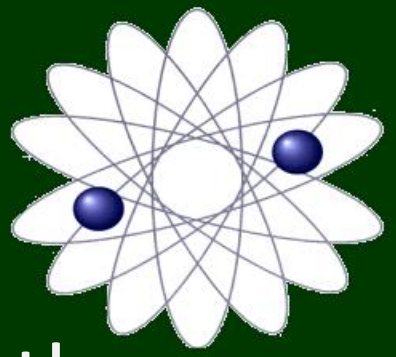
Using the TTC for evaluation of substances ingested at low levels through food: Challenges and perspectives

Alexandre Feigenbaum
scientific coordinator of ReSafe network

ReSafe: European research network for an independent REsearch on food SAFEty related to FCM

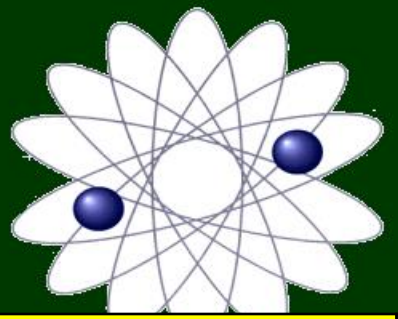
Food Packaging Forum, Zurich, 17 October 2013

Warning



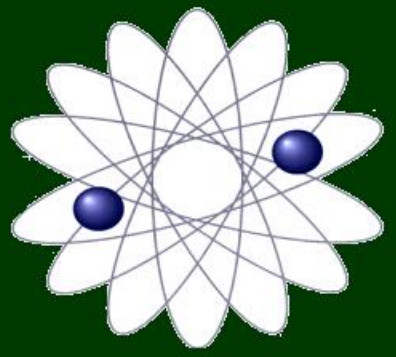
Any view presented here is under the sole responsibility of the speaker

The TTC thresholds & the TTC overall strategy



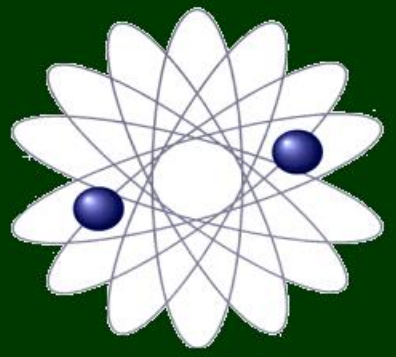
	mg/person per day	µg/kg b.w. per day
Exclusion categories:	TTC not applicable	
Possible carcinogens: STRUCTURAL ALERTS FOR GENOTOXICITY	0.00015	0.0025
Non-carcinogens		
NEUROTOXICITY ALERT	0.018	0.3
CRAMER CLASS III	0.090	1.5
CRAMER CLASS II	0.540	9
CRAMER CLASS I	1.800	30

Questions in this presentation



- **For which substances is TTC used as a tool for risk assessment?**
- **The limitations: when and why can the TTC overall strategy NOT be used?**
- **Challenges & perspectives:**
  Is the TTC principle an internationally recognised approach?

Questions in this presentation



- **For which substances is TTC used as a tool for risk assessment?**

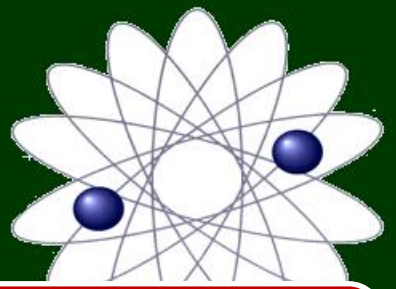
  ⇒ Flavouring substances

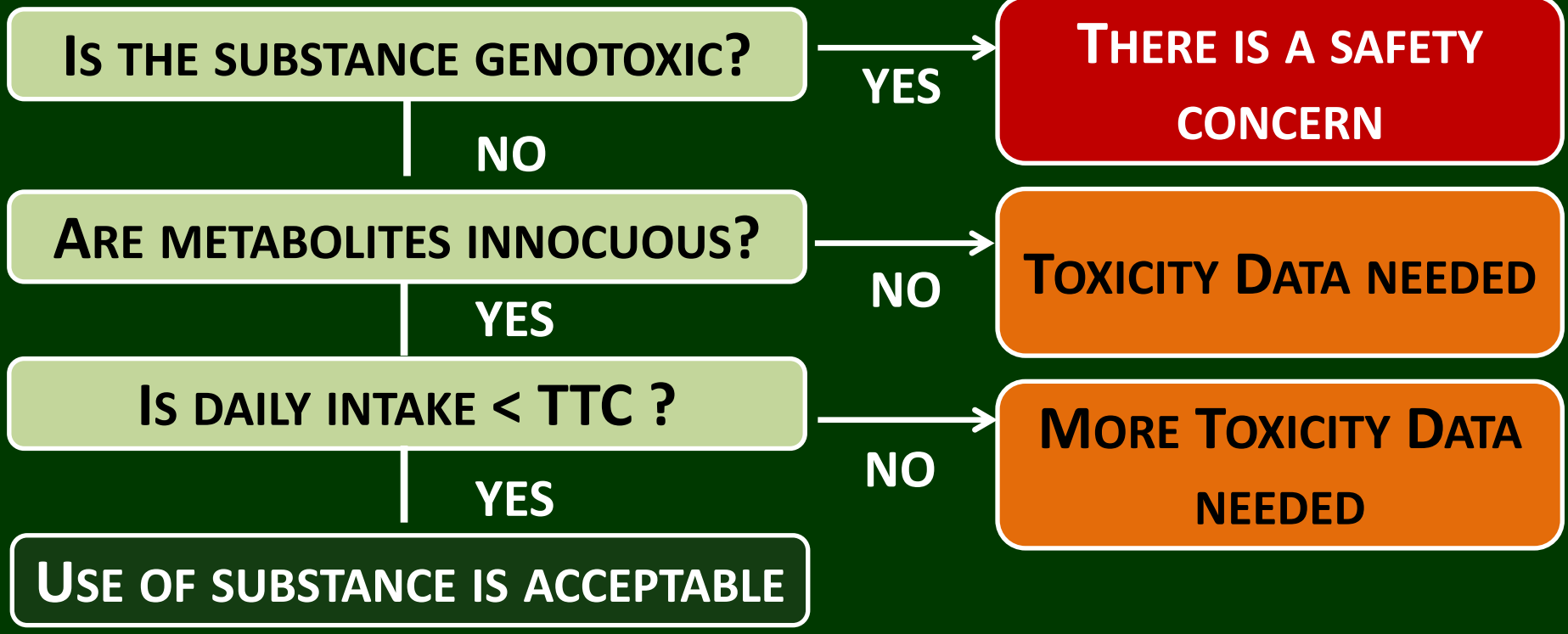
  ⇒ Non plastics Food Contact Materials

  ⇒ Food & feed contaminants (toxins)

