Moving from One-Size-Fits-All to Fit-for Purpose TTC Values

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Society of Toxicology, Computational Toxicology Specialty Section
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Conflict of Interest Statement

The presenters have no conflicts of interest to declare.

Caveats

- Owing to the short time available for the webinar, we will not be able to cover all of the important aspects of the TTC concept. However, we have included a reference list at the end of the slides that you can access at your convenience for more information.
- The views expressed herein are those of the presenter and do not necessarily reflect the views or policies of the US Environmental Protection Agency. Mention of tradenames or commercial products does not constitute endorsement or recommendation for use.

Overview

- Brief history of the TTC concept
- Examples of deriving of fit-for-purpose TTC values
- Comparing the chemical/biological space of two datasets
- Summary, next steps and vision for the future

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Threshold of Toxicological Concern (TTC) Concept and Regulatory Applications

What is it?

"TTC is a pragmatic risk assessment tool based on the principle of establishing a human exposure threshold value for all chemicals, below which there is a very low probability of an appreciable risk to human health." Kroes, 2004

See references provided at the end of the presentation (with PubMed links) for more information on the TTC concept.

Why do we need it?

TTC values can be used as a:

Screening/prioritization tool

Risk assessment tool

Applications of the TTC approach

Screening tool

1. **Screening/prioritizing substances for risk assessment:**
   - **food contact and food flavoring substances**
   - **impurities in manufacturing operations**
   - **genotoxic impurities in pharmaceuticals**
   - **substances that could leach out in medical devices**

2. **Facilitate risk-based prioritization of large numbers of data-poor substances that require triaging into categories of lower and higher concern to facilitate subsequent evaluation by other New Approach Methodologies (NAMs).**

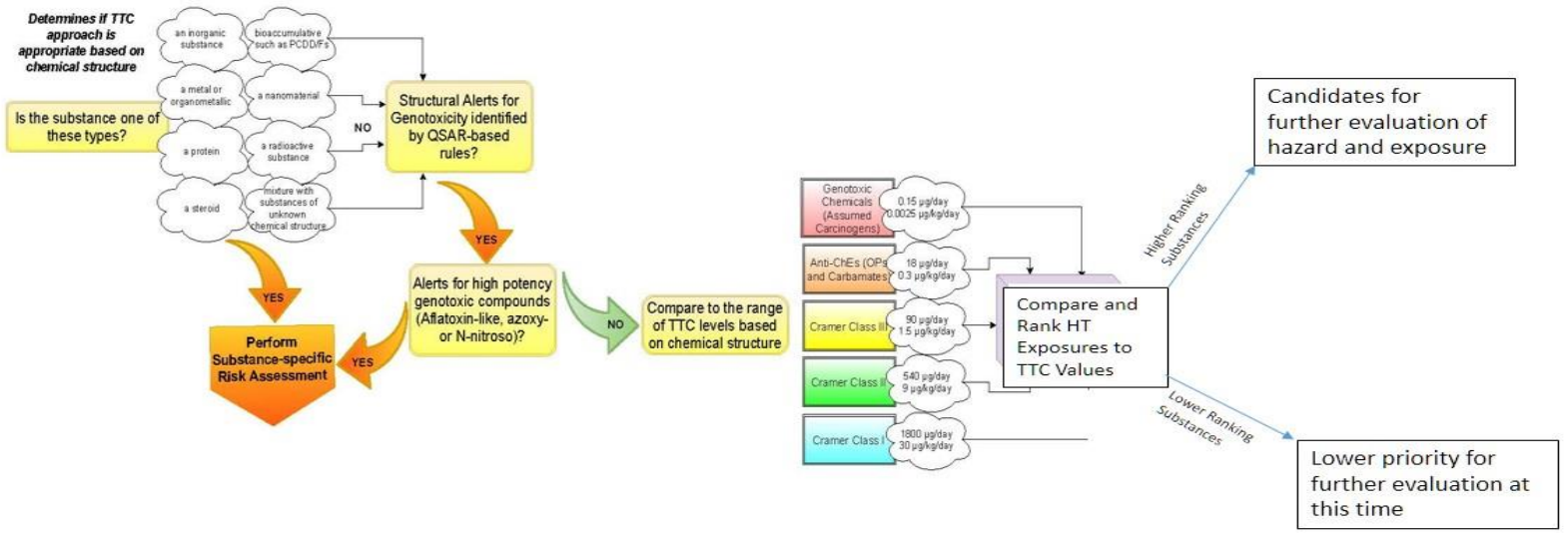
Applications of the TTC approach

Risk assessment tool

- For some regulatory purposes, TTC values can serve as a default Health Based Exposure Limit (HBEL) values in the absence of compound-specific toxicity data.

- However, use of the TTC approach is not an alternative to the use of the most appropriate dose-response toxicity data to derive HBEL values when the data are available.

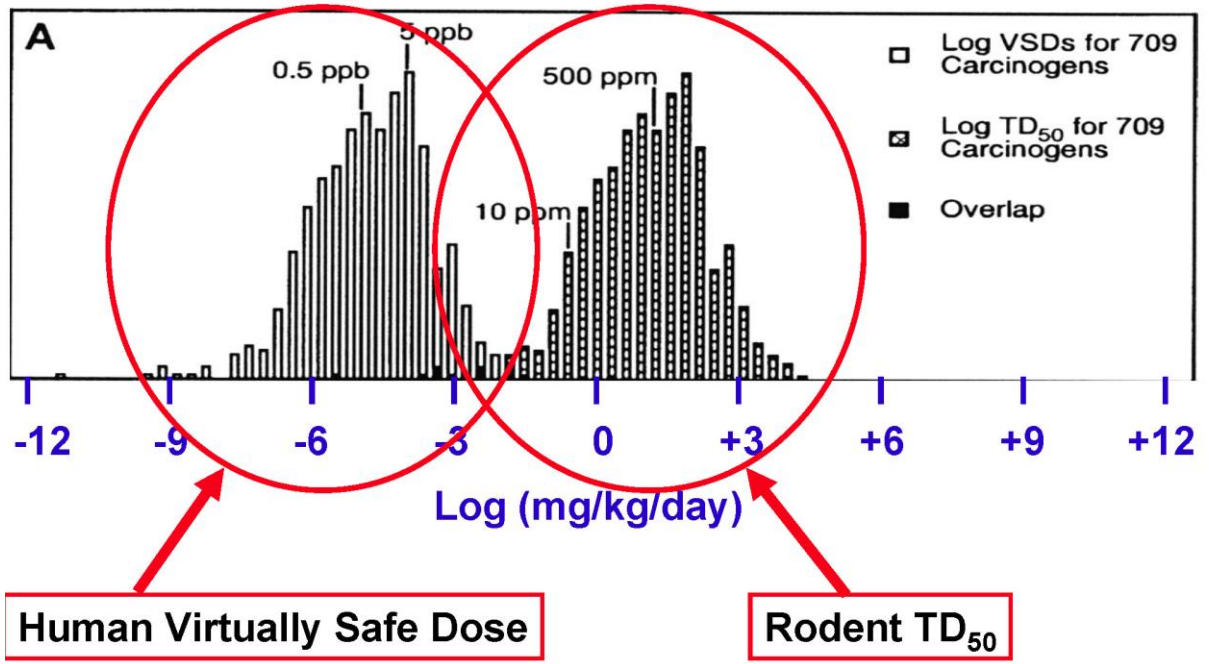
TTC used as part of a Risk-Based prioritization approach



- **Coupled Threshold of Toxicological Concern (TTC) values with High Throughput Exposure (HTE) modelling (predicted exposure values from Wambaugh et al (2014)) to rank order substances for further evaluation (Patlewicz et al., 2018).**
- **None of the substances categorized as Cramer Class I or Cramer Class II exceeded their respective TTC values.**
- **No more than 2% of substances categorised as Cramer Class III or acetylcholinesterase inhibitors exceeded their respective TTC values.**
- **Majority of chemicals with genotoxicity structural alerts did exceed the relevant TTC – recommendations were proposed for next steps.**

FDA Threshold of Regulation (1995)

- Precursor to the TTC concept
- FDA regulation specifies a limit for projected dietary exposure of 0.5 ppb (or 1.5 µg/day).
- No toxicity testing is required for chemicals w/o structure alerts for genotoxicity, or that are not known carcinogens or potent toxins, if estimated daily exposures are below this level.
- Such chemicals "Exempted from regulation."



Cheeseman et al. 1999

- USFDA. 1995. Food Additives: Threshold of Regulation for Substances Used in Food-Contact Articles; Final Rule. Fed Reg., 60: 36582-36596. July 17.

Slide provided by Kelly Coleman, Medtronic

Non-cancer TTC: Cramer classes

- **Class I** – Substances with simple structures and related data which suggest a low order of oral toxicity.
- **Class II** – Substances which are intermediate. Less innocuous than class I. Lack positive identification of toxicity.
- **Class III** – Substances that permit no initial presumptions on safety or may suggest significant toxicity.

Cramer et al. 1978

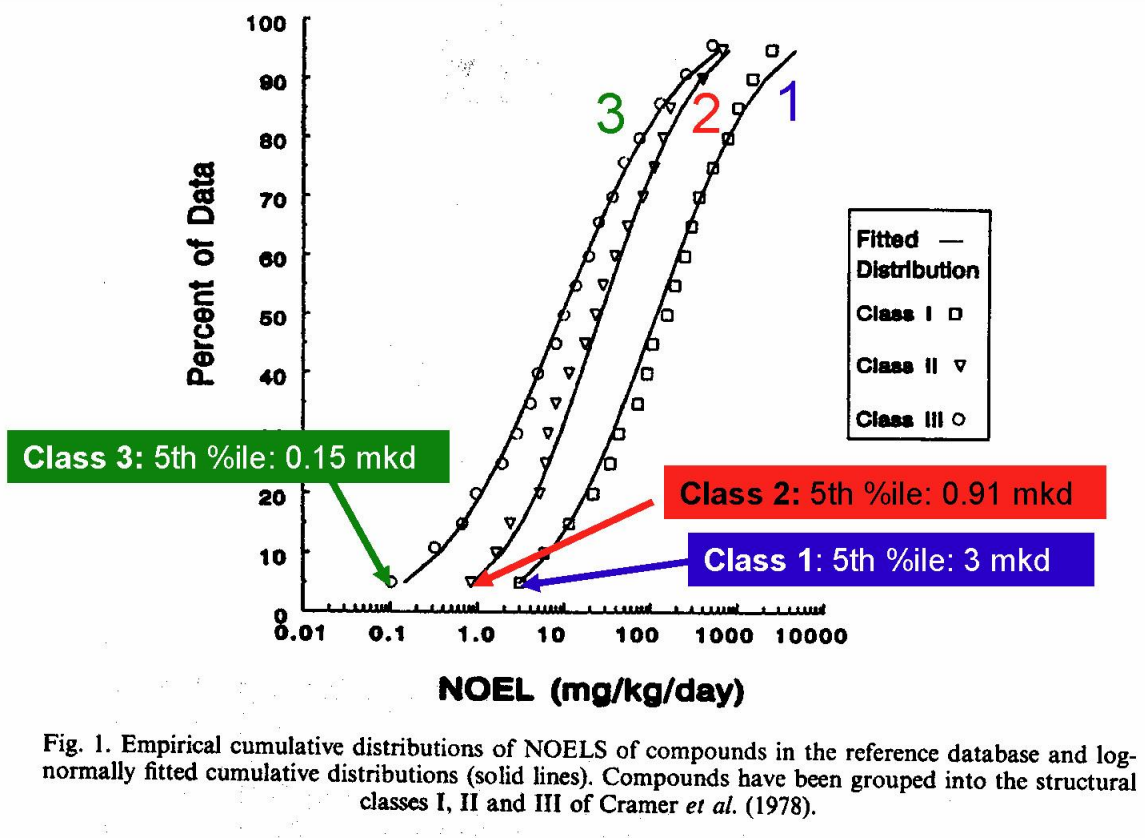


Fig. 1. Empirical cumulative distributions of NOELS of compounds in the reference database and log-normally fitted cumulative distributions (solid lines). Compounds have been grouped into the structural classes I, II and III of Cramer *et al.* (1978).

