Animal-Free Safety Assessment Education and Training Program

Covering Risk Assessment from start to finish

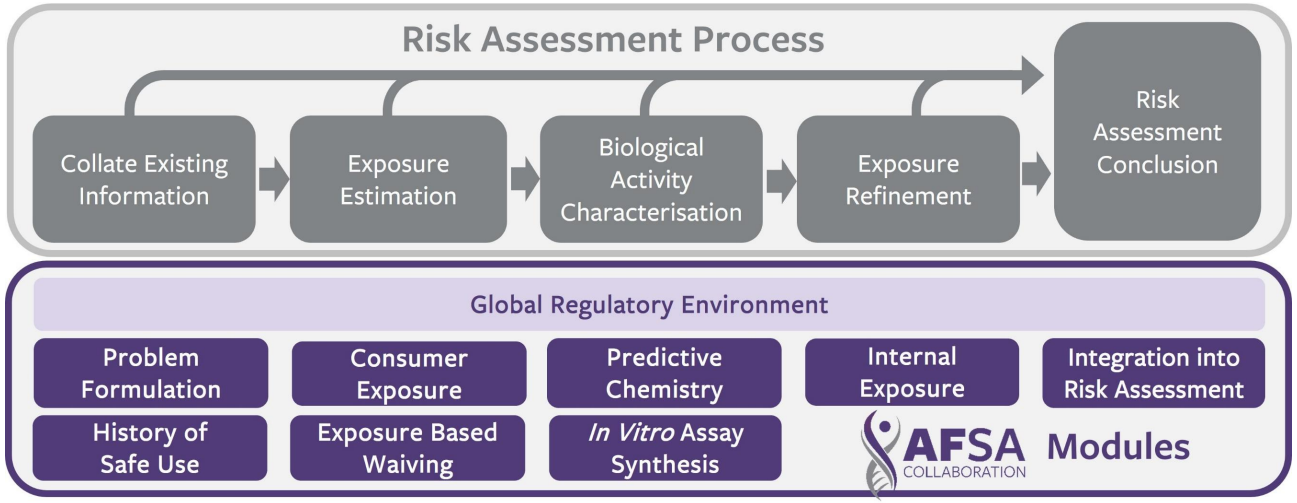
Predictive Chemistry: In silico tools and Read-Across

26 April 2022
11 am GMT/6:00 am EDT

Welcome and Introduction
Catherine Willett, Humane Society International

Predictive Chemistry: In silico tools and Read-Across
Ann Detroyer, L'Oréal
Wendy Simpson, Unilever

Slido Quiz and Q&A



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Overview: AFSA Cosmetics Education and Training

Catherine Willett
Humane Society International

26 April 2022

The Animal-Free Safety Assessment Collaboration

The HSI-coordinated **Animal-Free Safety Assessment** (**AFSA**) **Collaboration** works to accelerate global adoption of a modern, species-relevant approach to safety assessment that will better protect people and our planet, and hasten the replacement of animal testing

COSMETICS

CHEMICALS

BIOLOGICALS

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COSMETICS

AFSA Education and Training in Next Generation Risk Assessment

CHEMICALS

BIOLOGICALS

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AFSA Cosmetics E&T

A Global Training Program in Non-Animal Risk Assessment

Scope

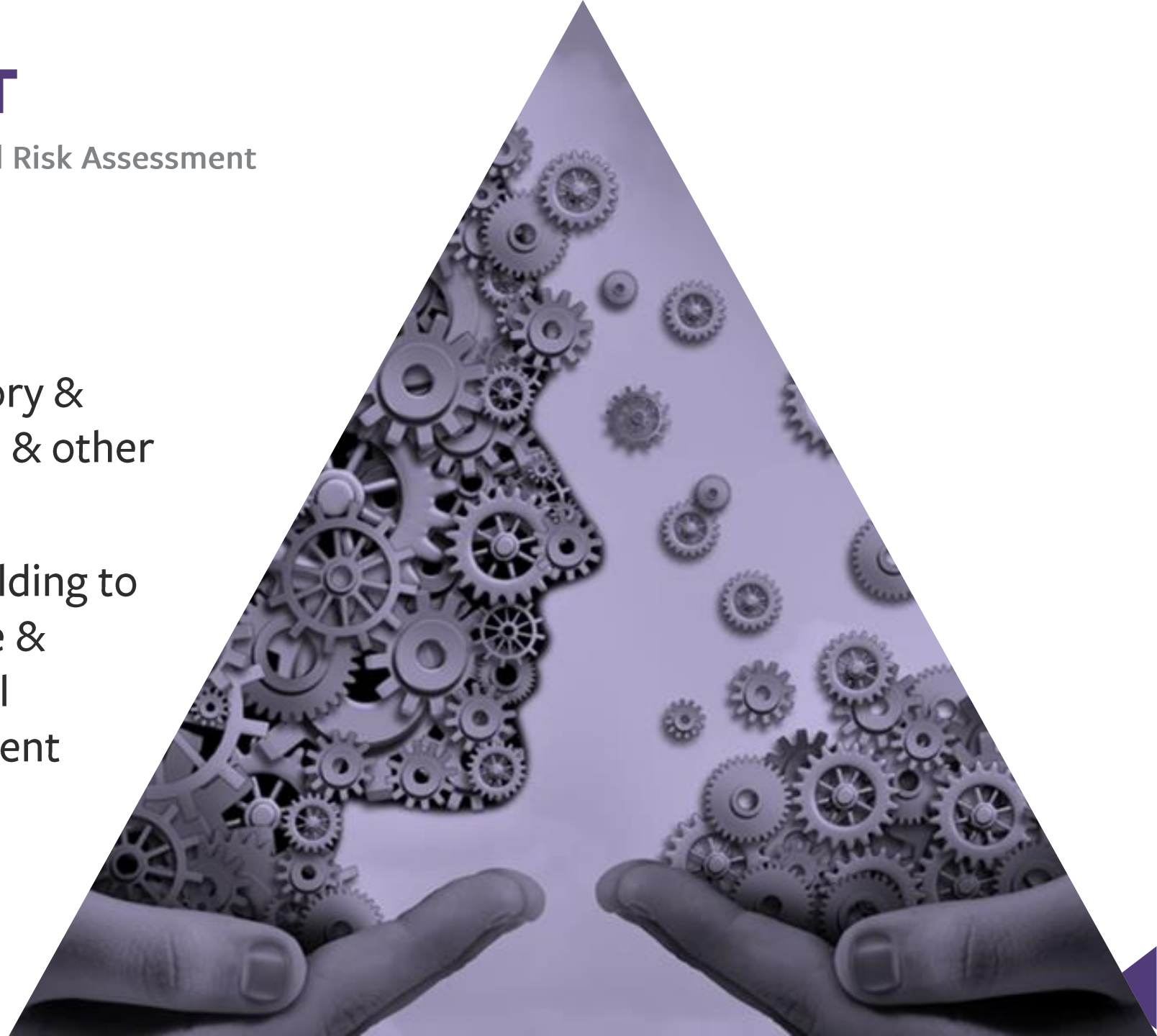
- Safety assessment of cosmetics and cosmetic ingredients without new animal data
- Covers all aspects of the process
  - Consumer exposure, external and internal
  - Acute local effects to systemic repeat effects
  - Information integration to make a risk decision
- Focus on *understanding* the information generated from the tools and *how to use* this information vs. how to perform or build the individual methods

AFSA Cosmetics E&T

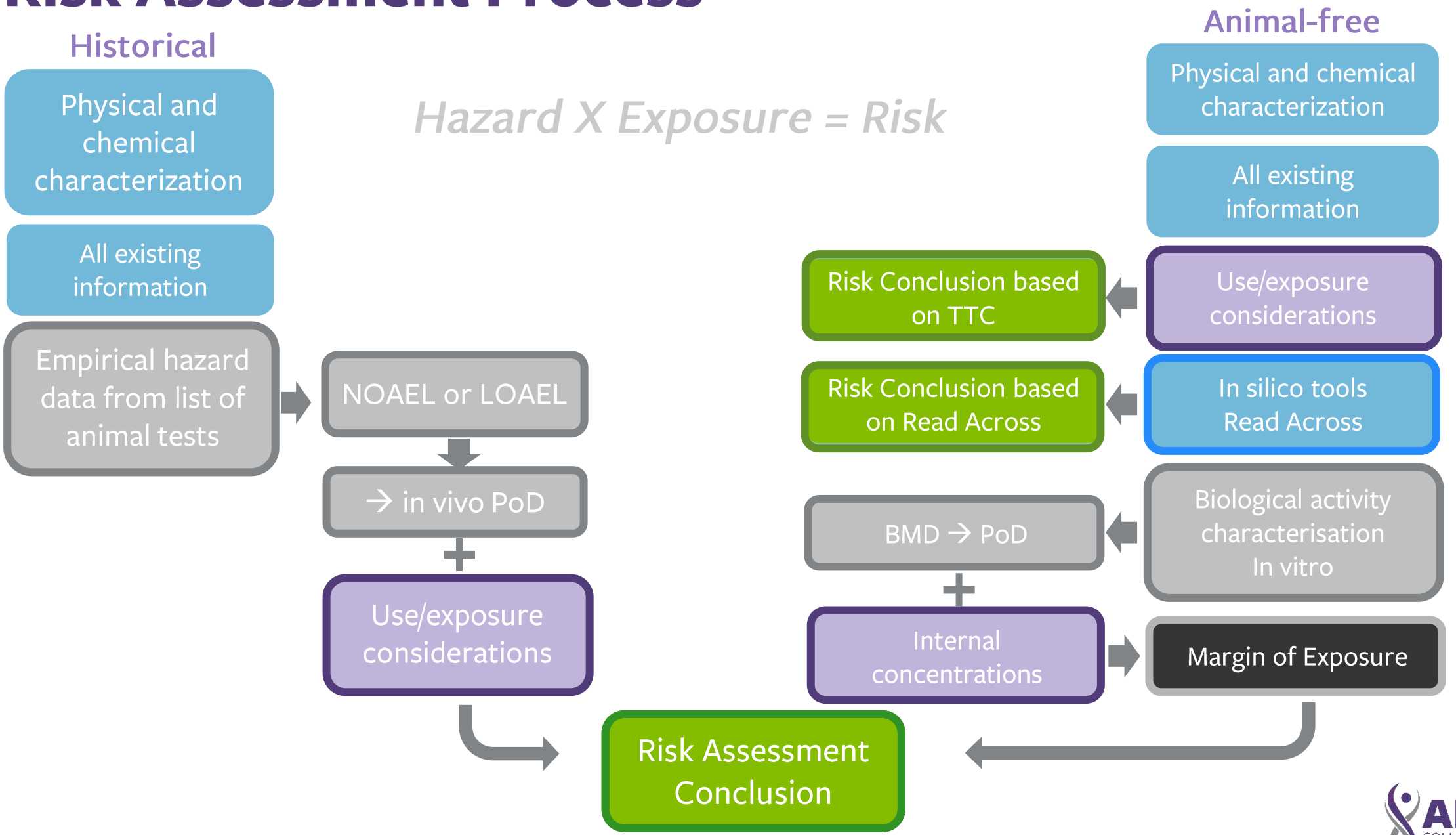
A Global Training Program in Non-Animal Risk Assessment

Purpose

- Address the needs of regulatory & regulated communities, CROs & other stakeholders
- Support regional capacity-building to achieve long-term acceptance & implementation of non-animal approaches to safety assessment