  ⇒ Pesticide metabolites (not presented here)

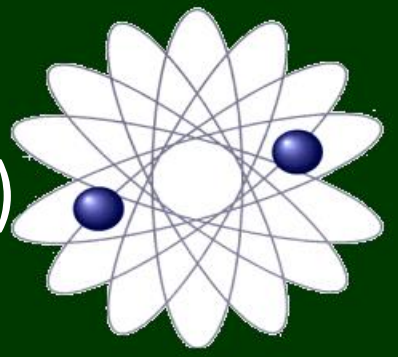
1- Strategy for evaluation of new flavouring substances





TAKE HOME MESSAGE 1: For risk assessment, the TTC approach is often integrated in a strategy making also use of data on toxicity & exposure

2- Case of non plastics Food Contact materials (ESCO, 2012)



This area includes paper and board, coatings, rubber, colorants, wood & cork, printing inks, responsible for crises in the 2000-2010 period (NOGE, ITX, MBP…)

3428 SUBSTANCES USED FOR NON-PLASTICS INVENTORIED IN MEMBER STATES REGULATIONS :

A European Scientific Cooperation (ESCO) Working Group of Member States delegates was appointed to propose solutions. http://www.efsa.europa.eu/en/supporting/doc/139e.pdf

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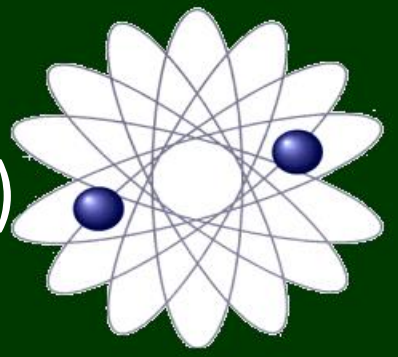
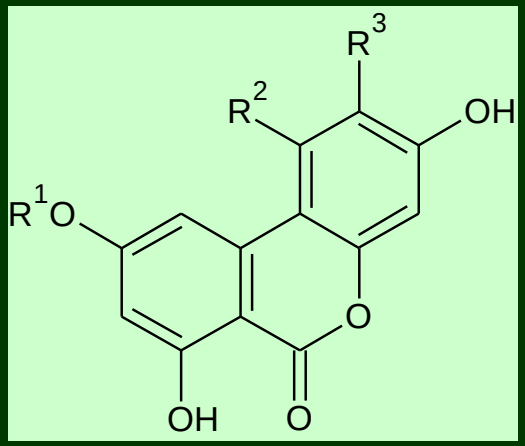


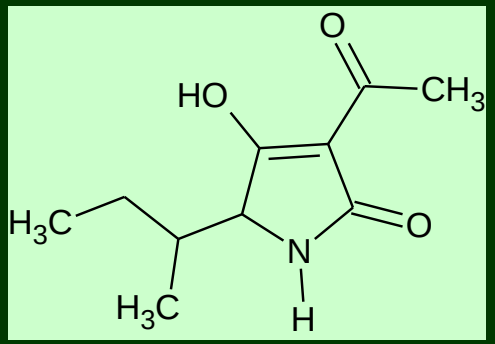
- **PRIORITIES FOR FUTURE EVALUATIONS: THEY ARE TO BE SET BY INDUSTRY, ON BASIS OF**
  - Technological interest of the substances & uses
  - TTC value
  - Estimated exposure compared to TTC value
  - …..
- **PRELIMINARY ADVICE IN CASE OF EMERGENCY SITUATION COULD BE PROVIDED BY FOOD SAFETY AGENCIES ON BASIS OF**
  - TTC approach
  - Read across if similar substances were evaluated
  - Conservative exposure scenarios
  - …..

3- Food contaminants: Case of Alternaria toxins (EFSA 2011)

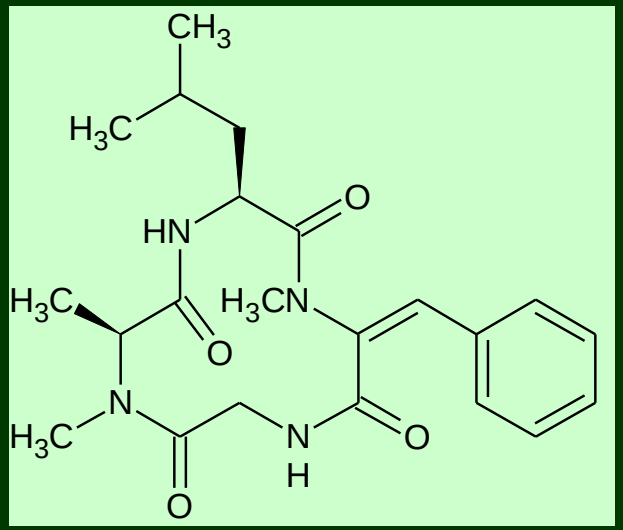
Alternaria toxins may contaminate cereals and seeds and cause plant diseases.



AOH, AME
(alternariol & Me ether)



TEA
(Tenuazonic acid)



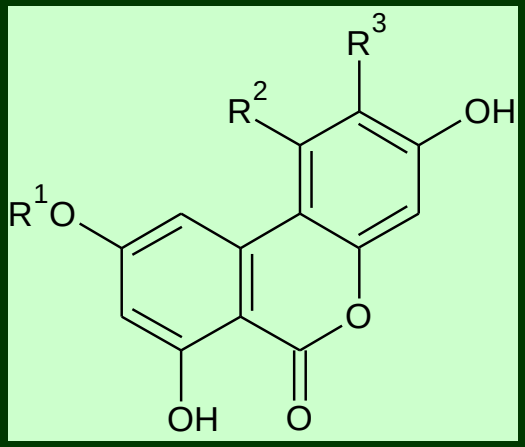
TEN (tentoxin)

3- Food contaminants: Case of Alternaria toxins (EFSA 2011)

Alternaria toxins may contaminate cereals and seeds and cause plant diseases.

