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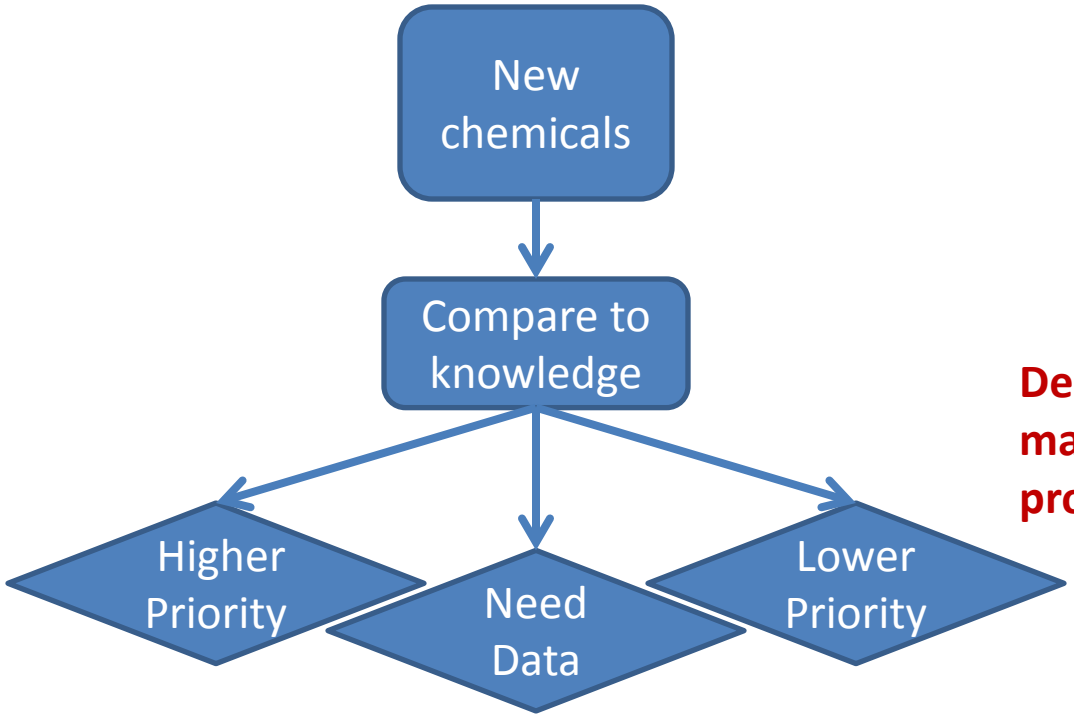
Risk Science Innovation and Application

An ILSI Research Foundation Center of Excellence

Chemoinformatics decision support for antimicrobial pesticides

Also known as the project to develop a thresholds of toxicological concern framework for antimicrobial pesticides decision support

Basic overarching question:
How can we use existing information to inform risk management decisions about new chemicals?



Decisions for risk management or product development

Specific question:
Can we apply the approach to enough classes of chemicals that are antimicrobials to aid decision making?

Benefits

- Use more of the existing data, so you only call for data when it is needed
- Agency and industry resources applied where needed most
- Focus animal testing to where needed most
- Enable product development decisions to identify safer product-use combinations
- Make data-need decisions more consistent, predictable and transparent

The Thresholds of Toxicological Concern Chemoinformatics Approach

1. Chemoinformatics-based decision rules to identify and sort classes of chemicals “covered” by the decision approach

   Includes structure- and property-based “triggers” for exclusions from the covered classes

2. Toxicity evaluations that evaluate distributions of effect levels and statistically derive “reasonable worst case” No Observed Effect Level values for the classes

   A low percentile NOEL divided by a safety factor

3. Evaluation of exposure for the specific decision context

   Confidence that exposure is less than the TTC for the class

4. A decision tree to put it all together

5. Experts to apply the approach, transparently and predictably

There are technical exclusions for the use of current TTC approaches

TTC cannot be applied if

- You do not know enough about the chemical or exposure to decide if TTC can be used
- The available TTC approaches exclude structures or properties that apply to the chemical that you are deciding about
- The chemical does not have enough nearest neighbors in the knowledge base used to set the TTC decision approach

Examples of TTC approaches in regulatory decision support

- FDA “Threshold of Regulation” for when to require additional data on migration from food contact materials to food
- WHO/FAO and European Food Safety Authority “procedure” for recommendations for additional data on new food flavourings

FDA's Threshold of Regulation

- Evolution of large toxicity databases during the 1970s and 1980s
- Registry of Toxic Effects of Chemical Substances
- Prioritized Assessment of Food Additives
- Integrated Risk information System
- Carcinogenic Potency Database

Slides from Mitch Cheeseman

FDA's Threshold of Regulation

- Can we determine a consumer exposure…
  - Likely to result in negligible risk
  - For an untested compound
  - If later shown to be a carcinogen?
- Assume cancer is the endpoint of most concern at lowest dietary concentrations.
- Analyze available carcinogenic potency data probabilistically.

