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Forming Chemical Categories..

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Overview

- What is a Category?
- What do we mean by Chemical Categories?
- Regulatory definitions e.g. OECD
- So what?
- How do we form Categories?
  - What guidance is out there, their strengths and limitations
- Possible approaches & examples
  - A couple of ECB activities
- Challenges?

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What is a Category?

Some potential definitions..

- A collection of objects sharing a common attribute
- A division of objects according to appearance, quality, functionality..
- A group of objects that have some features that are the same

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What do we mean by Chemical Categories?

- A group of chemicals that have some features that are common
  - Structurally similar e.g. common substructure
  - Property e.g. similar physicochemical, topological, geometrical, or surface properties
  - Behaviour e.g. (eco)toxicological response underpinned by a common Mechanism of Action
  - Functionality e.g. preservatives, flavourings, detergents, fragrances

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OECD Definition of Category

- A chemical category is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity
- These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and human health effects

OECD Manual for Investigation of High Production Volume (HPV) Chemicals. Chapter 3, Section 2.

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Annex IX of REACH

Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or "category" of substances.

Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for a reference substance within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint.

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So what?

Why might we want to develop categories?

- If we can characterize chemicals sufficiently in order to group similar chemicals together with respect to a given property/endpoint… then we can use that relationship to make predictions, rationalizations about the behaviour for new chemicals likely to belong to the same group.
- In the context of safety assessments – grouping has the potential to save resources and reduce hazard testing.
- BUT the challenge is to characterize chemicals appropriately in order to group them in the first place.

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How do we form a Category?

What Guidance is out there?

OECD HPV Manual

- This addresses:
  - Definitions and explanations of the chemical category concept.
  - General approach for developing categories.
  - Differences in grouping for different endpoints.
  - Use of (Q)SARs for the development of a category
  - Guidance on different types of categories
  - Provides a number of examples of categories that have been adopted within the OECD HPV Chemicals Programme. NB: Examples appear largely limited to chemical classes or structurally similar chemicals.
- **but** it lacks detail on the practical steps on how
  - to formulate a category,
  - justify it
  - document it

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How do we form a Category

What Guidance is out there?

- **In development for REACH (under the RIP 3.3 Task 3):**
  - To develop *non-prescriptive* guidance that explains and illustrates:
    - the commonalities and differences between SARs, read-across and categories (including sub-categories)
    - how to justify and report qualitative and quantitative read-across
    - how to build a category (practical details), including examples of qualitative and quantitative read-across
    - how to evaluate the robustness and applicability domain of a category
    - how to justify and report a category proposal

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Possible and Practical approaches

- Grouping could be nominally categorised into one of four classes:
  - knowledge-based
  - analogue-based
  - unsupervised
  - supervised

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Knowledge-based approach

- Encompasses "human expert rules". Human experience linked to specific endpoints is encoded in the form of structural alerts or chemical reactivity mechanisms.
- Examples include Cramer rules, Ashby Tennant alerts, Derek alerts..

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Example for Skin sensitization

- Skin sensitization results from a T-lymphocyte mediated immune response to a chemical allergen that comes into contact with the skin.
- A chemical need to overcome a number of hurdles in order to induce skin sensitization.
- These comprise:
  - Penetration into the viable epidermis across the *stratum corneum*.
  - **Formation of a stable association with protein** to create an immunogenic complex. This requires that a **chemical is** inherently **protein-reactive**, or can be transformed chemically or metabolically to a protein-reactive species. Typically the stable association is thought to be a **covalent** one
  - Deliver dermal trauma sufficient to induce and up-regulate those epidermal cytokines that are necessary for the mobilisation, migration and maturation of LC.
  - Be inherently immunogenic such that a T lymphocyte response of sufficient magnitude is stimulated.
- If these hurdles are not successful then skin sensitization will either not occur or will be sub-optimal.

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Example for Skin sensitization

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- The **KEY** step is the formation of a stable association (usually covalent) with a protein.
- Skin sensitization is underpinned by an understanding of chemical reactivity and chemical mechanisms.
- The chemical behaves as an electrophile whereas the protein behaves as a nucleophile.
- There are various types of electrophile-nucleophile reactions encountered in skin sensitization, perhaps the most common are: Michael-type reactions; SN2 reactions; SNAr reactions; acylation reactions and Schiff-base formation.
- It is possible to group chemicals and rationalise their skin sensitization potential on the basis of these chemical reaction mechanisms.