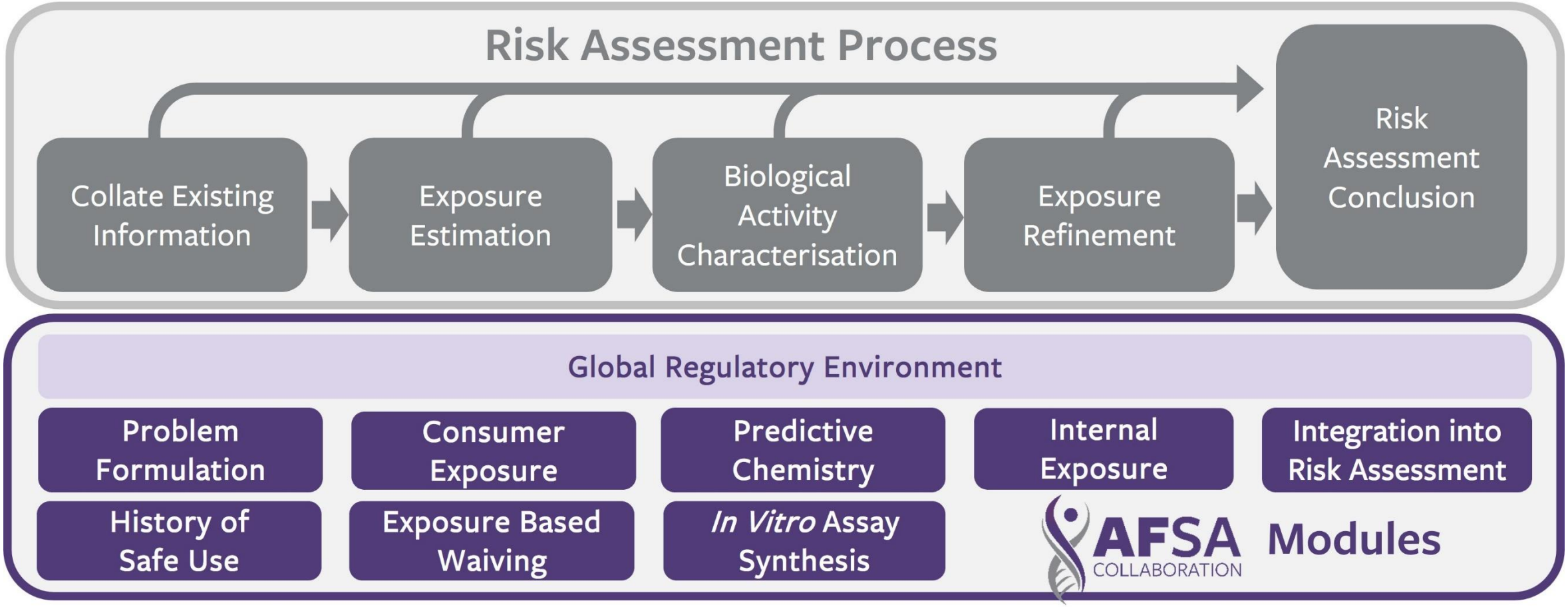


Risk Assessment Process

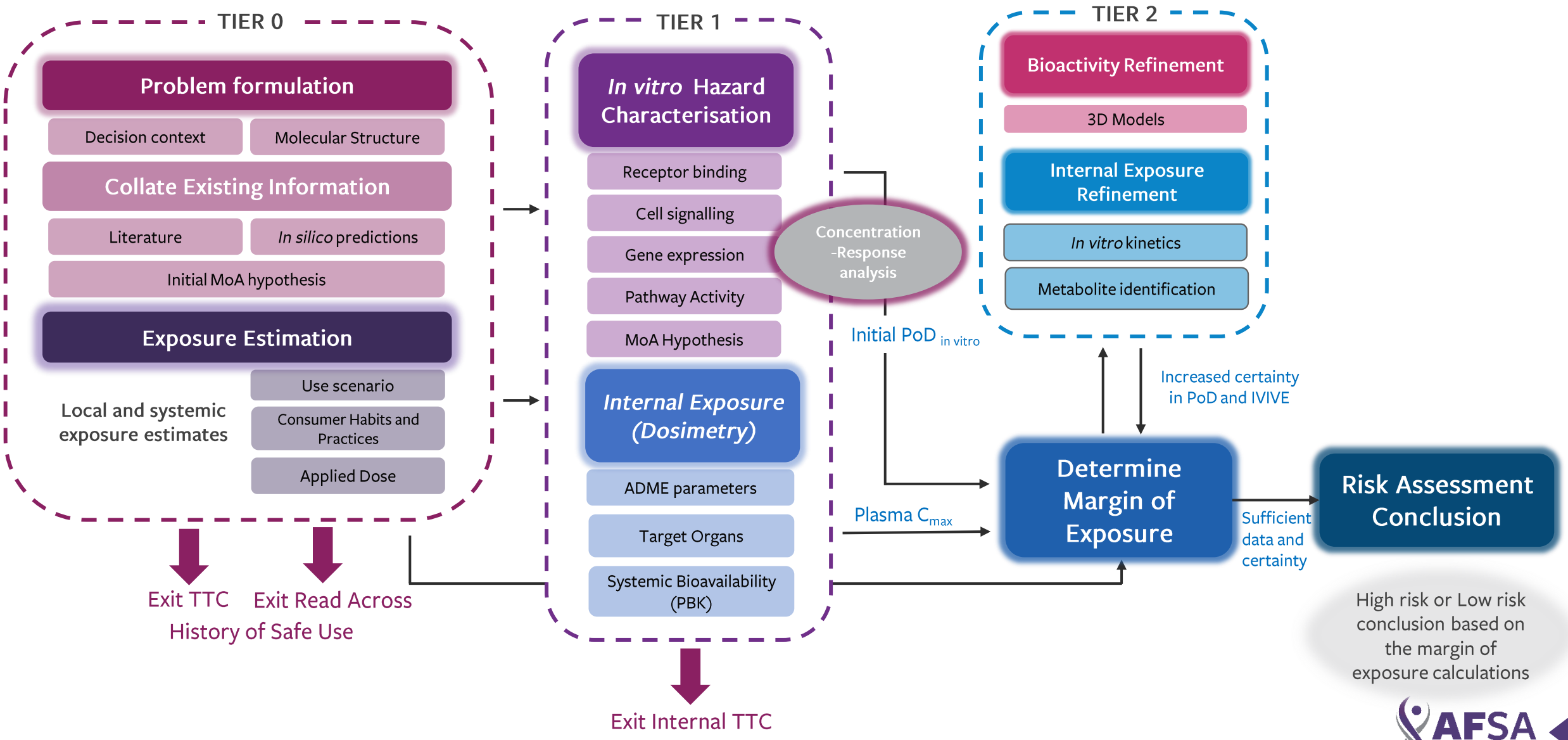


AFSA Cosmetics E&T

Covering Risk Assessment from start to finish



Next Generation Risk Assessment (NGRA) Framework



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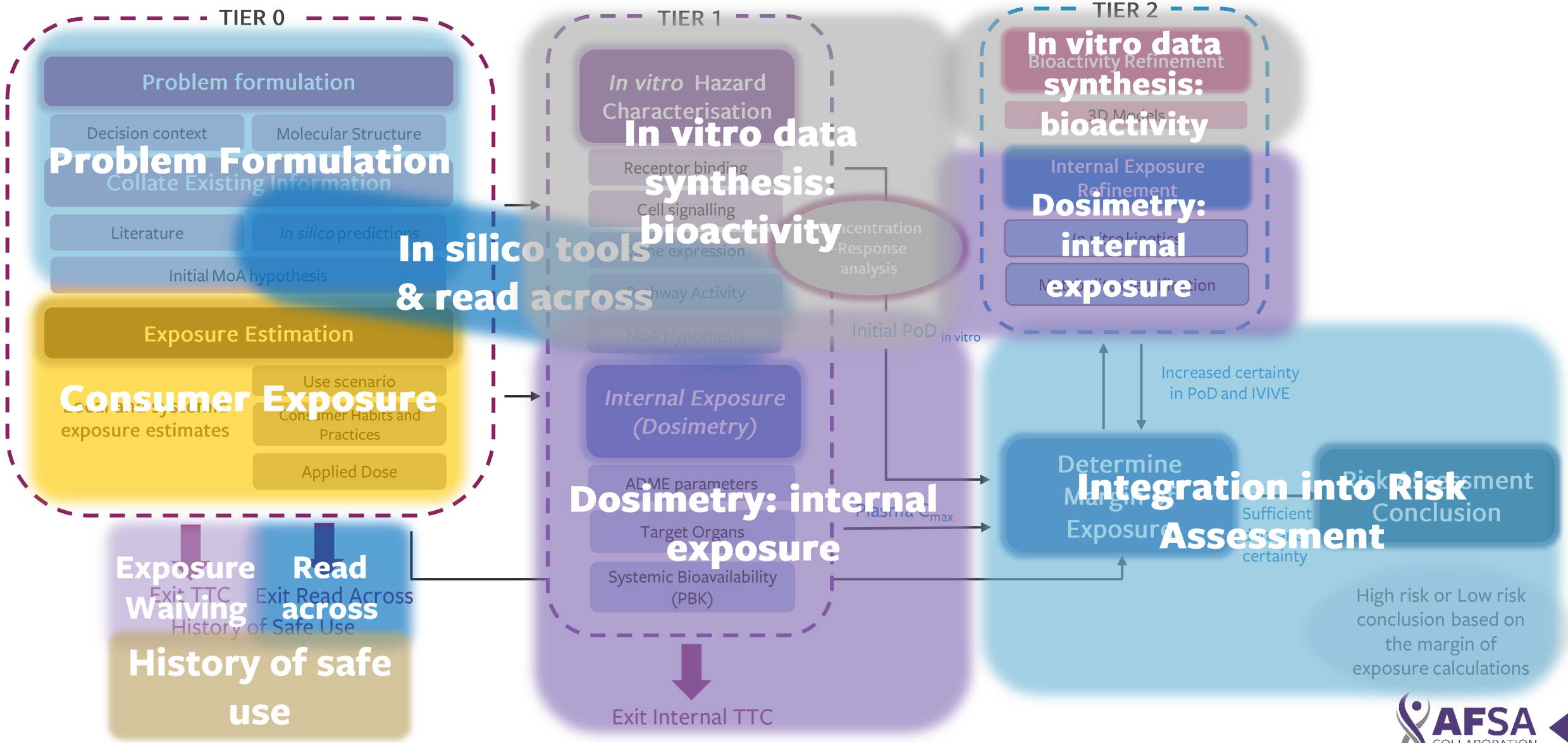
Next Generation Risk Assessment (NGRA) Framework



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Cosmetics Workstream Partners

HUMANE SOCIETY INTERNATIONAL

THE HUMANE SOCIETY OF THE UNITED STATES

Unilever

L'ORÉAL

P&G

Firmenich

AVON

iff

Givaudan

symrise

LUSH

Delphic HSE
SAFETY & REGULATORY SOLUTIONS

Lhasa Limited

IIVS
Institute for In Vitro Sciences

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Catherine Barrett	Unilever
Sage Begolly	IFF
Dagmar Bury	L'Oreal
Rebecca Clewell	21st Centruy Tox
Renato de Ávila	Unilever
Ann Detroyer	L'Oreal
Swatee Dey	Procter & Gamble
Hermine Dika Nguea	L'Oreal
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Corie Ellison	Procter & Gamble
Françoise Gautier	L'Oreal
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Gladys Ouédraogo	L'Oreal
Christian Pellevoisin	L'Oreal
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Chloe Raffalli	LUSH
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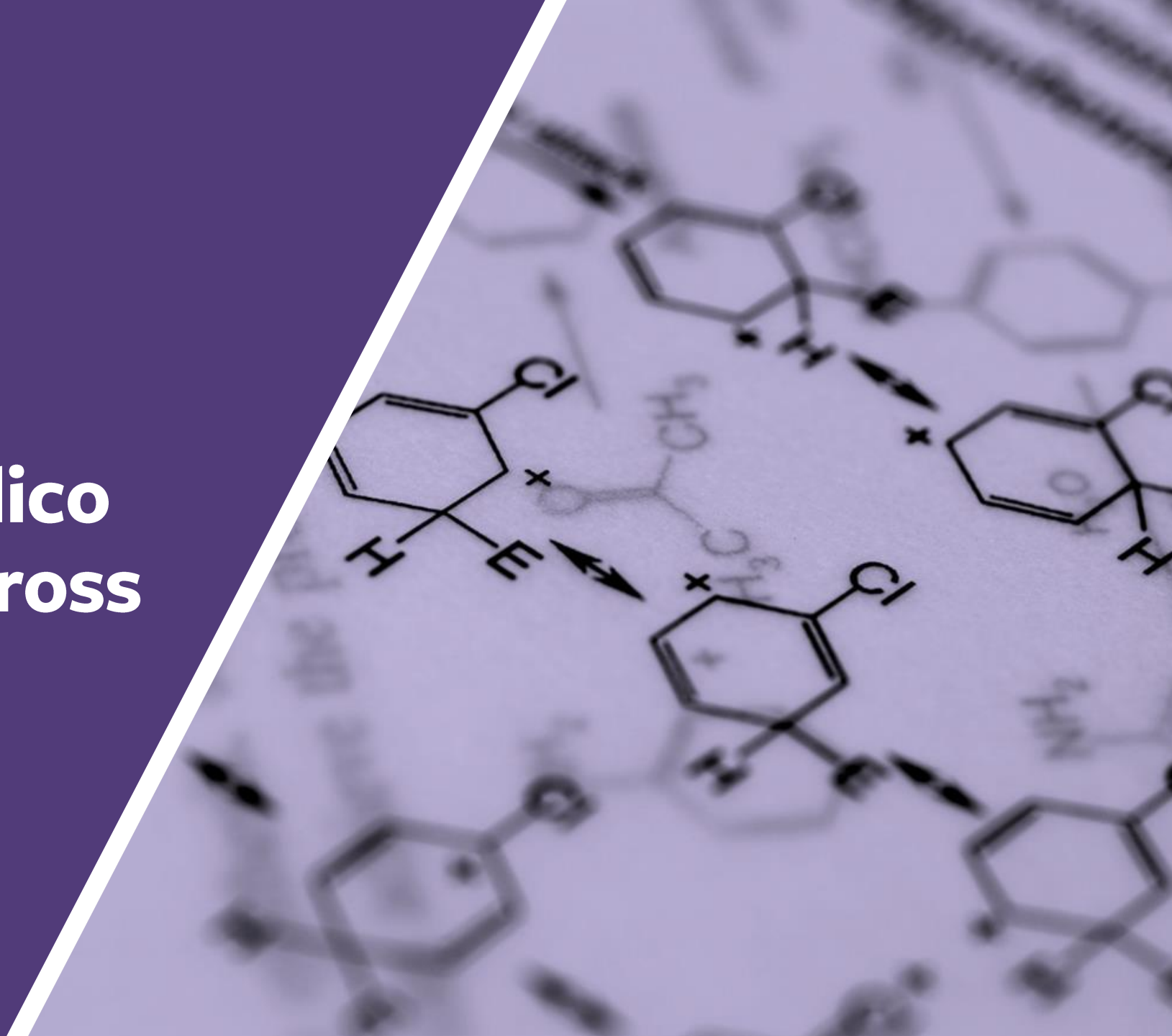
Predictive Chemistry: in silico tools & read-across

Ann Detroyer, L'ORÉAL R&I
Wendy Simpson, Unilever

April 26, 2022



Outline

- Learning Objectives
- Use context
- In silico tools
  - Definition
  - Develop
  - Apply
- Read-across
  - Process/framework
  - Target profiling
  - Source ID and evaluation
  - R-A outcome

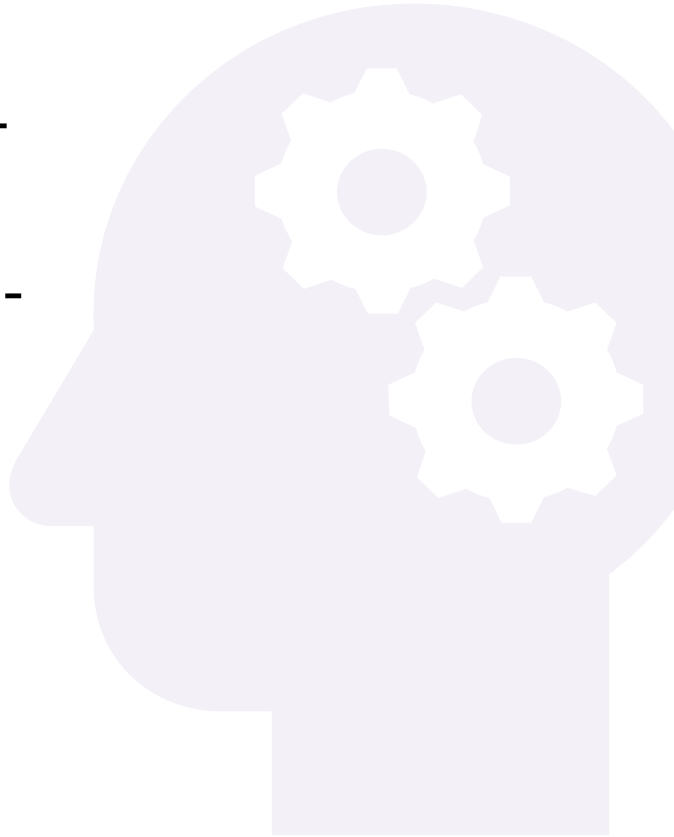
Learning Objectives

In silico tools

- Describe the typical process of in silico modelling
- Identify and describe SAR, QSAR, Hybrid and Consensus Models
- Outline process of using in silico models
- List the five elements of assessing reliability

Read-across

- Describe the different read-across approaches
- List the steps used in a read-across framework
- Outline how to search for source substances
- Identify factors which contribute to uncertainty in read-across



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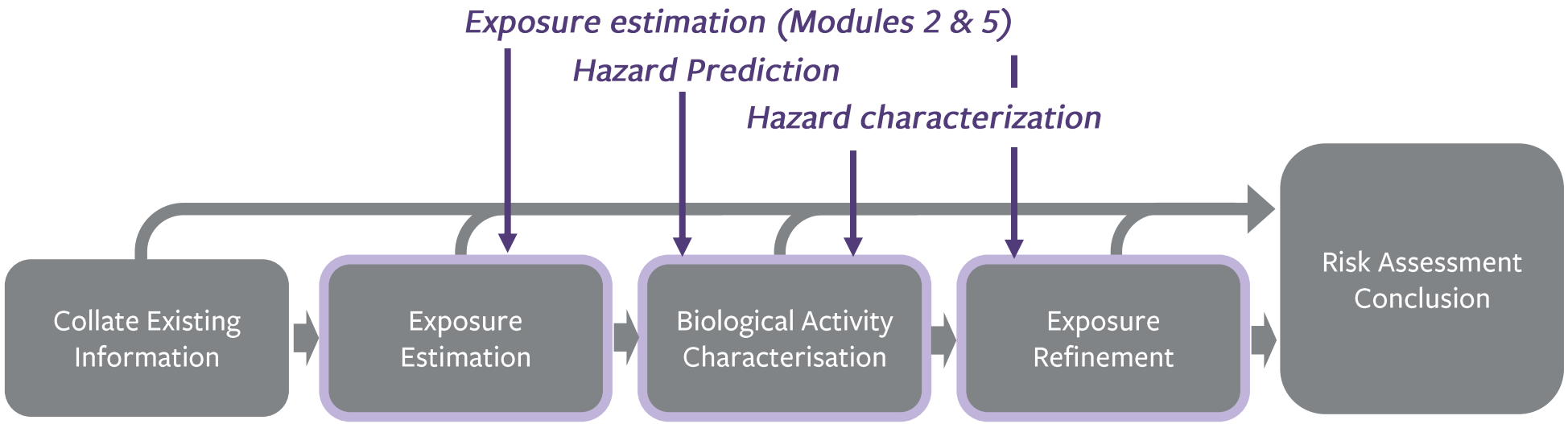
Predictive Chemistry using *in silico* tools

