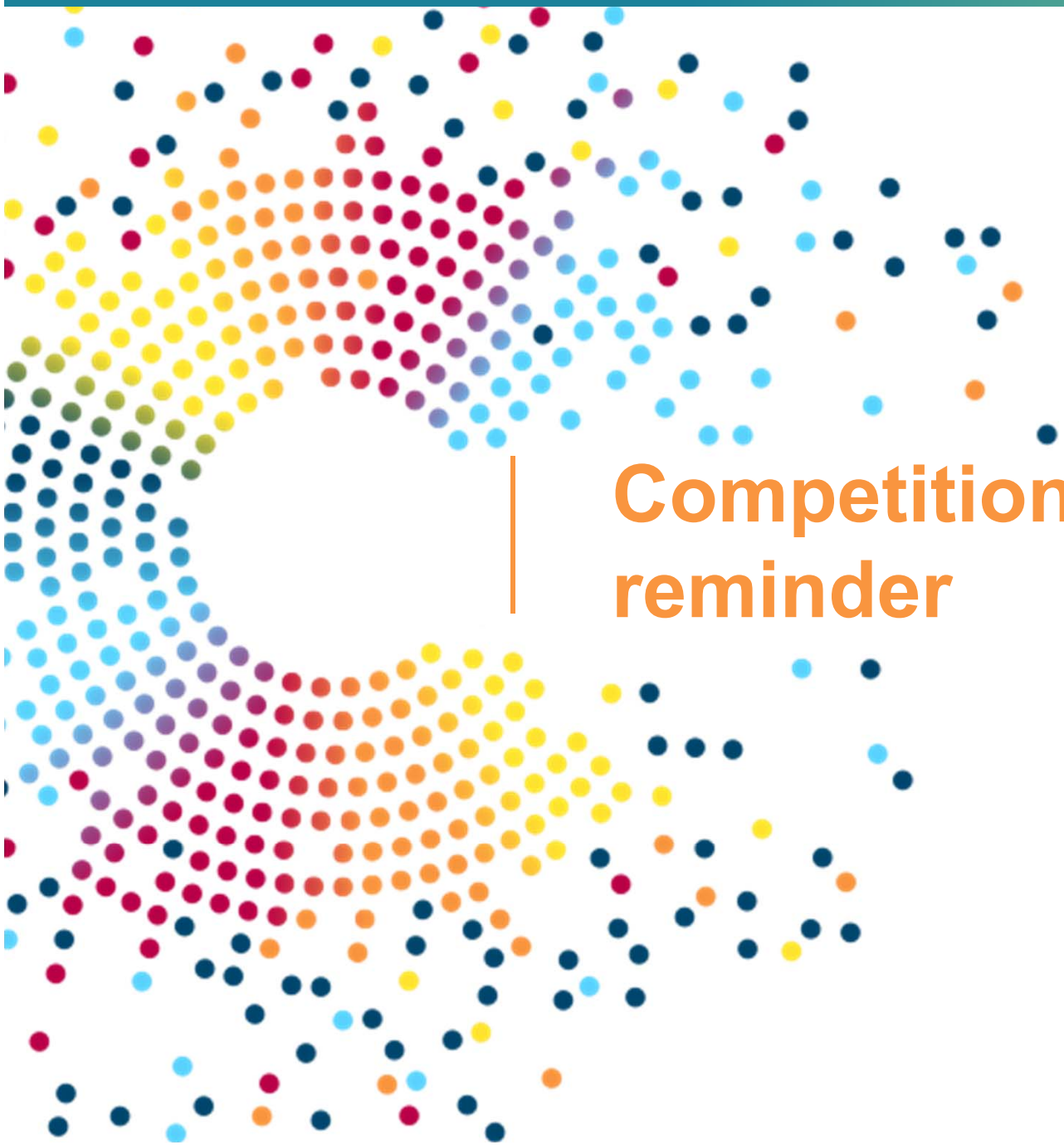
WELCOME to the Cat-App stakeholder workshop

"New Technologies to Underpin Category Approaches and Read-across in Regulatory Programmes"

