science and policy
for a healthy future

HBM4EU project

Introduction to Risk Assessment

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3rd HBM4EU Training School 2019

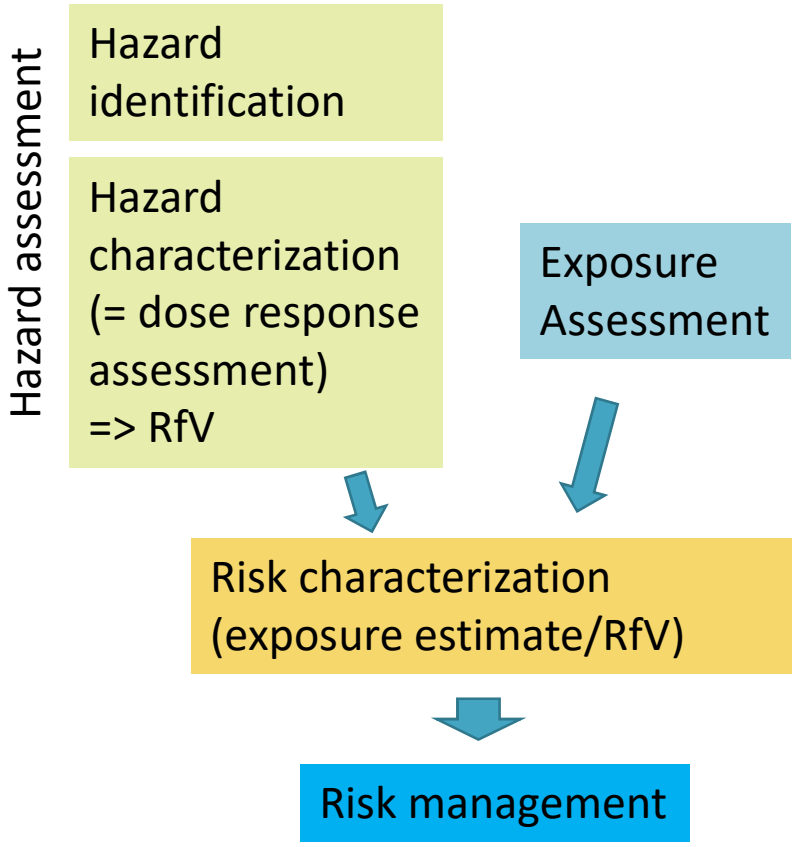
Topics

1. General RA paradigm and terminology
2. Risk Assessment Schemes; WHO and REACH as examples
3. Uncertainties in risk assessment
4. Mixture risk assessment

Terminology and RA process

- *Threshold/non-threshold*
- *NOAEL/NOAEC or LOAEL/LOAEC*
- *BMDL*
- *PoD*
- *Dose adjustment, human equivalent concentration*
- *Uncertainty factor/assessment factor*
- *Probabilistic/deterministic analysis*
- *Uncertainty analysis*
- *……*

Risk assessment process



WHO RA terminology:
https://www.who.int/ipcs/methods/harmonization/areas/terminology/en/

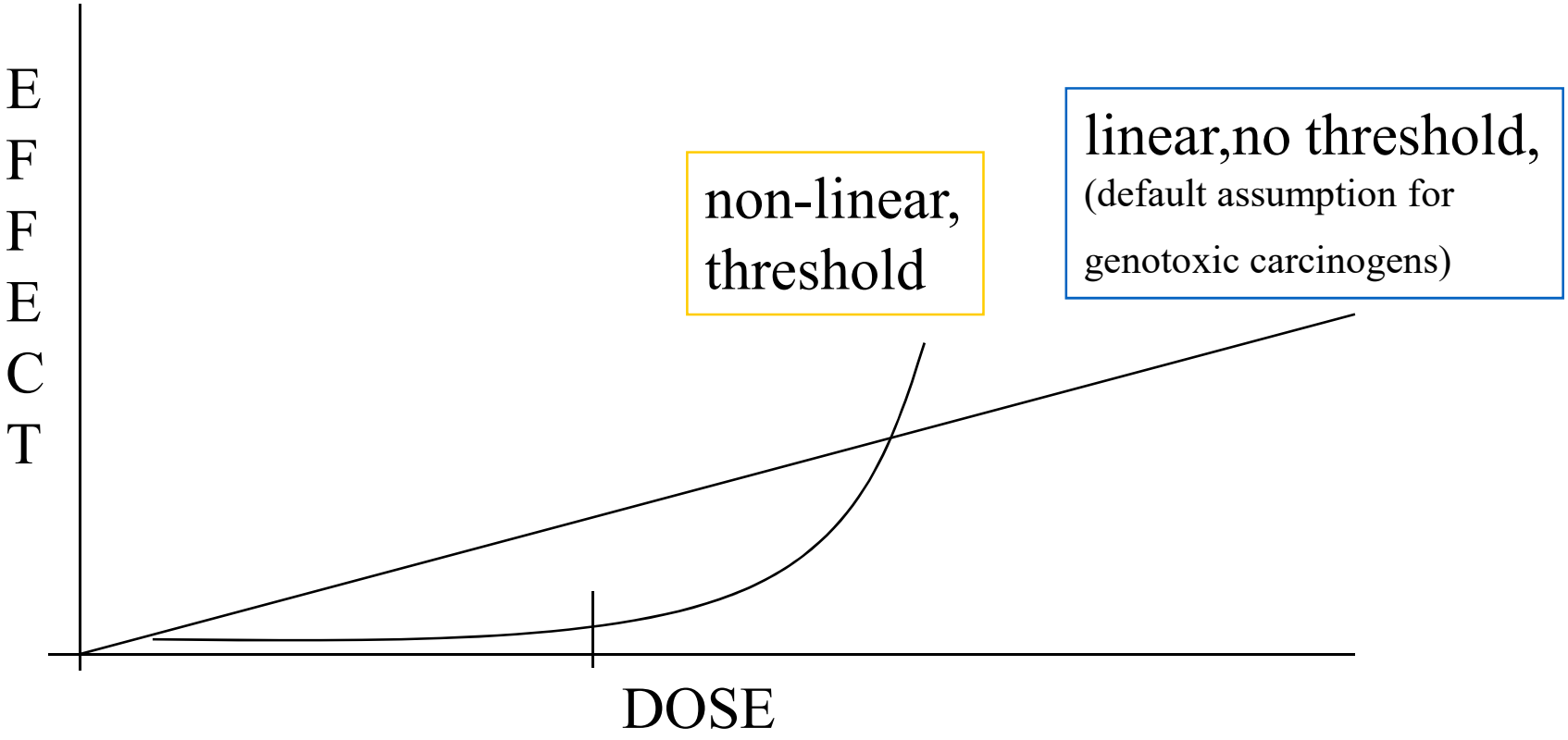
Classical hazard characterization process