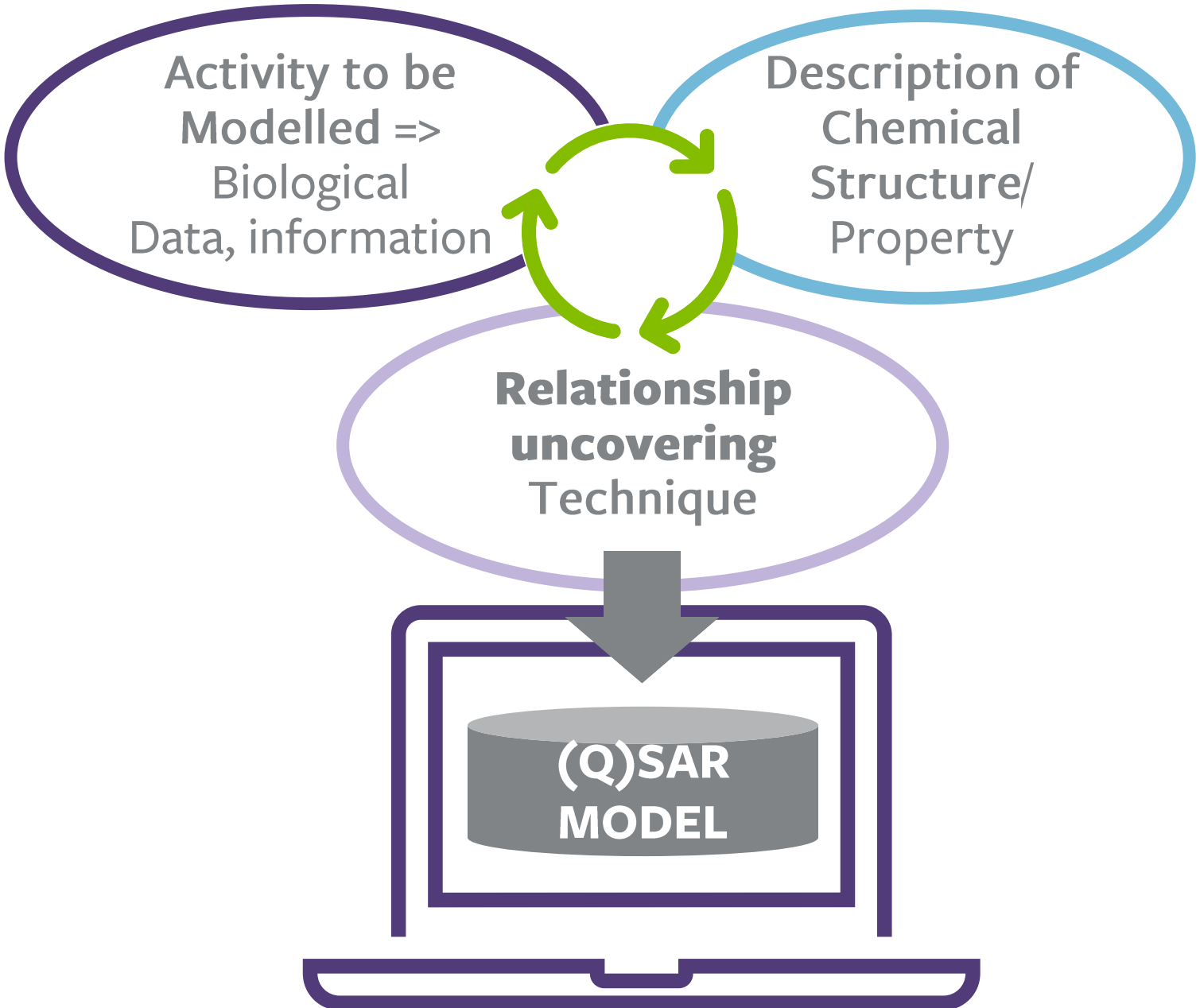
- *In silico* tools are used when the ability to generate new data is limited, by cost, time or regulatory framework (e.g. no animal testing)
- *In silico* predictions can:
  - → support risk assessment
  - → inform hypothesis generation
  - → predict biological properties
  - → add to weight of evidence
  - → reduce uncertainty
  - → support read-across to well-characterized chemicals

- *In silico* methods should be well documented to maintain full transparency
- Applicability domain should be well understood based upon the data upon which the model was built



Part 1: In Silico (prediction) Tools

In silico prediction models



Typical process of in silico modelling

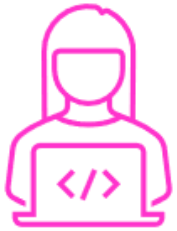
Find data

Curate data

Develop model using training set

Validate model (internal and external)

Run new data



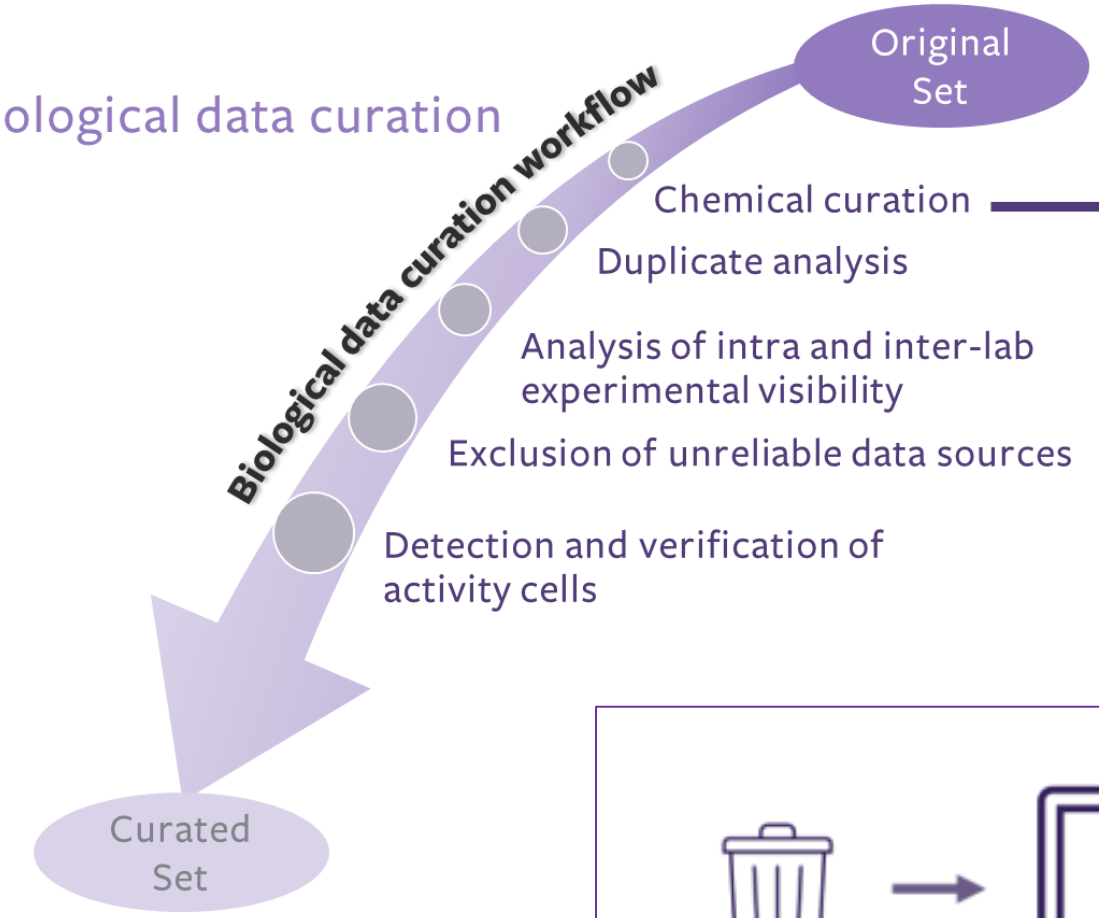
Use prediction

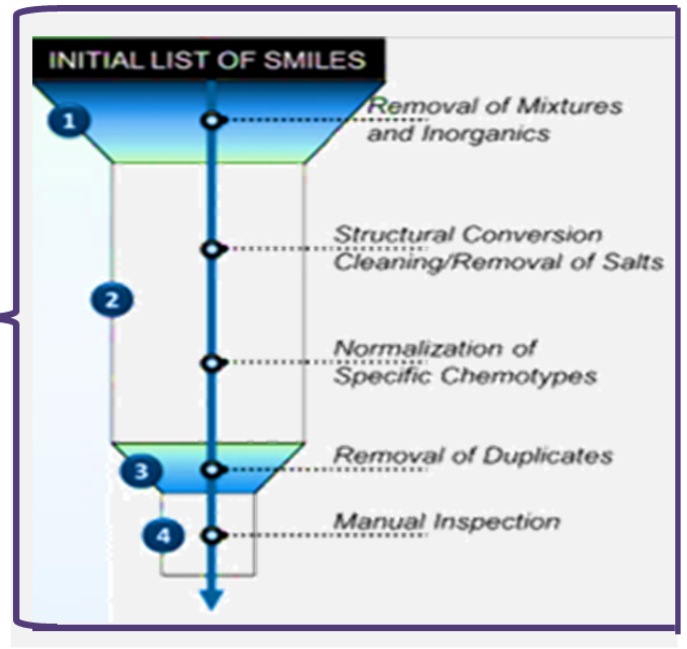
Develop

Apply

Develop : Data Curation

Biological data curation





Chemical data curation workflow

Adapted from Fourches et al. 2015. Curation of chemogenomics data. Nat Chem Biol 11, 535. https://doi.org/10.1038/nchembio.1881

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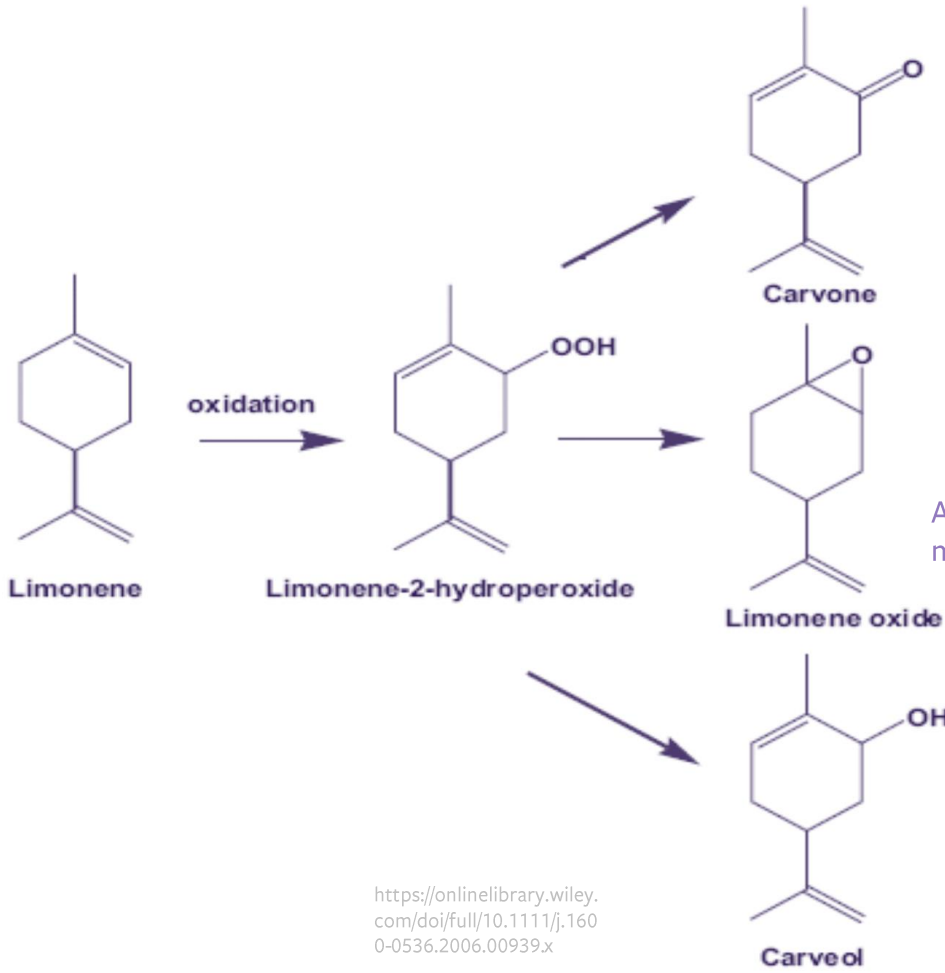
Develop : the right chemical structure

- When making predictions for toxicological activity, it is important to relate the correct chemical structure to the predicted activity
- Metabolism may increase or decrease the bioactivity of the parent chemical

- If you are not sure if metabolites may form and whether the parent or one of the metabolites is the active chemical, you can assess data for both the parent and the metabolite(s)
- *In silico* transformation (metabolism) simulators can predict likely metabolites

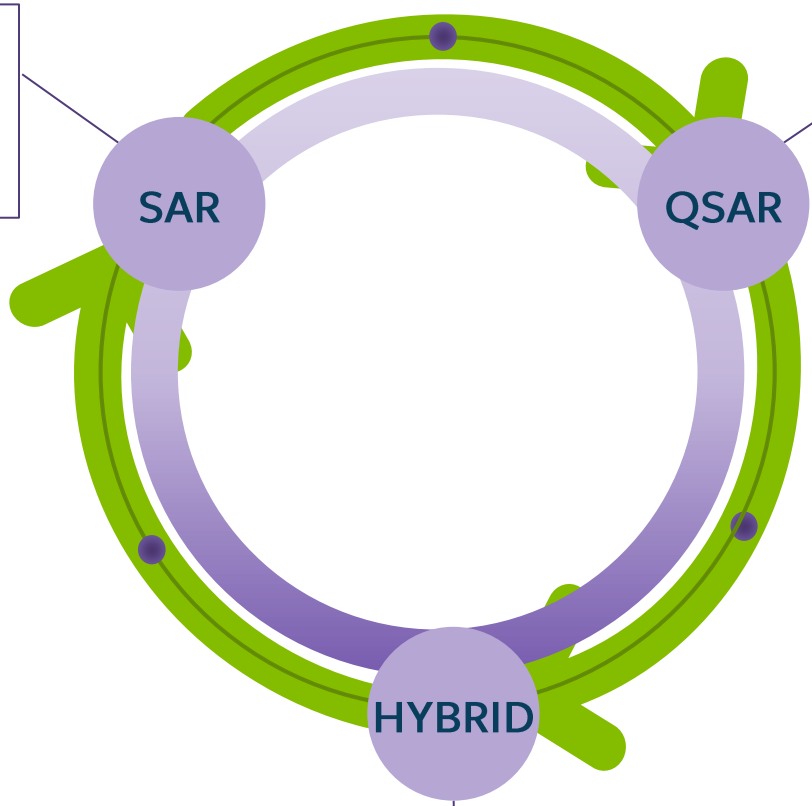
Example: Metabolism of limonene due to autooxidation