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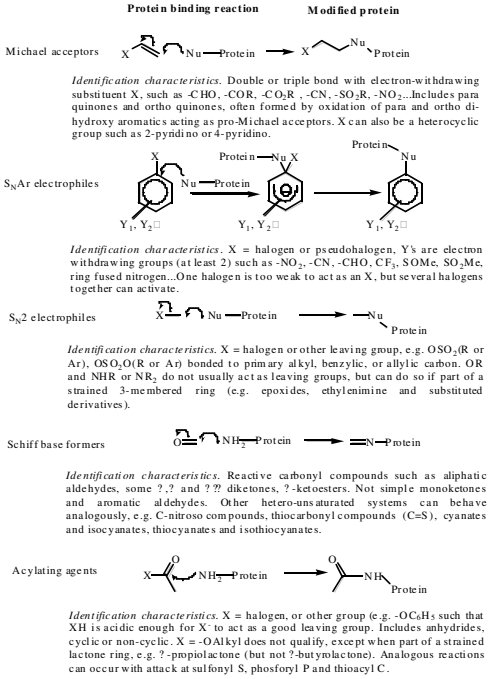

Figure taken from Aptula AO et al, 2006 *Tox in Vitro*, 20(2):239-47

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Analogue-based approaches

- Search and retrieval of structurally similar chemicals either on the basis of a substructure, fingerprint/fragment or on the basis of a similarity index measure such as Tanimoto
- The Tanimoto similarity index compares one compound with another on the basis of fingerprints to arrive at a number between zero and one. A index of 0 signifies that the two compounds have nothing in common whereas a value of 1 reveals them to be identical.

Tanimoto index =
(number of bits in common between A and B)/
(no of bits in molecule A + no of bits in molecule B - no of bits in common between A and B)

- There are a number of tools both freely available and commercially available to facilitate this type of searching.

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Analogue-based approaches: Search engines

- **AIM:** US EPA's Analog Identification Methodology identifies publicly available, experimental toxicity data on closely related chemical structures. Contains **31,031** records.
- **AMBIT (IDEA Consult Ltd):** Tool for defining applicability domain of QSAR models. Contains **463,426** records.
- **ChemFinder:** Portal of free and subscription scientific databases.
- **ChemID Plus Advanced:** Free database from the National Library of Medicine. Contains over **379,000** records.
- **Danish (Q)SAR Database:** Free internet-accessible version of a QSAR database originally developed by DK EPA. Contains **166,000** records.
- **Leadscope:** Commercial tool – databases + (Q)SAR functionalities

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Unsupervised

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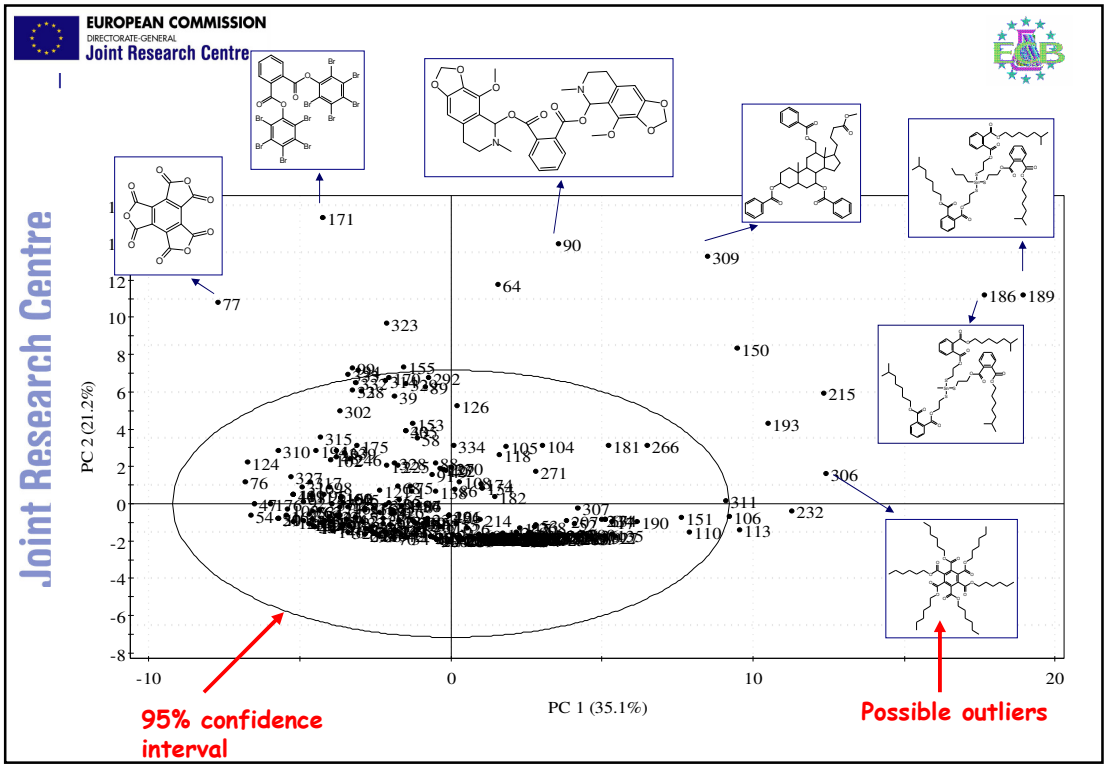
- Unsupervised approaches
- Based on independent variables (descriptors) only
- Methods involve the use of statistical techniques e.g. principal components analysis (PCA), clustering, self organising maps
- The approach relies on a starting dataset/inventory of chemicals and computing different numerical parameters (such as geometrical, topological, structural, physicochemical, electronic descriptors) for those chemicals or characterising them through the use of fingerprints or structural features.



