

# Horizon 2020 Proposal: CAT-APP

**“New methods to Underpin Category Approaches  
and Read Across in Regulatory Programmes”**

Hans Ketelslegers







› Fuels Quality & Emissions

› Air Quality

› Water, Soil & Waste

› Health

› Petroleum Products

› REACH Implementation

› CLP Notification

› Safety

› Oil Pipelines

› Refinery Technology

DISCLAIMER

The information that Concaawe provides on its Website represents opinions and is intended for guidance only. Whilst the information is provided in utmost good faith and has been based on the best information currently available, it is to be relied upon at the user's own risk. No representations or warranties are made with regards to its completeness or accuracy and no liability will be accepted for damages of any nature whatsoever resulting from the use of, or reliance on, the information.

Documents published by Concaawe are based on interpretations of Regulation (EC) 1907/2006 (REACH Regulation) and Regulation (EC) 1272/2008 (CLP Regulation) as well as guidance provided by and information obtained from the European Chemicals Agency (ECHA).

1. Background

2. Concaawe Inventory of Petroleum Substances

Concaawe has drawn up an inventory of petroleum substances, which can be downloaded [here](#).

3. REACH Implementation by Concaawe and its Member Companies

4. Collaboration among registrants of petroleum substances

5. Registration Dossiers

6. Facilitation of Substance Information Exchange Fora (SIEFs)

7. The sameness of petroleum substances

8. Import of petroleum substances into (and trading in) the European Economic Area (EEA)

9. Additives in preparations (crude oil, gas condensates, fuels/blending streams) imported into the EEA

10. List of Identified Uses and mapping against Generic Exposure Scenario titles and the Use Descriptor System

11. Specific Consumer Exposure Determinants (SCEDs)

12. Other relevant documentation

13. Contact

▶ [www.CONCAWE.eu](http://www.CONCAWE.eu)



1. Low Boiling Point Naphthas (Gasolines)
2. Kerosines
3. **Straight-run Gas Oils**
4. Cracked Gas Oils
5. **Vacuum Gas Oils, Hydrocracked**
6. **Other Gas Oils**
7. Heavy Fuel Oil Components
8. Unrefined / Acid Treated Oils
9. Other Lubricant Base Oils
10. Highly Refined Base Oils
11. Foots Oils
12. Paraffin and Hydrocarbon Waxes
13. Slack Wax
14. Petrolatum
15. Untreated Distillate Aromatic Extracts
16. Treated Distillate Aromatic Extracts
17. **Residual Aromatic Extracts**
18. **Bitumen**

Name	EINECS definition	CAS	EINECS
Asphalt	A very complex combination of high molecular weight organic compounds containing a relatively high proportion of hydrocarbons having carbon numbers predominantly greater than C25 with high carbon-to-hydrogen ratios. It also contains small amounts of various metals such as nickel, iron, or vanadium. It is obtained as the non-volatile residue from distillation of crude oil or by separation as the raffinate from a residual oil in a deasphalting or decarbonization process.	<b>8052-42-4</b>	232-490-9
Residues (petroleum), vacuum	A complex residuum from the vacuum distillation of the residuum from atmospheric distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly greater than C34 and boiling above approximately 495°C (923°F).	<b>64741-56-6</b>	265-057-8
Residues (petroleum), hydrodesulfurized vacuum	A complex combination of hydrocarbons obtained by treating a vacuum residuum with hydrogen in the presence of a catalyst under conditions primarily to remove organic sulfur compounds. It consists of hydrocarbons having carbon numbers predominantly greater than C34 and boiling approximately above 495°C (923°F).	<b>64742-85-4</b>	265-188-0
Residues (petroleum), thermal cracked vacuum	A complex combination of hydrocarbons obtained from the vacuum distillation of the products from a thermal cracking process. It consists predominantly of hydrocarbons having carbon numbers predominantly greater than C34 and boiling above approximately 495°C (923°F).	<b>92062-05-0</b>	295-518-9

In addition CONCAWE has prepared the joint parts of the Registration Dossier for the following stand-alone substances:

- MK1 diesel fuel (EC number 931-250-7),
- Oxidised Asphalt (EC number 265-196-4)
- Sulfur (EC number 231-722-6)



## Example: ECHA decision on Bitumen (dev. tox.)



CONFIDENTIAL 1(13)