KNOWN: chemical structures & dietary exposure

Examples of major chemical structures:



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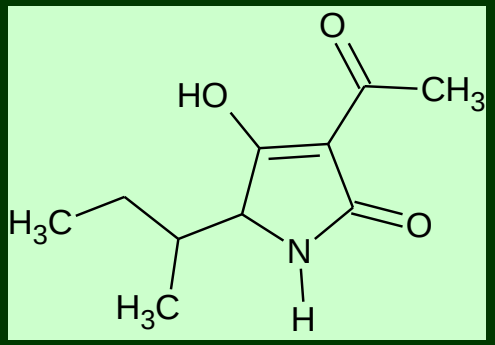

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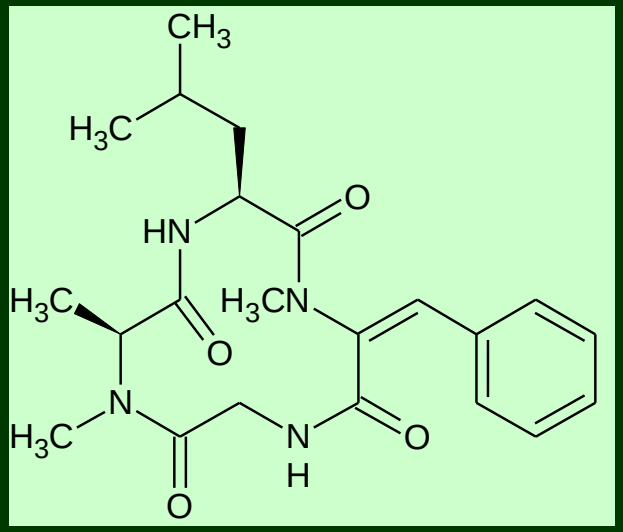


TEN (tentoxin)

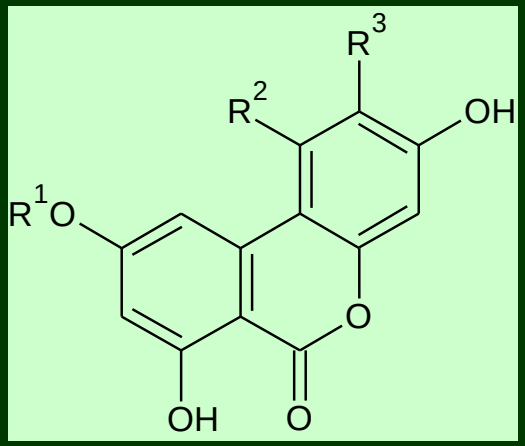
3- Food contaminants: Case of Alternaria toxins (EFSA 2011)

few toxicity data available

FOR TEA AND TEN:

- no suspicion of genotoxicity
- Estimated exposure < TTC Class III

⇒ **Evaluation: "unlikely to be a human health concern"**



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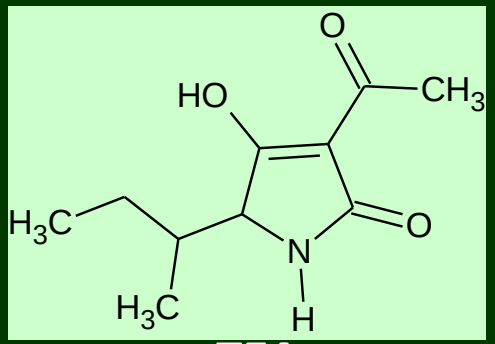

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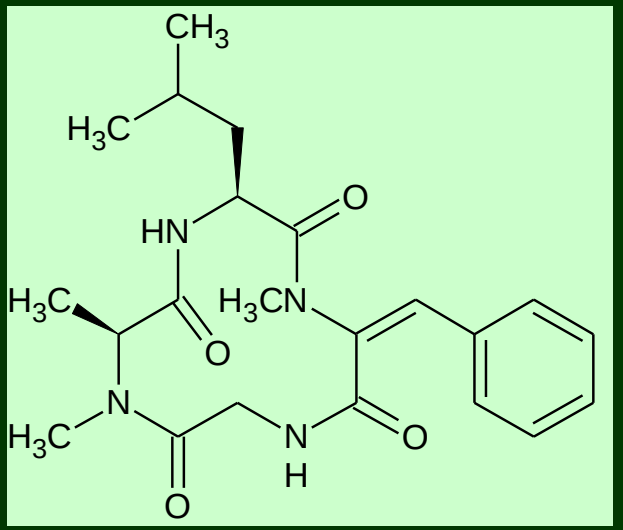


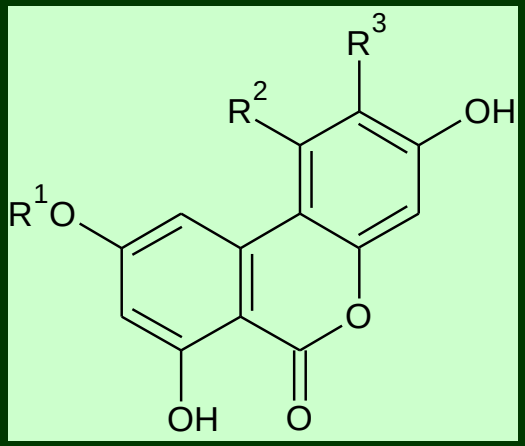
TEN (tentoxin)

3- Food contaminants: Case of Alternaria toxins (EFSA 2011)

FOR AOH AND AME > 0 in vitro genotoxicity data

The dietary exposure threshold for genotoxic substances (0.0025µg/kg b.w. per day) is exceeded

⇒ **evaluation was "need of genotoxicity data"**



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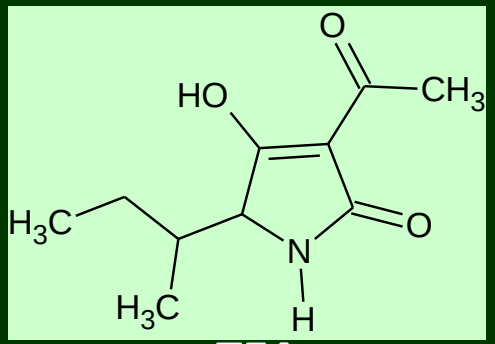

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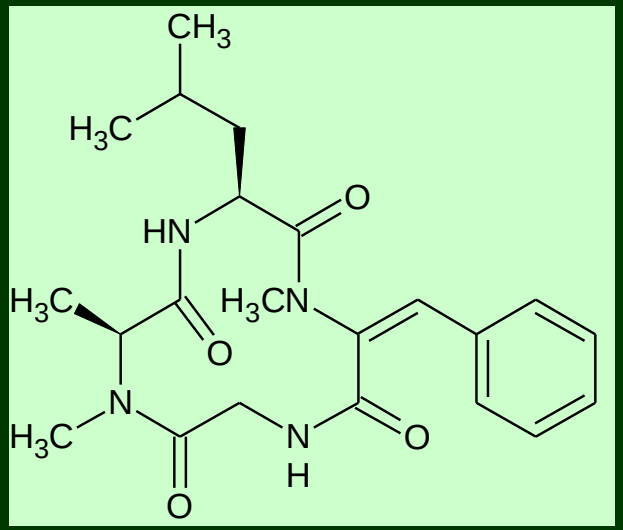
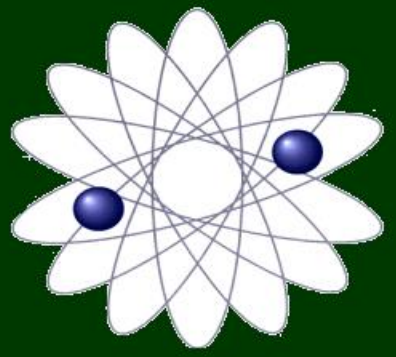