- Animal toxicity studies often the starting point
- Identification of the dose response (threshold, non-threshold)
  - Usually in relation to external intake
- Extrapolation to humans, covering of uncertainties
- Use of (in vitro) mechanistic data in the characterization of the dose response

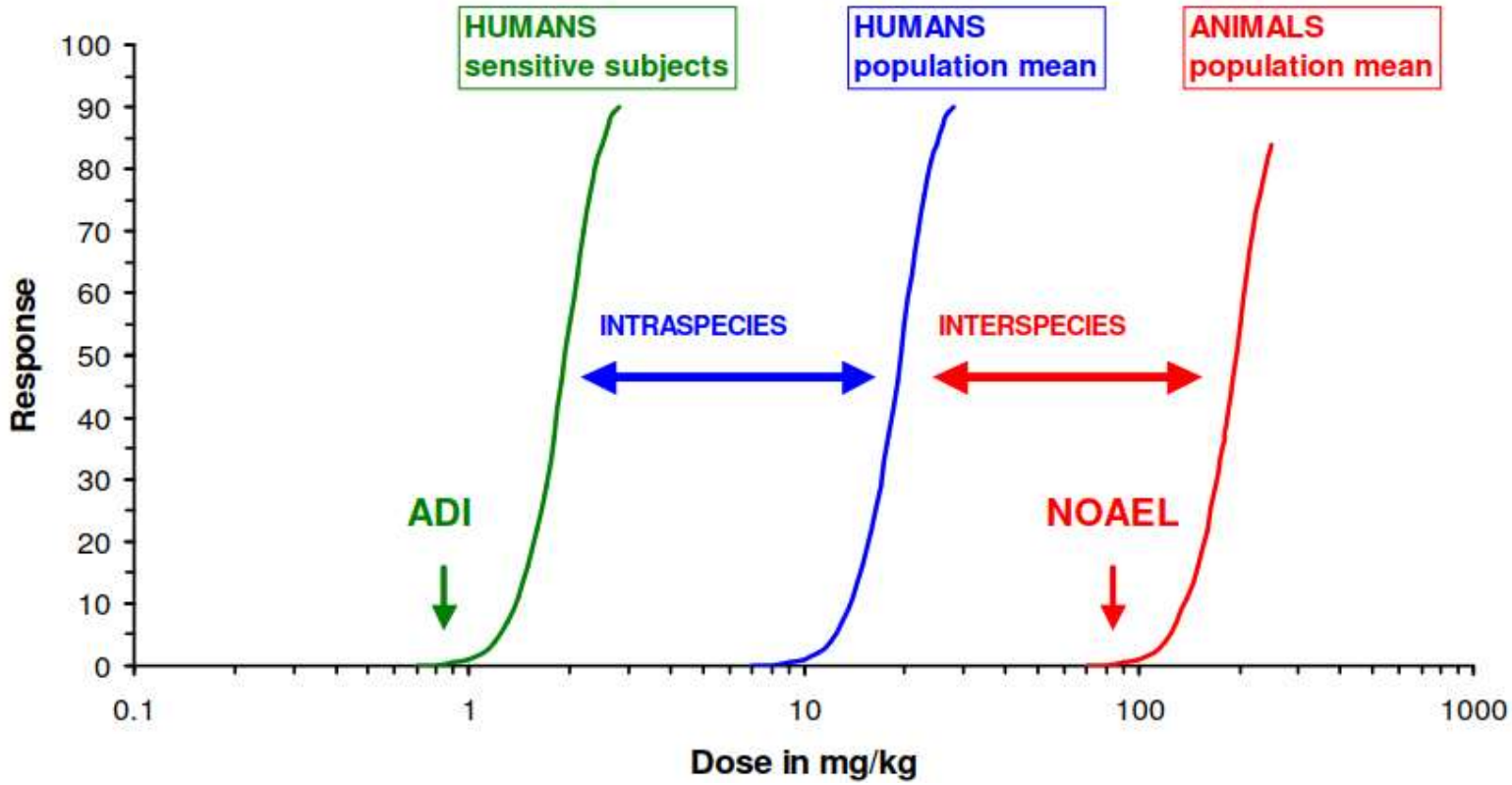
$\Rightarrow$ Health based limit value/RfD/TDI/ADI/DNEL…..

