Introduction to the TTC

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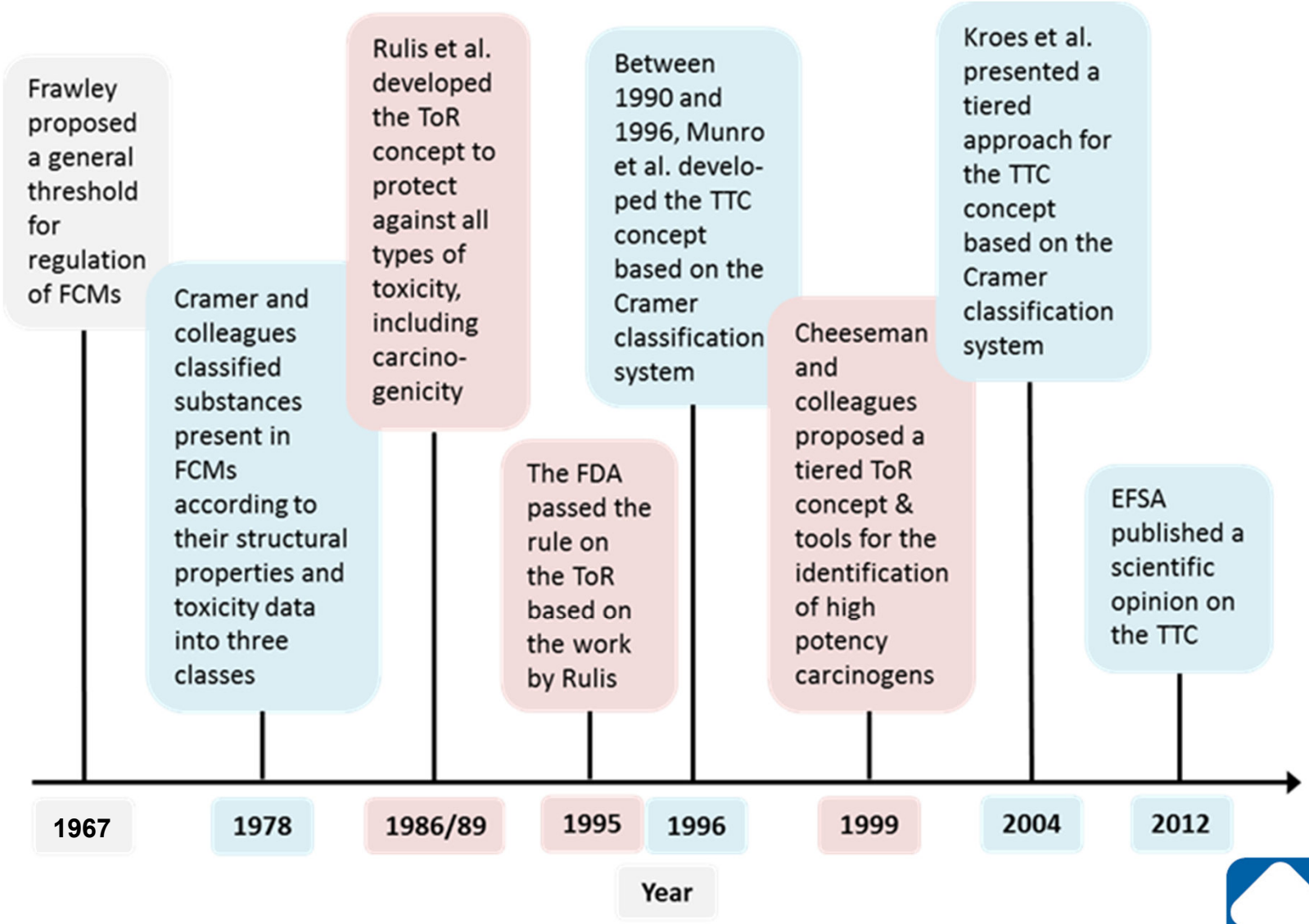
Historical milestones



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History: Beginnings

- Food and Drug Act Amendment of 1958: safety assessment of indirect food additives required
- 1967: J.P. Frawley of Hercules Incorporated "*Scientific evidence and common sense as a basis for food-packaging regulations*": proposed threshold **100 ppm**

Table 2. *Distribution of "no-effect" levels in 2-yr chronic studies*

"No-effect" level (ppm)	All compounds (220)	Heavy metals and pesticides (88)	Others (132)
<1	5	5	0
<10	19	19	0
<100	40	39	1
<1000	101	72	29
<10,000	151	86	65

Frawley JP. 1967. Fd Cosmet Toxicol. 5:293-308.

