OECD ACTIVITIES ON COMBINED EXPOSURES TO MULTIPLE CHEMICALS

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18-20 October 2021

BETTER POLICIES FOR BETTER LIVES

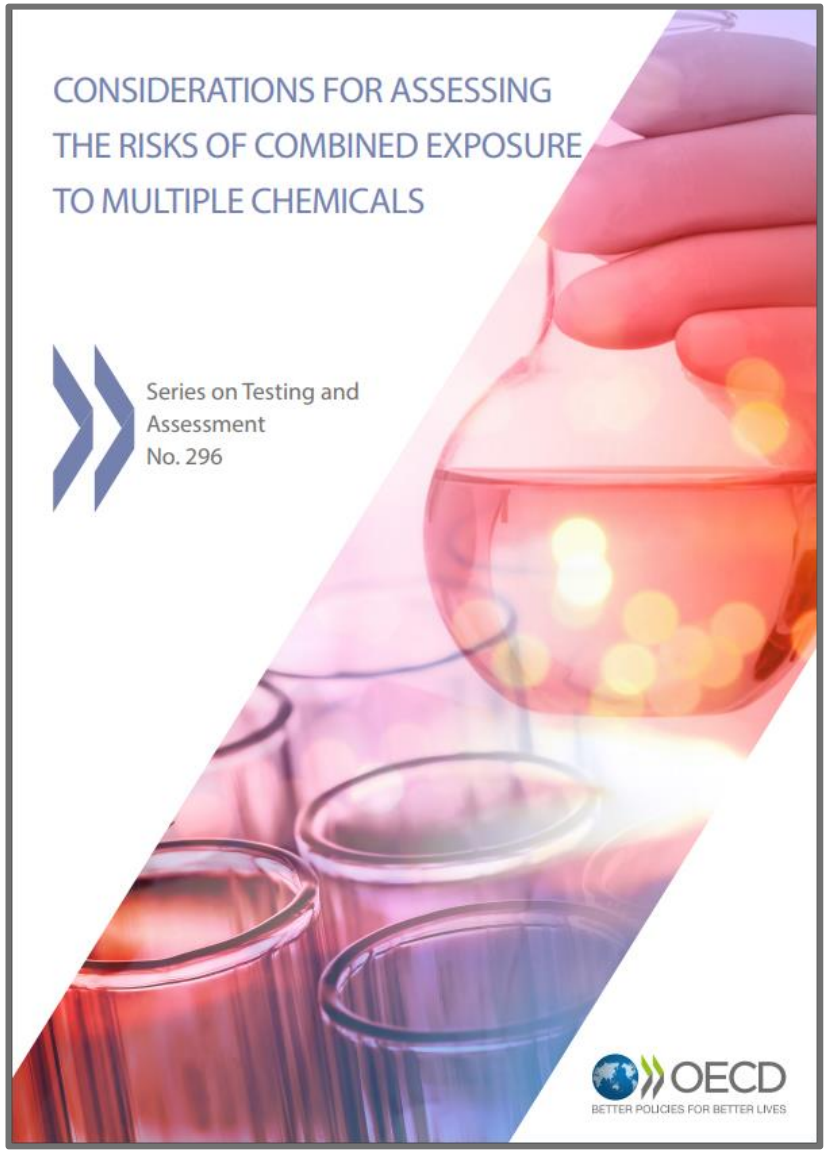
OECD work on mixtures: Test Guidelines

- While most test methods should be amenable to mixtures, generally not tested in the validation process
  - Standard language in TGs:

  "The test method was validated using single chemicals, therefore the applicability to test mixtures has not been addressed. The test method is nevertheless theoretically applicable to the testing of multi-constituent chemicals and mixtures."

