOELs

- **Why not use the TTC value for Cramer class II?**

  A. Not ruled out for future use but more work needed to support it

- **Why not revise the TTC value for Cramer Class III upwards given there is a lower value for OPs and carbamates?**

  A. No. Most substances fall into Class III; from a regulatory perspective it is desirable to maintain the overall conservative nature of the TTC approach

The public consultation: main issues raised

- **Does it require discussion with risk managers before using it?**

  A. The opinion discusses the science and the uncertainties behind the TTC approach and emphasises that it is a probability-based tool; risk managers will decide if the outcomes from using TTC can be accepted

Summary of potential benefits

- The TTC approach is a useful tool to add to EFSA's range of risk assessment approaches
- It would enable efficient use of resources in several areas of EFSA's work, e.g. low-level impurities, degradates and contaminants could be more readily evaluated, allowing a greater focus on substances more likely to pose risks
- It would help speed up urgent decision-making for low-level substances in food and feed
- It would contribute to reductions in the use of animals by avoiding unnecessary testing

Next steps

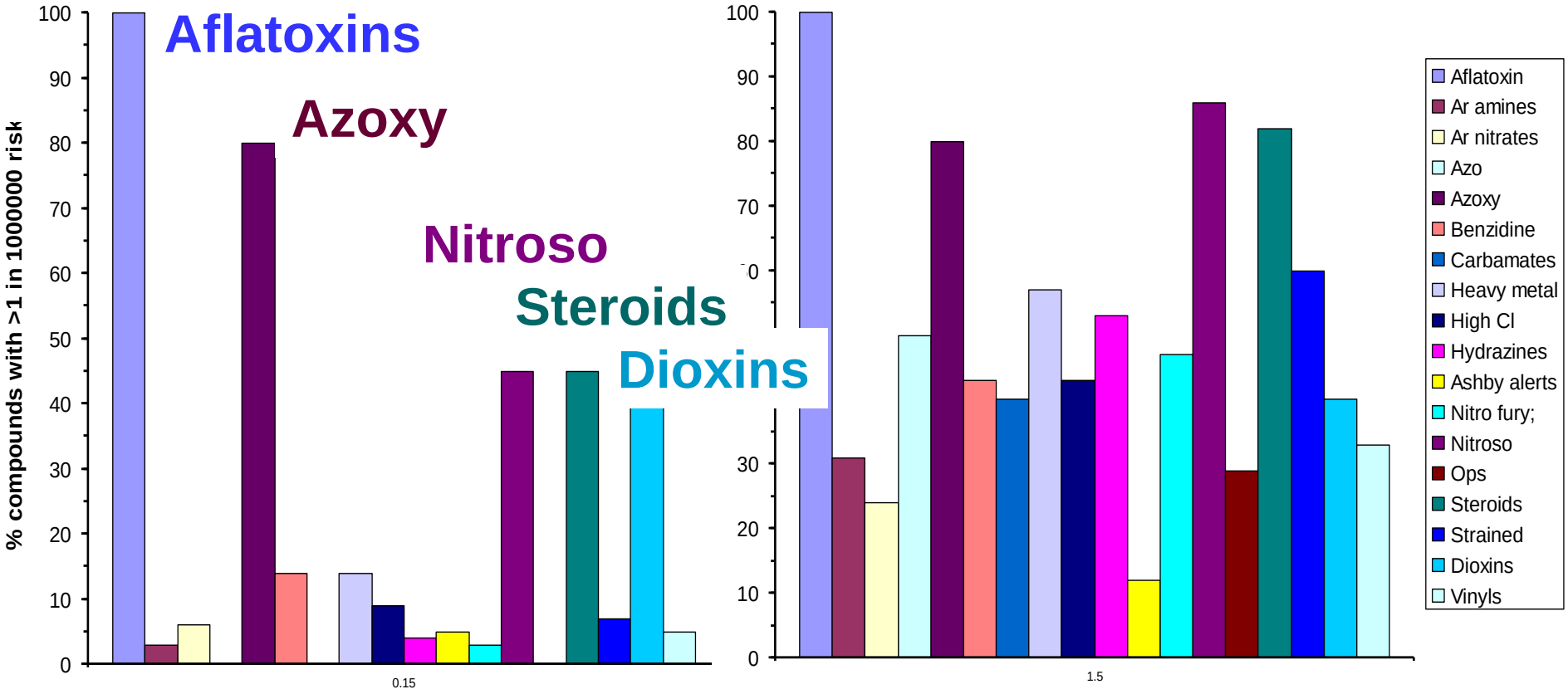
- The TTC WG is considering the public comments and will prepare a final draft to go to the Scientific Committee for its consideration and adoption
- EFSA is also in dialogue with the TTC WG of DG SANCO's non-food committees who are also developing an opinion
- Adoption of the EFSA opinion foreseen for early 2012

Thank you for your attention

Questions and comments?