Slides from Mitch Cheeseman

FDA's Threshold of Regulation

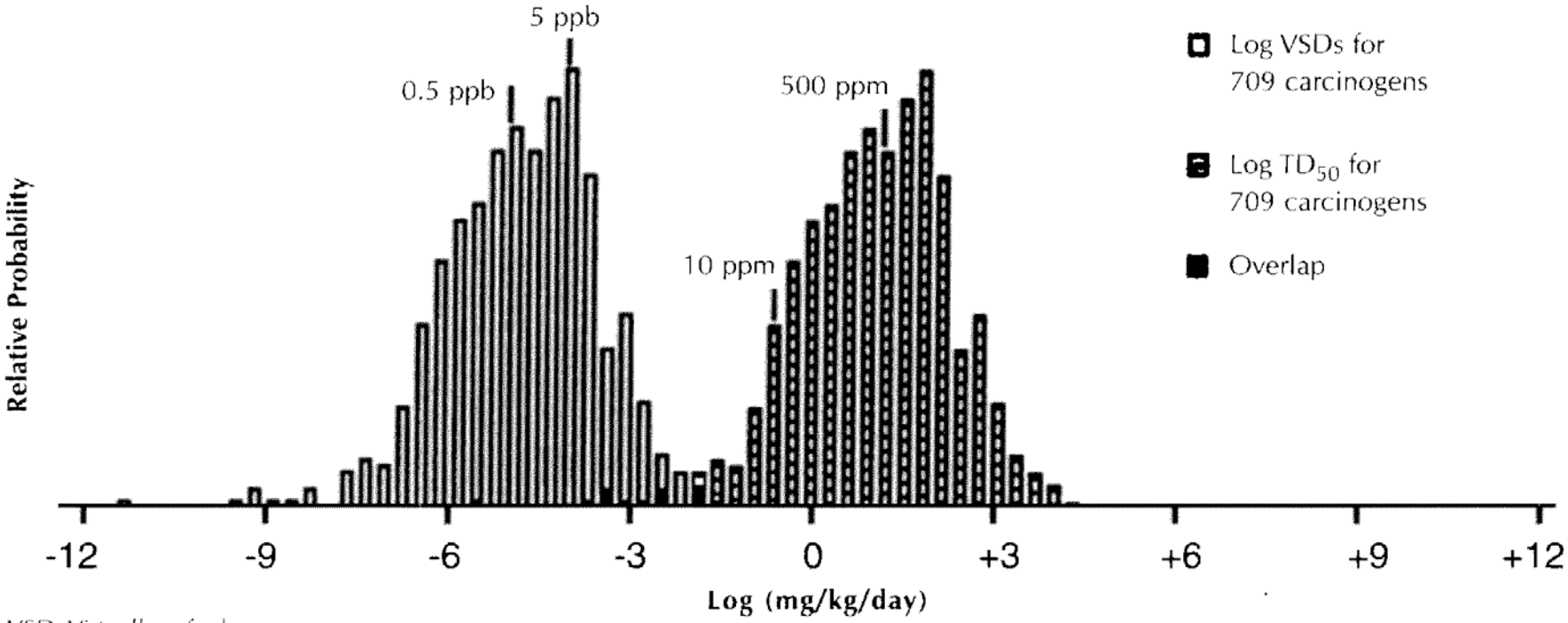
- Carcinogenic potency database Rulis (1987)
  - Compounds tested orally
  - Lowest statistically significant TD_{50} P = 0.01 or better
  - Potency modeled as $0.5/TD_{50}$
- When potencies are graphed logarithmically, they form a normal distribution spanning a broad but predictable range.
- Selection of a consumer exposure level based on the probabilistic distribution potencies and the capabilities of an abbreviated review.
  - Conservative database, linear extrapolation, and exposure assessments
  - Need for a practical level for decisions
  - Ability of trained toxicologists to identify compounds of concern
- Threshold of regulation formally established (1995) (0.5 ppb; 1.5 mcg/p/day)

Slides from Mitch Cheeseman

FDA's Threshold of Regulation

FIGURE 1

Distribution of TD_{50}s for chemical carcinogens and extrapolation to a 1 in a million risk



VSD: Virtually safe dose

Reprinted from *Food and Chemical Toxicology* Vol 37. Cheeseman MA, Machuga EJ and Bailey AB; A tiered approach to threshold of regulation, pp387-412, Copyright 1999, with permission from Elsevier.

Slides from Mitch Cheeseman

Another Early Challenge: Food Flavors

- The Challenge
  - Thousands of discrete chemicals
  - Most used in very small quantities (self-limiting)
  - Many chemicals naturally present in food
- Industry effort to independently assess safety
  - General Recognition of Safety (GRAS)
  - Expert panel
  - Established review process
  - Publication of data and assessment

Slides from Mitch Cheeseman

JECFA Food Flavor Review

- Need to prioritize reviews and address low exposure substances with little or no toxicity data
- Munro et al. 1996
  - Multi-dose studies from public databases
  - Most conservative NOEL
  - Structural Classification
    - Redbook
    - Cramer Decision tree
  - Probabilistic analysis similar to FDA's threshold of regulation analysis to set three safe human exposure levels
    - A threshold for each structural classification

