Risk Assessment of Chemicals: Recent Developments and Application to the General and the Occupational Environment

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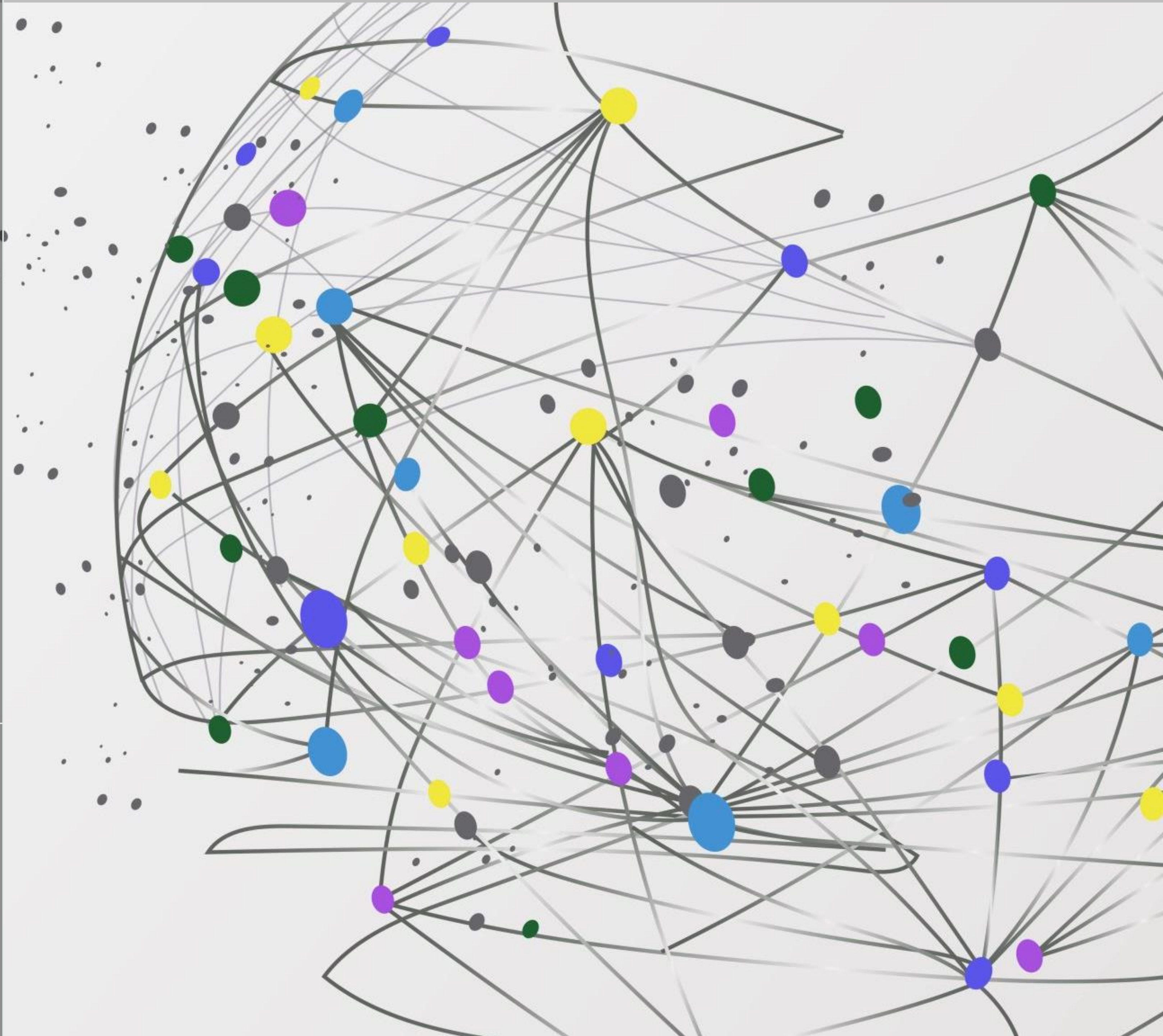


Outline

* Introduction: What is special about chemicals?
* The risk assessment process: The concept
* Development of health-based guidance values: Concept and new developments
* Challenges today
* Novel Approaches
* Outlook

Introduction: What is special about chemicals?

Chemicals: The broad context

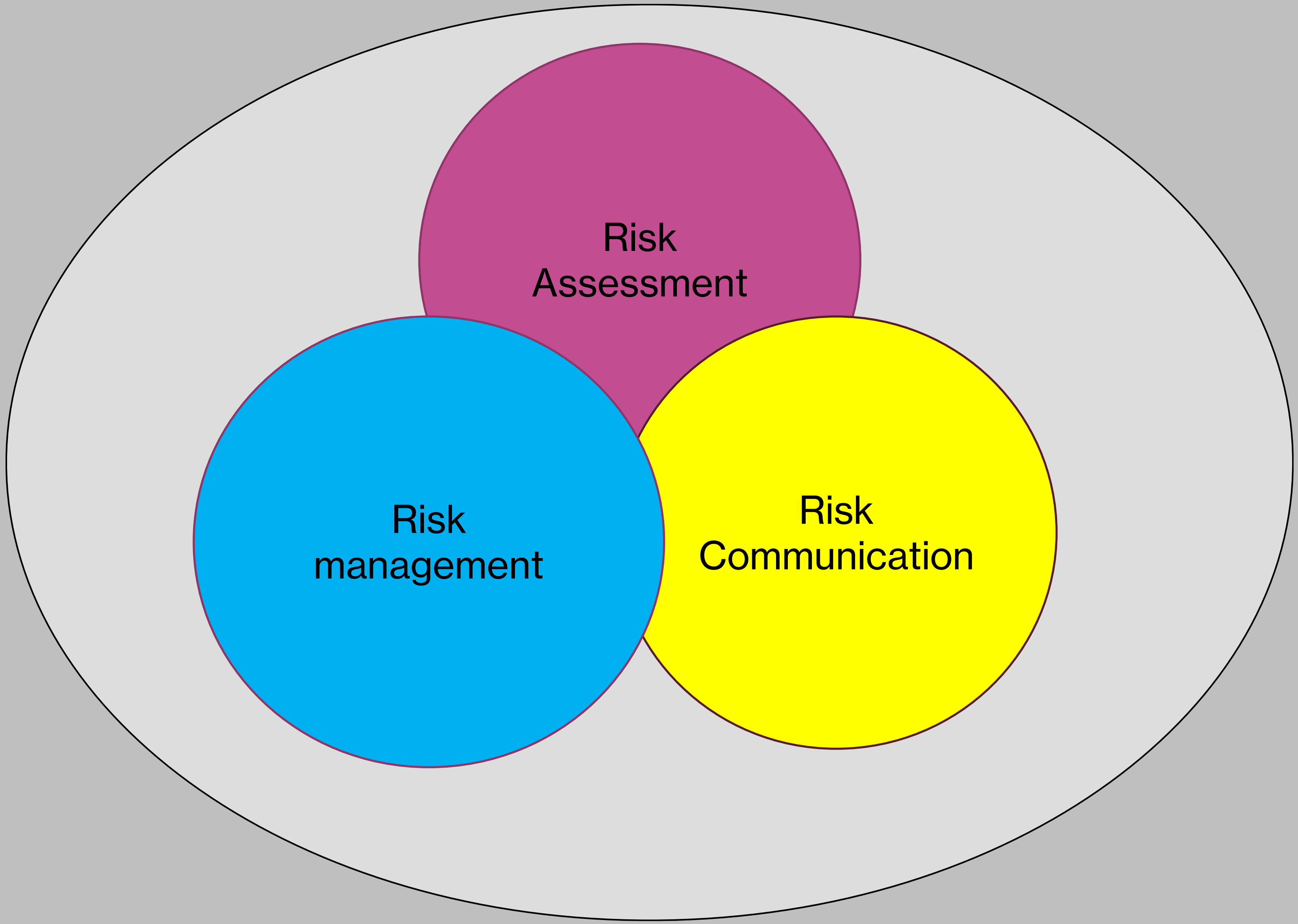
* Chemicals are integral to everyday life and key to economy
* Chemicals are part of many products and have manifold uses
* Important role in society due to the increased dependence on chemicals in products and services
* An integral component in the development of many sectors
* Chemicals can, however, have negative effects on health and environment if misused or badly managed