  - Usually given as external intake values: mg/kg bw (oral) or mg/m^3 (inhalation) or mg/cm^2 (dermal)

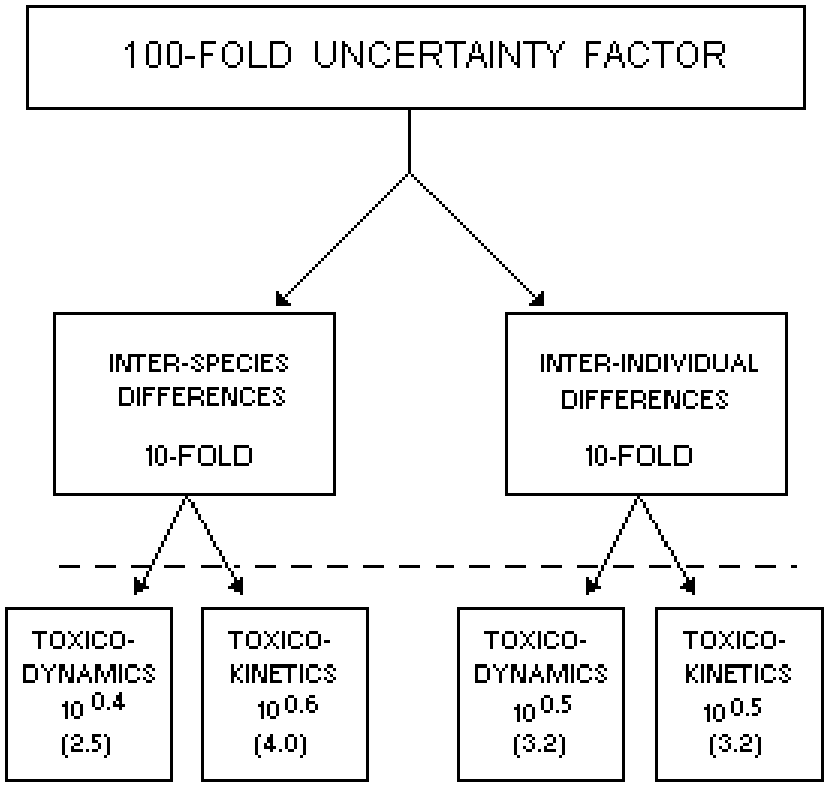
Shape of the dose-response



Assumptions in classical hazard characterization



Addressing uncertainties: uncertainty (assessment) factors



Substance specific data can be used to replace the default UFs

Fig. 1. Subdivision of the 100-fold uncertainty factor showing the relationship between the use of uncertainty factors (above the dashed line) and proposed subdivisions based on toxicokinetics and toxicodynamics (based on Renwick, 1993b). Actual data should be used to replace the default values if available.

Reference: WHO: EHC 210, 1999. Principles for the Assessment of Risks to Human Health from Exposure to Chemicals.

Non-threshold effects

- Estimation of risk at specific exposure levels
- What is the acceptable risk?
  - 1 extra cancer per 1 milj people per year?
  - 1 extra cancer per 100 000?
  - 1 extra cancer per 10 000?
  - ….
- In the end of the day, this is a risk management (=political) decision