Reserve slides for the discussion

Percent carcinogens with a calculated risk > 1 in a million at different levels of daily intake

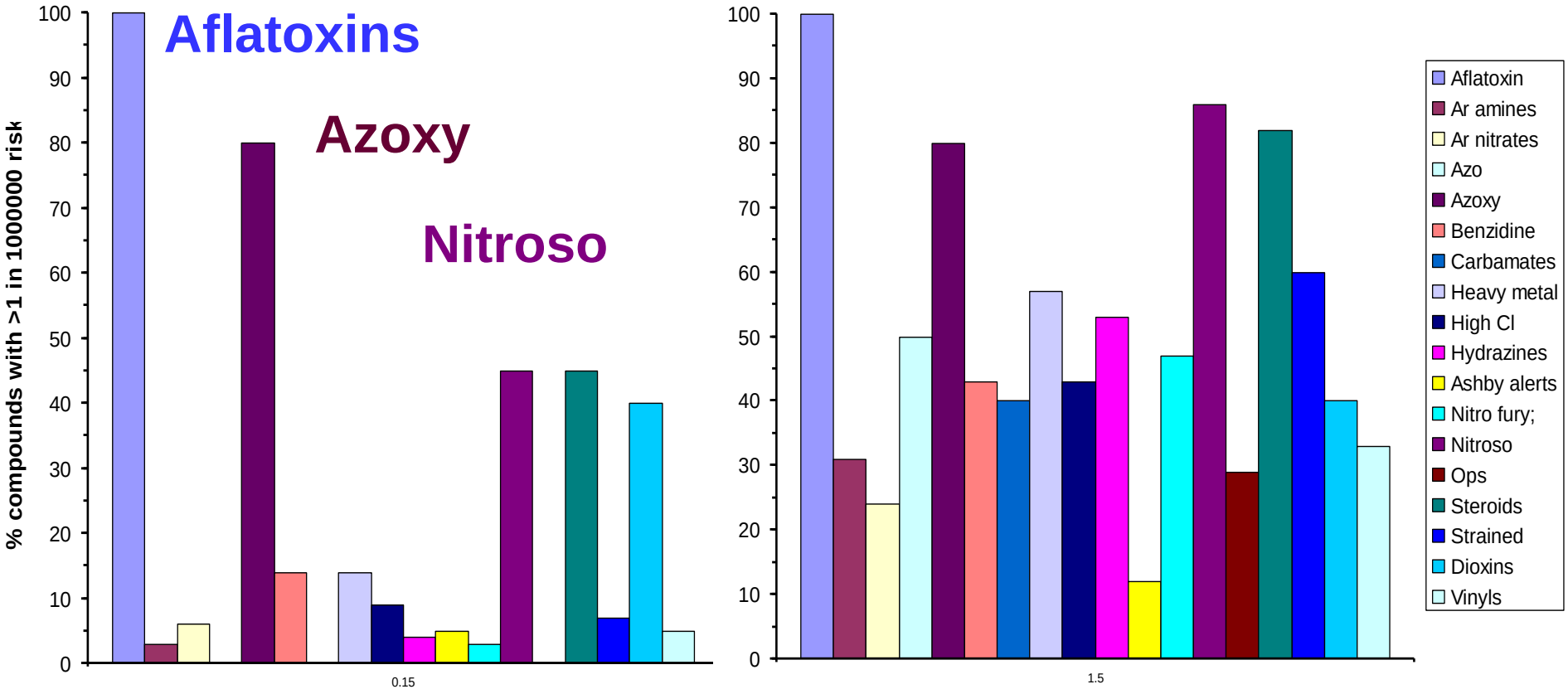


0.15µg/day

1.5µg/day

Next: Remove substances with a threshold

Percent carcinogens with a calculated risk > 1 in a million at different levels of daily intake

