## QSAR TOOLEOX

The OECD QSAR Toolbox for Grouping Chemicals into Categories

#### OECD QSAR Toolbox v.4.2

An example illustrating RAAF Scenario 2 and related assessment elements

#### **Outlook**

- Background
- Objectives
- Specific Aims
- Read Across Assessment Framework (RAAF)
- The exercise
- Workflow

#### Background

- This is a step-by-step presentation designed to take the Toolbox user through the workflow of a data gap filling exercise and justification of the outcome.
- The read-across prediction will be justified by fulfilling all information requirements according to the Read Across Assessment Framework (RAAF).

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#### **Objectives**

# This presentation demonstrates a number of functionalities of the Toolbox:

- Define target endpoint;
- Calculation of alert performance (AP) accounting for metabolism;
- Searching of analogues accounting for metabolism;
- Category consistency check;
- Selection of RAAF scenario;
- Filling in the report sections related to each read-across assessment element.

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#### **Specific Aims**

- To familiarize the user with the Read-Across Assessment Framework (RAAF) and more specifically with Scenario 2;
- To introduce to the user the read across assessment elements;
- To introduce to the user the report basket;
- To provide sufficient information allowing a scientific assessment of the outcome;
- To explain to the Toolbox user the rationale behind each step of the exercise.

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## Read-Across Assessment Framework (RAAF) Overview

- RAAF was developed by ECHA as an internal tool which provides a framework for a consistent and structured assessment of grouping and read across approaches under REACH.
- The outcome of the assessment is a conclusion on whether the read across is scientifically acceptable or not.
- The RAAF defines different scenarios for different read-across approaches.
- Each scenario is associated with particular aspects (assessment elements, AEs).
- Total six scenarios are available: two for analogue approach and four for category approach.

#### Read-Across Assessment Framework (RAAF) Selection of a RAAF scenario

SCENARIO	APPROACH	READ-ACROSS HYPOTHESIS BASED ON	QUANTITATIVE VARIATIONS
1	Analogue	(Bio)transformation to common compound(s)	Property of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach.
2	Analogue	Different compounds have qualitatively similar properties	Properties of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach.
3	Category	(Bio)transformation to common compound(s)	Variations in the properties observed among source substances. Prediction based on a regular pattern or on a worst-case approach.
4	Category	Different compounds have qualitatively similar properties	Variations in the properties observed among source substances. Prediction based on a regular pattern or on a worst-case approach.
5	Category	(Bio)transformation to common compound(s)	No relevant variations in properties observed among source substances and the same strength predicted for the target substance.
6	Category	Different compounds have qualitatively similar properties	No relevant variations in properties observed among source substances and the same strength predicted for the target substance

\*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf\_en.pdf

## Read-Across Assessment Framework (RAAF) Selection of a RAAF scenario

- Distinguish whether it is an analogue or a category approach\*
- To identify the basis of the read across hypothesis
  - (Bio)transformation to common compound(s) the read across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed
  - Different compounds have the same type of effect(s) the read across hypothesis is that the organism is not exposed to common compounds but rather, as a result of similarity, that different compounds have similar (eco)toxicological and fate properties. These compounds may be the source and target substances themselves or one or more of their (bio)transformation products.
- For a category approach there is a need to take further account whether or not quantitative variations in the properties are observed among the category members

## Read-Across Assessment Framework (RAAF) Selection of RAAF scenario

- Each scenario consists of a pre-defined set of assessment elements (AEs) that, when taken together, cover all of the essential scientific aspects that need to be addressed in the read-across approach for a particular scenario.\*
- Each AE reflects a critical scientific aspect of a read-across.
- The AEs could be:
  - common for all scenario within one approach common AEs for Scenario 1 and 2 (analogue approach) and common AEs for Scenario 3, 4, 5 and 6 (category approach)
  - **specific** addressing specific scenario.

\*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf\_en.pdf

#### **Outlook**

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- Specific Aims
- Read-Across Assessment Framework (RAAF)

#### • The example

• Workflow

#### **The Example**

- In this example we will predict the skin sensitization potential of 1,3-Propanediamine, N-(3-aminopropyl)- [CAS# 56-18-8], which will be the "target" chemical;
- The category will be defined by the mechanism of protein binding accounting for metabolism common to all the chemicals in the category;
- A read-across approach will be used for the prediction. The readacross will be based on analogue approach expressed as common underlying mechanism for metabolites of source and target substances;
- Read-across assessment elements will be included to the report;
- Examples for the possible content of each of AEs will be provided.

#### The Example Sidebar On Skin Sensitization

- Allergic contact dermatitis that results from skin sensitization is a significant health concern.
- Skin sensitization is a toxicological endpoint that is complex and conceptually difficult.
- However, there is growing agreement that most organic chemicals must react covalently with skin proteins in order to behave as skin sensitizers.
- Therefore, mechanisms by which organic chemicals bind with proteins are relevant to grouping chemicals that may be skin sensitizing agents.

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#### Workflow

- The Toolbox has six modules, which are used in a sequential workflow:
  - $\circ$  Input
  - $\circ$  Profiling
  - $\circ$  Data
  - $\odot$  Category Definition
  - Data Gap Filling
  - Report

The modules will be presented in different sequence than the one showed above.

#### **Input** Overview

- This module provides the user with several means of entering the chemical of interest or the target chemical.
- Since all subsequent functions are based on chemical structure, the goal here is to make sure the molecular structure assigned to the target chemical is the correct one.

#### Input Screen Input target chemical by CAS#



Click **CAS#** button (1); Type CAS **56-18-8** in the blank field (2) and click **Search** (3). When the structure appears, click **OK** (4).

#### **Input** Define target endpoint

Defining of the endpoint allows entering the endpoint of interest e.g. EC3, LC50, gene mutation etc., along with specific metadata information. Based on the metadata, different relevancy scores for profiles could be provided for same endpoint.

Calculation of alert performance (AP) is only possible if the target endpoint is preliminary selected.



