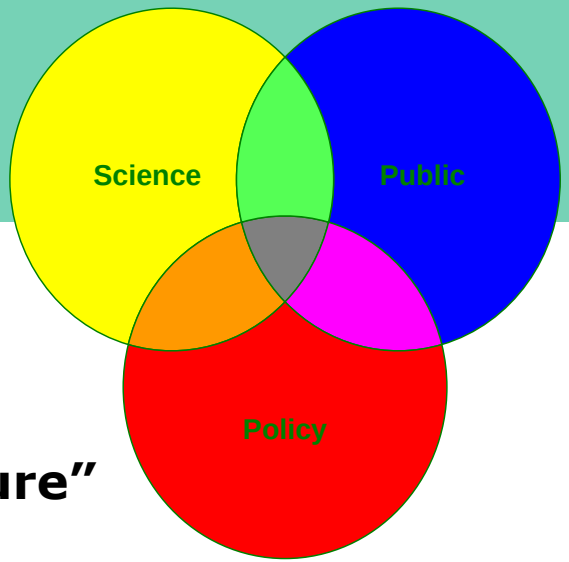
National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Chemical Mixtures: Research to support challenges in risk assessment

Erik Lebret



Mixtures; A mystifying concept?

No common widely shared definition of "mixture"

- To regulators: combination of substances falling under their regulatory context and jurisdiction
- To scientists: generically, any combination of substances circulating simultaneously in the body, depending on their scientific discipline
- To public: involuntary exposures and archetypical scare and suspicion that single-substance risk assessment aren't telling the whole story, depending on their core beliefs and worldviews

Mixtures in HBM

- Any combination of chemical substances or their metabolites, circulating in the human body at a given time

- Stemming from:
  - Joint simultaneous exposure from a single common source across single exposure routes
  - Joint simultaneous exposure from multiple different sources, possibly through different exposure routes and pathways
  - Past protracted or repeated exposure from multiple sources across multiple pathways

  - And combinations thereof

CEFIC report 2016. REACH Practical Guide on Safe Use Information for Mixtures under REACH

From ECHA website and from CEFIC report

Stakeholders, intentional mixtures

Mixture classification - ECHA

u/support/mixture-classification

ed

About Us | Regulations | Addressing Chemicals of Concern | Information on Chemicals | Chemica

Support > Mixture classification

ut Us
ulations
ressing Chemicals of cern
rmation on Chemicals
micals in our Life
port
Guidance
Getting started
Q&As Support

Mixture classification

©Uwe Völkner / Fotoagentur FOX, Lindlar

Are you an **importer** or a **formulator** of mixtures within EU/EEA?

If you are, you are **responsible** for the classification, lab and packaging of the mixture you place on the market (i. mixtures you import into the EU/EEA or formulate for furt supply) in accordance with the CLP Regulation. You need aware of the hazards of the mixture imported or formulat and you need to communicate them in your supply chain.

Distributors of mixtures also have obligations under CLP to make sure that the label and the packaging is in accor with CLP.

A further description of roles and obligations under CLP is in Chapter 2 of **the Introductory Guidance on the CLP Regulation.**