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Threshold of Regulation

- 1995: Rule on the 'Threshold of regulation for substances used in food-contact articles' (21 C.F.R. §170.39)
- Threshold follows the *de minimis* principle and is set at 0.5 ppb in the diet (1.5 µg per person and day)
- Carcinogens of most concern and have to be excluded
- Carcinogenicity was considered the most severe toxic effect

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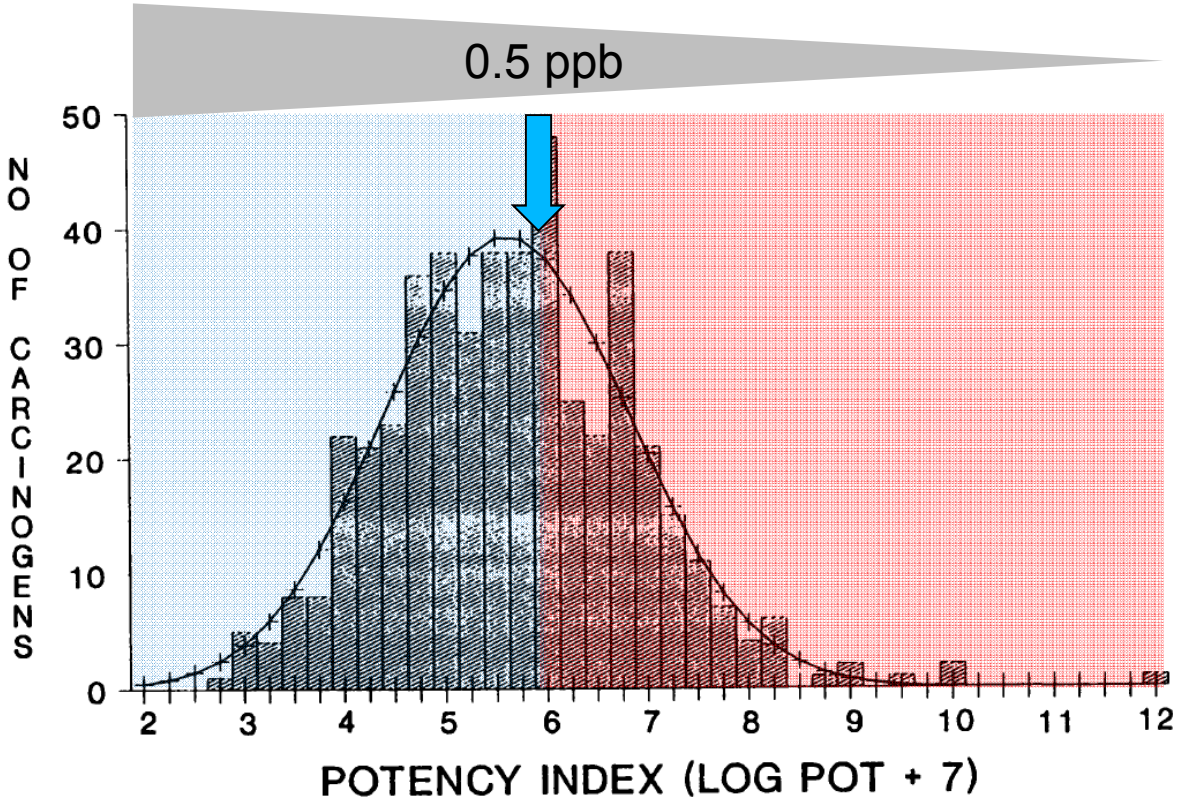
Scientific basis of the Threshold of Regulation (TOR)



The probability of an unknown carcinogen increasing the cancer risk of one in a million at a dietary intake of 0.5 ppb is 37%.

Figure 1. Probability distribution of carcinogen potencies based on the data base of Gold et al. (15-17) for 477 selected carcinogens.

Rulis AM: Threshold of Regulation - Options for Handling Minimal Risk Situations In Food Safety Assessment; Finley, J., et al.; ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

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Making expert judgment explicit

- 1978: “Estimation of toxic hazard - a decision tree approach”
- 33 questions about a substance’s structure, placing it into one of **three Cramer classes**
- “index of suspicion”
- Includes database of substances and no-effect levels that were tested according to this approach