Munro et al. 1996

Slide provided by Kelly Coleman, Medtronic

Cramer Class Values

Classification	Number of Chemicals	5th Percentile NOEL (mg/kg/day)	TTC Exposure Limit* (µg/day)
Cramer I	447	3	1800
Cramer II	28	0.91	540
Cramer III	137	0.15	90

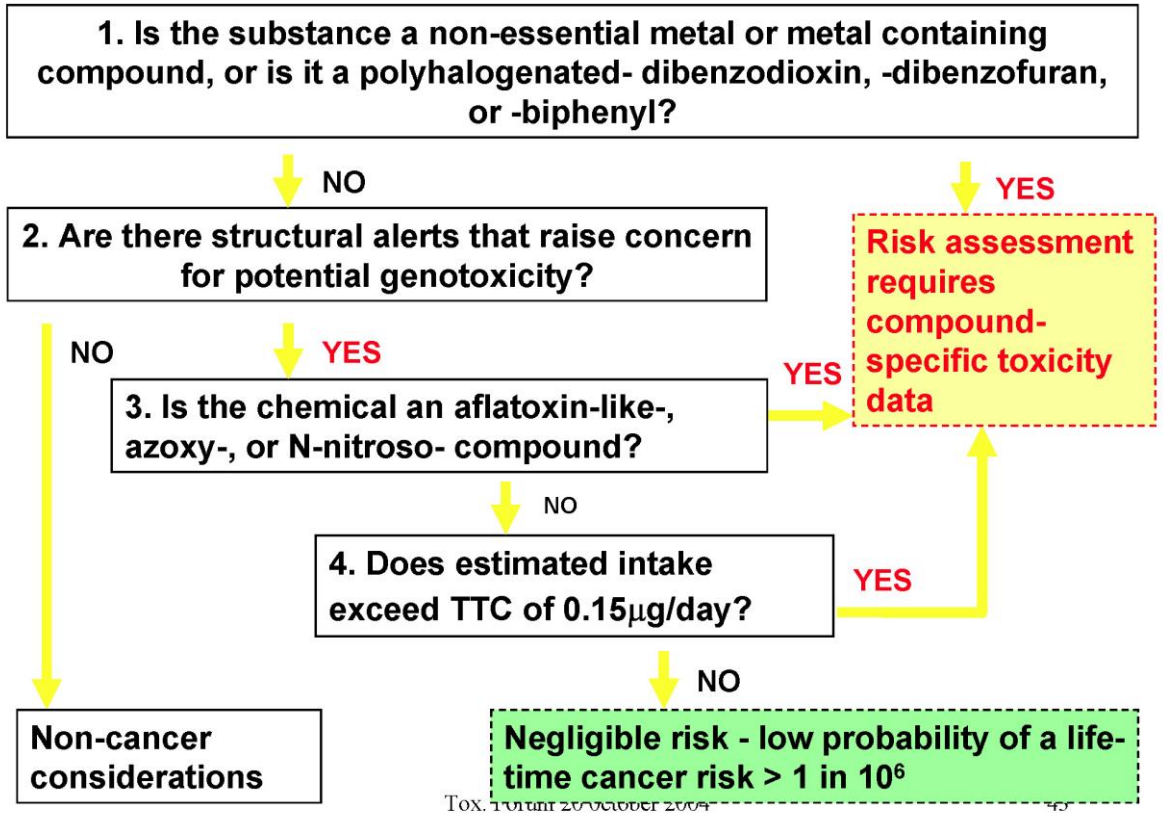
TTC Exposure Limit incorporates 100X uncertainty factor from adjusted chronic NOEL and assumes 60 kg body weight.

Munro et al. 1996

Slide provided by Kelly Coleman, Medtronic

TTC Decision Tree

- Kroes et al. (2004) created a new TTC decision tree that included genotoxins.
- Determined that an additional safety factor of 10 was needed for genotoxic compounds.
- TTC for chemicals with structural alerts for genotoxic carcinogenicity of 0.15 µg/day.
- Based on linear extrapolation to a theoretical upper-bound risk of 10^{-6} from TD_{50}.



Tox. Forum 20 October 2004

Slide provided by Kelly Coleman, Medtronic

Exclusions from the TTC Approach

Exclusions based on Kroes et al (2004) decision tree

- Polyhalogenated–dibenzodioxins & furans, and –biphenyls
- Heavy metals (elemental or ionic)
- Steroids
- Organophosphates
  - Aflatoxin-like compounds
  - *N*-Nitroso compounds
  - Azoxy compounds

Other compounds not in scope of the original Munro et al (1996) dataset

- Polycyclic amines
- Polymers
- Particles (including nanoparticles)
- Ceramics
- Proteins
- Radioactive constituents

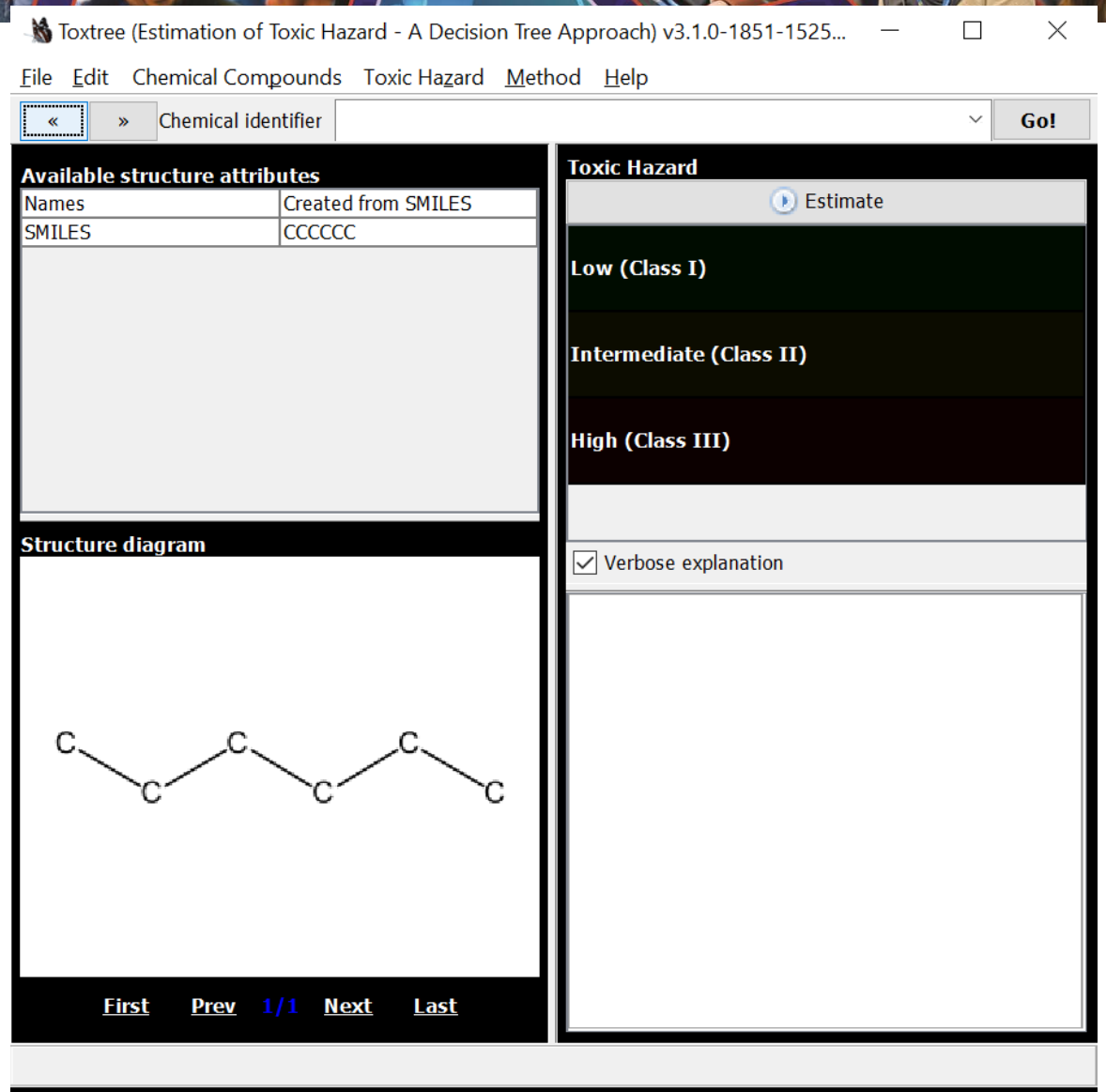
Summary of Oral TTC values

Type of substance	µg/person/day (µg/kg-day for 60 kg adult)
Alerts for potential genotoxic carcinogenicity	Kroes: 0.15 (0.0025 µg/kg-day) ICH: 1.5 (0.025 µg/kg-day)
Acetylcholinesterase inhibitors (AChEI) Organophosphate/carbamate	18 (0.3 µg/kg-day)
Cramer Class III	90 (1.5 µg/kg-day)
Cramer Class II	540 (9.0 µg/kg-day)
Cramer Class I	1800 (30 µg/kg-day)

