

Reliability of the TTC approach: learning from inclusion of pesticide active substances in the supporting database

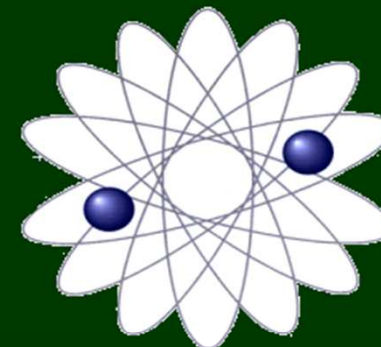
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Background



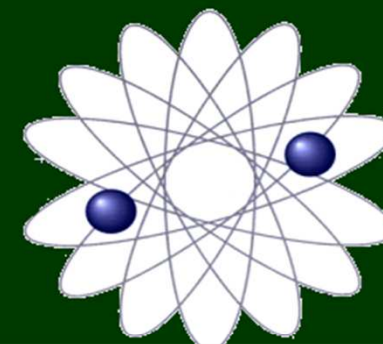
Need of approaches for the evaluation of substances currently used

- EFSA 2012 opinion on TTC (food)
- SCCS, SCHER, SCENIHR 2012 opinions on use of TTC (cosmetics & consumer products)

2-step practical approach:

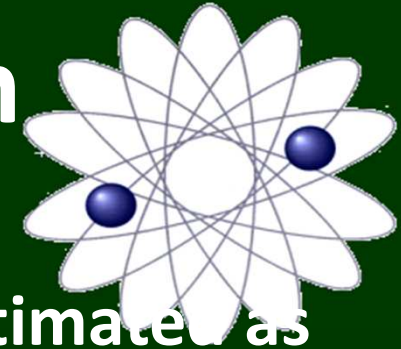
- ① Preliminary assessment of chemical structures: exclusion of substances which cannot be evaluated through the TTC approach
- ② If OK, classify the substance into the structural classes and allocate the corresponding threshold

Exclusion categories: examination of chemical structures in the preliminary assessment



EXAMPLES OF CHEMICAL STRUCTURES	
HIGH POTENCY CARCINOGENS	Aflatoxin-like, azoxy ($\text{RN}=\text{N}^+(\text{O}^-)\text{R}$ and N-nitroso ($\text{RR}'\text{N}-\text{N}=\text{O}$) compounds, benzidines, hydrazines
SUBSTANCES KNOWN OR PREDICTED TO BIOACCUMULATE	Polyhalogenated dibenzodioxins, -dibenzofurans and -biphenyls, heavy metals
STEROIDS	Substances which have not been tested for their endocrine properties, other than steroids, can be evaluated using the TTC approach (EFSA 2012)
SUBSTANCES WHICH ARE NOT INCLUDED IN THE CRAMER OR MUNRO DATABASES	Inorganic substances, organometallics, proteins, nanomaterials, radioactive substances, mixtures of substances containing unknown chemical structures.

Reliability of the TTC approach

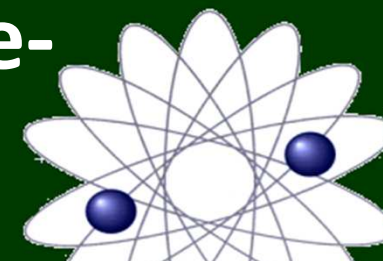


- The reliability of the TTC approach can be estimated as the % of substances for which $\psi > 1$ in a database
= for which the TTC approach is conservative compared to evaluation based on experimental data

$\psi = \frac{ADI}{TTC} > 1$: TTC approach is conservative

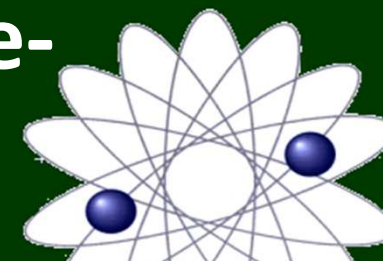
$\psi \leq 1$: toxicity is under-evaluated through the TTC approach. TTC approach not conservative. How far, to what extent is it conservative reliable?