Different risk assessment schemes

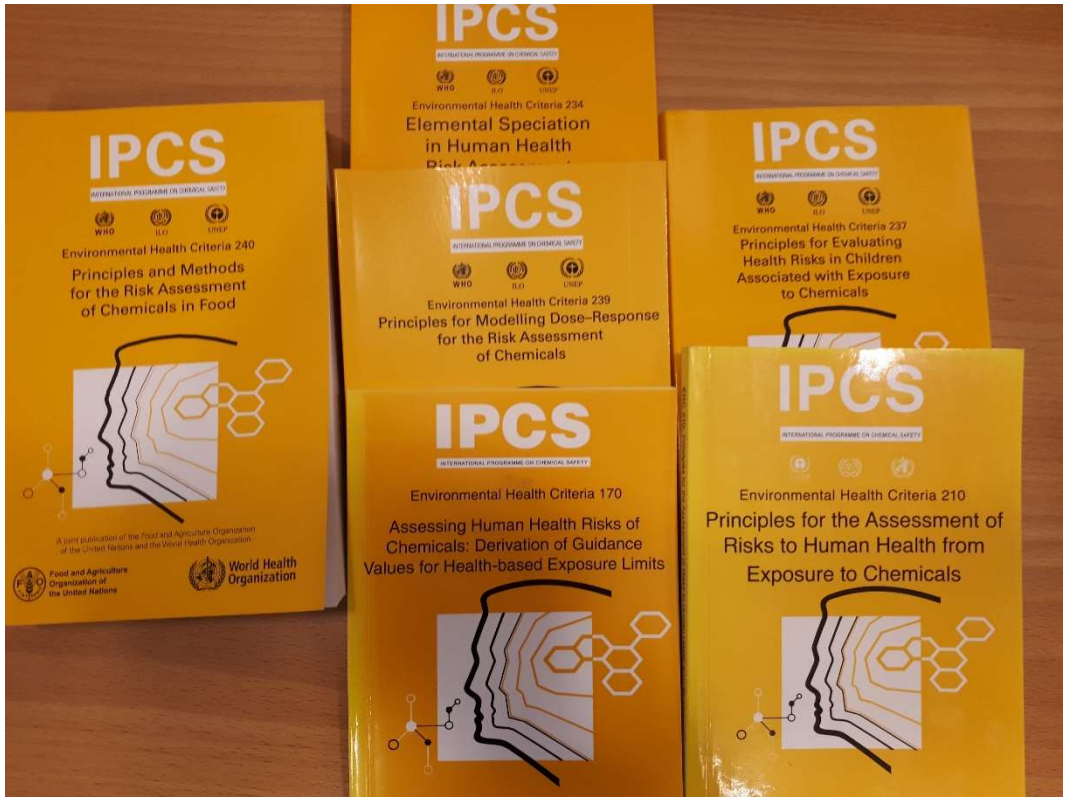
Global schemes

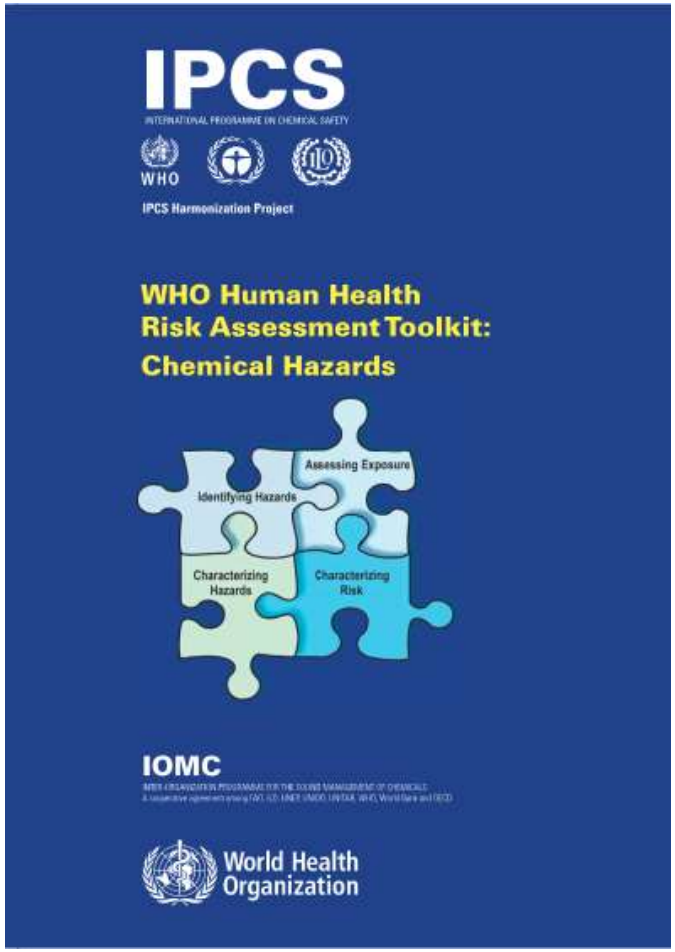
- WHO RA scheme
- FAO RA scheme
- WHOPES RA schemes

EU schemes

- EU chemicals legislation (REACH)
- EFSA: Food safety
- RA under PPP regulation
- RA under biocides regulation
- RA of cosmetics in EU
- RA under EU OSH regulation

WHO Risk assessment guidance





https://www.who.int/ipcs/publications/ehc/methodology_alphabetical/en/

WHO/IPCS Paradigm of Risk Assessment

Step	Description	Content
Problem formulation	Establishes de scope and objectives of the assessment	Defining the question Prior knowledge Desired outcomes
Hazard identification	Identifies the type and nature of the adverse health effects	Human studies Animal-based toxicology studies In vitro toxicology studies Structure-activity studies
Hazard characterization	Quantitative or qualitative description of the inherent properties of an agent having properties to cause adverse health effect	Selection of critical dataset Modes/mechanism of action Kinetic variability Dynamic variability Dose-response for critical effect
Exposure assessment	Evaluation of the concentration or amount of a particular agent that reaches the target population	Magnitude Frequency Duration Route Extent
Risk characterization	Advice for decision-making	Probability of occurrence Severity Given population Uncertainties

Table 2: Output from the framework for chemical risk assessment in the context of the Toolkit.

