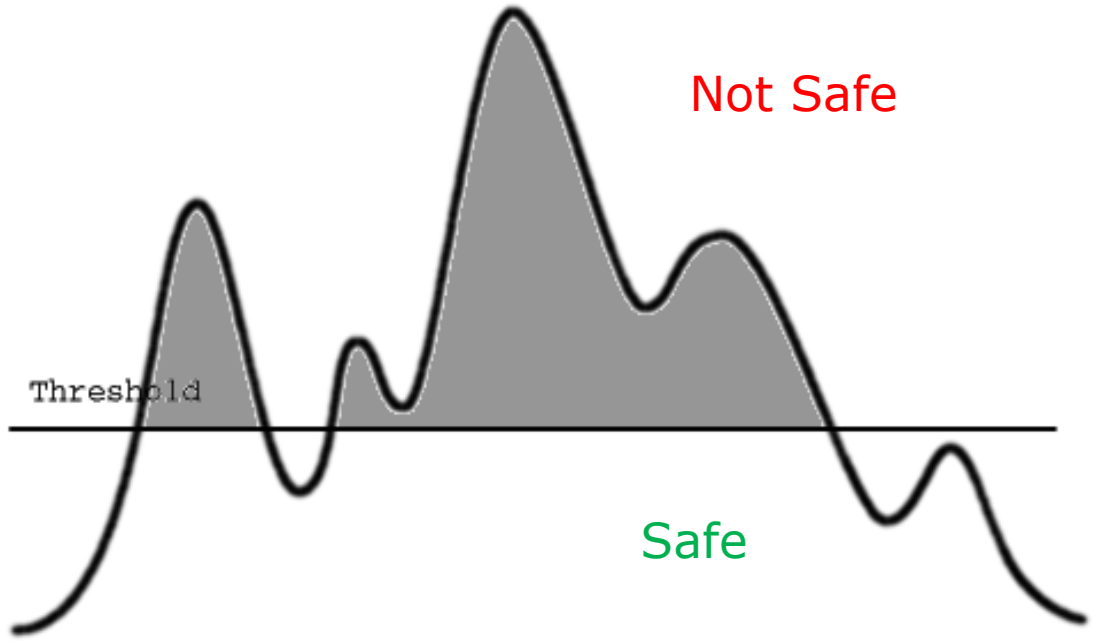
Using the Threshold of Toxicological Concern as an exposure-based waiving approach

On utilizing the existing animal data



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Recalibrating the existing inhalation TTC datasets to develop refined strategies for inhalation safety evaluation

Api AM[1], Patlewicz G[2], Rose J[3], Sadekar N[1]

[1]RIFM

[2]US EPA

[3]Procter & Gamble

Presentation Agenda

General Introduction to TTC

Introduction to Inhalation TTC

Case Study For the Application of Inhalation TTC

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Making the best use of existing animal data

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Brief History of TTC

- **Two main tiers of TTC**: Genetox/Cancer tier and non-cancer tiers
- **Genetox/Cancer TTC** based on a predicted tumor risk of 1 in a million derived through an analysis of cancer potency data
- **For non-cancer tiers**, Munro et al (1996) evaluated a large database of ~600 chemicals distributed into 3 Cramer classes and revealed how structural class has an important bearing on toxicological potency.
- Kroes et al. (2004) presented a tiered TTC approach that established several human exposure thresholds over four orders of magnitude, ranging from 0.15 µg/d to 1800 µg/d.
- These thresholds were established for **lifetime exposures** by the **oral route**.

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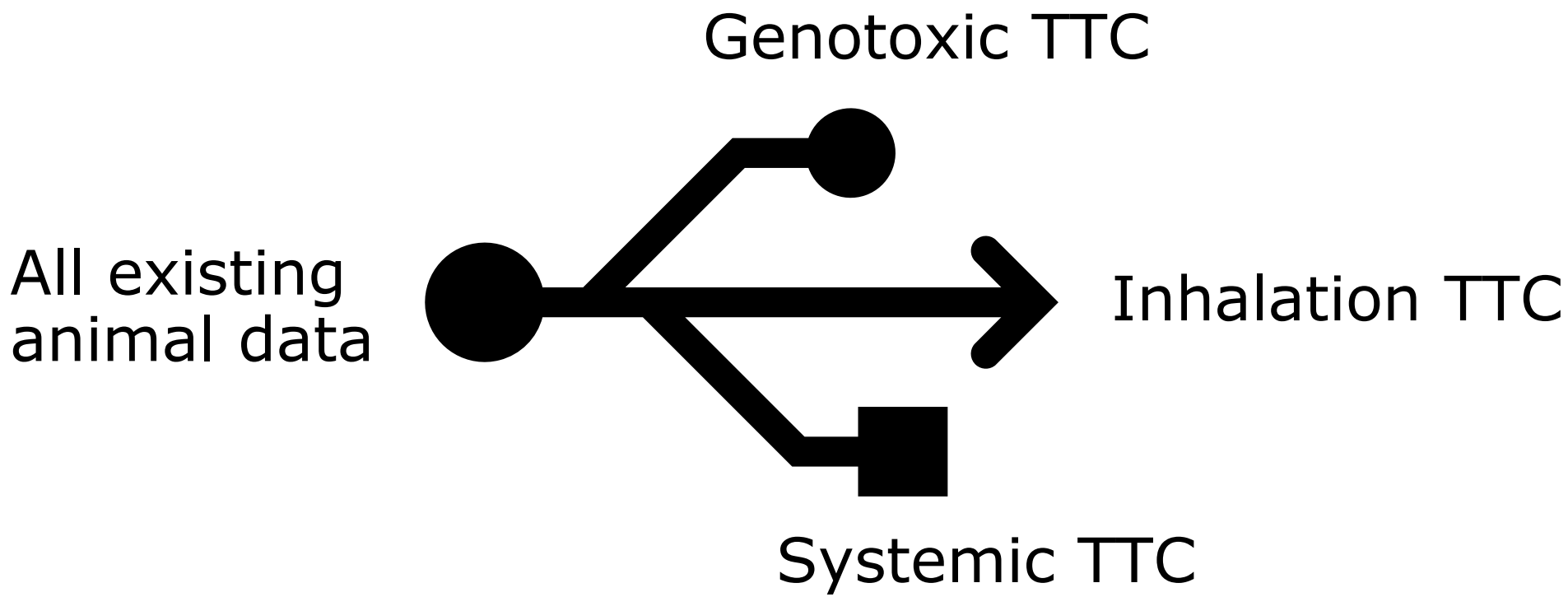
Application of TTC in chemical risk assessment