How is the % of under-evaluations decreased? Example of Munro's Class III



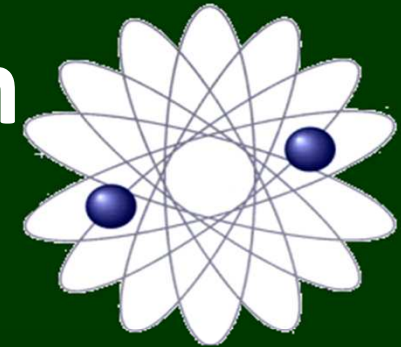
	Nr substances	% of total
1996: NUMBER OF CLASS III SUBSTANCES	448	
2004: Kroes Structural alerts for neurotoxicity (organophosphates, carbamates)	40	
2012: UPDATED NR. OF CLASS III SUBSTANCES	408	
CLASS III SUBSTANCES WITH $\Psi \leq 1$	14	
* Steroids	2	TTC approach not applicable (8 substances excluded <i>a priori</i>)
* Polyhalogenated	5	
* nitroarene	1	
* miscellaneous	6	
Under-evaluated		
SUBSTANCES FOR WHICH THE TTC APPROACH IS CONSERVATIVE		

How is the % of under-evaluations decreased? Example of Munro's Class III



	Nr substances	% of total
1996: NUMBER OF CLASS III SUBSTANCES	448	
2004: Kroes Structural alerts for neurotoxicity (organophosphates, carbamates)	40	
2012: SUBSTANCES EXCLUDED A PRIORI	8	
2012: UPDATED NR. OF CLASS III SUBSTANCES	400	
CLASS III SUBSTANCES WITH $\Psi \leq 1$	14	
* miscellaneous	Under-evaluated	
	6	1.5%
SUBSTANCES FOR WHICH THE TTC APPROACH IS CONSERVATIVE (448-40-8=400 ; 400-6=394)	394	98.5%

Reliability of the TTC approach



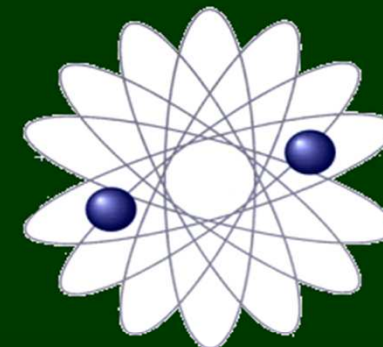
- We investigated pesticide active substances as worst case substances for risk assessment to challenge thresholds and exclusion criteria

What is then the reliability of the TTC approach?

- How do exclusion criteria in preliminary assessment apply (bioaccumulation)?
- Are the ADIs not too conservative?

