PRIORITIZATION OF CHEMICALS ACCORDING TO THEIR HUMAN HEALTH TOXICITY

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GOAL

To propose a system for prioritizing chemicals according to their human health toxicity
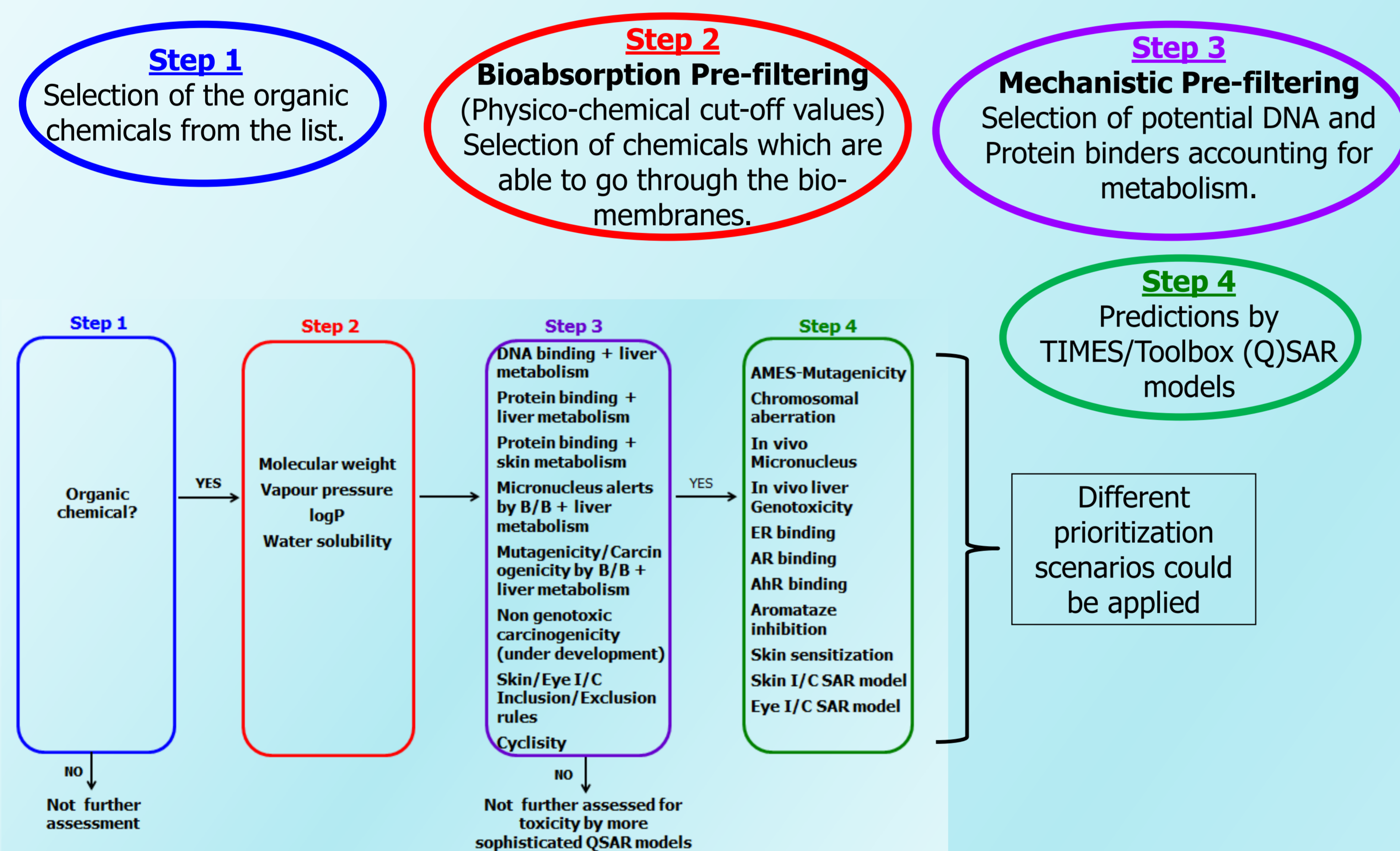
The development of new chemicals requires their rapid prioritization with respect to the possible impact on human health and the environment. In many cases, this prioritization even precedes the experimental syntheses of new products. In turn, the regulatory authorities are also interested in prioritization of their inventories for exisiting and new chemicals to identify the potentially most hazardous chemicals which deserve to be tested. Thus, the time taken to assess the risk of thousands of chemicals that are in current use can be reduced significantly. The use of the QSAR approach for prioritization of chemicals could save time and resources and give satisfactory results.