Slides from Mitch Cheeseman

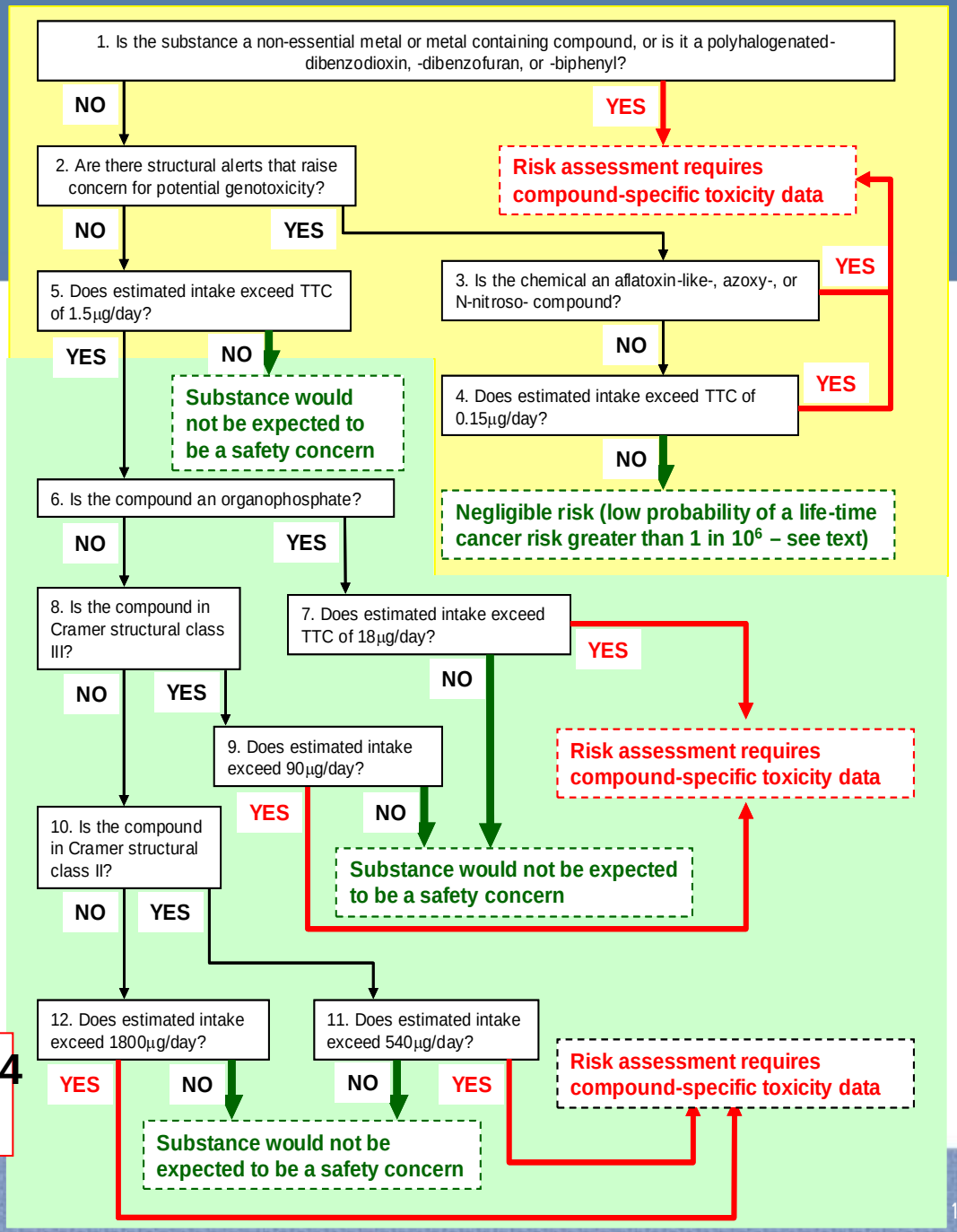
The Tiered TTC Approach

- By mid-1990s, two key parts of what would become the tiered TTC established:
  - **FDA's Threshold of Regulation**
    - 0.5 ppb (1.5 ug/day) based on distribution of carcinogenic potencies
  - **Three noncancer tiers ("Cramer Classes")**
    - Established for evaluating flavor chemicals which are present in the diet at very low levels

Slides from Susan Felter, Procter & Gamble

CANCER

NON-CANCER



Kroes et al., 2004
FCT, 42, 65-83

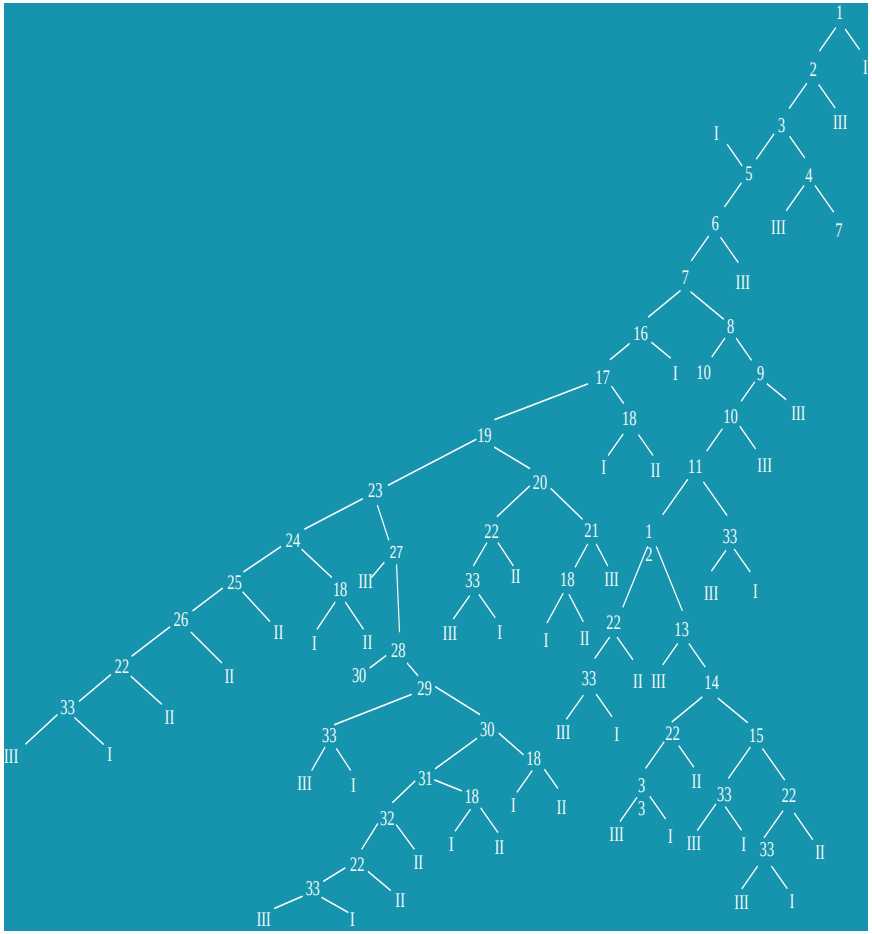
The "Cramer Classes"

- In the late 1970s, Cramer *et al.* proposed a decision tree approach that could be used to group chemicals into three broad structural classes based on a review on chronic and sub-chronic data for non-cancer endpoints.
  - Class 1: low order of toxicity
  - Class 2: Intermediate
  - Class 3: Possible significant toxicity
- *Tool* for classifying chemicals according to levels of concern based on chemical structure.

Slides from Susan Felter, Procter & Gamble

The Cramer Classification Tree

- Sorting questions
  - Is the substance heterocyclic?
    - Yes – Proceed to Q#8
    - No – Proceed to Q#16
  - Is the substance readily hydrolyzed to mononuclear residues?
    - Yes – Proceed to Q#22
    - No – Proceed to Q#33
- Classification questions
  - Does the substance contain any of the following functional groups: aliphatic secondary amine, cyano, *N*–nitroso, diazo, triazeno groups?
    - Yes – Classification III
    - No – Proceed to Q#3



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Basis for TTC Limits for the "Cramer Classes"

The Munro (1996) database

Pergamon

Food and Chemical Toxicology 34 (1996) 829–867

Food and Chemical Toxicology

Regulatory

Correlation of Structural Class with No-Observed-Effect Levels: A Proposal for Establishing a Threshold of Concern

I. C. MUNRO, R. A. FORD*, E. KENNEPOHL† and J. G. SPRENGER

CanTox Inc., 2233 Argentia Road, Suite 308, Mississauga, Ontario, Canada L5N 2X7 and *Research Institute for Fragrance Materials, Inc., Two University Plaza, Suite 408, Hackensack, NJ 07601, USA

Susan Felter, Procter & Gamble

The Munro (1996) Database

- A reference database of 613 organic substances representing wide range of chemicals likely to be encountered in commerce
  - Industrial chemicals, pharmaceuticals, food substances and environmental, agricultural and consumer chemicals
- Total of 2941 NOELs.
- For each of the 613 substances, the most conservative NOEL was selected, based on the most sensitive species, sex and endpoint.