  Some external activities to validate OECD test guidelines
  - *e.g.* Test of agrochemical formulations in *in vitro/ex vivo* methods for eye irritation undertaken by NTP/EPA/JRC
    DOI: 10.1080/15569527.2021.1910291

OECD work on mixtures: Hazard Assessment



Published December 2018

http://www.oecd.org/chemicalsafety/risk-assessment/considerations-for-assessing-the-risks-of-combined-exposure-to-multiple-chemicals.pdf

What it is … what it is not …

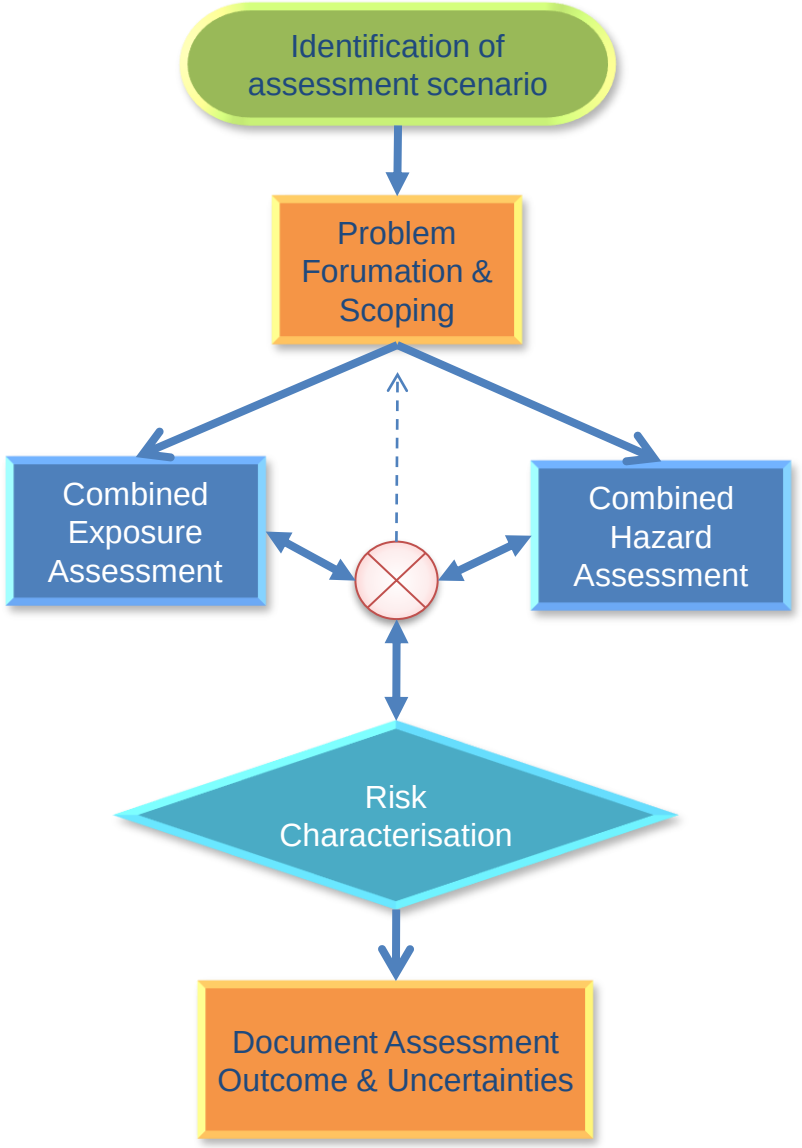
- Overview the technical aspects of the various approaches and methodologies
- Draws from approaches applied and experience gained in the regulatory context
- Not strict guidance
  - what to consider in assessing combined exposures to multiple chemicals
- Concepts presented at general level
  - multiple assessment scenarios of different types of combined exposures

What it is … what it is not …

- Both human health and environmental risk assessment aspects are considered
  - Some aspects further developed in one field or the other

- Non-chemical stressors are not a focus of the document
  - e.g. disease state, nutritional status/diet, psychological stressors, etc. are out of the scope

Framework for combined exposure assessment



Identify potential scenario for assessment of risk from combined exposures

- Formulate assessment question
- Determine scope of the assessment
- Identify data availability, generate data
- Confirm potential for co-exposure

