The second phase of the (Q)SAR Application Toolbox

Doris Hirmann

CAESAR-Workshop

Milano, 10-11 March 2009

REACH: Generation of information

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.

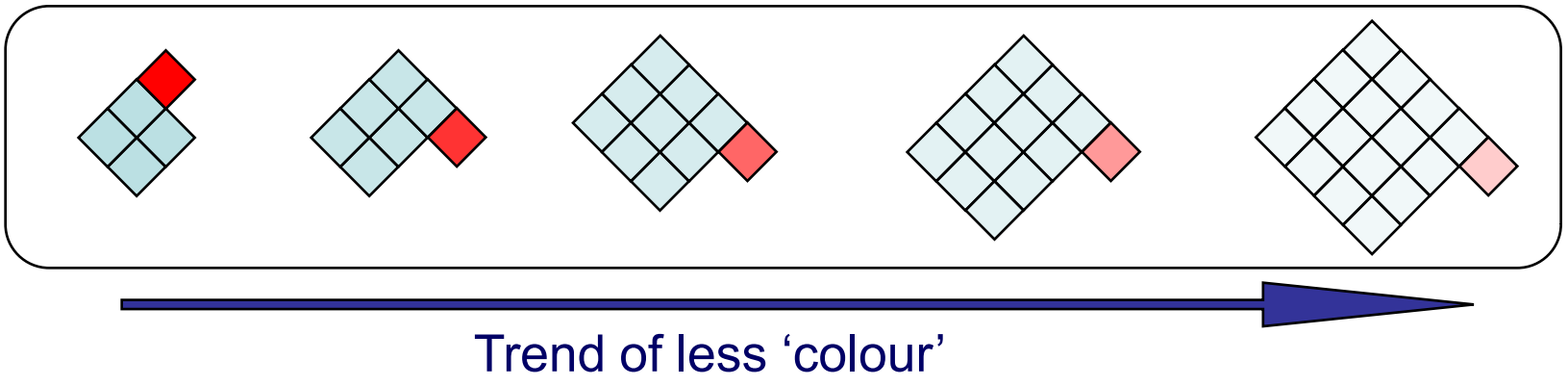
What is a Chemical Category ? (1)

- group of chemicals with structural similarity (or other similarity characteristics), resulting in
  - Physicochemical properties,
  - Human health properties and/or
  - Ecotoxicological properties

  which 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



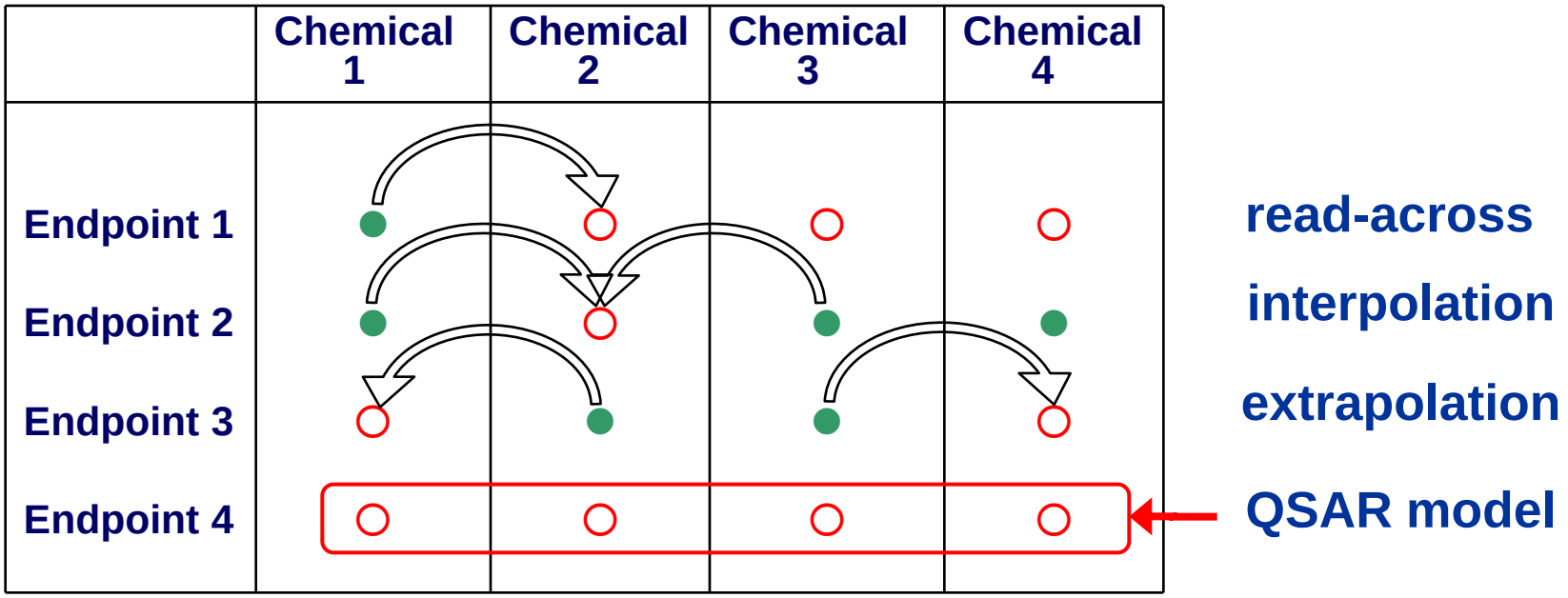
What is a Chemical Category ? (3)