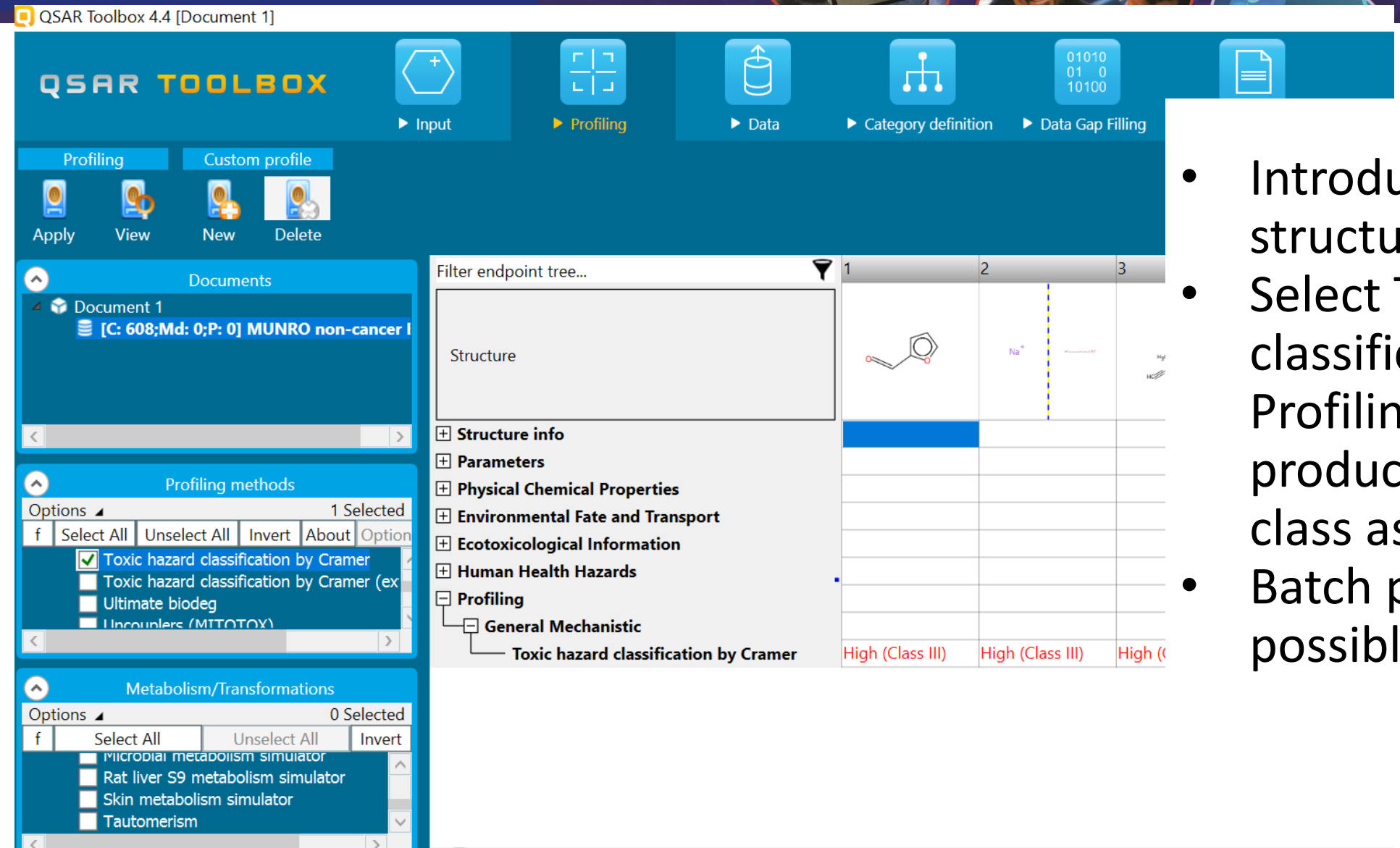
TTC values span several orders of magnitude

Tools to assist in TTC determinations: Toxtree

- Toxtree – select Cramer rules
- Introduce chemical structure
- Click **Estimate** to produce the Cramer class assignment
- Batch processing of files possible



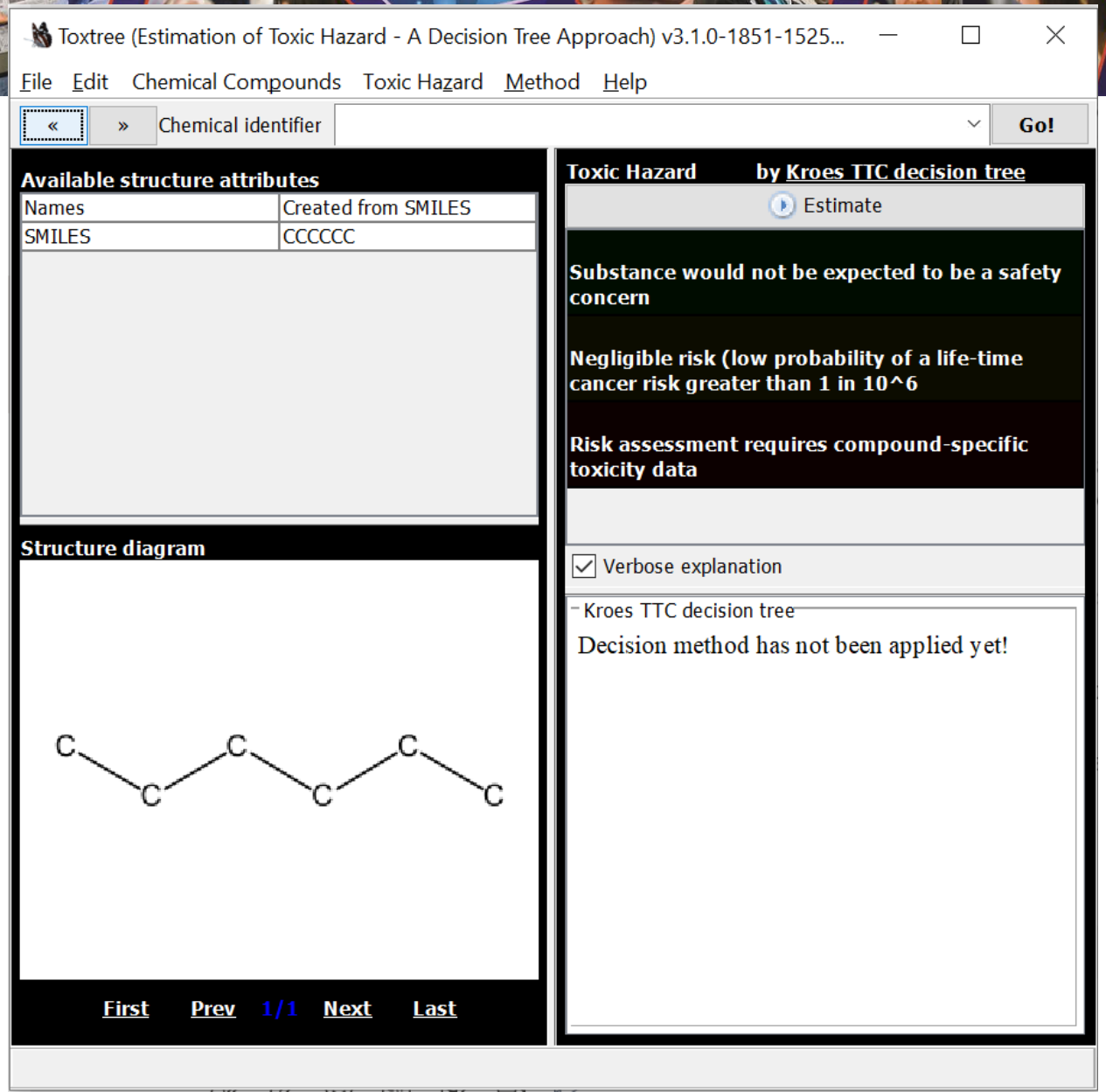
Tools to assist in TTC determinations: Toolbox



- Introduce chemical structure(s)
- Select Toxic hazard classification under the Profiling methods to produce the Cramer class assignment
- Batch processing possible

Tools to assist in TTC determinations: Toxtree

- Mimics the overall Kroes decision tree
- Introduce chemical of interest
- Introduce exposure level (required)
- Process substance through Kroes workflow to determine appropriate TTC value or whether a substance specific risk assessment is merited
- Batch processing possible if exposure is known otherwise consult Patlewicz et al (2018) for a hack!



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Why do we need fit-for-purpose TTC values?

Food and Chemical Toxicology 109 (2017) 170–193

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Thresholds of Toxicological Concern for cosmetics-related substances: New database, thresholds, and enrichment of chemical space

Chihae Yang [a,b], Susan M. Barlow [c], Kristi L. Muldoon Jacobs [d,1], Vessela Vitcheva [a,b,e], Alan R. Boobis [f], Susan P. Felter [g], Kirk B. Arvidson [d], Detlef Keller [h], Mark T.D. Cronin [i], Steven Enoch [i], Andrew Worth [j], Heli M. Hollnagel [k,*]

The original reference dataset (Munro et al., 1996) consisted of 613 organic substances representing a "range of industrial chemicals, pharmaceuticals, food substances and environmental, agricultural and consumer chemicals likely to be encountered in commerce". Although the intent was to cover a broad chemical domain, the dataset is now over 20 years old, and questions have been raised as to whether it is adequately representative of chemicals and structures used in contexts other than its original application in food (Dewhurst and Renwick, 2013).

Examples of how the representativeness of compounds in the development dataset was evaluated for compounds in a specific use class or for specific toxicological endpoints

Use classes

- Drugs/antimicrobials
- Fragrances
- Cosmetics/Botanicals
- Medical devices
- Occupational exposures
- Environmentally relevant compounds

Toxicological endpoints

- Reproductive/developmental toxicity
- Skin sensitization

References to papers providing examples of how the representativeness of compounds in the development dataset was evaluated for an application dataset are provided at the end of the presentation.

Are compounds in the development dataset representative of those in the application dataset?

Yes

- **Compounds are relevant and representative.**

No

- **Compounds are missing from the development set that are representative of those in the application dataset.**

- **Compounds are present in the development dataset that are not representative of those in the application dataset.**

Options to consider when evaluating the applicability domain of datasets used to derive TTC values

Retain existing dataset

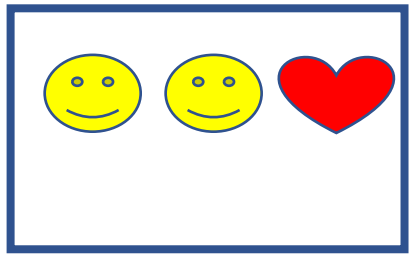
- Is the applicability domain of the existing dataset relevant for the compounds in the new dataset?
- Are the TTC values derived from an existing dataset adequately protective (or maybe overly conservative) for compounds in a new dataset?

Revise existing dataset

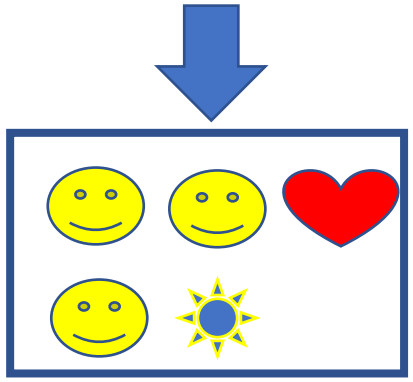
Is it necessary to modify an existing data set by:

- Adding toxicity data for new compounds?
- Removing compounds that are not relevant/out of domain?
- Completely revising the dataset?