#### **Input** Define target endpoint



By clicking **Define** (1) you could select the target endpoint. Select **Sensitisation** in the *Human health hazards* category (2) and click **Next** (3). Select **EC3** endpoint (4) from the drop-down menu and then consecutively the following metadata: *Assay*: **LLNA**, *Organ*: **Skin**, *Type of method*: **In Vivo** (5). Finally click on **Finish** (6).

#### **Input** Define target endpoint

Once the endpoint is defined along with its metadata, they appear in the endpoint tree and the corresponding row of the data matrix is highlighted.

QSAR TOOLBOX	► Input ► Profiling	Data     Category definition	01010 01 0 10100 > Data Gap Filling > Report		X 8 5 7 8
Document       Image: Second seco	Single Chemical       Image: CAS#     Name     Structure     Composition	Chemic Chemic Select ChemiDs Database Inventor	📑 - 🖌	Target Endpoint       Output       Output       Output	The OECD QSAR Toolbox for Grouping Chemicals into Categories Developed by LMC, Bulga
Documents  *  Document 1  # CAS: 56188	Filter endpoint tree Structure Human Health Hazards Acute Toxicity Bioaccumulation Carcinogenicity Developmental Toxicity Genetic Toxicity Immunotoxicity Photoinduced toxicity Photoinduced toxicity Repeated Dose Toxicity Skin Skin Skin Skin ToxCast Toxicity to Reproduction Toxicokinetics, Metabol	AW SW AOP .			

#### **Data** Overview

- "Data" refers to the electronic process of retrieving the environmental fate, ecotoxicity and toxicity data that are stored in the Toolbox.
- Data gathering can be executed in a global fashion (i.e., collecting all data for all endpoints) or on a more narrowly defined basis (e.g., collecting data for a single or limited number of endpoints).

#### **Data** Gather data



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#### **Data** Gather data

- Toxicity information on the target chemical is electronically collected from the selected dataset(s).
- It should be kept in mind that the search for data and analogues (and further calculation of AP) is performed only among the chemicals which are listed in the selected databases. In this example only the *Skin sensitization database* and *REACH Skin sensitization database* (normalized) are selected.
- In this example, a pop-up window appears stating there are 5 experimental data points for the target chemical. Positive experimental data are available.
- Go to the *Profiling* module to check for the possible reasons of the positive effect (to check for an alert identified in the target chemical).

#### **Profiling** Overview

- "Profiling" refers to the electronic process of retrieving relevant information on the target compound, other than environmental fate, ecotoxicity and toxicity data, which are stored in the Toolbox database.
- Available information includes likely mechanism(s) of action, as well as observed or simulated metabolites.

#### **Profiling** Profiling the target chemical

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1	<ul> <li>✓ Protein binding alerts for skin sensit</li> <li>✓ Protein binding by OASIS</li> <li>✓ Plausible</li> </ul>	tization by	<ul> <li>Human Health Hazards</li> <li>Acute Toxicity</li> </ul>	i					
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	Metabolism/Transformations Options f Select All Unselect All	Invert	Neurotoxicity     Photoinduced toxici     Repeated Dose Toxic     Sensitisation	city	W AOP				
1	Suitable Autoxidation simulator Skin metabolism simulator Plausible Autoxidation simulator (alkaline mer	dium)	Skin Gin Vivo LLNA EC3						
	<ul> <li>Dissociation simulator</li> <li>Hydrolysis simulator (neutral)</li> <li>Unclassified</li> <li>Hydrolysis simulator (acidic)</li> <li>Hydrolysis simulator (basic)</li> <li>in vivo Rat metabolism simulator</li> <li>Microbial metabolism simulator</li> </ul>		ToxCast Toxicity to Reproduction Toxicokinetics, Meta		buti				

#### **Profiling** Profiling results

- 1) No alerts are identified in the target structure as a parent;
- No metabolites are produced as a result of abiotic activation (Autoxidation simulator);
- 3) 5 metabolites are produced as a result of biotic activation (*Skin metabolism simulator*);
- 4) Endpoint specific protein binding alerts are identified in the metabolites produced by the Skin metabolism simulator.

#### **Profiling** Profiling results

QSAR TOOLBOX	Profiling     > Data     > Category definition     > Data Gap Filling     > Report	X 9 5 4 8
Profiling Custom profile		The OECD QSAR Toolbox for Grouping Chemicals into Categories
Apply View New Delete		Developed by LMC, Bulg
<ul> <li>Documents</li> </ul>	Filter endpoint tree 🝸 1 [target]	
Profiling methods     Options ▲     f Select All Unselect All Invert     Suitable     ✓ Protein binding alerts for skin sensitization ac	Structure H2N~~_NY~~_ANH2	
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	3 x Schiff base formation >> Schiff base formation with carbonyl compounds	

The OECD QSAR Toolbox for Grouping Chemicals into Categories

#### Recap

- In module one, you entered the target chemical and defined the target endpoint.
- In the *Data* module, you saw the database corresponding to the defined target endpoint. You also found some experimental data for the target available in the selected databases.
- In the *Profiling* module, you profiled the target chemical with profiling schemes and metabolic simulators, suitable for the selected target endpoint.
- Protein binding alerts for skin sensitization were identified for some of the metabolites produced by simulating of biotic activation.
- Click "Category Definition" to move to the next module.

#### Category Definition Overview

- This module provides the user with several means of grouping chemicals into a toxicologically meaningful category that includes the target molecule.
- This is the critical step in the workflow.
- Several options are available in the Toolbox to assist the user in refining the category definition.

#### **Category Definition** Grouping methods

- The different grouping methods allow the user to group chemicals into chemical categories according to different measures of "similarity" so that within a category data gaps can be filled by read-across.
- For example, starting from a target chemical for which a specific protein binding mechanism is identified, analogues can be found which can bind by the same mechanism and for which experimental results are available.
- If no alert is identified in the target structure, but is identified in its metabolites, analogues can be searched accounting for metabolism. In this way the target chemical and the identified analogues will have similar metabolic pattern.
- When more than one alert is found in the target structure before or after metabolic activation, Alert performance could be used to define which of them is the most suitable for primary categorization.