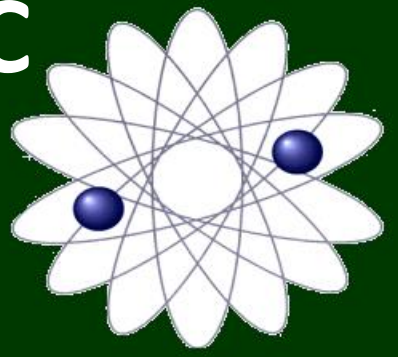
TEN (tentoxin)

Questions in this presentation



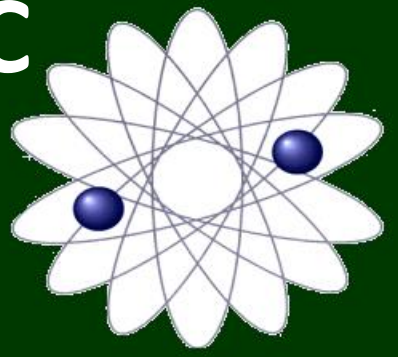
- **For which substances is TTC used as a tool for risk assessment?**
- **The limitations: when and why can the TTC overall strategy NOT be used?**
- **Challenges & perspectives:**
  Is the TTC principle an internationally recognised approach?

When & why can/should the TTC overall strategy NOT be used?



When ⇓ Why⇒	Toxicity reasons	Background data bases
Exclusion categories	X	X
Pharmacollogically active substances residues in food & feed		X

When & why can/should the TTC overall strategy NOT be used?



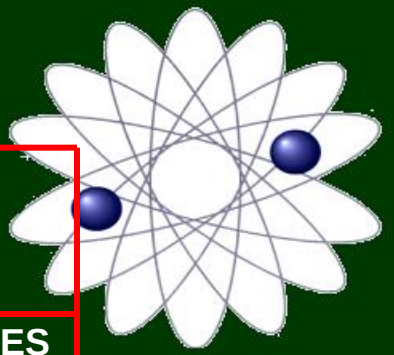
1- Exclusion categories

OVERALL STRATEGY FOR THE TTC APPROACH (EFSA 2012)**:**

Question 1: is the substance member of an exclusion category?
If yes, the approach cannot be applied.

Overall strategy

EFSA 2012



Is the substance a member of an exclusion category? *

NO

Is there a structural alert for genotoxicity (including metabolites)?

YES

Exposure > 0.0025 µg/kg bw/day?

YES

NO

Low probability of health effect **

NO

Substance requires non-TTC approach (toxicity data, read-across etc.)

Low probability of health effect **

NO

Exposure > 0.3 µg/kg bw/day? ***

YES

Is substance an OP/Carbamate?

YES

NO

NO

Exposure > 1.5 µg/kg bw/day? ***

YES

Is substance in Cramer Class II or III?

YES

NO

NO

Exposure > 30 µg/kg bw/day? ***

YES

* Exclusion categories
–

** If exposure of infants < 12 weeks is in range of TTC
→ consider if TTC is applicable

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

strategy

Is the substance a member of an exclusion category? *

NO

Is there a structural alert for genotoxicity (including metabolites)?

YES

Exposure > 0.0025 µg/kg bw/day?

YES

NO

Low probability of health effect **

NO

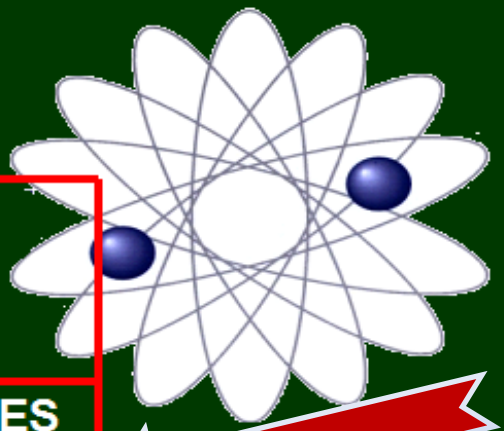
Exposure > 0.3 µg/kg bw/day? ***

YES

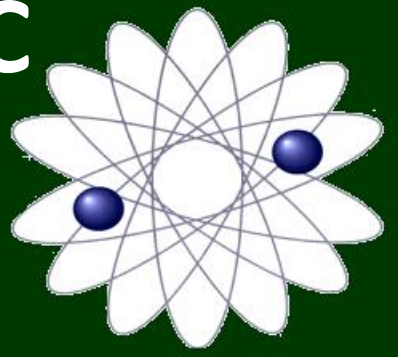
Is substance an OP/Carbamate?

YES

Substance requires non-TTC approach (toxicity data, read-across etc.)



When & why can/should the TTC overall strategy NOT be used?

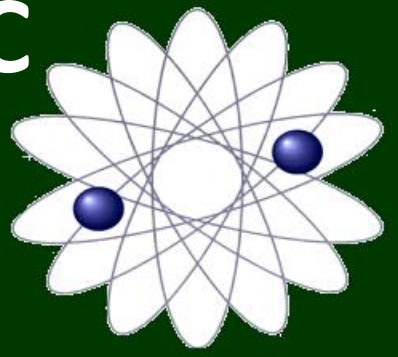


1- Exclusion categories

a) Substances suspected of very high toxicity
due to structural similarity with toxic substances

b) Substances not represented / foreseen in the Cramer and in the Munro databases

When & why can/should the TTC overall strategy NOT be used?

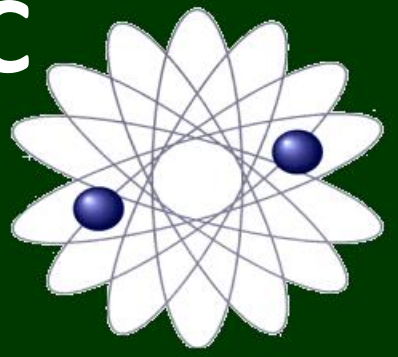


1- Exclusion categories

a) Substances suspected of very high toxicity due to structural similarity with toxic substances

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

When & why can/should the TTC overall strategy NOT be used?

