LOW LEVEL CONTAMINANTS

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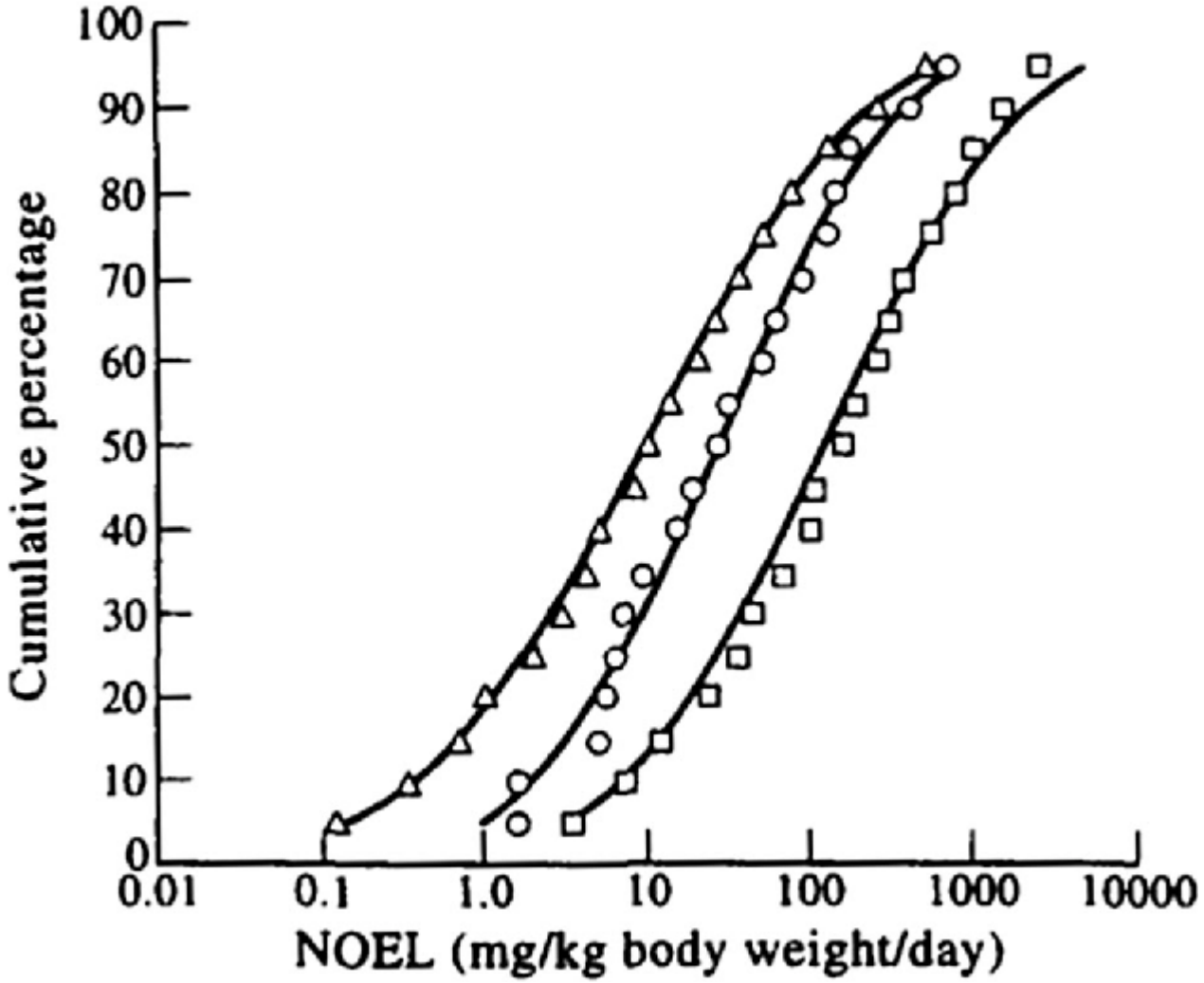
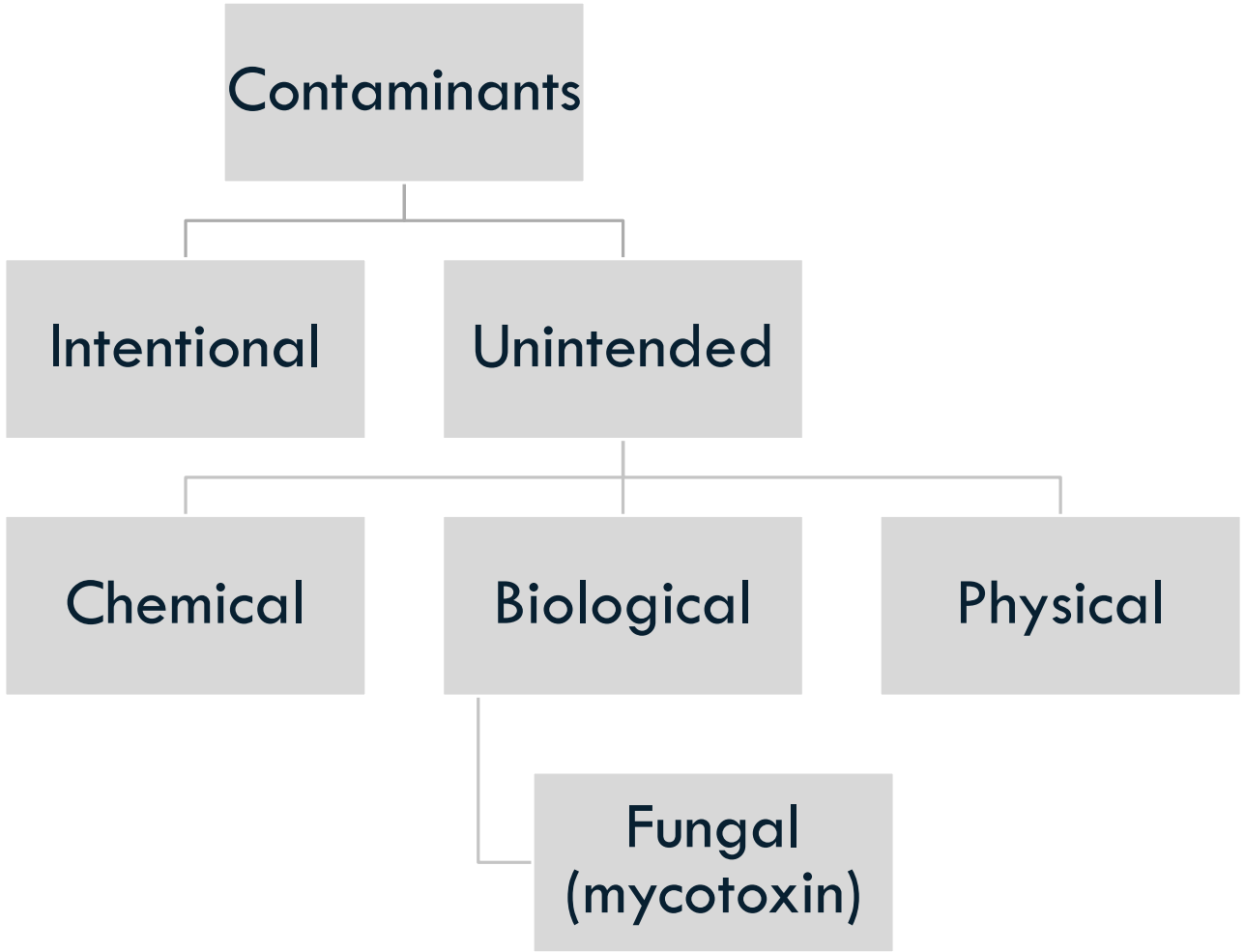