MATERIALS AND METHODS

OECD QSAR Toolbox functionalities and OASIS TIMES models were used in the prioritization process

The prioritization scheme consists of two stages. The first one is pre-filtering and it is based on OECD QSAR Toolbox [1] categorization profiles. Bio-absorption thresholds, mechanistic and endpoint specific alerts applied to parents and metabolites are used for pre-filtering purposes. The second stage includes (Q)SAR predictions based on TIMES [2-5] and OECD Toolbox models applied to already pre-filtered chemicals. Based on the endpoint hierarchy the chemicals are grouped into toxic categories.

After defining toxicity categories, two layers of confidence are associated with each of the toxicity category. The first layer provides "degree of certainty" of predictions depending on the structural target of these predictions: parent chemical, their metabolites or structural alerts, respectively. The second layer of confidence, called "reliability of prediction" is defined according to belonging of chemical structures to model applicability domain.


Step 1 — Selection of the organic chemicals from the list.

Step 2 — Bioabsorption Pre-filtering (Physico-chemical cut-off values) Selection of chemicals which are able to go through the bio-membranes.

Step 3 — Mechanistic Pre-filtering Selection of potential DNA and Protein binders accounting for metabolism.

Step 4 — Predictions by TIMES/Toolbox (Q)SAR models

Different prioritization scenarios could be applied

Proposed requirements for toxic priorities
(could be dynamically modified)

| Toxicity Priority	Carcinogenicity		Genotoxicity		Reproductive/ Developmental Toxicity		Acute toxicity	Repeat dose toxicity	Sensitization		Irritation	
	Genotoxic	Non Genotoxic	In vitro	In vivo	ER binding	AR binding			Skin	Lung	skin	eye
Class I (Highest)	+						+/-	+/-	+/-		+/-	
Class II (High)	-		+		+/-			+/-		+/-		+/-
Class III (Moderate)	-				-		+		+/-		+/-	
Class IV (Weak)	-				-		-		+		+/-	
Class V (Low)	-				-		-		-		+	
Class VI (Lowest)	-						-	-	-		-	