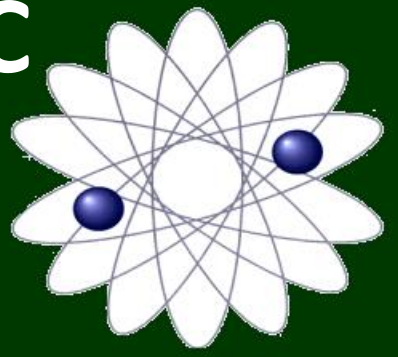


1- Exclusion categories

b) Substances not represented / foreseen in the Cramer and in the Munro databases:

- Nanomaterials
- Mixtures
- Radioactive substances
- Inorganic substances
- Metals and organometallics
- Proteins

When & why can/should the TTC overall strategy NOT be used?



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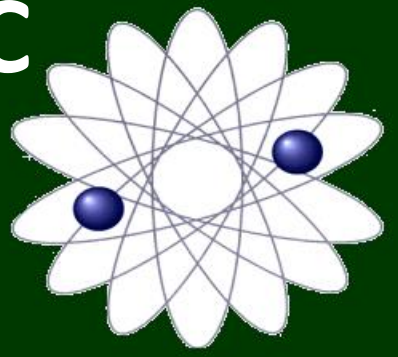
When & why can/should the TTC overall strategy NOT be used?

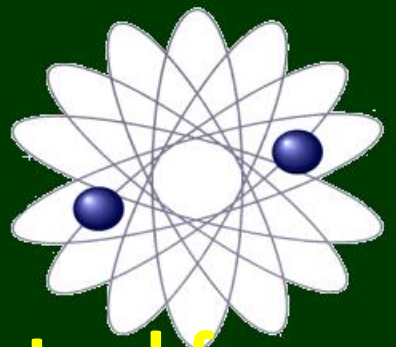


2- Non-allowed pharmacologically active substances residues in food (EFSA 2013)

The TTC concept was considered **not applicable** for deriving Toxicological Screening Values, as:

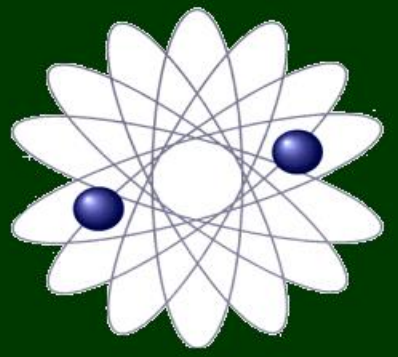
- some substances that are common in this area (e.g. steroids) are excluded from the TTC approach
- the database underlying the TTC concept only contains a small number of pharmacologically active substances.

Questions in this presentation



- **For which substances is TTC used as a tool for risk assessment?**
- **Limitations: when and why can the TTC overall strategy NOT be used?**
- **Challenges & perspectives:**
  Is the TTC principle an internationally recognised approach?
  - **⇒Example of use**
  - **⇒International recognition**
  - **⇒Conservatism**

1. Example of a possible use of the TTC approach with NIAS



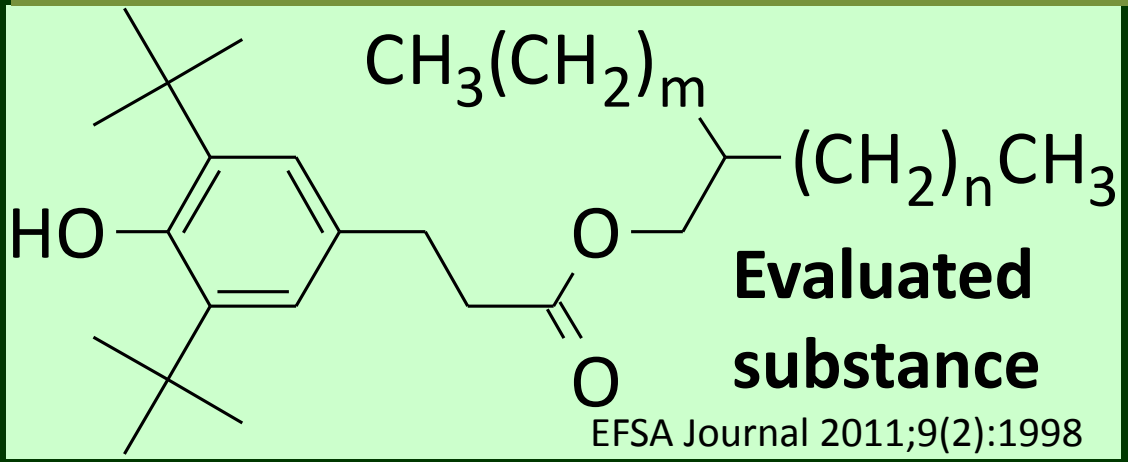
The substances used to manufacture plastic FCM are evaluated on basis of toxicity data, as requested in guidelines.

Often, there is little to no information on impurities and degradation products, which are **present in very low amounts**. They are the NIAS ("Non Intentionally Added Substances")

Example: evaluation of an impurity of a process stabiliser

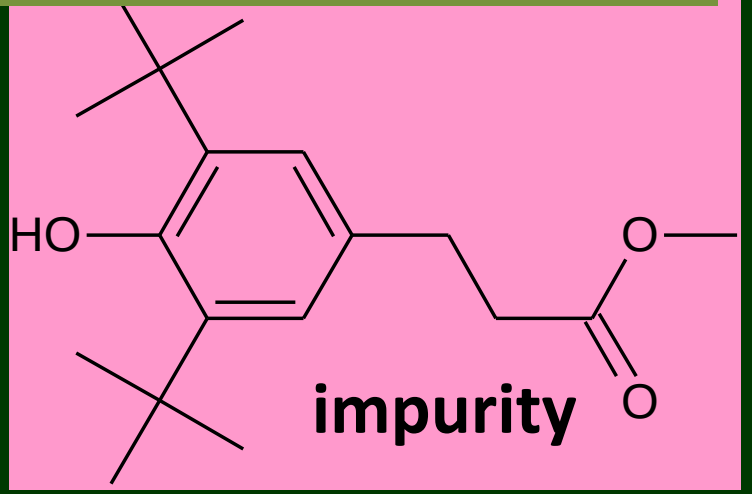
1. Example of a possible use of the TTC approach with NIAS

The stabilizer was evaluated on basis of all requested data. There were no data on the impurity