Decision number: TPE-D-0000004028-78-04/F Helsinki, 19 February 2014

### DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For Residues (petroleum), vacuum, CAS No 64741-56-6 (EC No 265-057-8), registration number: [REDACTED]

Addressee: [REDACTED]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

#### I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for Residues (petroleum), vacuum, CAS No 64741-56-6 (EC No 265-057-8), by [REDACTED] (Registrant):

- Prenatal Developmental Toxicity Study (OECD Guideline 414), in rats, inhalation route using tank fume condensate derived from Residues (petroleum), thermal cracked vacuum (CAS No 92062-05-0); and
- Two-Generation Reproduction Toxicity Study (OECD Guideline 416), in rats, inhalation route using Tank fume condensate derived from Residues (petroleum), thermal cracked vacuum (CAS No 92062-05-0).

The present decision relates to the examination of the testing proposal for pre-natal developmental toxicity study. The testing proposal for the two-generation reproductive toxicity study is addressed in a separate decision although both testing proposals were initially addressed together in the same draft decision.

This decision is based on the registration dossier as submitted with submission number [REDACTED], for the tonnage band of 1000 tonnes or more per year. In order to follow the procedure outlined in Articles 50(1) and 51 of the REACH Regulation and to allow ECHA complete the necessary administrative practices for the Member States Competent Authorities' referral, ECHA has taken into consideration dossier updates pertinent to the decision received by the deadline of 29 April 2013 agreed between ECHA and the Registrant. Furthermore, ECHA has exceptionally taken into account the data provided by the Registrant, after the deadline, in the informal communication, as Registrant notified it of the incorrectness of some information contained in the relevant update.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

On 26 October 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu





CONFIDENTIAL

6(13)

In that line, the Registrant has considered the compositional profiles of the substances (listed above) and proposes to use Residues (petroleum), thermal cracked vacuum (CAS No 92062-05-0) as the substance to be tested.

- d) ECHA's analysis of the grouping approach in light of the requirements of Annex XI, 1.5

ECHA understands that the grouping approach is based on the refining processes by which these substances are produced and on two basic physico-chemical properties.

The REACH Regulation allows for the adaptation of the standard testing regime by means of grouping and read-across as outlined in Annex XI, 1.5: "*Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or category of substances*".

ECHA notes that "petroleum substances" are specifically addressed in ECHA's Guidance for identification and naming of substances under REACH and CLP (version: 1.2; March 2012), Section 4.3.2.2 Substances obtained from oil and oil like sources. This Guidance document acknowledges that UVCB (*substances of Unknown or Variable composition, Complex reaction products or Biological materials*) petroleum substances, such as the substance subject to the present decision, may have a considerable intrinsic compositional variability, which may exceed the compositional variability normally observed for other UVCBs.

Nevertheless, ECHA stresses that the requirements for grouping set out in Annex XI 1.5 pursue the objective of identifying hazards of the substances concerned. For that specific objective, the intrinsic compositional variability between substances shall be taken into account by any registrant relying upon a category, because it may influence the outcome of the hazard assessment. This would imply at least that this registrant qualifies the compositional variability in order to justify the relevance of the category.

- ▶ ECHA acknowledges (petroleum) UVCBs...
- ▶ ...but stresses the need for qualification of compositional variability





## Example: ECHA decision on Bitumen; grouping (2)

In relation to the present category, ECHA took note of the generic compilation of compositional information that was submitted by the Registrant in the updated category justification document, following the request of ECHA within the draft decision previously notified. However, while this generic data reveals structural similarity to some degree among the category members, ECHA stresses several deficiencies.

Firstly, contrary to the explicit requirement of Annex XI, 1.5, the Registrant does not define the category based on the structural similarity of the substances concerned, but persists in relying exclusively on manufacturing processes and performance characteristics to justify the grouping approach.

Secondly, the Registrant does not sufficiently qualify the compositional variability of the substances concerned by the category in order to justify that the compositional variability would not be such as to affect the determination of the actual hazard of the substances concerned.

Thirdly, the generic compositional data submitted only refers to the average carbon number distribution and average relative mass (%) of four major hydrocarbon classes. However, in the absence of detailed compositional information on the substances concerned by the category, including representative ranges of hydrocarbon classes content, ECHA considers that the respective hazards of these substances cannot be identified in a representative way which does not underestimate the hazard.