$$\Psi = \frac{ADI}{TTC} > 1$$

The database of pesticide active substances evaluated by EU & EFSA

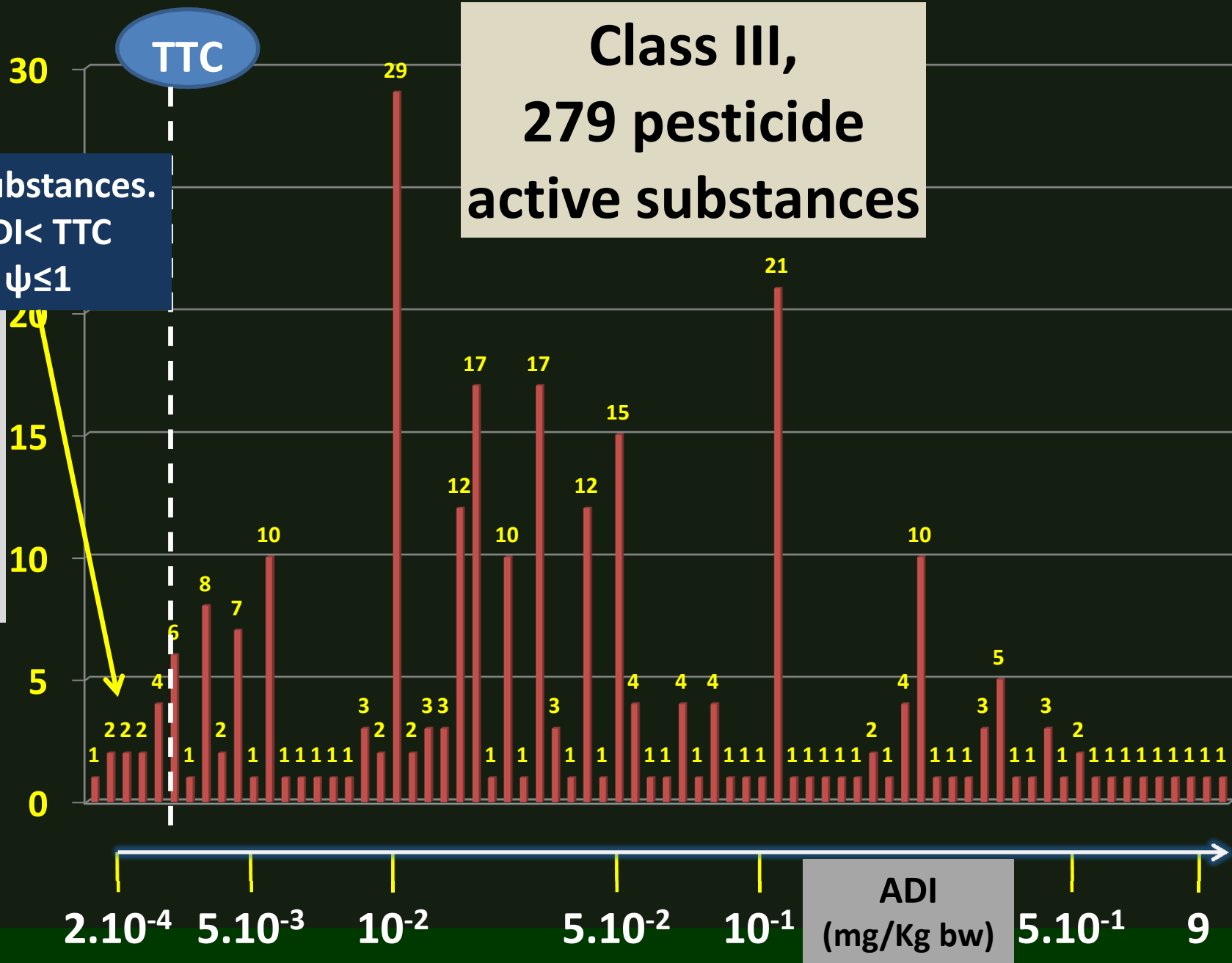


STRUCTURAL CLASS	Number of substances
Exclusion category	1
Neurotoxicity alert (AChE inhibitors)	43
Cramer Structural class III	279
Cramer Structural Class II	3
Cramer Structural Class I	2
TOTAL	328