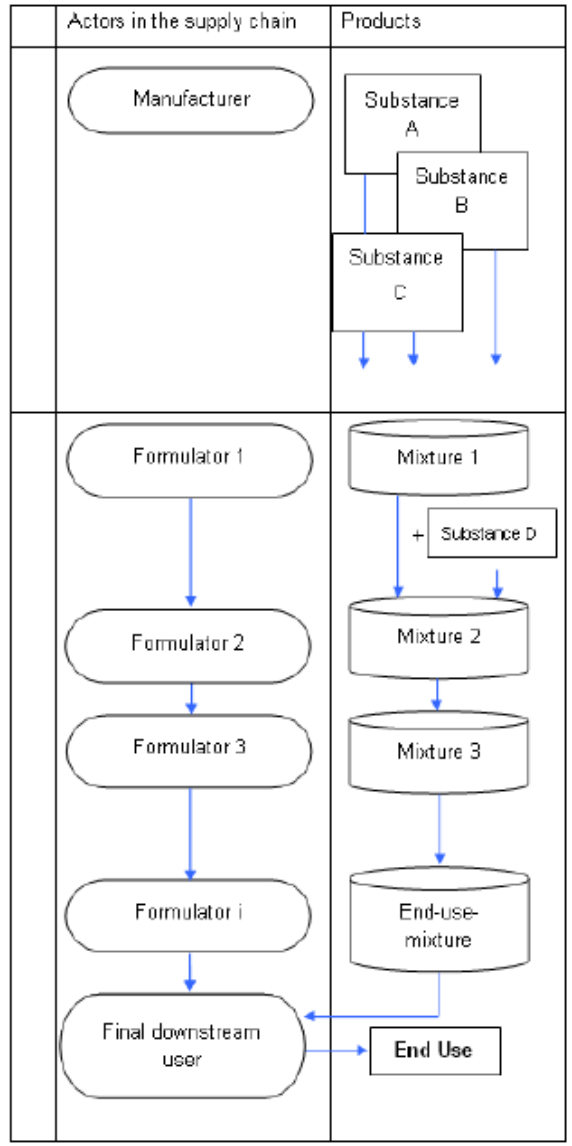
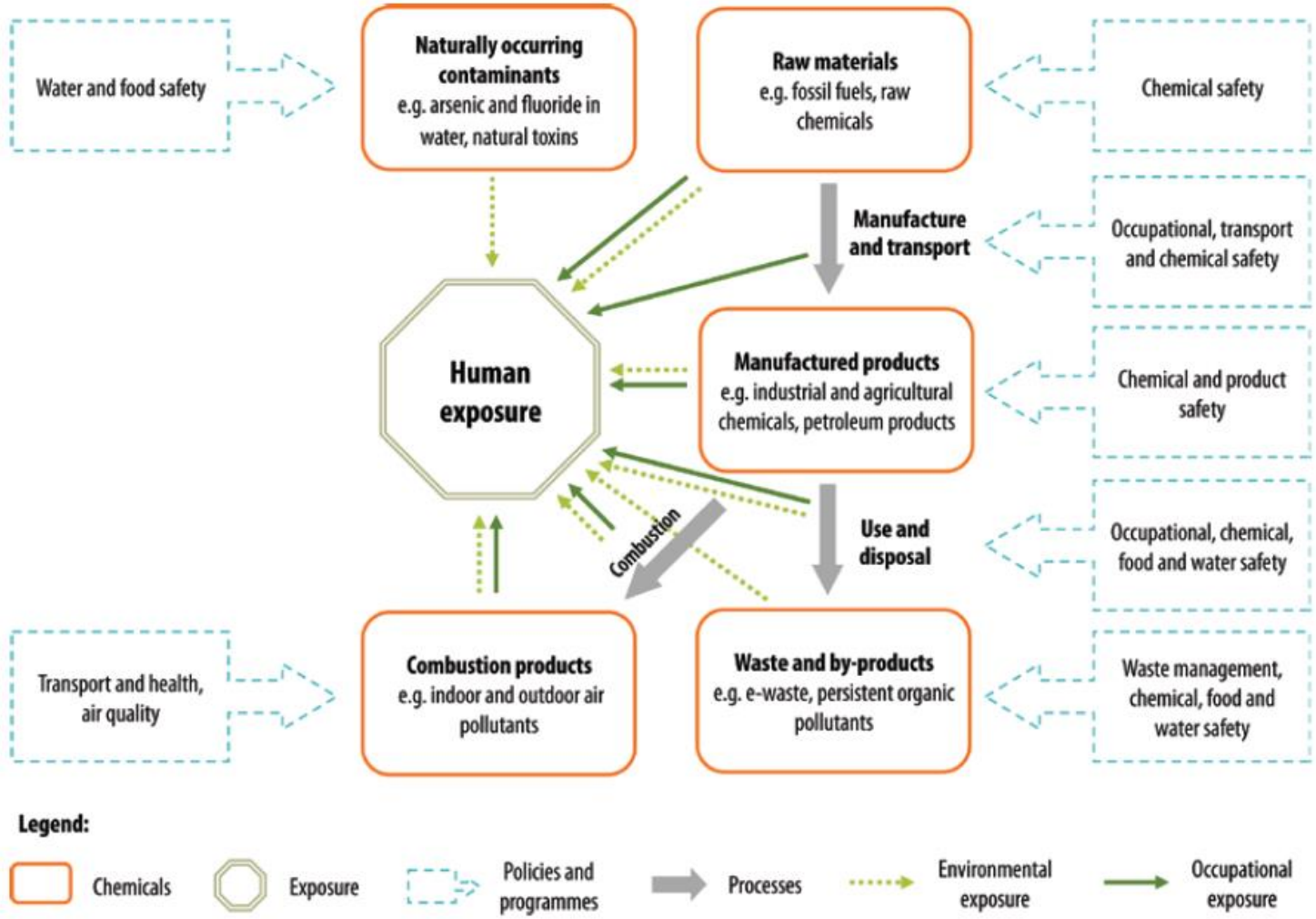