- Conduct assessments in parallel
- Apply tiered approach starting with conservative assumptions and progressing until regulatory question can be answered
- May result in need to modify the scope of the assessment or gather more information

- Document outcome of assessment
- Identify and document key uncertainties

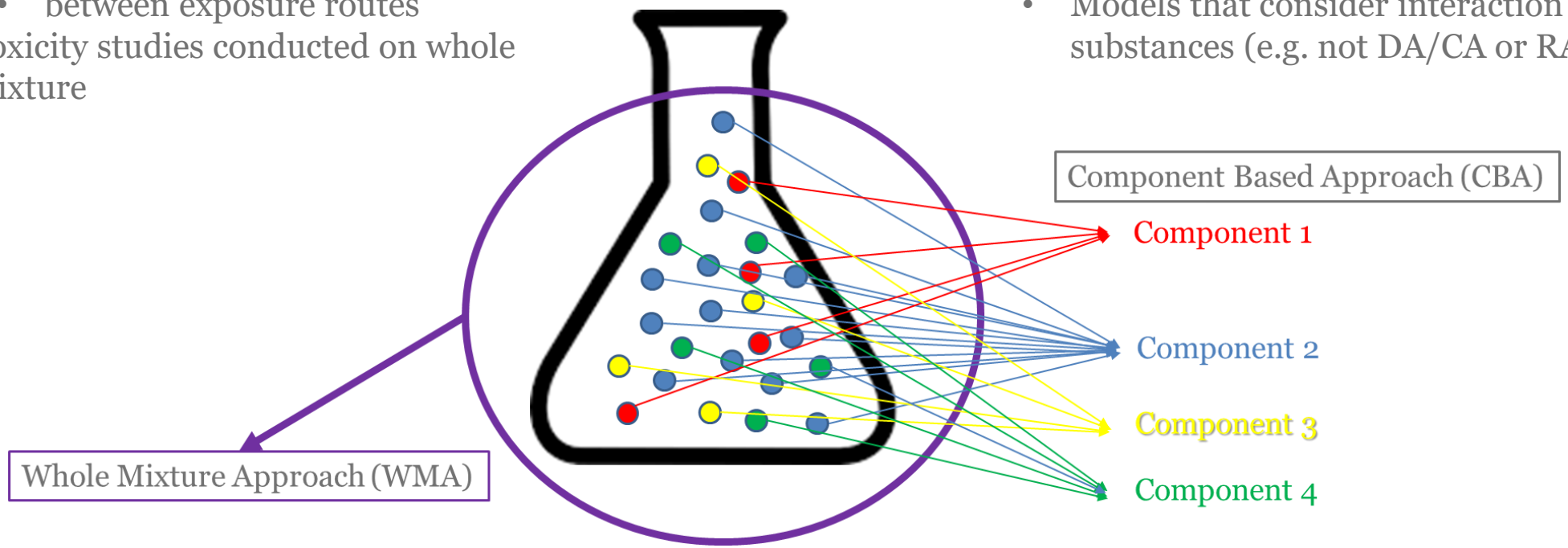
Two fundamental approaches

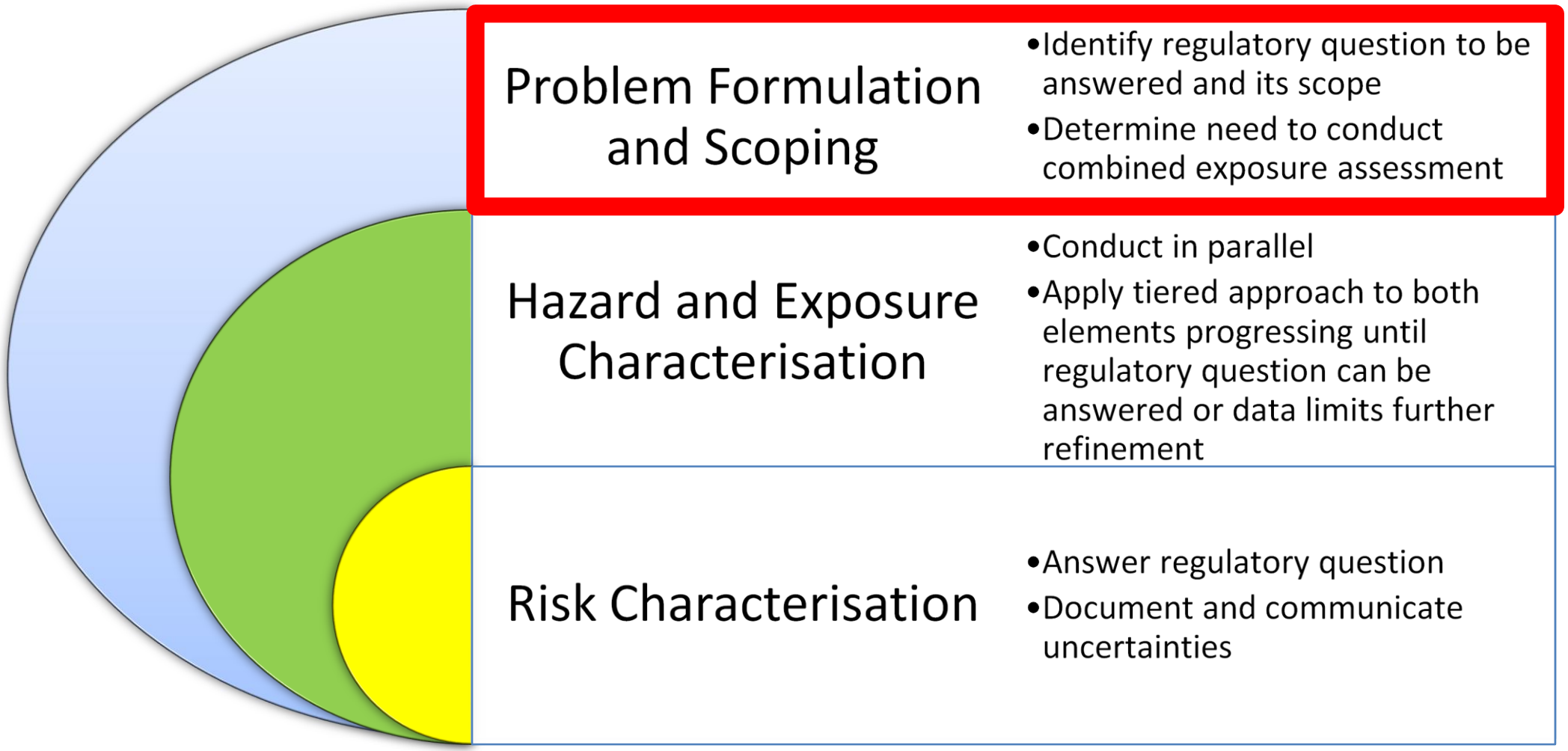
Considers group as a single unit

- Components/concentrations do not vary:
  - over time,
  - across individuals,
  - between exposure routes
- Toxicity studies conducted on whole mixture