Consequently, ECHA considers that the category '*Bitumens*' does not fulfil the requirement defined in Annex XI, 1.5. and does not allow the Registrant to meet the objective pursued by the REACH Regulation. As a result and based on the information analysed by ECHA,

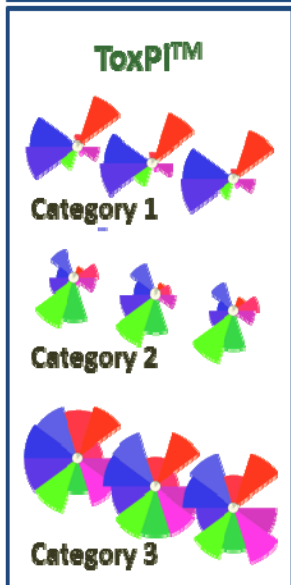
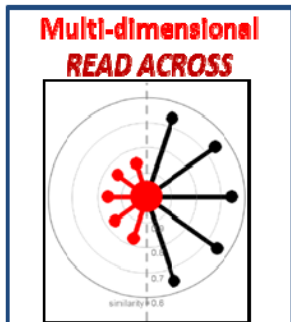
Anankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

these substances cannot be considered as a group, or category of substances under the REACH Regulation, irrespective of the status of these substances under other legal systems.

- ▶ No similarity principle, but rely on manufacturing process
- ▶ Compositional variability not sufficiently addressed to justify determination of hazard (via read across)
- ▶ Category or grouping not accepted



## Data Integration and visualization



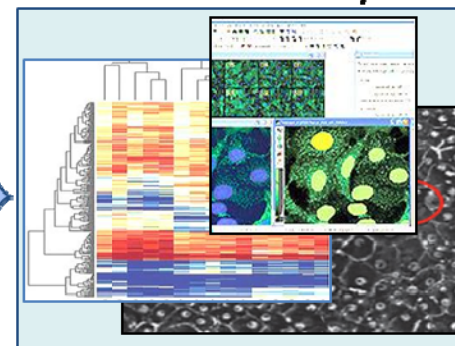
	TYPE	DESCRIPTION
<b>Analogue approach</b>	Identical toxicants through biotransformation	<u>Chemical or biological transformation</u> results in exposure to the same toxicants, and subsequently the same effects
	Different ultimate toxicants	Source and target are known to belong to a group of substances that cause effects by means of an identical <u>mode of action</u> with identical tox endpoints. Identical interactions or endpoints imply predictability of effects.
<b>Category approach</b>	Trend in the property to read across	A plot of the property under consideration on another property shows a clear trend for a group of substances, this trend alone may suffice for prediction
	Trend in the property to read across plus a mechanistic explanation	A plot of the property under consideration on another property shows a trend for a group of substances; moreover, there is a <u>mechanistic explanation</u> why group membership goes with predictive power
	Trend in other properties	Trends observed for other properties than the property under consideration go with possibilities to predict effects.