- 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

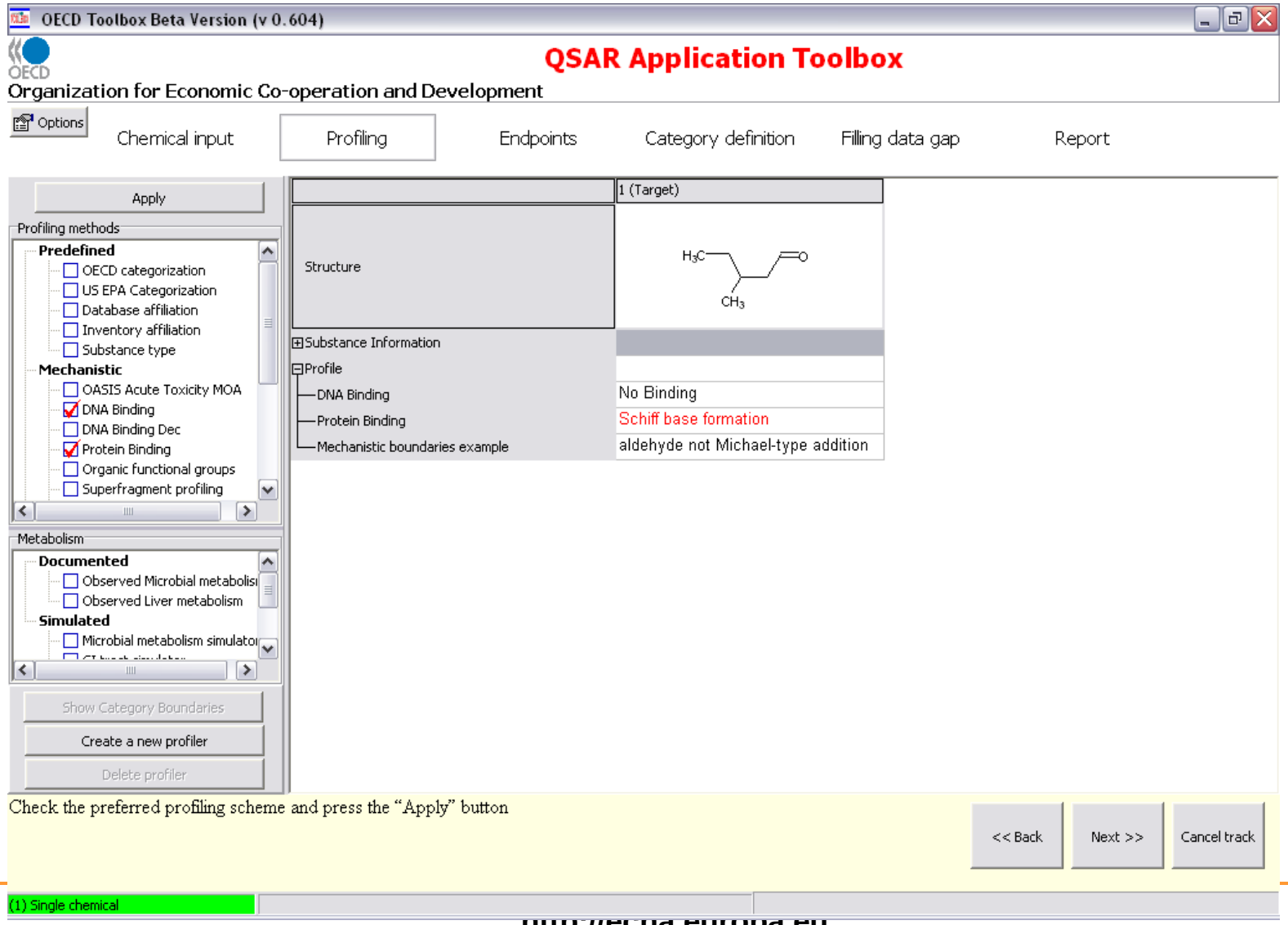
OECD Guidance on grouping of chemicals

http://appli1.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

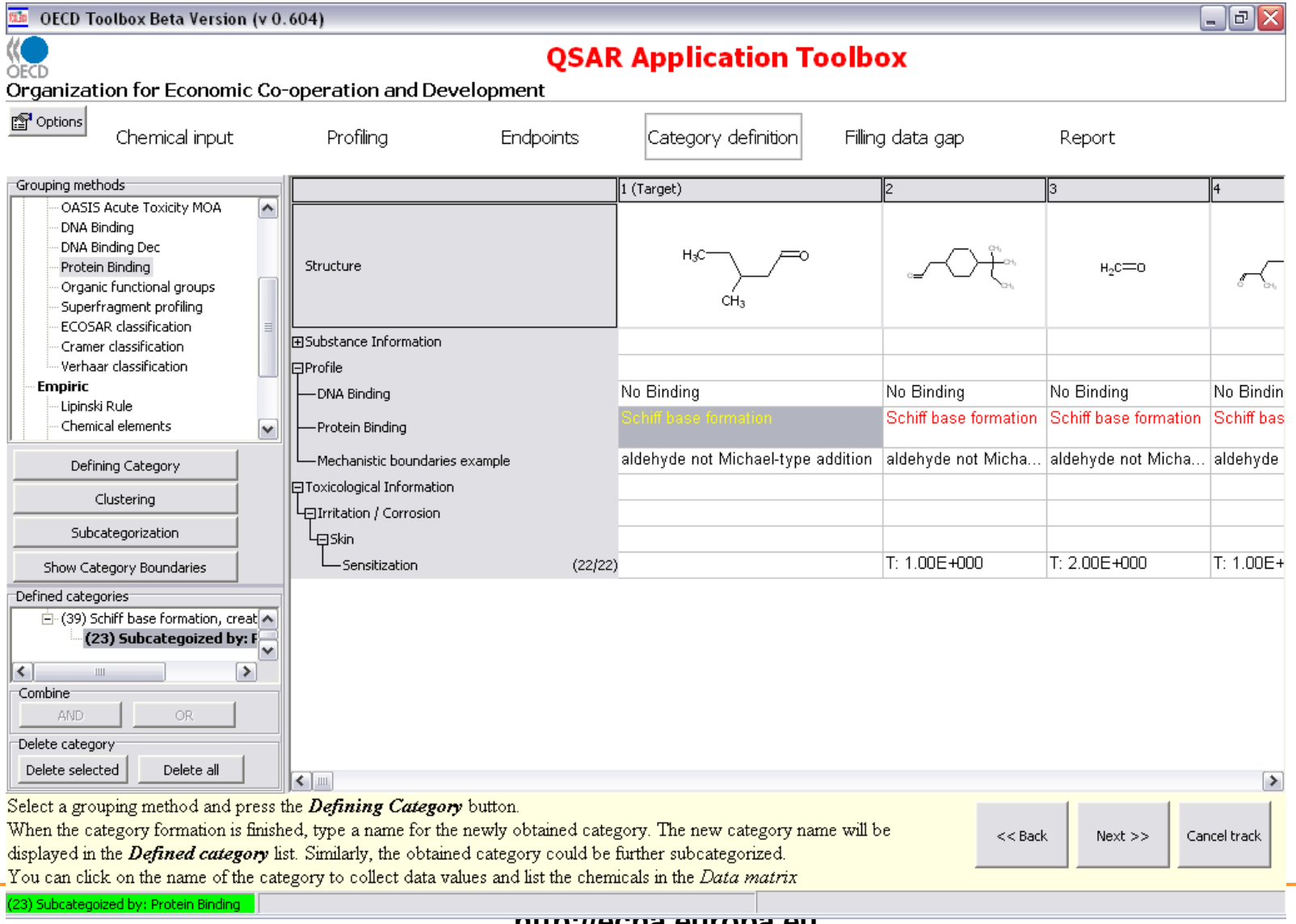
Grouping of chemicals



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