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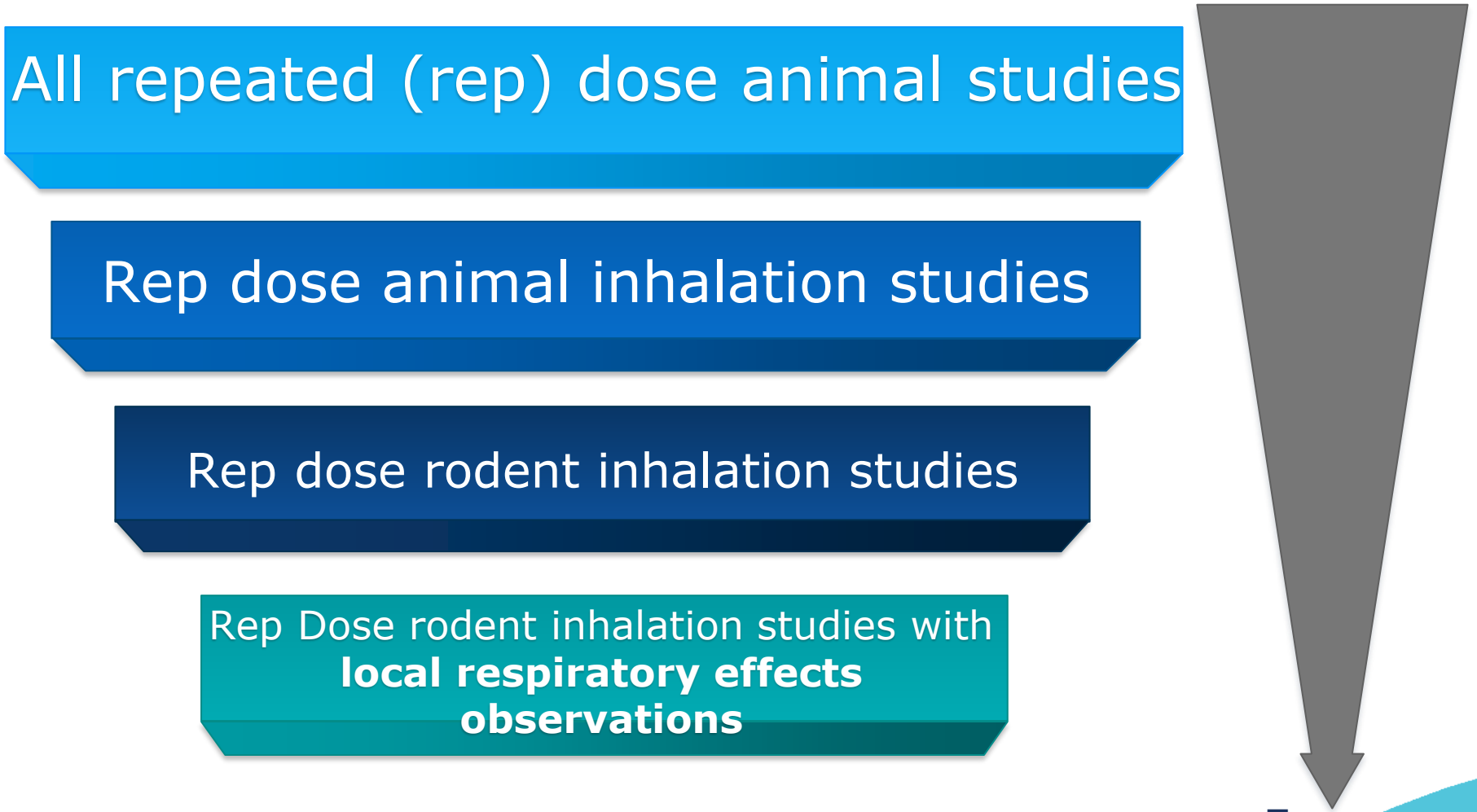
Compared to the oral database, the pool of available repeated dose inhalation exposure studies is scarce



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Use of TTC helps **overcome the challenge of local respiratory effects safety assessment** from inhalation exposures

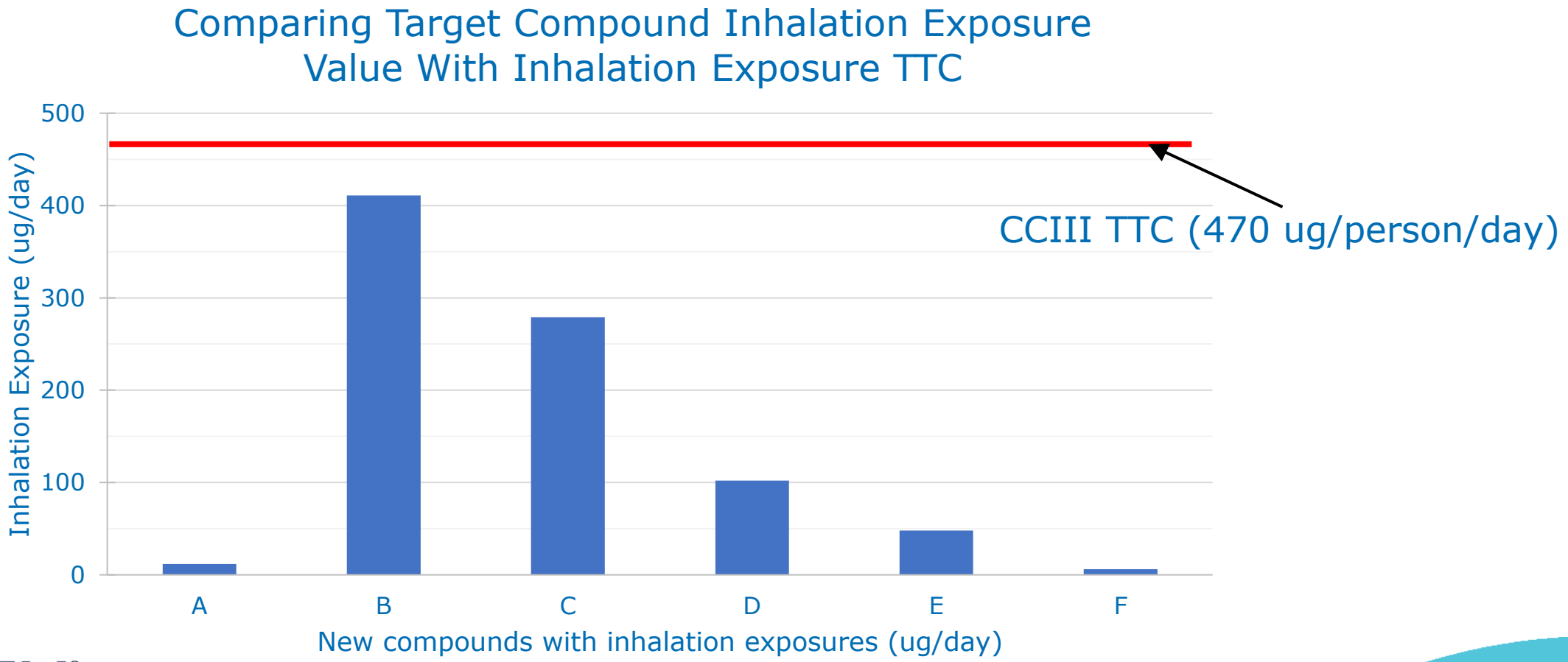

Figure example for illustration purpose only

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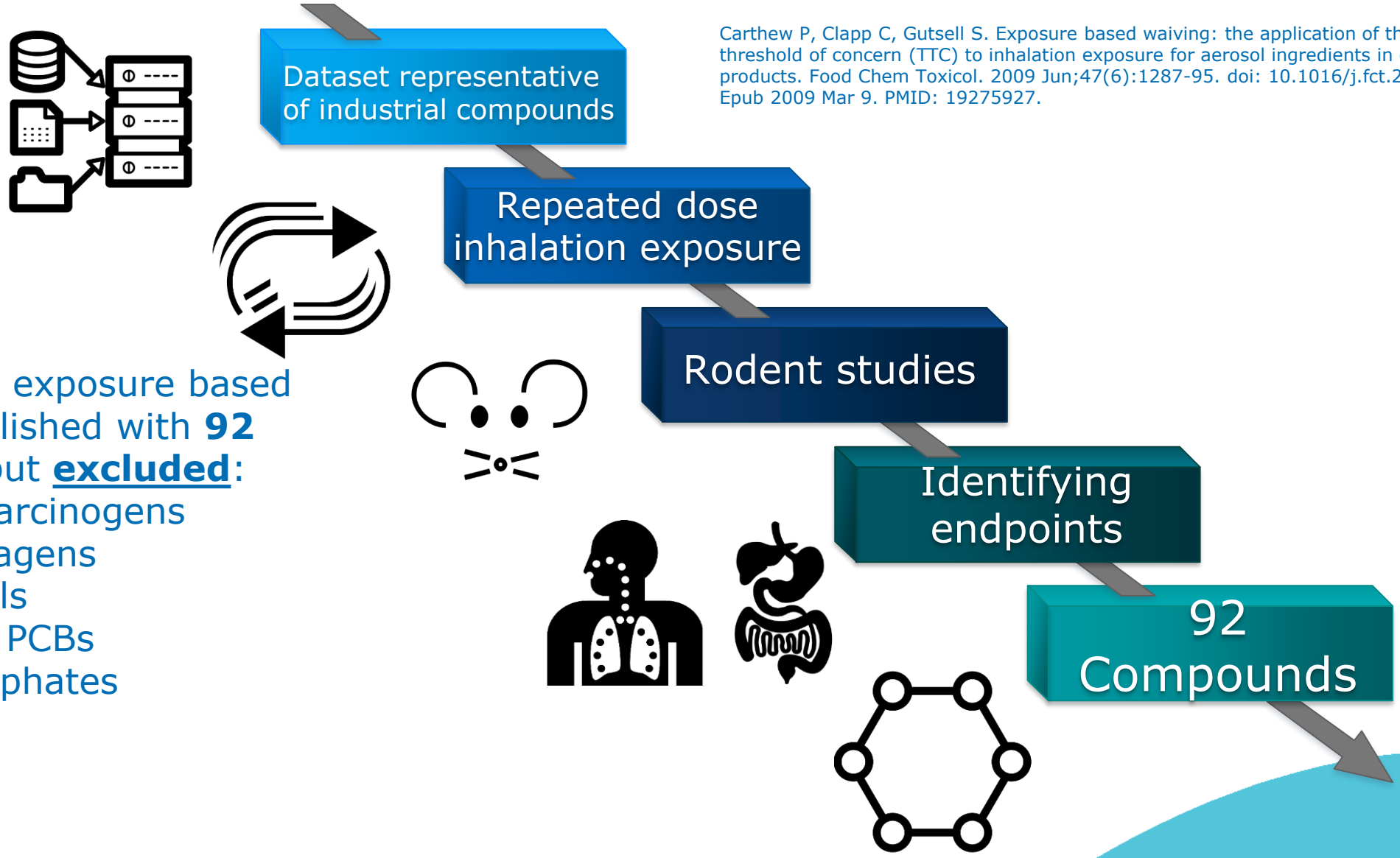
Carthew et al. 2009- Derivation of Inhalation TTC based on **systemic** & **portal of entry effects** from inhalation studies