https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0536.2006.00939.x

Develop : types (techniques) of in silico models

- Decision tree-based
- Expert knowledge-based



- Statistical models
- Machine learning

Combination of SAR and QSAR

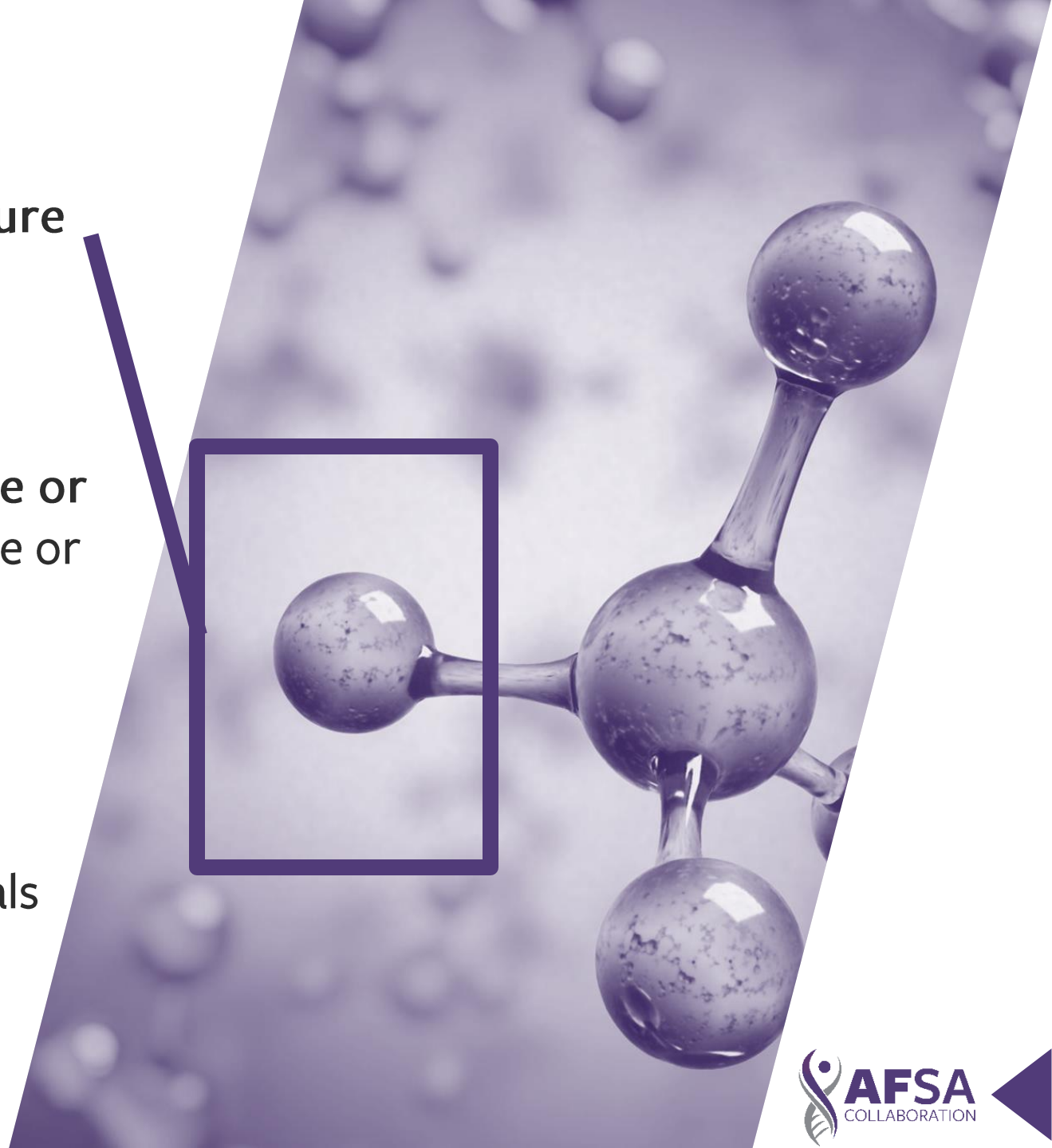
SAR Models

A SAR model uses a chemical's **(sub)-structure** to predict its (qualitative) biological activity-toxicity.

Very often based **on mechanistic knowledge or expert knowledge.** "Rules" relating presence or absence of activity to (a) specific chemical feature(s) are thus created and encoded.

⇒ also called "Alert models"

⇒ also widely used for grouping chemicals into categories which share the same mechanism of action ("Profilers")



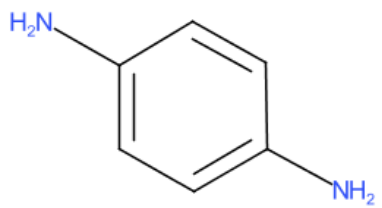
SAR - Decision tree-based expert system

ex. Toxtree Skin sensitization reactivity domain

Available structure attributes

Alert for Acyl Transfer age...	NO
Alert for Michael Acceptor i...	YES
Alert for SN2 identified.	NO
Alert for SNAr Identified.	NO
Alert for Schiff base forma...	NO
No skin sensitisation reacti...	NO
SMILES	Nc1ccc(N)cc1
cdk:Comment	Created from SMILES
cdk:Title	

Structure diagram



Toxic Hazard

Alert for SNAr Identified.

Alert for Schiff base formation identified.

Alert for Michael Acceptor identified.

Alert for Acyl Transfer agent identified.

Alert for SN2 identified.

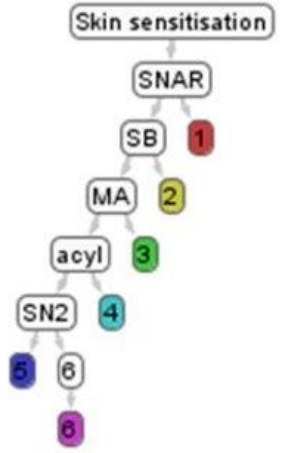
No skin sensitisation reactivity domains alerts identified.

☑ Verbose explanation

Skin sensitisation reactivity domains

- QSNAR.SNAr-Nucleophilic Aromatic Substitution **No** Nc1ccc(N)cc1
- QSB.Schiff Base Formation **No** Nc1ccc(N)cc1
- QMA.Michael Acceptor **Yes** Class Alert for Michael Acceptor identified. Nc1ccc(N)cc1
- Qacyl.Acyl Transfer Agents **No** Nc1ccc(N)cc1
- QSN2.SN2-Nucleophilic Aliphatic Substitution **No** Nc1ccc(N)cc1
- Q6.At least one alert for skin sensitisation? **Yes** Nc1ccc(N)cc1

- ToxTree applies the decision tree and alerts matched within the structural domains indicate skin sensitization potential



→ Para-phenylene diamine has matched the QMA Michael Acceptor mechanistic domain with at least one alert (Q6) so is considered to be a skin sensitiser

http://toxtree.sourceforge.net/index.html

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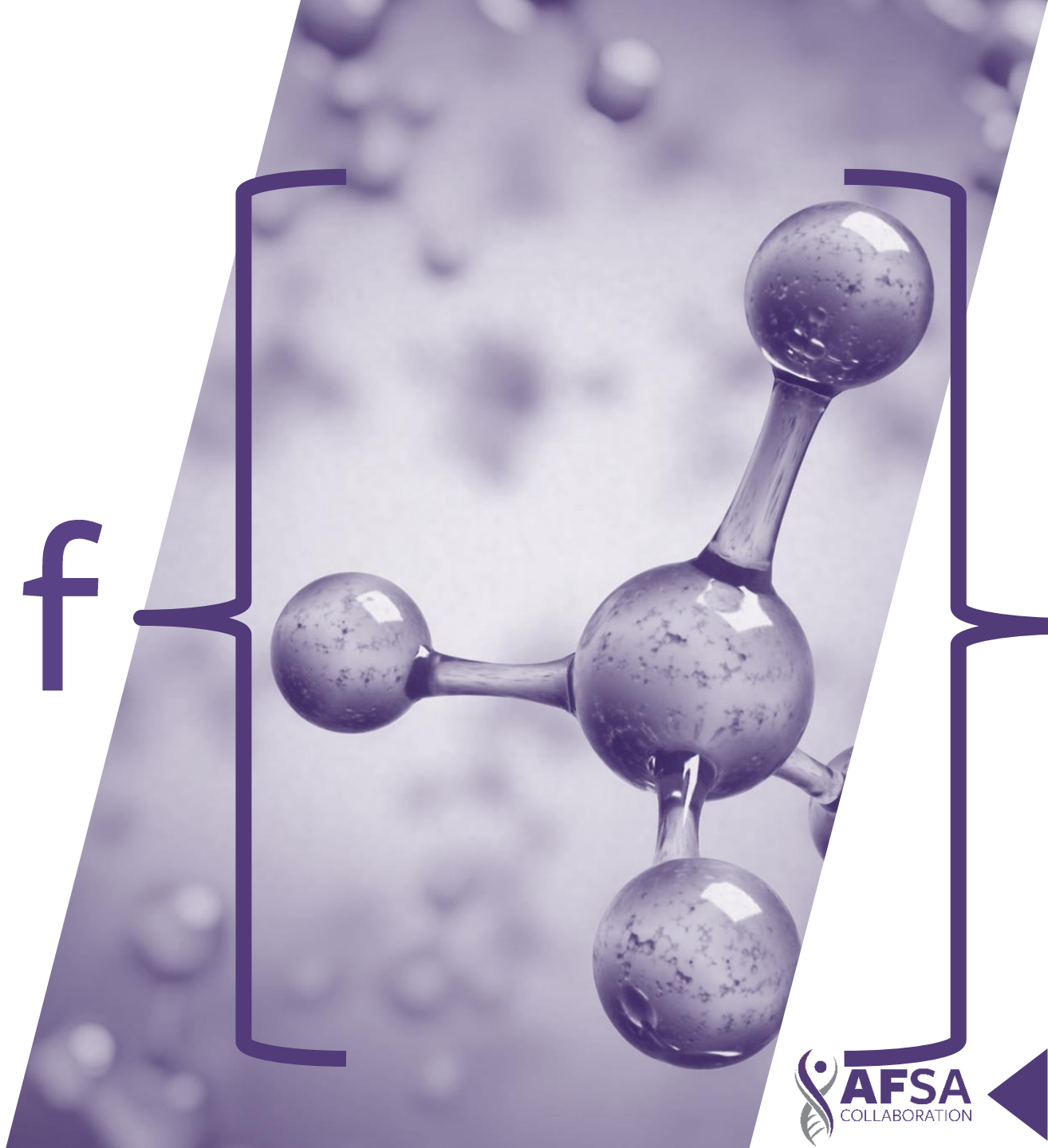
QSAR Models

QSAR differs from SAR in that they :

use quantitative measures of chemical structures (defined as **descriptors**)

+

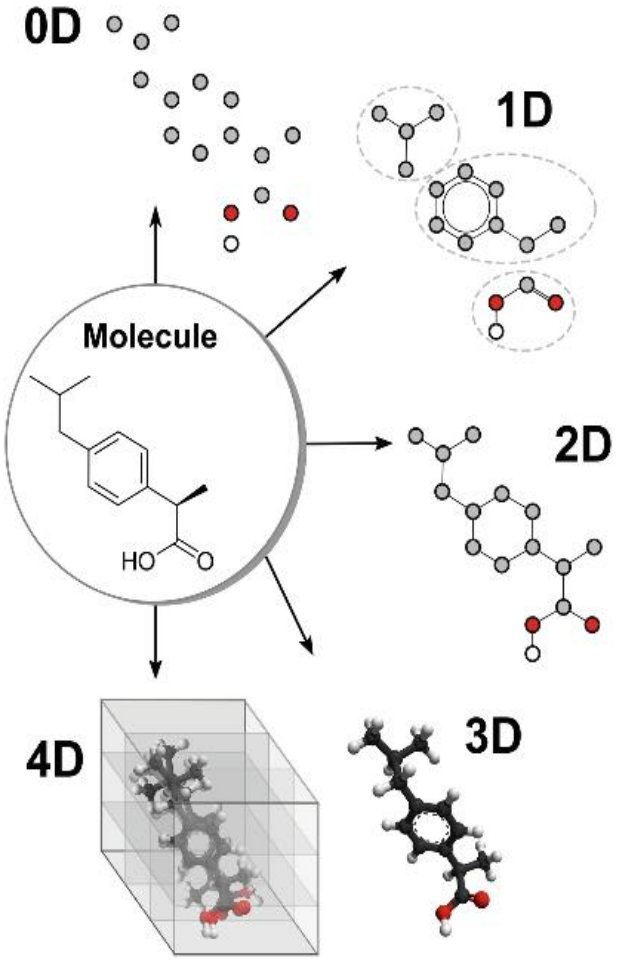
correlate one or more of these to a biological activity of interest using a **statistical technique**



Molecular descriptors

Molecular descriptors are a quantification of the various molecular properties of a chemical compound

Descriptor Types	Description	Examples
Constitutional	They represent a molecular structure, which take into account only chemical composition	molecular weight, the number of atoms and bonds, number of aromatic rings
Electrostatic	They represent properties related to electronic nature of the compound	atomic and partial charges
Topological	They are derived from the topological representation of molecular structures i.e., molecular graph	Wiener descriptors, Kappa shape
Geometric	They are derived from a 3-dimensional graph representation of the molecule, taking into account not only the positions of the atoms but also the connections among them	Geometry, Topology, and Atom-Weights Assembly (GETAWAY) descriptors
Quantum	They express all of the electronic and geometric properties of molecules and their interactions	highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO)



Grisoni et al., (2018) Impact of Molecular Descriptors on Computational Models. In: Brown J. (eds) Computational Chemogenomics. Methods in Molecular Biology, vol 1825.

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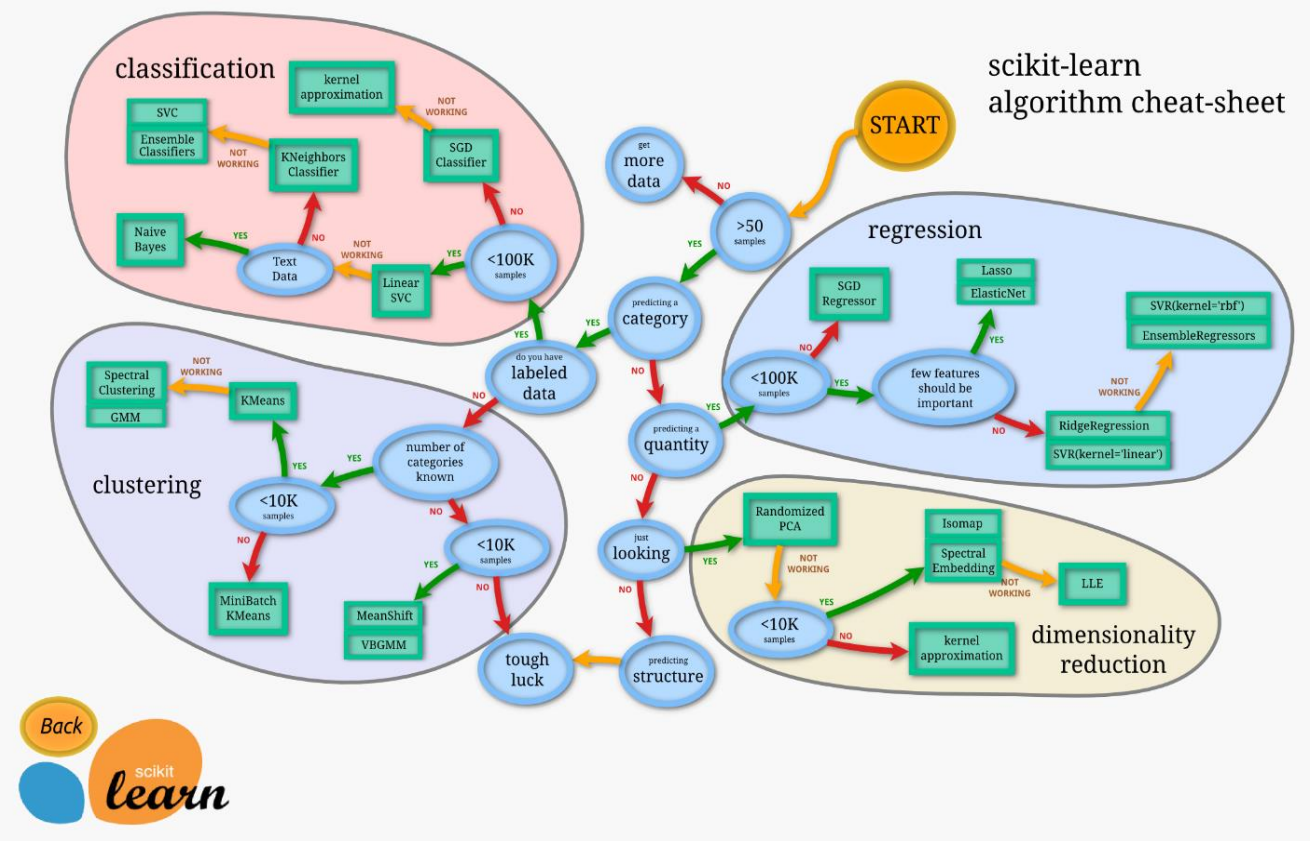
Statistical technique ?