#### QSAR TOOLEOX

### Category Definition Searching for analogues accounting for skin metabolism



#### Category Definition Searching for analogues accounting for skin metabolism

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	-				tabalitaa				
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#### **Category Definition** Alert performance calculation

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#### **Category Definition** Alert performance calculation



#### Keep in mind that the statistic is obtained from the chemicals and data, available in the selected databases
# Category Definition Searching for analogues accounting for skin metabolism

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Aquatic toxicity cla Chemical elements Groups of element Keratinocyte gene Lipinski Rule Oasis OECD HPV Chemic Organic functional Organic functional	Metabolite 2 nythere are the second	criteria.		Invert result Strict	3	> X Cancel
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The OECD QSAR Toolbox for Grouping Chemicals into Categories

## **Category Definition** Summary information for Analogues

17 chemicals with 44 experimental results related to the defined target endpoint are found across all 29 analogues.

qsi	AR TOOLBOX	+ Input		Data	Category definition	01010 01 0 10100 ► Data Gap Filling	► Report				X 0 5 0 0	
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US	ibstance type G-EPA New Chemical Categories		EC3		44 M: 0.882 %			M: 1.68 %		M: Positive		M: Ne
		atistic	s presenting t erimental data	he numl	ber of ch	emicals	and					

#### Data Gap Filling Overview

- "Data Gap Filling" module give access to five different data gap filling tools:
  - $\circ$  Read-across
  - Trend analysis
  - (Q)SAR models
  - Standardized workflow
  - Automated workflow
- Depending on the situation, the most relevant data gap mechanism should be chosen, taking into account the following considerations:
  - Read-across is the appropriate data-gap filling method for "qualitative" endpoints like skin sensitisation or mutagenicity for which a limited number of results are possible (e.g. positive, negative, equivocal). Furthermore read-across is recommended for "quantitative endpoints" (e.g., 96h-LC50 for fish) if only a low number of analogues with experimental results are identified.
  - Trend analysis is the appropriate data-gap filling method for "quantitative endpoints" (e.g., 96h-LC50 for fish) if a high number of analogues with experimental results are identified.
  - "(Q)SAR models" can be used to fill a data gap if no adequate analogues are found for a target chemical.

#### In this example we will use the read-across approach.

## **Data Gap Filling** Apply Read-across



## **Data Gap Filling** Apply Read-across



Open **Select/filter data** and **Subcategorize** by: 1) *Protein binding alerts for skin sensitization by OASIS* profiler in combination with *Autoxidation simulator, 2*) Remove the different analogues; 3) *Structural similarity 4*) *Select* all analogues (3) similar less than 30% to the target chemical, by hold Ctrl button; 5) Click *Remove* 

March, 2010

#### **Data Gap Filling** Apply Category consistency elements

SAR	TOOLBOX	t input	► Profiling	► Data	► Cat	egory definition	01 0 10100 Data Gap Filling	► Report			
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Aquatic Chemica		Add / Remove									Mark chemicals by descriptor valu
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category elements<sup>\*</sup> (1). No different selection than the default is needed – click **OK** (2). Once the category elements are applied **accept the prediction** (3).

\*For more information on category elements see Tutorial\_1\_TB 4.2. Category consistency

#### Recap

- In the *Category definition* module you found analogues based on the alert with the best performance accounting for skin metabolism.
- In *Data gap filling* module you applied a read-across approach. Readacross is the appropriate data-gap filling method for "qualitative" endpoints like skin sensitisation. Since the most of the analogues and all five neighbouring tested chemicals in the category were positive, it was easy to accepting the prediction of positive for the target chemical.
- Category consistency was checked by applying the category elements.
- You are now ready to complete the final module and to create the report.
- Click "Report" to proceed to the last module.

#### **Report** Overview

- Report module allows generating a report for any of the predictions performed within the Toolbox.
- The report module contains predefined report template which users can customize.
- Additionally specific RAAF scenario could be chosen. Selection of one of the scenarios will append automatically the related assessment elements related to the corresponding report sections.

#### **Report** Selection of RAAF scenario

To select the applicable RAAF scenario for assessment, the following aspect should be identified\*:

- the type of approach applied analogue approach or category approach;
- the read-across hypothesis;
- For category approach whether quantitative variations in the properties are observed among the category members must be considered.



\*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf\_en.pdf

The OECD QSAR Toolbox for Grouping Chemicals into Categories

#### **Report** Selection of RAAF scenario

For the current example:

- the type of approach applied analogue approach is used (threshold of ≤3 analogues is proposed by LMC for the analogue approach);
- the read-across hypothesis different compounds with common underlying mechanism for metabolites of source and target substances;

Based on that Scenario II was identified as appropriated for the current example.



# Read-Across Assessment Framework (RAAF) Scenario 2

- Scenario 2 covers the analogue approach for which the read-across hypothesis is based on different compounds with qualitatively similar properties.
- For the REACH information requirement under consideration, the property investigated in a study conducted with one source substance is used to predict properties that would be observed in a study with the target substance if it were to be conducted.
- The current case corresponds to Example 2 for Scenario 2 of the RAAF\*. The target (B) and the source chemicals (A) are biotransformed to substances causing the same type of effects through a common mechanism (A1 and B1). The rest of the obtained compounds, non-common for the target and the source substance does not influence the prediction of the property under the consideration.