Carthew P, Clapp C, Gutsell S. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem Toxicol. 2009 Jun;47(6):1287-95. doi: 10.1016/j.fct.2009.02.024. Epub 2009 Mar 9. PMID: 19275927.

This inhalation exposure based TTC was established with **92 compounds** but **excluded**:

- Genotoxic carcinogens
- In vivo mutagens
- Heavy metals
- Dioxins and PCBs
- Organophosphates
- Polymers

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Carthew used the **Cramer Decision Tree** to classify chemicals in the dataset

Of the 92 total chemicals:

- 40% (38 chemicals) Cramer Class I
- 54% (50 chemicals) Cramer Class III
- Four chemicals in Cramer Class II

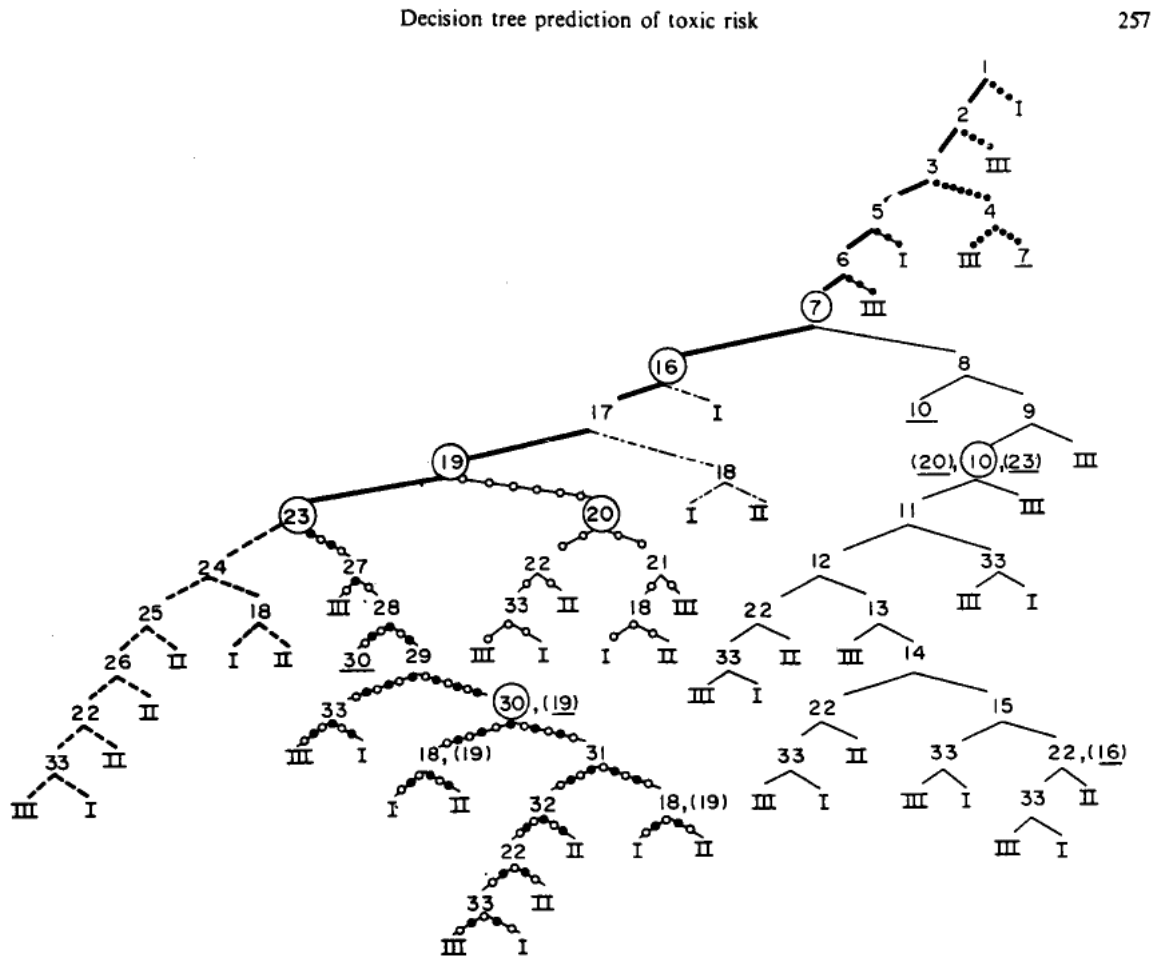

Fig. 1. A schematic diagram of a decision tree for the estimation of probable toxicity. Assessors should (a) start with question 1, (b) proceed by 'no' ↙ or ↘ 'yes', (c) move from any underscored number encountered to same circled number and (d) proceed to final classes I, II or III. Working downwards 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 (– – –).

https://doi.org/10.1016/S0015-6264(76)80522-6

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TTC thresholds identified by Carthew et al. to **assess local and systemic effects from inhalation exposure**

Effect Type	Cramer Class	Number of compounds per Cramer Class	TTC (ug/person/day)
Local (n=92)	**1**	**38**	**1400**
	2	**4**	
	3	**50**	**470**
Systemic (n=92)	1	38	980
	2	4	
	3	50	170

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Carthew et al. built a **conservative yet practical dataset**