WHO WE ARE

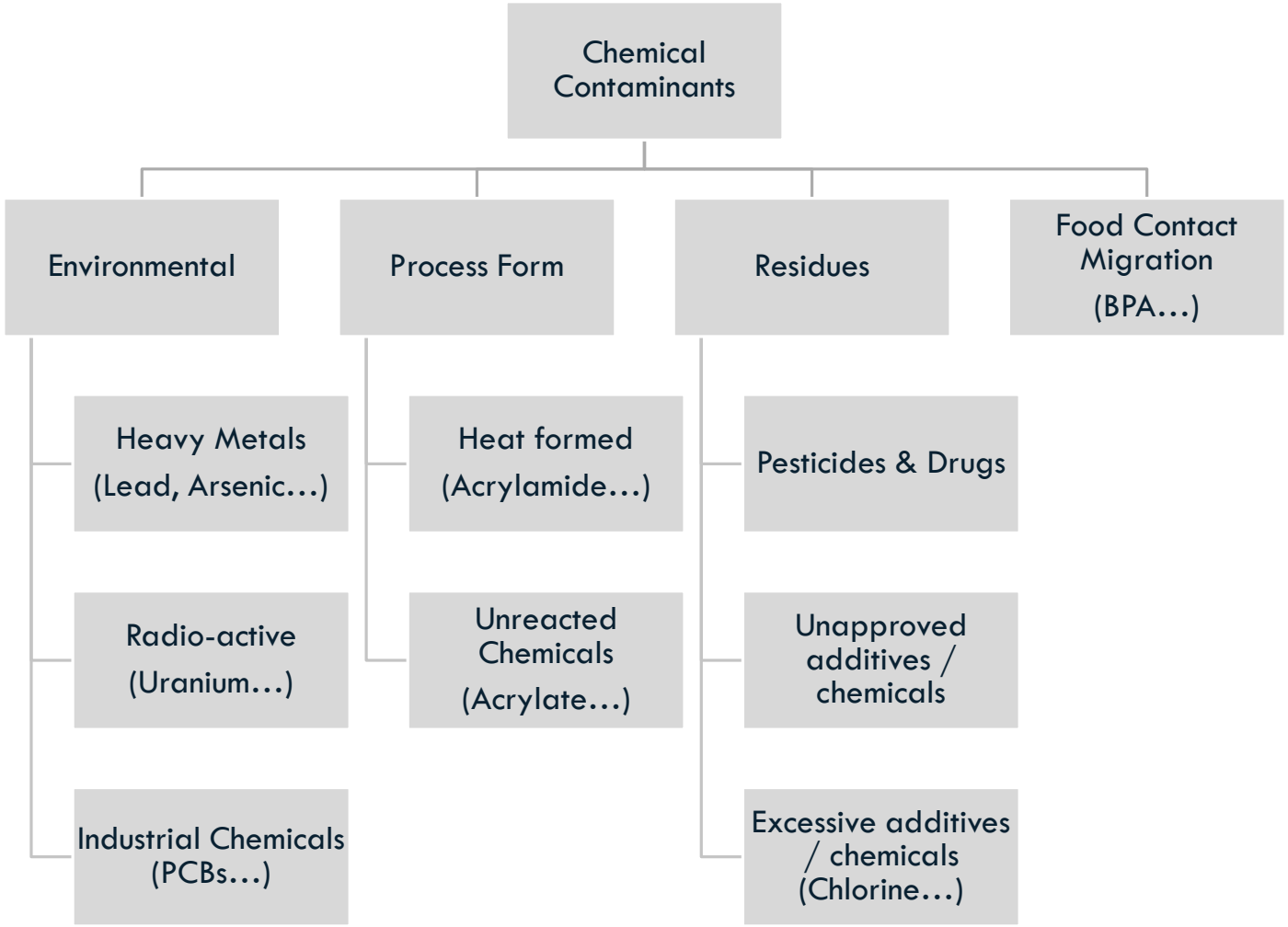
- **GMA is the voice of consumer-facing brands.** Our members' products touch the lives of Americans every single day.

- **Our mission is to empower growth for the CPG industry.** We advocate for policies that ensure consumers have access to and their choice of affordable products that they can trust.