March 22nd 2017
From 9:00 to 13:00

Radisson Blue Astrid Hotel
Koningin Astridplein 7, 2018 Antwerp, Belgium



Competition law reminder

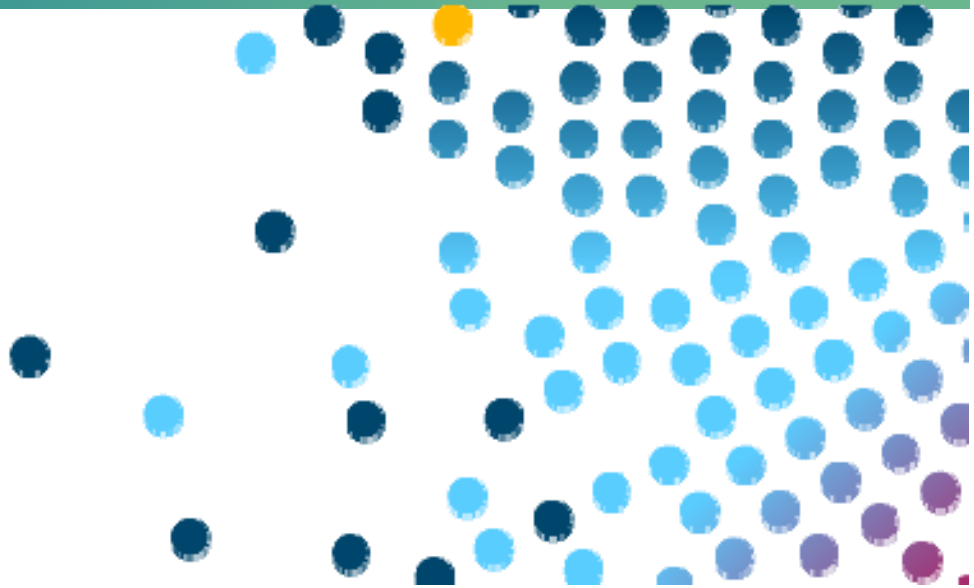
Brussels 22 March 2016

Agenda

9:00	**Registration and Welcome Coffee**	
9:30	Role of Cat-App in Concawe REACH strategy	Hans Ketelslegers, Concawe
9:50	State of the art and progress made in high throughput testing	Ivan Rusyn, Texas A&M University
10:30	Progress at PHE and overview on ongoing activities in the field	Tim Gant, Public Health England