- **Pentafluoroethane**

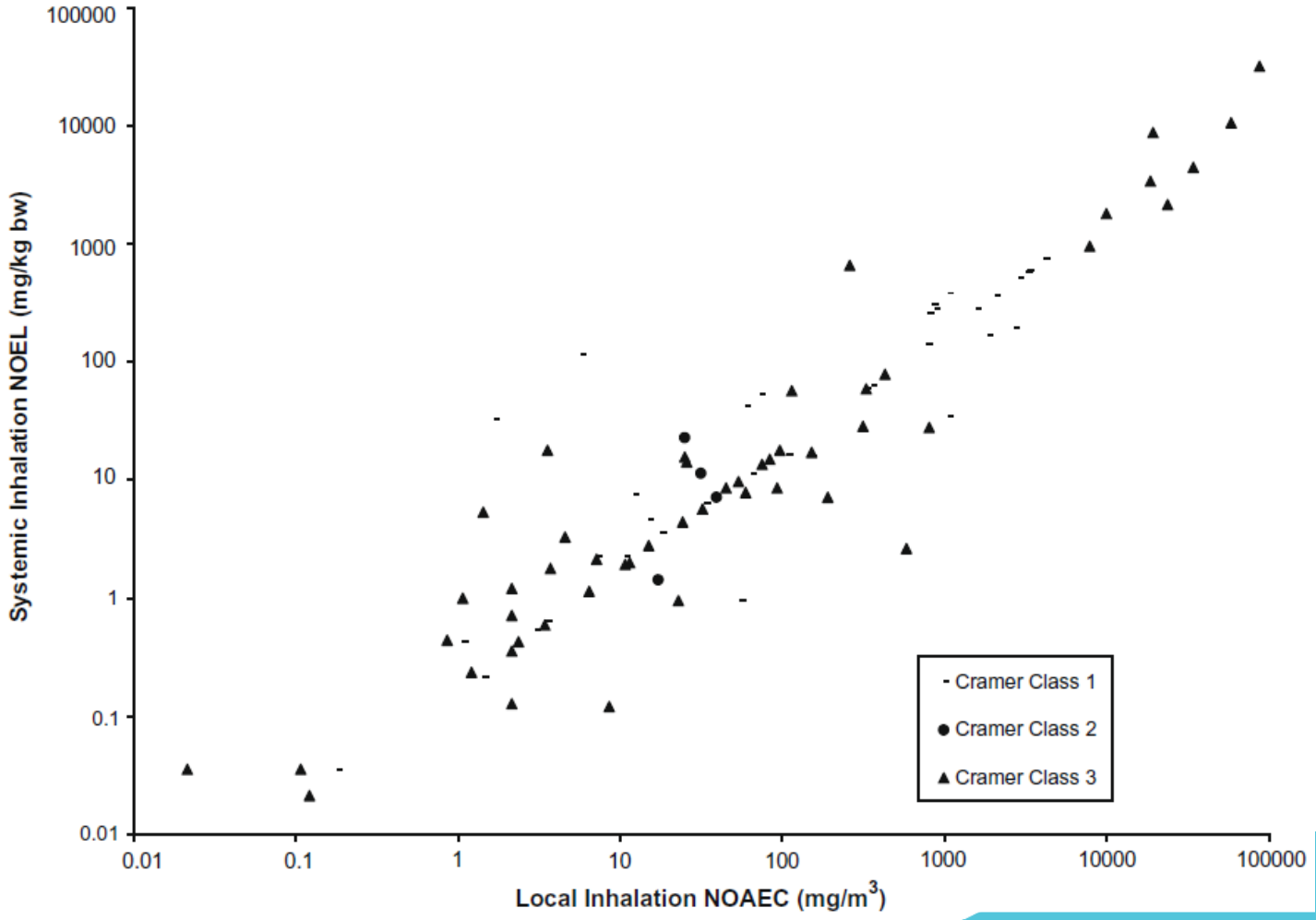
Local NOAEC – 87,500 mg/m3

Systemic NOAEC – 31,800 mg/kg/day

- **Hydrogen peroxide**

Local NOAEC – 0.9 mg/m3

Systemic NOAEC – 0.4 mg/kg/day



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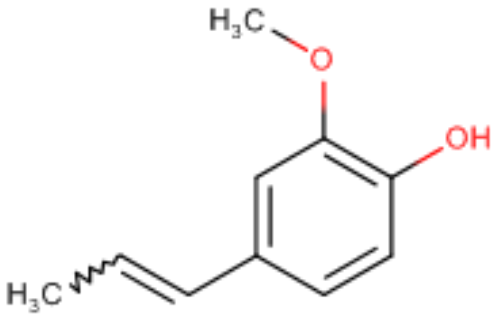
Case study example for exposure based waiving approach: **Isoeugenol**



Chronic Aggregate Inhalation Exposure = 0.005 mg/person/day
Cramer Class = 1
Corresponding TTC limit = 1.4 mg/person/day
Margin of Safety = 280

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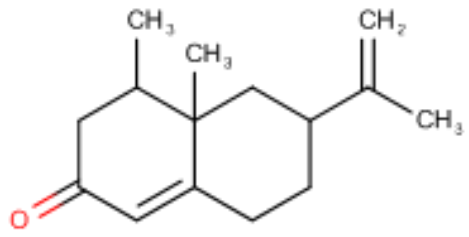
Case study example for exposure based waiving approach: **Nootkatone**



Chronic Aggregate Inhalation Exposure = 0.0003 mg/person/day
Cramer Class = 2
Corresponding TTC limit = 0.47 mg/person/day (Cramer 3 Threshold)
Margin of Safety = 1567

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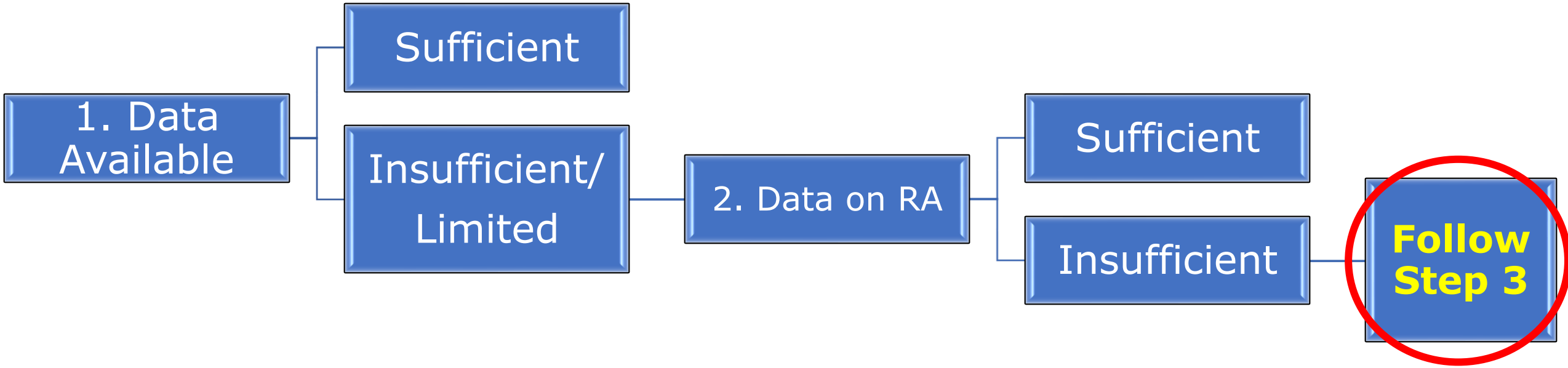
Exposure based waiving approach is Step 3 of the RIFM safety assessment process



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RIFM is working on **advancing the science for inhalation TTC** similar to the efforts in the area of oral TTC

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Food and Chemical Toxicology

Volume 109, Part 1, November 2017, Pages 170-193

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]

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Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Bolstering the existing database supporting the non-cancer Threshold of Toxicological Concern values with toxicity data on fragrance-related materials

Atish Patel [a,1], Kaushal Joshi [a], Jane Rose [b], Michael Laufersweiler [b], Susan P. Felter [b], Anne Marie Api [a,*]

[a] Research Institute for Fragrance Materials, Inc., Woodcliff Lake, NJ, USA
[b] Procter & Gamble, Mason, OH, USA