Question	*Output*
Hazard identification	
Is the identity of the chemical known?	Clear identification of chemical in question through CAS registry number
Is the chemical potentially hazardous to humans?	Description of health hazards obtained from internationally available information
Hazard characterization/guidance or guideline value identification	
What properties of the chemical have the potential to cause adverse health effects?	Qualitative or quantitative description of the inherent properties of the agent having the potential to cause adverse health effects
Do guidance or guideline values from international organizations exist for the chemical?	List of guidance or guideline values (rates or concentrations) for the chemical obtained from internationally available resources
What assumptions about exposure and dose are incorporated into guidance/guideline values for the chemical?	List of assumptions about contact rates, absorption and other factors incorporated into the guidance or guideline values
Do those assumptions reflect conditions specific to the local population?	A reference value that reflects exposure and dose parameters specific to the local culture and demographics
Exposure assessment	
In what ways could people come into contact with the chemical?	Qualitative description of the relevant media and exposure routes
What metric of exposure is appropriate for characterizing health risks?	Determination from the guidance or guideline value of whether an exposure concentration or exposure rate is needed to perform the risk characterization
Risk characterization	
How does the estimated exposure compare with guidance/guideline values for the chemical?	A quantitative or qualitative statement of non-cancer or cancer risk

CAS, Chemical Abstracts Service

Source: IPCS, Chemical risk assessment toolbox

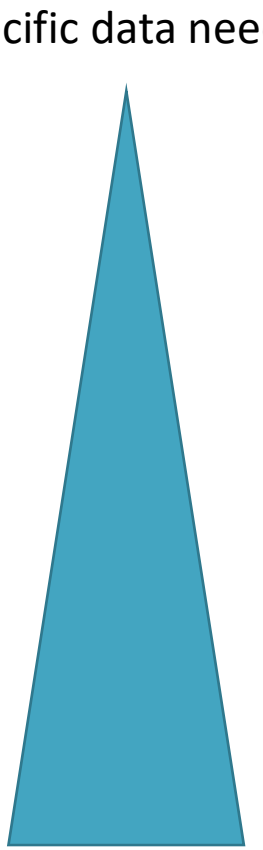
Tiered approach for the RA (according to WHO)

Tier 1 (screening)

Tier 2 (adaptive)

Tier 3 (modelling/field based RA)

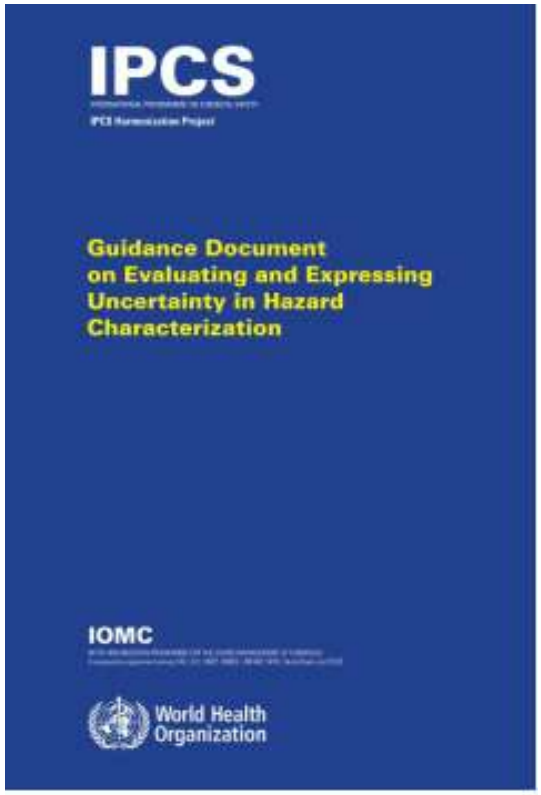
Tier 4 (Full in depth RA)



Analysing uncertainty/confidence in final RA

Voltaire: Uncertainty is an uncomfortable position. But certainty is an absurd one.