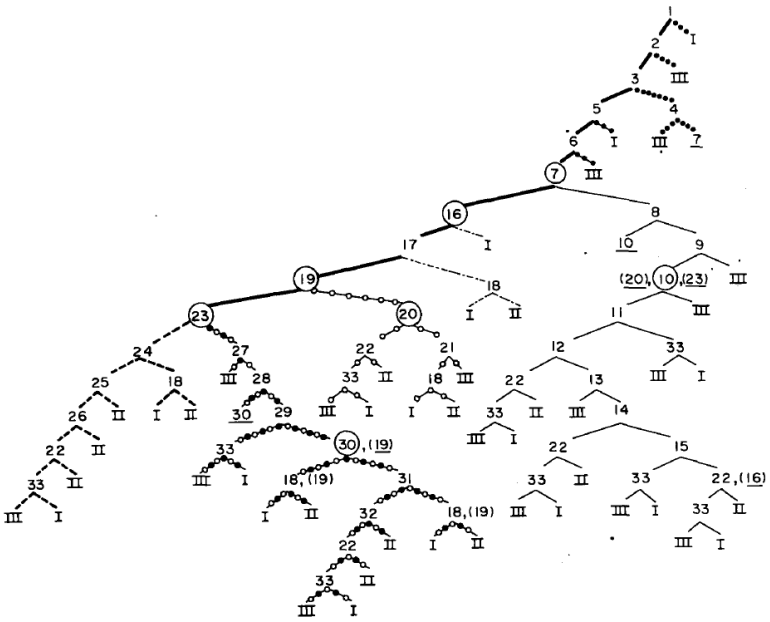

Fig. 1. A schematic diagram of a decision tree for the estimation of probable toxicity. Assessors should (a) start with question 1, (b) proceed by 'no' ↙ or ↘ 'yes', (c) move from any underscored number encountered to same circled number and (d) proceed to final classes I, II or III. Working downwards through the tree, the symbols designate the following groupings: biological normality (●●●), high and low toxicity (●–●–●); heterocyclics (——); terpenoids (–·–·–); aliphatics (–O–O–O); aromatics (–O–●–O); alicyclics (– – –).

Cramer GM et al. 1978. Food Cosmet Toxicol. 16:255-76.

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Threshold of Toxicological Concern

1. 613 Chemicals

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2. Cramer classification

Table 1. Number of reference database substances in each Cramer *et al.* (1978) structural class

Structural class	No. of chemicals
I	137
II	28
III	448

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3. Cumulative distribution

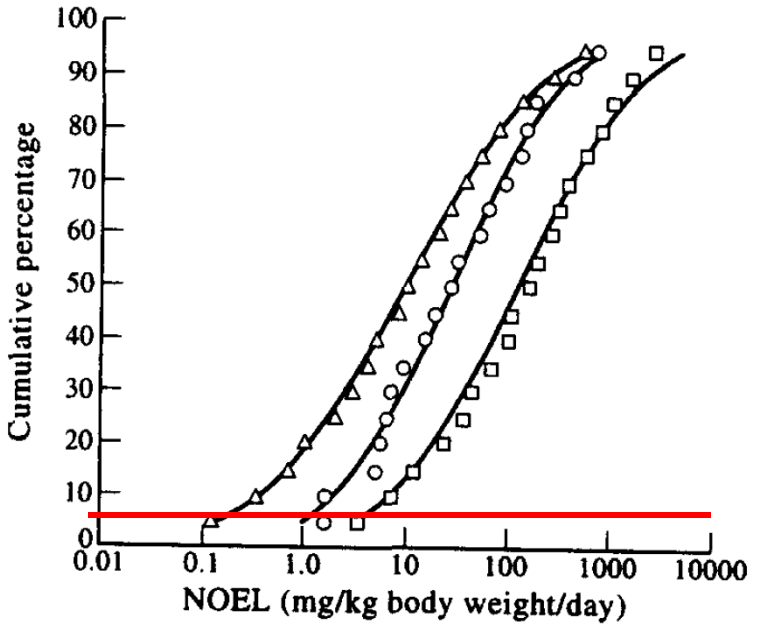

Fig. 2. Cumulative distribution of the most conservative NOELs for compounds in the reference database grouped into Cramer *et al.* (1978) structural classes I, II and III (□, class I percentiles; ○, class II percentiles; Δ, class III percentiles; — fitted lognormal distribution).

Munro IC et al. 1996. Food Chem Toxicol. 34:829-67.

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Threshold of Toxicological Concern

4. Calculation of thresholds

Table 2. Fifth percentile NOELs and human exposure thresholds for each Cramer (1978) structural class

Structural class	Fifth percentile NOEL (mg/kg body weight/day)	Human exposure threshold (mg/day)*
I	3.0	1.8
II	0.91	0.54
III	0.15	0.09

*The human exposure threshold was calculated by multiplying the fifth percentile NOEL by 60 (assuming an individual weighs 60 kg) and dividing by a safety factor of 100, as discussed in the text.

Munro IC et al. 1996. Food Chem Toxicol. 34:829-67.