- Some statistical techniques are more suitable for specific types of data or different sizes of datasets

- How to choose:
  - → Flowcharts
  - → Visualization of the data (e.g. using Principal Component Analysis)
  - → Literature for similar problems

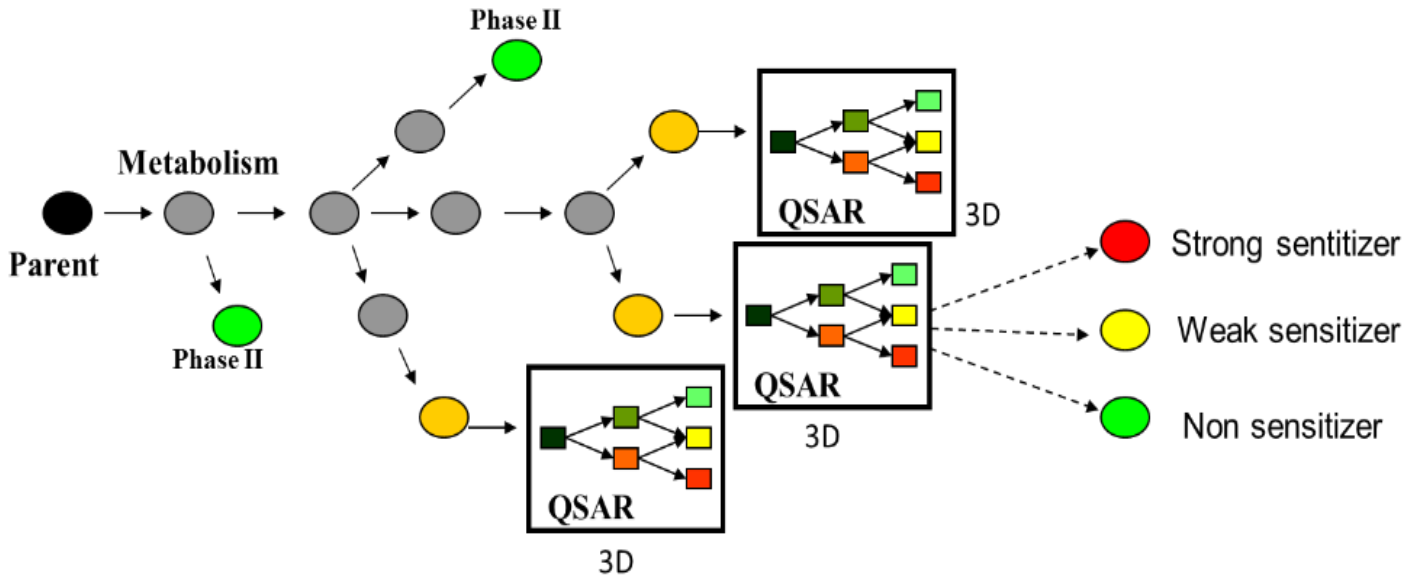
- Usually, several techniques would be tried and the best “performing” one chosen



Best of both : Hybrid Models

ex. TIMES Skin sensitization model with Autooxidation

This figure illustrates different interconnections between simulator of skin metabolism, classification and 3D-QSAR models in TIMES.



TIMES SS assessment

- Matching parent molecule against 420 hierarchical metabolic transformations
- For all matches, reactive or metabolic species and their respective protein (or Phase II) adducts are then generated
- The propagation of metabolism is stopped when protein conjugation reactions classifying the chemical as strong (or weak) sensitizer or Phase II reactions are applied.
- For some reactive species, additional information is required and 3D-QSARs are invoked to determine their sensitization effect.

Consensus models

Models that take the predictions of several (Q)SAR models and combine them to provide a single prediction.

Approaches that provide a consensus prediction include:

- Taking the predominant prediction
- Taking the average prediction
- Combining the predictions into a combined linear regression model

PRO

May provide more accurate and higher confidence predictions

CON

May put alert models at same level as prediction models, be too complex and lack transparency

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Typical process of in silico modelling

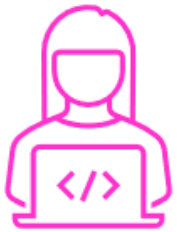
Find data

Curate data

Develop model using training set

Validate model (internal and external)

Run new data



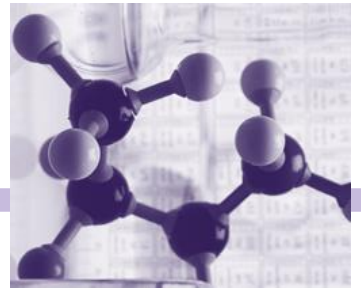
Use prediction

Develop

Apply

Applying in silico predictions

1 Ensure you have the correct chemical structure for input into the model



Ex.

- If you are not sure if metabolites may form and whether the parent or one of the metabolites is the active chemical, you can assess data for both the parent and the metabolite(s)
- *In silico* transformation (metabolism) simulators can predict likely metabolites

Applying in silico predictions

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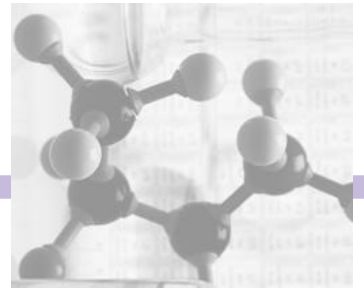

(Q)SAR MODEL

2 Choose a model that is applicable for your endpoint of interest

Generate a prediction using the protocol for the model

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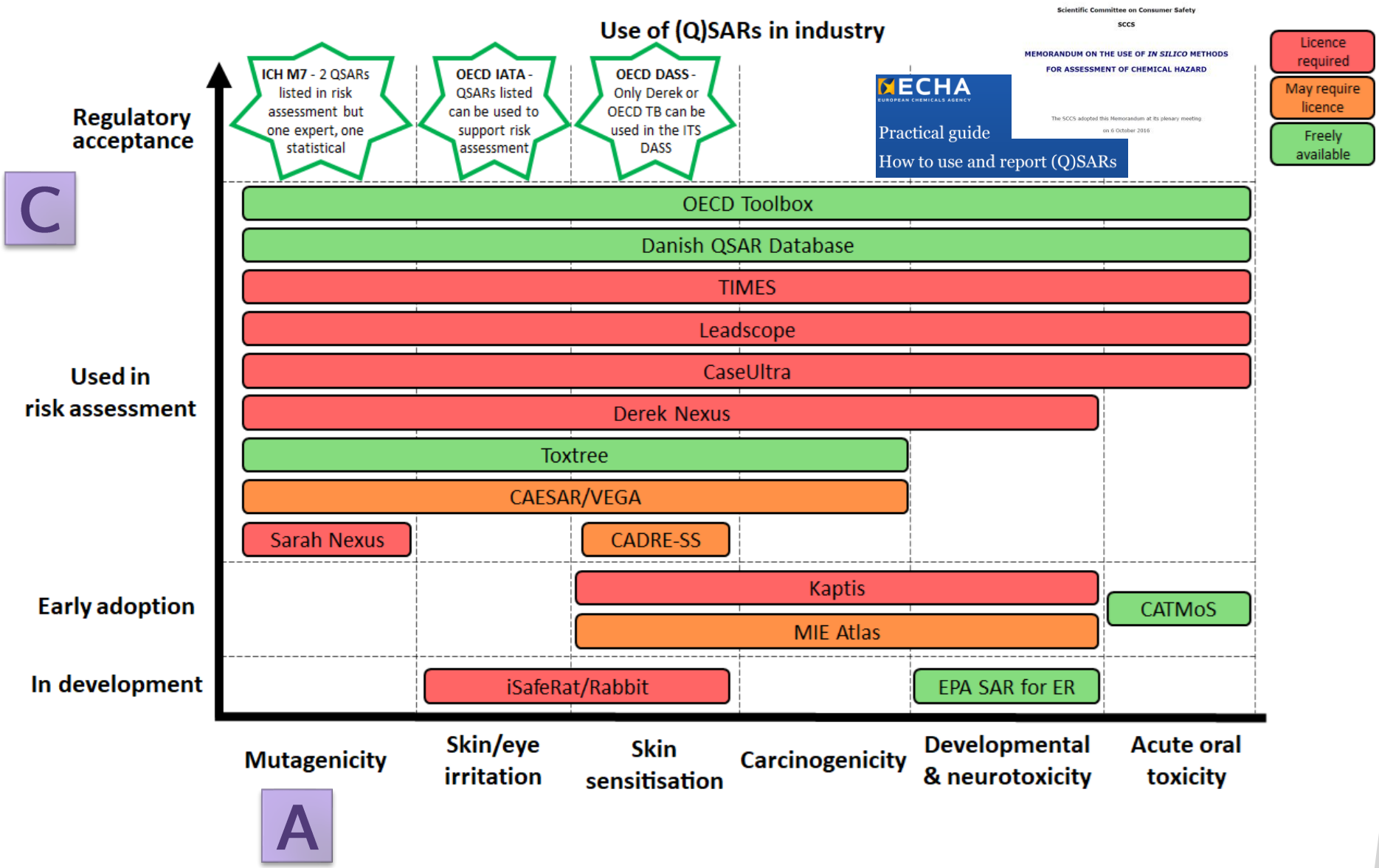
Choice of the model

C

B



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Applying in silico predictions

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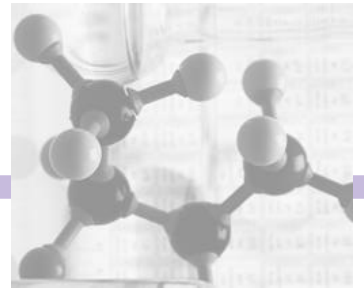

2 Choose a model that is applicable for your endpoint of interest

Generate a prediction using the protocol for the model

(Q)SAR MODEL

3 Assess reliability:

Understand whether the prediction is in the applicability domain of the model

Characterize and document uncertainty

Use the prediction!

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Assessing reliability

Applicability Domain	Uncertainty	Variability	Validation	Reporting
Usually dependent on the training set used to develop the model.	Expresses the limitation in knowledge or lack of data. It can be reduced or eliminated.	Refers to inherent heterogeneity in the data. It cannot be reduced but it can be characterised.	Allows to evaluate the predictivity and reliability of the model. It can be internal or external.	(Q)SAR Model Reporting Format (QMRF)* is a harmonised template structured according to the OECD validation principles.

What the prediction can / cannot tell us

Be transparent about it

*http://ihcp.jrc.ec.europa.eu/our_databases/jrc-qsar-inventory

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Summary (Part 1): *In silico* tools

In silico models can be used to predict toxicity. There are many types, which include:

- SAR models, which uses a chemical's (sub)-structure to predict its (qualitative) biological activity (toxicity).
- QSAR models use chemical sub-structures as well as other physico-chemical properties and/or biological activity, and converts to quantitative descriptors which statistical techniques are applied to predict toxicity
- Hybrid models combine elements of more than one model
- Consensus models take the predictions of several (Q)SAR models and combine them to provide a single prediction

Using in silico tools:

- Make sure you know the identity of the chemical whose activity you are trying to predict
- Chose a model that is appropriate for both the chemical type and your endpoint of interest
- check whether the chemical you are interested in is within the **applicability domain** of the model
- Characterize and describe sources of uncertainty, both in the model and in the application of the model
- It is important to undergo the correct validation processes, as well as assess uncertainty and reliability of *in silico* data.

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Part 2: Read-Across

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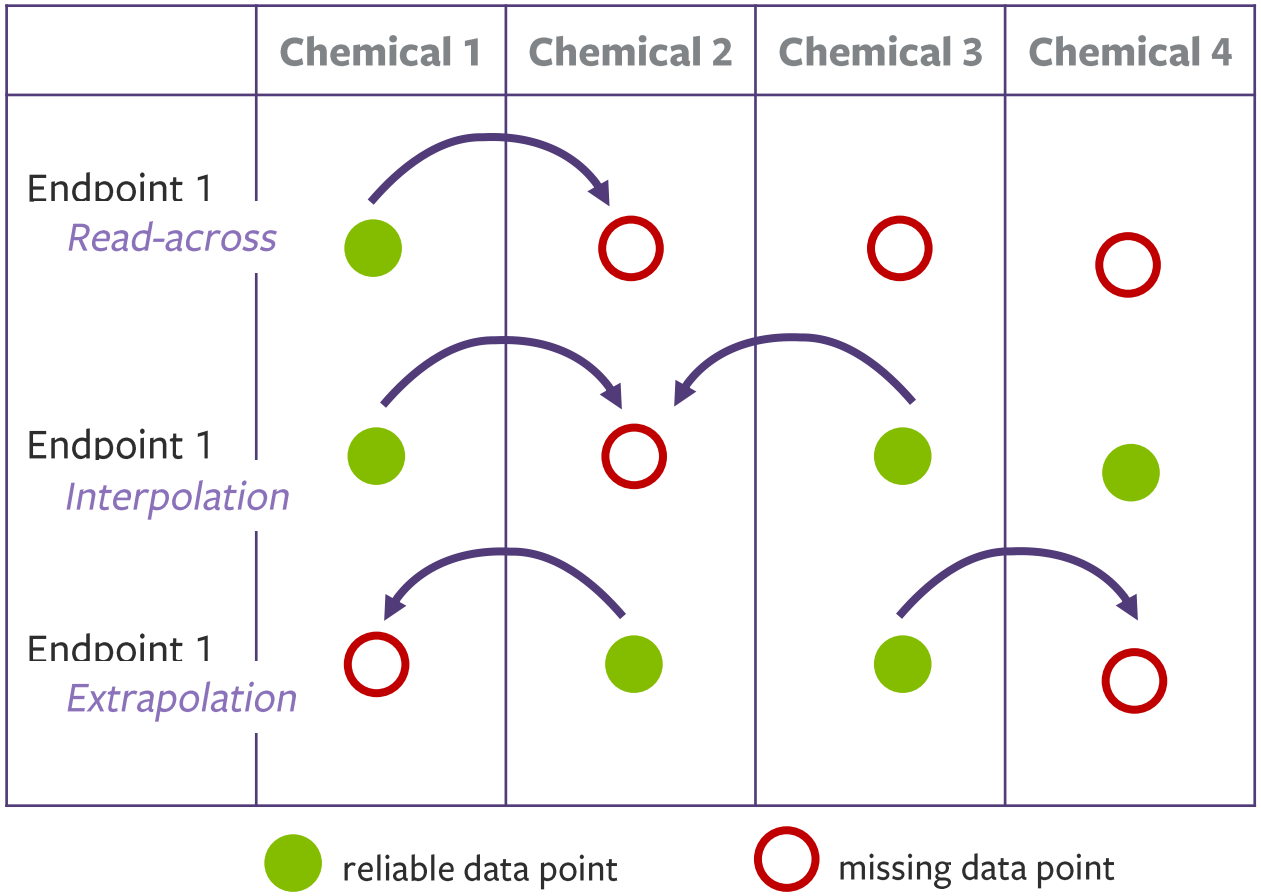
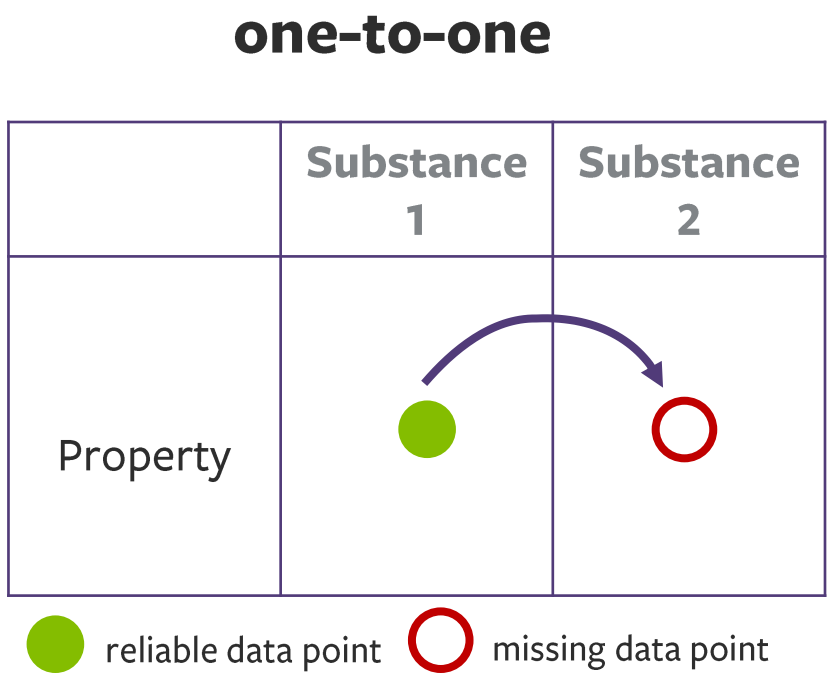
What is read-across?