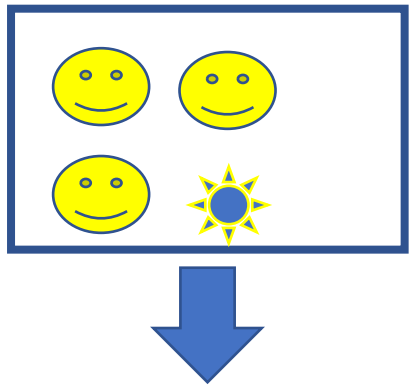
Strategies to modify dataset of toxicity values that serve as the basis for TTC values



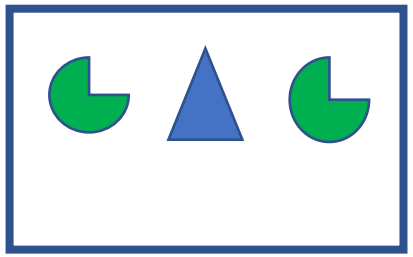
Keep existing dataset intact



Enrich dataset



Remove dissimilar compounds



Develop new dataset

Option 1: Keep dataset intact

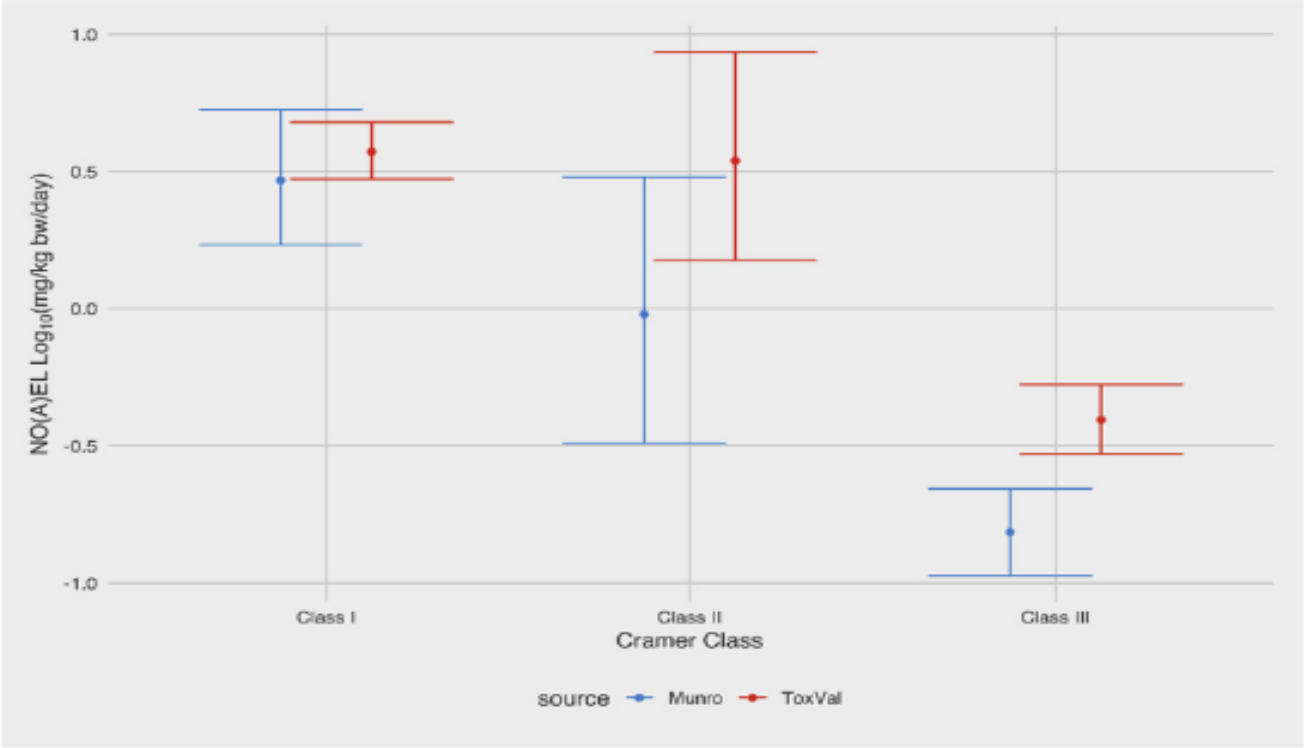
Overall, given the overlap in the 90th percentile confidence intervals with the TTC values for Classes I and III from the other databases, the Munro TTC values are interpreted as being sufficiently protective against potential health hazards over a wide range of chemical sectors. Therefore, the Munro TTC values are robust enough for use in risk assessment, including in the case of substances pertinent to food safety. (Reilly et al., 1999)

Are the existing TTC values adequately protective?

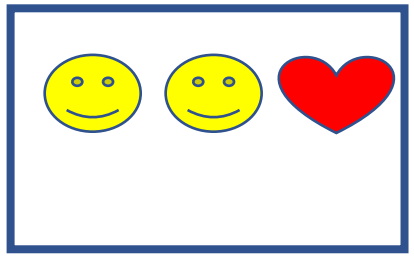
- **Compare the existing TTC values to the distribution of HBEL values in the application dataset. Evaluate whether the existing TTC values adequately protective for compounds in the application dataset.**

Option 1

- Bootstrapped the 5th percentiles to compare those from the Munro set and the ToxValDB to determine whether they were significantly different.
- The Cramer class III 5th percentiles were different, hence an enrichment analysis on the basis of structural features was informative to probe what structures in the 2 different datasets could be responsible for the differences observed in the 5th percentile.
- OPs in the Munro dataset captured in Cramer III were responsible for the differences.



Strategies to modify dataset of toxicity values that serve as the basis for TTC values



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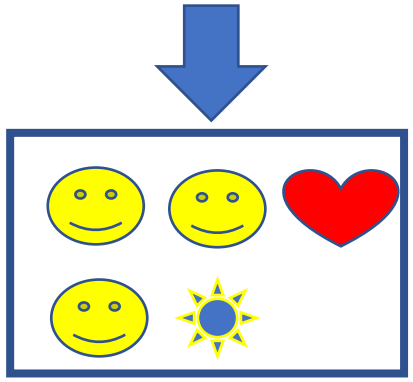

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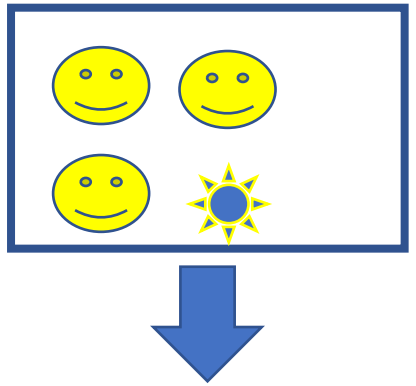
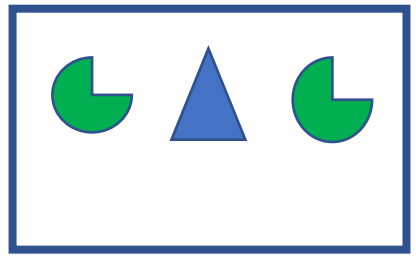


Remove dissimilar compounds



Develop new dataset

Option 2: Enrich dataset

Yang et al. (2017)

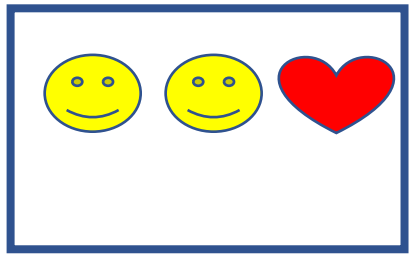
Federated set = Munro + COSMOS database

Table 10
Comparison of human exposure threshold values.[a]

Datasets (number of chemicals)	Human exposure threshold values (μg/person/day)		
	Cramer Class I	Cramer Class II	Cramer Class III
COSMOS (552)	2500	NA	470
Munro-1996[b] (613)	1800	540	90
Munro-2016 (606)	2900	640	90
Federated set (963)	2700	370	140

Enriching the Munro et al. (1996) with compounds from the COSMOS data set had little effect on resulting TTC values.

Strategies to modify dataset of toxicity values that serve as the basis for TTC values



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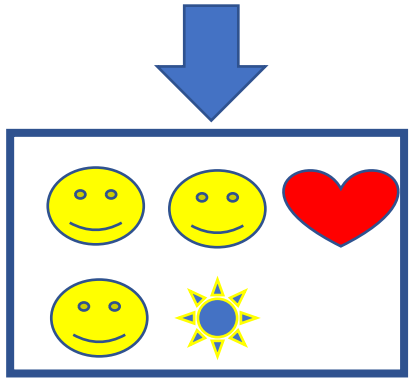

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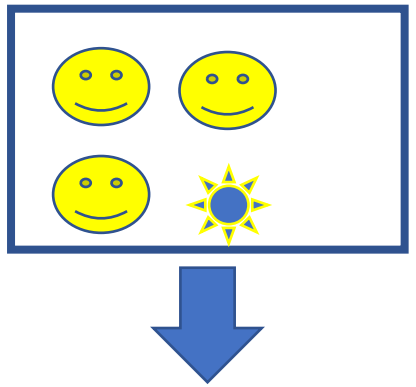

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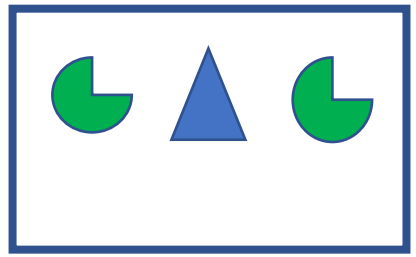


Develop new dataset

Option 3: Remove dissimilar compounds

Develop fit-for-purpose inhalation TTC value for VOCs released from respiratory devices

Started with inhalation dataset from Escher et al. (2010); used as the basis for inhalation TTC values.

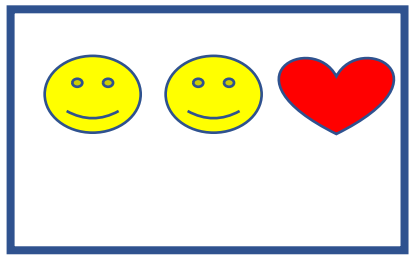
Is this dataset relevant for VOCs released from medical device polymers?

Removed nonrelevant compounds: pesticides, drugs, chemical warfare agents

Removing these compounds had a significant on the TTC based on 5th percentile of distribution of PoD values

Study	Inhalation TTC value	
	mg/m^3	µg/day
Cramer Class I (5th percentile)		
This study (Modified Escher)	0.04	800
Escher et al. (2010)[a]	0.009	180
Carthew et al. (2009)[b]		200
Cramer Class II/III (5th percentile)		
This study (Modified Escher)	0.002	40
Escher et al. (2010)[a]	0.0002	4
Carthew et al. (2009)[b]		67 (local) 170 (systemic)
ISO 18562-1		40

Strategies to modify dataset of toxicity values that serve as the basis for TTC values



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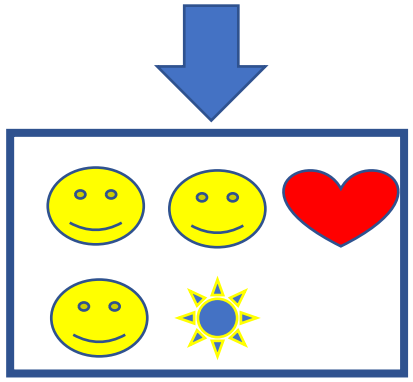

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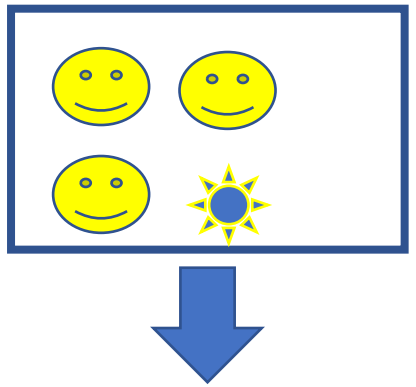

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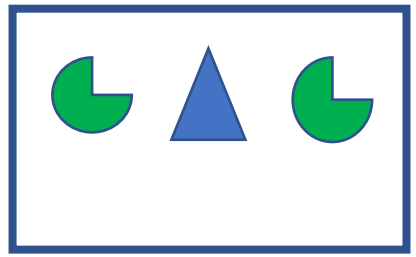


Develop new dataset

Option 4: Develop new dataset of toxicity values

Toxicology Letters 314 (2019) 117–123

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Testing the thresholds of toxicological concern values using a new database for food-related substances

Linda Reilly[a,b], Rositsa Serafimova[a], Falko Partosch[c], Ursula Gundert-Remy[d], José Cortiñas Abrahantes[a], Jean-Lou M.C. Dorne[a], George E.N. Kass[a,*]

The TTC approach has repeatedly been demonstrated to be a conservative approach to identify exposure levels below which no toxicity is expected to occur. The TTC approach has been found applicable to different chemicals subject to different applications or uses. However, there was a need to check whether the TTC approach is protective enough for the substances found in the food/feed chain. This study gathered data from EFSA's OpenFoodTox database with the aim of specifically testing the TTC application with chemicals relevant to food safety.