Actions to date

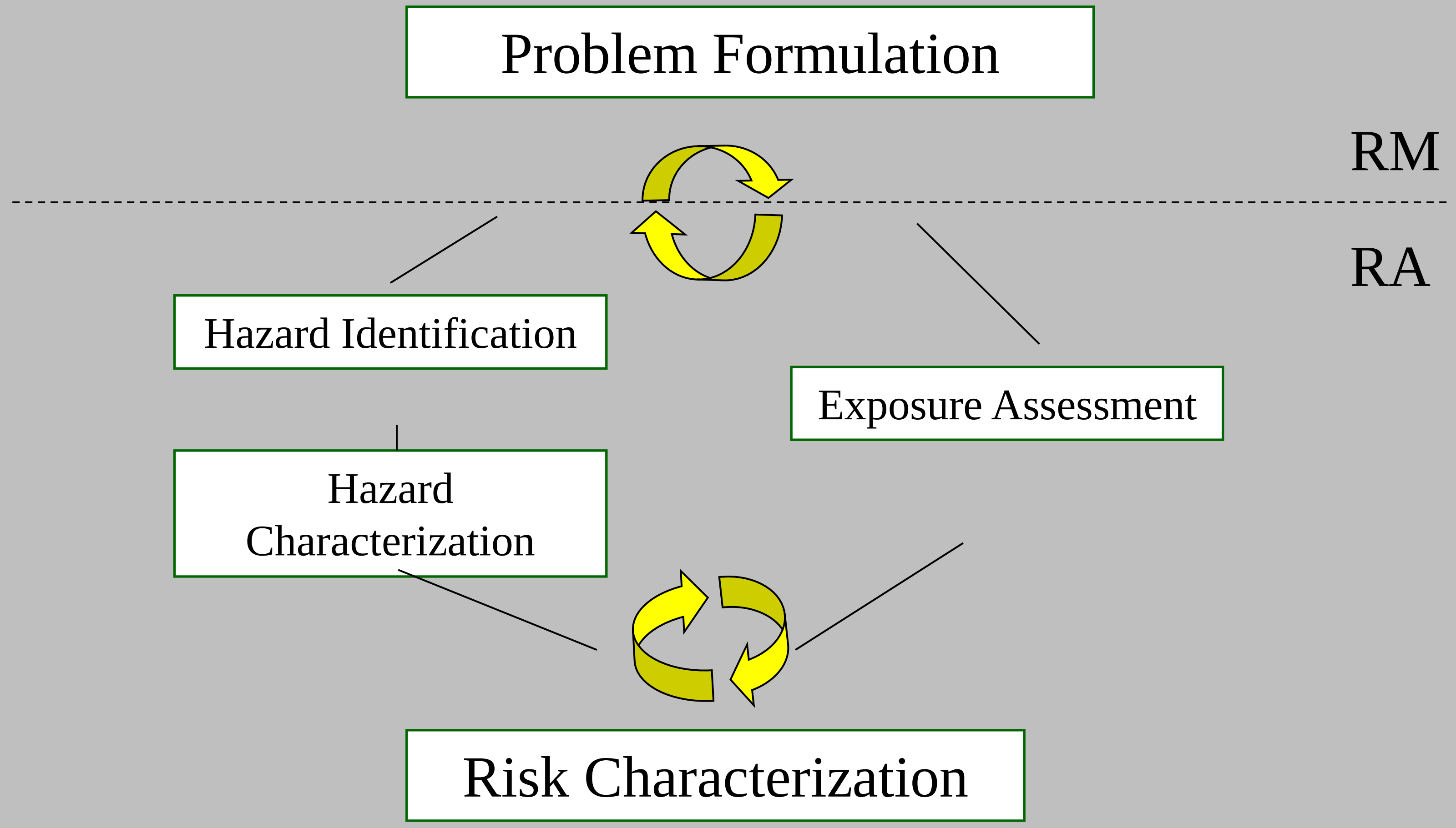
- National systems for environmental and occupational management of chemicals
- International work (OECD, WHO, FAO, ILO, UNEP and others)
- European level: ECHA, EFSA, EMA, European Commission, JRC
- Chemicals Strategy for sustainability / The Green Deal
- Science underpins all this work: A central role for research

The risk assessment process: The concept

Risk analysis : a stepwise approach



Risk Assessment: A Scientific Process



Development of health-based guidance values: Concept and new developments

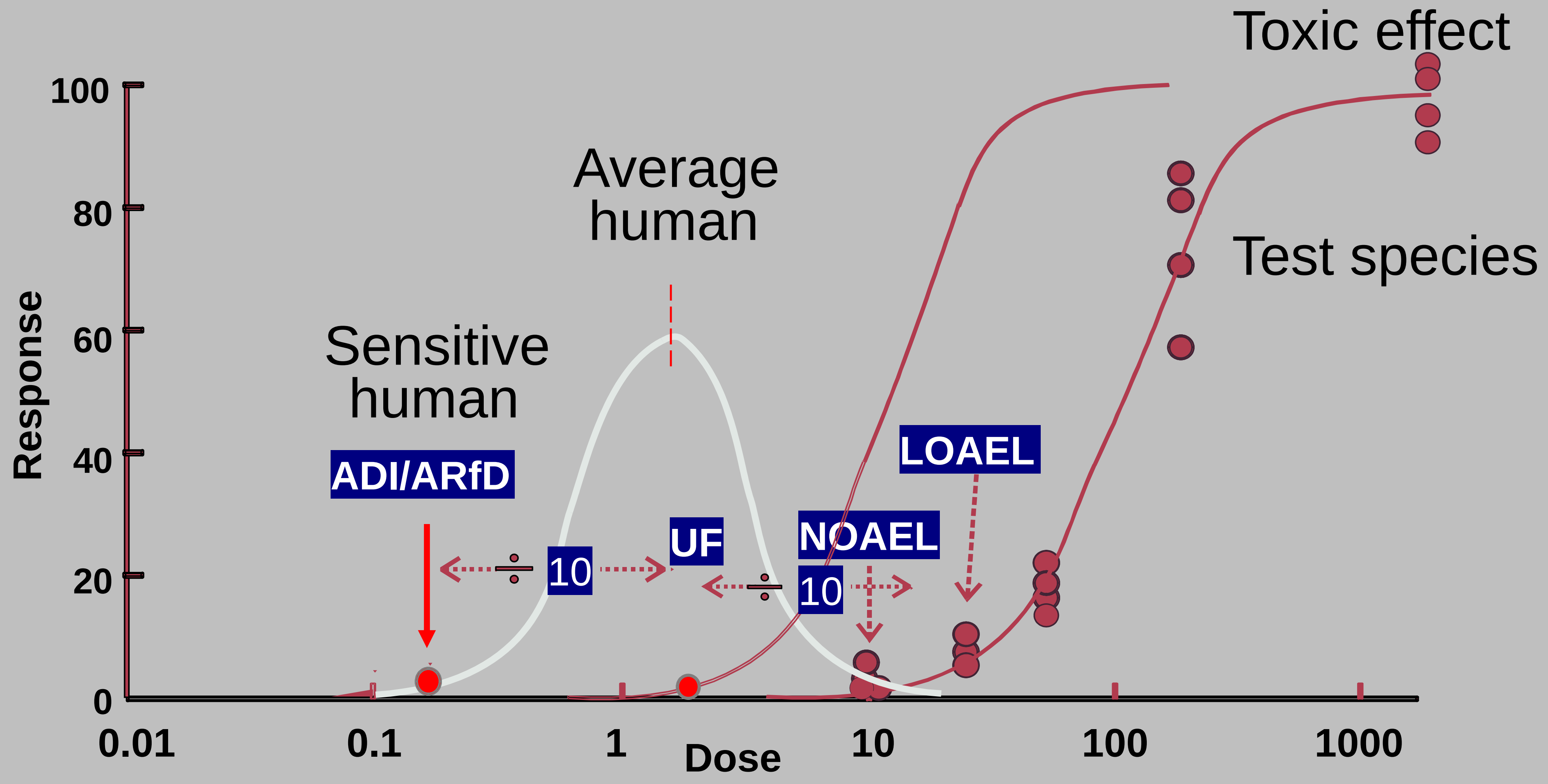
Setting health-based guidance values (HBGVs)

- Use of human, animal or alternative data
- Assessment of dose-response relationship for particular endpoints
- Derivation of a point of departure on the dose-response curve (NO(A)EL; LO(A)EL; BMDL)
- Application of uncertainty factors (UF) if necessary
- Setting of HBGV for comparison with current exposures
- Decision by risk managers on standards