Read-across is an alternative approach that is used to fill a data gap for a substance (the target), for a specific endpoint, by using the data from another structurally/ mechanistically similar substance (the source).



Read-across approaches

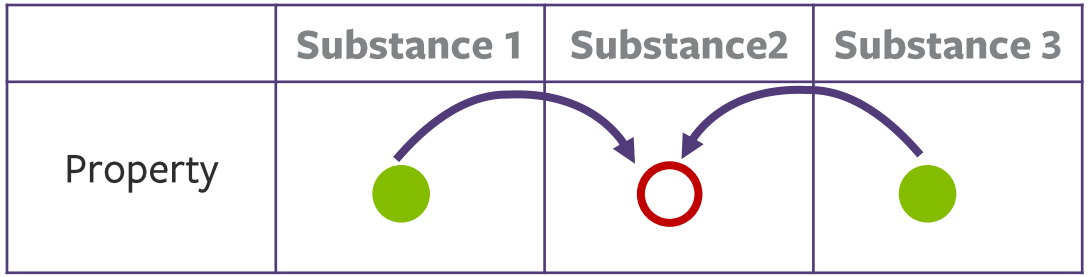
- The way in which source data are used in the read-across is dependent on the available data and the properties of the target and source substances.
- If there is only one source substance with data, this is a one-to-one read-across:



Read-across approaches

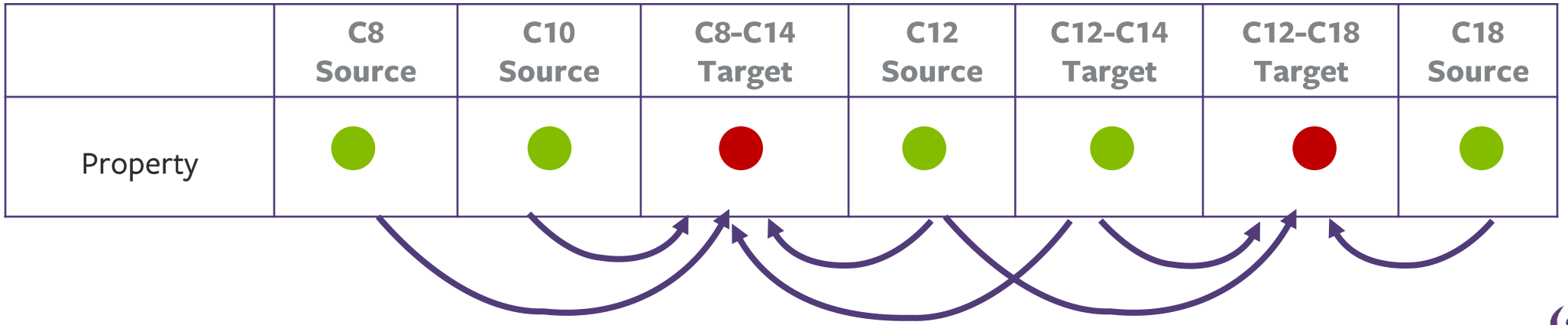
If there are multiple source substances, this is many-to-one:

many-to-one



If there are multiple substances which are structurally similar, but which do not follow a trend or pattern in their properties, this is called an **Analogue** approach.

Where there are multiple substances that have similar properties, or which follow a pattern because of structural similarity, these may be considered as a **Group** (or **Category**).

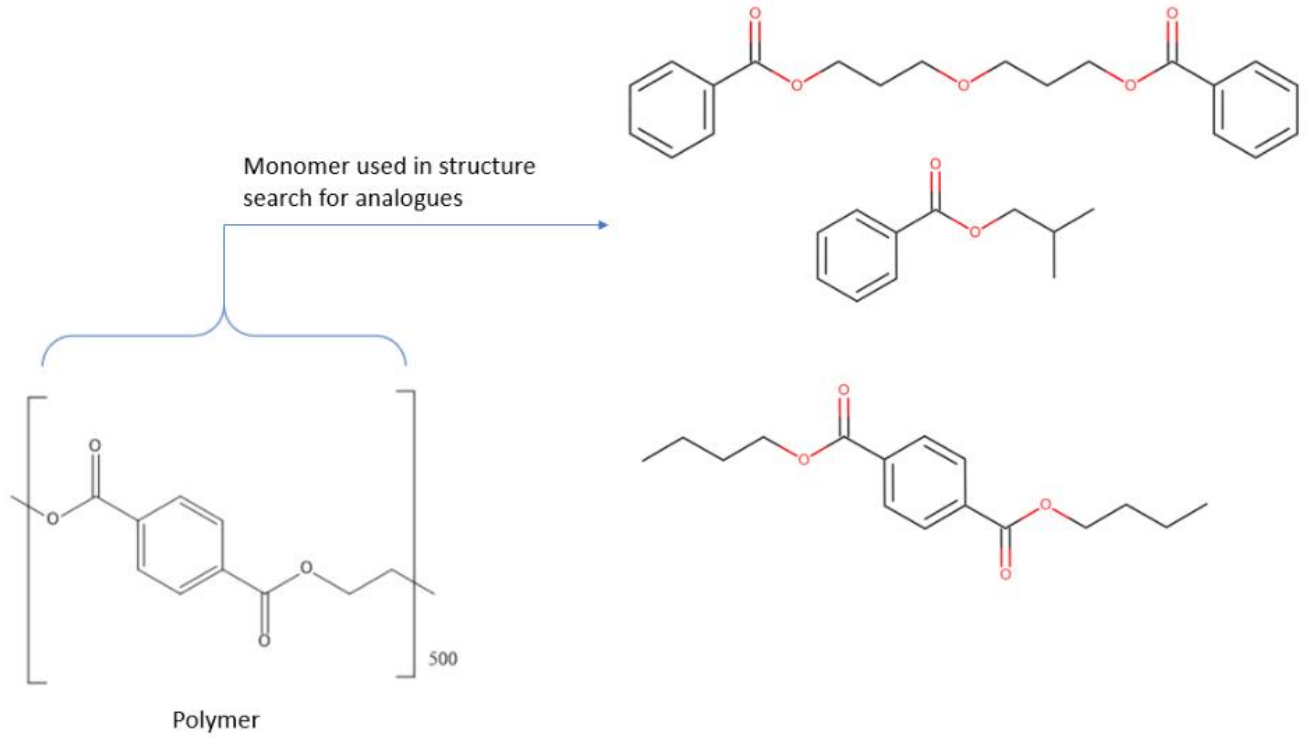


What can be done when read-across is challenging?

If the target or source is complex and does not have a single chemical structure, it may still be possible to perform read-across.

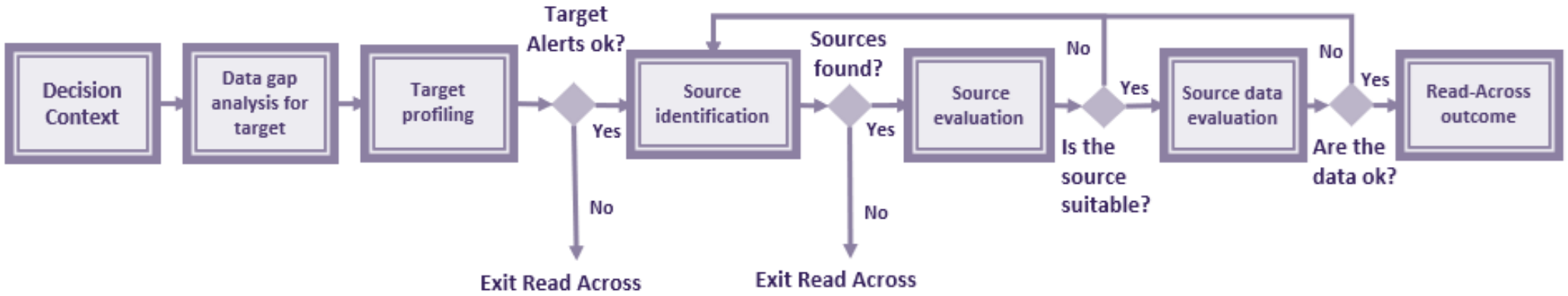
It is possible to base the read-across on:

- The component parts of a UVCB or a natural substance.
- The monomers which make up a polymer.
- Alternative data sources for inorganic substances.



The read-across process / framework

In summary, the key steps involved in read-across are:



- Define decision context
- Data gap analysis for the target
- Define hypothesis
- Target profiling
- Source identification
- Source evaluation
- Source data evaluation
- Read-across outcome

Defining the read-across hypothesis

For any read-across, there must be a hypothesis which describes why it is possible to use the data from a source substance to risk assess the target substance.

If the target and source substances are shown to have the same features, properties, and behavior, the hypothesis is that the target would exhibit the same biological response in an assay as the source substance. Therefore, justifying the use of the source data to support the target.

The hypothesis is supported by all the information gathered from the steps in the read-across and so develops as more information is collected.

The decision context

This step in the framework describes the problem and gives a reason why read-across is needed. At this step, it is important to know:

The Purpose	Is it for safety risk assessment or regulatory submission?
Target Details	The substance common name, synonyms, CAS, structure etc.
Exposure Scenario	How is the product containing the ingredient used? How often it is used? How is it administered (dermally, orally, inhaled?) How much is used per use? If it enters the body, how is it metabolised?

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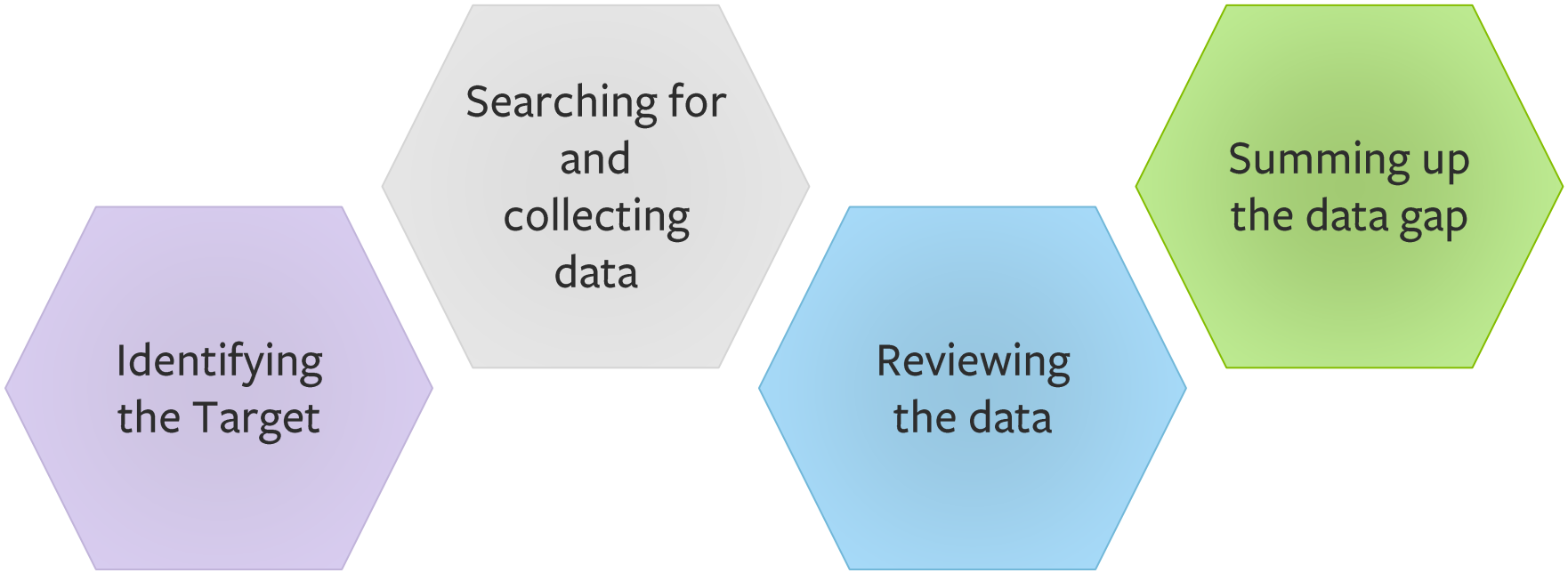
Data gap analysis for the target

Before a read-across is performed, it is important to know as much as possible about the target substance. This includes:



All the information collected about the Target can be stored in a series of tables in a data matrix.

Data gap analysis for the target: Summarising the data gaps

It is important to define the data gaps to be filled by read-across.

The data gap could be from missing endpoint studies, or from poor quality endpoint data which are not good enough to be used in the risk assessment.

As read-across is endpoint specific, read-across must be performed for each individual data gap / endpoint.