UNIVERSE OF CONTAMINANTS



CHEMICAL CONTAMINANTS



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THRESHOLD SETTING

"All things are poison and nothing is without poison; only the dose makes a thing not a poison"

Toxicology: Defining substances with hazard potential and determining thresholds for safe use

TTC: Very low dose – No real risk (setting a pragmatic threshold below which concerns become negligible)

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NEED FOR A TTC APPROACH

- Prioritizing Resources
- Analytical Detection Methods
- Reduce Animal Testing

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THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

TTC: A Risk Assessment Concept

- For chemicals lacking sufficient toxicity data
  - Establishing a exposure threshold
  - Low probability of adverse effect
- Based on analysis of the distribution of toxicity data
  - Use of Existing databases
  - Potential for toxicity
- Criticism
  - Risk Characterization without toxicity data
  - Validity of databases

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HISTORY OF TTC

- John P Frawley 1967: "**Scientific evidence and common sense** as a basis for food-packaging regulations"
  - Manage exposure from indirect food additives
  - Proposed a 10 ppm threshold for food packaging material (0.1 ppm with safety factor)

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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HISTORY OF TTC

- 1995: Rule on the 'Threshold of regulation for substances used in food-contact articles' (21 C.F.R. §170.39)
  - 1960-1972 FDA performs toxicity studies on ~50 of 1100 flavor ingredients
  - 1974 FEMA collects safety data 1100 on flavor ingredients in use
  - 1974-1979 FEMA publishes data on ~1100 flavoring ingredients organized into 69 scientific literature reviews (SLRs)
  - 1978 Based on SLRs, Cramer et al. publish sequence of structure-based questions. CDT is born
  - 1996 Munro assigns 5th% NOEL each class and proposes TTC for each class. TTC is born

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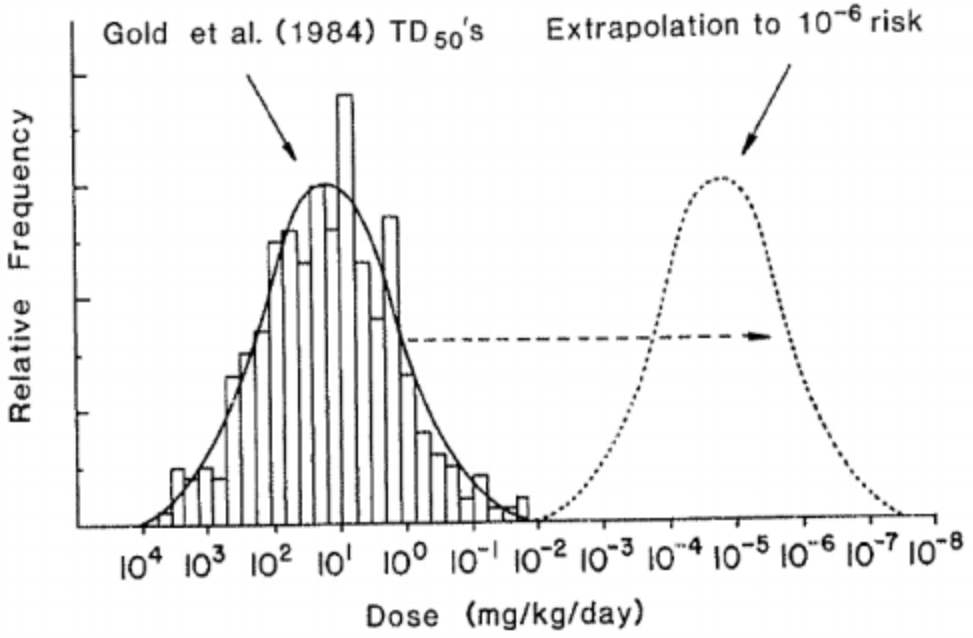
THRESHOLD OF REGULATION