Munro NOELs & Cramer Classes

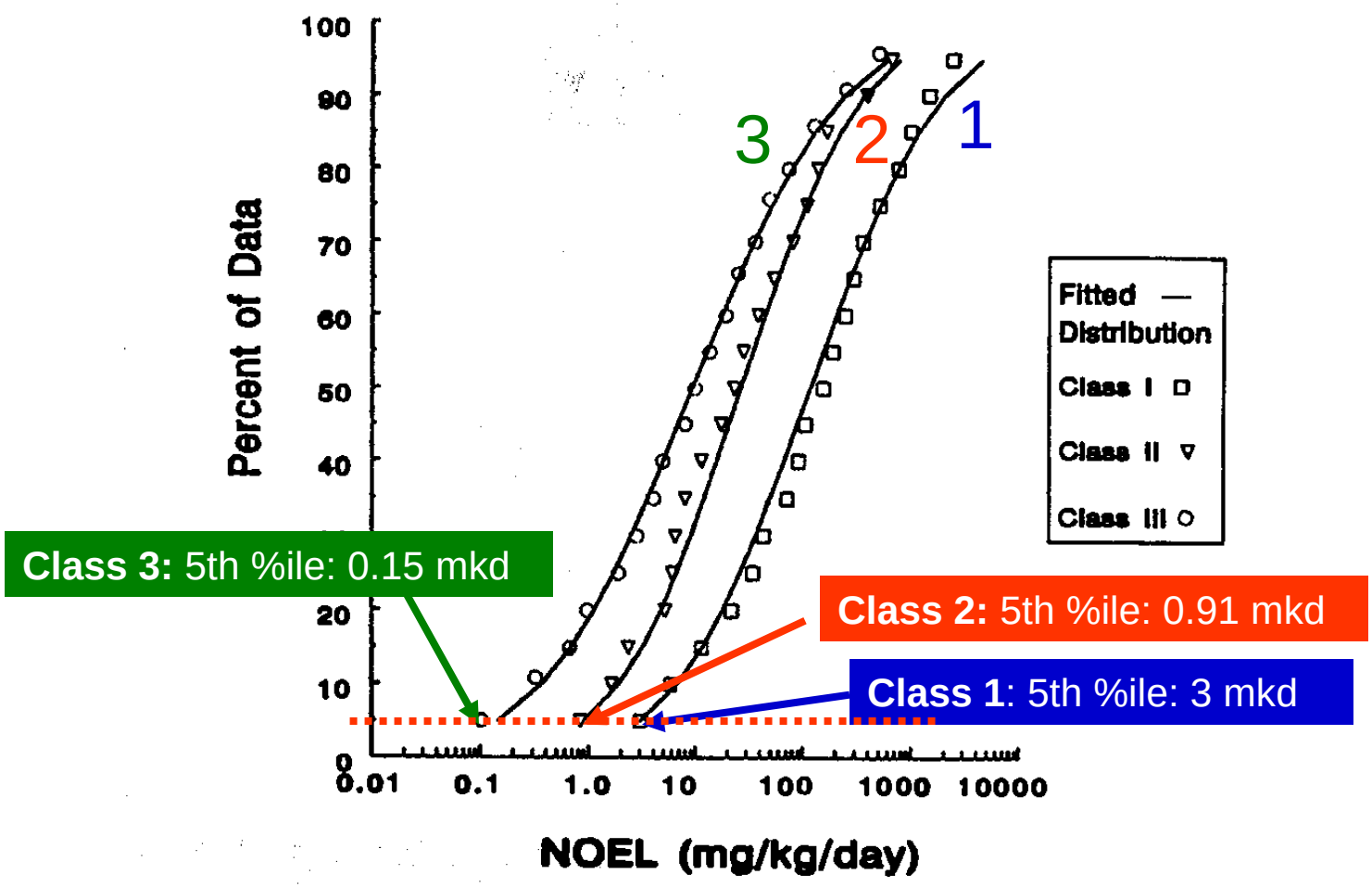

Fig. 1. Empirical cumulative distributions of NOELS of compounds in the reference database and log-normally fitted cumulative distributions (solid lines). Compounds have been grouped into the structural classes I, II and III of Cramer *et al.* (1978).

Munro "5th percentile NOELs" and Human Exposure Thresholds

Cramer Class	N	5th percentile NOEL	HET*
Cramer Class III (most toxic)	137	0.15 mg/kg/d	90 ug/d
Cramer Class II (intermediate)	28	0.91 mg/kg/day	540 ug/d
Cramer Class I (least toxic)	447	3 mg/kg/day	1800 ug/d

* HET = Human Exposure Threshold. Assumes bw of 60 kg and incorporates 100X UF

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Tiered TTC Limits: from Kroes et al., 2004

TTC Tier	Exposure Limit
Excluded chemicals	--
Chemical with Structural Alerts or positive genetox	0.15 ug/d
No SA's or other concern for genetox	1.5 ug/d
Organophosphates	18 ug/d
Cramer Class III	90 ug/d **
Cramer Class II	540 ug/d
Cramer Class I	1800 ug/d

FDA's ToR

"Cancer Tiers"

"Non-cancer Tiers"

** Increased to 180 ug/d when re-evaluated by Munro (2008)

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Congruent findings with another NOEL data set

- Data from a regulatory database selected from studies performed according to OECD 407 and 408
- 813 chemicals.
- NO overlap with Munro database

Cramer Class	Munro TTC (ug/day)	(ug/kg/day)	Kalkhof TTC (ug/kg/day)
III	90 ug/day	1.5 ug/kg/day	13 ug/kg/day
II	540 ug/day	9 ug/kg/day	25 ug/kg/day
I	1800 ug/day	30 ug/kg/day	25 ug/kg/day