Figure 1 Supply chain and mixtures



Source: Knowns and unknowns on burden of disease due to chemicals: A systematic review, Prüss-Ustün et al (2011).

What mixtures are we talking about?

- Essentially, all the priority substances of HBM4EU are classes of mixtures by themselves; they can be grouped by:
  - Chemical family, e.g. phtalates, metals and PAH's
  - Application, e.g. plasticisers, flame retardants, pesticides, food additives, medication, recreational drugs
  - Supposed joint working mechanism of effect, e.g. endocrine disruptors
- These groups overlap and are not mutually exclusive

Challenge for mixtures in HBM4EU

"We encourage the consortium to start addressing identification of chemical mixtures to which humans are exposed and develop concrete activities, across all three pillars, which would be carried out in the second half of the project. The pre-defined mixtures of substances having common mode of action could frame the initial perspective on this topic."

Overarching objective

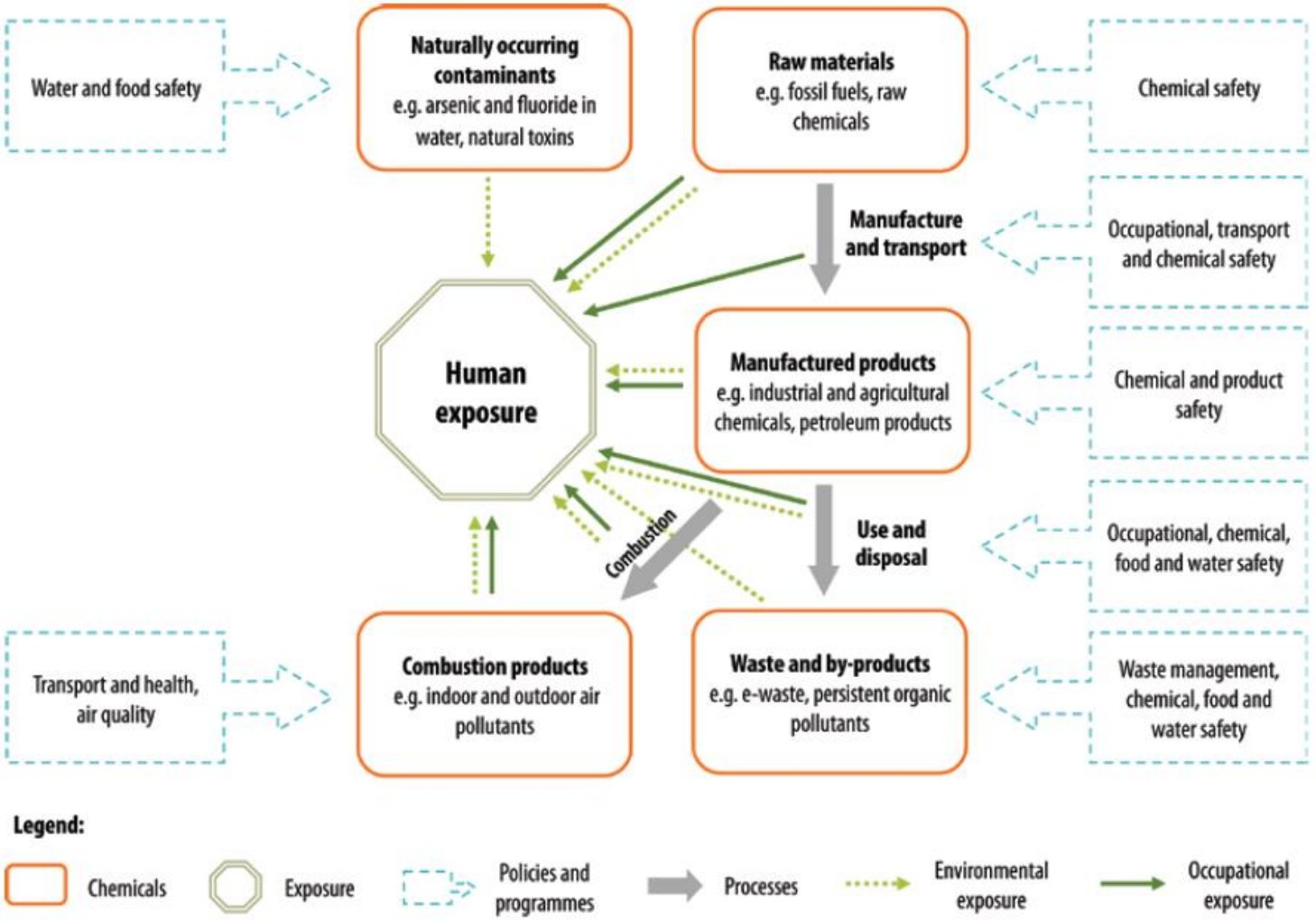
To improve the efficacy of HBM to inform science, policy/regulatory actions and societal debate with respect to dealing with mixtures