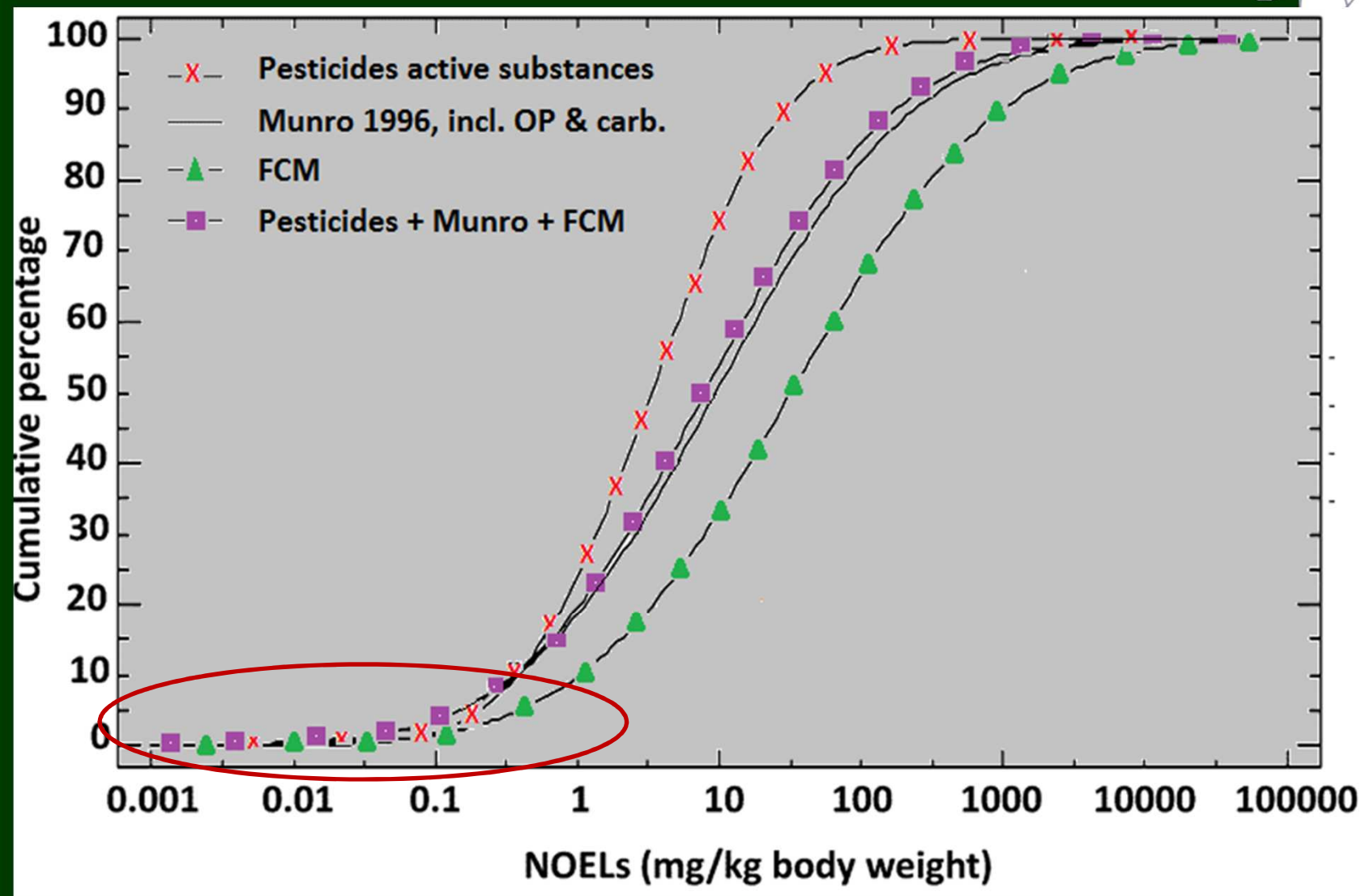
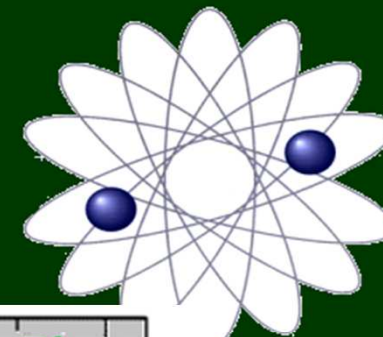
**Class III,
279 pesticide
active substances**