Special Considerations

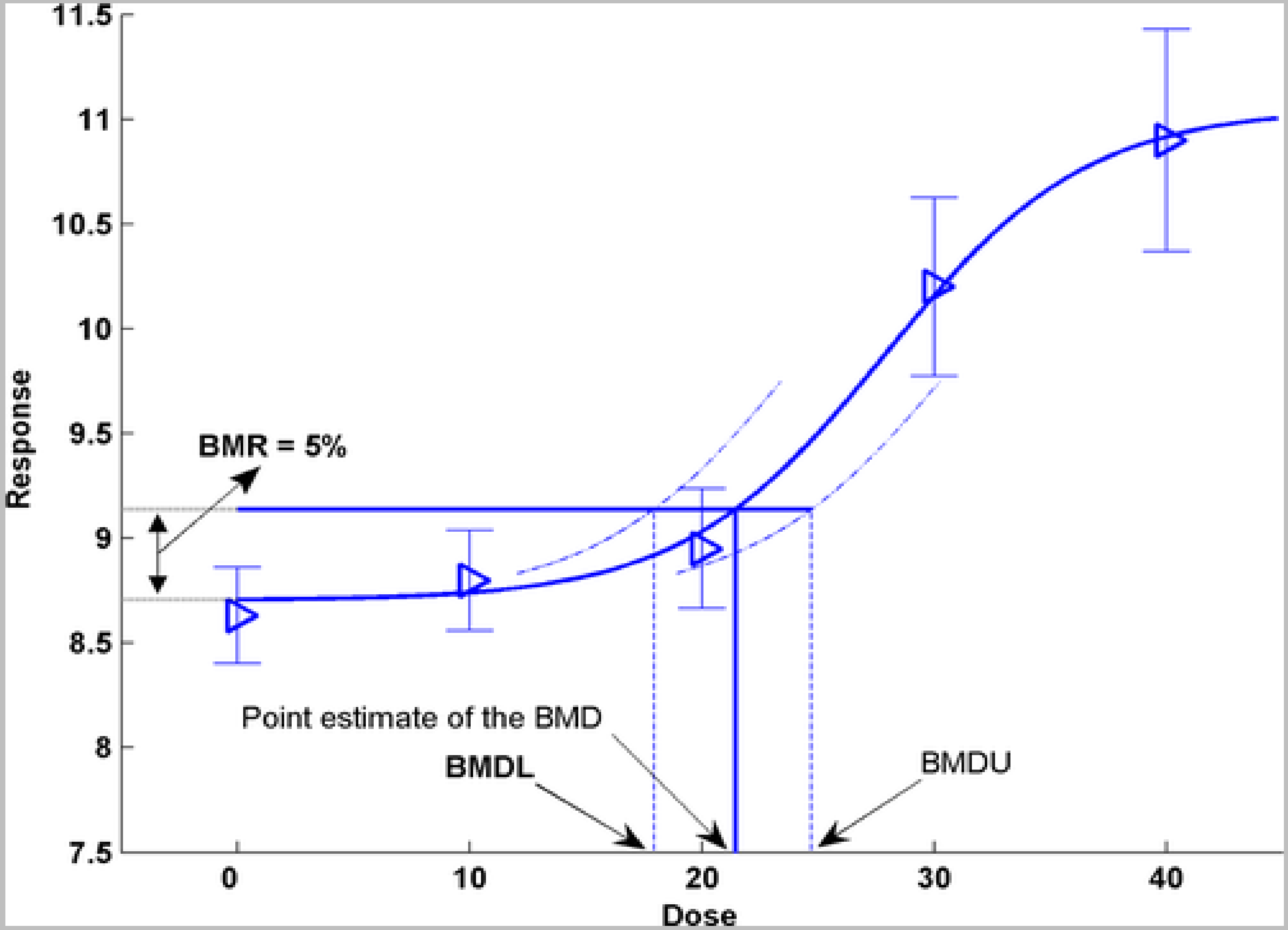
* Sensitive population groups (pregnant women, newborns, children, elderly)
* Genotoxic carcinogens (HBGV-setting not applicable)

Derivation of HBGV (e.g. TDI or ADI)

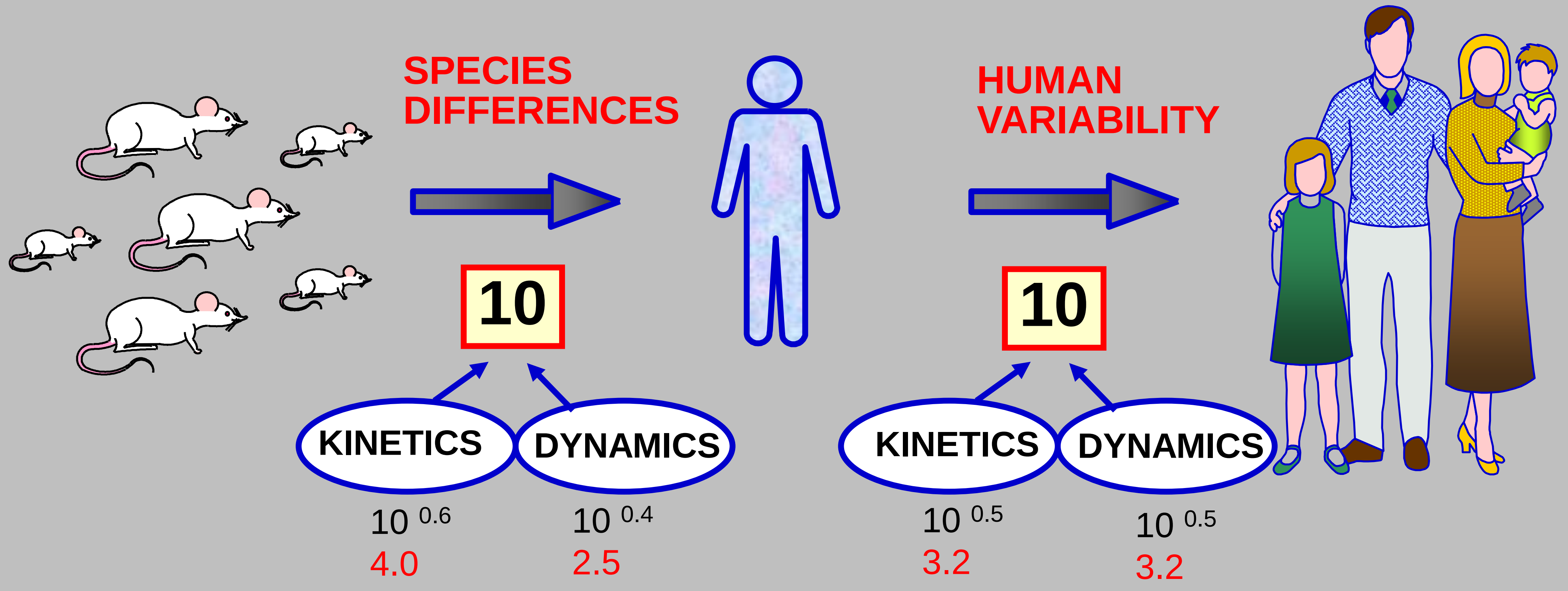


Benchmark dose approach

https://doi.org/10.2903/j.efsa.2017.4658



Default Uncertainty Factors (UF)

