

# The second phase of the (Q)SAR Application Toolbox

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CAESAR-Workshop

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## REACH Article 13(1)

### ***General requirements for generation of information on intrinsic properties of substances***

*„Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across).“*

## (Q)SAR Application Toolbox

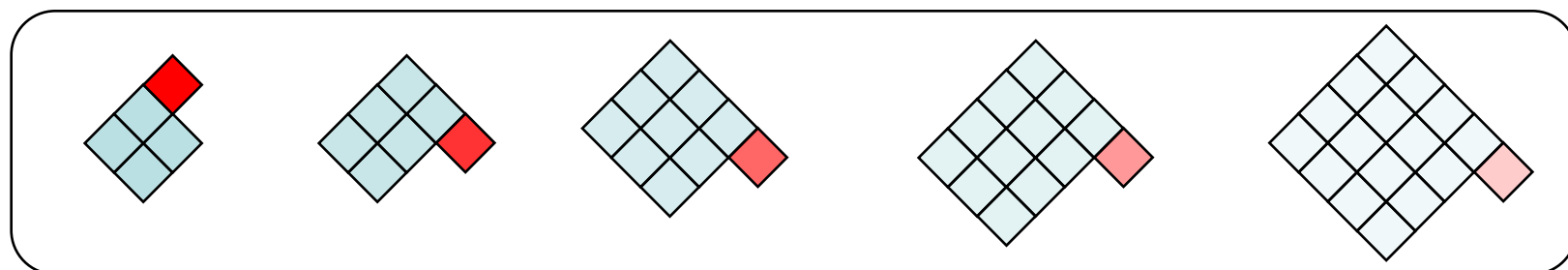
A computer application to help the user **to build chemical categories** or apply the simplified analogue approach.

## What is a Chemical Category ? (1)

- group of chemicals with structural similarity (or other similarity characteristics), resulting in
  - Physicochemical properties,
  - Human health properties and/or
  - Ecotoxicological propertieswhich are likely to be similar or follow a regular pattern

## What is a Chemical Category ? (2)

- Chemicals are selected based on the hypothesis that properties of a series of chemicals with common structural features will show coherent trends in their physicochemical properties and toxicological effects (human health, ecotoxicity) or environmental fate properties



Trend of less 'colour'

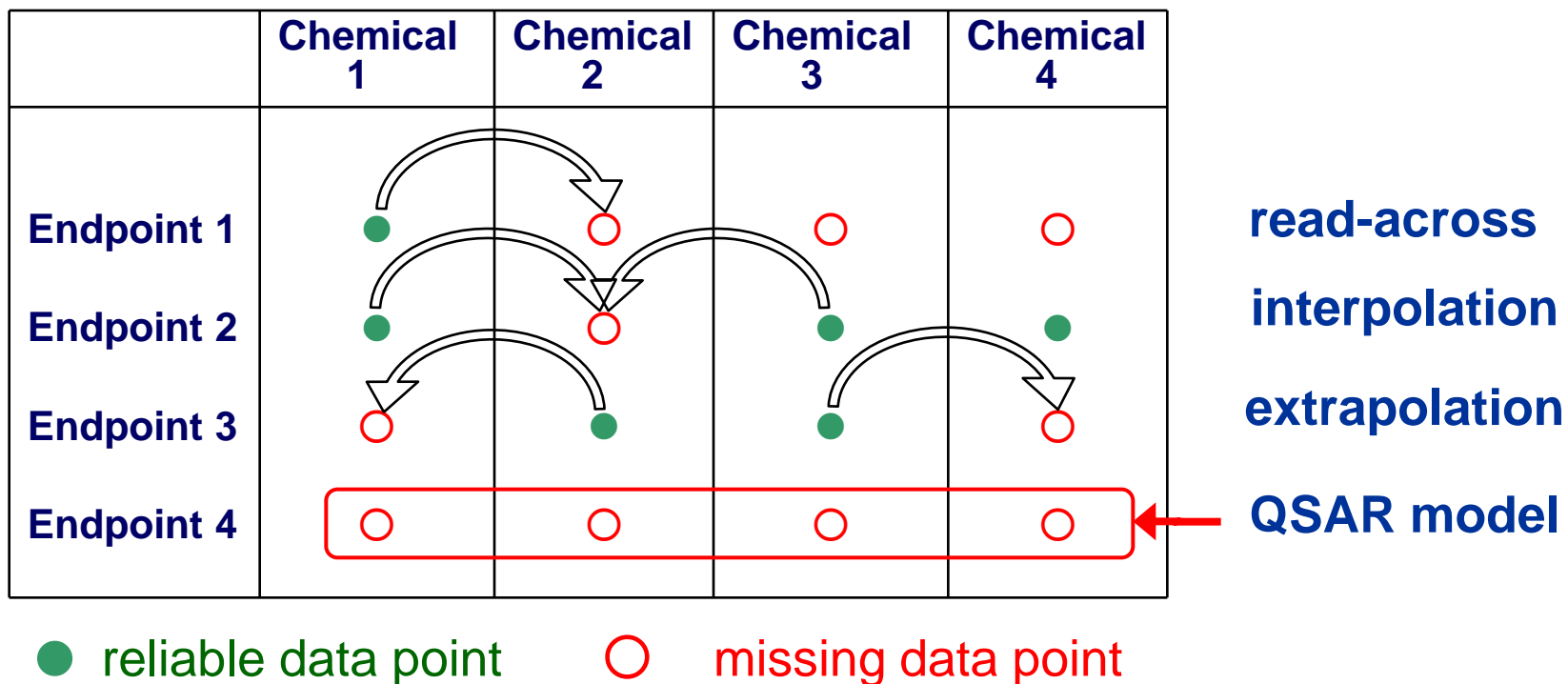
## What is a Chemical Category ? (3)