	PARENT SUBSTANCES	(BIO)TRANSFORMATION	COMMON COMPOUND	NON-COMMON COMPOUNDS
SOURCE	A	A → A1+ A2	A1	A2
TARGET	В	B → B1	B1	-

\*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf\_en.pdf

#### Report

#### Generation report according to RAAF-Scenario 2

QSAR TOOLBOX	*	<u></u>	Ê	H	01010 01 0 10100			X 0 5 4 0	
Reports	Input	Profiling	► Data	Category definition	Data Gap Filling     Data Customize report content a	Report ind appearance			>
ediction 2 gory QMRF		Filter endpoint tree		💙 1 [target]	Wizard pages			cking/unchecking the correspon uttons "Move Up" and "Move Do	
Docut     CAS: 56188      # CAS: 56188      Grouping with metabolism: 'Sk      F Enter GF(RA) with 17 chemica      G Ch: 9] Data: 9 Subcategori      G Ch: 9] Data: 9 Subcategori	ls, 44 data po	Structure		1/2~~~10~~~10	Customization Customize report Prediction	Add RAAF	<sup>F</sup> scenario	Scenar	io 2
교 편 Ch: 외 Data: 9 Subcategori [@ Ch: 4] Data: 4 Subcategori		Human Health Hazards     Acute Toxicity				3 Target and pred Prediction deta	ails (I)		
		Bioaccumulation     Carcinogenicity     Developmental Toxici	ty / Teratogenicit	y .	Prediction details (l)	<ul> <li>✓ Target profiles</li> <li>✓ Analogues sele</li> </ul>	ection details		
		Genetic Toxicity     Immunotoxicity     Irritation / Corrosion			Prediction details (II) Target profiles		uping / subcategorization cific report explanations		
		Neurotoxicity     Photoinduced toxicity     Repeated Dose Toxici	ty		Analogues selection details	Category defin Consistency ch	iition and members neck		
		Skin in Vivo	AW SW /		Category Category definition and members	Data matrix			
		⊕ GPMT ⊕ HRIPT ⊖ LLNA		16/21 M: Category 1B 1/2	Consistency check Options			Mor	ve Up Move Do
		ToxCast	ous 1	17/45 M: 0.882 % M: Category C	<b>Data matrix</b> Options		sword protection of the tion is removed, this will be	PDF files. specified in the first page of	the report
		Toxicity to Reproduct     Toxicokinetics, Metab     Profile     General Mechanistic		u :			Back	Next Ca	Create rep
1. Go to the <b>Rep</b>	ort mo	<b></b>	on the	cell with th	ne prediction:	2 Click the	Prediction	hutton: 3 Ch	eck the

1. Go to the **<u>Report</u>** module and click on the cell with the prediction; 2. Click the **Prediction** button; 3. Check the box at the top to add RAAF scenario; 4. Select **Scenario 2** from the drop-down menu.

## Report

#### Generation report according to RAAF-Scenario 2



corresponding sections of the report automatically. AEs appear in the following report sections: **Target profiles** (2). **Category definition and members** (3) and **Consistency check** (4).

Each of the AEs will be considered in the next slides.

Customize report content an	nd appearance	🗨 💽 Report basket	↔ _		
	3	Options  f Select All	11 1 4 4		
Wizard pages			Unselect All	Invert	-
wizaru pages		□ □ Category □ □ □ □ Chemical profile ("Protein bindin	in alerts for skin sensitization accord	ing to GHS")	
		Profiling similarity accounting for			
Customization		Profiling similarity accounting for	. 💽 Create new items 🛛 😁	_	
Customiza raport	Select profiles to report	 □ 耳 Chemical profile ("Protein bindin □ 耳 Chemical profile ("Protein bindin	Options 🖌		
Customize report		Profiling similarity accounting for		Unselect Al	l Inve
Prediction	Show profiles in report	Profiling similarity accounting for			
Target and		Profiling similarity accounting for			
prediction	Export profiles in Excel file	Profiling similarity accounting for			
summary		Category members	電Chemical profile		
	Active descriptor value(s) Automatically populated I	☐ 및 Scruccului similaric) □ 및 Chemical profile ("Organic funct	山Mechanistic similarity 描Structural similarity		
Prediction details	• AE 2.1: Compounds the test organism is exposed to	🔲 🛱 Chemical profile ("Structure sim	A External content		
(I)	Hint	the Endpoint data variation (5 selection)		r	
Prediction (	PURPOSE:	<ul> <li>□ □ Parameter variation (5 selected</li> <li>□ □ Parameter values</li> </ul>	A Text provided by user		
<b>↓</b>	In this scenario, it is claimed that different compounds hav				
(  )	consideration. Such different compounds may be the source	🔺 🗌 Grouping			
Target profiles	(bio)transformation products. It has to be assessed whethe				
	<ul> <li>the compounds to which the test organism is exposed (at</li> </ul>	Input Target substance			
Analogues	substances) have been established in the documentation; a - the provided evidence supports the explanation.			ОК	Cancel
selection details	- the provided evidence supports the explanation.		L		
Category			¬ T		
Category defi	Add / Remove			>	
and members 2		<u> </u>			
			Create new OK	Cancel	
Consistency check					_

Hint for each of the assessment elements is available (1). Information can be included by clicking the **Add/Remove** button (2) located below the corresponding AE. The *Add/Remove* button invokes the so-called "*Report basket*" (3). The latter contain different items triggered by the actions of the user during the workflow (e.g. Alert performance calculation, applying of category elements, etc.).

Additionally, new items (including items with external content) can be created (4).

Items with external content (picture and text) will be added for AE 2.1. Compounds the test organism is exposed to

Customize report content and	opearance ++ ×	
Wizard pages	Report basket     Options ₄     Options ↓     Options ↓     Options ↓     Options ↓     Options ↓     Options ↓	
Customization Customize report	□ □ Chemical profile Options ⊿	rce D
Prediction Target and prediction	Show profiles in tep     Defiling similarity     f     Select All     Unselec     Defiling similarity     f     Select All     Unselec     Defiling similarity     f     Category     The control of	
summary Prediction details	Active descriptor value → AE 2.1: Compound → Profiling similarity → AE 2.1: Compound → Profiling similarity →	
(l) Prediction details (ll)	♦ Hint       □ \$ Structural similar       \$ Structural similar       \$ Structural similarity         PURPOSE:       □ \$ Chemical profile       ▲ External content       Image width, % 75         In this scenario, it is       □ \$ Chemical profile       ▲ External content	
Target profiles Analogues	Image: State and the state	Cancel
selection details	substances) have be - the provided evide Add / Remove Add / Remove Grouping Imput Cancel	
Category defi and members		
Consistency check Options	Create new OK Cancel	

Click the **Add/Remove** button (1) and then **Create new** (2). Select to create an item with external content – **Image provided by user** (3) and click **OK** (4). New window appears where you can add your custom picture by Copy/Paste or browsing (5) to the directory in your PC where the desired picture is saved\*. Finally confirm by **OK** (6).