**12 substances.
ADI < TTC
 $\psi \leq 1$**

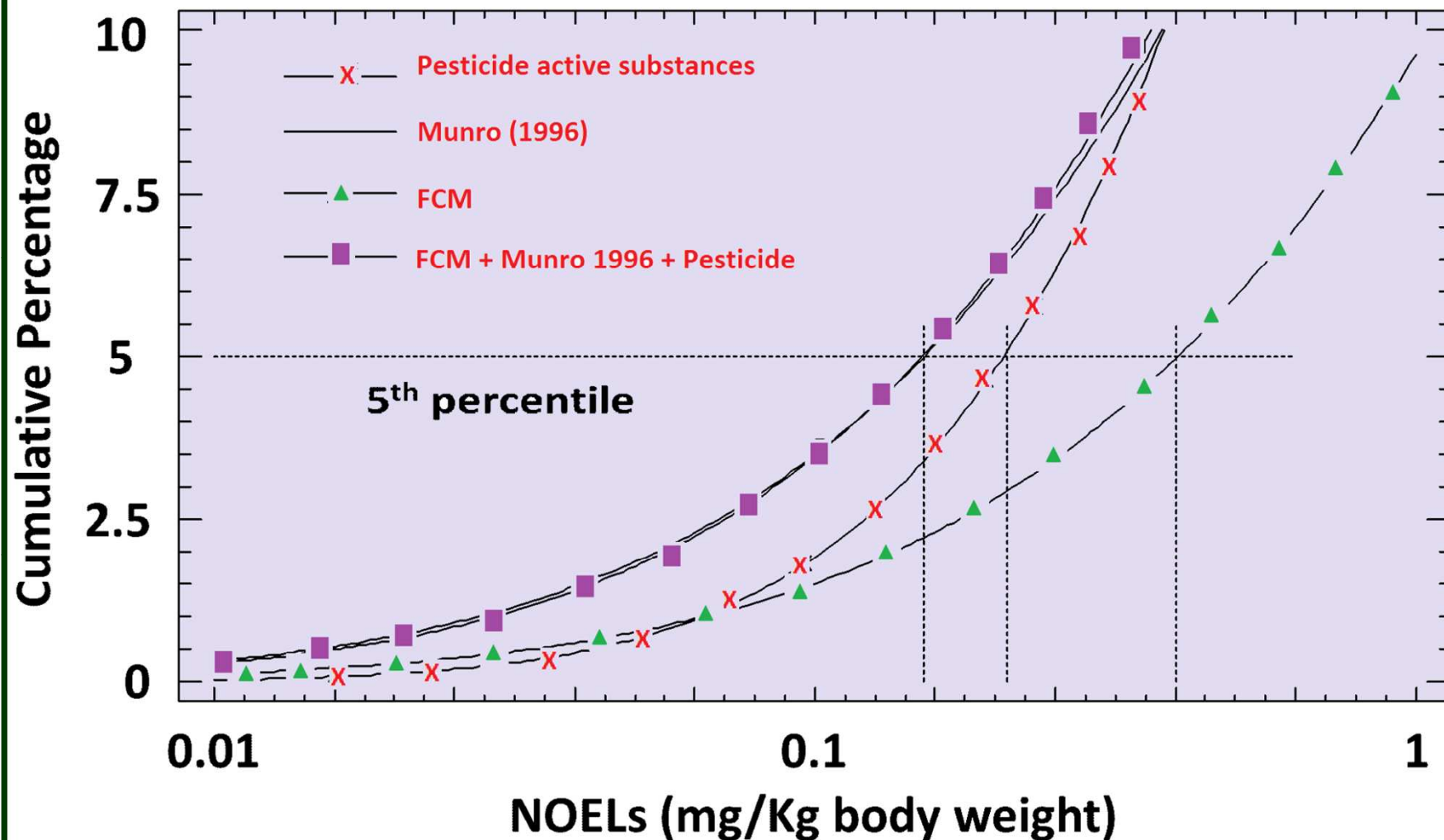
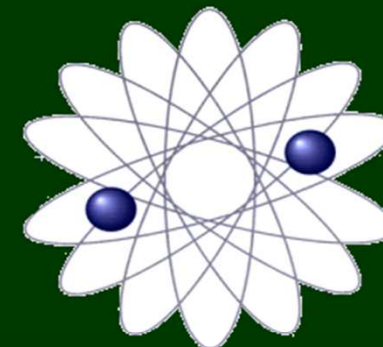
Number of substan



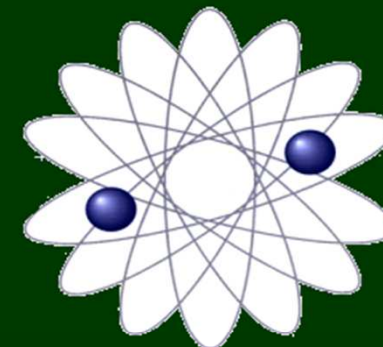
Comparison of Class III cumulated distribution curves



Comparison of Class III cumulated distribution curves



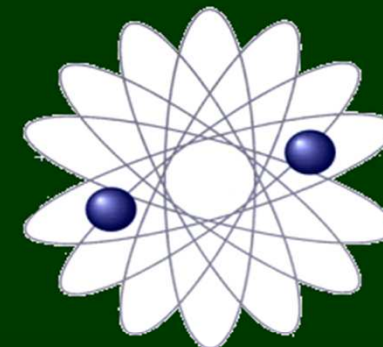
Comparison of Class III cumulated distribution curves: 5th pc (mg/kg bw per day)



Structural classification	Pesticide active subst.	Munro 1996 database	Pesticide + FCM + Munro
Class III, <u>including</u> substances with neurotoxicity alert		0.15 (448 substances)	0.15 (840 substances)
Class III <u>without</u> substances having a neurotoxicity alert	0.20 (279 substances)	0.3 (408 substances)	

**Worst case
value**

Pesticide active substances with $\Psi < 1$ (overview)

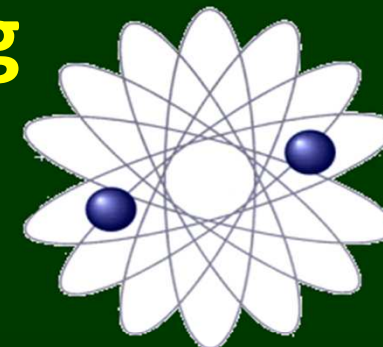


- 12 substances (4.3 %) in Class III of the pesticide database have $\Psi \leq 1$:
- The toxicity of these substances would have been under-evaluated if only the TTC approach had been available
- However the und-evaluation is of small magnitude for these substances, since:

$$0.1 < \Psi < 1$$

How is the reliability increased, using updated rules?