- Common behaviour / consistent trends are generally associated with a **common underlying mechanism of action**
- As a result, it is possible to extend the use of measured data to similar untested chemicals, and **reliable estimates** adequate for classification and labelling and/or risk assessment can be made without further testing.

# Grouping of chemicals

Within a chemical category, data gaps may be filled by

- read-across,
- trend analysis and
- QSARs



# Grouping of chemicals

Guidance on information requirements and chemical safety assessment: R6: QSARs and grouping of chemicals

[http://guidance.echa.europa.eu/docs/guidance\\_document/information\\_requirements\\_en.htm?time=1236156888#r6](http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm?time=1236156888#r6)

OECD Guidance on grouping of chemicals

[http://apli1.oecd.org/olis/2007doc.nsf/linkto/env-jm-mono\(2007\)28](http://apli1.oecd.org/olis/2007doc.nsf/linkto/env-jm-mono(2007)28)

## **Main features of the Toolbox are:**

1. Identification of **structural characteristics** and **potential mechanism** or **mode of action** of a target chemical

# Grouping of chemicals

OECD Toolbox Beta Version (v 0.604)

**QSAR Application Toolbox**  
Organization for Economic Co-operation and Development

Options | Chemical input | **Profiling** | Endpoints | Category definition | Filling data gap | Report

Apply

Profiling methods

**Predefined**

- OECD categorization
- US EPA Categorization
- Database affiliation
- Inventory affiliation
- Substance type

**Mechanistic**

- OASIS Acute Toxicity MOA
- DNA Binding
- DNA Binding Dec
- Protein Binding
- Organic functional groups
- Superfragment profiling

Metabolism

**Documented**

- Observed Microbial metabolism
- Observed Liver metabolism

**Simulated**

- Microbial metabolism simulator
- CT-based simulator

Show Category Boundaries

Create a new profiler

Delete profiler

1 (Target)

Structure

CC(C)CC=O

Substance Information

Profile

- DNA Binding
- Protein Binding
- Mechanistic boundaries example

No Binding

Schiff base formation

aldehyde not Michael-type addition

Check the preferred profiling scheme and press the "Apply" button

<< Back | Next >> | Cancel track

(1) Single chemical

## **Main features of the Toolbox are:**

1. Identification of structural characteristics and potential mechanism or mode of action of a target chemical
2. Identification of other chemicals that have the same structural characteristics and/or mechanism or mode of action

# Grouping of chemicals

OECD Toolbox Beta Version (v 0.604)

OECD  
Organization for Economic Co-operation and Development

Options | Chemical input | Profiling | Endpoints | **Category definition** | Filling data gap | Report

Grouping methods

- ...OASIS Acute Toxicity MOA
- ...DNA Binding
- ...DNA Binding Dec
- ...Protein Binding
- ...Organic functional groups
- ...Superfragment profiling
- ...ECOSAR classification
- ...Cramer classification
- ...Verhaar classification
- Empiric**
- ...Lipinski Rule
- ...Chemical elements