Some underlying questions:

- What is the information need of regulatory bodies and stakeholders?
- What are common HBM mixture patterns in the European population?
- Can we identify hotspots or risk groups with high mixture exposures?
- Which sources & pathways contribute most to HBM mixture values?
- Which effect markers can we use to assess health risks of mixtures?
- What action perspectives are available to reduce mixture levels?

More specific objectives

- Develop summary indicators to describe the exposure and body burdens of mixtures with an emphasis on defining priority mixtures and drivers of mixture toxicity
- Re-evaluate existing HBM mixture data to identify real-life exposure patterns to mixtures
- Collect new HBM mixture data in selected European countries
- Further develop and apply practical approaches to assess the potential health risks and impacts of mixtures
- Inform policy makers, stakeholders and the public at large about mixture exposures, possible health risks and action perspectives



Source: Knowns and unknowns on burden of disease due to chemicals: A systematic review, Prüss-Ustün et al (2011).

First tasks

1. Together with WP4 further articulate the ‘mental models’ and information needs of policy makers and stakeholders regarding mixtures with respect to envisaged policy use

2. Develop approaches and aggregate indicators to describe HBM mixtures to analyse existing HBM mixture data
   a) Data driven approaches
   b) Existing approaches in participating countries
   c) Mode of Action / Adverse Outcome Pathway approaches, e.g. EFSA’s Cumulative Assessment Groups (CAG’s)

3. Prepare the development of a protocol for the joint collection of HBM data of mixtures in 3-5 countries

4. Prepare the development of approaches to identify mixture health effects and description of the functionality of mixture effect biomarkers

Subsequent tasks

- Perform the joint collection of HBM data of mixtures
- Perform topical case studies on mixture health effects; proof of concept
- Perform a risk assessment of the observed mixtures in existing and newly collected HBM data
- Apply overarching analysis over all HBM data compiled/generated in HBM4EU to strenghten HBM mixture profiles
- Translate aggregated indicator analysis into policy recommendations and future research recommendations

In conclusion:

- Targeted approaches to dealing with mixtures are needed, tuned to information needs of regulators and stakeholders
- Existing data as well as newly collected data will be used
- New approaches in analysing HBM mixture data and health effects will be tested
- Alternative action perspectives for dealing with mixtures will be needed; consistent but likely tailor-made