11:00	Coffee Break	
11:30	Data Science: Integrative data analysis and visualization	Fred Wright, North Carolina State University
12.00	Gene expression connectivity mapping and its application in Cat-App	Shu-Dong Zhang, University of Ulster
12:30	Discussion and conclusions	Hans Ketelslegers, Concawe
13:00	Networking Lunch	

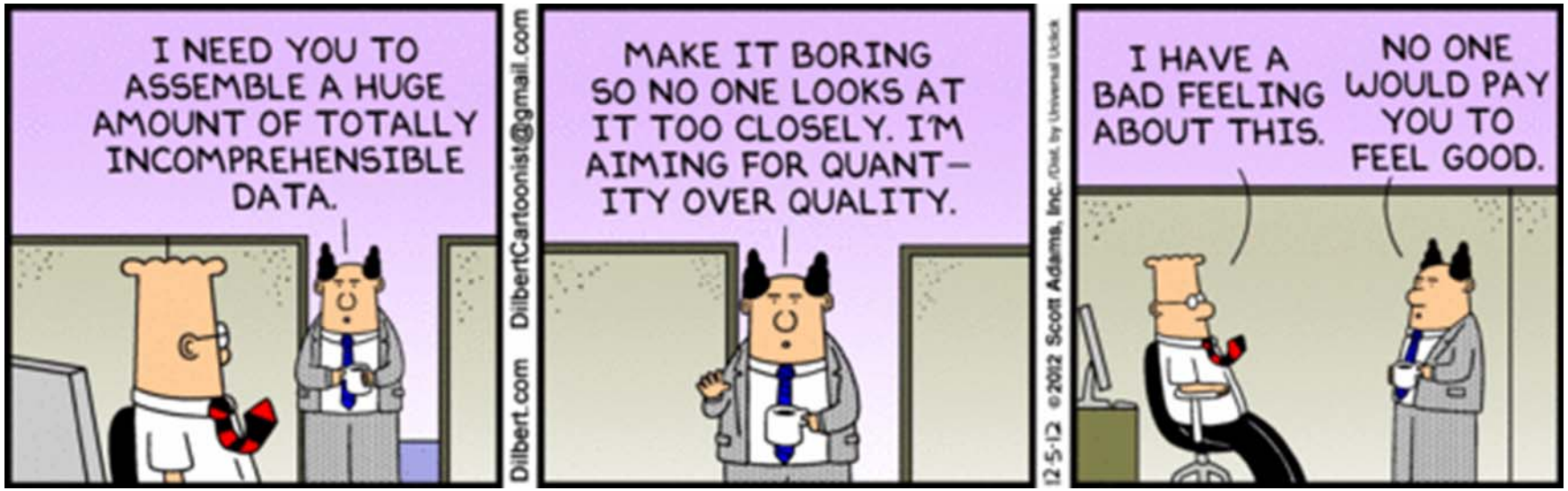
Cat-App

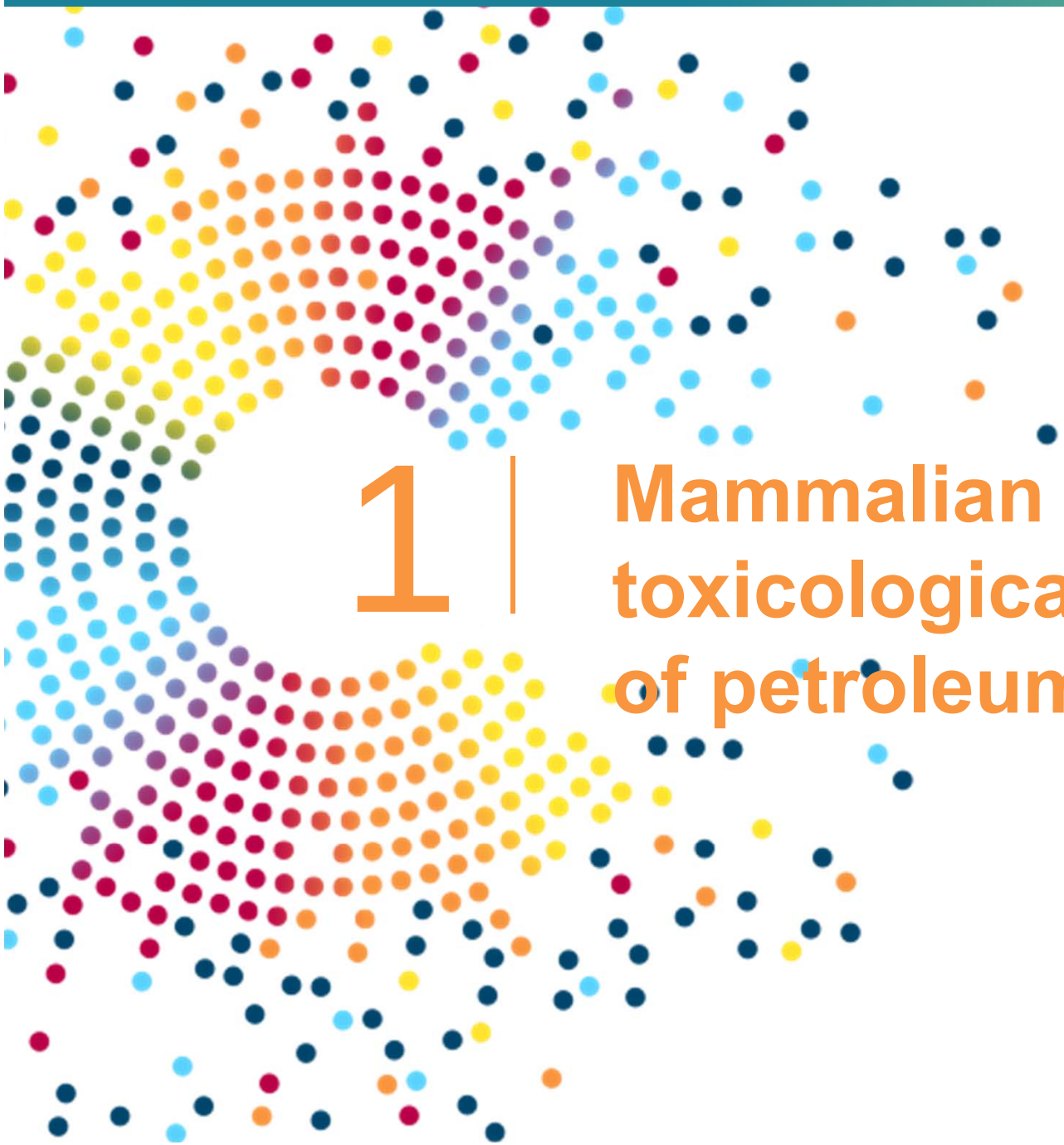
Underpinning
Category and Read Across ***App***roaches
under REACH



