

*39th Joint Meeting of the Chemicals Committee and the Working Party on Chemicals,  
Pesticides and Biotechnology  
15-17 February 2006*

**Focus Session: Experiences using integrated approaches to fulfil information requirements  
for Testing and Assessment**

**Contribution by OECD  
(Development and use of chemical categories)**

## Development and use of Chemical Categories

Bob Diderich (OECD/EHS)

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. The similarities may be based on the following:

- a common functional group (e.g. aldehyde, epoxide, ester, metal ion, etc.); or
- the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (e.g. the “metabolic pathway approach” of examining related chemicals such as acid/ester/salt); and
- an incremental and constant change across the category (e.g. a chain-length category).

Read-across can be regarded as using data available for some members of a category to estimate values (qualitatively or quantitatively) for category members for which no such data exist.

Developing chemical categories can be considered a stepwise process:

- Identify proposed category and its members.
- Gather published and unpublished data for each category member.
- Evaluate available data for adequacy.
- Construct a matrix of data availability.
- Perform an internal assessment of the category.
- Prepare category test plan.
- Conduct the necessary testing.
- Perform an external assessment of the category and fill data gaps.

Different types of categories can be developed:


Chain length. These are defined as categories showing an incremental, and usually constant, increase in chain length across the category. There is an assumption that each category member exhibits the same toxic mode of action. Examples are the homologous series of alpha-olefins where each category member differs by a  $-CH_2-$  unit and the ethylene glycols where there is an incremental increase in the number of  $CH_2CH_2O$  groups.

Metabolic pathways. The underlying hypothesis for a metabolic series is a sequential metabolism of a parent chemical to downstream blood metabolites that are chemicals of interest. Hazard identification studies with the parent compound could then be used to identify the hazards associated with systemic blood levels of the downstream primary and secondary metabolites and, once quantified, can be used in place of studies using direct exposure to primary and secondary metabolites themselves.

Chemical mixtures. Categories can sometimes apply to series of chemical reaction products or chemical mixtures that are, again, related in some regular fashion. Analogous to the basic “discrete chemical” category model, in a mixture category some, but not all, of the individual mixtures may undergo testing.


Metal and metal compounds. There are a number of assumptions underlying any grouping of metal compounds for estimating their biological properties. The main assumption is that it is the metal ion that is responsible for the effects to be assessed. This is considered to be a reasonable assumption for the majority of the inorganic and some organic anions. This implies that in the case of inorganic salts, the toxicity of the counter ion is assumed to be largely irrelevant in producing the effects to be assessed.

Slide 1




**Development and use of chemical categories**

**Bob Diderich**  
**OECD**


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Slide 2



**History**

- Introduced for US HPV Challenge Program and OECD HPV Chemicals Programme in 1998
- OECD Workshop in January 2004
- Revised guidance document in May 2005

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## Slide 3

### What is a Chemical Category ?

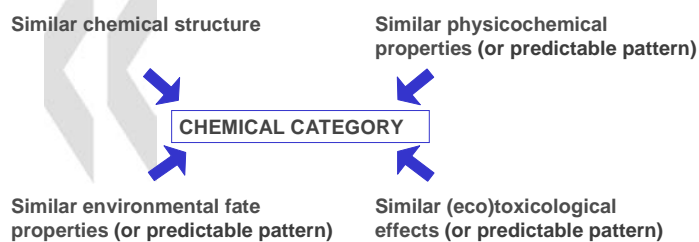
“... a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity.

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 HPV Chemicals. Chapter 3, Section 2.

## Slide 4

### Rationales for Chemical Categories

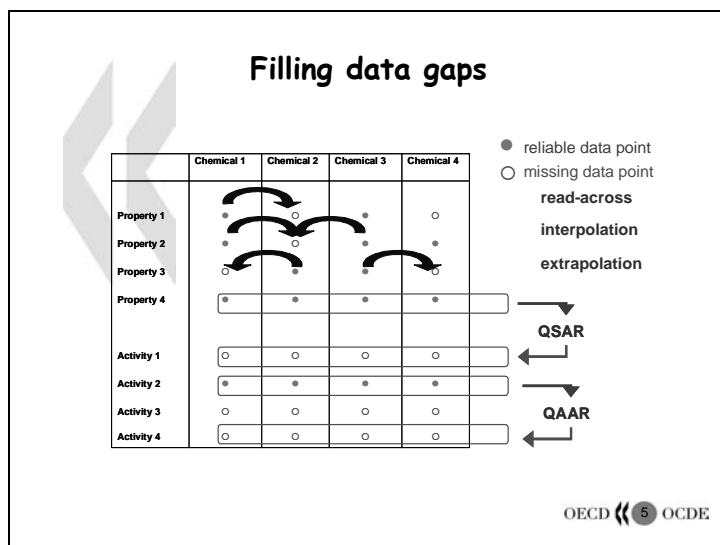


**Key words:**

Structural similarity (structural analogy) → SAR

Predictable pattern (trend) → QSAR

## Slide 5



## Slide 6

### A stepwise procedure


- **Step 1:** Identify proposed category and its members:
  - The relational features of the category: the chemical similarities and trends in properties and or activities that collectively generate an association between the members.
  - The applicability domain i.e. identify the ranges of values within which reliable estimations can be made for category members.