Effects of group are based on individual components

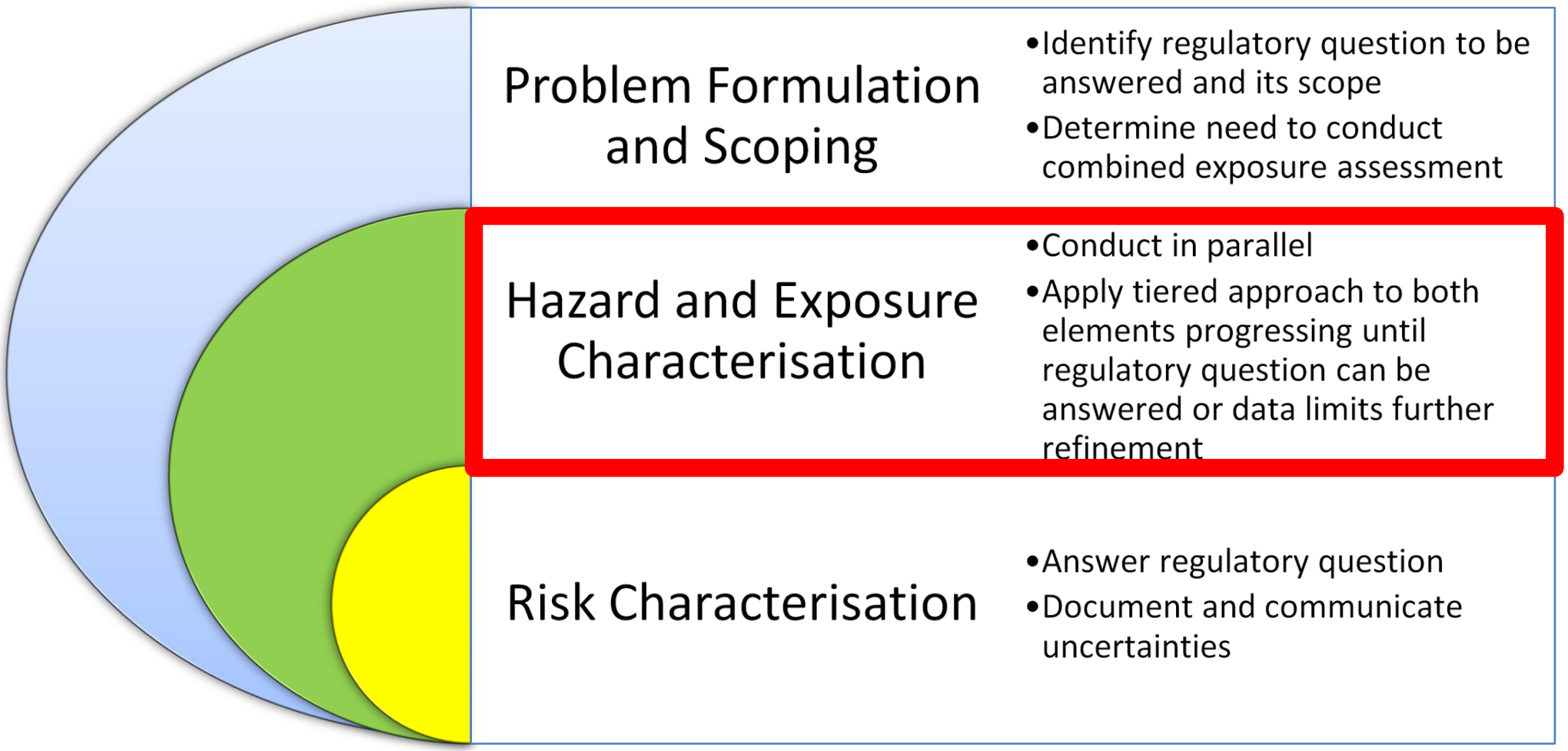
- Need to select an appropriate model for calculating toxicity (based on MOA or AOP)
  - Dose Addition (DA)/Concentration Addition (CA)
  - Response Addition (RA)/ Independent Action (IA)
  - Models that consider interaction between substances (e.g. not DA/CA or RA/IA)




Problem Formulation and Scoping
•Identify regulatory question to be answered and its scope
•Determine need to conduct combined exposure assessment
Hazard and Exposure Characterisation
•Conduct in parallel
•Apply tiered approach to both elements progressing until regulatory question can be answered or data limits further refinement
Risk Characterisation
•Answer regulatory question
•Document and communicate uncertainties