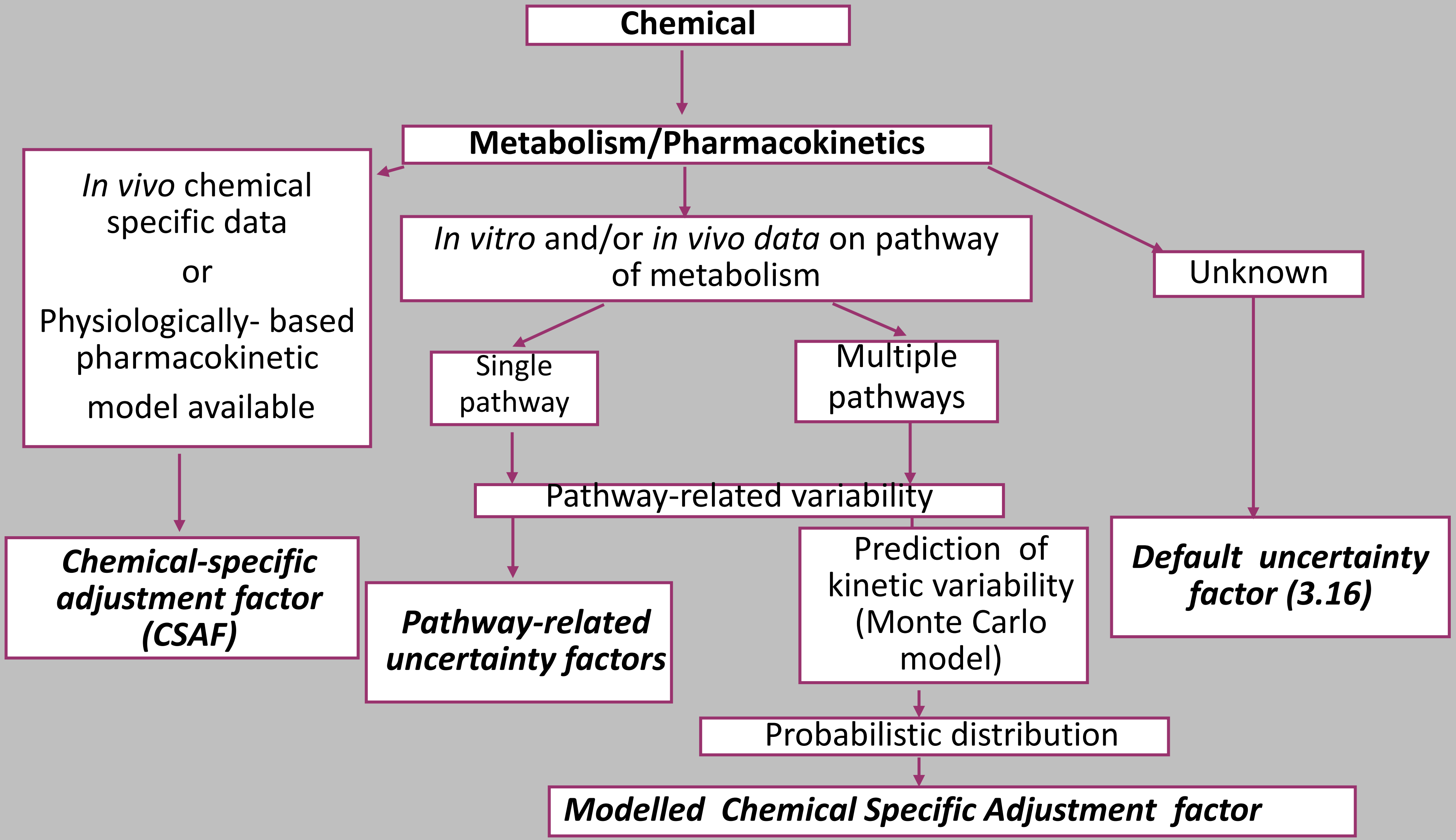


Options to replace default uncertainty Factors (UF)

-**Chemical specific adjustment factors** using physiologically-based models (PB-TK/PB-TK-TD)(WHO, 2006)

-**Categorical uncertainty factors e.g for humanTK pathway-related UF** (Dorne and Renwick, 2005)

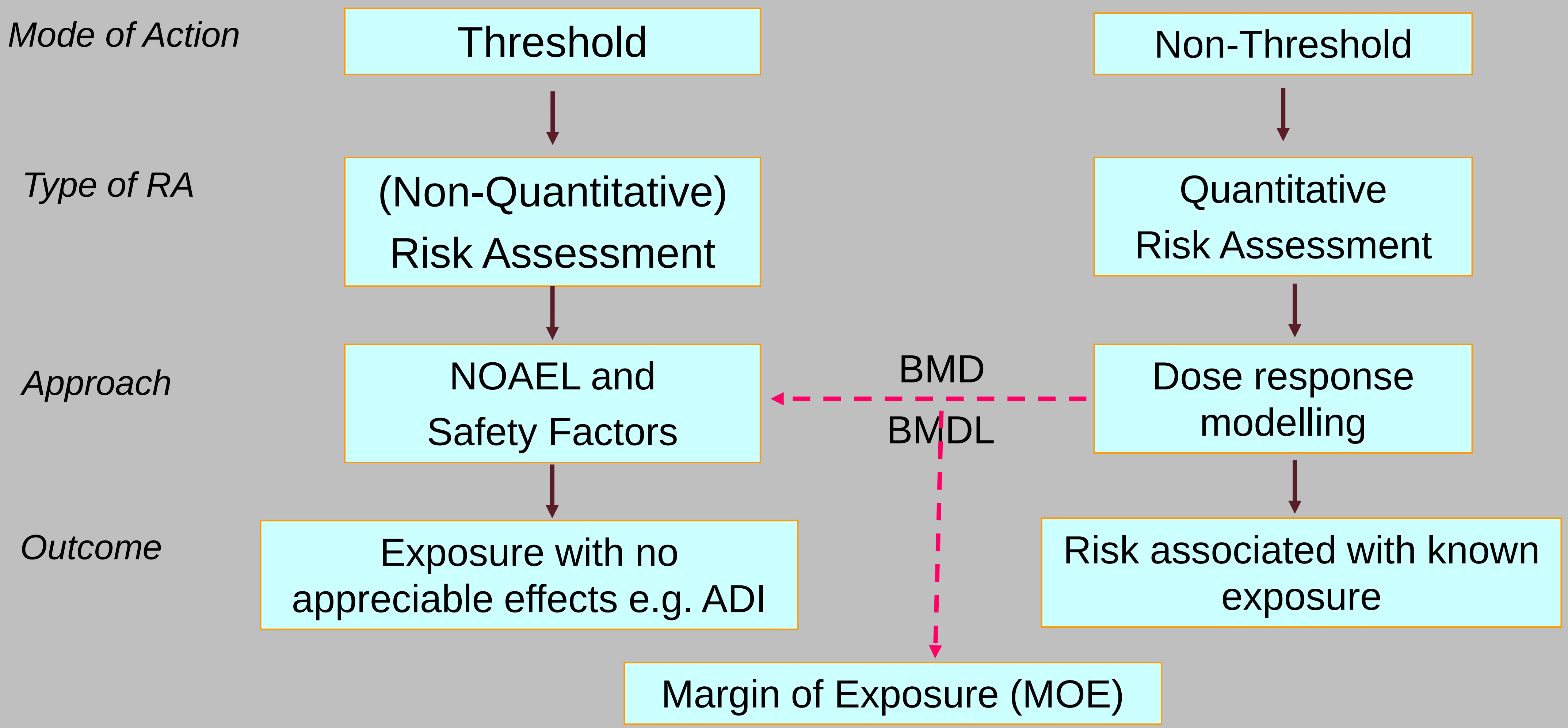
Example TK: Pathway-related UF



Carcinogens

- Traditionally: HBGV possible for non-genotoxic carcinogens
- No HBGV for genotoxic carcinogens
- Low-dose extrapolation use not generally accepted
- Margin of exposure
- Special considerations

Mechanism-based approach to RA



Probabilistic approaches

- A group of techniques that incorporate variability and uncertainty into risk assessment
- Alternative to deterministic risk assessment
- Provides estimates of the range and likelihood of a hazard, exposure or risk, rather than a single point estimate
- Population-based
- Allows risk managers to decide on specified target level of protection (e.g. 95^{th} percentile)