Defining Category

Clustering

Subcategorization

Show Category Boundaries

Defined categories

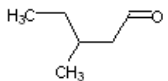
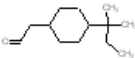

(39) Schiff base formation, creat...  
(23) Subcategorized by: F

Combine

AND OR

Delete category

Delete selected Delete all

	1 (Target)	2	3	4
Structure			<chem>H2C=O</chem>	
Substance Information				
Profile				
DNA Binding	No Binding	No Binding	No Binding	No Bindin
Protein Binding	Schiff base formation	Schiff base formation	Schiff base formation	Schiff bas
Mechanistic boundaries example	aldehyde not Michael-type addition	aldehyde not Micha...	aldehyde not Micha...	aldehyde
Toxicological Information				
Irritation / Corrosion				
Skin				
Sensitization	(22/22)	T: 1.00E+000	T: 2.00E+000	T: 1.00E+

Select a grouping method and press the **Defining Category** button.

When the category formation is finished, type a name for the newly obtained category. The new category name will be displayed in the **Defined category** list. Similarly, the obtained category could be further subcategorized.

You can click on the name of the category to collect data values and list the chemicals in the *Data matrix*

(23) Subcategorized by: Protein Binding

## **Main features of the Toolbox are:**

1. Identification of structural characteristics and potential mechanism or mode of action of a target chemical
2. Identification of other chemicals that have the same structural characteristics and/or mechanism or mode of action
3. Facilitate the use of existing experimental data for read-across to **fill data gap**

# Grouping of chemicals

OECD Toolbox Beta Version (v 0.604)

**QSAR Application Toolbox**

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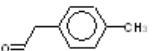
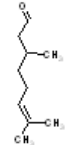
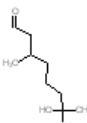
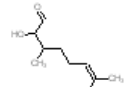
Options | Chemical input | Profiling | Endpoints | Category definition | **Filling data gap** | Report

Read-across | Trend analysis | (Q)SAR models | Apply

**Target endpoint:**  
Toxicological Information Irritation / Corrosion Skin Sensitization

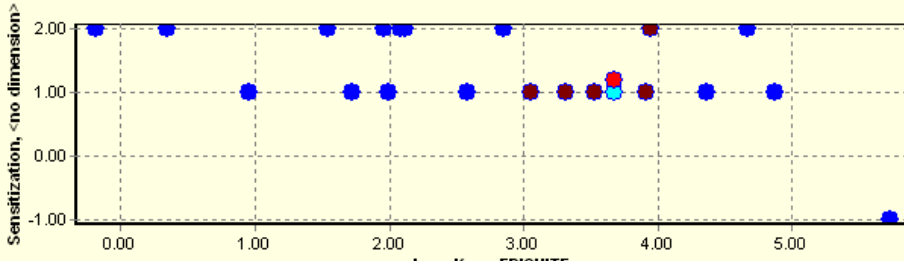
Select data points...

Data:  
 All values  
 Average value  
 Min value  
 Max value

Structure	20	23	27	28
				
Sensitization (39/39)	T: 2.00E+000	T: 1.00E+000	T: 2.00E+000	T: 1.00E+000

Descriptors | Endpoint | Adequacy | Cumul. frequency | Statistic

**Read across evaluation, taking the average from the nearest 5 neighbours based on 'Current subcategory', containing 22 data points in 22 analogue structures**  
Observed target value: 1.00; Predicted target value: 1.20



Descriptors: Log\_Kow\_EPISUITE  
 show descriptors in use only

**Prediction**  
Accept  
Cancel

**Data points**  
Subcategor.  
Back Fwd  
Restore

**Model**  
Read across options:  
Average  
on nearest 5  
Save model

Select the preferred data gap filling approach and press the “Apply” button. The data points corresponding to analogous chemicals (training set) could be by filtered according to the study details - press “Select data points...”. Check the respective radio buttons for preferred endpoint function and data manipulation approaches.