Problem Formulation and scoping

- Problem Formulation
  - Determining whether to conduct a risk assessment of combined exposures
    - Evidence regarding co-exposure/co-occurrence
      - Monitoring data measuring substance in same media
      - Data on likelihood of finding co-occurring substances (release or fate information, market penetration information, use information)
      - Intentionally produced mixtures/products containing several components (mostly with known composition)
        - » pesticide/biocide formulations, cosmetic products, commercial mixtures of industrial chemicals, mixtures of food/feed additives etc.
      - Information on intended uses for regulated substances, under potentially multiple legislations.
    - Evidence regarding common hazard
      - Are the chemicals causing the same/similar adverse effects on the same target organs (i.e. is the biological outcome the same)?
      - Are chemicals known to follow the same AOP/MOA? Different AOPs/MOAs but the same target organ? Do they share $\geq$ 1 key events (KE) between AOPs?
      - Is there evidence suggesting that the compounds may interfere with relevant metabolic pathway(s)?
- Defining the Scope of the Risk Assessment of Combined Exposures
  - Boundaries for hazard and exposure; regulatory considerations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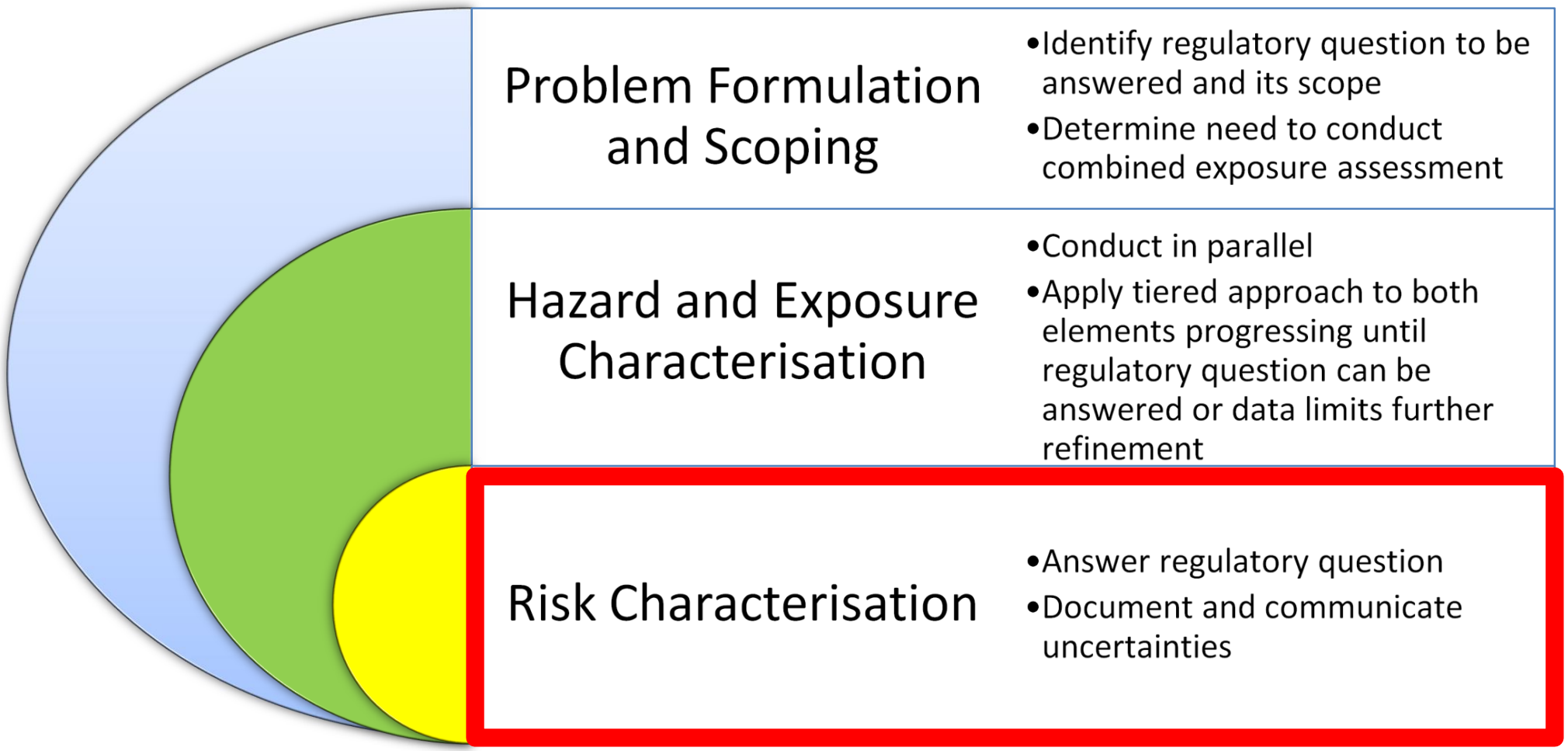
Hazard and Exposure Characterisation