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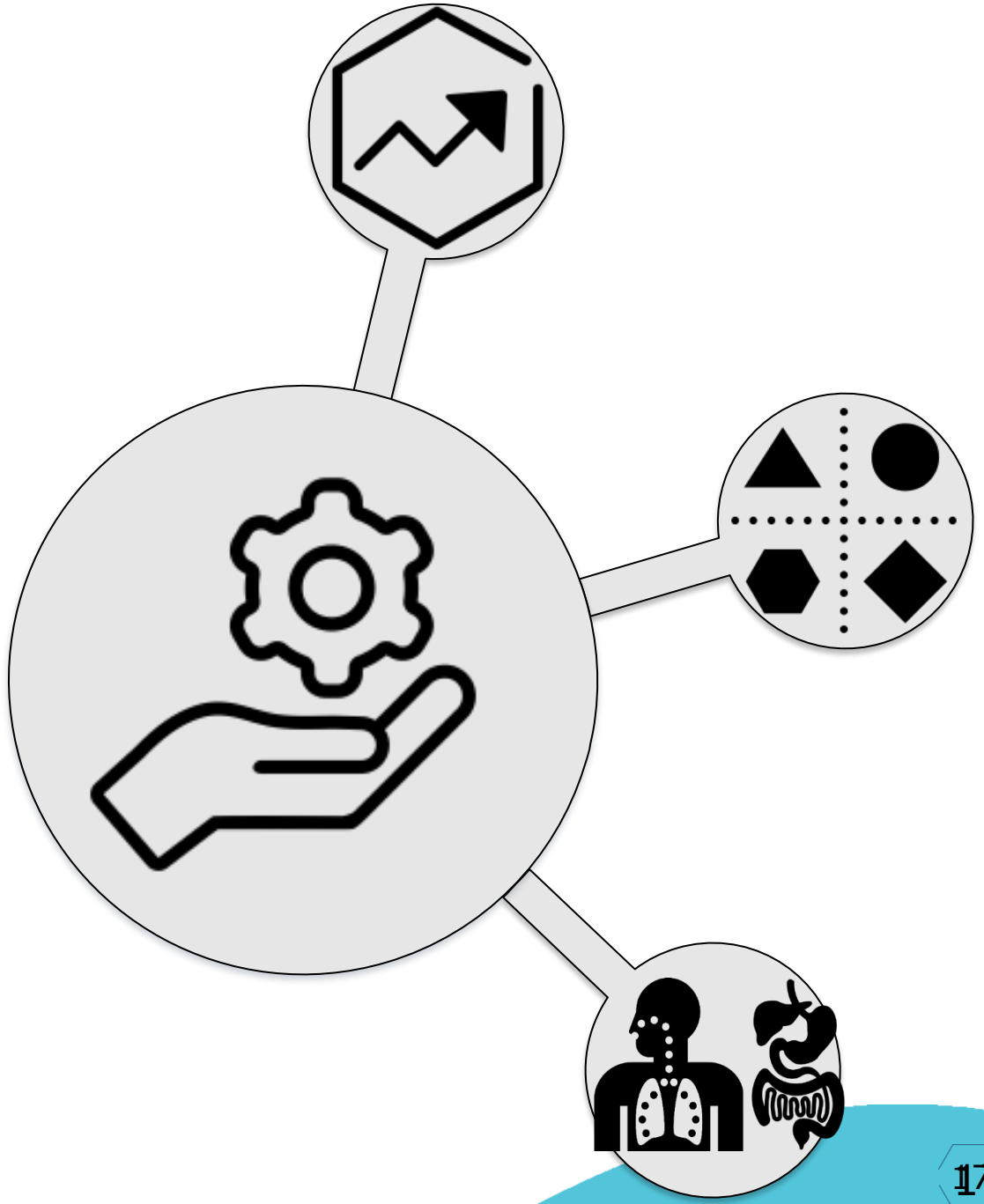
The project was planned to bolster the Carthew et al. 2009 approach for inhalation TTC



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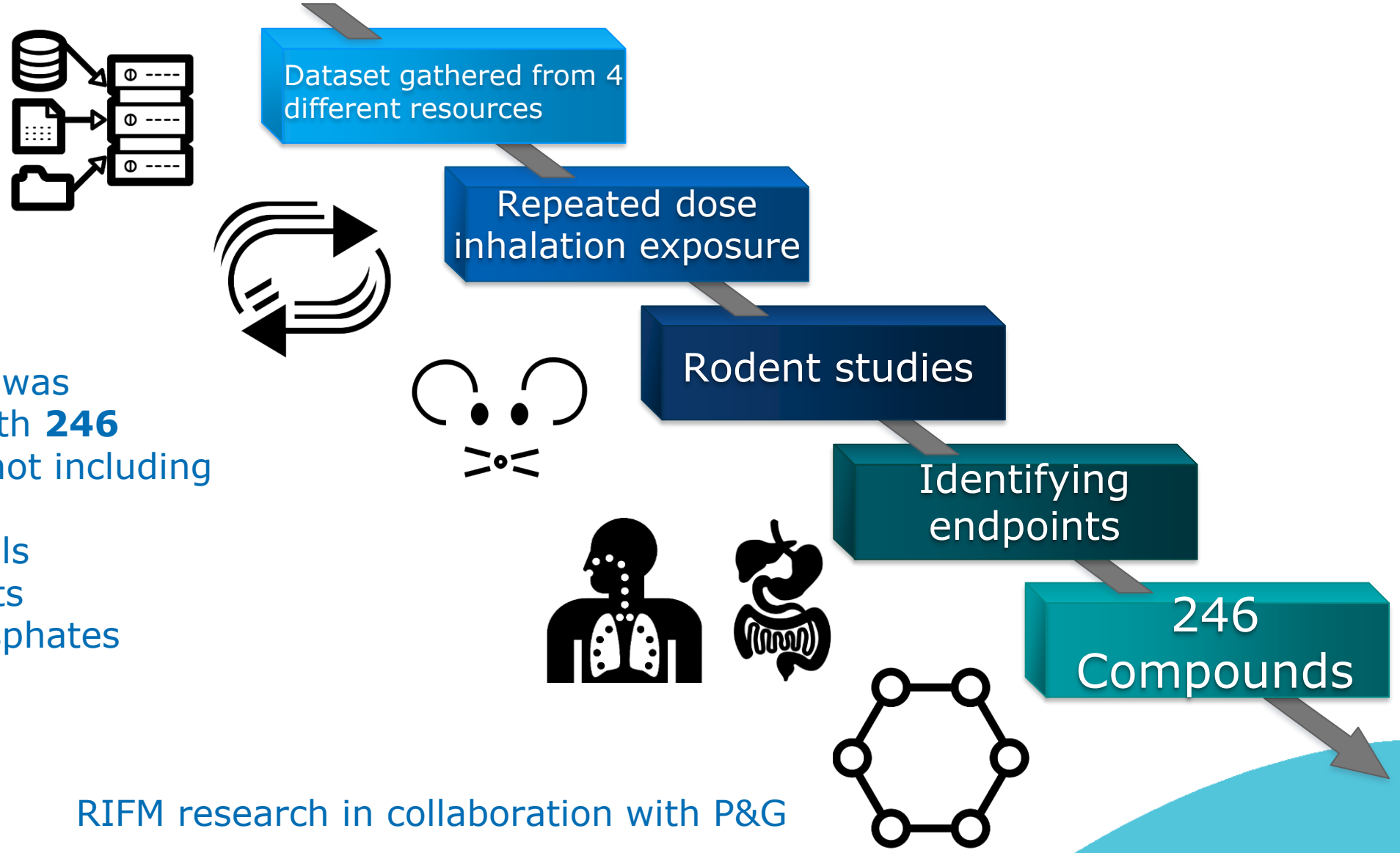
Broad Goal project for Inhalation TTC has **increased the dataset 2+ times** that of Carthew's