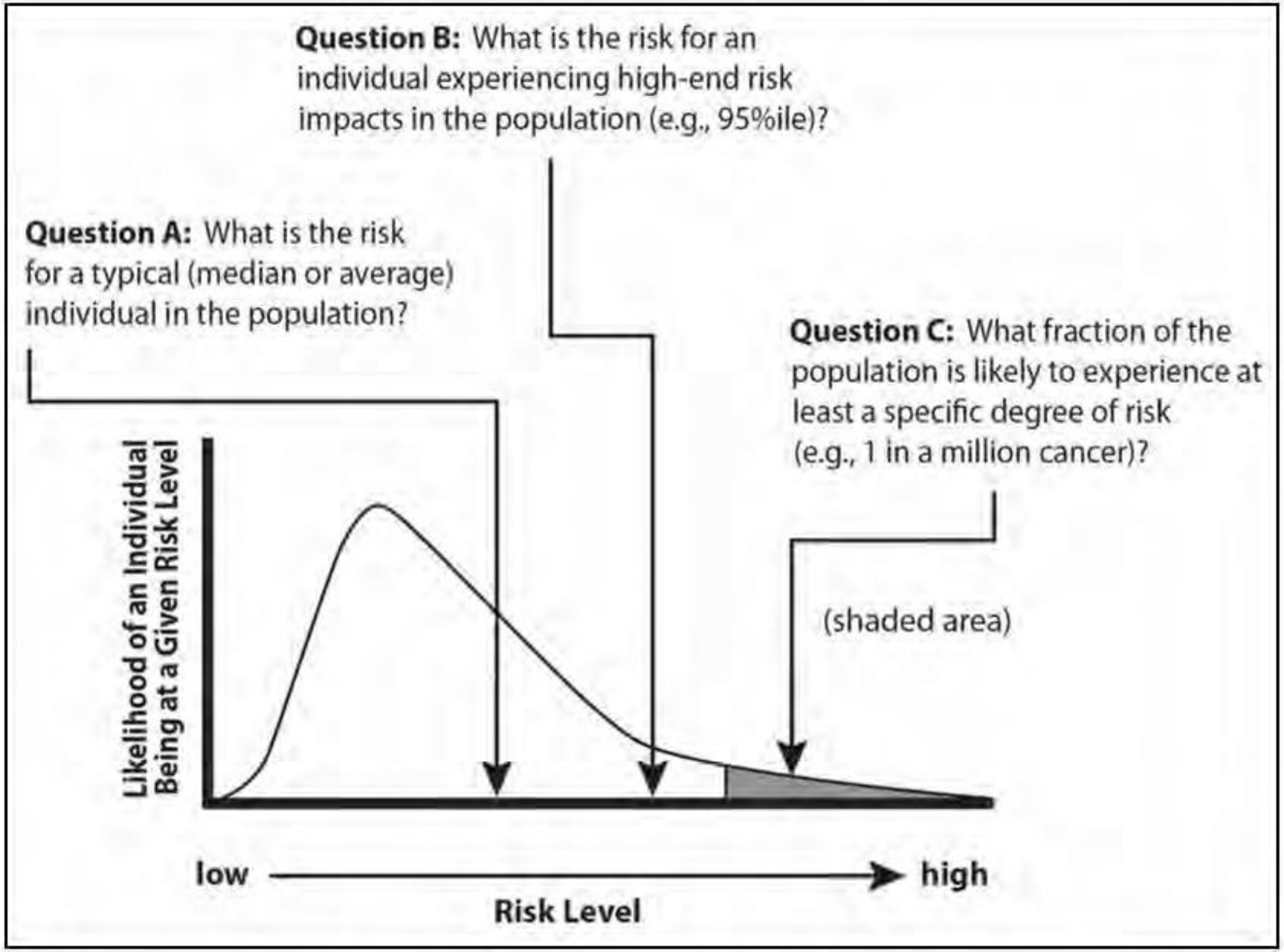
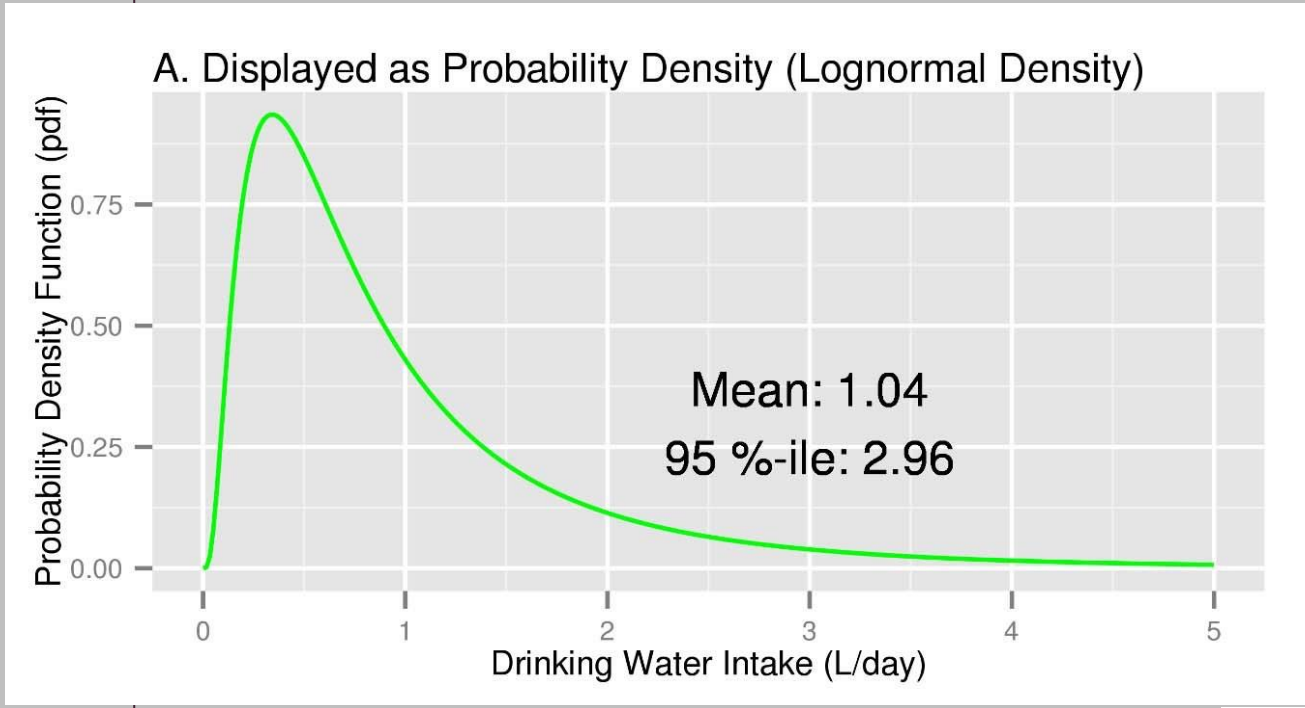
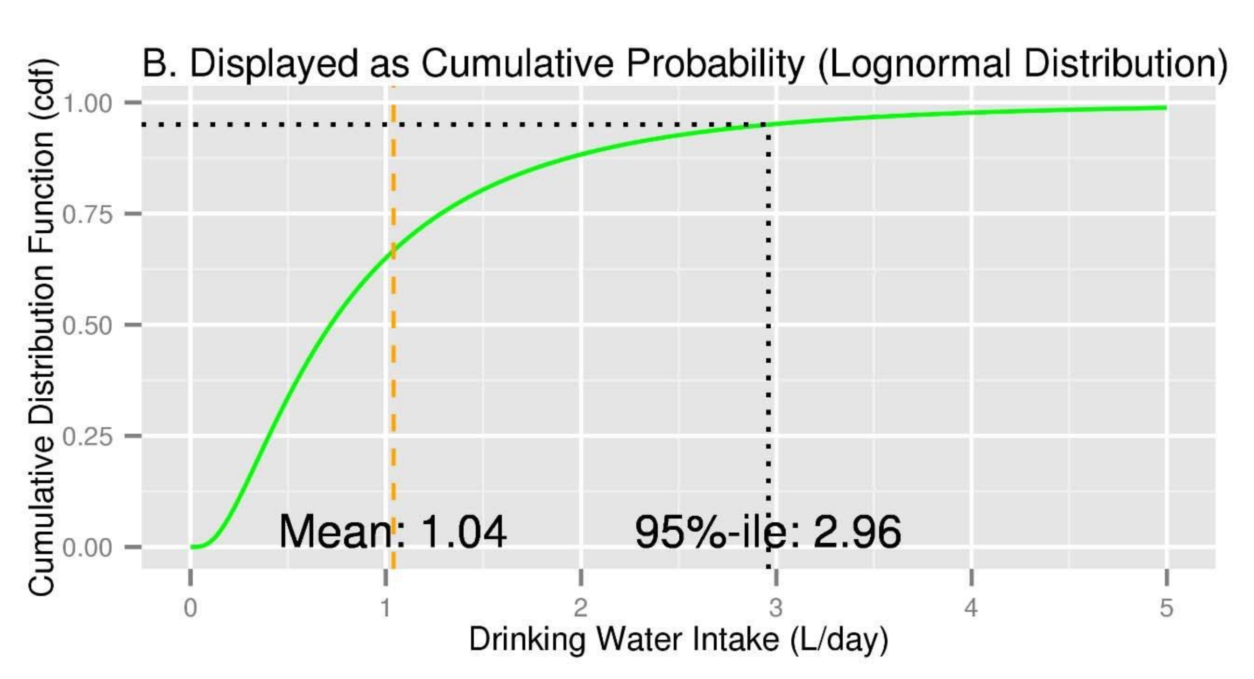


Figure 4. What Questions Can PRA Address? PRA can be used to determine the likelihood of exposure or risk in a specific fraction of the population.