Evaluated substance

EFSA Journal 2011;9(2):1998

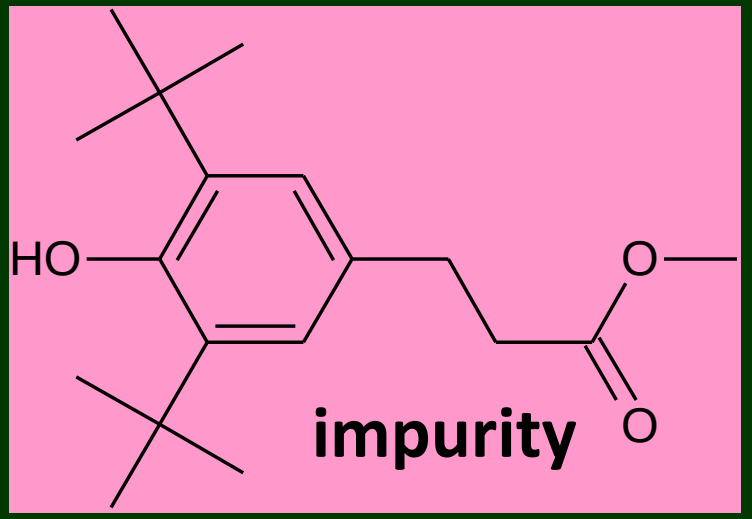


impurity

The evaluation was based on read across. Conclusion was: *"Due to its expected low migration the impurity, that is chemically related to the parent substance, is not considered to be of a safety concern."*

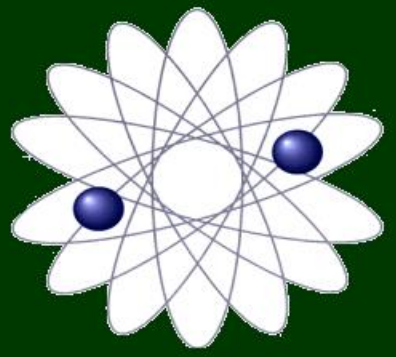
Example of a possible use of the TTC approach with NIAS

If the TTC approach had been used for the evaluation of the impurity, the conclusion could have been as follows:



Class II, TTC = 0.54 mg/person per day to be compared with the low dietary exposure (0.006 mg/person per day). Hence no safety concern.

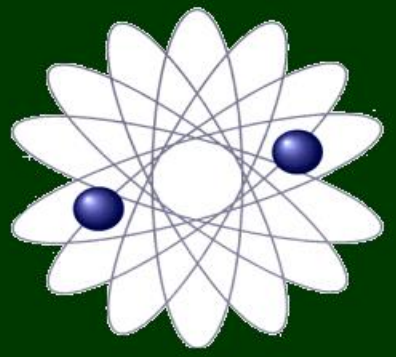
2. International recognition



Recital nr. 20 of the plastic FCM Regulation (2010/11):

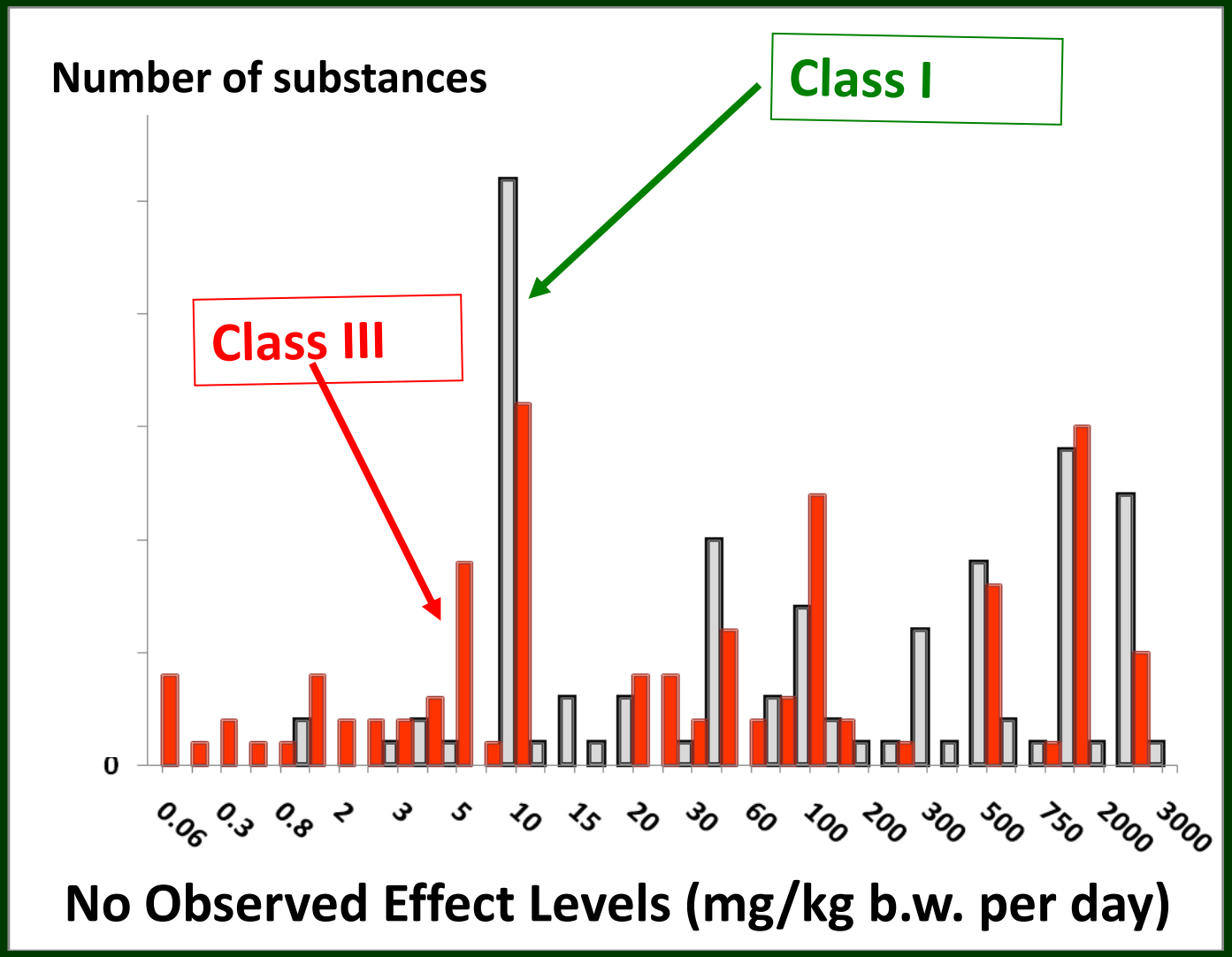
"*Any potential health risk in the final material or article arising from reaction and degradation products should be assessed by the manufacturer in accordance with* ***internationally recognised*** *scientific principles on risk assessment."*