Cat-App workshop 22 March 2017, Antwerp
Hans Ketelslegers

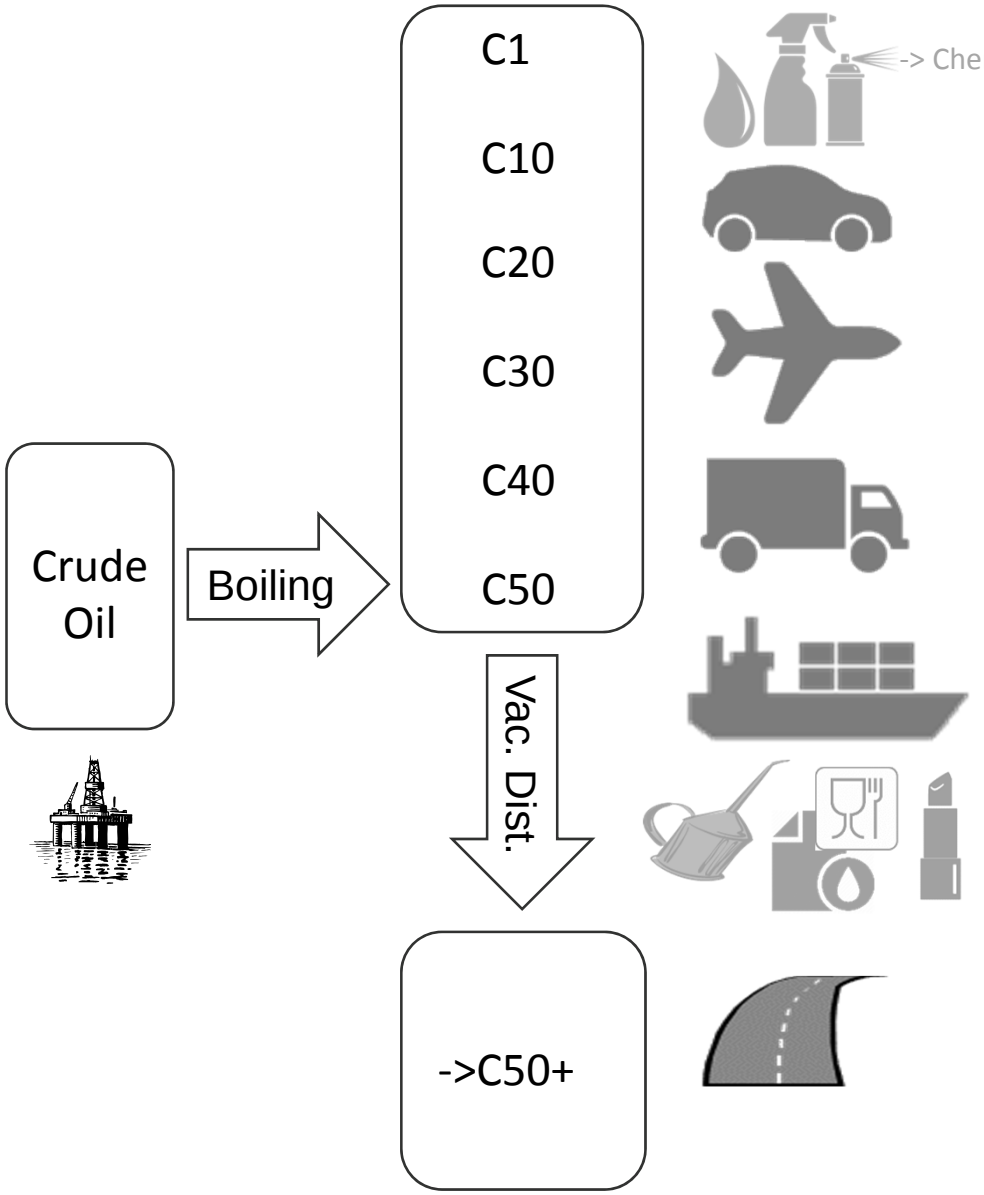
Cat-App: what it’s not…





1 Mammalian toxicological hazards of petroleum products

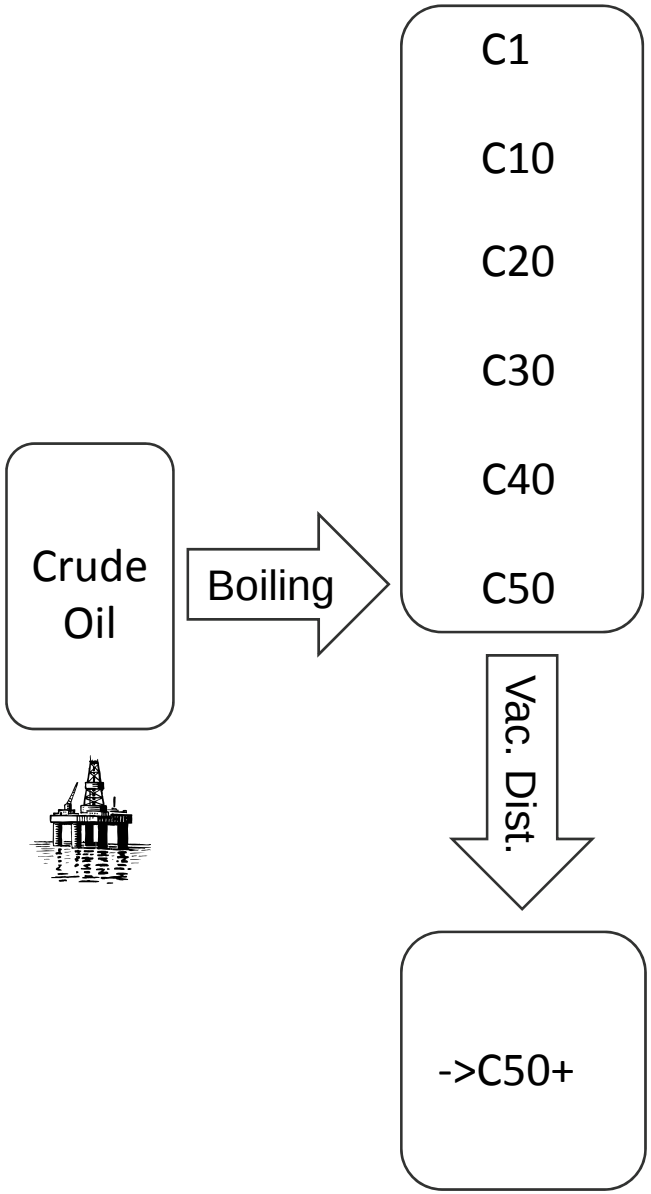
Petroleum products



- 207 petroleum products
- Thousands to billions of molecules (isomers) per product
- **U**nknown or
  Variable composition,
  Complex reaction products,
  Biological materials
  (UVCB)

https://www.fuelseurope.eu/knowledge/how-refining-works

Hazard Classification of Petroleum substances (PS)



1,3-Butadiene

Toluene, Benzene, n-Hexane

PAHs

PAHs

<u>Gases, Naphthas, Kero's</u>

Presence of these molecules drives classification of these substances, **not intrinsic hazard of PS**