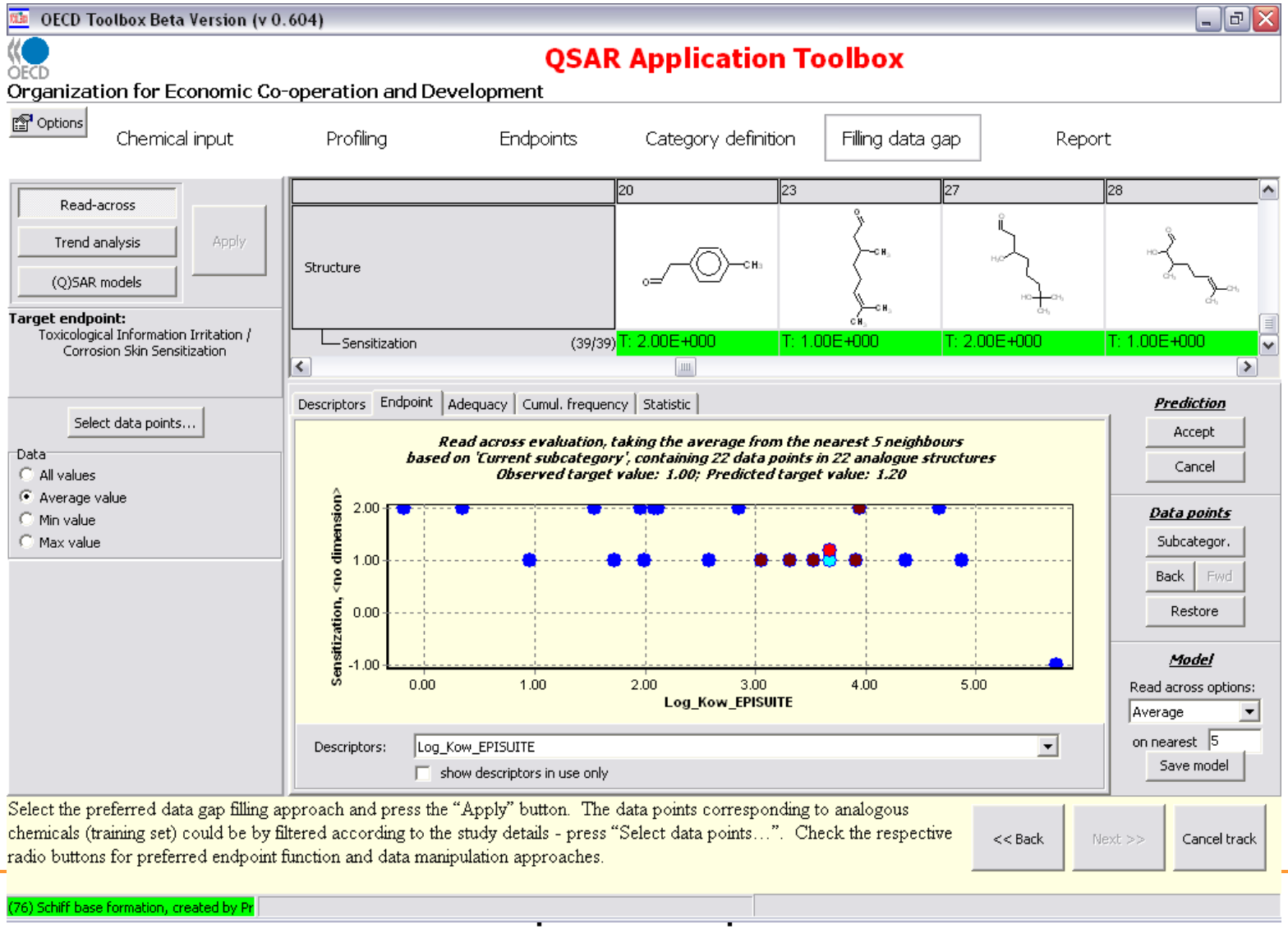
Grouping of chemicals



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



(Q)SAR Application Toolbox

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

Work Plan Project Areas

Phase 2 of the QSAR Application Toolbox