From: EPA/100/R-14/003; 2014

Example





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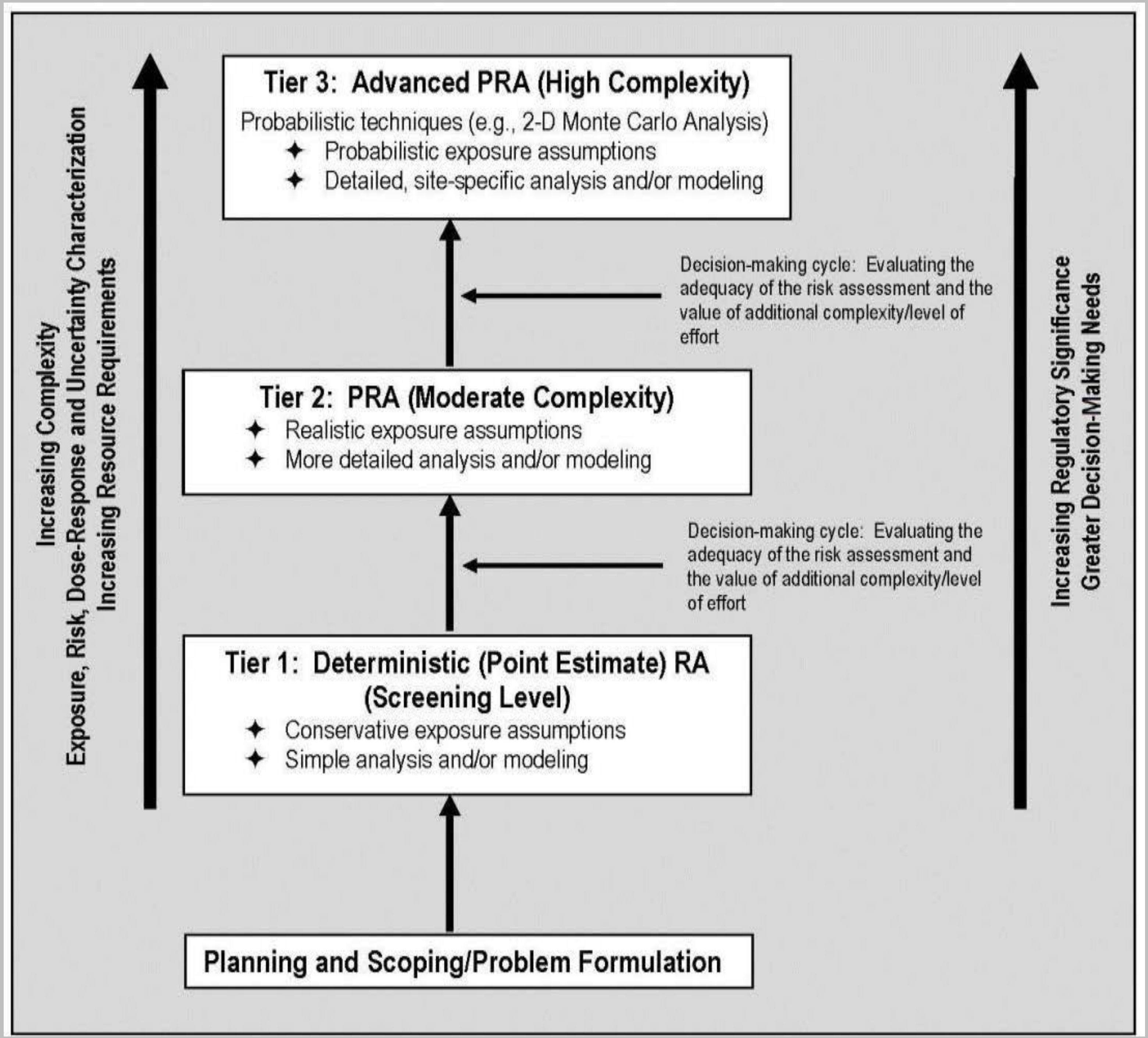


Tiered Approach for Risk Assessment. The applicability of a probabilistic approach depends on the needs of decision makers and potential stakeholders. Assessments that are high in complexity and regulatory significance benefit from the application of probabilistic techniques. Source: Adapted from USEPA 2004 and WHO 2008.

Standard setting

* Environmental standards (air, drinking and recreational water, food, soil) are based on HBGVs, taking into account overall exposures and exposure patterns and covering the general population
* Can be translated to emission standards
* Occupational standards are based on workplace exposure patterns and covering exposure at the workplace (and bystanders?)
* Probabilistic approaches permit consideration of the true exposure patterns in setting standards

Main challenges today:

* Need to accelerate chemicals assessment
* Rational Handling of data (and big data)
* Need to reduce/replace animal testing
* Mixtures/Combined exposures
* Transparency and sound assessment frameworks – Systematic approaches
* Integration of novel and diverse data
* Assessing uncertainty

Some recent developments

- Systematic review of literature and assessment protocols
- Appraisal and integration of data
- Assessing biological relevance
- Weight of evidence approaches
- Uncertainty assessment and communication
- Adverse Outcome Pathways
- Use of data from New Approach Methodologies (NAMs)
- *Specific considerations for nanomaterials and mixtures (not covered in this lecture)*

Evidence Use (Source. EFSA; EFSA Journal 2015;13:4121)

STEPS:

- Problem formulation
- Data collection (systematic)
- Appraisal of data (data quality, risk of bias assessment)
- Evidence integration (WoE!)
- Outcome assessment

Examples:

- EFSA (Prometheus): Overall process
- OHAT: Risk of Bias Handbook and Tool (US-NIEHS)

Evidence use

Define to the extent possible beforehand the strategy applied for:

- Collecting and selecting data
- Appraising the relevant evidence
- Analysing and integrating the evidence in order to draw conclusion

(Protocol)

Systematic reviews

- Aim (OHAT, NTP, 2019):
  - Enhance transparency, foster greater consistency in methods, and increase efficiency in summarizing and synthesizing findings for literature-based health assessments
- Explicit, pre-specified approach to identify, select, assess, and synthesize the data from studies in order to address a specific scientific or public health question (Protocol)
- Does not replace expert opinions, but supports experts in assessing, evaluating and integrating studies. Possibility of applying Expert Knowledge Elicitation (EKE)