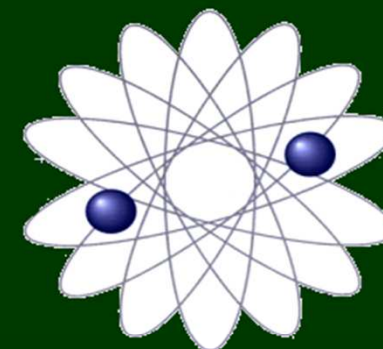
Case of pesticides active substances



To optimise the reliability, we investigated more closely the 12 substances:

- **Would/could they have been excluded *a priori*?**
 - because of $\log P_{ow} > 3$ (possible bioaccumulation)
 - Should the exclusion rules be improved?
- **Are evaluations by EU/EFSA overly cautious?**
(ψ would then be ≈ 1 or even ≥ 1)

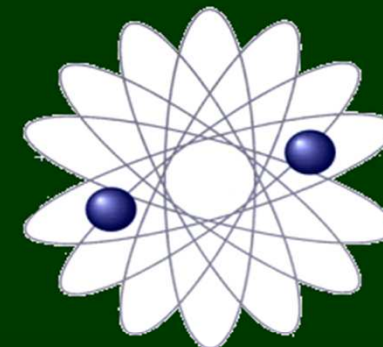
The 12 pesticides active substances with $\psi \leq 1$: could LogPo/w be used to exclude them *a priori*?



The 12 Substances	logPo/w
Fluometuron	2.36
Amitrole	-1.24
Fipronil	3.75
Tembotrione	-1.7
Sulcotrione	-1.7
Emamectin	5.0
Haloxypop	4.0
Haloxypop R	4.0
Chloropicrin	2.5
Methyl bromide	1.15
Diclofop	4.8
Metam-sodium	- 2.91

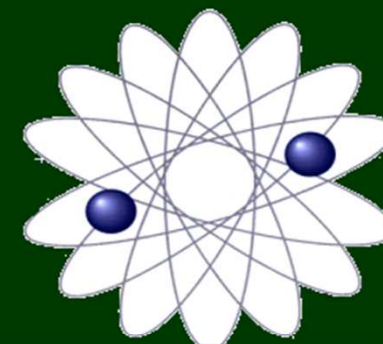
If we had used only $\text{logPo/w} > 3$ for preliminary assessment, these 5 substances would be excluded *a priori* from the TTC approach

The 12 pesticides active substances with $\psi \leq 1$: could LogPo/w be used to exclude them *a priori*?

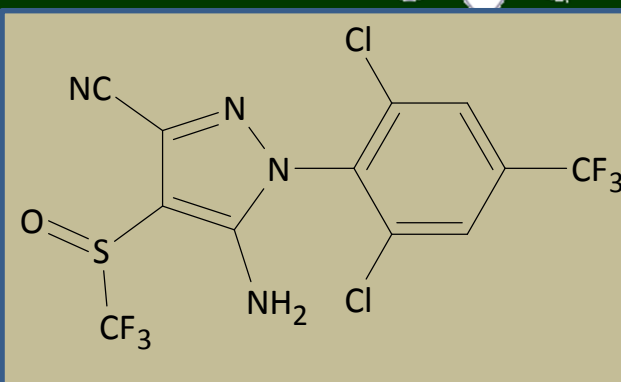


- If logPo/w was used to exclude substances *a priori*, 5 of the 12 substances with $\psi \leq 1$ would be excluded from the TTC approach. Only 7 would be under-evaluated by the approach
- However many other substances with $\psi > 1$ would also be excluded *a priori*
- The logPo/w parameter should be used with caution to exclude substances *a priori* from the TTC approach.