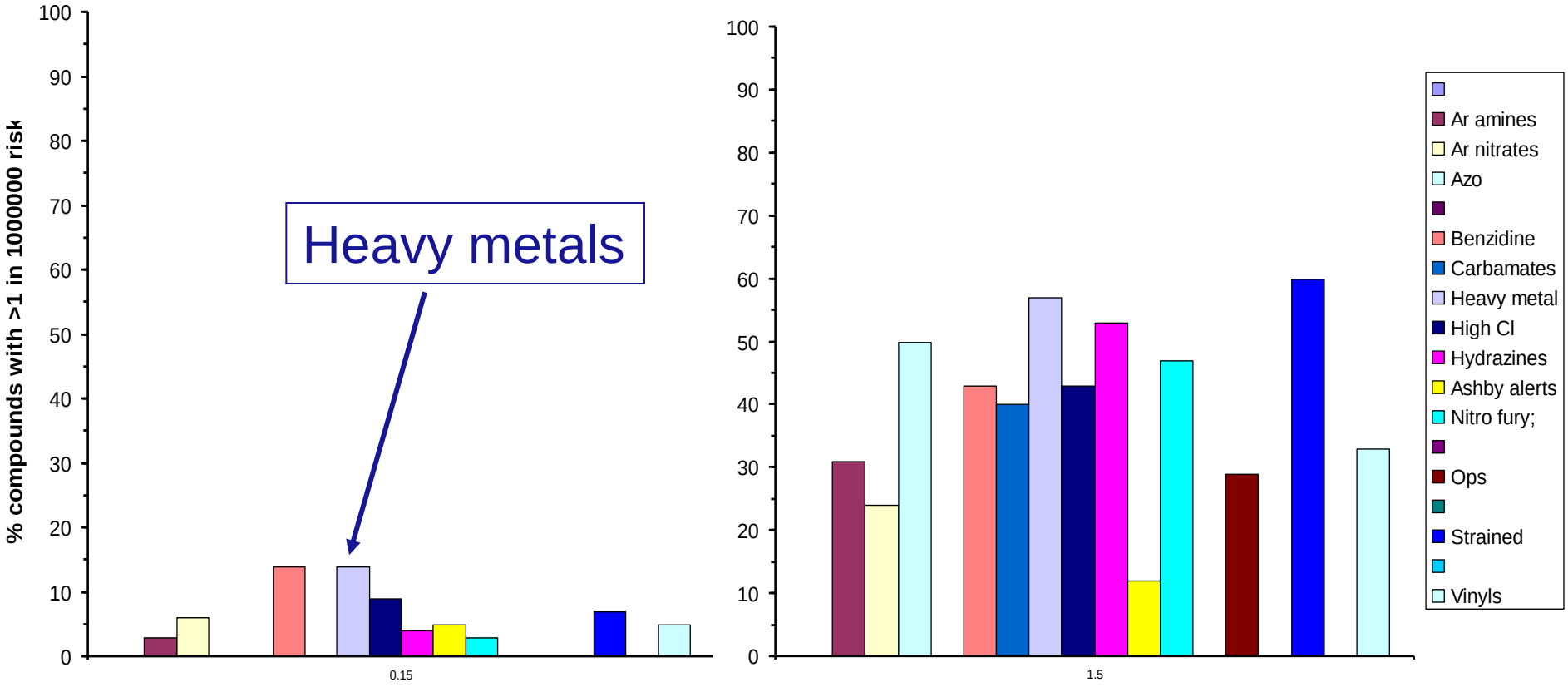


0.15µg/day

1.5µg/day

Next: Remove substances the most potent

Percent carcinogens with a calculated risk > 1 in a million at different levels of daily intake



0.15µg/day

1.5µg/day

For remaining substances there is a high probability that any cancer risk would be less than 1 in a million at an intake of 0.15 µg/day

How reliable are the TTC values for the endpoint of cancer?

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Probability analysis by Munro (1990) for exposures of 0.15 and 1.5 µg/person per day

	Percentage of chemicals presumed carcinogenic			
	100%	50%	20%	10%
Exposure	% probability risk of 1 in a million will not be exceeded			
0.15 µg/day	86	93	97	99
1.5 µg/day	63	82	93	96

Assuming that 1 in10 untested chemicals might be carcinogenic a generic TTC of 0.15 µg per day would give a 1% probability of a lifetime cancer risk of more than1 in a million

This also assumes that any untested substance would be as potent as the 15% most potent carcinogens in the CPDB

EFSA analysis of reproductive and developmental NOELs

- **Reproductive & developmental toxicity:**

  TTC values for Cramer Class I and III are adequately protective.

  Based on EFSA analysis of EU database on industrial chemicals classified for reproductive and developmental toxicity.

  EFSA analysis confirms findings of Kroes et al 2004, Bernauer et al 2009, van Ravenzwaay et al 2010, who also looked at data on reproductive toxicants.

Database	5th percentile NOEL (µg/kg bw per day)	
	Cramer Class I	Cramer Class III
Munro	3000	150
EU CPL	3840 (13) *	550 (83) *
	* Number of substances	

Endocrine mediated toxicity

- **Endocrine-mediated toxicity**

Adequately covered by existing TTC values

- Standard OECD protocols for reproductive, developmental, subchronic and chronic toxicity will detect many endocrine-mediated effects
- Such studies were included in the Munro database
- Homeostatic mechanisms limit adversity at low doses