- Qualitative communication of uncertainties in the assessment
- Quantitative: WHO quantitative (probabilistic) approach for the evaluation of uncertainties in hazard and exposure assessment



Also: Guidance document on characterizing and communicating uncertainty in exposure assessment, IPCS, 2008

https://www.who.int/ipcs/methods/harmonization/en/

Mixtures: WHO/IPCS 2009

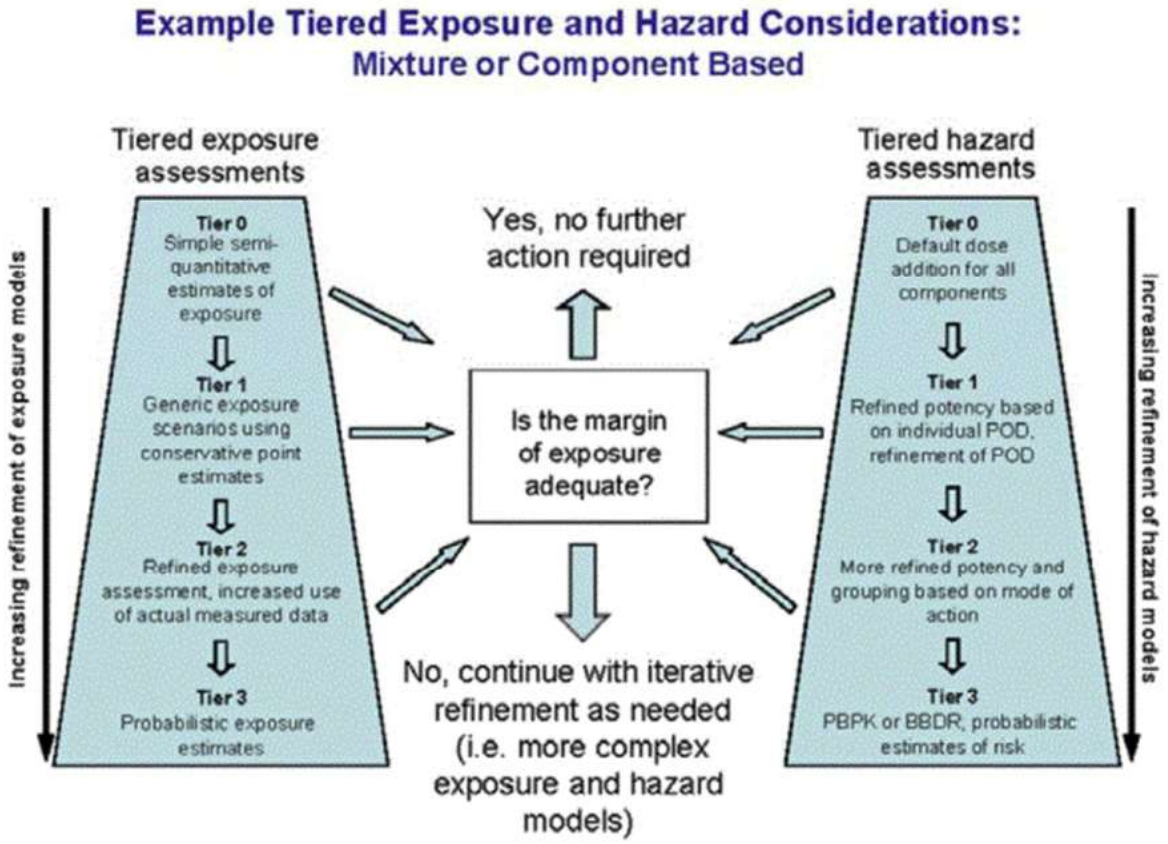


Figure 2: A conceptual representation of the WHO/IPCS framework (from Meek et al., 2011)