<< Back | Next >> | Cancel track

## Phase 1

- First version emphasised proof-of-concept, published in March 2008
- Extensive training material available
- Version 1.1 with additional profiling tools and additional databases released in November 2008

## Phase 2

- Joint project between OECD and ECHA
- 48 month work plan
- Beginning November 2008

Free download from

[www.oecd.org/env/existingchemicals/qsar](http://www.oecd.org/env/existingchemicals/qsar)

## **Phase 2 of the QSAR Application Toolbox**

- Information Technology
- Chassis Development and Additional Functionalities
- Database Compilation
- (Q)SAR Library and Expert System Compilation
- Training

- **Toolbox versions, updates & architectures**
  - Version 2.0 planned release end 2010
  - Version 3.0 planned release end 2012
  - Beginning with Version 2.0 auto-updates and a server-based and stand-alone architecture will be available
- **Docking with other instruments**
  - For server-based architectures, docking with e.g. IUCLID 5
- **Using harmonized templates & import/export functions**
- **Automatic summary of Toolbox predictions**
  - Reporting to document the case

# Chassis Development & Additional Functionalities

- Streamlining the operation of the Toolbox
  - Improve the operation of the Toolbox
  - Make it more intuitive and more user friendly
- Inventory query and database property searching
- Chemical speciation
- Metabolism
- 3D-descriptors
- Assessment of mixtures

# Database Compilation

- Identification of additional suitable databases
- Establishing agreements with database holders
- Quality assurance of chemical identifications

# (Q)SAR Library & Expert System Compilation

- Structural alerts & re-evaluation of existing chemical reactivity categories
  - Strength of Toolbox, expand to include other endpoints
  - Especially DNA and protein binding
- Development of toxicological categories
  - New categories to be developed and implemented in the Toolbox
- Expert system compilation for databases
  - cut offs for categories and/or endpoints, e.g. minimum vapour pressure for inhalation toxicants, maximum molecular size for bioconcentration
- (Q)SAR models
  - To be proposed to and approved by OECD Management Group
- Novel methods for analogues and categories
  - To reach our goal of placing all chemicals in a category we need to get much better at forming categories

- Aids currently being developed
- Advanced interactive help would be accessed from a HELP hot-link any time during an evaluation
- Guided tutorials would navigate the first time users through the Toolbox functions in a step-by-step and self-paced fashion

Guidance Document for using the (Q)SAR Application Toolbox to develop chemical categories according to the OECD Guidance on Grouping of Chemicals

[http://www.olis.oecd.org/olis/2009doc.nsf/linkto/env-jm-mono\(2009\)5](http://www.olis.oecd.org/olis/2009doc.nsf/linkto/env-jm-mono(2009)5)