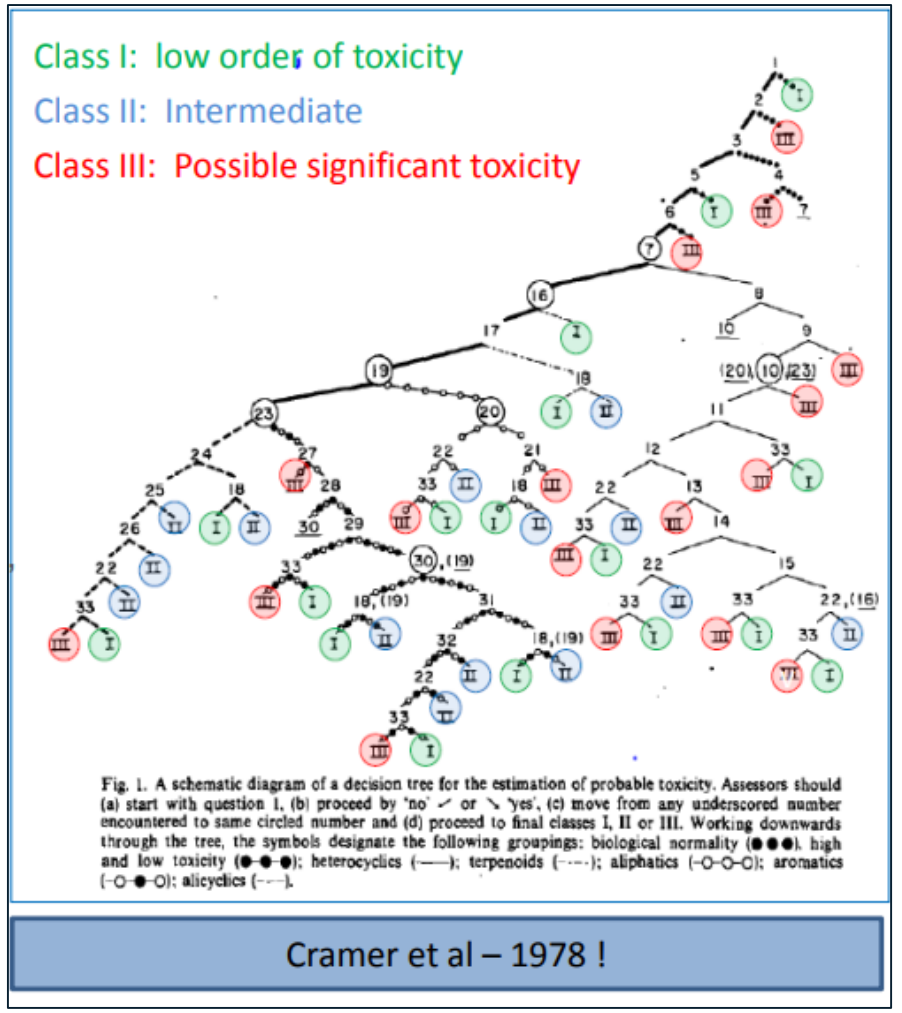
- Statistical Analysis of the Carcinogenic Potency Database (CPDB) published by Gold et al. (1984)
  - Database included 477 chemicals
- Threshold follows the *de minimis* principle and is set at 0.5 ppb in the diet (1.5 µg/person/day)
  - Carcinogens of most concern excluded
  - Carcinogenicity considered the most severe effect