PRIORITIZATION SCENARIOS

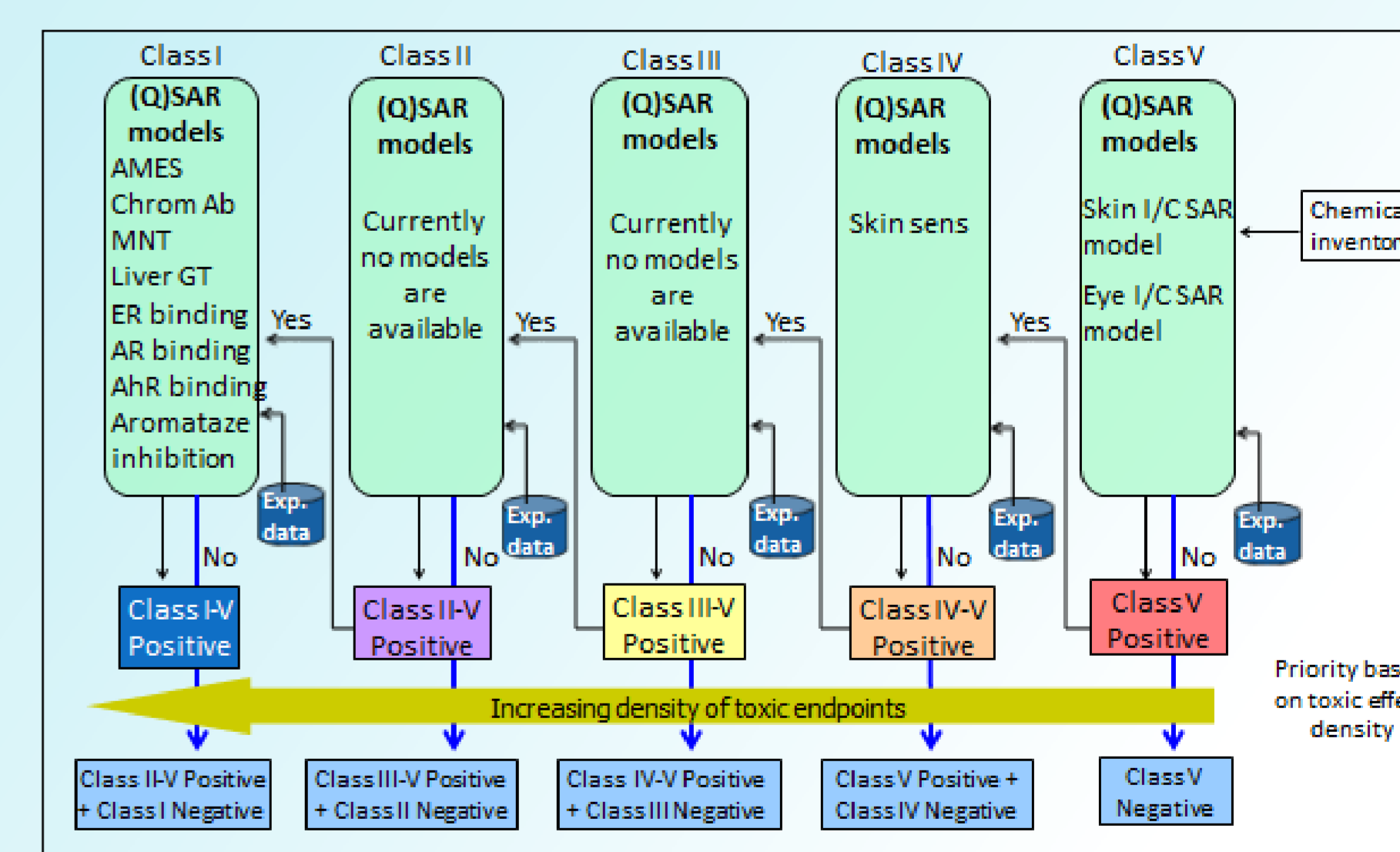**Simplified prioritization**
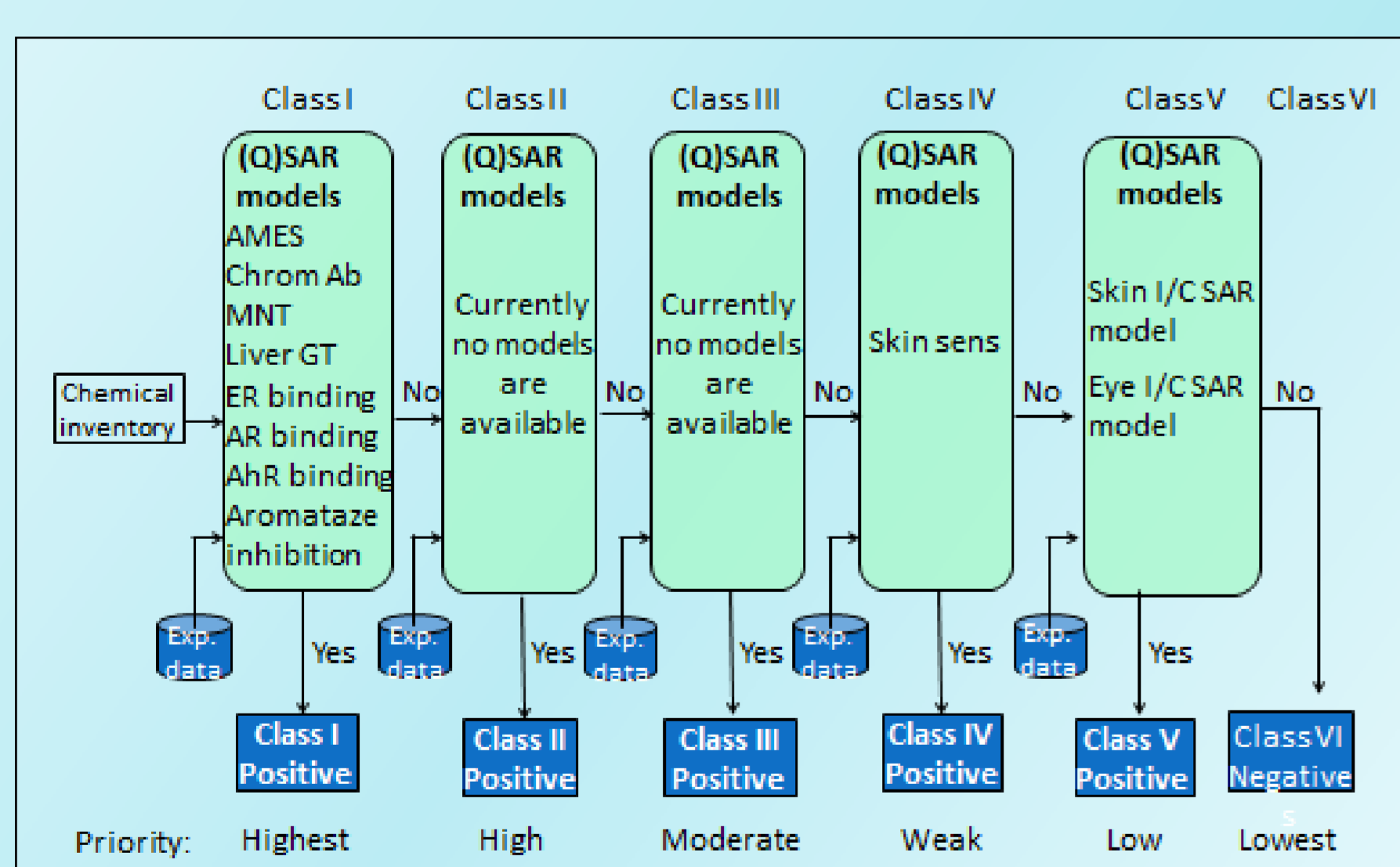
Prioritization based on accumulated toxic effects