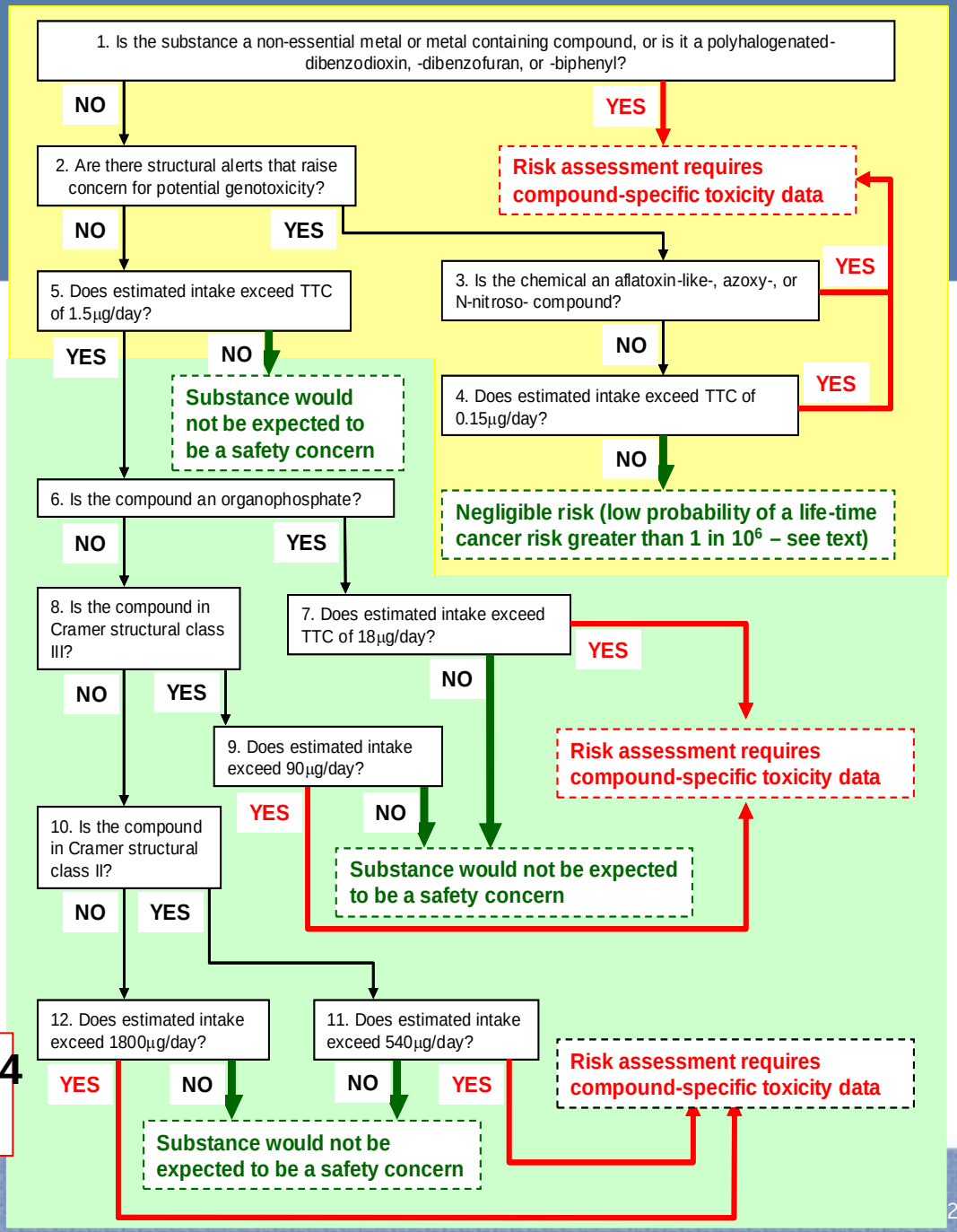
  - Kalkhof H, Herzler M, Stahlmann R, Gundert-Remy U (2012). Threshold of toxicological concern values for non-genotoxic effects in industrial chemicals: re-evaluation of the Cramer classification. Archives of Toxicology 86: 17-25.

Determining “Chemosphere” coverage

- A TTC decision framework works within a “knowledge base” to form rules for what the TTCs do and do not address
- Some of the knowledge forms exclusions
  - Structural alerts
  - Bioaccumulation
  - Specific chemical classes
- Some of the knowledge forms basis for inclusion in a range or category