2. International recognition



- **JECFA** (Joint FAO/ WHO Expert Committee on Food Additives) applied the Munro approach in 1997 for the evaluation of flavouring substances
- **OECD** toolbox offers the use of TTC for assessment of chemicals
- **FDA** has first introduced TTC and threshold approaches

3. The TTC approach does not predict ADI nor NOEL values



There is NO correlation between TTC and NOEL

4. Conservatism, deduced from the definition of TTC by Munro

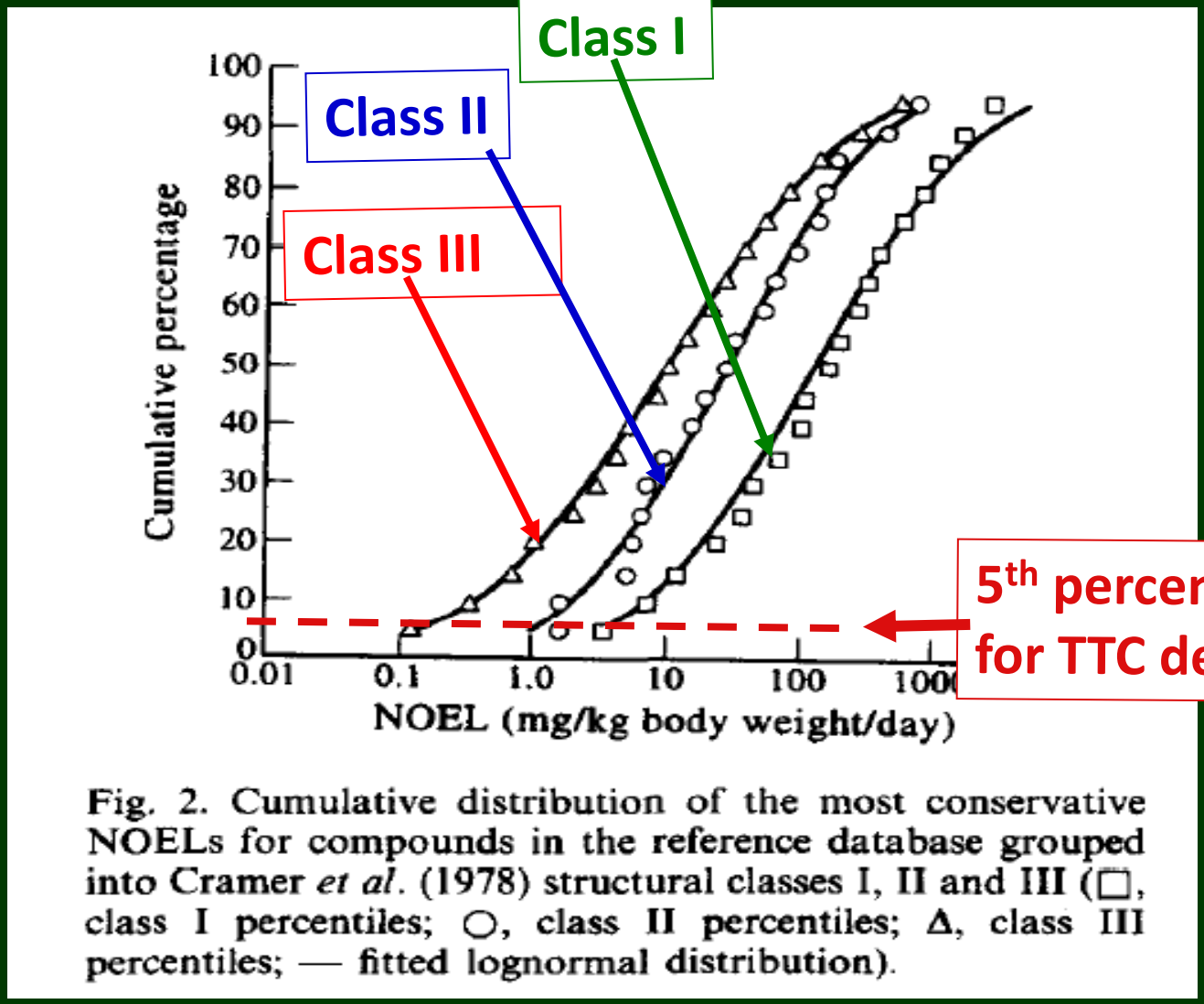


Fig. 2. Cumulative distribution of the most conservative NOELs for compounds in the reference database grouped into Cramer *et al*. (1978) structural classes I, II and III (□, class I percentiles; ○, class II percentiles; Δ, class III percentiles; — fitted lognormal distribution).

5th percentile NOEL, used for TTC definition

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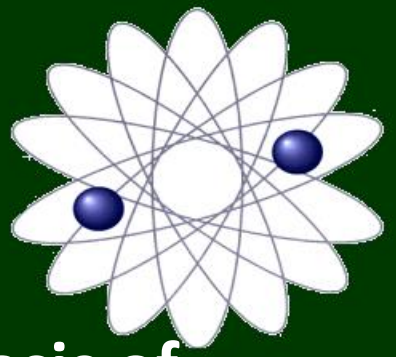


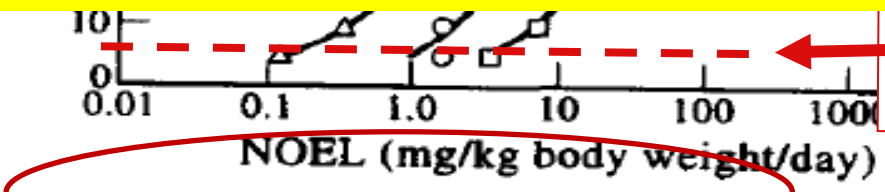
Munro has defined the TTC thresholds on basis of the 5th pc of the NOEL cumulated distribution curve.

$\Rightarrow$± 95 % of the substances in the database have a NOEL above the threshold. They are evaluated in a conservative way by considering the Munro TTC

$\Rightarrow$What about the remaining 5%?

4. Conservatism, deduced from the definition of TTC by Munro

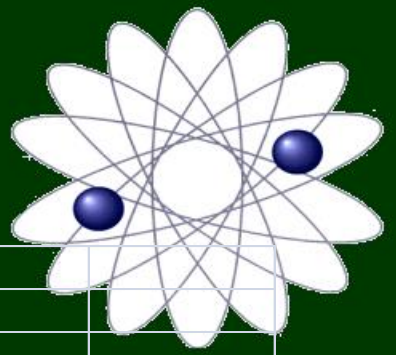
These substances are the most toxic, while the TTC is higher than NOEL determined from experimental toxicity studies.
For these substances the Munro TTC thresholds are not conservative.