N = 329 compounds, 69 (21%) overlap with Munro et al. (1996) dataset

Table 4
TTC values (in μg/kg bw per day) across different databases.

	Munro database (Munro et al., 1996) *n* = 613	Munro database (Leeman et al., 2014)*	RepDose (Tluczkiewicz et al., 2011) *n* = 554	ELINCS (Kalkhof et al., 2012) *n* = 824	COSMOS (Yang et al., 2017) *n* = 552	OpenFoodTox (this paper) *n* = 329
Substances	chemicals mixed origin	chemicals mixed orrigin	chemicals mixed origin	industrial chemicals	cosmetics-related chemicals	chemicals in food and feed
Cramer Class						
I	30	30	32	25	42	17
III	1.5	4.0	1.0	13	8	1.5

*Only Class III compounds were re-analyzed.

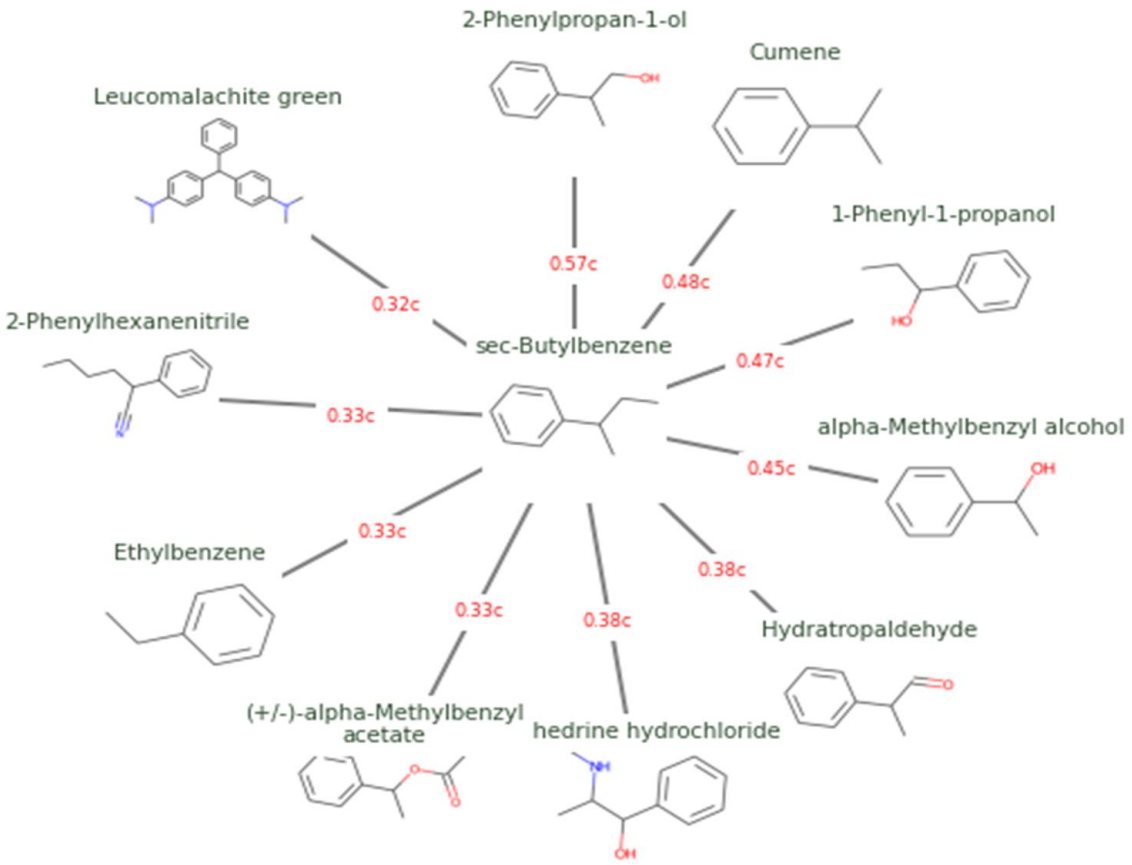
TTC values (in μg/day for a 60 kg person) across different databases

Cramer class	Munro	Munro	RepDose	ELINCS	COSMOS	OpenFoodTox
I	1800	1800	1920	1500	2520	1020
III	90	240	60	780	480	90

Option 4: Develop new dataset

- **Often not possible due to the lack of toxicity data.**
- **However, TTC like values could be potentially derived for neighbourhoods of (structurally) similar groups of compounds i.e. a read-across approach.**
- **Rather than make a specific prediction for a chemicals based on a read-across approach – take the 5th percentile of the neighbourhood to derive a conservative estimate of toxicity across the neighbourhood (pertinent given the inherent variability of the *in vivo* data typically used) and potentially effective for classes of substances that are known exclusions from the current TTC approach.**

Option 4: Develop new dataset



- **Approach could be along the lines of characterize substances by structural features/fingerprints.**
- **Determine the ‘mean’ and compute pairwise similarities relative to the central substance now designated as the ‘seed’.**
- **Derive the 5th percentile of the local neighbourhood to derive a health protective estimate of toxicity.**

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Approaches to compare the chemical and biological space of two datasets

Chemical space

- Principal Component Analysis (PCA) to visually compare chemical space
- Comparison of the relative proportion of specified structural elements in each data set (Toxprint Chemotyper)

Biological space

- Cumulative frequency distribution of toxicity values in each dataset.
- Heatmaps, linear and non-linear dimension reduction algorithms

National Toxicology Program
U.S. Department of Health and Human Services

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ICE v3.4 Release

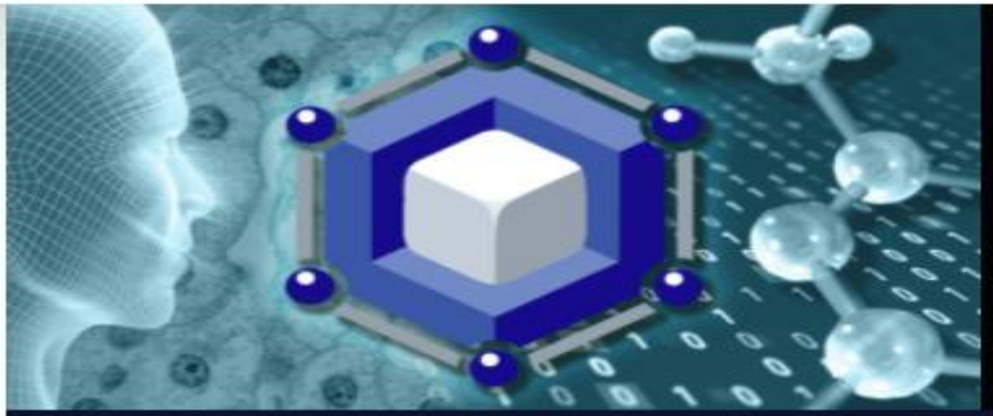
ICE updates include:

New tools and expanded capabilities:

- Chemical Quest (Beta)
- Drawing of 2D structures
- Query by multiple chemical identifiers
- Send Assays to other ICE tools

Learn about ICE updates

UPDATES



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The Chemical Characterization tool allows you to view and compare one or two chemical lists based on their physicochemical properties. Comp
along with principal component analysis plots of list against subsets of the ICE chemical inventory.

Run | Reset

List Name EPA Pesticide Active Ingredients

Select Chemicals | 1 chemical quick list selected.

Quick List CASRNs

103-90-2
107-02-8
61-82-5
84-65-1
1912-24-9
86-50-0
65-85-0
82657-04-3
10043-35-3
133-06-2
63-25-2
1563-66-2
999-81-5
76-06-2
1897-45-6
56-72-4

User Chemical Identifiers

List Name NTP Cancer Bioassay Chemicals

Select Chemicals | 1 chemical quick list selected.

Quick List CASRNs

67-66-3
143-50-0
79-01-6
71-55-6
60-51-5
952-23-8
18662-53-8
139-13-9
834-28-6
57-74-9
76-44-8
62-73-7
150-38-9
72-20-8
127-18-4
58-89-9