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Slide 7

**A stepwise procedure**

- **Step 2:** Gather published and unpublished data for each category
- **Step 3:** Evaluate available data for adequacy
- **Step 4:** construct a matrix of data availability

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Slide 8

**Matrix of Available and Adequate Data on Alpha-Olefin Category Members**

**Human Health Effects**

Test	Hexene	Octene	Decene	Dodecene	Tetradecene
Acute Oral	√	√	√	√	√
Acute Inhalation	√	√	√	√	√
Acute Dermal	√	√	√	√	√
Repeated Dose	√	√	-	-	-
Genotoxicity (in vitro - bacteria)	√	√	√	√	√
Genotoxicity (in vitro - non-bacterial)	√	√	-	√	√
Genotoxicity (in vivo)	√	-	-	-	-
Repro/Developmental	-	-	-	-	-

(√) = Data available and considered adequate; (-) = No data available, or available data considered inadequate.

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### A stepwise procedure

- **Step 5:** Perform an internal assessment of the category
  - identification of the relational features that collectively generate the association between the category members.
  - use of the relational features to fill data gaps (empty cells in the category matrix).
- **Step 6:** Prepare category test plan

#### Alpha-Olefin Proposed SIDS Test Plan

Selected SIDS Endpoint	Hexene	Octene	Decene	Dodecene	Tetradecene
Repeated Dose	√/+	√/+	-	-	- <sup>2</sup>
Repro/Developmental	-	-	-	-	- <sup>2</sup>


<sup>1</sup> KEY: √/- = data available, but not adequate; √/+ = data available and considered adequate; - = no data available. Shaded cells represent those SIDS endpoints for which testing was recommended.

<sup>2</sup> A combined repeated dose and reproductive/developmental toxicity screen study design was recommended.

Slide 11

**A stepwise procedure**


- **Step 8:** Perform an external assessment of the category
- and fill data gaps
  - Qualitative
  - Quantitative

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Slide 12

**Results and Interpolation of Alpha-olefin SIDS Category Testing**


Selected SIDS Endpoint	Hexene	Octene	Decene	Dodecene	Tetradecene
Repeated Dose	NOEL <sub>oral</sub> = 101 mg/kg (males) and >1000 mg/kg (females)	NOEL = 50 mg/kg (males)	SIMILARLY TOXIC		NOEL <sub>oral</sub> = 100 mg/kg (males) and >1000 mg/kg (females)
Repro/ Developmental	NOEL <sub>repro</sub> and NOEL <sub>dev</sub> = >1000 mg/kg	SIMILARLY TOXIC			NOEL <sub>repro</sub> and NOEL <sub>dev</sub> = >1000 mg/kg

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Slide 13

**Different types of Categories**


- Chain length
- Metabolic pathways
- Chemical mixtures
- Isomers and their mixtures
- Complex substances
- Metal and metal compounds

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Slide 14

**Metabolic pathways**

- Sequential metabolism of a parent chemical to downstream blood metabolites.
- Primary metabolite is the predominant chemical found in the blood.
- Proof of metabolism preferably *in vivo* (direct measurement of both parent compound and metabolite).
- Limited to hazards related to systemic blood levels.


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Slide 15




### Chemical mixtures (1)

- Tentative, further guidance to be developed
- Simple mixtures e.g. Lineal Alkylbenzenes
- Isomers and their mixtures
  - Chain isomers, Position isomers, Stereoisomers ?
  - Metabolic data may be needed.


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Slide 16



### Chemical mixtures (2)

- Complex substances
  - Composition and impurities
  - Identify representative components and outliers
  - Properties of repr. components can be applied to the complex mixture
  - Properties of complex mixture can be applied to another similar complex mixture
  - Quantitative read-across difficult

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## Slide 17

### **Metal and metal compounds**

- Assumption: metal ion is responsible for the effects to be assessed (same oxidation state).
- Possible basis for grouping: water solubility
  - Transformation/dissolution of insoluble compounds
  - Bioavailability of the metal ion in the environment
  - Solubility in biological fluids
  - Persistence in the body
- Not applicable to local effects
- Not applicable to organically based metals

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### **Further developments needed**

- Systematic approach for category identification
- Quantitative validation criteria
- Guidance on quantitative filling of data gaps
- Guidance for complex substances
- Compatibility with classification criteria

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