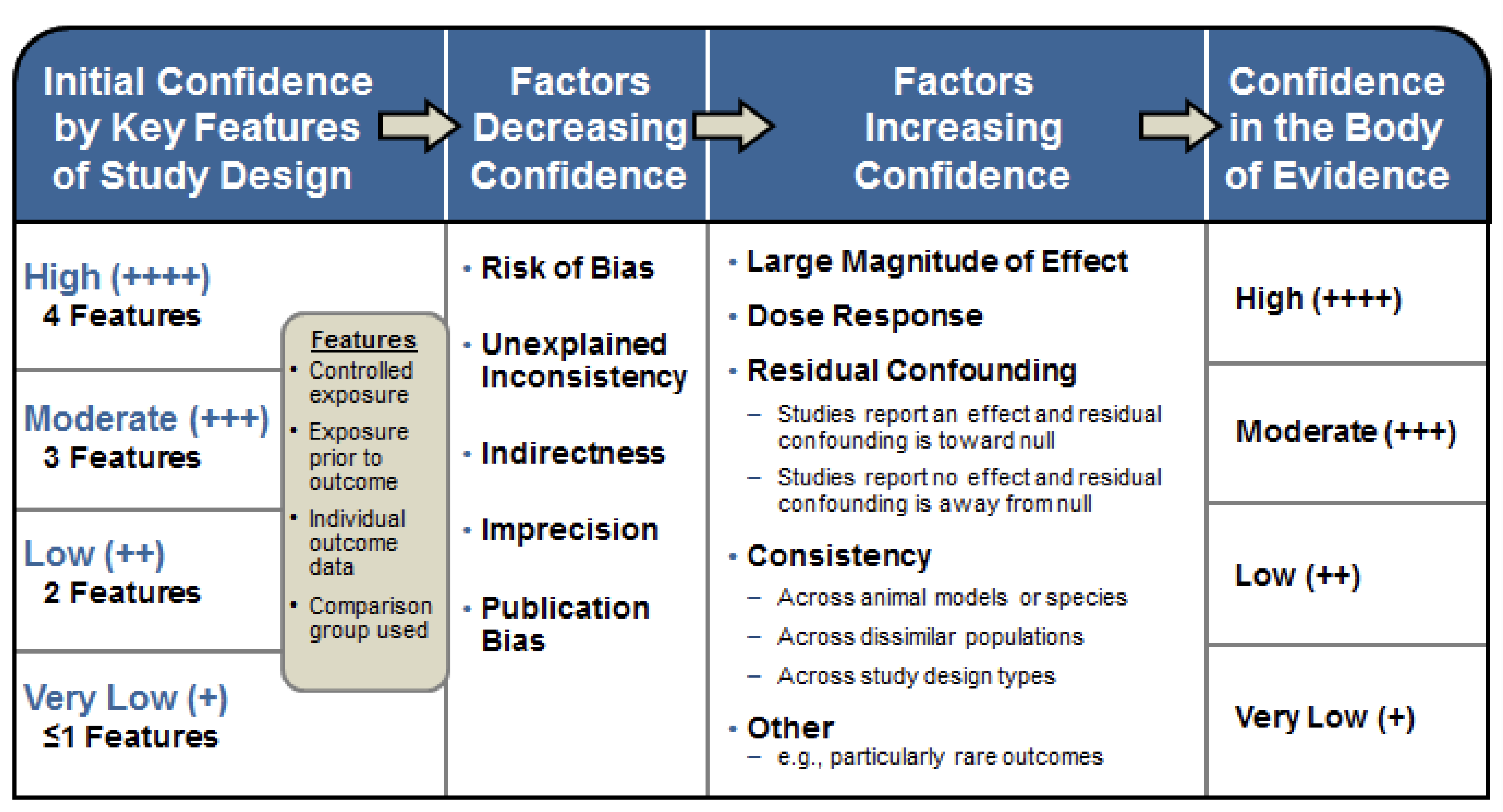
Systematic reviews-2

* Protocol development:
  * Agreement on literature search strategy (including endpoints, dates, etc.)
  * Description of how studies will be selected for inclusion (stepwise approach)
  * Identification of endpoints to assess
  * Description of how the quality of selected studies will be assessed (risk of bias)
  * Description of the approach to evidence synthesis and the assessment of confidence in the body of evidence
  * Description of how the confidence in the evidence will be translated into level of evidence for health effects
  * Process for integration of the evidence to conclude on risk assessment question(s)

Systematic reviews-3

* In applying the protocol:
  * Inclusion/exclusion criteria for studies may include date, language, relevance, endpoints considered, etc.
  * Risk of bias covers issues such as sample size, controls, randomization, blinding, etc. Result: tiers (subject to upgrading or downgrading based on concerns)
  * Weighing of the body of evidence using quantitative or qualitative approaches
  * Description of uncertainties

Systematic reviews-4 (OHAT Handbook, 2019)

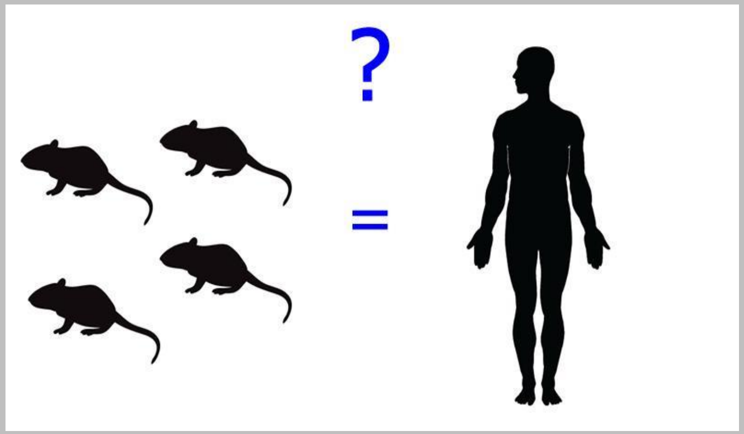


Big Data

* Handling large datasets and historical data
* Automation? Machine review?
* Do benefits outweigh potential risks?
* Assessment still by experts

Biological relevance

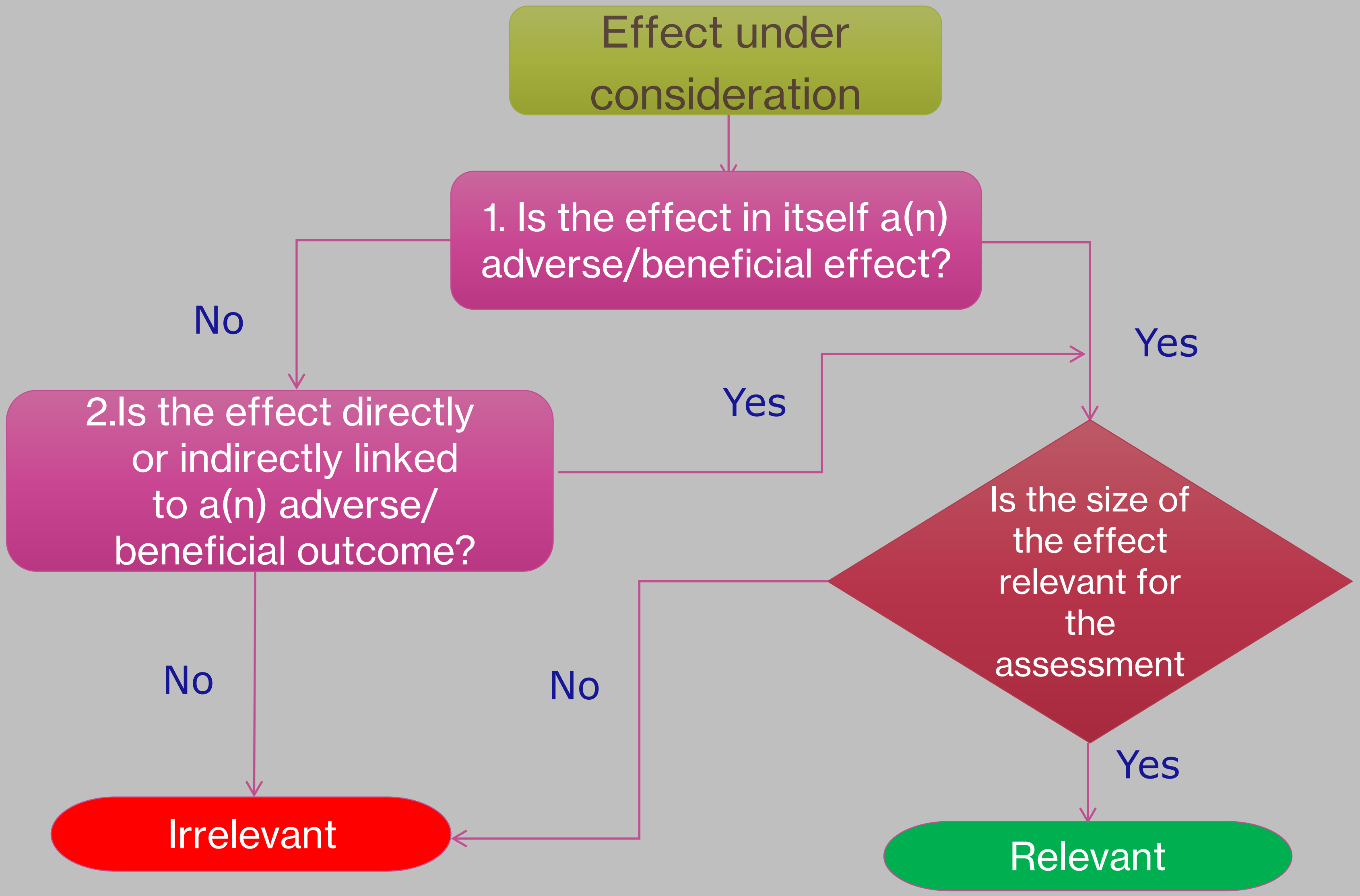
* Which generic issues and criteria are needed to consider biological relevance in relation to evidence used in Scientific Assessments?
(EFSA, EFSA Journal 2017;15(8):4970)