User Chemical Identifiers

Results

Help

Report an issue

Chemical Characterization Results

Click on the arrows to show results

> Chemical Properties Summary

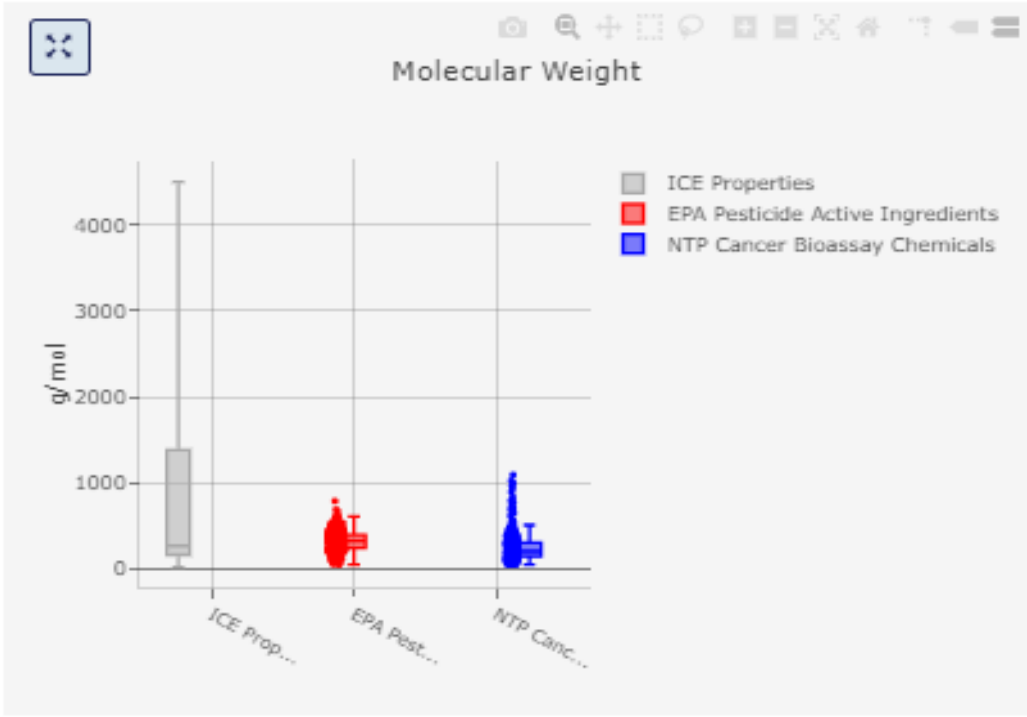
∨ Visualization of Chemical Properties

Visualization of Chemical Property Data

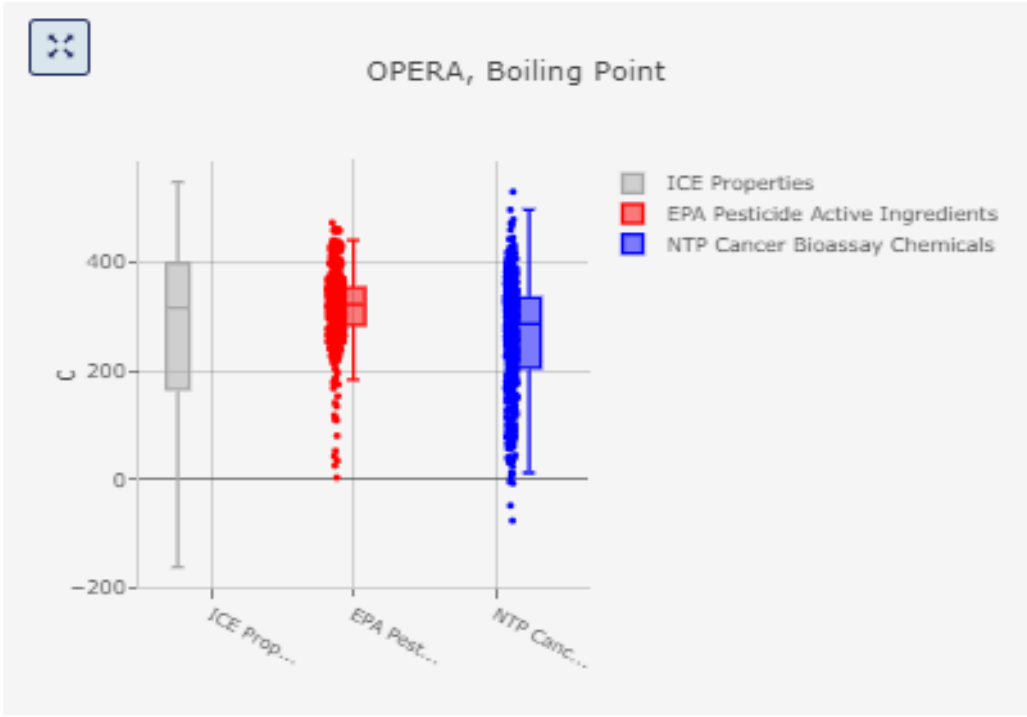
> All Chemical Identifiers Not Returned by Query (112)

Hover over graphic for interactive tools. View interactive tools user guide.

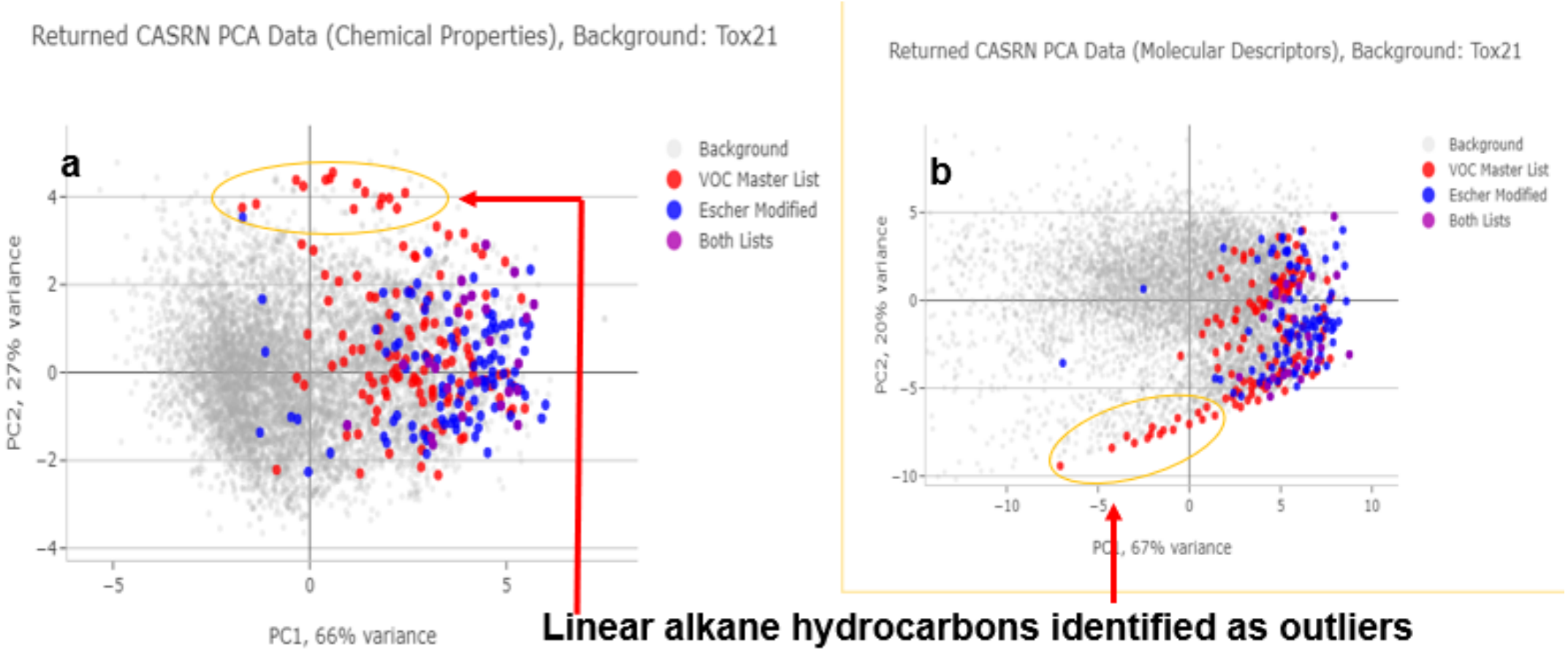
Molecular Weight



OPERA, Boiling Point



Example: Visualization of chemical space to identify outliers using NTP ICE



Comparison of datasets from VOC Master List (released from devices) and modified list from Escher et al. (2010)

Use of PCA to compare chemical space
Yang et al. (2017)