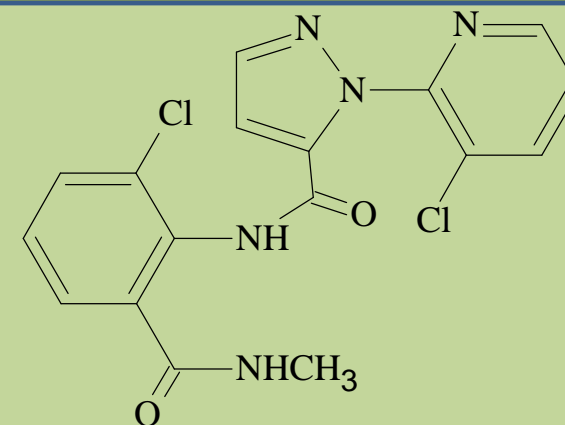
Arylpyrazole derivatives (group of analogs of fipronil)



substances	ADI (mg/kg bw)	Ψ (ADI/TTC)
Fipronil	0.0002	0.13
Fenpyroximate	0.01	6.67
Tebufenpyrad	0.01	6.67
Fluxapyroxad	0.02	13.3
Bixafen	0.02	13.3
Pyraclostrobin	0.03	20.0
Isopyrazam	0.03	20.0
Penflufen	0.04	26.7
Halosulfuron	0.063	42.0
Metazachlor	0.08	53.3
Penthiopyrad	0.1	66.7
Sedaxane	0.11	73.3
Pyraflufen-ethyl	0.2	133
Chlorantraniliprole	1.56	1040



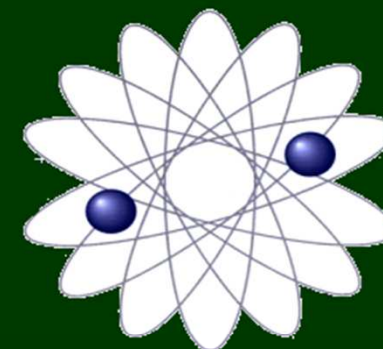
Fipronil ($\psi=0.13$)



Chlorantraniliprole ($\psi=1040$)

Arylpyrazole derivatives

LogPo/W

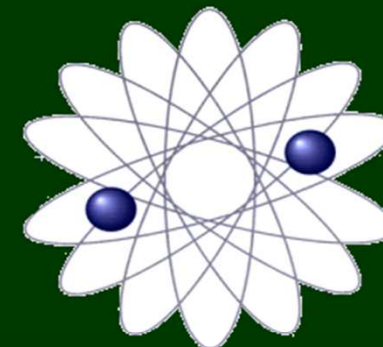


substances	ADI (mg/kg bw)	Ψ (ADI/TTC)	logPo/w
Fipronil	0.0002	0.13	3.75
Fenpyroximate	0.01	6.67	5.01
Tebufenpyrad	0.01	6.67	4.93
Fluxapyroxad	0.02	13.3	3.13
Bixafen	0.02	13.3	3.3
Pyraclostrobin	0.03	20.0	3.99
Isopyrazam	0.03	20.0	4.25
Penflufen	0.04	26.7	3.3
Halosulfuron	0.063	42.0	-0.02
Metazachlor	0.08	53.3	2.49
Penthiopyrad	0.1	66.7	4.5
Sedaxane	0.11	73.3	3.3
Pyraflufen-ethyl	0.2	133	3.49
Chlorantraniliprole	1.56	1040	2.86

Most of these substances have $\log Po/w > 3$ but their toxicity is not under-evaluated through the TTC approach.

The $\log Po/w$ should be used with caution

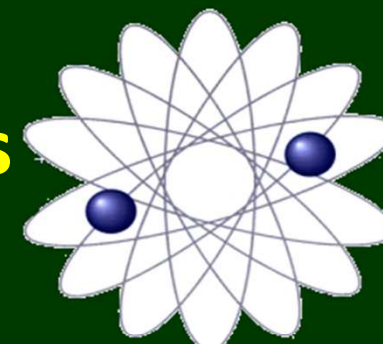
Are the NOAELs set by EU/EFSA of the 12 substances overly cautious?



- The evaluations of the 12 substances with $\psi \leq 1$ were compared with those of JMPR/WHO
- Where the NOAEL set by EU/EFSA was overly cautious, it was considered that the substance is not under-evaluated using the TTC approach.

How is the reliability increased?