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

Information Technology

- 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

Training

- 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

Vision for the Toolbox

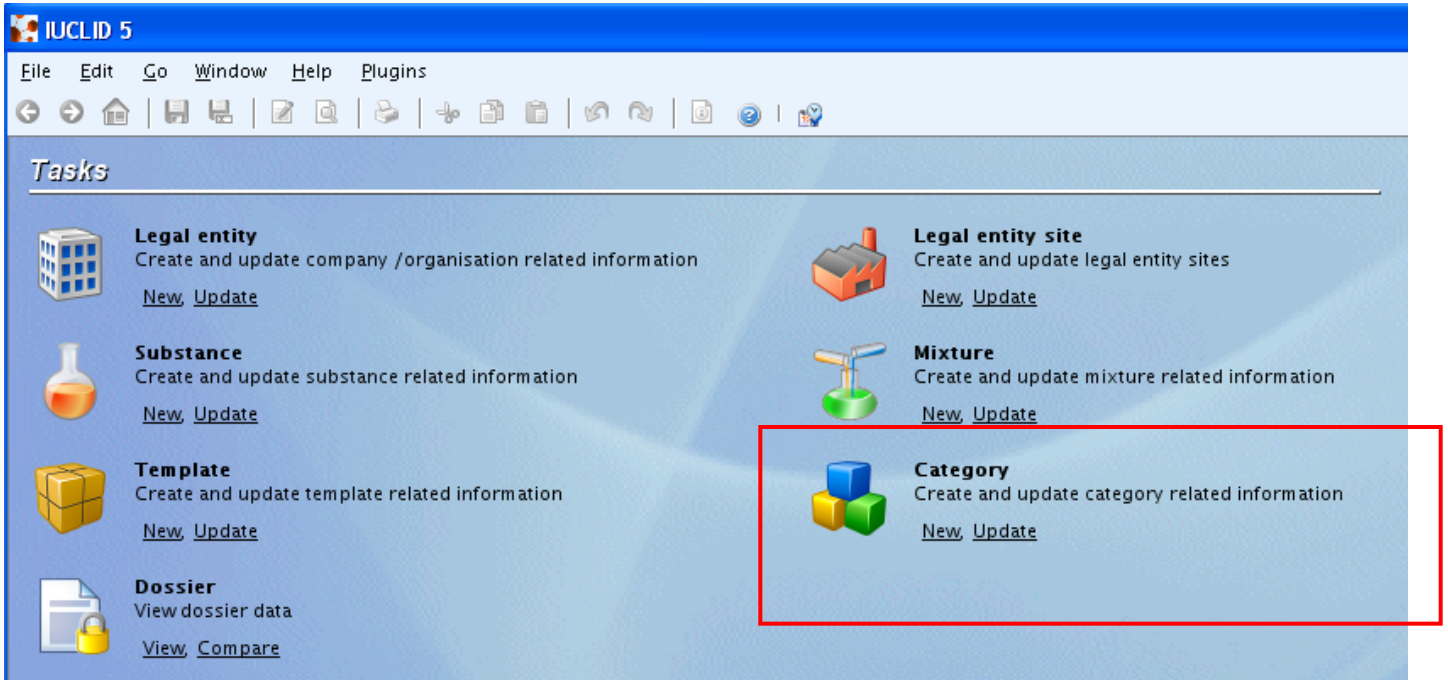