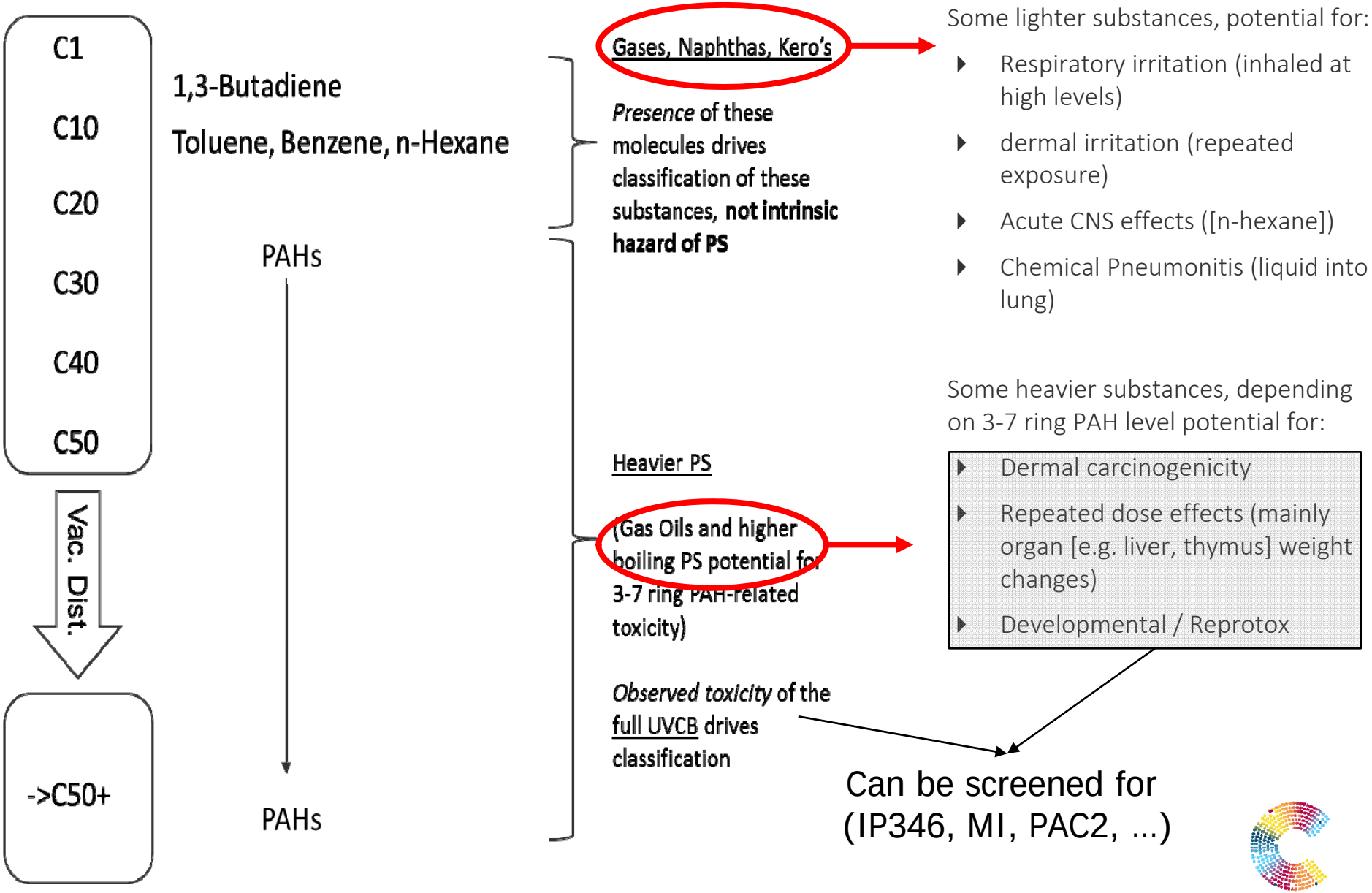
<u>Heavier PS</u>

(Gas Oils and higher boiling PS potential for 3-7 ring PAH-related toxicity)

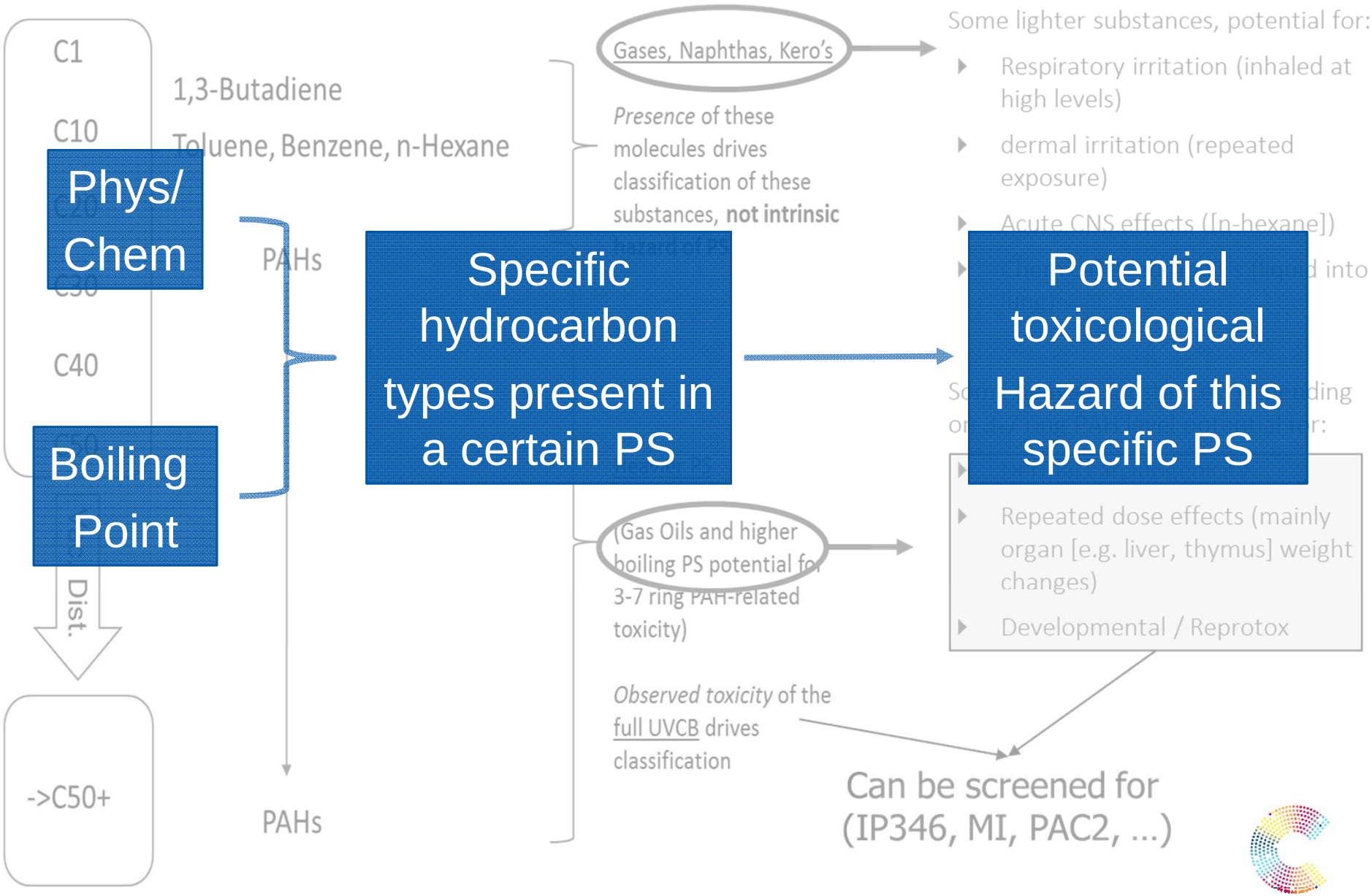
Observed toxicity of the <u>full UVCB</u> drives classification

https://www.fuelseurope.eu/knowledge/how-refining-works

Mammalian toxicological hazards of PS



Mammalian toxicological hazards of PS: chemical-biological interaction



2 Grouping petroleum substances

to support chemical biological read-across

Concawe “Categories”

1. Low Boiling Point Naphthas (Gasolines)
2. Kerosines
3. **Straight-run Gas Oils**
4. Cracked Gas Oils
5. **Vacuum Gas Oils, Hydrocracked Gas Oils&**
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**

In addition CONCAWE has prepared the joint parts alone substances:

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

Name	EINECS definition	CAS
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.	**8052-42-4**
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).	**64741-56-6**
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).	**64742-85-4**
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).	**92062-05-0**

Example: ECHA decision on Bitumen/Asphalt (dev. tox.)