Hazard

- Key considerations for grouping chemicals into hazard categories
  - structural similarities
  - similarities in toxicological or biological responses/effects
  - Considerations for incorporating chemicals with limited data
- Using a Tiered Approach and Considerations for Addressing Potency
- Interactions of chemicals and influence of potency

Exposure

- Factors affecting co-exposure
  - Sources, use patterns and lifecycle of exposure
  - Pathways and routes of exposure
  - Physico-chemical and fate properties
  - Magnitude, frequency and duration of exposure
  - Specific target populations
  - Toxicokinetics
- Data for evidence of co-exposure – data types and data sources
- Interpretation of monitoring data
- Data needs, limitations and uncertainties moving through tiers of exposure assessment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Risk Characterisation

Characterising the risk from combined exposures to multiple chemicals aims to:

- Identify whether there are concerns
- Quantify the magnitude of the risks of the combined exposure and the conditions under which such risks are likely to manifest using a weight of evidence approach that considers multiple lines of evidence.
- Identify the groups of chemicals that are particularly important risk drivers that should be targeted by risk management activities or controls.
- Illustration of the use of tiered approaches to assess the risk of combined exposures to humans or the environment
  - starting with less data and less resources
  - increasing accuracy when moving through the tiers

Consideration and Documentation of Uncertainty

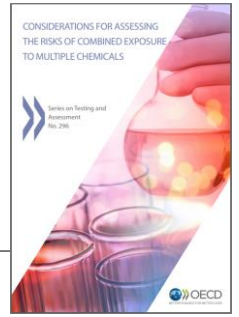
Considerations

- All of the uncertainties of assessing individual chemicals +
  - The accuracy with which the components have been characterised.
  - The accuracy with which the exposure has been characterised
  - The evidence supporting the co-exposure
  - The evidence supporting the common hazard (e.g. assumptions about additivity (or departure from additivity), shape of the dose response curves for dose/concentration addition).
  - Methods used to fill data gaps (read-across data, allometric scaling, PBPK modelling and alternative approaches (HTS data, in vitro, in silico)).
- Generally uncertainties are greater for ecological assessment than for human health assessment of combined exposures:
  - More complex
  - Different species, different sensitivities/vulnerabilities towards individual components;
  - Differing modes of action of chemicals in different types of organisms (bacteria, plants, invertebrates, vertebrates).

Document

- Key limitations, assumptions and uncertainties associated with approaches used in the assessment
- Consider the magnitude and impact of the sources of uncertainty and if reductions would be likely to lead to a different outcome to inform regulatory decisions
- Uncertainty analysis should also follow a tiered approach that can be refined as necessary (and as the data allows)
- Should be communicated in way that is understandable by decision-makers