Forward approach
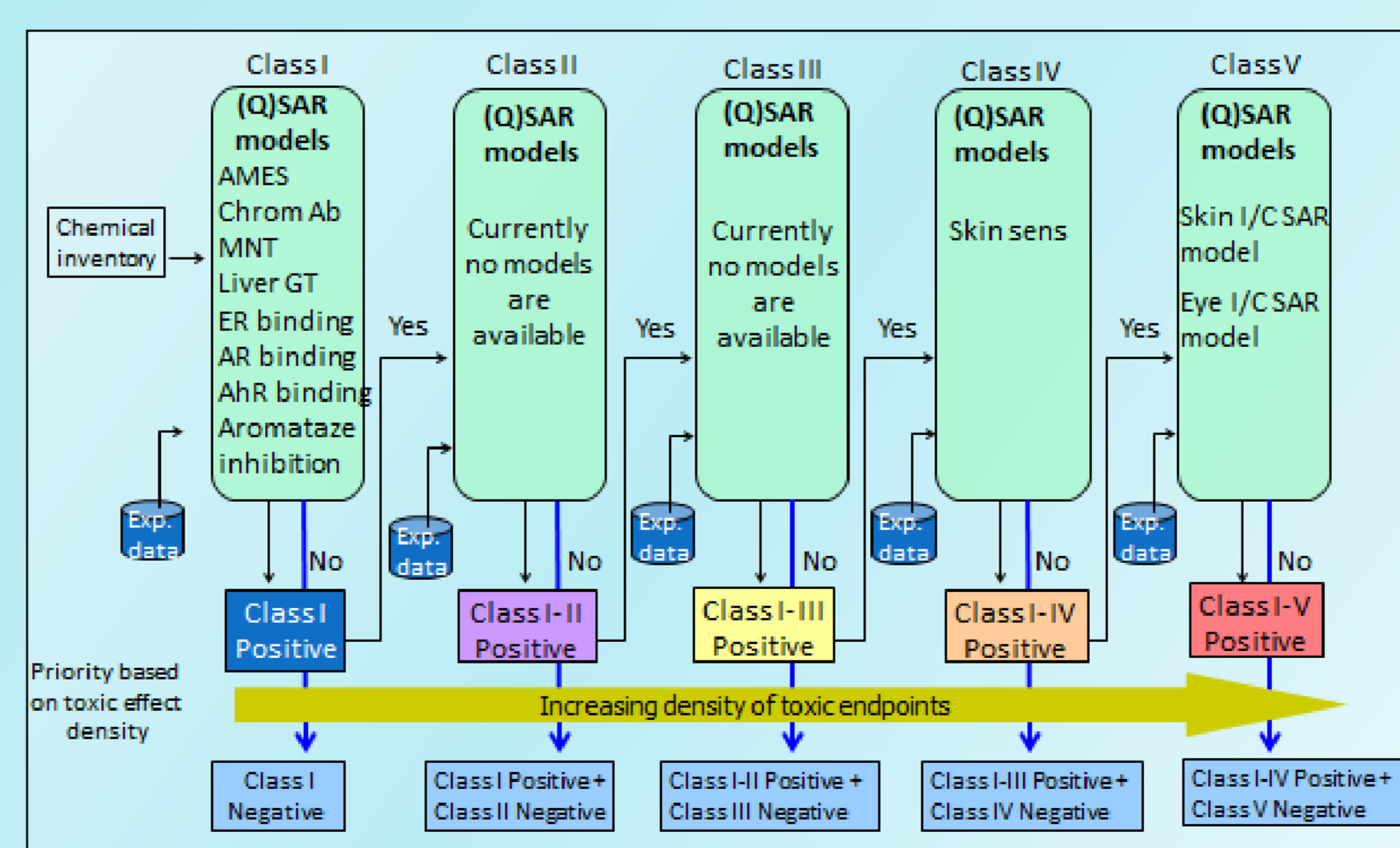
Backward approach

SUMMARY

❖ Human Health Toxicity prioritization scheme has been proposed

❖ OECD Toolbox and OASIS-TIMES platforms are used as endpoint assessment tools and data sources

❖ Six classes of toxicity have been proposed

❖ Two layers of confidence have been added to each of the toxicity classes depending on:
  • Degree of certainty, i.e. whether toxicity is due to parent, metabolites or structural alerts
  • Reliability of prediction, i.e. belonging to model domain

❖ Two prioritization schemes are proposed based on:
  • Hierarchy of toxicity classes
  • Accumulated toxic effects

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