\*In the current example a picture illustrating the target chemical marked as **Target A** and source chemicals marked as **Source A**, **B** and **C** was prepared in advance.

		💽 Report basket	↔ _		×		~	1					
Customize report content and	appearanc	Options 🖌					×						
		f Select All	Unselect All		Invert								
Wizard pages		▲ Category □ □ Chemical profile ("Protein")	Create new items		↔	-		×					
		Profiling similarity account In Profiling similarity account	options ∡ f Select All	Unseleo	+ ΔII	Invert	_				-		
Customization	🕑 Sele	□ 铒 Chemical profile ("Protein	Category     Endpoint data variation	Unselex		intere	0			5	-		Х
Customize report	Jen		#Parameter variation				Enter y	our tex	t here:				
Prediction	✓ Show		電Chemical profile <b>业</b> Mechanistic similarity						nces (analogues) B, C	and D has sam	e primary aliph	atic amin	e ^
Target and		Profiling similarity account	In the second						substance A;				
prediction	Expor	The Structural similarit	External content Image provided by user					-	d source substances a				
summary	Active de	E Chemical profile (	A Text provided by user						wo alerting groups and is defined based on t				
Prediction details	🔿 AE 2.	, 🔲 🛱 Endpoint data variation (							ording to Protein bindi				
(I)	Hin	ー □ 国 Parameter variation (5 se ロ □ 国 Parameter values		4					r SS metabolism;				
Prediction details	PURPO	□ 国 Endpoint data values				юĸ	Positiv	e exper	imental data is availab	le for the sour	e substances E	B, C and D	2
(11)	In this	External content	image from cliphoard No. 1.)			ler	Substa	nces B,	C and D are used to p	redict the toxic	effect of subs	tance A.	
Target profiles	1	Grouping				nd/or the							$\vee$
Analogues	substa	A Target substance				ie target				6 5	> OK	Cano	el
selection details	- the p												
Category	Add				>								
Category definition	Add		Create new OK	Ca	ncel								
and members													

The newly created item appears in the *Report basket* (1). Now text will be also included. Click **Create new** (2), select **Text provided by user** (3) and click **OK** (4). Copy the following example text:

- Source substances (analogues) B, C and D has same primary aliphatic amine as the target substance A;
- The target and source substances are activated as a result of skin metabolism. Two alerting groups are identified: Aldehyde and Bis aldehyde;
- Primary group is defined based on the alert with highest performance: Bis aldehyde according to Protein binding alerts for skin sensitization profiler accounting for SS metabolism;
- Positive experimental data is available for the source substances B, C and D (references for the data could be also included)
- Substances B, C and D are used to predict the toxic effect of substance A.

and paste it in the new window (5). Finally confirm by **OK** (6).

#### **Report** Assessment elements <u>of Scenario 2</u>

Customize report content and	appearance ↔ _		×		Target profiles (OECD principle 5 - Chemical and biological mechanisms)
					Profiles used for grouping/subcategorization
Wizard pages					Using of "Skin metabolism simulator" Combined parent Parent and 5 metabolites:; and products requirements: Schiff base formation >> Schiff base formation with carbonyl compounds >> Bis didehydes (Protein binding alerts for skin sensitization by OASIS) (primary grouping) Has the following additional categories: No alert
Customize report	<ul> <li>Select profiles to report</li> </ul>				found, Schiff base formation, Schiff base formation >> Schiff base formation with
diction	✓ Show profiles in report				carbonyl compounds, Schiff base formation >> Schiff base formation with carbonyl compounds
Target and prediction	Export profiles in Excel file			4	
summary	Active descriptor value(s) Automatically populated by the system			•	ructure similarity (subcategorization) [90%,100%]
Prediction details					vog Kow (calculated): -1.15
(I)	AE 2.1: Compounds the test organism is exposed to				AE 2.1: Compounds the test organism is exposed to
	© Hint 2	3			1. Image provided by user (image from clipboard No.1)
Prediction details (II)	Add / Remove				Target A Source B Source C Source D
Target profiles	Image provided by user (image from clipboard No.1)	Preview			
Analogue selection	A Text provided by user (Target substance A and three source s Edit	Preview			Target substance A and three source substances (B, C and D); Source substances (analogues) B, C and D has same primary aliphatic amine as
egory			_		the target substance A;
Category definition					The target and source substances are activated as a result of skin metabolism. Two positive alerting groups are obtained: Aldehyde and Bis aldehyde;
and members					Primary group is defined based on the alert with highest performance: Bis
Consistency check					aldehyde according to Protein binding alerts for skin sensitization profiler
					accounting for SS metabolism; Substances B, C and D are used to predict the toxic effect of substance A.
Options					Substances B, C and D are used to predict the toxic effect of substance A.
ta matrix					
Options					
h newly create	ed items appear under the <b>AE 2.1</b> . (1). Each	of the	<b>_</b> ~		
	ed (2) or just previewed (3) in a <i>.pdf</i> format.		ort		
	the AE 2.1. and related description will look	in th		_	
				09	AR Toolbox 4.2 OSAR TOOLBOX