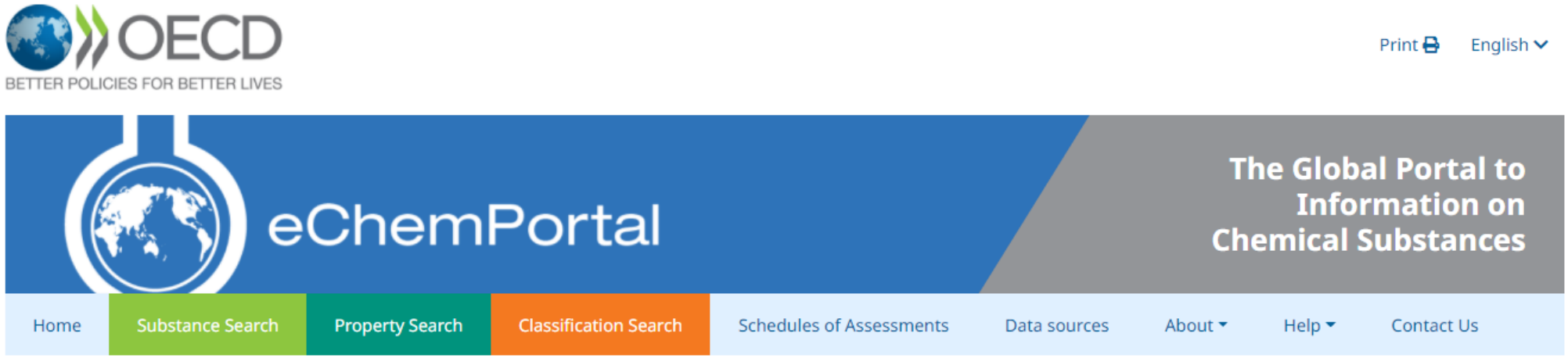
Take aways from the document



- Number of limitations and uncertainties associated with the various approaches
  - also true of single substance assessment methods

- Need to gain of experience from use of the methods and the identification of key gaps and uncertainties during the application
  - will help build experience and refine methodologies moving forward

2020 New Project: **eChemPortal**



2020 New Project: **eChemPortal**

- OECD secretariat sends requests to WPHA/WPEA members for information on combined exposure assessments
  - webpage lists the documents and chemicals included.
  - Initial responses limited but more in 2021

EFSA, Craig P.S. et al., (2020), Scientific report on cumulative dietary risk characterisation of pesticides that have acute effects on the nervous system. EFSA Journal 2020;18(4):6087, 79 pp.
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2019 Joint Projects: **Occupational biomonitoring** to address risks due to exposures in the workplace

- CH + 39 institutions from many countries
- National approaches are variable and no harmonised guidance for biomonitoring
- Goals:
  - Compare existing methods in deriving OBL (Occupational Biomonitoring Levels)
  - Identify data gaps and future research needs.
  - Propose quality criteria and minimum requirements for OBLs, (including toxicokinetic data).
  - Elaborate general tiered guidance on the derivation of OBL with respect to accepted points of departure in risk assessment.
  - Propose different OBL derivation methods for screening purposes and for more advanced regulatory risk assessment contexts.
  - Recommend general biomonitoring options in occupational settings
  - Provide a characterization and outlook for the use of effect-based biomarker monitoring

2020 Joint Project:
Occupational Exposure Limits

- CA joined by DE/CH/NL
- Examine approaches and guidance for OEL development,
  - As a first step, a survey was circulated to collect information on:
    - How occupational exposure limits are established in different jurisdictions (including roles of various governments/groups/committees, lessons learned)
    - How priorities for OEL development are set in different jurisdictions
    - Document approaches for development of exposure limits in the workplace
    - Identify current chemicals with existing workplace exposure limits
    - Role of monitoring and/or modelling in the development of workplace exposure limits
- Next steps:
  - Explore opportunities to harmonize OEL development
  - Identify areas for collaboration and pilot through a case study

2021 Joint Project: **Using AOPs to address combined exposures** to chemicals using biomarkers

- New project CH/US/NL/LUX
- Evaluate known and unknown components of mixtures using effects biomarkers
- Improve understanding of biomarkers relevance to apical hazard and/or what levels of response indicate a strong probability for hazard.

Further Information

- Website
  - http://www.oecd.org/chemicalsafety
- EHS Newsletters (sign up to receive automatically)
  - http://www.oecd.org/chemicalsafety/environment-health-safety-news.htm

- Email: patience.browne@oecd.org