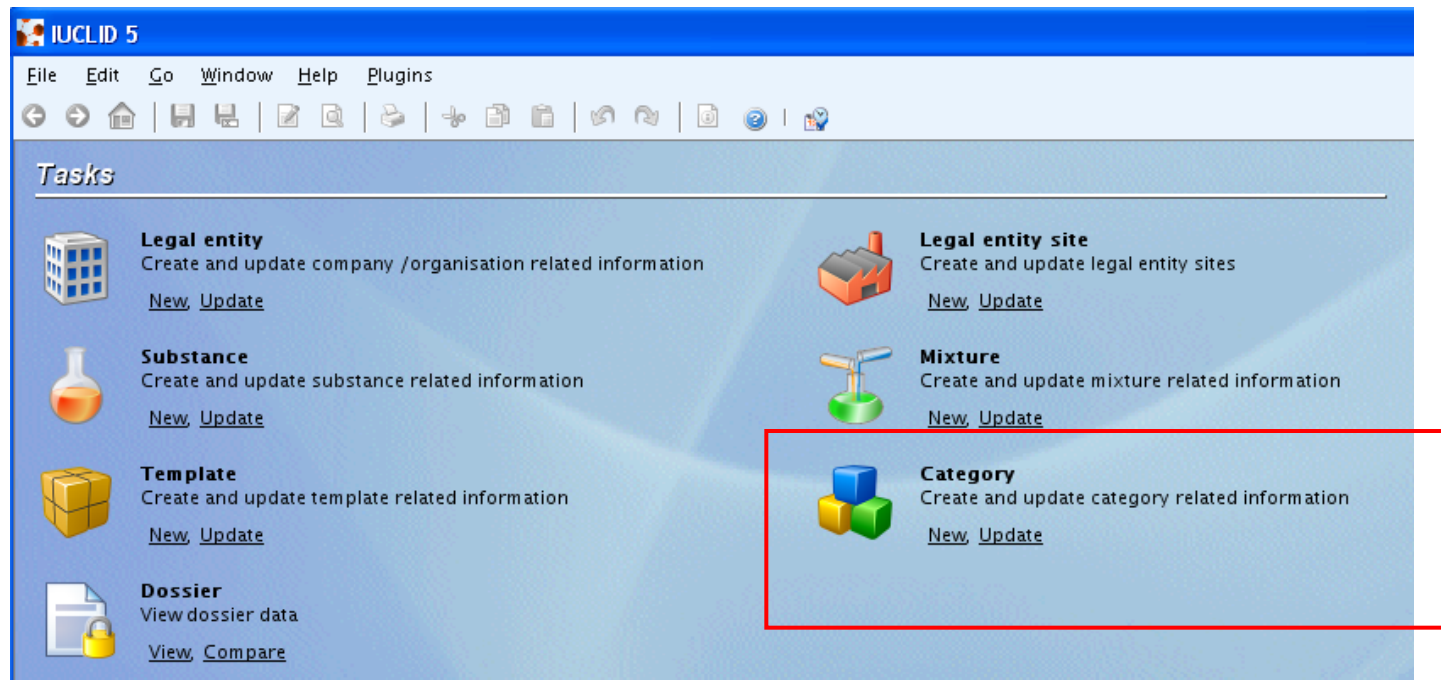
## Vision for the Toolbox

- To ensure that the categories approach to filling data gaps works uniformly for all discrete organic chemicals and for all regulatory endpoints

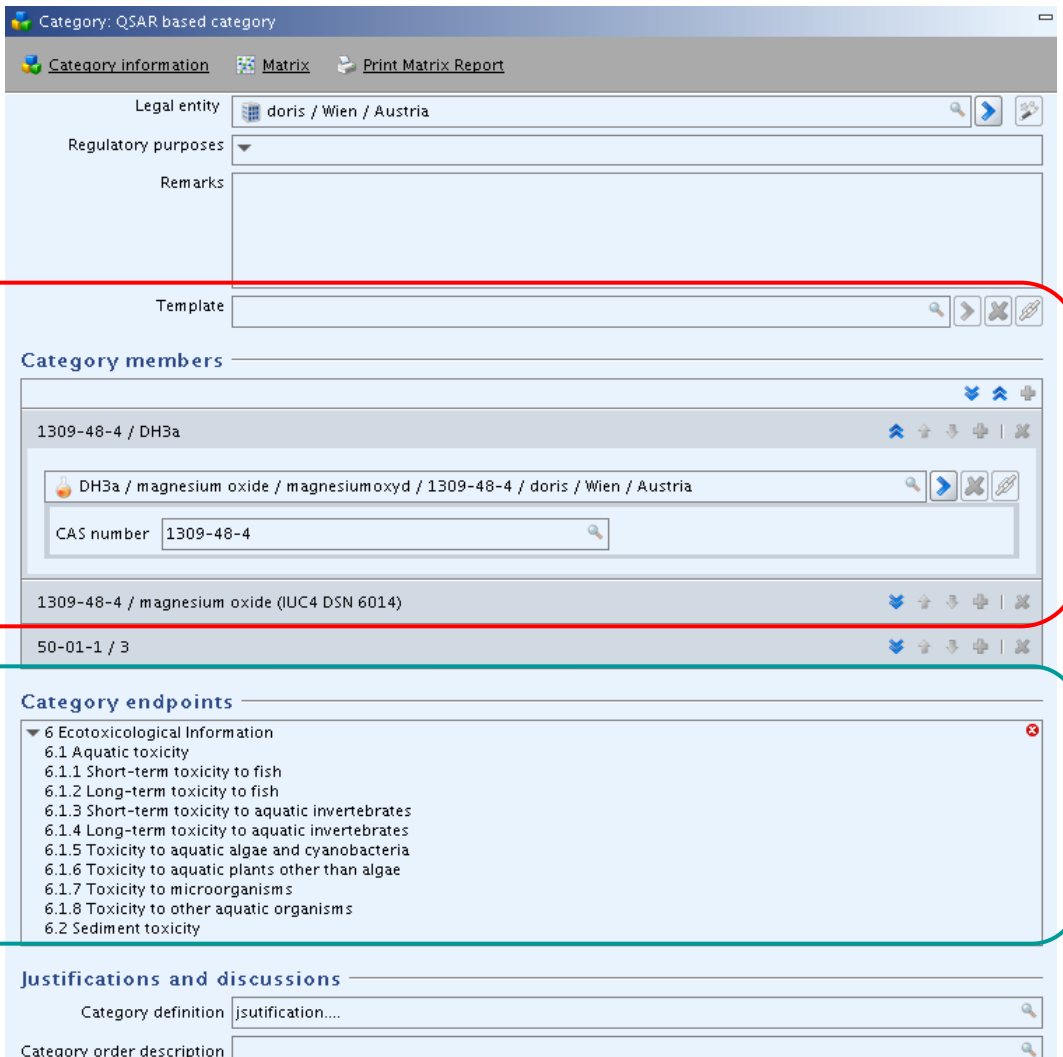
## Importance for REACH

- The (Q)SAR Application Toolbox shall provide a **COMMON BASIS** for the chemical industry, ECHA, and any other stakeholder