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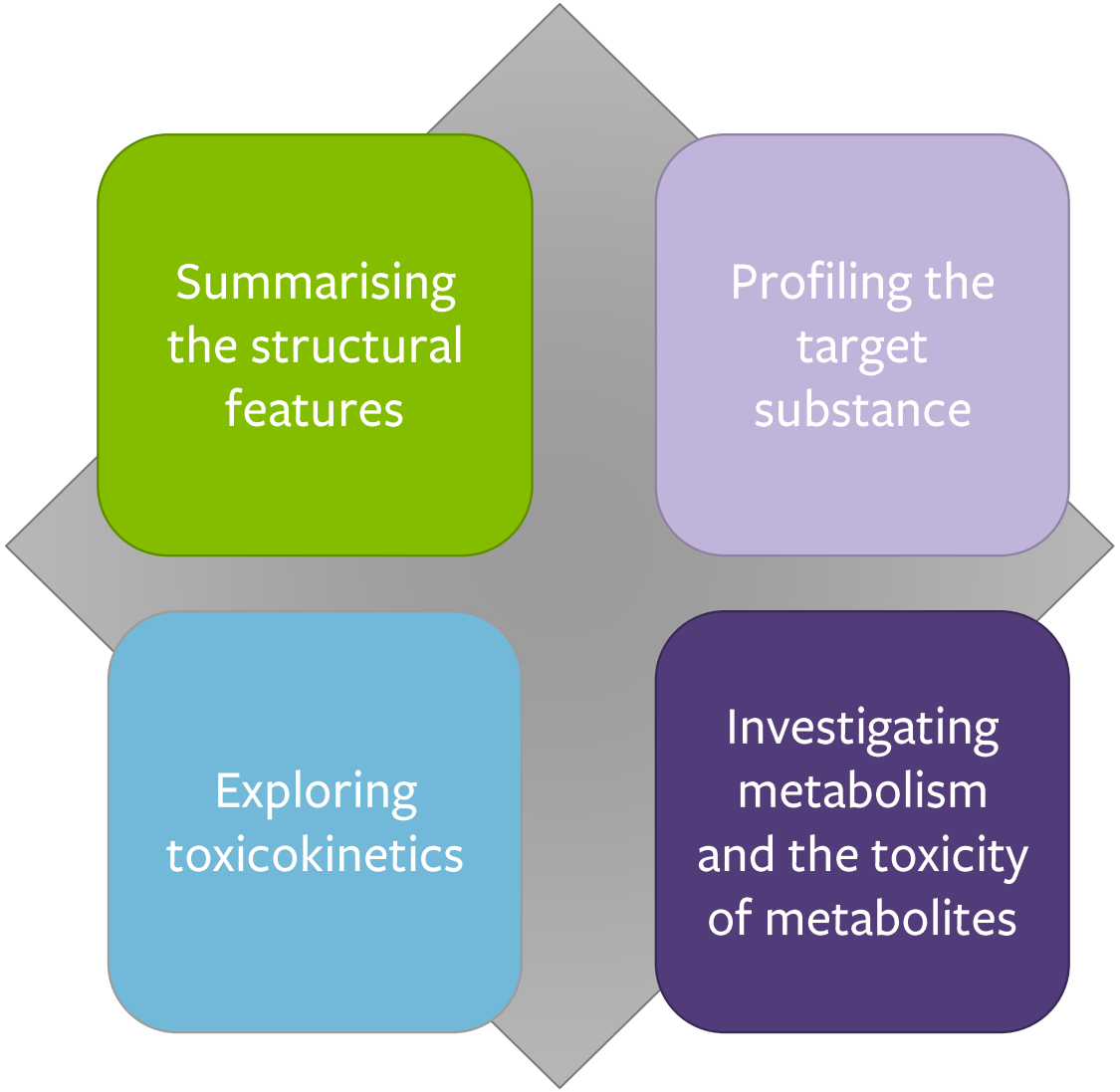
Target profiling

As well as creating a data matrix of existing data, further investigation is needed to completely understand the target substance. This includes:

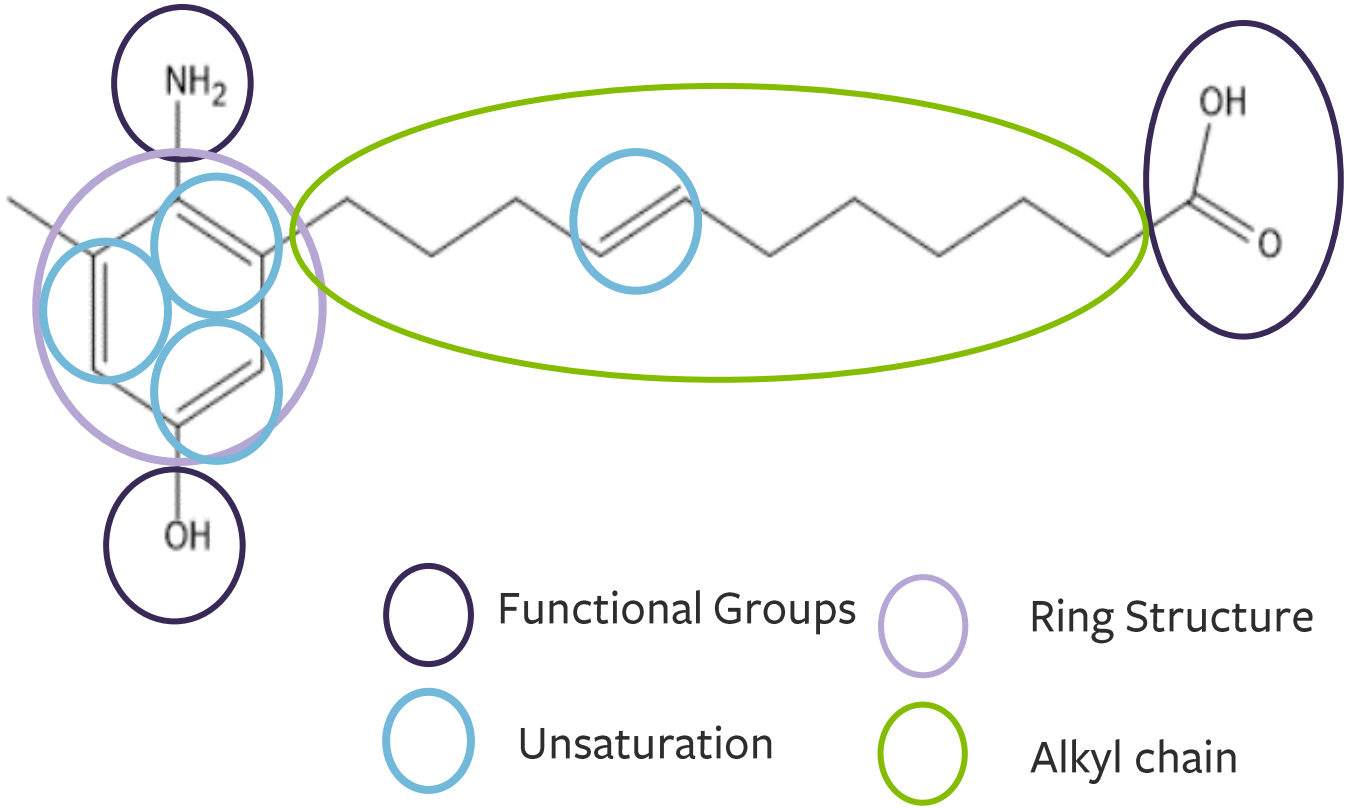


Target profiling: Summarising the structural features

Once the composition of the target is known, its chemical structure (or structures) are reviewed to identify th key features.

For example: key features may include functional groups, alkyl chains and ring structures.

Identifying the structural features can help to determine how a substance may react or metabolize.



The structural features can be stored in a table in the data matrix.

Target profiling: Identifying potential alerts/bioactivity

Profiling the target identifies any potential for toxicity. This can be identified from the existing data, but if there is little or no available data, toxicity can also be predicted using in silico tools.

In this case, the target's chemical structure is used to:

- Predict toxicity by using in silico tools to identify structural features associated with toxicity.

For example, the presence of a halogenated alkene may be associated with carcinogenicity.

- Predict physchem properties, which can help to inform a group or category read-across.

If the target is a mixture, this step is repeated for each component of the mixture. The output from each tool run is recorded in a table in the data matrix.

Target profiling: Identifying potential alerts/bioactivity

There are many free and commercial tools available to predict the toxicity of the target.

These tools can predict the toxicity for multiple endpoints for human health and ecotoxicology.

The tools can also indicate how the target reacts (i.e. mechanism of action, or molecular initiating event).

Prediction Tools	
Public	**Commercial**
OECD QSAR Toolbox	DEREK NEXUS
VEGA	TIMES by OASIS
OPERA	ChemTunes ToxGPS
EPA CompTox Chemicals Dashboard	Leadscope tools
Danish (Q)SAR Database (and models)	MultiCASE

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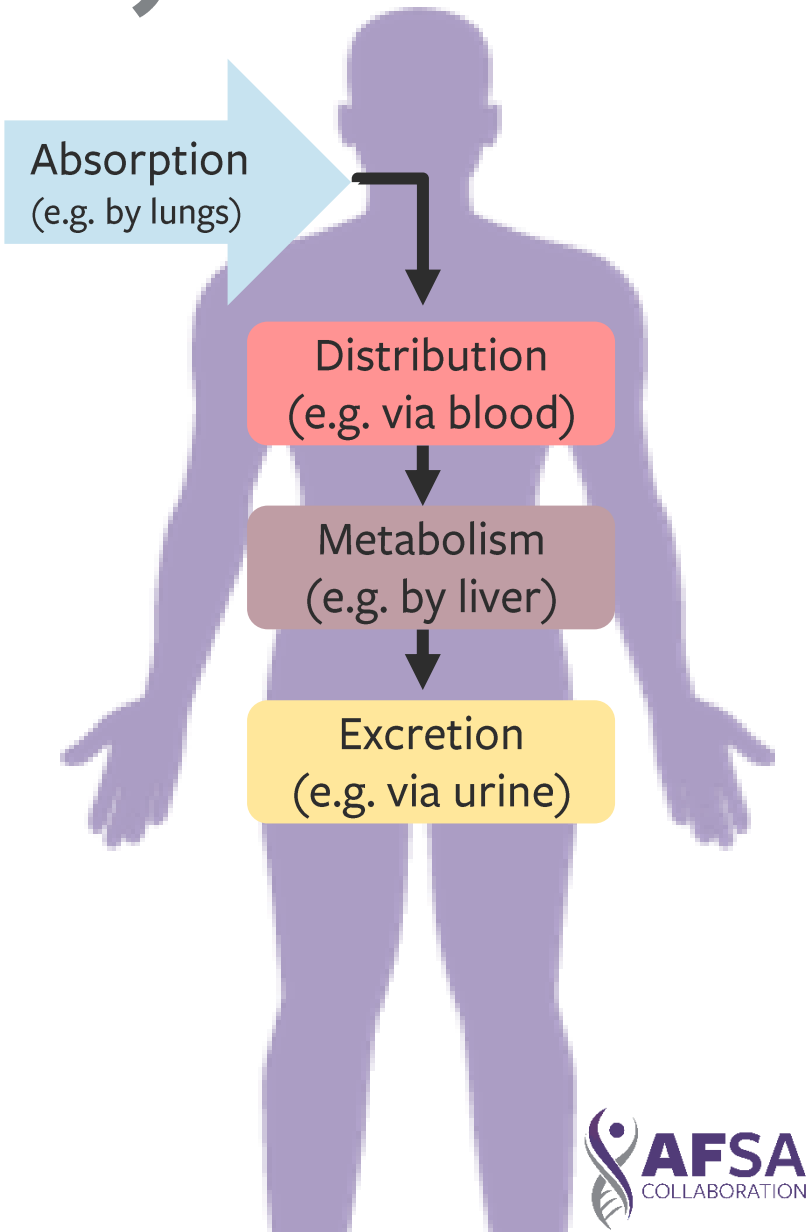
Target profiling: Exploring toxico(bio)kinetics

- Knowing the exposure that a person may have to the target substance is an important part of a risk assessment. This not only includes how a product is used, but what happens when (and if) the product ingredients enter the body.

- If the read-across is for a systemic endpoint data gap, it is important to consider toxicokinetics, which is a measure of ADME (absorption, distribution, metabolism/biotransformation, and excretion).

- Literature and data sources can be searched to find relevant experimental data. However, if this is not available, toxicokinetics can be predicted using in silico tools [**see Module 5: Internal Exposure/Dosimetry**]

- All data should be added to a table in the data matrix.



Target Profiling: Summarising the target (and metabolite toxicity)

As already suggested, it is important to record the output for each stage of the read-across framework. Once all the information about the target is available, a summary can be prepared which gives an overall view of the target substance (and metabolites).

The data in the data matrix can be used to prepare the summary and can include a summary of:

- Structural features.
- Existing toxicity data.
- Predicted toxicity alerts.
- Predicted physchem properties.
- Summary of toxicokinetics predictions.
- Key metabolic biotransformations.
- Metabolite toxicity alerts

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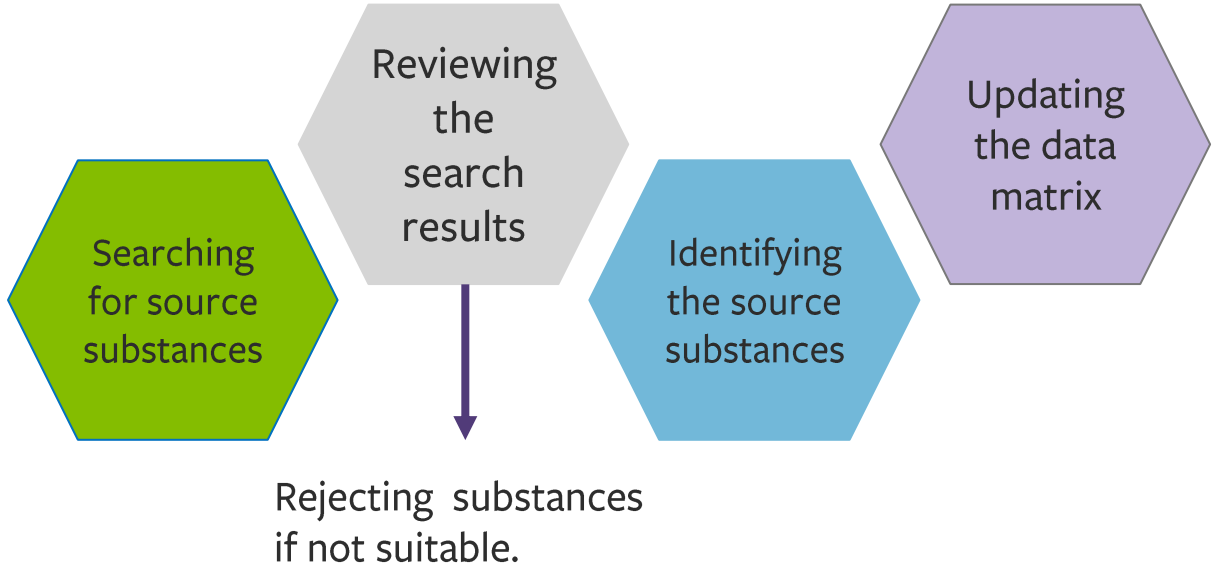
Source identification

Source substances may be found in literature or regulatory dossiers. In these cases, the source substances are evaluated for their suitability for use in the read-across.

If a source substance has not been proposed or found, suitable substances must be identified, and this includes:



Source identification: Searching for source substances

To find source substances, the target's structure is used as input into a search tool. Searches can be based on:

- **Similarity**. In this case, the whole target structure is used to find source substances which are structurally similar (that is, contain the same structural features).

- **Substructure**. In this case only part of the target structure is used. This is usually part of the structure which has already been identified as having potential to cause toxicity during the profiling step.

The query can also contain a requirement that the search results must have the required data for the risk assessment.

Source identification: Similarity searches

Similarity searches use the whole target structure to find other chemicals which have a similar chemical structure.

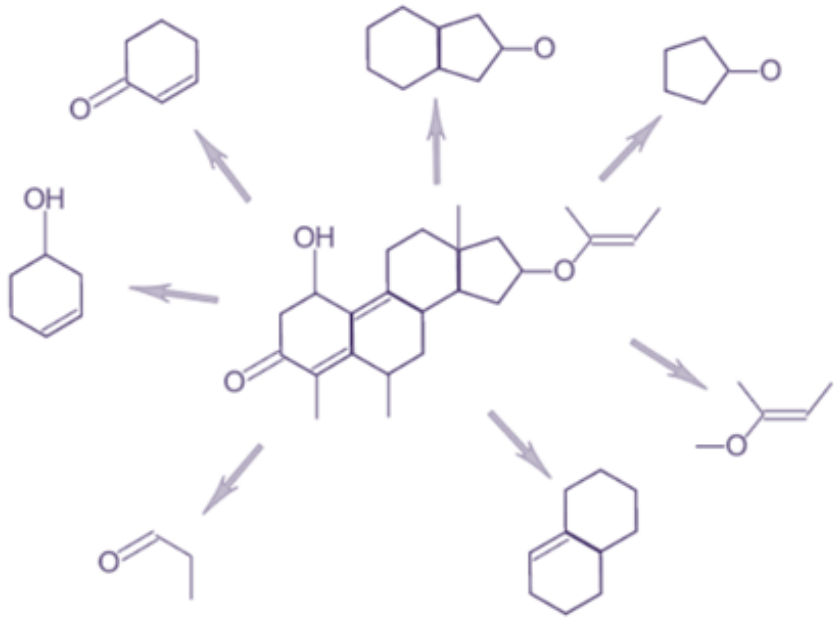
The target structure is converted into fingerprints, which contain the structural features encoded into strings. These strings are then compared with the fingerprints of other structures.

The query can also contain a condition relating to the data required for the risk assessment. For example, the search results must contain substances which have specific assay or endpoint data.

Source identification: Substructure searches

If the target has structural features (which may or may not be associated with toxicity), these features can be used as the basis for a search for source substances. In this case the input is a structural fragment (substructure).

For example:



Source: https://open-babel.readthedocs.io/en/latest/Cheminf101/search.html

The substructure is converted into fingerprints (in the same way as for similarity searches).