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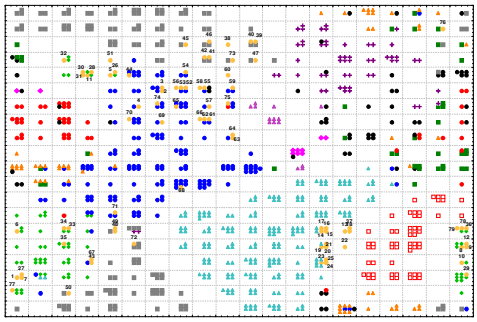
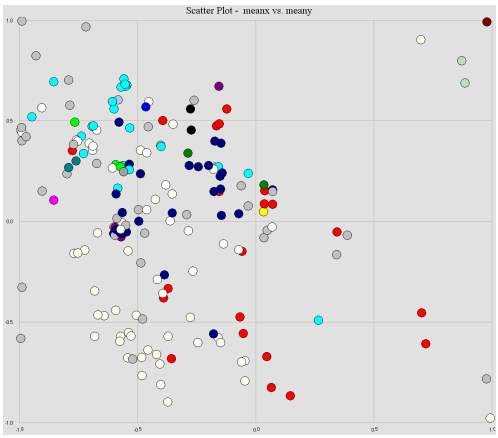
Examples of SOMs



- Aromatics
- Diox+Furans
- PAHs
- PCBs
- Pest. various
- Aliphatics
- List6
- OrgCl
- OrgPh
- Phenylureas
- Triazines
- Carbammates
- Dinitrobenzenes

With permission from M. Pavan

Grouping using descriptors thought to be relevant for the endpoint of concern



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Supervised learning

- Many of the same statistical techniques that might be applied.
- The key difference is that information about the activity/toxicity of chemicals is taken into account in addition to the structural/descriptor information
- For example
  - Clustering techniques employed with the criteria that clusters are extracted to discriminate for the toxicity present.
  - Recursive partitioning and simulated annealing which aims to find active or statistically correlated subsets based on the presence or absence of a particular combination of substructural features.

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ECB contributions: REACH work on Categories

- Application of QSAR and ranking methods to organic chemicals
- Application of ranking methods to organic chemicals
- Investigation of similarity-based grouping methods
- Review of examples discussed in EU Working groups

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ECB contributions: Other

- ECB Tool for Chemical Similarity
  - ECB contract with IdeaConsult Ltd, Sofia, Bulgaria
    - to facilitate the development of generic (atom environments) and endpoint-specific categories
    - inclusion of functionality for read-across
    - prototype (due end year) is being developed using several endpoints as examples including skin sensitization, skin irritation, aquatic toxicity and bioaccumulation

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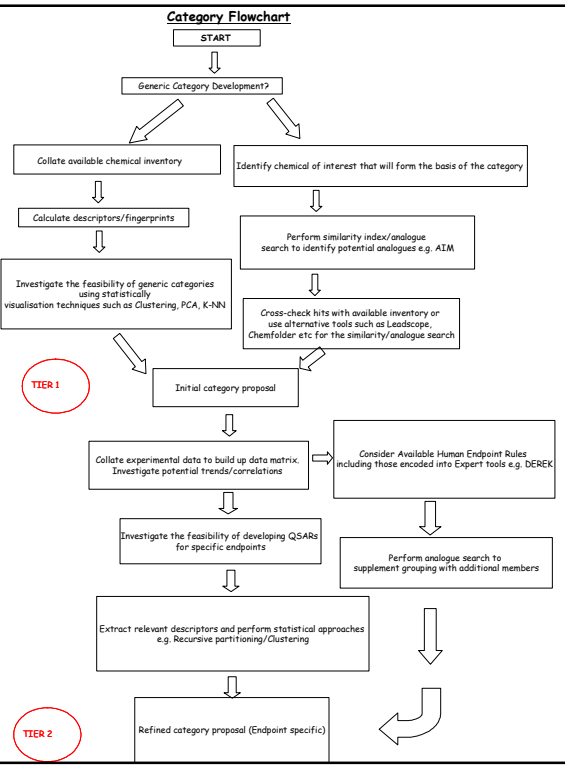

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Challenges?

- Guidance is in development for regulatory use to provide more practical guidance on how to formulate categories
- BUT More work needs to be done to characterize chemicals appropriately for the formation of groupings i.e. what are the drivers for a particular endpoint
  - Gaining the mechanistic understanding to underpin each endpoint
    - Being able to characterize reactivity
      - Through extracting insights from properly structured toxicity databases
      - Through appropriate experimentation where necessary

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