ECHA
EUROPEAN CHEMICALS AGENCY

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.

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Example: ECHA decision on Bitumen; grouping (1)

ECHA
EUROPEAN CHEMICALS AGENCY

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 complexity of 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 numbe 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 wa 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,

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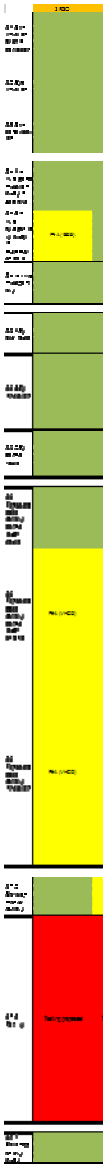
these substances cannot be considered as a group, or category of substances under the REACH Regulation, irrespective of the status of these substances under other legal systems.

- reliance on manufacturing process instead of similarity principle
- Compositional variability not sufficiently addressed to justify determination of hazard (via read across)
- **Category or grouping not accepted**

Datagap Analysis – overall groups

207 Petroleum Products into ~20 groups

Human Health Hazard Endpoint



Datagap analysis – within group

SRGOs as example -> comprising 4 out of 207 substances (CAS #s)

Human Health Hazard Endpoint

CAS No.	64741-43-1	64741-44-2	68814-87-9	68915-96-8
Name	Gas oils (petroleum), straight-run	Distillates (petroleum), straight-run middle	Distillates (petroleum), full-range straight-run middle	Distillates (petroleum), heavy straight-run
Concawe Registered substance (Y/N)	Y	Y	Y	Y
8.1 Skin irritation or skin corrosion	Not irritating	**Not irritating**	*Not irritating*	*Not irritating*
8.2 Eye irritation	Not irritating	**Not irritating**	*Not irritating*	*Not irritating*
8.3 Skin sensitisation	*Not sensitising*	**Not sensitising**	*Not sensitising*	*Not sensitising*
Genetic toxicity				
8.4.1 In vitro gene mutation study in bacteria	**Negative TA98 only (Modified Ames Test)**	Weak positive TA98 only	Negative TA98 only (Modified Ames Test)	Negative TA98 only (Modified Ames Test)
8.4.2 In vitro cytogenicity study in mammalian cells	*Sister chromatid exchange (CHO) negative –S9, ambiguous +S9 [R-A from OGO - CAS No.64742-80-9]*	*Sister chromatid exchange (CHO) negative –S9, ambiguous +S9 [R-A from OGO - CAS No.64742-80-9]*	*Sister chromatid exchange (CHO) negative –S9, ambiguous +S9 [R-A from OGO - CAS No.64742-80-9]*	*Sister chromatid exchange (CHO) negative –S9, ambiguous +S9 [R-A from OGO - CAS No.64742-80-9]*
8.4 In vivo mutagenicity	*Negative*	**Negative rat cytogenetic tests**	*Negative*	*Negative*
Acute toxicity				
8.5.1 By oral route	LD_{50} > 5000 mg/kg	**LD_{50} > 5000 mg/kg**	*LD_{50} > 5000 mg/kg*	*LD_{50} > 5000 mg/kg*
8.5.2 By inhalation	*LC_{50} > 2530 mg/m³*	**LC_{50} > 2530 mg/m³**	*LC_{50} > 2530 mg/m³*	*LC_{50} > 2530 mg/m³*
8.5.3 By dermal route	LD_{50} > 2000 mg/kg	**LD_{50} > 2000 mg/kg**	*LD_{50} > 2000 mg/kg*	*LD_{50} > 2000 mg/kg*
Repeated dose toxicity				
8.6 Repeated dose toxicity dermal (sub-acute)	28d rat systemic NOAEL > 0.5 mL/kg [dose levels tested: 0, 0.01, 0.10, 0.50 mL/kg] *28d rat and rabbit systemic NOAEL >2000 mg/kg/day*	28d rabbit systemic NOAEL >2000 mg/kg/day [dose levels tested: 0, 200, 1000, 2000 mg/kg/day]	*28d rat and rabbit systemic NOAEL >2000 mg/kg/day*	*28d rat and rabbit systemic NOAEL >2000 mg/kg/day*
8.6 Repeated dose toxicity dermal (sub-chronic)	*90d NOAEL 30 mg/kg/day [R-A from VHGO - CAS No.64741-49-7; dose levels tested: 30, 125, 500 mg/kg/day]*	*90d NOAEL 30 mg/kg/day [R-A from VHGO - CAS No.64741-49-7; dose levels tested: 30, 125, 500 mg/kg/day]*	*90d NOAEL 30 mg/kg/day [R-A from VHGO - CAS No.64741-49-7; dose levels tested: 30, 125, 500 mg/kg/day]*	*90d NOAEL 30 mg/kg/day [R-A from VHGO - CAS No.64741-49-7; dose levels tested: 30, 125, 500 mg/kg/day]*
8.6 Repeated dose toxicity inhalation	*90d NOAEC ≥ 1710 mg/m3 (systemic); 880 mg/m3 (local, lung) [R-A from VHGO - CAS No. 68334-30-5 (most likely); dose levels tested: 0, 0.35, 0.88, 1.71 mg/L]*	*90d NOAEC ≥ 1710 mg/m3 (systemic); 880 mg/m3 (local, lung) [R-A from VHGO - CAS No. 68334-30-5 (most likely); dose levels tested: 0, 0.35, 0.88, 1.71 mg/L]*	*90d NOAEC ≥ 1710 mg/m3 (systemic); 880 mg/m3 (local, lung) [R-A from VHGO - CAS No. 68334-30-5 (most likely); dose levels tested: 0, 0.35, 0.88, 1.71 mg/L]*	*90d NOAEC ≥ 1710 mg/m3 (systemic); 880 mg/m3 (local, lung) [R-A from VHGO - CAS No. 68334-30-5 (most likely); dose levels tested: 0, 0.35, 0.88, 1.71 mg/L]*
Reproductive toxicity				
8.7.2 Developmental toxicity	**NOAEL 50 mg/kg/day** [dose levels tested: 0, 50, 250, 500 mg/kg/day]	*NOAEL 50 mg/kg/day*	*NOAEL 50 mg/kg/day*	*NOAEL 50 mg/kg/day*
8.7.3. Fertility	Testing proposed *	Testing proposed *	Testing proposed *	Testing proposed *
Carcinogenicity				
8.9.1 Carcinogenicity study	*Not considered a carcinogenic hazard*	**Weakly tumorigenic on the skin secondary to skin irritation; long latent period. Not considered a carcinogenic hazard**	Weak initiator and promoter with borderline effects *Not considered a carcinogenic hazard*	*Not considered a carcinogenic hazard*