The search results include all substances which contain the same structural feature. However, the substances may also contain other features which may be associated with toxicity.

The query can also contain a condition relating to the data required for the risk assessment. For example, the search results must contain substances which have specific assay or endpoint data.

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Source identification: Rejecting source substances

Potential source substances may be rejected because of differences in structural features compared to the target.

To ensure transparency and traceability in the read-across, any rejected substances must be recorded, along with the reason why there were rejected.

Missing functional groups	...which may affect how the substance reacts.
Additional functional groups	...which may have a different mechanism of action.
Ring versus Linear	... the structural feature may be part of a ring structure vs. part of an alkyl chain in the target.
Features that impact properties	...the structural feature impacts the substance's physchem properties. E.g. the presence of a long alkyl chain.
Missing endpoint data	... the data needed to risk assess the Target is missing.

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Source identification: Identifying the source substance(s) fully

- Following the searches, there maybe one or more potential source substances.

- The identity of the source substances must be known before read-across can be performed. As with the target, it is important to determine what the source substance is by searching for alternative names (synonyms) and specific identifiers such as CAS or EC numbers. The same search tools used to find the target identifiers can be used for the source substances.

- The source may be a single component or a mixture, in which case, all the component parts of the mixture (and any impurities) must be identified. Ideally, the substance has been characterized using an analytical technique to determine what the substance is.

- The source substance details can then be stored in the data matrix alongside the details for the Target.

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Source identification: Searching for existing data

- When source substances have been identified, it is important to find what data already exist as this can inform how the substance reacts, but more, importantly it will include the data which may be used to risk assess the target.
- The sources used to search for source substances can be used to find any associated toxicity data and details of any physchem experiments. The toxicity data and physChem properties associated with each source substance must be recorded. This can be added to the data matrix tables alongside the data for Target.

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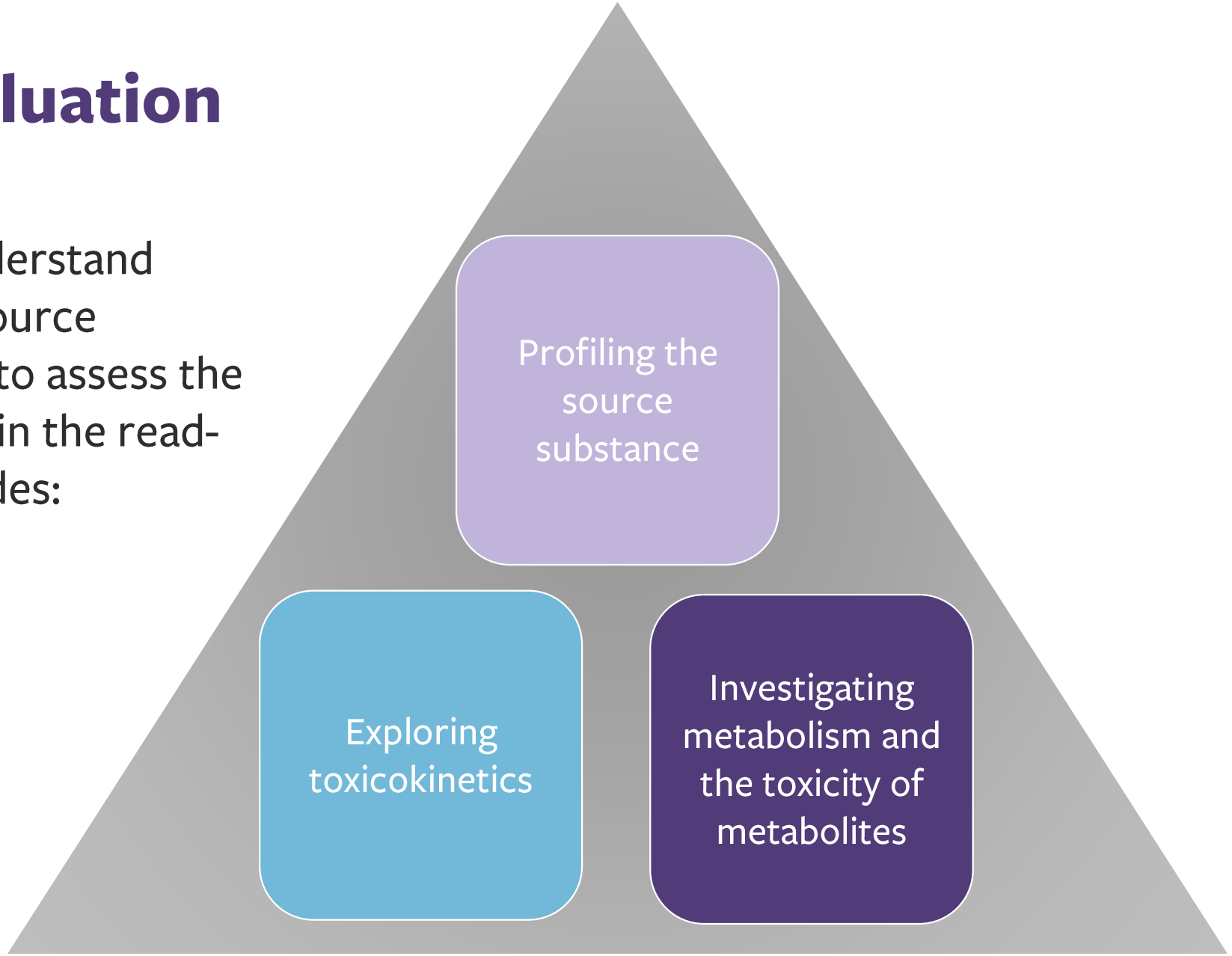
Source evaluation

This step is to understand more about the source substance(s) and to assess the suitability for use in the read-across. This includes:



Source evaluation: Comparing the target and source substances

The following characteristics of the target and source substance are compared to rate the potential read-across hypothesis:

- Structural features.
- Potential toxicity (existing data and / or in Silico predictions).
- Physchem properties (existing data and / or in Silico predictions).
- Toxicokinetics (experimental or predicted).
- Metabolism (experimental or predicted).

Differences are recorded and appropriate read-across ratings can then be assigned to each source substance:

1. Suitable
2. Suitable with Interpretation
3. Suitable with Pre-Condition
4. Not suitable

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Opportunities to strengthen read-across

Use of New Approach Method (NAMs)

For example:

- Metabolism studies may confirm which metabolites are formed.
- Targeted in vitro studies may help to fill a data gap for a specific endpoint, and / or to confirm any toxicity predictions. For example:
  - → Tox Tracker from Toxys is a stem cell reporter assay which gives mechanistic insights into genotoxic properties of chemicals.
  - → ToxProfiler from Toxys uses human liver cells to quantitatively measure cell stress responses.
- High throughput assays (e.g. transcriptomics) may help to identify toxicity which may not have been identified by the available experimental data or in Silico tools.

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Read-across outcome

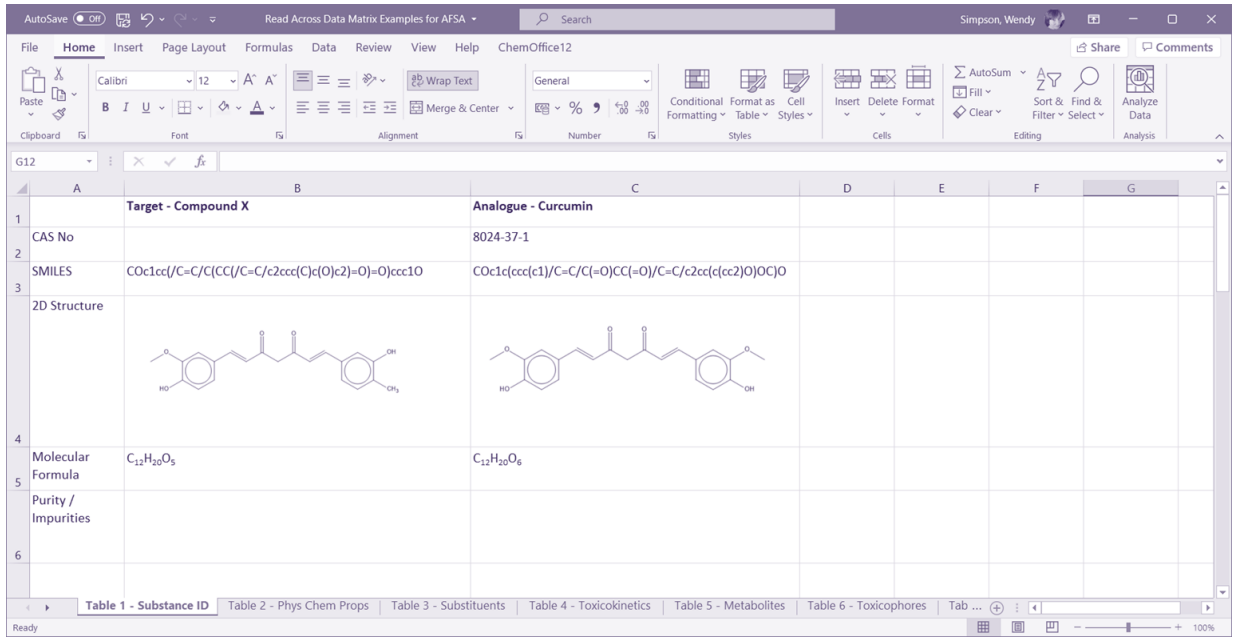
The read-across outcome is a conclusion as to whether the data from the source substance(s) can be used to risk assess the target.

All the information gathered in the process is reviewed. This includes:

- The comparison between the target and source substance(s). Are the substances similar enough in structure and behavior?
- Is there enough evidence to support the hypothesis?
- Is the data of good quality?

After the review, it is confirmed or refuted as to whether the source substance data can be used. It may be identified that additional data generation is needed to support the hypothesis.

The conclusion is recorded and stored along with all data collected during the read-across steps.



Uncertainty

It is key to describe the type and degree of uncertainty in a read-across. Any areas of uncertainty must be recorded in the read-across documentation.

Sources of uncertainty can include:

- Context and relevance to risk assessment / regulation.
- Data for the end point under consideration. For example, the quality of the study data for the source substance(s).
- Argumentation of the read-across:
  - → Hypothesis.
  - → Plausibility of the mechanism.
  - → Weight of Evidence.
- Similarity between the target and source substances:
  - → Structure.
  - → PhysChem.
  - → Toxicodynamics.
  - → Toxicokinetics.

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Documenting the read-across

It is important to document all stages of the read-across. The read-across must be transparent and it must be possible to understand which substances and data are used to support the hypothesis.

Several templates have been developed to support documenting a read-across. These include:

- A strategy for structuring and reporting a read-across prediction of toxicity, Schultz et al 2015. OECD doc
- ECHA Read Across Assessment Framework (RAAF).

However, in reality, it is more often necessary to adapt these or use an in-house designed reporting format.

Regulatory acceptance

Read-across can be used to inform a risk assessment or used to support a regulatory submission.

Read-across is one of the most applied alternative approaches (adaptations) for data filling in registrations submitted under the REACH Regulations. By using read-across, unnecessary animal testing may be avoided.

The conditions under which 'Read-across and grouping' can be used to adapt the standard testing regime for REACH are listed in Annex XI, 1.5 of the REACH Regulations:

1.5.: Grouping of substances and read-across approach
The similarities may be based on:
(1) a common functional group;
(2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or
(3) a constant pattern in the changing of the potency of the properties across the category.
In all cases results should:
—be adequate for the purpose of classification and labelling and/or risk assessment,
—have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),
—cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and
—adequate and reliable documentation of the applied method shall be provided.

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Using both read-across and *in silico* tools in a weight of evidence approach

How do you apply a weight?

- Take into account the robustness and reliability of the different data sources
- Depends on factors such as:
  - → the quality of the data
  - → consistency of results
  - → nature and severity of effects (for in vivo/in vitro studies)
  - → relevance of the information

- The weight of evidence approach requires use of scientific judgment and as a general principle, the more information you provide, the stronger your weight of evidence is.

For more information:
See module 7 for more on WoE and integration of results in risk assessment

Summary: Read-across

- The following are steps of a read-across process:
  - → Hypothesis
  - → Decision Context
  - → Data gap analysis for the target
  - → Target profiling
  - → Source identification
  - → Source evaluation,
  - → Source data evaluation,
  - → Read-across framework/outcome
- There are different read-across approaches:
  - → one-to-one
  - → many-to-one
  - → Analogue
  - → Group (or category)
- If the target or source is complex, it may still be possible to perform read-across
- When evaluating the read-across outcome, the following should be considered:
  - → Is there enough similarity between the target and source substance(s)?
  - → Is there enough evidence to support the hypothesis?
  - → Is the data of good quality?
- Sources of uncertainty should also be considered
- The read-across process must be appropriately documented, and

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We value your feedback! As the AFSA Collaboration works to complete its free Master Class on Animal-Free Cosmetic Safety Assessment, we would appreciate your input on what we've developed so far and presented via this webinar preview series. Please take our FEEDBACK SURVEY

Thank You !

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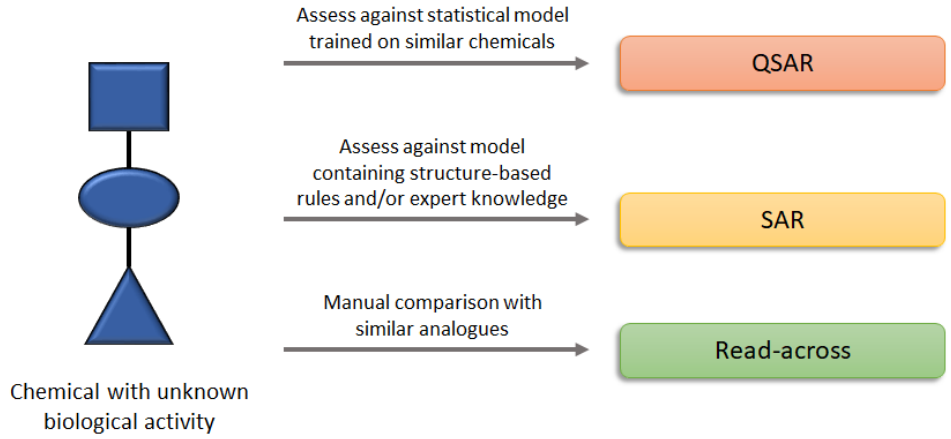
https://www.afsacollaboration.org

Definitions

- ***In silico* prediction:** any method of prediction using a computational approach
- ***(Q)SAR (Quantitative) Structure-Activity Relationship models:*** models that predict the physicochemical, biological and environmental fate properties of compounds from the knowledge of their chemical structure.
  - **SAR** is a qualitative relationship that relates a (sub)structure to the presence or absence of a property or activity of interest, usually using rules or patterns.
  - **QSAR** is a mathematical (statistical) model relating one or more quantitative parameters (molecular descriptors) that are derived from the chemical structure to a quantitative measure of a property or activity

- ***Read-Across***: is an approach that uses the data from a structurally/mechanistically similar substance (the source) to infer information for a substance (the target) for a specific endpoint or activity. Read-across is often conducted using one or more *in silico* model to identify analogues.



Abbreviations

- ADME: Absorption, distribution, metabolism, and excretion
- AOP: Adverse outcome pathway
- DPRA: Direct peptide reactivity assay
- DST: Dermal Sensitisation Threshold
- ECHA: European Chemicals Agency
- EFSA: European Food Safety Authority
- ITS: Integrated Testing Strategy
- LLNA: Local lymph node assay
- MA: Michael Acceptor
- MAD: Mutual acceptance of data
- MPS: Microphysiological systems
- NN: Nearest neighbours
- OECD: Organisation for Economic Cooperation and Development
- QSAR: Quantitative structure activity relationship
- SAR: Structure activity relationship
- SB: Schiff Base
- SNAr: Nucleophilic Aromatic Substitution

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