5th percentile NOEL, used for TTC definition

Fig. 2. Cumulative distribution of the most conservative NOELs for compounds in the reference database grouped into Cramer *et al.* (1978) structural classes I, II and III (□, class I percentiles; ○, class II percentiles; Δ, class III percentiles; — fitted lognormal distribution).

How to express the conservatism of TTC approach?



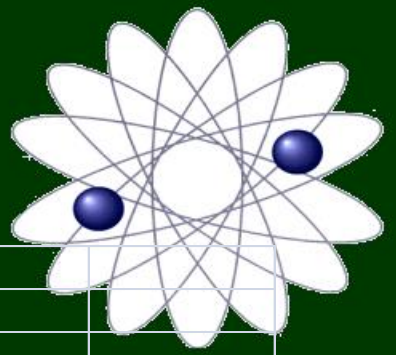
Determined from experimental toxicity data

$$\psi = \frac{\text{ADI or TDI (mg/kg b.w. per day)}}{\text{TTC (mg/kg b.w. per day)}}$$

Deduced from chemical structure

Assuming for simplicity an Uncertainty Factor of 100 between NOEL or NOAEL and ADI

How to express the conservatism of TTC approach?



$\Psi \leq 1$: TTC ≥ ADI

If these substances had been evaluated only by TTC, their toxicity would be under-evaluated. The approach is not conservative for these substances.

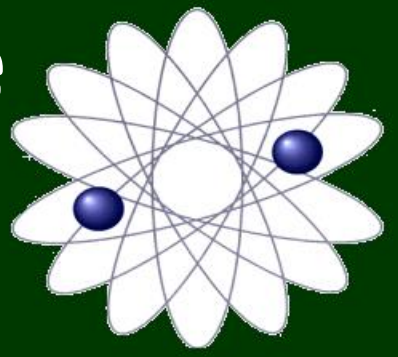
Overview of substances allocated to Class III in Munro database (1996)

	Number of substances	Percentage
TOTAL NR OF SUBSTANCES IN CLASS III	449	100 %
SUBSTANCES WITH $\Psi \leq 1$	24	5.3 %

Substances allocated to Class III in Munro database in 1996

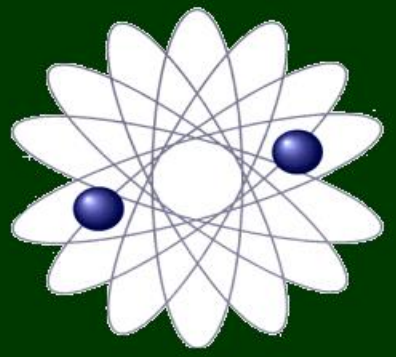
	Number of substances	Percentage
TOTAL NR OF SUBSTANCES IN CLASS III	449	100 %
SUBSTANCES WITH $\Psi \leq 1$	24	5.3 %
Steroids (members of exclusion categories)	2	
Polyhalogenated subst. (bioaccumulate)	5	
Neurotoxicity alerts (organophosphates, carbamates)	10	
SUBSTANCES WITH $\Psi \leq 1$ NOT BELONGING TO A STRUCTURAL ALERT GROUP NOR TO AN EXCLUSION CATEGORY	7	1.3%
SUBSTANCES EVALUATED IN A CONSERVATIVE WAY		98.7 %

Substances in Class III in database of pesticide active substances



	Number of substances	Percentage
TOTAL NR OF SUBSTANCES IN CLASS III	328	100 %
SUBSTANCES WITH $\Psi \leq 1$	9	2.7 %
SUBSTANCES EVALUATED IN A CONSERVATIVE WAY THROUGH THE TTC OVERALL STRATEGY		97.3 %

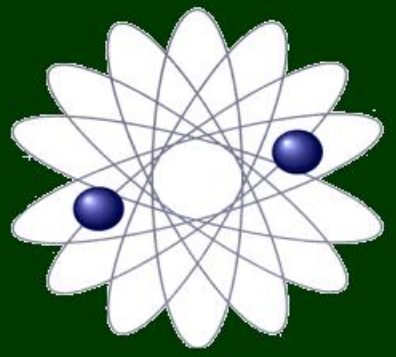
Future developments: to improve conservatism for risk assessment



The conservatism of the approach could still be improved, opening the way to international recognition for risk assessment:

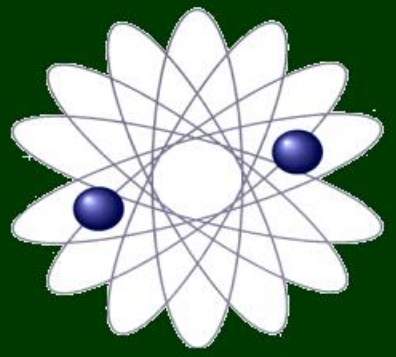
- by better documenting exclusion categories, e.g. with help of QSAR approaches
- by studying larger databases

Take home message 2



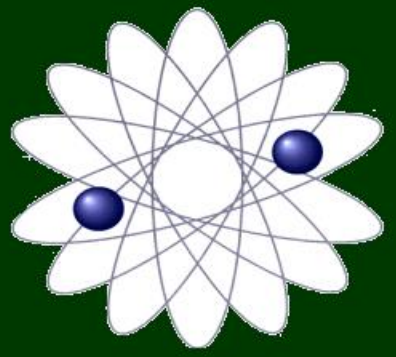
- **The TTC approach is conservative in the vast majority of cases**
- There is more and more understanding about the reasons for the (few) cases of under-evaluation.

Conclusions



- **TAKE HOME MESSAGE 1: For risk assessment, the TTC approach is often integrated in a strategy making also use of data on toxicity & exposure**
- **TAKE HOME MESSAGE 2: The TTC approach is conservative in the vast majority of cases.** Improving conservatism % is making it an internationally recognised approach

To know more



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- A. Worth, T. Platzek, A. Feigenbaum (2013). Progress towards the acceptance and application of the TTC concept in the food and cosmetics areas - an EU perspective, M. Cheeseman and B. Safford editors, Wiley

- A. Feigenbaum, R. Pinalli, M. Gianetto (2013). The TTC approach: learning from a database with biological active substances (publication in progress)

Thank you
for your kind attention

Da Vinci, Scapigliata, 1500, Parma
The source of inspiration?