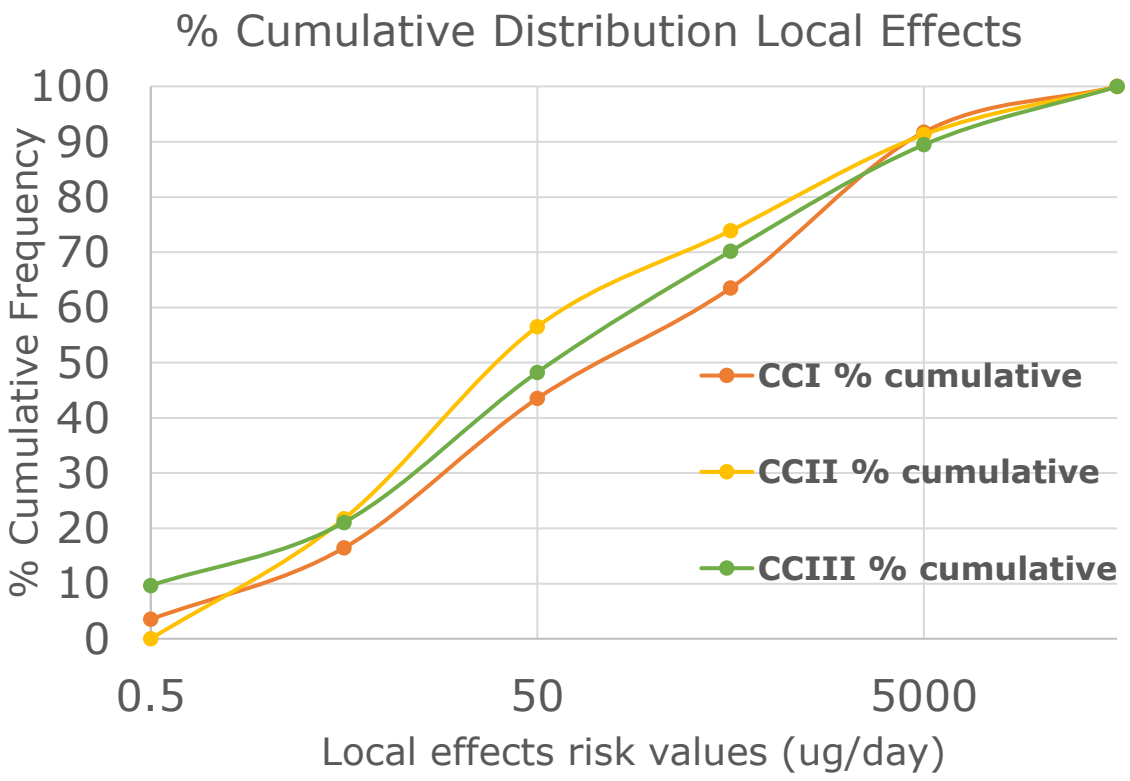


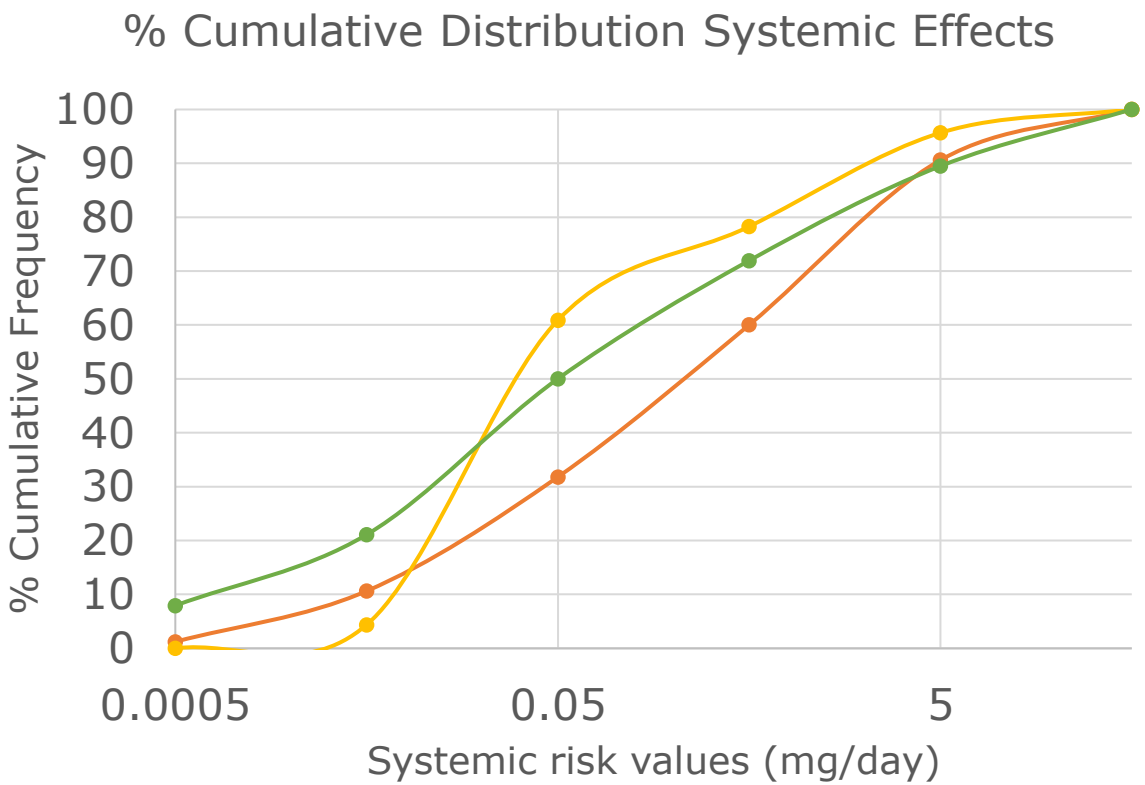
The inventory was established with **246 compounds** not including

- Genotoxic
- Heavy metals
- Nerve agents
- Organophosphates

RIFM research in collaboration with P&G

There is a clear distinction between CCI and CCIII material local and systemic effect values





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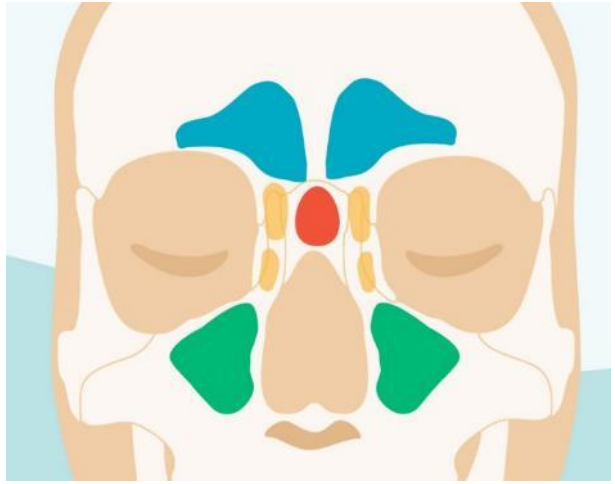
Materials were also categorized based on **site-specific effects**