- To ensure that the categories approach to filling data gaps works uniformly for all discrete organic chemicals and for all regulatory endpoints

Importance for REACH

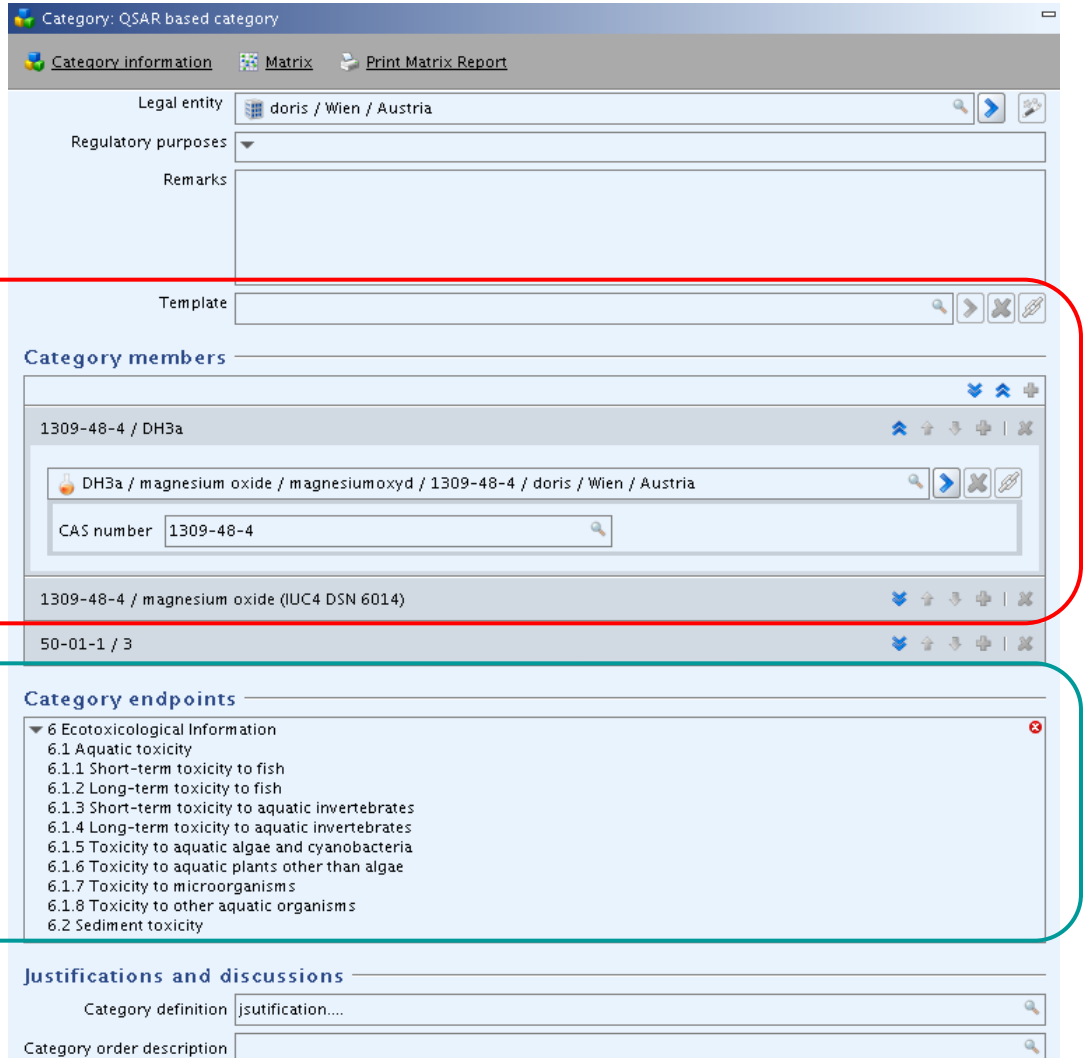
- The (Q)SAR Application Toolbox shall provide a **COMMON BASIS** for the chemical industry, ECHA, and any other stakeholder