Mixtures: WHO/IPCS 2009

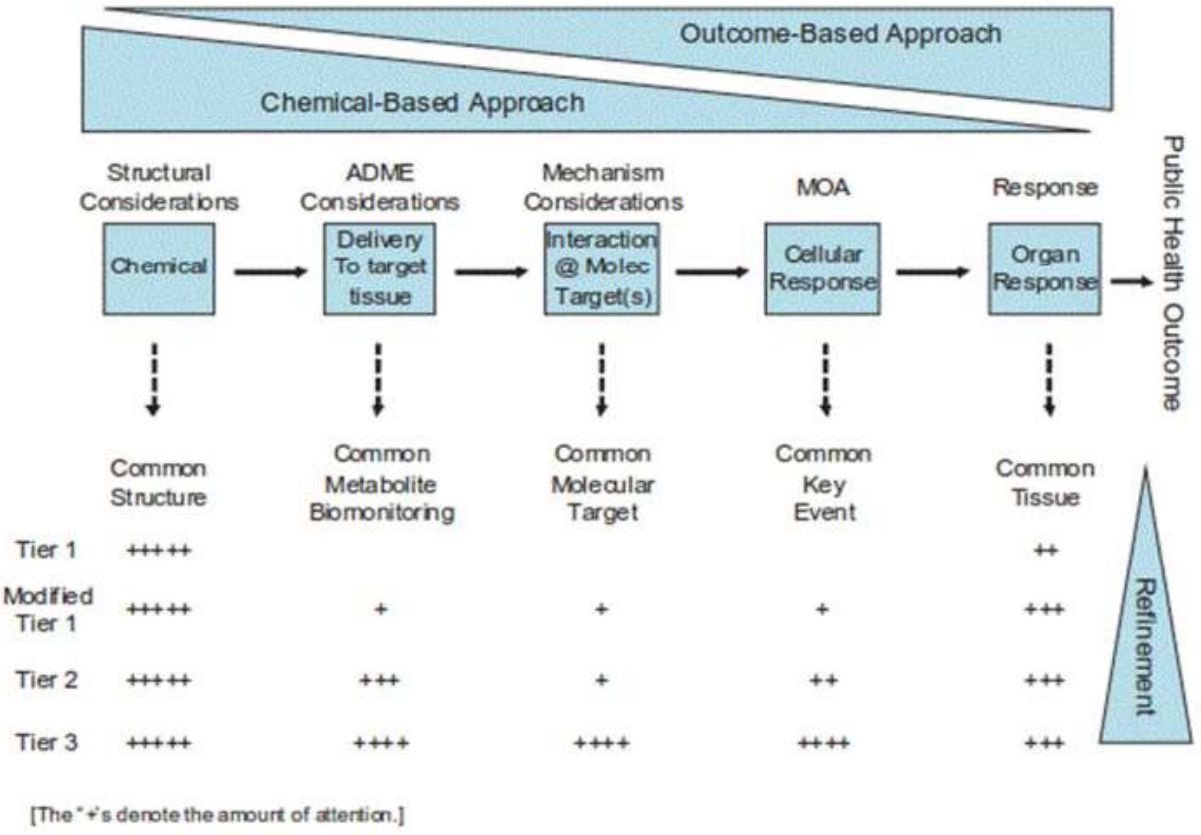
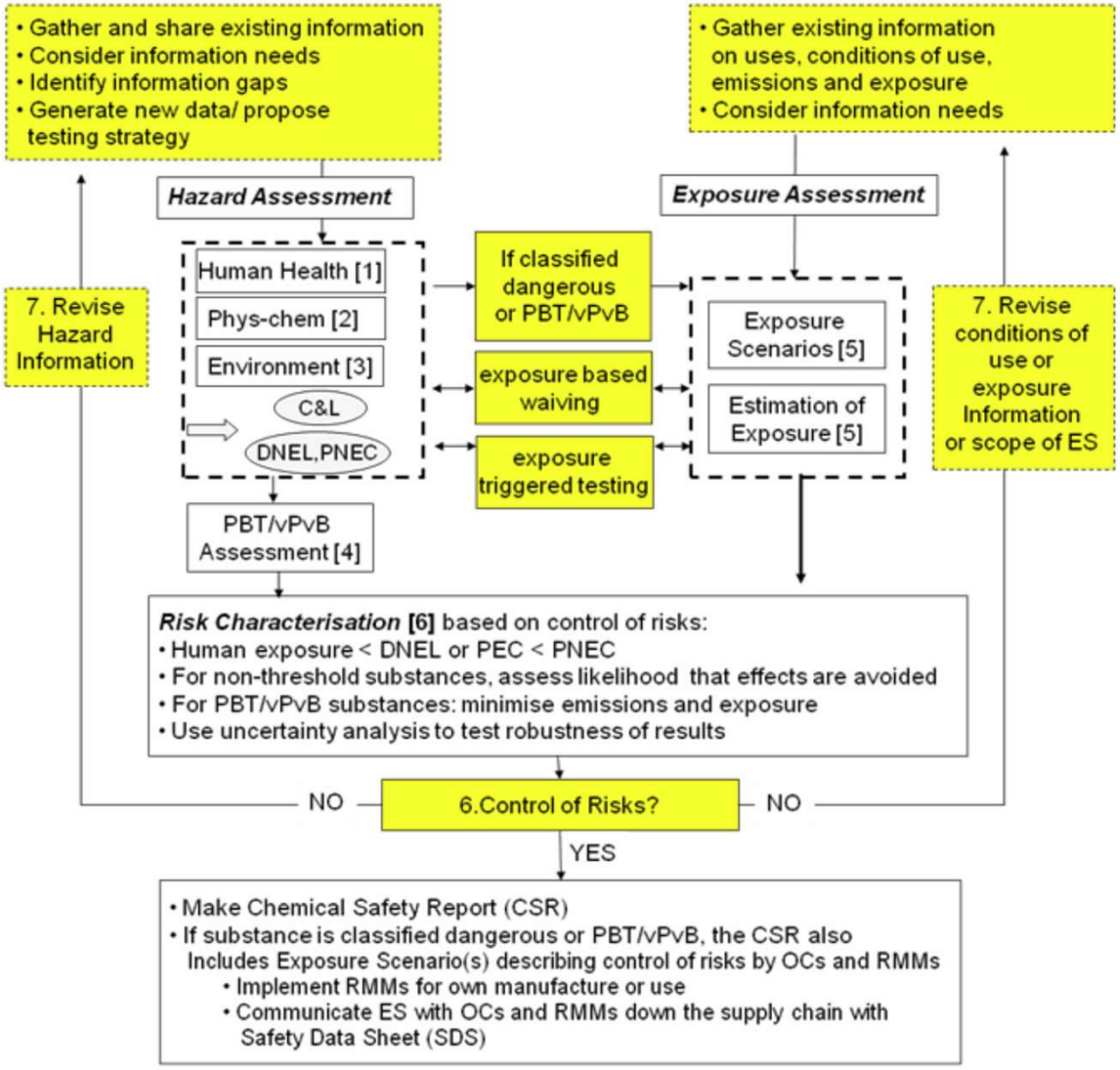