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Modifications of the TTC

2004

- Threshold for genotoxic carcinogens (0.15 µg/person/day)
- 5 Groups of carcinogens were excluded (aflatoxin-like compounds, N-nitroso-compounds and azoxy-compounds, steroids and polyhalogenated dibenzo-p-dioxins and dibenzofurans)
- Threshold for carbamate and organophosphates (18 µg/person/day)

2012

- Cramer class II should be included into class III
- Further exclusion categories: inorganic substances, metals, organometallics, proteins, chemicals that (might) bioaccumulate, nanomaterials, radioactive substances and mixtures of unknown chemical structures

Kroes R et al. 2004. Food Chem Toxicol. 42:65-83.
Scientific Opinion. 2012. EFSA Journal 10:2750.

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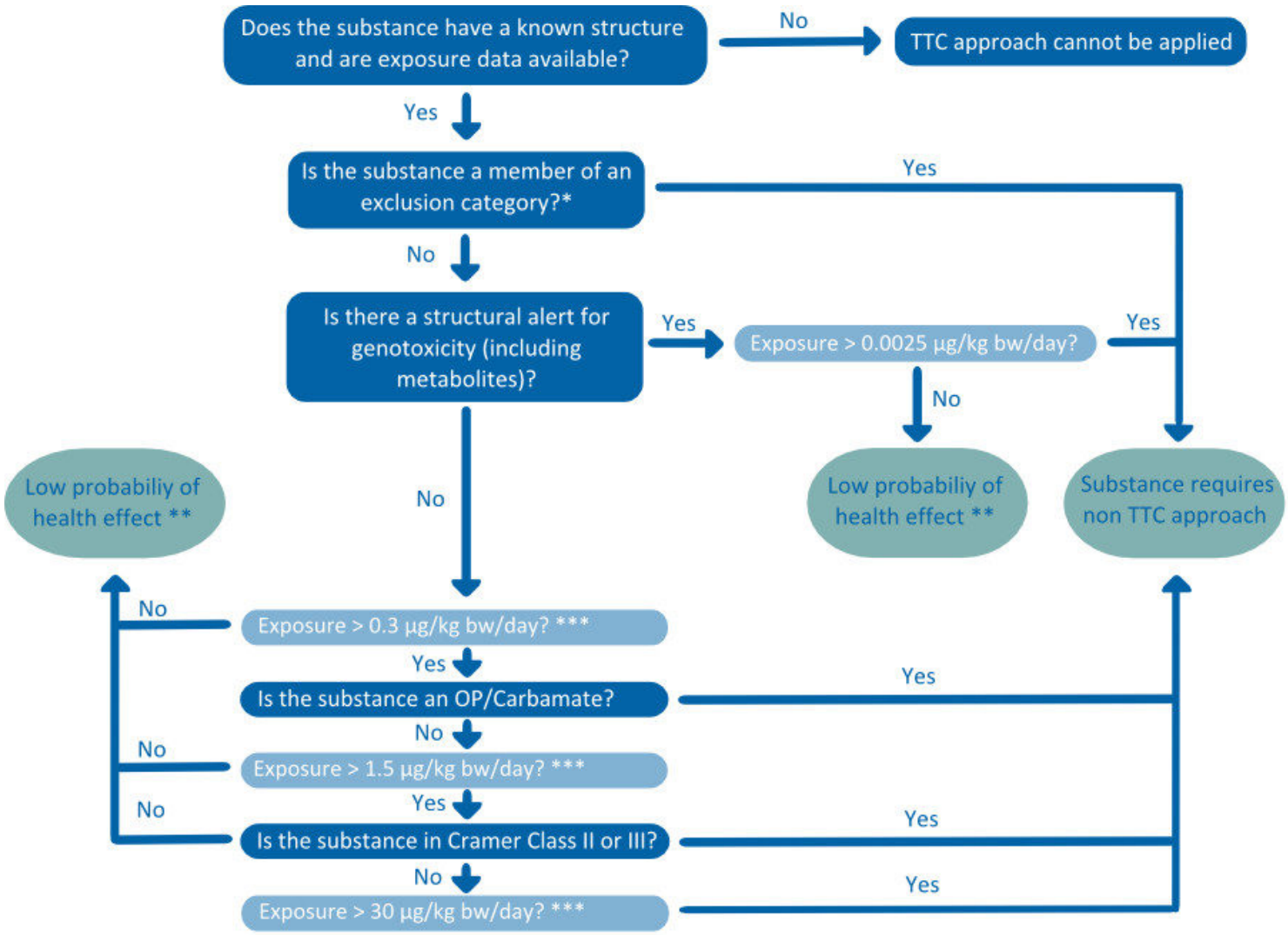
EFSA`s decision tree



Adopted from EFSA Journal 2012;10(7):2750