Chemical Categories in REACH

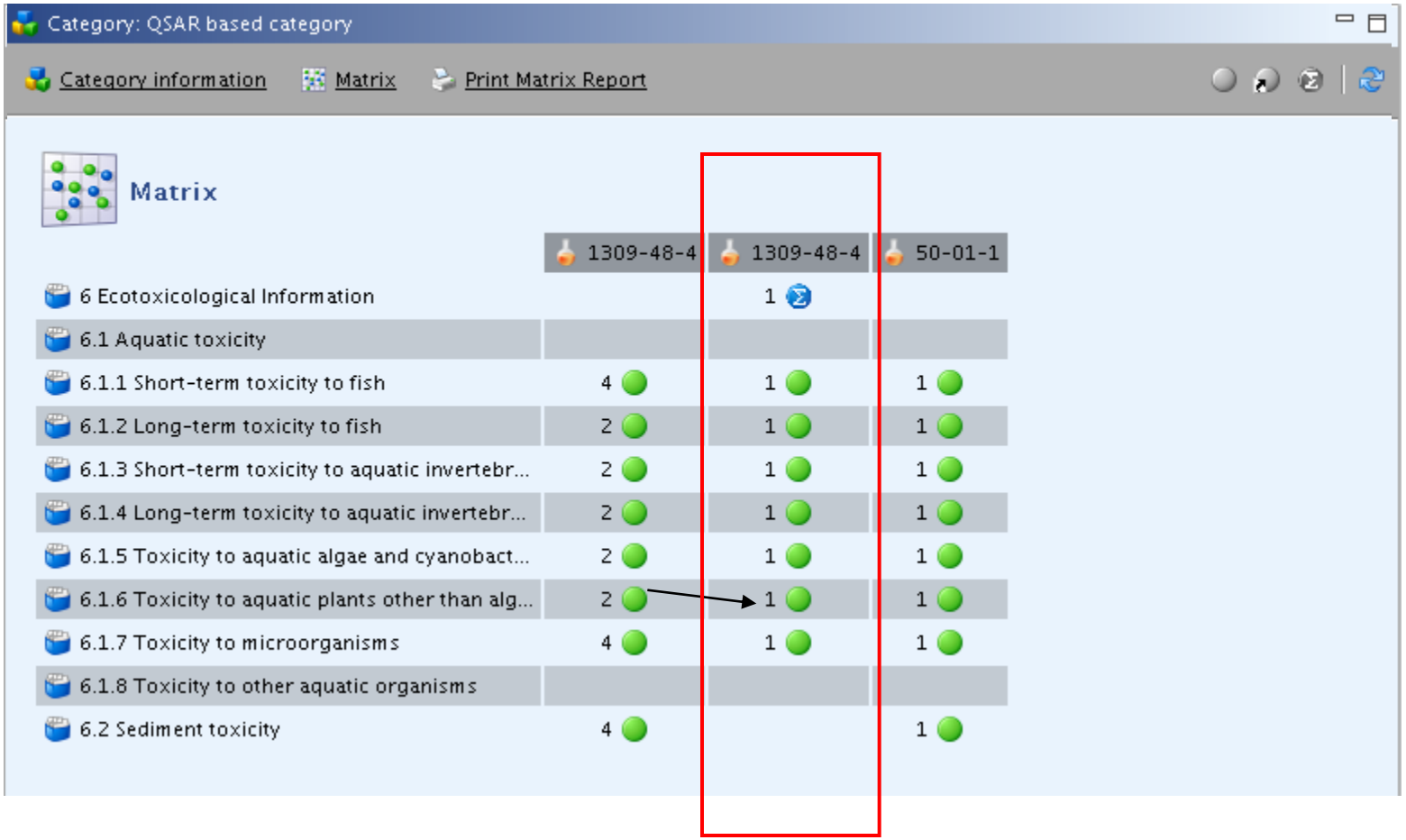
IUCLID 5 provides category functionality:



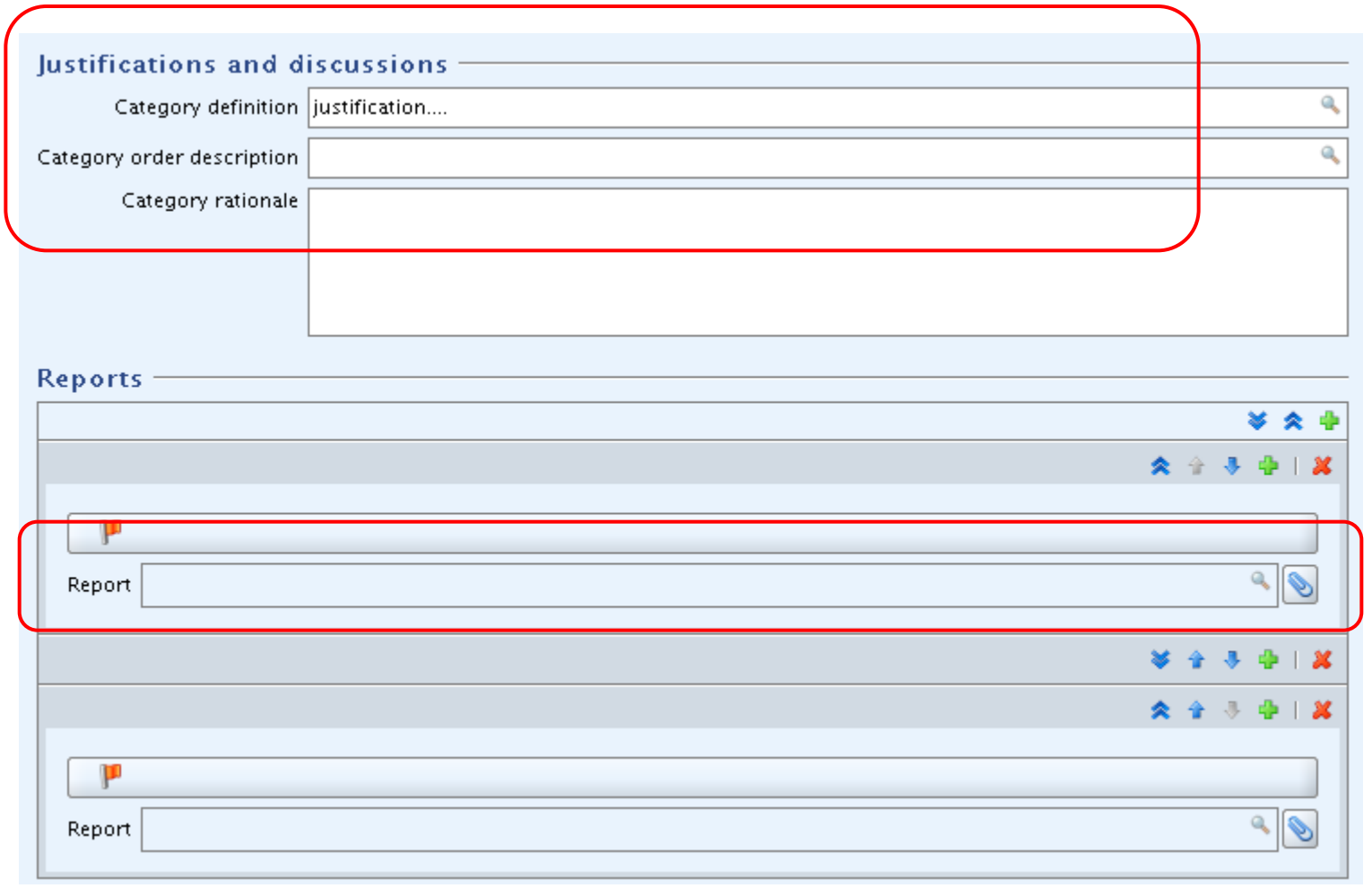
Chemical Categories in REACH



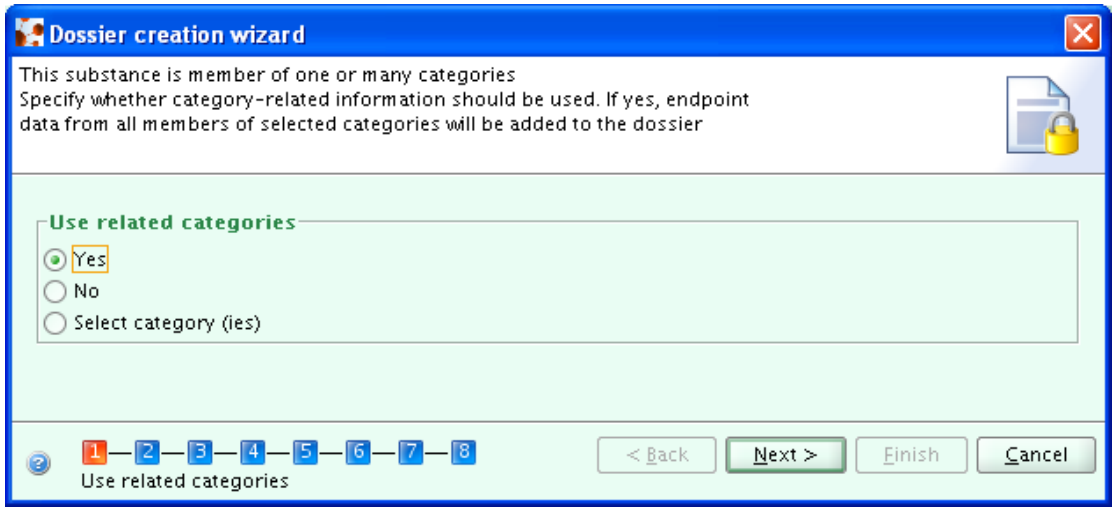
Chemical Categories in REACH