**UVCB chemical descriptors:**  
Generic fragments, G SMILES, G graphs

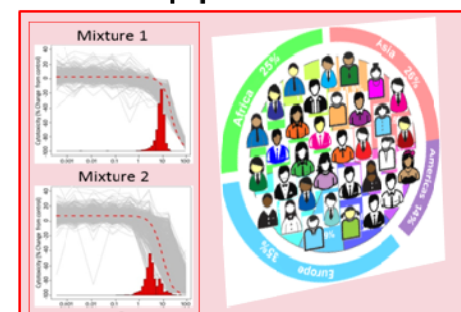
**Data from *In vivo* studies:**



**Data from *In vitro* model systems:**



**Data from a population-based model**

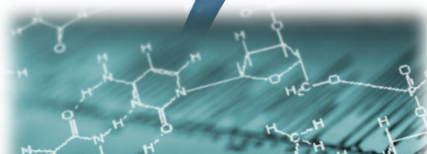




# Need to address grouping of PP... Exploration and exploitation of *novel data streams*

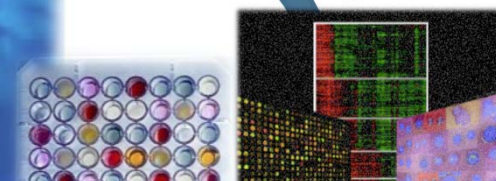
## Cheminformatics

Making predictions over multiple chemicals



## Bioinformatics

Collecting data over multiple biological assays



Integrate **chemical-** and short-term toxicity assay data

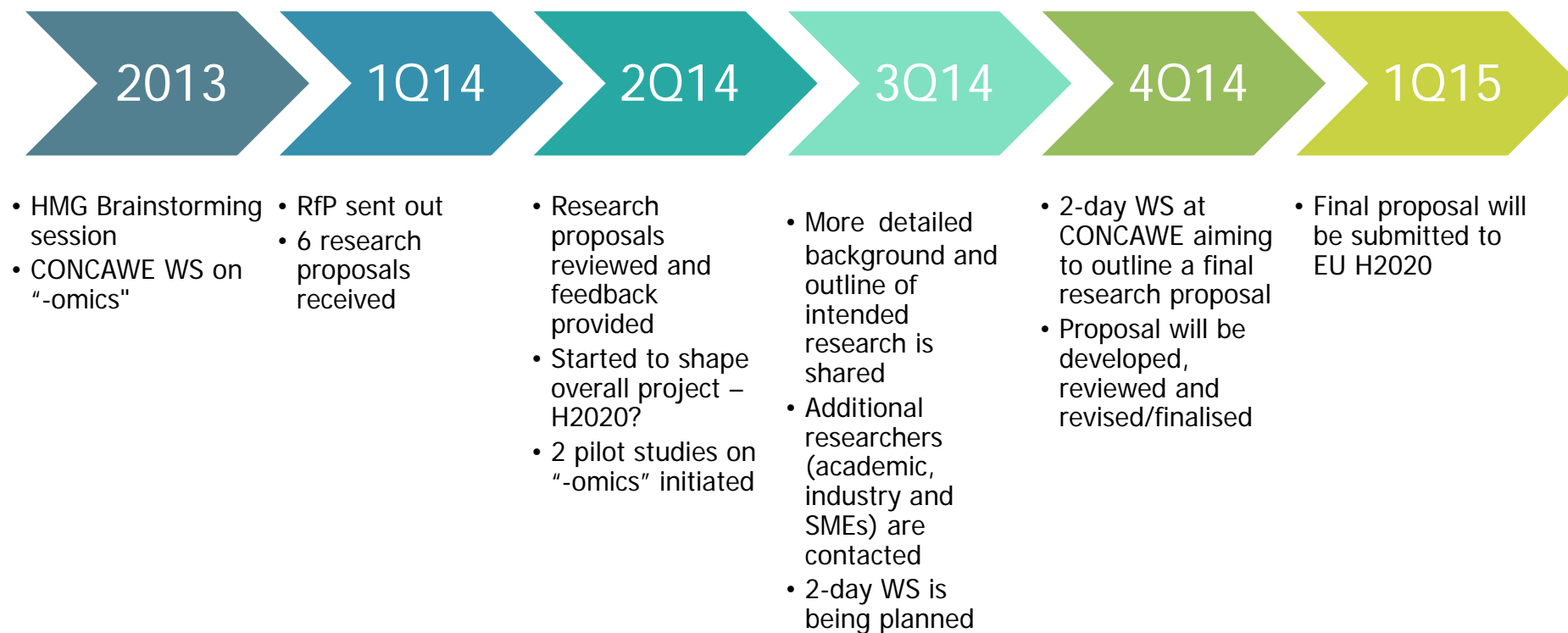
**QSAR** descriptors  
 Tanimoto  
 molecular  
 bond  
 chain **hydrophobic**  
 similarity ring SAR aromatic acid  
 size order  
 chemical logP benzene  
 aliphatic connectivity fragments  
 electrostatic  
**cheminformatics**

## TOXICITY TESTING IN THE 21ST CENTURY: A VISION AND STRATEGY



pathways High-throughput  
 mechanisms points  
 Vitro investigators doses  
 pathway chemicals characterization Biology  
 large allow vision approaches over away  
 breakdown adverse proteomics possible between operate  
 make modeling dose-response environment  
 associating human microarray toxicity alone platforms  
 models being application perturbations key main elements  
 cells future direct predict exposure Dose multiple  
 animal cell larger function approach uses molecular NRC  
 data field examine addressed issue any  
 lines **genes** physical biological approaching allows  
 discussed full information-based elucidate potential Systems  
 response population-based combination interpret testing  
 efficient each observation combination interpret testing  
 diverse integrate PK/PD cellular including  
 numbers substances metabolomics metabolites

## Broadening CONCAWE's horizon: toxicology of the 21<sup>st</sup> century





The EU's 2014-20 programme for research and innovation



*“Strengthening the EU’s global position in research, innovation and technology”*