Graph adapted from Munro et al., 1990, Rulis 1986

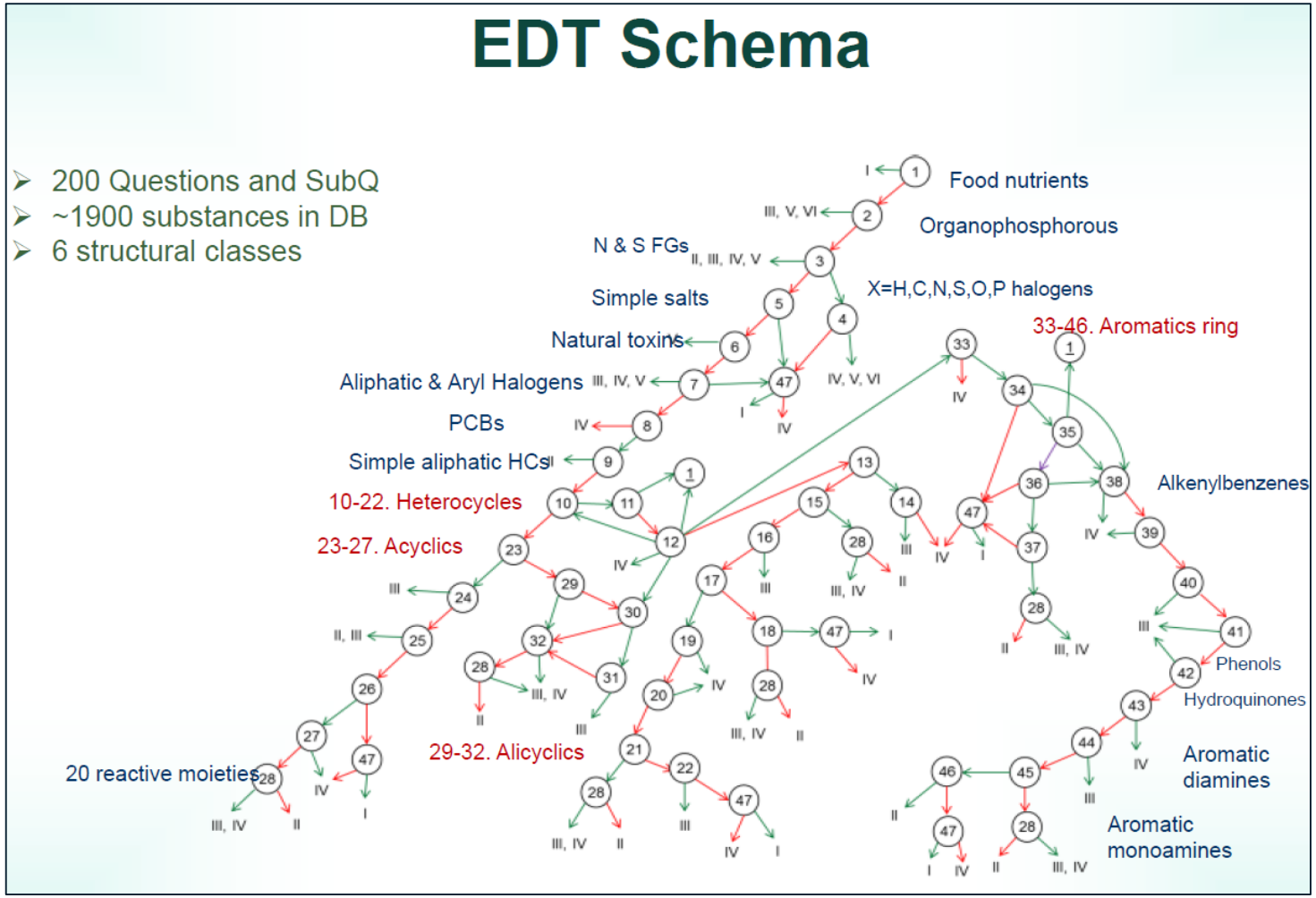
CRAMER STRUCTURAL CLASSES

- Classify Chemicals based on chemical structure
- Use decision tree to group chemicals into three broad structural classes (non-cancer endpoints)
  - Class I: low order of toxicity
  - Class II: Intermediate
  - Class III: Possible significant toxicity