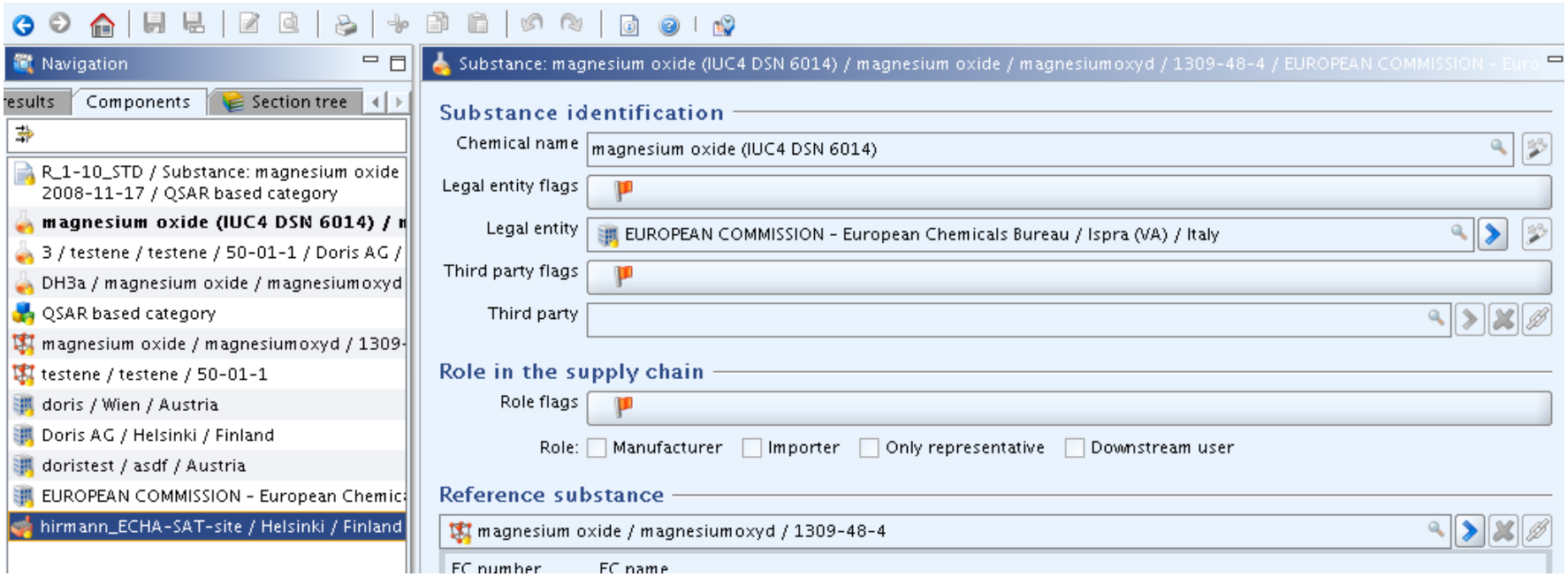


Chemical Categories in REACH



Chemical Categories in REACH





Thank you for your attention!