CANCER

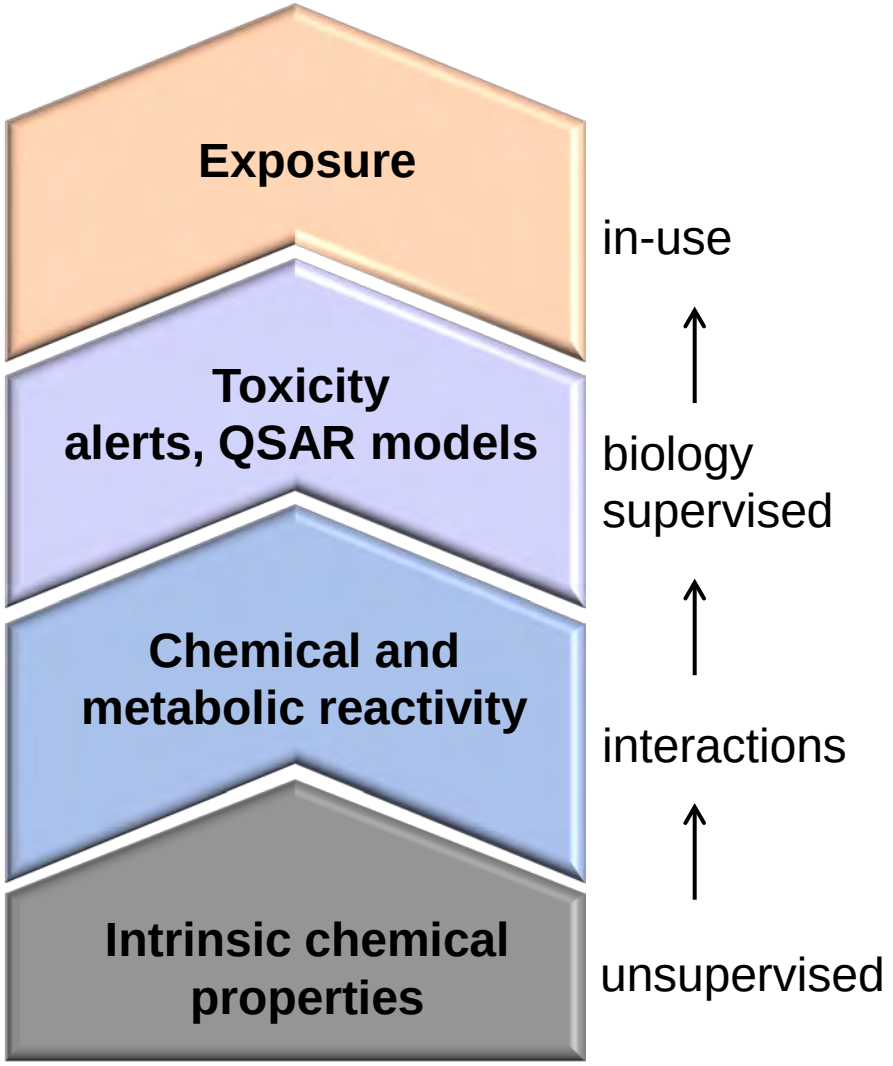
NON-CANCER



Kroes et al., 2004
FCT, 42, 65-83

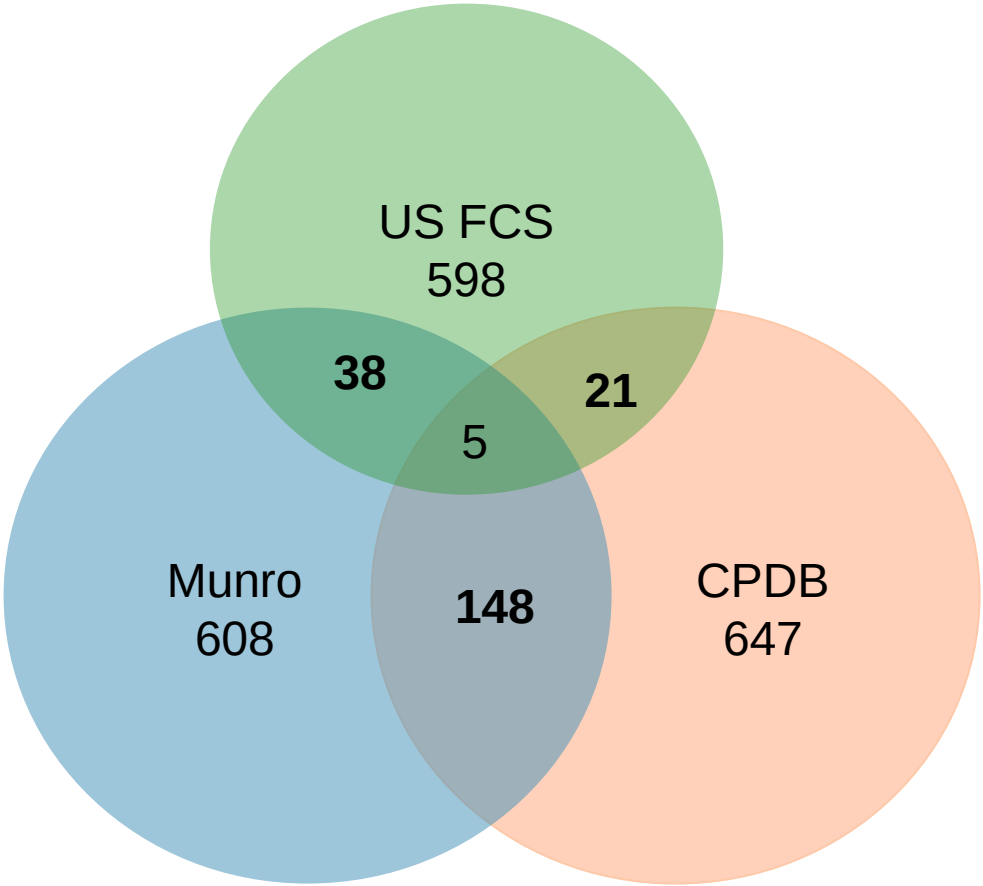
Chemical Inherency: domain characterization

- Chemicals span a sparse and rugged terrain in a very high dimensional space
- Chemical inherency
  - stages of linking chemical structures to toxicity, and eventually to risk assessment



Slides from Chihae Yang, Altamira

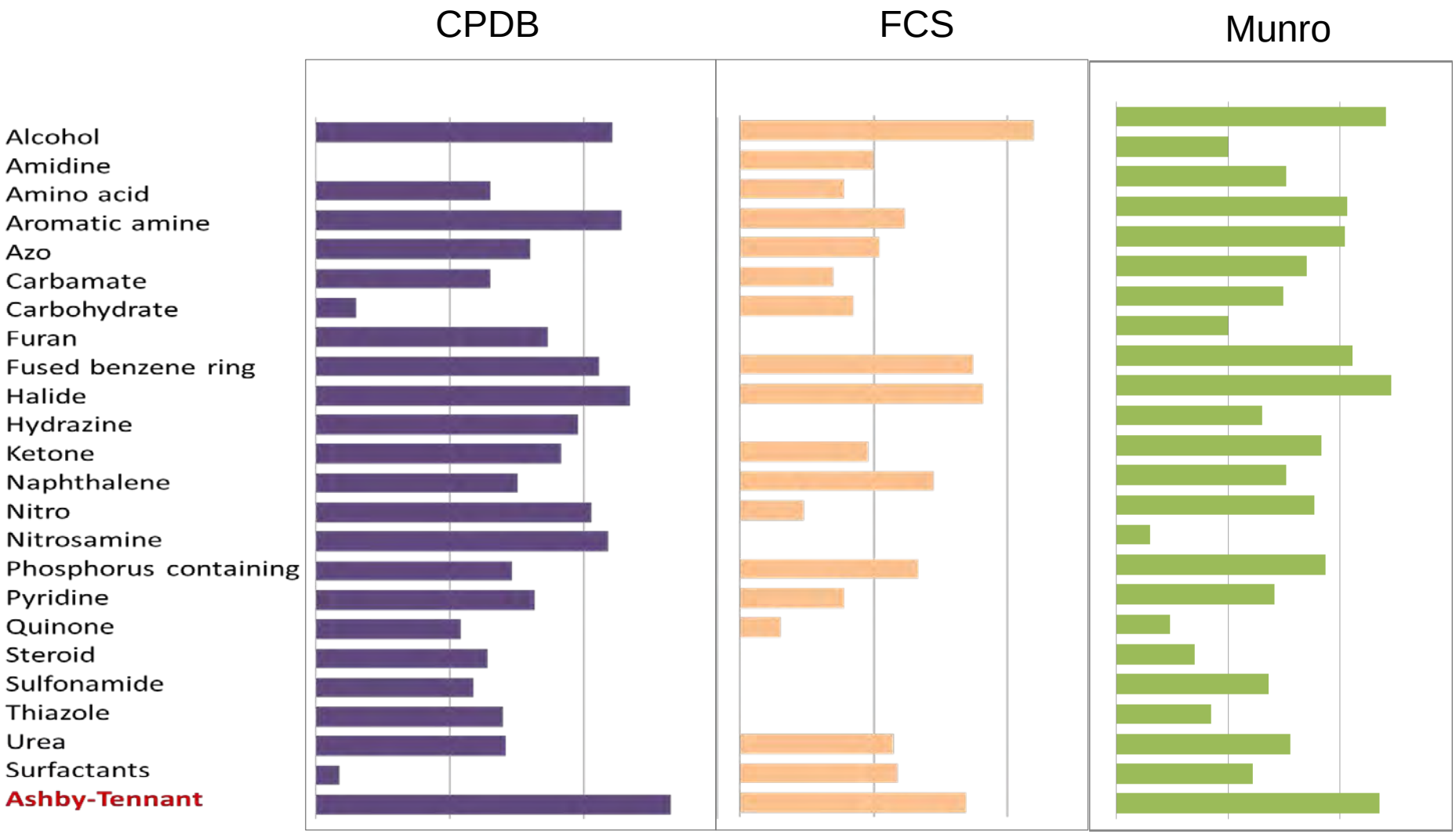
Example of the overlap of chemicals



- US FCS (US Food Contact Substance) http://www.fda.gov/food/foodingredientspackaging/foodcontactsubstancesfcs/default.htm
- Cancer Potency DB TTC
  - Altamira website with detailed tox data) http://www.altamira-llc.com
  - EFSA site http://www.efsa.europa.eu/fr/supporting/pub/159e.htm
- Munro/EFSA http://www.efsa.europa.eu/fr/supporting/pub/159e.htm