- Where we have data over multiple CAS in a group: alignment – indicating (biological) similarity

- Datagaps: cannot test all endpoints for each and every CAS across all petroleum streams based on practical (time and testing cost) and animal welfare constraints

Need more pragmatic and informed approach: Cat-App

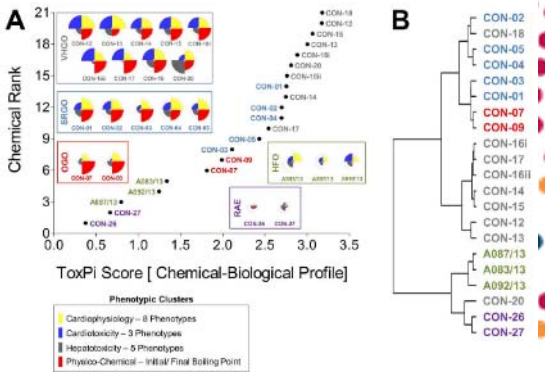
Implementation of a chemical-biological framework to minimize animal testing

Implementation of a chemical-biological framework to minimize animal testing

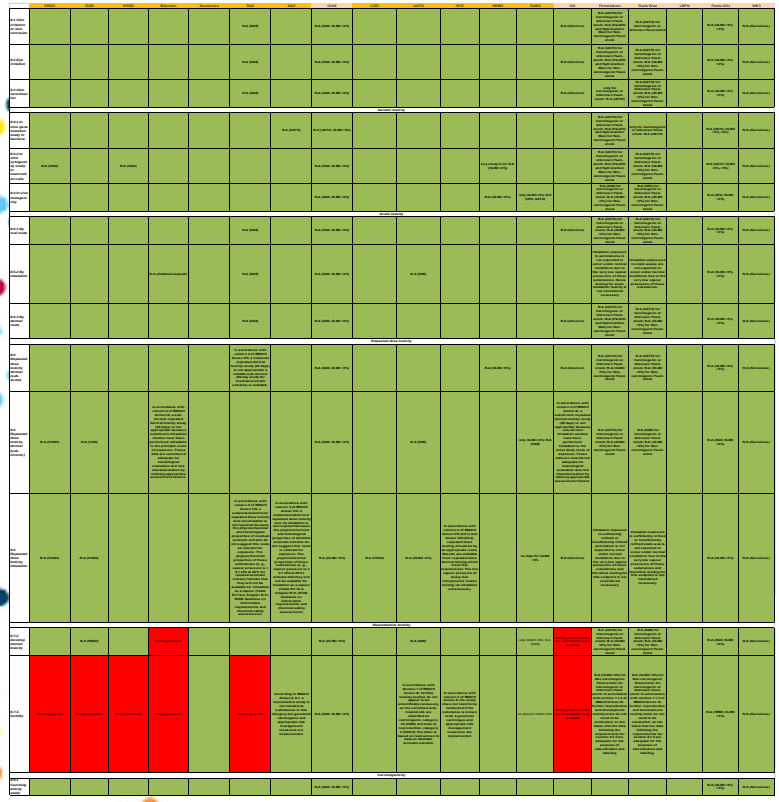
All available ***substance*** data:

- Phys/Chem
- Analytical-chemical
- Environmental
- In-vivo HH
- In-vitro HH
- Transcriptomics

Integrated analysis framework which…



…supports grouping of 207 PS into ~20 groups



and

Chemical-Biological Read Across

To fill datagaps…

…and prioritize animal testing as a last resort

Cat-App Workflow

CAT-APP: New technologies to underpin the category approaches and read across in regulatory programmes
Project Management: Hans Ketelslegers / Concawe
Steering: Scientific Committee / Concawe

WP1

Setting up **database with all available data** and infrastructure for data to be generated in the project (and in other Concawe activities?)

Presentation 3 – Fred Wright (NCSU)

DMSO extracts prep by Tim Roy (PR) of PS to be used for WP2&3

WP2

Evaluation of **mechanistic toxicology (e.g. phenotypical) changes** in stem cells (Ivan) and human cell-lines (Tim) in response to PS exposure

Presentation 1 – Ivan Rusyn (TAMU)
Presentation 2 - Tim Gant (PHE)

WP3

Generation of **gene expression data** in stem cells and most appropriate human cell-line models in response to PS exposure

Presentation 1 – Ivan Rusyn (TAMU)

WP4

Integrative analysis of all available data to support and **visualize** groupings for **transparent communication** of all data (eventually supporting chemical-biological read across of available hazard data to fill datagaps)

Presentation 3 – Fred Wright (NCSU)
Presentation 4 – Shu-Dong Zhang (UU)

4a.4 Perform ToxPi analysis

WP4.b (Shu-Dong Zhang/ Ulster)

4b.1 Perform connectivity mapping
4b.2 Develop and apply an-alysis algorithms to robust-ness testing, inves-tigate grouping accuracy and profiling cost