Prediction of EC3 for Iminobis-3-propylamine

4/6

Customize report content an	d appearance		+	- 0	×		1	egory members	ation of source substa		
						- 1	*	CAS	Name	SMILES	Structure
Wizard pages						3	1	56-18-8	Iminobis-3- propylamine	NCCCNCCCN	
<b>tomization</b> Customize report	Profiles/Metabolisms										H2N~NHNH2
diction	Category members				$\neg$		2	109-55-7	3.	CN(C)CCCN	
	AE A.1: Characterisation of sou	urce substance					-	105-55-7	aminopropyldimethy		
Target and	Hint								amine		H3C
prediction	PURPOSE:										CH3
summary		the source substance needs to have	ve a clear substance c	haracterization. It has to							
Prediction details	be assessed whether:						3	107-15-3	Ethylenediamine	NCCN	
(1)	<ul> <li>the chemical identity of the an- across; and</li> </ul>	alogue is sufficiently clear for a m	eaningful assessment	of the proposed read-							
Prediction details	- the impurity profile is clear.										H <sub>2</sub> N NH2
(11)	Name CAS and/or FC number of	hemical structure should be provi	ided								tunz (
Target pro			laca.								
Analogues 1	Add / Remove								•		•
selection c											
gory	Category members			Preview							
Category definition and members	Purity / Impurity					QS	R Toolbox 4	1.2	OSAR	TOOLBO	( TPRF
Consistency check					-	Datz	ibase versio	n: 4.2			
Options	AE A.1: Characterisation of sou	irce substance									
a matrix	Hint					Che	nicals categ				3
Options 2	PURPOSE:										
	Impurity profiles for the source s	substance should be provided (wit	th identifiers as define	2d above).	_		4	111-40-0	Diethylenetriamine	NCCNCCN	
	Add / Remove										
											H2N NH NH2
	AE A.3: Reliability and adequad	:y of the source study									
	Hint										
-	Add / Remove							<b>Impurity</b> provided by the			manually editable field
					$\sim$				e user ation of source substa	nce	
				Cancel Create re				provided by us			

Two AE (AE A.1 and A.3) related to Scenario 2 are included in the Category definition and members section.

- AE A.1 Characterization of source substance is automatically filled by the system using the available items in the *Report* basket. In this example Category members item (1) is appended, only. If impurities/additives of the used analogues are available, they will appear under the *AE A.1* in *Purity / Impurity* (2). The current analogues have no additives/impurities. Example of how the AE A.1. will look in the generated report is shown on the right(3).
- AE A.3 Reliability and adequacy of the source study should be filled in manually (4) (see on the next slide)

Customize report content and	appearance ** - $\Box$ ×	
Wizard pages		
Customization Customize report		
Prediction	Category members	
Target and	AE A.1: Characterisation of source substance	
prediction summary	Purity / Impurity	+ ypu     + Andreg + (unit + Calegory definition + Data Capering + Apport     Cape Calegory     the      -      X
Prediction details	✓ AE A.1: Characterisation of source substance	Use ubcategorisation We ubcategorisation Combine categories
(I)	AE A.3: Reliability and adequacy of the source study	Vez Vez Matrials/Mrthods
Prediction details (II) Target profiles Analogues selection details Category Category definition and members	<ul> <li>→ Hint</li> <li>PURPOSE: The source study needs to match the default REACH requirements in terms of reliability and adequacy as requested for any other key study. It has to be assessed whether: - the study design reported for the source study is adequate and reliable for the purpose of the prediction based on read-across: - the study design should cover the key parameters in the corresponding test method referred to in Article 13(3); - the study design should cover an exposure duration comparable to or longer than the corresponding method referred to in Article 13(3); and - there is adequate and reliable documentation of the applied test method, i.e. a robust study summary should be provided. The test material used represents the source substance as described in the</li> </ul>	Duality of guideline The method / duality of the method / dua
Consistenc Options Data matrix	hypothesis in terms of purity and impurities. Add / Remove	Database Description Database Clearered from 5.802 to 53%, Predicted 2.27%. Prediction Predictin Prediction Prediction Prediction Prediction Pr
Options	A Text provided by user (• The all three source substance are Edit Preview	Ter material kately (kote) Ter material dentely (kote) Ter material dentely (kote) URL Material dentely (kote) URL Select different URL Select different
2	Image provided by user (image from clipboard No.1)         Edit         Preview           Back         Next         Cancel         Create report	

**AE A.3:** Click the **Add/Remove** button (1) and create new item with textual content (2) (see slide 52).

In the text field paste the following example text:

"The all three source substance are tested according to the Local lymph node assay (LLNA)

The study is used to predict the skin sensitization effect concerning LLNA study for the target substance"

Additionally a snapshot of the filter by test conditions window (2) could be added to confirm the consistency regarding the assay.

Customize report content and     Wizard pages	appearance ↔ — □	×	AE A.3: Reliability and adequacy of the source study • The all three source substance are tested in a local lymph node assay (LLNA) • The study is used to predict the skins sensitization effect concerning LLNA study for the target substance
Customization Customize report Prediction Target and prediction summary Prediction details (I)			Image provided by user (Image from clipboard No.1)
Prediction details (II) Target profiles Analogues selection details <b>Category</b> Category definition and members Consistency check	<ul> <li>AE A.3: Reliability and adequacy of the source study</li> <li>→ Hint</li> <li>PURPOSE:</li> <li>The source study needs to match the default REACH requirements in terms of reliability and adequacy as requested for any other key study. It has to be assessed whether:</li> <li>the study design reported for the source study is adequate and reliable for the purpose of the prediction based on read-across:</li> <li>the study design should cover the key parameters in the corresponding test method referred to in Article 13(3);</li> <li>the study design should cover an exposure duration comparable to or longer than the corresponding method referred to in Article 13(3); and</li> <li>there is adequate and reliable documentation of the applied test method, i.e. a robust study summary should be provided. The test material used represents the source substance as described in the hypothesis in terms of purity and impurities.</li> </ul>		QSAR Toolbox 4.2 Database version: 4.2       QSAR TOOLBOX       TPRF v4.2         Chemicals category       3/12
	Add / Remove Text provided by user (• The all three source substance are Edit Preview Image provided by user (image from clipboard No.1) Back Next Cancel Create rep How the <b>AE A.3</b> . will look in the port is shown on the right.	ort	