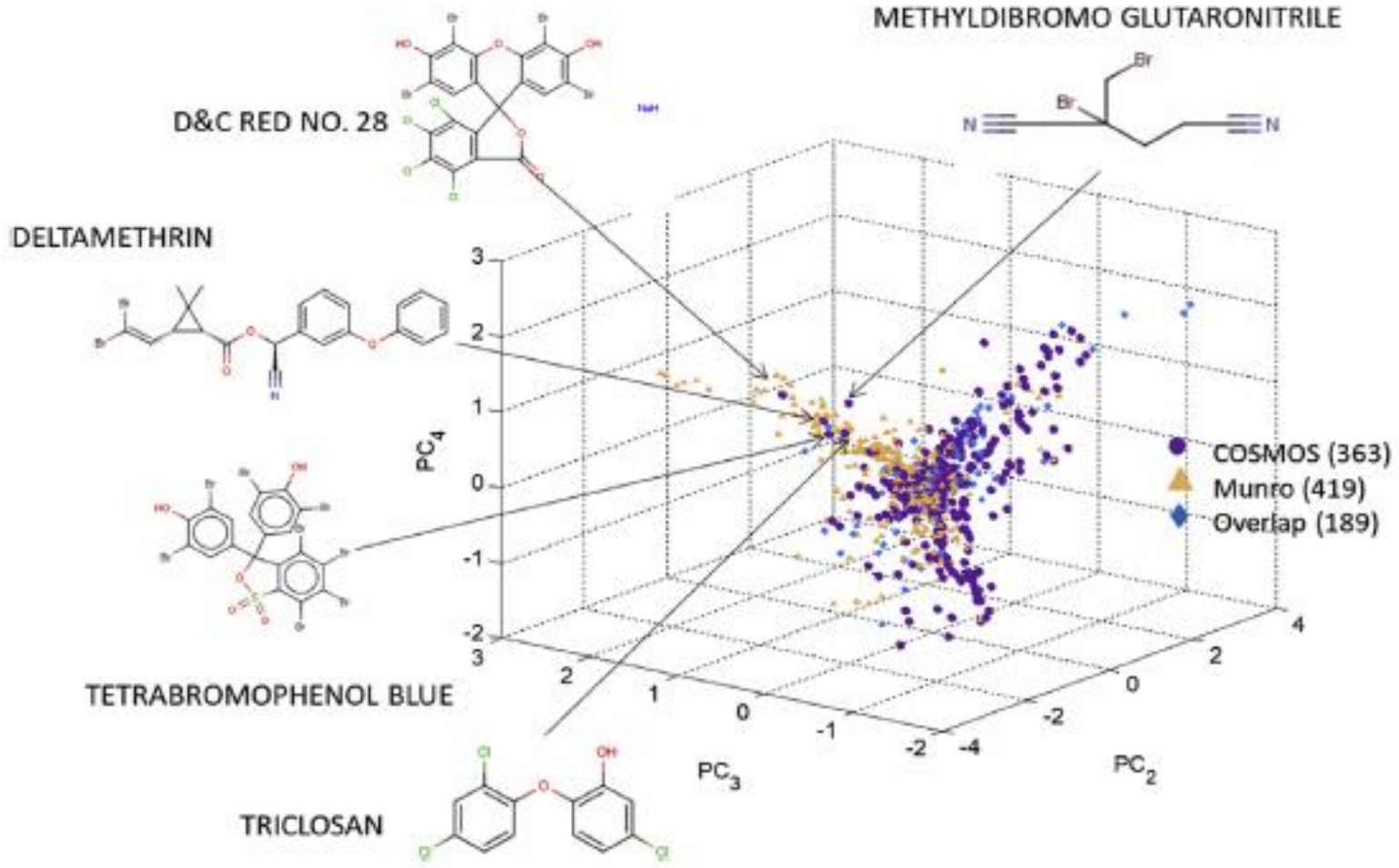


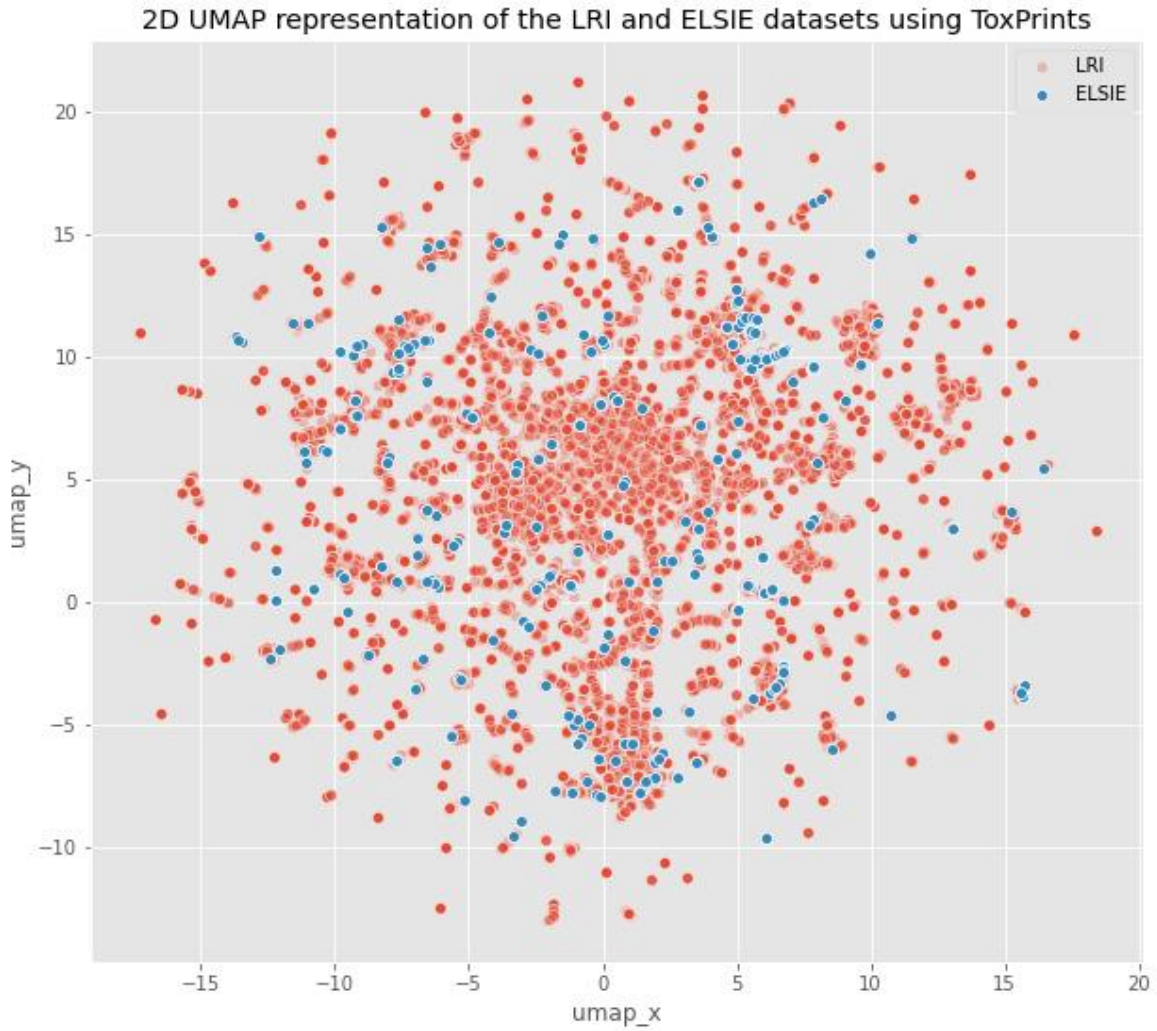
Fig. 7. Principal Component Scores projection for COSMOS and Munro TTC datasets.

Use of UMAP for compare LRI dataset with ELSIE

- LRI dataset comprised 45K substances drawn from many sources including the CERAPP list and others sourced from the EPA CompTox Chemicals Dashboard

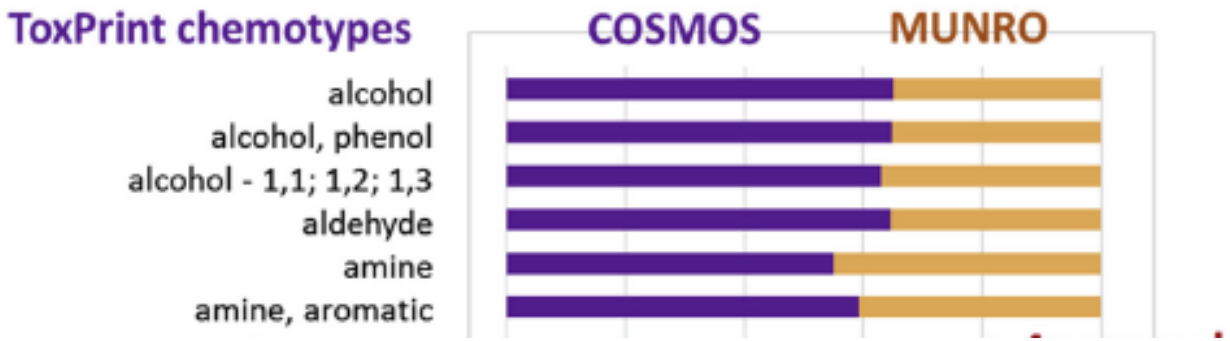
- ELSIE Extractables Leachables Substances Information Exchange

- Both sets of chemicals characterized by ToxPrint fingerprints and projected into 2D using UMAP (Uniform Manifold Approximation and Projection)

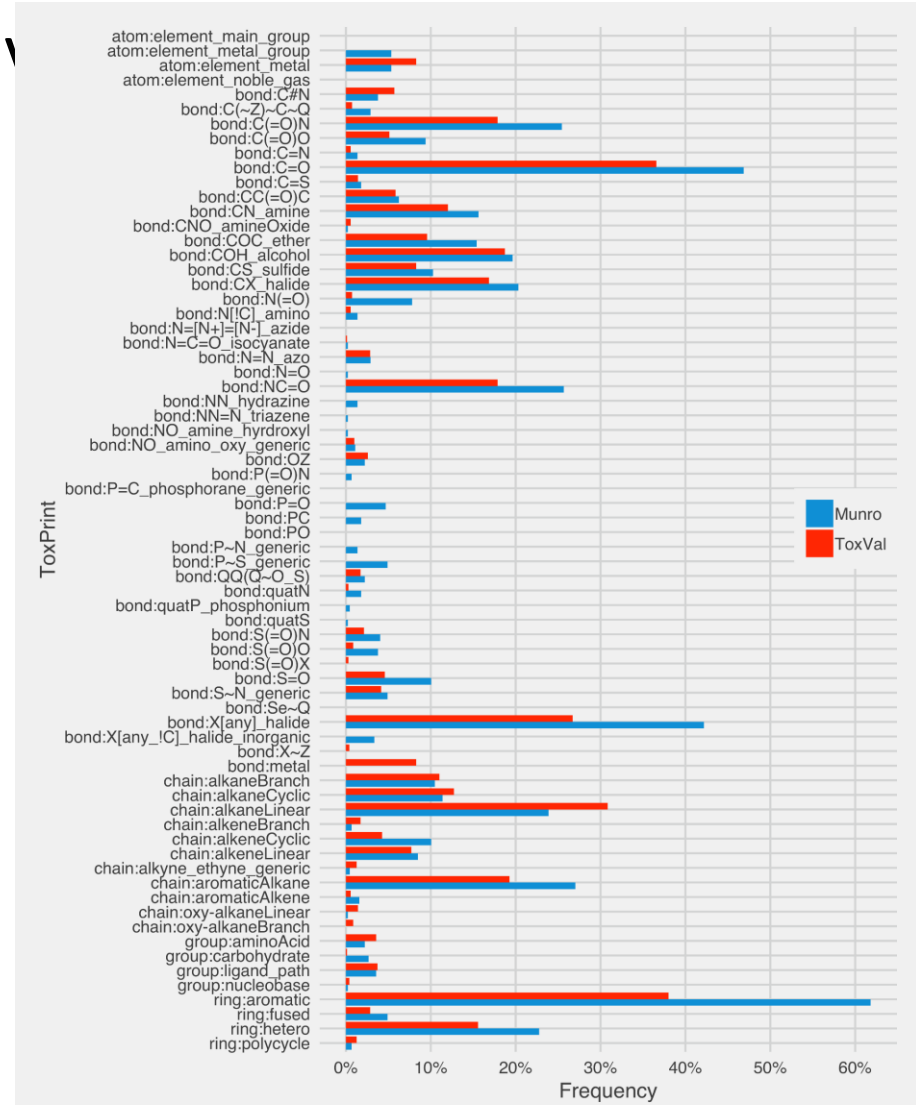


Approaches to compare the chemical space

Use Toxprint Chemotyper to identify relati
groups



Yang et al. (2017)



Nelms et al. (2019)

Approaches to compare the chemical and biological space of two datasets

Chemical space

- Principal Component Analysis (PCA) to visually compare chemical space
- Comparison of the relative proportion of specified structural elements in each data set (Toxprint Chemotyper)

Biological space

- Cumulative frequency distribution of toxicity values in each dataset.
- Heatmaps, linear and non-linear dimension reduction algorithms

Characterization of potency differences between datasets Nelms et al. (2019)