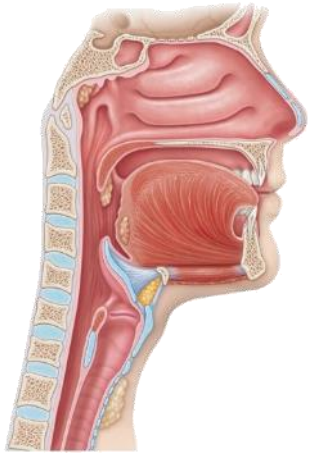


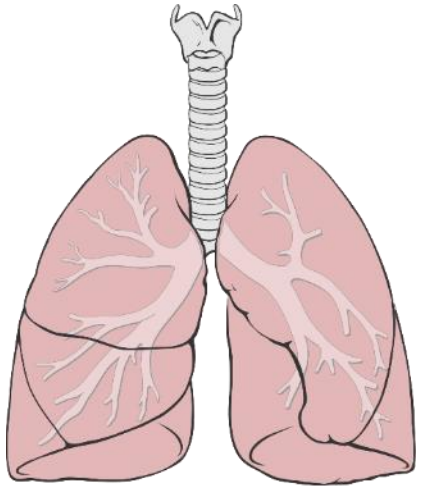
A: Local Irritation Effects

Nose and eye irritation observations only

B: Upper Respiratory Effects

Observations in nose, larynx and pharynx only



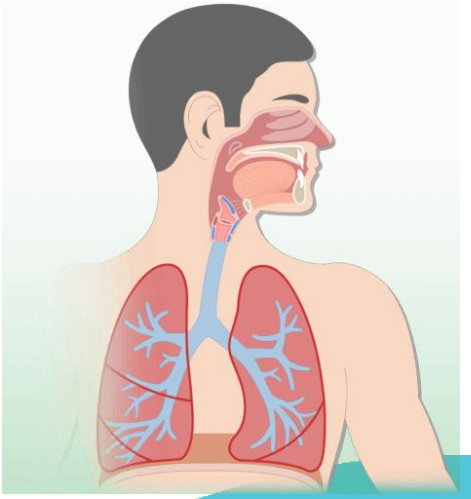


C: Lower Respiratory Effects

Observations in trachea and lungs only

D and E: Entire Respiratory Tract Effects

All tissues in the respiratory system observed



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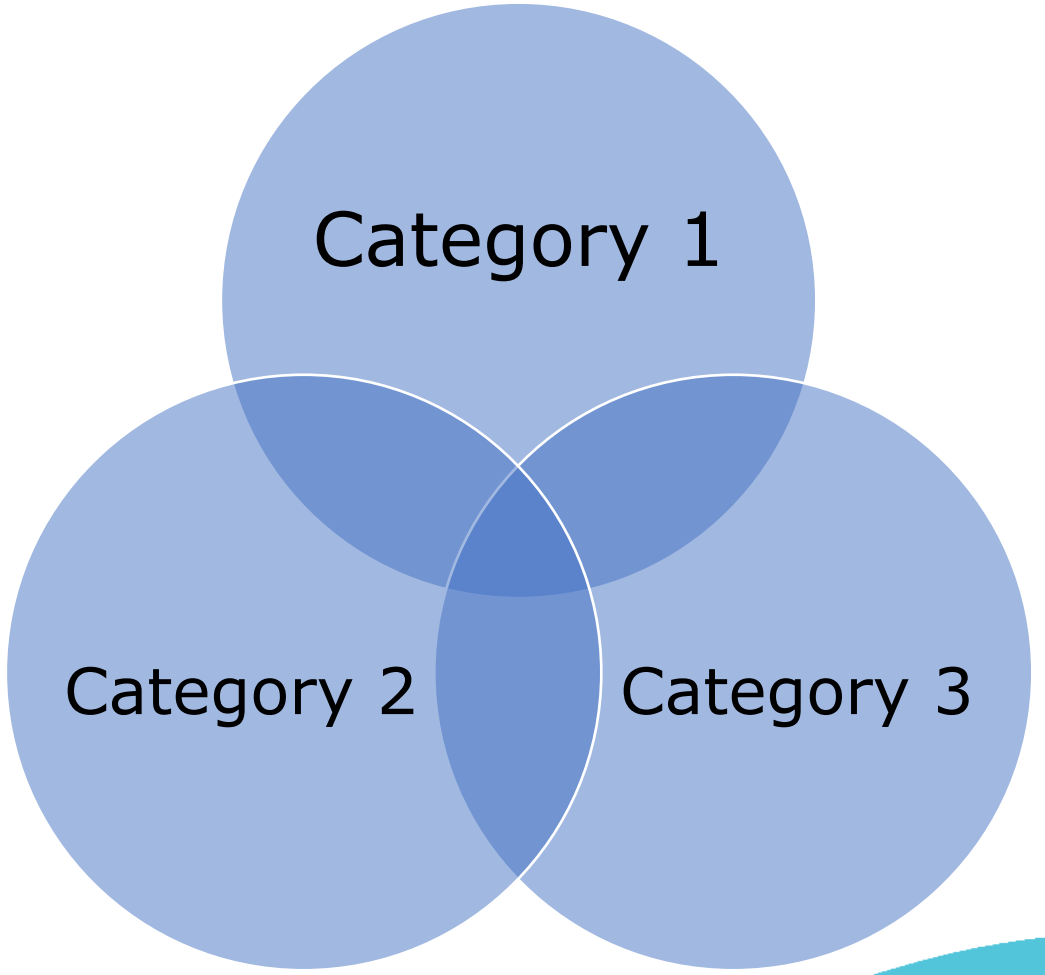
Machine Learning: Moving forward from previous attempts at categorizing the dataset

Earlier attempts at categorizing the inventory saw no clear separation of the dataset



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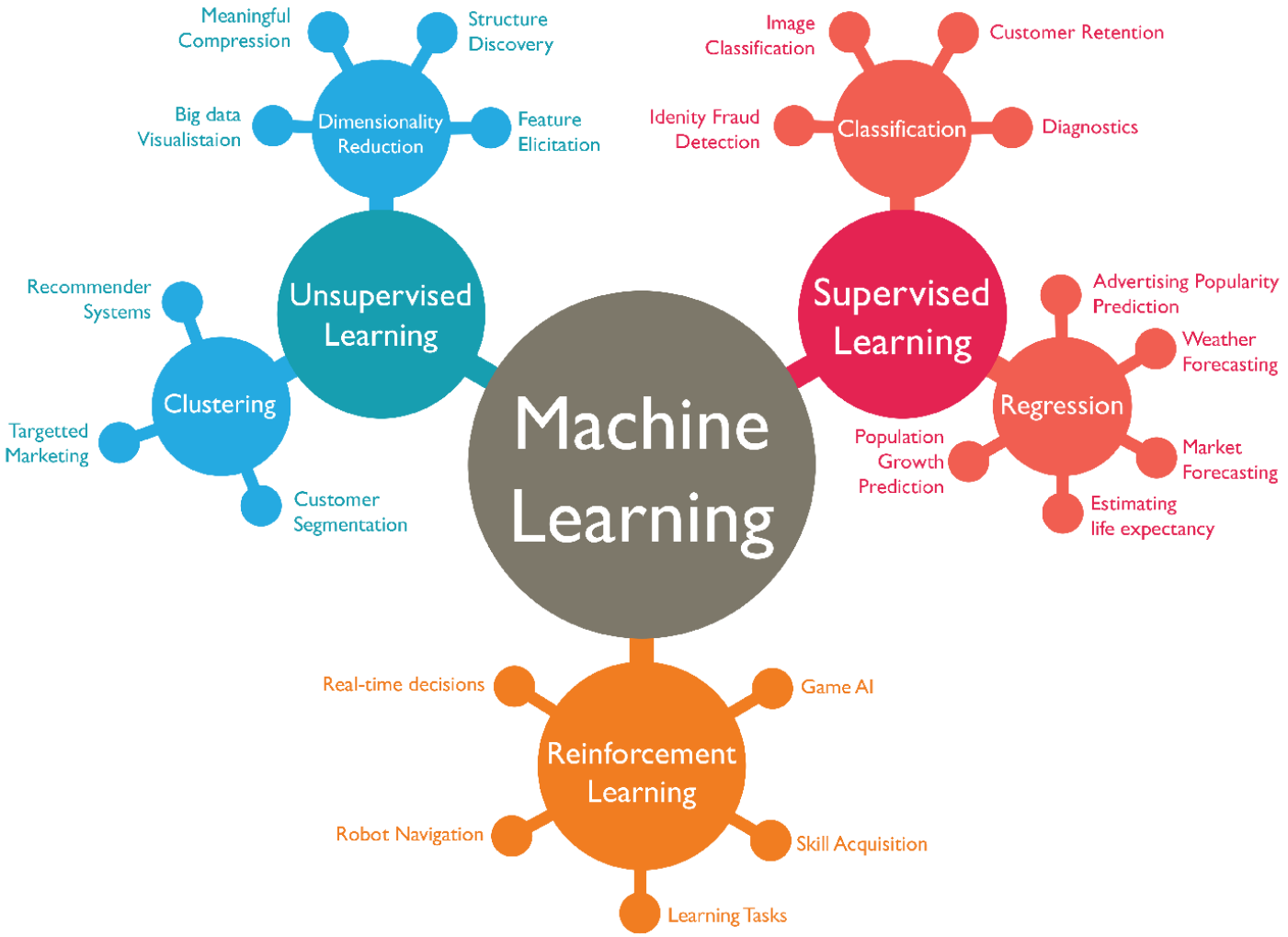
Ability to learn without explicit programming



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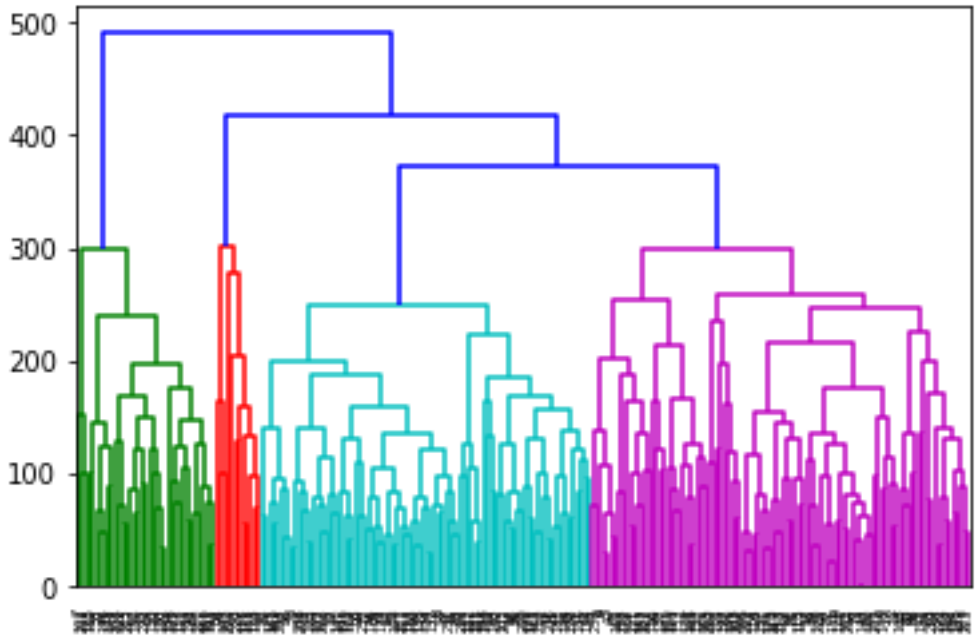
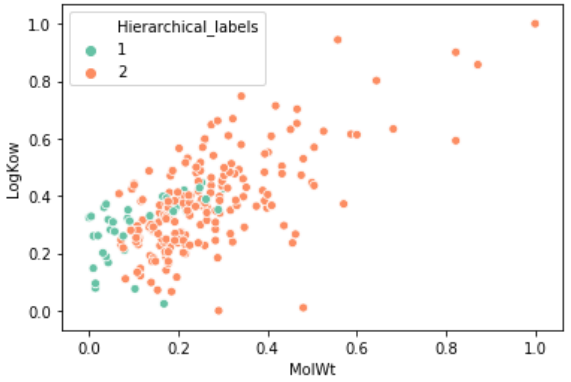
Visualizing Hierarchical Clusters