Slides from Chihae Yang, Altamira

Chemical inherency class comparisons: CPDB, FCS, Munro



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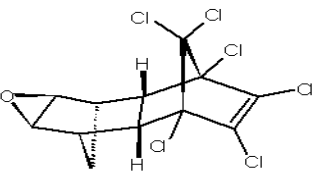
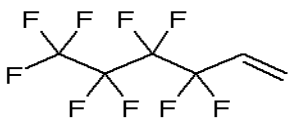
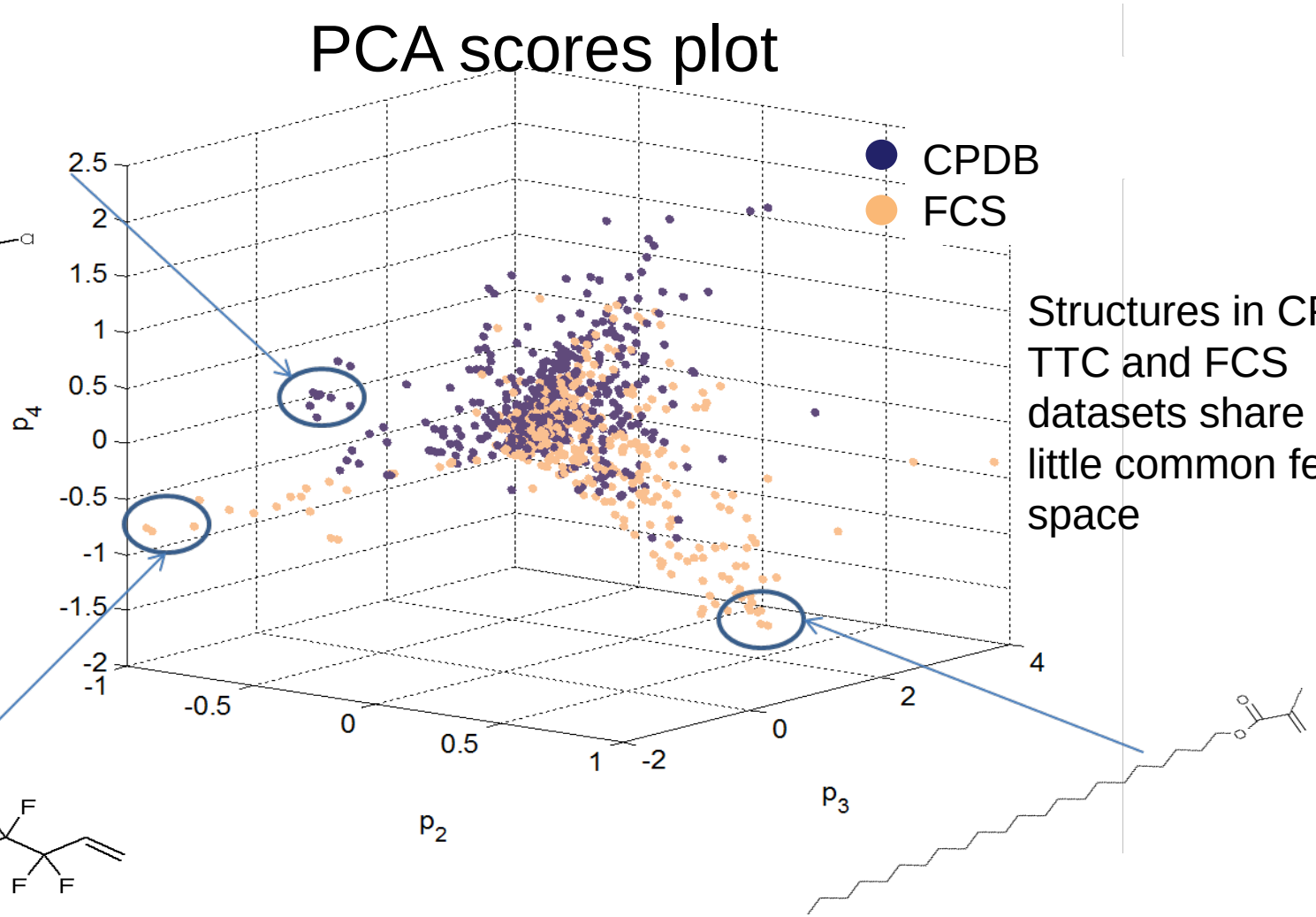
Chemical inherency
Structural features: CPDB TTC, US FCS







Structures in CPDB TTC and FCS datasets share very little common feature space

Slides from Chihae Yang, Altamira

The Antimicrobial TTC project

Major workstreams:

1. Curate and evaluate toxicity data (ToxRefDB)
2. Establish categories based on chemical structure/function domain analysis
3. Identify categories in the chemosphere of existing TTCs
4. Develop decision approaches for categories for categories outside of the existing TTCs
5. Develop decision approach to assessing AM dermal exposures for use with oral TTC tox data
6. Address special issues: inorganic AMs; first-pass metabolism

Project Structure:
Overall Project Steering Team

Kirk Arvidson	US FDA
Mitch Cheeseman	Steptoe & Johnson
Vicki Dellarco	US EPA
Susan Felter	Procter & Gamble
Tim Leighton	US EPA
Steve Olin	ILSI-RF
Richard Canady	ILSI-RF
Troy Seidle	Humane Society

Dermal Exposure Group

James McDougal (chair)	Wright State University
Robert Bronaugh	FDA/CFSAN/OCC
Richard Guy	University of Bath, UK
P.V. Shah	US EPA
Tim Leighton	US EPA
Tim O'Brien	Ecolab
Stephen Olin	ILSI RF
Brannon Walsh	US EPA

Database/Framework Group

Alan Boobis	Imperial College London, UK
Richard Canady	ILSI Research Foundation
Mitchell Cheeseman	Steptoe & Johnson
Vicki Dellarco	US EPA
Matt Martin	US EPA NCCT
Tim McMahon	US EPA
Stephen Olin	ILSI Research Foundation
Paul Price	Dow Chemical
Chihae Yang	Altamira, LLC
Mike Laufersweiler	Procter & Gamble
Kristi Jacobs	US FDA