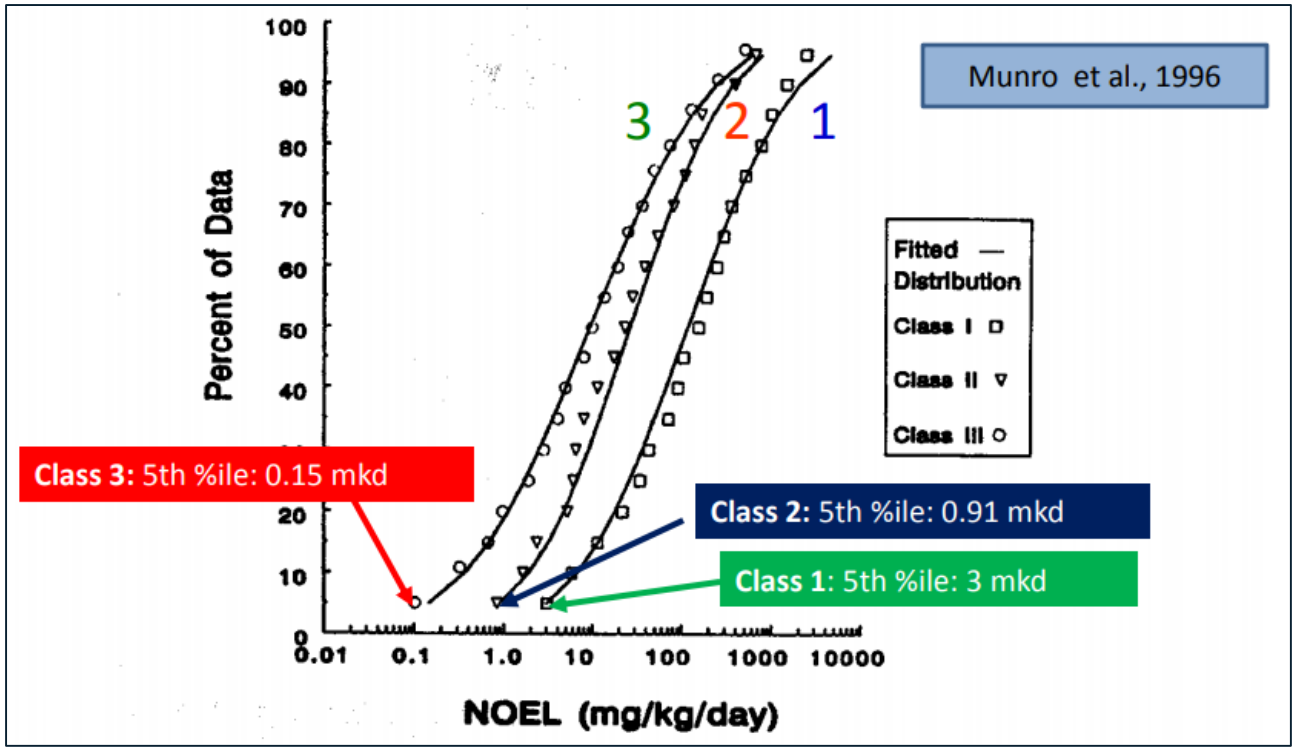


Cramer et al – 1978 !

FDA: EXPANDED DT



MUNRO 5TH PERCENTILE NOEL: CRAMER DT



Cramer Class	Number of Chemicals	5th percentile NOEL	TTC Exposure Limit*
Cramer Class III (most toxic)	137	0.15 mg/kg/d	90 ug/d (1.5µg/kg/d)
Cramer Class II (intermediate)	28	0.91 mg/kg/day	540 ug/d (9 µg/kg/d)
Cramer Class I (least toxic)	447	3 mg/kg/day	1800 ug/d (30 µg/kg/d)

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CURRENT REGULATORY ACCEPTANCE

Area	Authority
Food packaging migrants and flavoring agents	US FDA, JECFA, WHO
Food flavorings and pesticide metabolites in groundwater; *Under discussion for:* food contact materials; impurities and breakdown/reaction products in food and feed additives; plant metabolites and degradants of pesticides; metabolites of feed additives; technological feed additives; flavoring substances in feed	EFSA
Genotoxic impurities in (veterinary and human) pharmaceutical preparations and genotoxic constituents in herbal substances and preparations	EMEA, EMA
Genotoxic and carcinogenic impurities in drugs	US FDA
Within REACH registrations for industrial chemicals	ECHA

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CHALLENGES

Can a Robust TTC be established?

When to use TTC?

Data Access & Quality

TTC - NOAEL

Uncertainty Factor

Changes in Exposure

Mixtures

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SUMMARY

- The TTC approach is a pragmatic screening and prioritization tool for low level exposures used > 20 years
- Application of TTC should be done on a case-by-case basis taking into account information on toxicity and exposure
- No distinction between toxicity induced by intentionally added ingredients or inadvertent contaminants

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THANK YOU

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