Wizard pages		Example text for AE 2.4. Exposure to other compounds than to those linked to the prediction:
. 5		•Target substance A and source substances B,C and D are al metabolized to aldehydes and bis aldehydes;
Customization Customize report Prediction Target and prediction summary	AE 2.4: Exposure to other compounds than to those linked to the prediction     Hint     PURPOSE:     Other compounds than those linked in the hypothesis to the prediction may be formed via other (bic)transformation pathways or may be     intermediates/metabolites of the identified pathway. In addition, the impurity profiles associated with the source and target substances     may have an impact on the prediction. The other compounds may have been identified by the hypothesis, but not linked to the prediction.	<ul> <li>Bis aldehydes functionality is responsible for the toxic effect;</li> <li>Aldehydes are not expected to cause skin sensitization effect by the expert knowledge;</li> <li>The latter is confirmed with the smaller value of aler performance of the group</li> </ul>
Prediction details (I) Prediction details (II)	Another possibility is that the occurrence of such compounds has been identified by the assessing expert. It has to be assessed whether: - other compounds that those linked to the prediction may be formed (e.g. via another (bio)transformation pathway or as intermediates) or are present as impurities (see AE A1); and - indications are available that such compounds could influence the prediction of the property under consideration. Add / Remove	Example text for AE 2.5. Occurrence of othe effects than covered by the hypothesis and justification:
(II) Target profiles Analogues selection details <b>Category</b> Category definition and members	AE 2.5: Occurrence of other effects than covered by the hypothesis and justification     Hint     PURPOSE:     It has to be assessed whether:     - additional mechanisms than those identified in the hypothesis may be acting on the basis of mechanistic insights or derived from     information in the data matrix; and     - these additional mechanisms affect the prediction for the property under consideration.	<ul> <li>Target substance A and source substances B,C and D ar metabolized by skin metabolism simulator;</li> <li>Protein binding alerts (PBA) for skin sensitization ar identified in the metabolites of the target and source substances;</li> <li>No PBA for chromosomal aberration are identified in the</li> </ul>
Consistency check	Add / Remove	target and source substances, nor in the structures of the metabolites.
Data matrix Options	At A: bias that influences the prediction     Hint     PURPOSE:     It has to be assessed whether:     - It is clear from the documentation how the source substance(s) have been chosen, for example, what methods/tools have been used to     map the field of potential source substance(s), which other substances have been considered and why they have been discarded;     - there are additional, structurally-similar substances which are currently not used in the analogue approach and which arguably could be     used;     - there are additional, structurally-similar substances which are currently not used in the analogue approach and which arguably could be     used;     - there are additional substances in the prediction (possibility of underestimation of hazard).     Add / Remove     uded to the Consistency check section.	<ul> <li>Example text for AE A.4. Bias that influences the prediction:</li> <li>Alert performance is used to define the alert with the best prediction purposes with respect to the target endpoint. Buddehyde functionality is selected for searching for analogues.</li> <li>All identified analogues that have PBA as a result of Autoxidation simulator are removed. The most dissimilar chemicals (with similarity below 30%) are also removed. Expert can provide additional literature search of similarity</li> </ul>

Customize report content and	appearance	+	- 🗆	×	Γ	Calculated st	ructure simi	larity	
Wizard pages						Chemical 1 Chemical 1 100% Chemical 2 37.5 %		Chemical 61.5 % 36.4 %	3 Chemical 4 87.5 % 28.6 %
Customization Customize report Prediction	Structural similarity  Justification for selected structure similarity profilers					Chemical 3 61.5 % Chemical 4 87.5 %	36.4 %	100% 72.7 %	72.7 % 100%
Targo pred 1 sumi	Add / Remove	Edit	Preview			Chemical profile ("Organic f	unctional groups"; 2	3	
Prediction details (I) Prediction details	Chemical profile ("Organic functional groups, Norbert Haider (check     Chemical profile ("Organic functional groups")	mc Edit Edit	Preview Preview			H <sub>2</sub> N NH NH <sub>2</sub>	H <sub>3</sub> C CH <sub>3</sub>	∼ <sub>NH2</sub> H	H <sub>2</sub> N NH <sub>2</sub>
(II) Target profiles	Chemical profile ("Structure similarity")	Edit	Preview						
Analogues selection details <b>Category</b>	structural similarity					Amine, primary Amine, secondary Aliphatic amine, primary Aliphatic amine, secondary	Amine, primary Amine, tertiary Aliphatic amine, p Aliphatic amine, te	Alip rimary	ine, primary ohatic amine, primary
Category definition and members Consistency check Option Data matrix Option 2	AE A.2: Link of structural similarity and differences with the proposed prediction     Hint     PURPOSE:     The aim of this AE is to verify that the source and target substances are covered by the n     be assessed whether:     - the scientific hypothesis establishes the structural similarities and differences of source     - structural similarities and differences are linked with the possibility to predict similar pr     - the provided evidence supports the proposed link between structural similarities and th     Add / Remove	and target; operties; and		20		4 H <sub>2</sub> N			

#### **AE A.2**. Link of structural similarity and differences with the proposed prediction is related to the structural similarity of the final category.

All items in the report basket related to the structural consistency of the category (1) are added automatically. The following example text can be added for AE A.2. (2) by analyzing the structural similarity items:

- Structural similarity between Target substance A and 3 source substances B, C and D according to Str.similarity profiler is in the range of [29-88%]
- They all have primary aliphatic amine based on the OFG profiler, while the target substance A and source substance D have additional secondary aliphatic amine and the source substance B has additional tertiary amine functional group.