WP5

Advisory Board

George Daston
Procter & Gamble

Shirley Price
University of Surrey

Chris Rowat
Health Canada

Xiaowei Zhang
Nanjing University

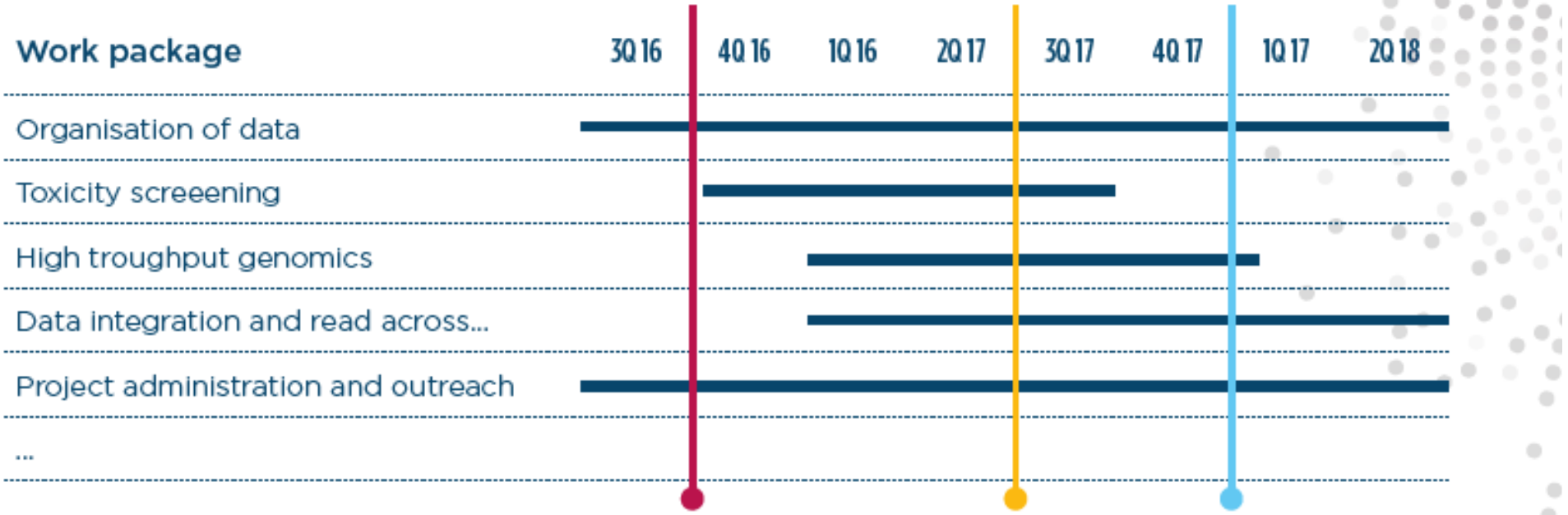
ina State University - PHE: Public Health England
g GmbH

Cat-App timeline

MS1: All petroleum substances available as DMSO extracts for testing in in vitro assays

MS2: Quality control report of preliminary in vitro analyses

MS3: Initial workflow for Chemical-Biological Read-across and ToxPi visualisation available

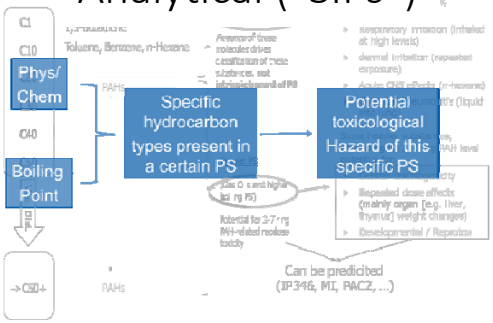


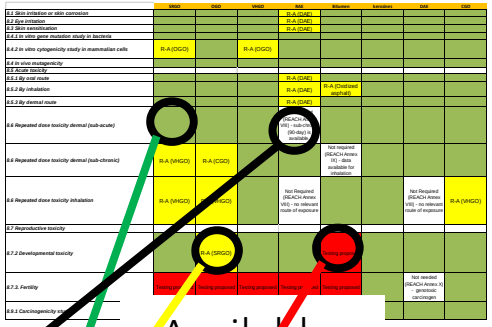
3 Pulling it all together…

- analytical composition PS after boiling crude oil;
- "natural" groupings with limits by SIPs (SIPs per CAS RN)

- Biological response is related, and limited, to analytical composition provides mechanistic support for "natural" PS grouping

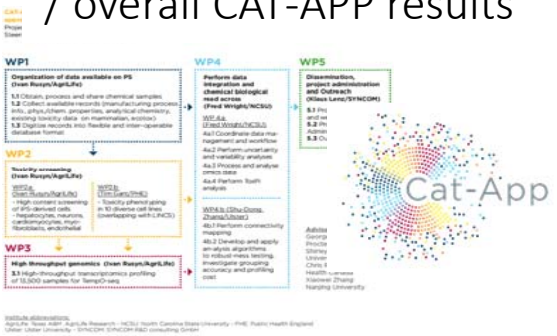
BP, Phys/Chem, Analytical ("SIPs")





Available in-vivo data

In-vitro data / overall CAT-APP results



- Within PS, in-vivo tox data can then be read across based on similarities in phys/chem, SIPs & biological profiles
- Only where
  - no in-vivo data are available for a certain endpoint across members of a PS,
  - no WoE to support non-requirement of an endpoint can be developed (e.g., exposure based waiving)
  - and no worst-case analogue read across (from other PS) can be supported,

  testing might be required as a last resort
- Worst case test sample selected based on analytical data related to testing hypothesis (tox and mechanistic data)

Overall result of implementing CAT-APP:
Chemical-Biological Read Across will prioritize testing needs

Thank you for your attention!