### H2020 Personalising Health Care (PHC) – PHC-33-2015

*New approaches to improve predictive human safety testing (30M€)*

#### Proposal and Interest:

**“New methods to Underpin Category Approaches and Read Across in Regulatory Programmes”**

- ▶ Develop the *framework* to utilize cutting-edge in vitro technologies to underpin the category and read-across approach for petroleum substances

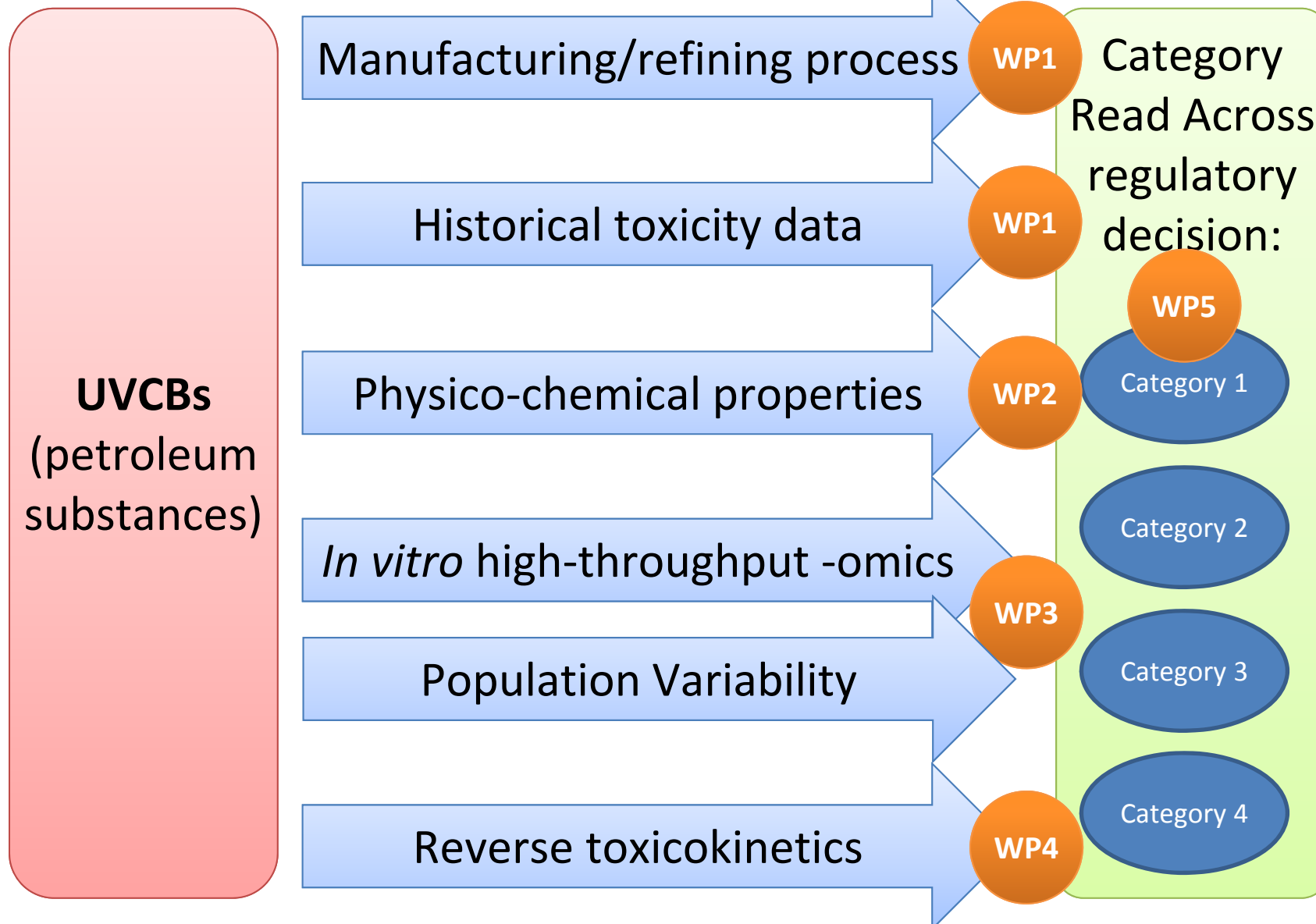
#### Benefits to CONCAWE/Petroleum industry:

- ▶ Reduce long-term REACH compliance costs and shorten the overall timeline
- ▶ Design & data to evolve category approach and read-across for PS UVCBs
- ▶ Reduction of animal testing
  - ▶ some minimal testing will be required to verify approach
  - ▶ new approach will eventually lead to significant reduction in animal use
- ▶ Peer-review publications (& regular reports to EC)

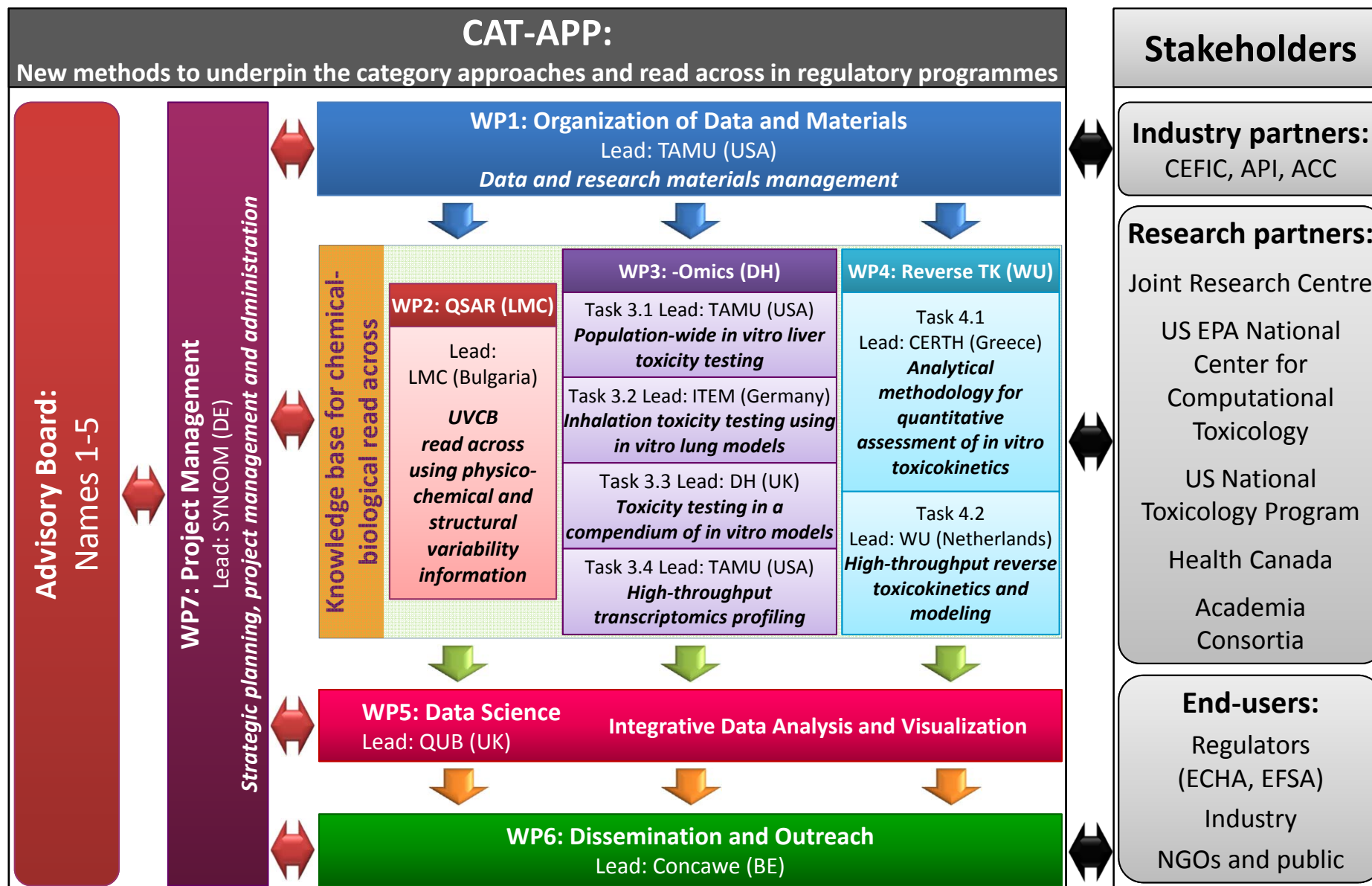




## CAT-APP: Conceptual Design

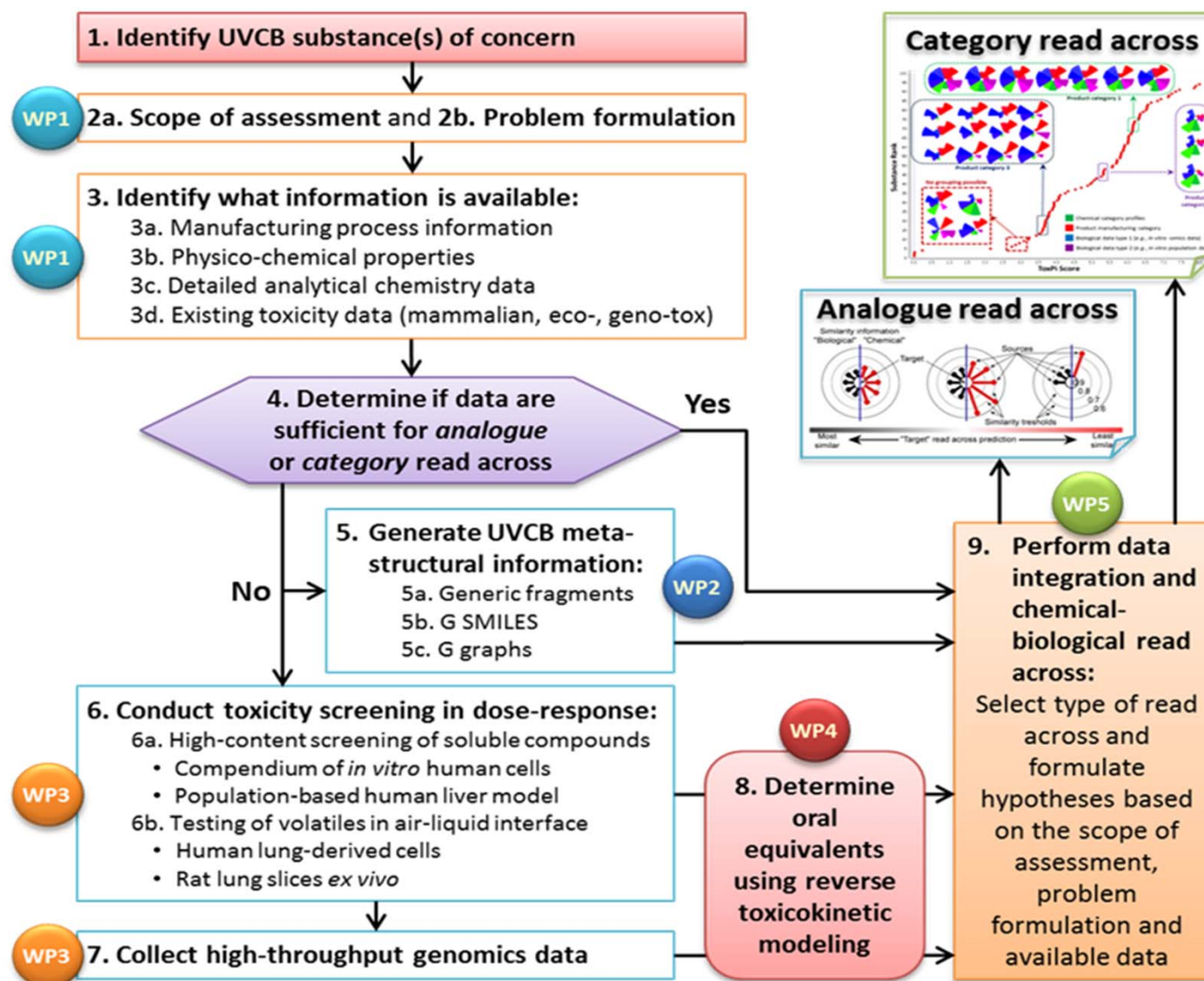






**Abbreviations:** Texas A&M University (TAMU), Laboratory of Mathematical Chemistry (LMC), Department of Public Health England (DH), Centre for Research & Technology, Hellas (CERTH), Wageningen University (WU), Queen's University of Belfast (QUB), European Chemical Industry Council (CEFIC), American Petroleum Institute (API), American Chemistry Council (ACC), European Chemicals Agency (ECHA), European Food Safety Authority (EFSA)

# “Hypothetical output”: Proposed framework for read across of UVCBs



Thank you for your attention!



11 partners  
4 stakeholders  
5 advisors

Jan 2016



Dec 2019