Figure 3: A proposed approach to tiered consideration of hazard for exposure to multiple chemicals (from WHO/IPCS 2009b)

REACH risk assessment



Terminology

CSA = Chemical Safety Assessment

CSR = Chemical Safety Report

DNEL= derived no-effect level (mg/kg bw or mg/m3)

DMEL= derived minimal effect level

Exposure Scenario=description of the specific situations in which exposure may occur

Read-across= extrapolation of the hazardous properties of the compound on the basis of related substances

(Q)SAR = (Quantitative) Structure-Activity Relations

REACH DNELs for different exposure scenarios

Exposure pattern	DNEL/DMEL (appropriate unit)	
	Workers	**General population** [3]
Acute – inhalation, systemic effects[1]	worker-DNEL acute for inhalation route-systemic	General population-DNEL acute for inhalation route-systemic
Acute – dermal, local effects[2]	worker-DNEL acute for dermal route-local	General population-DNEL acute for dermal route-local
Acute – inhalation, local effects[2]	worker-DNEL acute for inhalation route-local	General population-DNEL acute for inhalation route-local
Long-term – dermal, systemic effects[1]	worker-DNEL long-term for dermal route-systemic	General population-DNEL long-term for dermal route-systemic
Long-term – inhalation, systemic effects[1]	worker-DNEL long-term for inhalation route-systemic	General population-DNEL long-term for inhalation route-systemic
Long-term – oral, systemic effects[1]	Not relevant	General population-DNEL long-term for oral route-systemic
Long-term – dermal, local effects[2]	worker-DNEL long-term for dermal route-local	General population-DNEL long-term for dermal route-local
Long-term – inhalation, local effects[2]	worker-DNEL long-term for inhalation route-local	General population-DNEL long-term for inhalation route-local

[1] Units for systemic exposure are mg/m^3 for inhalation, and mg/kg bw for oral and dermal exposure

[2] Units for local effects are mg/m^3 for inhalation; and for dermal exposure: mg/cm^2 skin, mg/person/day (e.g., calculated based on the deposited amount per cm^2 times the actually exposed body area), or a measure of concentration (% or ppm)

[3] General population includes consumers and humans via the environment. In rare cases it may also be relevant to derive a DNEL for specific subpolulations, such as children.

REACH exposure assessment: example

WCS	PROC	Inhalation exposure (mg/m3)	Dermal exposure (mg/kg)	Contribution to daily operator exposure		Inhalation exposure 8 hour TWA (mg/m3)	Dermal exposure 8 hour TWA (mg/kg)
				Daily duration	frequency		
ES1	1	0.05	0.03	0,125	1	0.01	0.00
ES2	3	5.5	0.7	0.41	1	2.26	0.29
ES3	3	5.5	0.7	0.41	1	2.26	0.29
ES4	8b	6.84	2.7	0.125	0.2	0.17	0.07
ES5	8a	16.4	0.555	Full*	0.2	3.28	0.11
ES6	8a	4.1	0.27	Full*	0.05	0.21	0.01
ES97	15	5.5	0.07	0.125	0.2	0.17	0.00
SUM						**8.34**	**0.77**

Man via Environment – inhalation	Local PEC: 6.673E-4 mg/m^3
Man via Environment - oral	Exposure via food consumption: 1.625E-6 mg/kg bw/day

Exposure assessment is often based on models. Often measured data is limited.

Refinement of the exposure assessment with measured data

- More hazardous the substance is, or when exposure estimate is close to DNEL => more refined exposure assessment needed
- Usually external contaminant levels in air, food, surfaces, consumer products etc….
- Still challenges related to the actual intake and combined exposure from different sources

$\Rightarrow$ biomonitoring could provide invaluable data for exposure assessment

Contacts

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Speaker's information

Tiina Santonen, MD, PhD, MSc in Applied Toxicology, ERT, works as Chief Specialist at Finnish Institute of Occupational Health. Her main tasks at the institute relate to chemical risk assessment and biomonitoring. She is the former member of Scientific Committee on Occupational Exposure limits (SCOEL) and a member of ECHA Risk Assessment Committee (RAC). In HBM4EU she is responsible for tasks 5.3 related to the better use of HBM in the risk assessment of chemicals and task 8.5 related to targeted occupational surveys.

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