Customize report content and	appearance ↔ – □ ×			Alert performance Scale=Skin sensitisation II	(ECETOC); E	ndpoint=EC3; M	letabolism=Sl	in metabolism s
Wizard pages			#	Alert name	Alert pe	rformance, %	Number	of chemicals
ustomization					Positive	Negative	Positive	Negative
Customize report	✓ Mechanistic similarity	^	1	Using of "Skin metabolism	78.57	21.43	11	3
ediction	Justification for selected mechanistic similarity profiles/metabolisms			simulator" Combined parent and				
Target and	Add / Remove			products requirements:				
prediction summary				No alert				
	The Chemical profile ("Protein binding alerts for skin sensitization by OASIS Edit Preview			found <and>Aldehydes<an< td=""><td></td><td></td><td></td><td></td></an<></and>				
Prediction (I)	백 Chemical profile ("Protein binding alerts for skin sensitization according Edit Preview			D>Bis aldehydes (Protein				
Prediction	The Chemical profile ("Protein binding by OASIS")			binding alerts for skin sensitization by OASIS)				
				Using of "Skin metabolism	45.35	54.65	575	693
Target profiles	Profiling similarity accounting for metabolism ("Autoxidation simulator Edit Preview		2	simulator"	45.55	54.05	5/5	093
Analogues	📥 Profiling similarity accol 🥘 Report basket 🦷 🚽 🗆	×		Combined parent and				
selection details	Profiling similarity accord Options ⊿			products requirements:				
tegory	f Select All Upselect All Invert About O	otions		No alert found (Protein				
Category definition	Profiling similarity accol			binding alerts for skin				
and members	Profiling similarity accounting for metabolism ("Skin metabolism Endpoint data variation (5 selected: Human Health Hazards#)			sensitization by OASIS) Using of "Skin metabolism	48.99	51.01	169	176
Consistency check	▲ Profiling similarity acco		<b>X</b> °	simulator"	40.99	51.01	109	170
Options		ula		Combined parent and				
<b>ta matrix</b> Options	Comments on 目間 Parameter values mechanistic similarity 目目 Endpoint data values			products requirements:				
Options	internalistic similarity int			Aldehydes (Protein binding				
	A E 2.2: Common underlying m			alerts for skin sensitization				
	⊘ Hint Select All			by OASIS)	02.25	17.05		2
	PURPOSE: Unselect All		4	Using of "Skin metabolism simulator"	82.35	17.65	14	3
	of effects / absence of effects   b	<u>`</u>		Combined parent and				
	- the documentation has establis Invert			products requirements:				
2	qualitatively similar type of effec	el 📗		Bis aldehydes (Protein				
2	- the provided evidence support			binding alerts for skin				
	Add / Remove			sensitization by OASIS)				

AE A.2.2. Common underlying mechanism, qualitative aspects is related to the mechanistic similarity of the final category.

All items in the report basket related to the mechanistic consistency of the category (1) are added automatically. Only the Alert performance item have to be included here manually (2). Right-click on Alert performance in order to preview it. The following example text summarizing the results of the provided mechanistic similarity items can be added:

- Target substance A and source substances B, C and D are all metabolized to Bis aldehydes
- Bis aldehydes is taken as alerting groups responsible for the toxic effect based on the expert knowledge
- Bis aldehydes are taken as alerting group supported by the higher alert performance (82 %) as compared with aldehyde group (47%)

Additionally, metabolic maps (for each of the analogues), produced by external software or found in the literature, could be included to AE in order to support the mechanistic similarity of the category.

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Wizard pages		<b>AE A.2.3. Common underlying mechanism,</b> <b>quantitative aspects</b> is also related to the mechanistic similarity of the final category. The
Customization Customize report Prediction Target and prediction summary Prediction details	AE 2.2: Common underlying mechanism, qualitative aspects     Hint     Add / Remove     Alert performance     Preview Additional endpoints	following information could be included here: 1) textual or illustrated explanation why the common underlying mechanism leads to the same quantitative outcome (for source and target) with regard to the prediction of the property under consideration; and
(l) Prediction details (ll)	Image: Construction of the second	Example text: • Target substance A is metabolized to Aldehydes and Bis aldehydes
Target profiles Analogues selection details	<ul> <li>Category values for selected additional endpoints</li> <li>Comments on additional endpoints</li> </ul>	• It is expected that Bis-aldehydes as the alert with higher alert performance is could be responsible for the toxic effect
Category Category definition and members Consistency check	Additional comments	<ul> <li>Source substances B, C and D are metabolized to aldehydes and bis-aldehydes, too</li> <li>The available experimental EC3 values for the source</li> </ul>
Options Data matrix Options	<ul> <li>AE 2.3: Common underlying mechanism, quantitative aspects</li> <li>→ Hint PURPOSE: Under this scenario, there should be no biologically significant quantitative differences for the same type of effects caused by the underlying mechanism or the differences should be used in a conservative prediction (i.e. effects for the target substance are not likely to be under-predicted, worst case approach). It has to be assessed whether:</li> <li>the documentation has provided an explanation why a common underlying mechanism leads to the same quantitative outcome (for source and target) with regard to the prediction of the property under consideration; and</li> </ul>	
	- the provided evidence supports the explanation.      Add / Remove      Back Next Cancel Create re	2) evidences supporting the explanation. Include all available SS EC3 data for the target chemical and the source substances in all Toolbox database. See how to do this on the next two slides.

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Customization Customize report Prediction Target and prediction summary Prediction details (I) Prediction details (II) Target profiles Analogues selection details Category Category definition and members Consistency check Options Data matrix Options	<ul> <li>AE 2.2: Common underlying me</li></ul>	Physical Chemical Properties Environmental Fate and Transport Ecotoxicological Information Acute Toxicity Bioaccumulation Carcinogenicity Developmental Toxicity / Teratogenicity Genetic Toxicity Invert A Neurotoxicity Irritation / Corrosion Neurotoxicity Photoinduced toxicity Repeated Dose Toxicity Sensitisation Y Sensitisati

Click **Add/Remove** button (1) and **create new** item (2). Select **Endpoint data variation** (3) and confirm by **OK** (4). A new window with the endpoint tree organization appears. Select **EC3** and click **OK** (5). This new item will provide information not only for the used, but for all available EC3 data for the chemicals of the category.

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Customization Customize report	Category values for selected ad	lditional endpoints			^		AE 2.3: Common underlying m	nechanism, quantitative asp	ects
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After creating of the new item, it appears below the AE 2.3. along with the created text item (1). Example on how the **AE 2.3**. will look in the generated report is shown in right (2).

#### **Report** Generation

After clicking *Create report* button, *Generated report files* window appears. It contains three type of files:

- **1) Prediction report** a PDF file containing the prediction information related to the target.
- 2) Category report a PDF file containing information for the consistency of the final category (target plus used analogues)
- **3) Data matrix** a MS Excel file containing chemicals used for prediction along with their data for selected parameters, profiles and endpoint tree positions.

RAAF AEs are included in the first two files.

All generated files should be provided when submit a prediction.



## **Report** Generated report files

ction of EC3 for Iminobis	s-3-propyla	mine							1/6	6	<u></u>	emicals category					1/31
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#### Congratulation

- You have now been introduced to the RAAF scenario;
- You have now been introduced to the *Report basket*.
- You have now been introduced to the AEs related to Scenario 2.
- Note proficiency comes with practice.