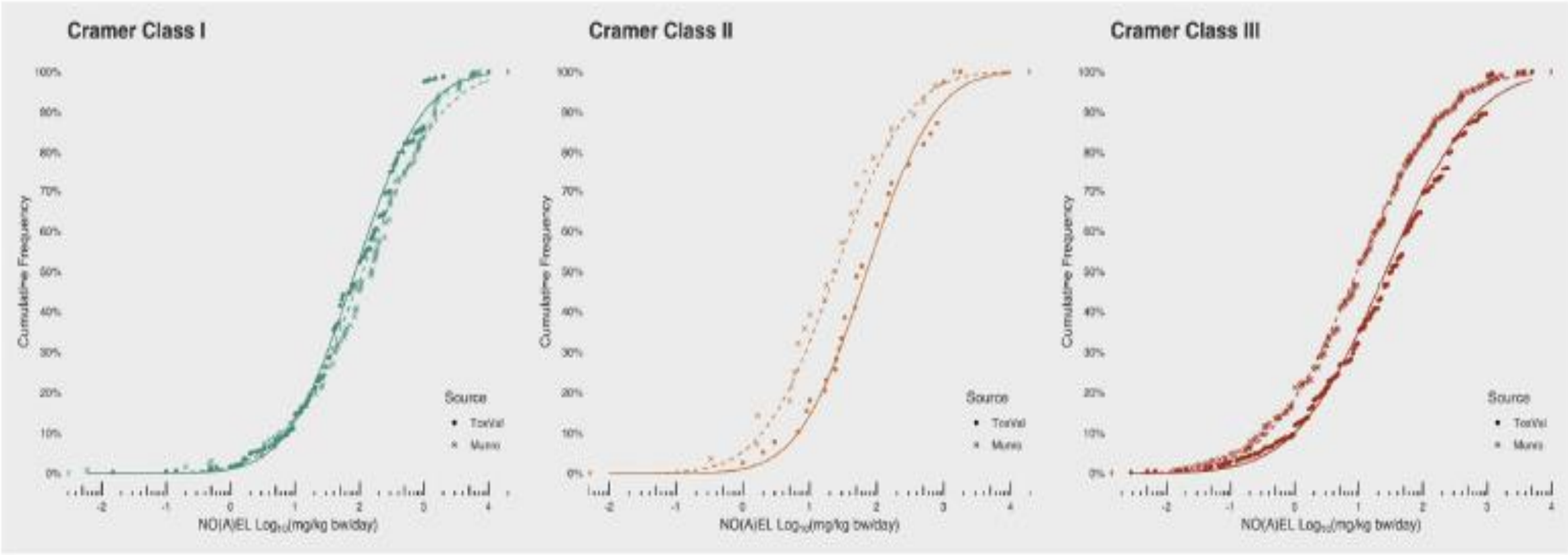
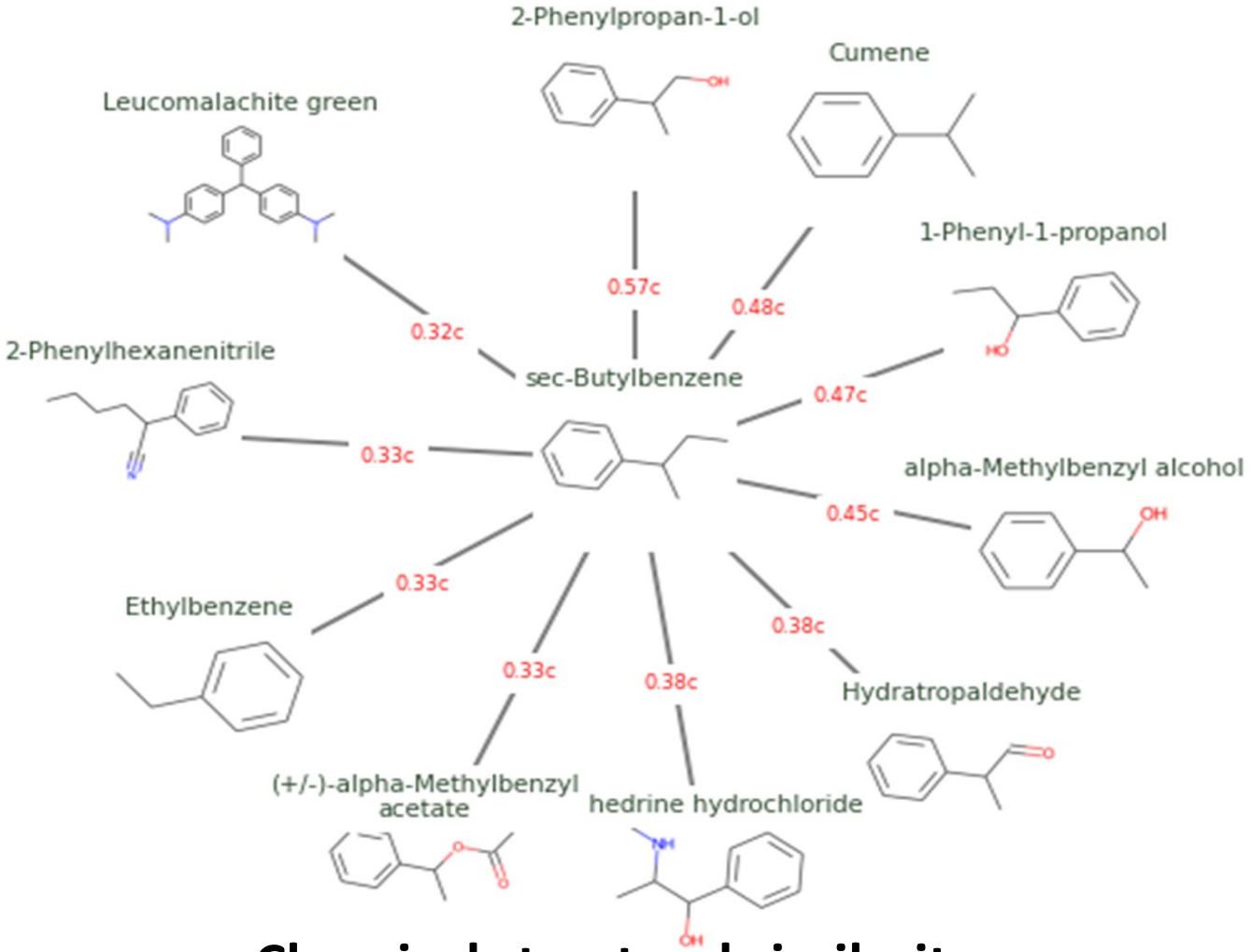
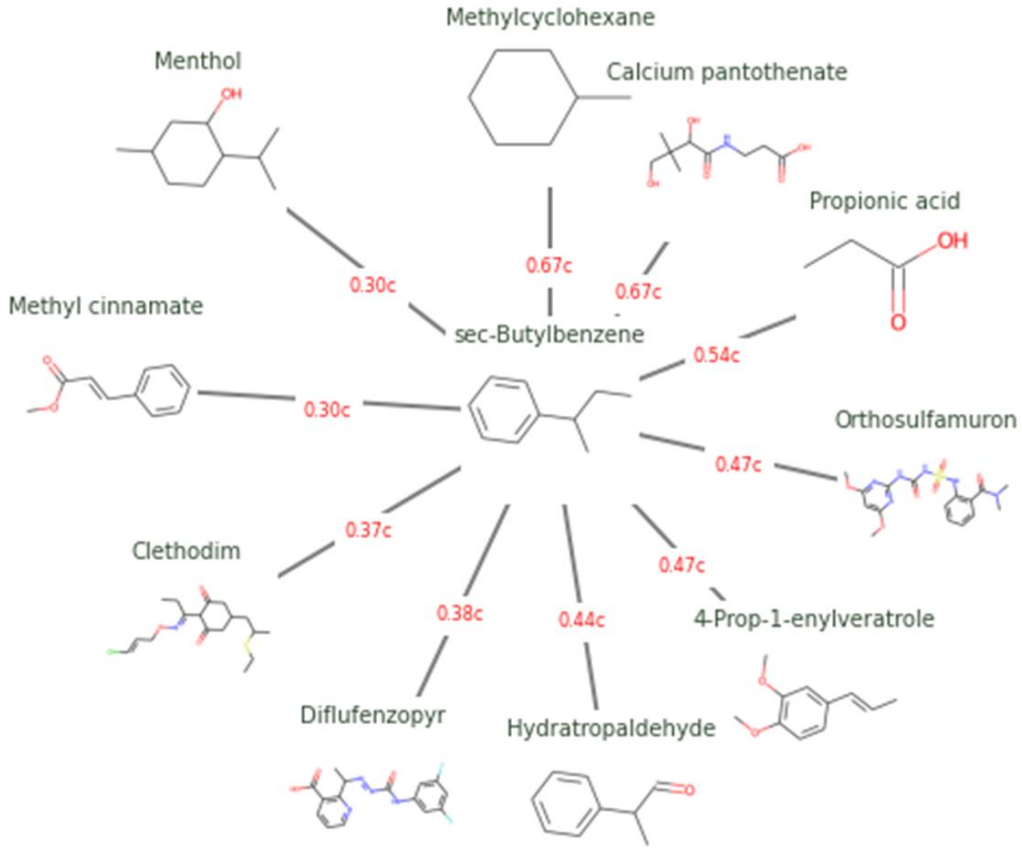


Fig. 2. Comparison of the cumulative and fitted lognormal distributions for the ToxValDB and Munro NO(A)EL data for each Cramer class. The ToxValDB and Munro Cramer class I and II distributions were not significantly different ($p > 0.05$). Meanwhile, the Cramer class III distributions were significantly different between the two datasets ($p < 0.05$).

How do neighbourhoods change depending on similarity context?



Chemical structural similarity



Biological activity similarity

Overview

- Brief history of the TTC concept
- Examples of deriving of fit-for-purpose TTC values
- Comparing the chemical/biological space of two datasets
- Summary, next steps and vision for the future

Summary

- **The TTC approach is a practical means to screen/prioritize compounds for toxicity evaluation and, in some cases, to provide default HBEL values for data-poor compounds.**

- **The values are intentionally conservative and are intended to be protective for compounds in a wide range of use and structural classes, with the exception of excluded Cohort of Concern compounds. Therefore, the TTC values in common use can be considered to be "one-size fits all".**

- **However, the need may exist to develop "fit-for-purpose" TTC values that are chemically and biologically representative of compounds in specific use or structural classes.**

Summary

- Determining whether compounds used to derive TTC values are representative of those in an application dataset is aided by a comparison of the chemical and biological space of compounds in each dataset.

- Tools and approaches are available to compare the chemical and biological space of different datasets of toxicity values:
  - Chemical space: PCA, comparison of structural alerts
  - Biological space: Dimensionality reduction techniques, clustering, heatmaps, ECDFs

Ongoing and future work

- Broadening the scope of the Cramer structural classes – FDA's work on the Extended Decision Tree
- TTC-like approach to read-across for neighbourhoods of chemicals characterized by their similarity (chemical and/or bioactivity)
- Chemoinformatic approaches to subcategorise substances for TTC rather than necessarily relying on the rulebase systems such as the Cramer decision tree
- TTC on the basis of NAM data in lieu of traditional toxicity data e.g. Paul Friedman et al (2020) Utility of in vitro Bioactivity as a Lower Bound Estimate of in vivo adverse effect levels and in risk-based prioritization
- Examples of ongoing work is showcased in this special issue: https://www.frontiersin.org/research-topics/13793/advances-and-refinements-in-the-development-and-application-of-threshold-of-toxicological-concern-tt#articles

References: Historical perspective

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- Cramer et al. (1978) https://pubmed.ncbi.nlm.nih.gov/357272/
- Hartung et al. (2017) https://pubmed.ncbi.nlm.nih.gov/28735337/
- Kroes et al. (2004) https://pubmed.ncbi.nlm.nih.gov/14630131/
- Munro et al. (1996) https://pubmed.ncbi.nlm.nih.gov/8972878/

References: TTC values for specific use/exposure categories

Environmentally relevant compounds

- Nelms et al. https://pubmed.ncbi.nlm.nih.gov/31639428/

Cosmetics

- Yang et al. https://pubmed.ncbi.nlm.nih.gov/28867342/
- Kroes et al. https://pubmed.ncbi.nlm.nih.gov/17664037/
- Bury et al. https://pubmed.ncbi.nlm.nih.gov/34023455/

Botanicals

- Mahony et al. https://pubmed.ncbi.nlm.nih.gov/32058013/
- Re et al. https://pubmed.ncbi.nlm.nih.gov/19249334/

References: TTC values for specific use/exposure categories

Drugs/Antimicrobials

- Stanard et al. https://pubmed.ncbi.nlm.nih.gov/26025210/
- Bercu et al. https://pubmed.ncbi.nlm.nih.gov/22732128/
- Yang et al. https://pubmed.ncbi.nlm.nih.gov/32640338/

Fragrances

- Patel et al. https://pubmed.ncbi.nlm.nih.gov/32603678/

Food related compounds

- Reilly et al. https://pubmed.ncbi.nlm.nih.gov/31325634/

References: TTC values for specific routes of exposure

Inhalation

- Nelms and Patlewicz (2020)

https://www.frontiersin.org/articles/10.3389/ftox.2020.580347/full

- Escher et al. https://pubmed.ncbi.nlm.nih.gov/20600457/
- Tluckiewicz et al. https://pubmed.ncbi.nlm.nih.gov/27041393/

Internal/Systemic

- Partosch et al. https://pubmed.ncbi.nlm.nih.gov/24915937/
- Ellison et al. https://pubmed.ncbi.nlm.nih.gov/30653989/

References: TTC values for specific toxicity endpoints

Reproductive/developmental toxicity

- Lauferswiler et al. https://pubmed.ncbi.nlm.nih.gov/22019814/
- Van Ravenzwaay et al. https://pubmed.ncbi.nlm.nih.gov/22705707/

Skin sensitization

- Safford https://pubmed.ncbi.nlm.nih.gov/18406502/
- Safford et al https://pubmed.ncbi.nlm.nih.gov/25934255/
- Roberts et al. https://pubmed.ncbi.nlm.nih.gov/25765509/