IUCLID 5 provides category functionality:



# Chemical Categories in REACH



Category: QSAR based category

Category information Matrix Print Matrix Report

Legal entity doris / Wien / Austria

Regulatory purposes

Remarks

Template

**Category members**

- 1309-48-4 / DH3a
  - DH3a / magnesium oxide / magnesiumoxyd / 1309-48-4 / doris / Wien / Austria
  - CAS number 1309-48-4
- 1309-48-4 / magnesium oxide (IUC4 DSN 6014)
- 50-01-1 / 3

**Category endpoints**

- 6 Ecotoxicological Information
  - 6.1 Aquatic toxicity
    - 6.1.1 Short-term toxicity to fish
    - 6.1.2 Long-term toxicity to fish
    - 6.1.3 Short-term toxicity to aquatic invertebrates
    - 6.1.4 Long-term toxicity to aquatic invertebrates
    - 6.1.5 Toxicity to aquatic algae and cyanobacteria
    - 6.1.6 Toxicity to aquatic plants other than algae
    - 6.1.7 Toxicity to microorganisms
    - 6.1.8 Toxicity to other aquatic organisms
  - 6.2 Sediment toxicity

**Justifications and discussions**


Category definition jsutification...







































Category order description

# Chemical Categories in REACH

Category: QSAR based category

[Category information](#) [Matrix](#) [Print Matrix Report](#)

 **Matrix**

	 1309-48-4	 1309-48-4	 50-01-1
 6 Ecotoxicological Information		1 	
 6.1 Aquatic toxicity			
 6.1.1 Short-term toxicity to fish	4 	1 	1 
 6.1.2 Long-term toxicity to fish	2 	1 	1 
 6.1.3 Short-term toxicity to aquatic invertebr...	2 	1 	1 
 6.1.4 Long-term toxicity to aquatic invertebr...	2 	1 	1 
 6.1.5 Toxicity to aquatic algae and cyanobact...	2 	1 	1 
 6.1.6 Toxicity to aquatic plants other than alg...	2 	1 	1 
 6.1.7 Toxicity to microorganisms	4 	1 	1 
 6.1.8 Toxicity to other aquatic organisms			
 6.2 Sediment toxicity	4 		1 

# Chemical Categories in REACH

**Justifications and discussions**

Category definition

Category order description

Category rationale

**Reports**

Report

Report

# Chemical Categories in REACH

**Dossier creation wizard**

This substance is member of one or many categories  
Specify whether category-related information should be used. If yes, endpoint data from all members of selected categories will be added to the dossier

**Use related categories**

Yes  
 No  
 Select category (ies)

1 2 3 4 5 6 7 8  
Use related categories

< Back Next > Finish Cancel

Navigation

Substance: magnesium oxide (IUC4 DSN 6014) / magnesium oxide / magnesiumoxyd / 1309-48-4 / EUROPEAN COMMISSION - Euro

results Components Section tree

R\_1-10\_STD / Substance: magnesium oxide 2008-11-17 / QSAR based category

**magnesium oxide (IUC4 DSN 6014) / n**

3 / testene / testene / 50-01-1 / Doris AG /

DH3a / magnesium oxide / magnesiumoxyd / QSAR based category

magnesium oxide / magnesiumoxyd / 1309-48-4 / testene / testene / 50-01-1

doris / Wien / Austria

Doris AG / Helsinki / Finland

doristest / asdf / Austria

EUROPEAN COMMISSION - European Chemi

hirmann\_ECHA-SAT-site / Helsinki / Finland

**Substance identification**

Chemical name: magnesium oxide (IUC4 DSN 6014)

Legal entity flags:

Legal entity: EUROPEAN COMMISSION - European Chemicals Bureau / Ispra (VA) / Italy

Third party flags:

Third party:

**Role in the supply chain**

Role flags:

Role:  Manufacturer  Importer  Only representative  Downstream user

**Reference substance**

magnesium oxide / magnesiumoxyd / 1309-48-4

FC number	FC name
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Thank you for your attention!