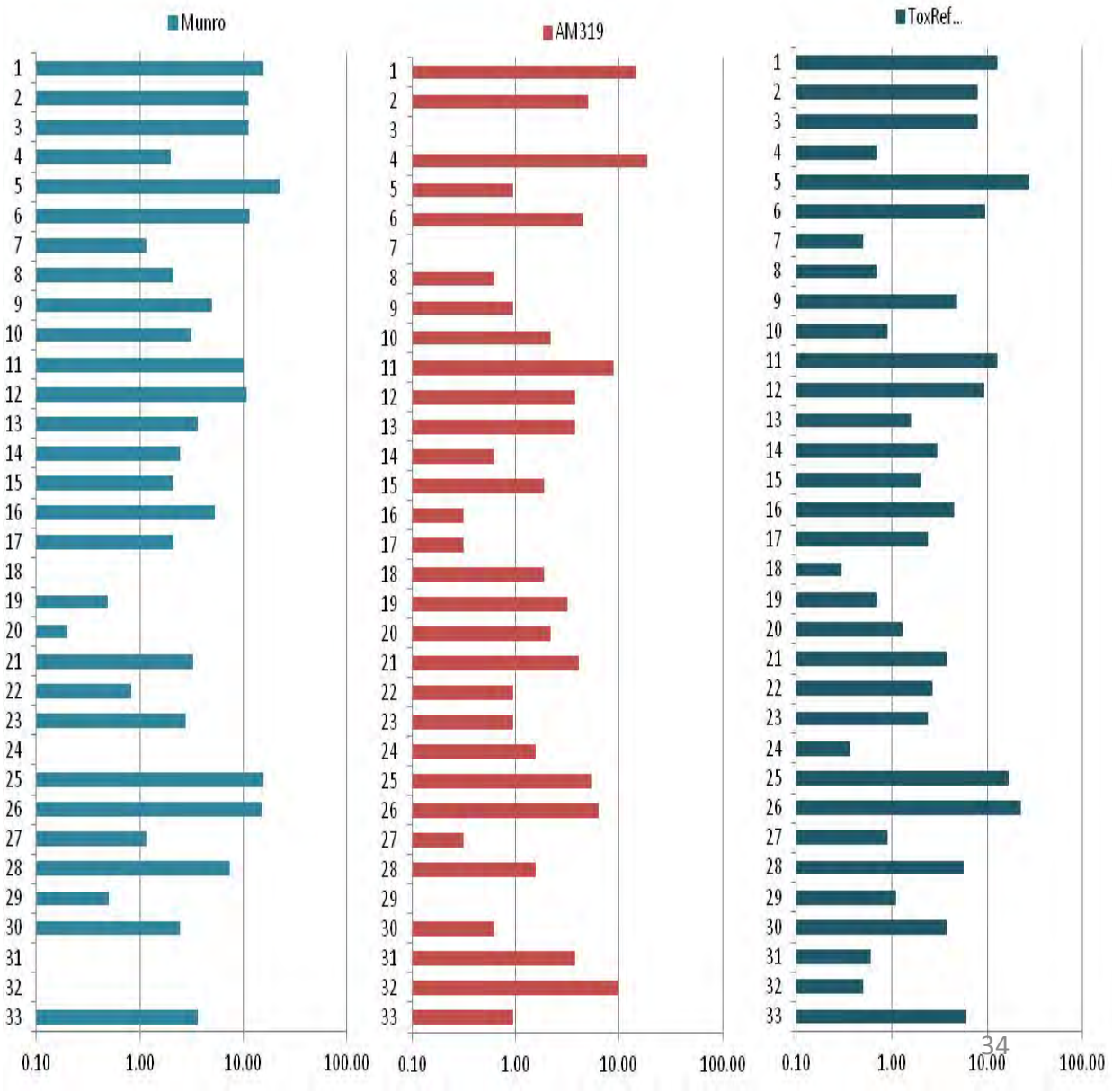
AM TTC Status

- Data entered
  - Major effort by EPA to enter data from registered AMs into ToxRef DB
  - Public announcement and QC done
- Tiered dermal exposure estimation method developed
- Chemical classifications developed
  - A “master” chemical ontology for TTC databases derived and applied across other major TTC data sets so that broad comparisons can be done

"Coverage" comparison of number of NOELS per general chemical category in Munro/EFSA, the AM data set, and ToxRef DB **(DRAFT work product of the project!)**

Structure classification and analysis by Chihae Yang of Altamira

#	Selected Category Names (AM319)
1	Alcohol, aliphatic
2	Alcohol, aromatic
3	Alcohol - Phenol (OH)
4	Aldehyde
5	Amine, aliphatic
6	Amine, aromatic
7	Amino acid
8	Azo
9	Carbamate/thiocarbamate
10	Carbohydrate
11	Carboxamide
12	Carboxylic acid
13	Carboxylic acid, aliphatic C<=4
14	Carboxylic acid, aromatic
15	Carboxylic acid, aromatic - benzoic acid
16	Carboxylic ester, aromatic - hydroxybenzoic ester
17	Fused ring - carbocycle
18	Heterocycle - 1,3,5-triazine, 2,4,6-oxo/oxy (iso/cyanurate)
19	Heterocycle - imidazole dione, generic (hydantoin)
20	Heterocycle - oxazole, generic
21	Heterocycle - triazine, generic
22	Heterocyclic conazole - ring5 N-aliphatic positive sigma-charge
23	Hydrocarbon - bridged diphenyl
24	Nitro, aliphatic
25	Organohalide - aliphatic halide
26	Organohalide - aromatic halide
27	Organohalide - diphenyl ether, polyhalogenated
28	Organophosphorus
29	Steroid ring
30	Sulfonamide
31	Surfactant, anionic
32	Surfactant, cationic - QUAT
33	Urea



Rough cut on the categories

- 30% are inorganic/metalics/organometallics “IOM”
- An additional ~25% are not directly covered by the Munro “chemosphere”
- So, we can develop TTC decision rules for about 50% of the antimicrobial chemical classes now
- And may be able to include up to 25%
- But we need to address the IOMs in order to have a complete picture of antimicrobials

Next steps

- Publish dermal exposure framework (submit late 2012)
  - Tiered approach to estimating exposure dose
  - Include case studies
- Develop a draft decision tree for the AMs that we can now (in next 3-6 months)
  - Evaluate chemosphere coverage
  - Evaluate toxicity coverage (Are the AMs more or less toxic than Munro data set equivalents)
  - Develop rules for application of TTCs
  - Issue draft report for peer review (mechanism to be determined)
- Separate track for inorganics/metals
  - Small expert group to evaluate approaches
  - Workshop to explore approaches (late 2012)
  - Issue draft report of recommendations of the expert group for peer review (early 2013)

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Thank you

Richard Canady, PhD DABT

Director, RSIA

rcanady@ilsi.org

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