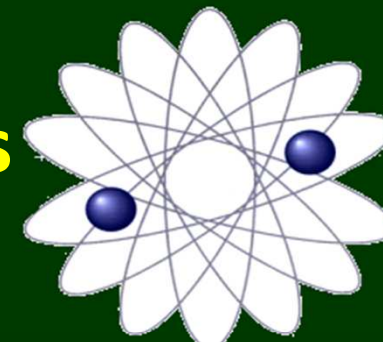
Comparison with JMPR/WHO evaluations of the 12 substances with $\psi \leq 1$



Substance	EU ADI is cautious or overly cautious	EU ADI is justified
Fluometuron	X	
Amitrole	X	
Fipronil	X	
Temboatrione	X	
Sulcotrione		X
Emamectin		X
Haloxypop		X
Haloxypop R		X
Chloropicrin		X
Methyl bromide		X
Diclofop		X
Metam-sodium		X

How is the reliability increased?

Comparison with JMPR/WHO evaluations of the 12 substances with $\psi \leq 1$



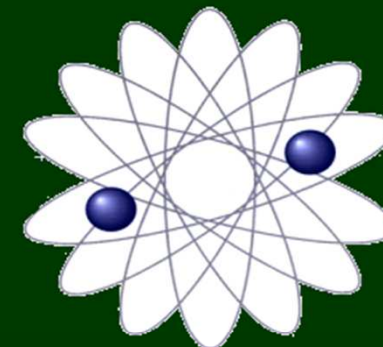
Substance	EU ADI is cautious or overly cautious	EU ADI is justified
Fluometuron	X	
Amitrole	X	
Fipronil	X	
Temboatrione	X	
Sulcotrione		X
Emamectin		X
Haloxyfop		X
Haloxyfop R		X
Chloropicrin		X
Methyl bromide		X
Diclofop		X
Metam-sodium		X

These substances are NOT under-evaluated / TTC

These 8 Class III substances (out of 279 = 2.8 %) are under-evaluated by the TTC approach

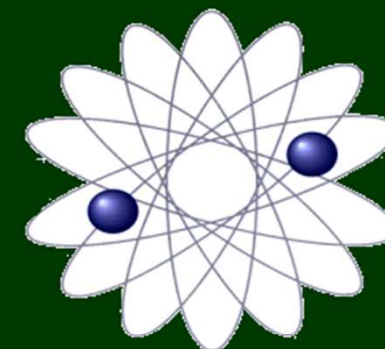
Reliability is 97.2% (100-2.8)

Take home message 1/3



- **Given 2012 practical implementation of the approach, the reliability is strongly increased.**
 - **Members of exclusion categories**
 - **Structural similarities with carcinogenic substances**
 - **Structural alerts for neurotoxicity**
 - **Cramer Classes III and II**
 - **Cramer Class I**

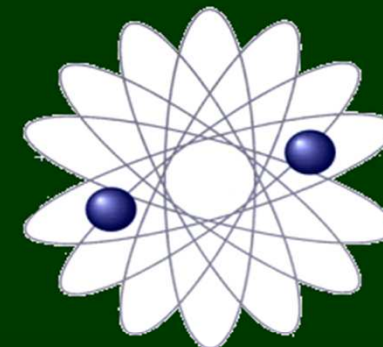
Take home message 2/3



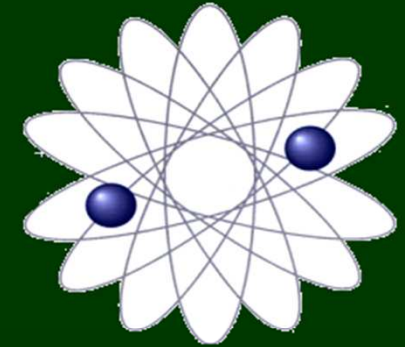
**Historical TTC threshold of Class III
is supported**

	TTC value (mg/person per day)	TTC value ($\mu\text{g}/\text{kg}$ bw per day)
CARCINOGENS Substances with structural alerts for genotoxicity	0.00015	0.0025
NON-CARCINOGENS Neurotoxicity alert	0.018	0.3
Cramer Structural Class III	0.090	1.5
Cramer Structural Class II	0.540	9
Cramer Structural Class I	1.800	30

Take home message 3/3



- The work with pesticide active substances as worst case supports the historical TTC threshold value for Class III.
- The approach is reliable and conservative
- It passed the test of worst case substances and can be used for evaluations, setting priorities, evaluations in case of urgent need, NIAS ...



Thank you for your attention

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