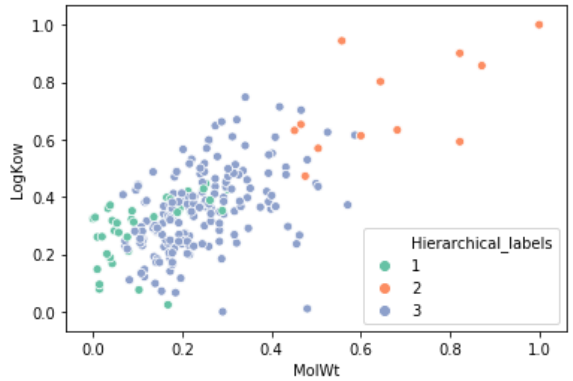
Complete + Canberra



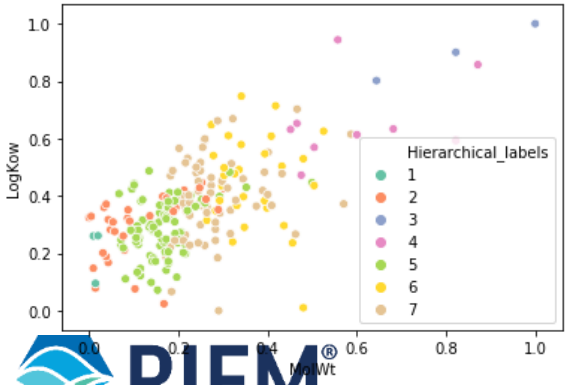
2-membered



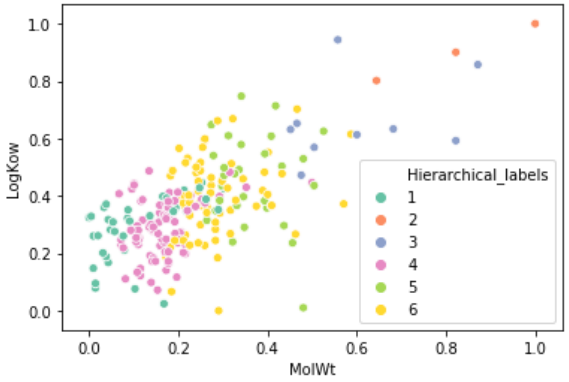
3-membered



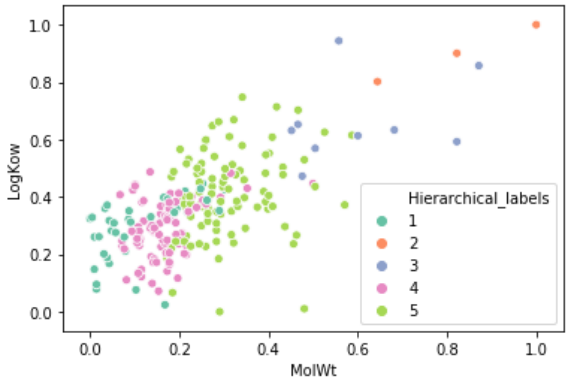
7-membered



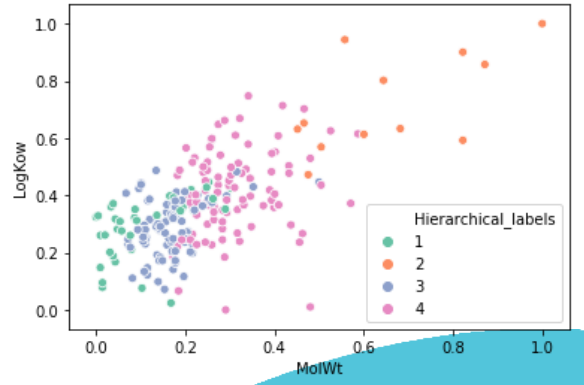
6-membered



5-membered



4-membered



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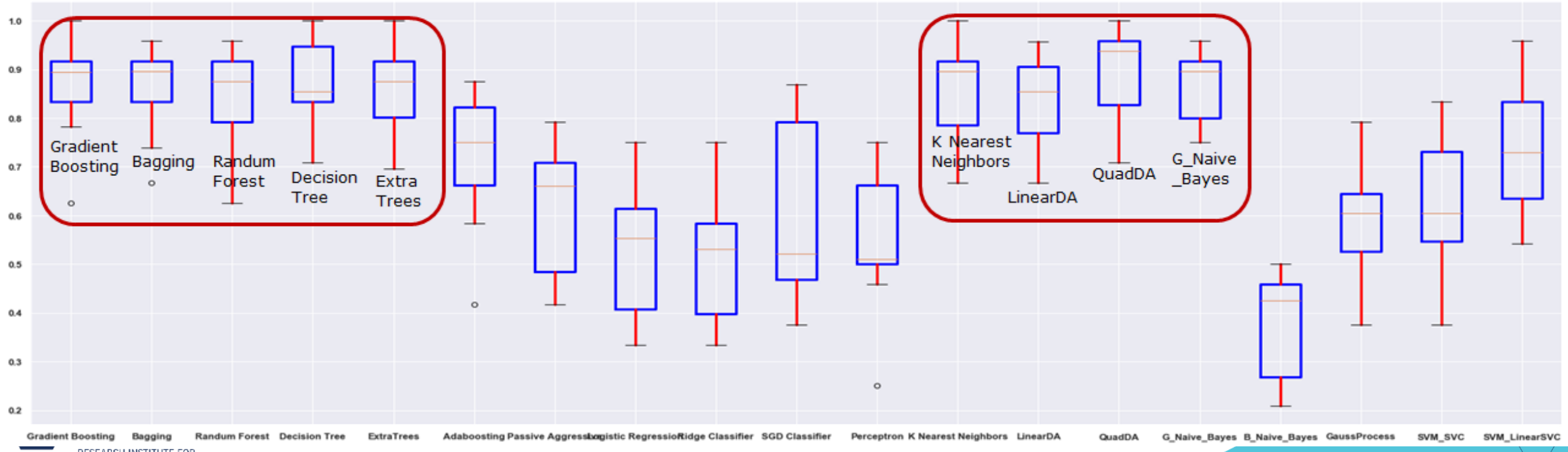
Hierarchical 5 Clusters: Classification Analysis using 4 Features

nAtom = No. of Atoms
Sv = Sum of constitutional weighted by van der Waals volume
ECIndex = Eccentric connectivity index
Radius = Radius of a molecule



Conclusions

FIVE clusters using Artificial Intelligence-based Hierarchical Clustering have been identified to classify inhalation TTC materials

Classification of inhalation TTC materials is decided by four features:

Number of atoms
van der Waals Volume
Shape and size of a molecule

Any of following machine learning methods is recommended for studying inhalation TTC materials:

Bagging
QuadDA
Random Forest
G_Naive_Bayes

K-Nearest Neighbor
Gradient Boosting
ExtraTrees

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Cosmetics Europe Workshop for Inhalation TTC was held in November 2020

- Several groups participated and provided their research insights both in the area of TTC and in inhalation toxicity
- Knowledge gaps in inhalation TTC were identified
- Fostered new partnerships to be established to work together to address these knowledge gaps

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The next steps are all about growth and expansion

Questions?

Nikaeta Sadekar, Scientist
nsadekar@rifm.org

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