Evidence from test models

Relevance in target species

Decision tree on biological relevance

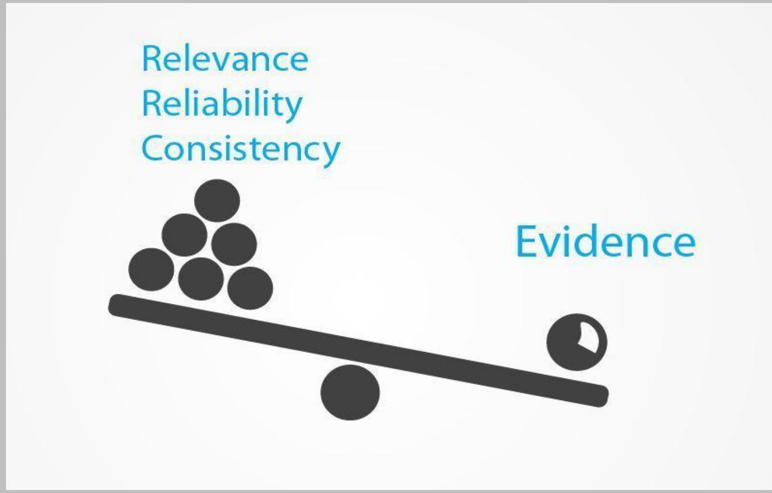


Weight of evidence (WoE) (EFSA Journal 2017;15:4971)

- Weight of evidence is the extent to which evidence supports possible answers to a scientific question
- Reached by weight of evidence assessment, and can be expressed qualitatively or quantitatively
- Organisation of the evidence is generally useful:

  Piece of evidence: Distinct element of information (observation, model, experience)

  Line of evidence: Set of evidence of similar type



Weight of evidence (WoE)-3

A 3-step process:

Overall scientific assessment

Problem formulation

- Define the question(s) for assessment
- Identify which questions require weight of evidence assessment

Weight of evidence assessment

1. Assemble the evidence
2. Weigh the evidence
3. Integrate the evidence

may occur at one or more points in the assessment, where evidence integration is needed

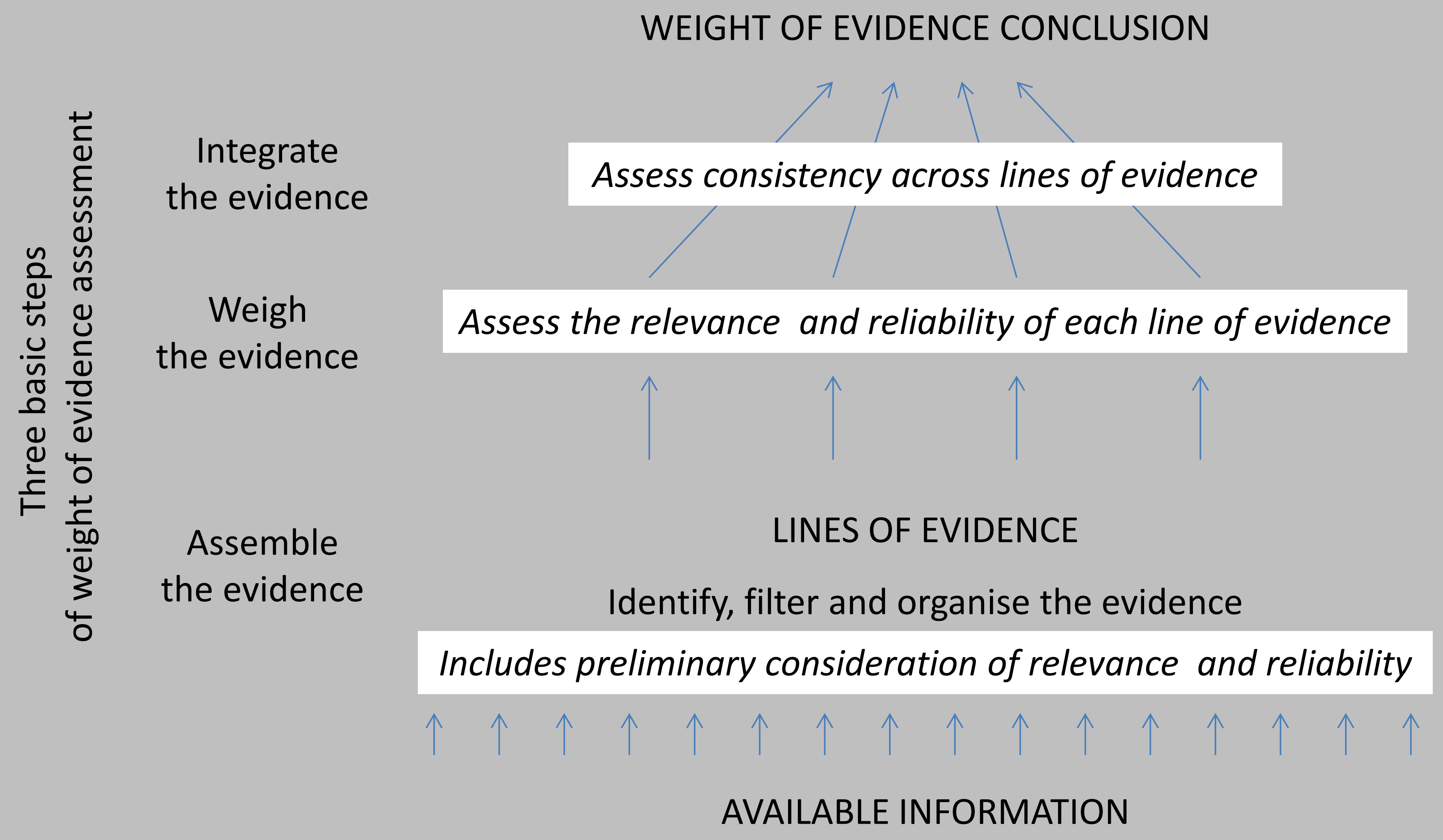
Uncertainty analysis

- Assess and combine uncertainties from all parts of the overall assessment
- Identify data gaps

Conclusion of overall assessment

Weight of evidence (WoE)-4

The approach:



Weight of evidence (WoE)-5

WoE methods:

Examples of WoE approaches

- Listing evidence
- Best professional judgement
- Causal criteria
- Rating
- Quantification

Criteria for choosing WoE methods

- ✓ Availability of guidance
- ✓ Expertise needed
- ✓ Ease of understanding for the non-specialist
- ✓ Time needed
- ✓ Transparency and reproducibility
- ✓ Variability and uncertainty

Weight of evidence (WoE)-6

WoE methods:

- Listing evidence:
  - Presentation of individual lines of evidence without attempt at integration
- Best professional judgement:
  - Qualitative integration of multiple lines of evidence
- Causal criteria:
  - A criteria-based methodology for determining cause and effect relationships
- Rating:
  - assess and integrate based on several factors, often derived from the Bradford-Hill considerations (e.g. Grade, IARC, OSHA)
- Quantification:
  - Various statistcal methods including meta-analysis

WoE Steps - 1

- Assemble the evidence:
  - Identify potentially relevant evidence (consider data gaps)
  - Select the evidence to be included
  - Group into lines of evidence
- Weigh the evidence:
  - Assess reliability, relevance and consistency
  - Decide on method(s) for weighing and integrating the evidence (qualitative, quantitative, several)
  - Apply chosen methods and summarise results in form allowing integration

WoE Steps - 2

- Integrate the evidence:
  - Consider conceptual model for evidence integration (e.g. combining evidence with differing weight)
  - Assess consistency of the evidence (e.g. compatibility of lines of evidence)
  - Apply methods chosen for integration
  - Develop conclusion for WoE assessment (summary of results, the way the conclusion will be expressed, and procedure for expert judgement if applied)
- Uncertainty and influence assessment
- Potential for iterative refinement

Reporting Weight of Evidence

Question		*Insert text of question here*
Assemble evidence	Select evidence	*Briefly summarise the methods used to search, select and extract the evidence (see Note 1).*
	Lines of evidence	*List the line(s) of evidence into which the evidence were assembled for assessment (see Note 2).*
Weigh the evidence	Methods	*Briefly summarise the method(s) used to weigh the lines of evidence (see Note 3).*
	Results	*Give a reference to the section of the assessment where the results of weighing the lines of evidence are presented (see Note 4).*
Integrate the evidence	Methods	*Briefly summarise the methods used to integrate the lines of evidence (see Note 5).*
	Results	*State the conclusions of integrating the evidence for this question (see Note 6).*

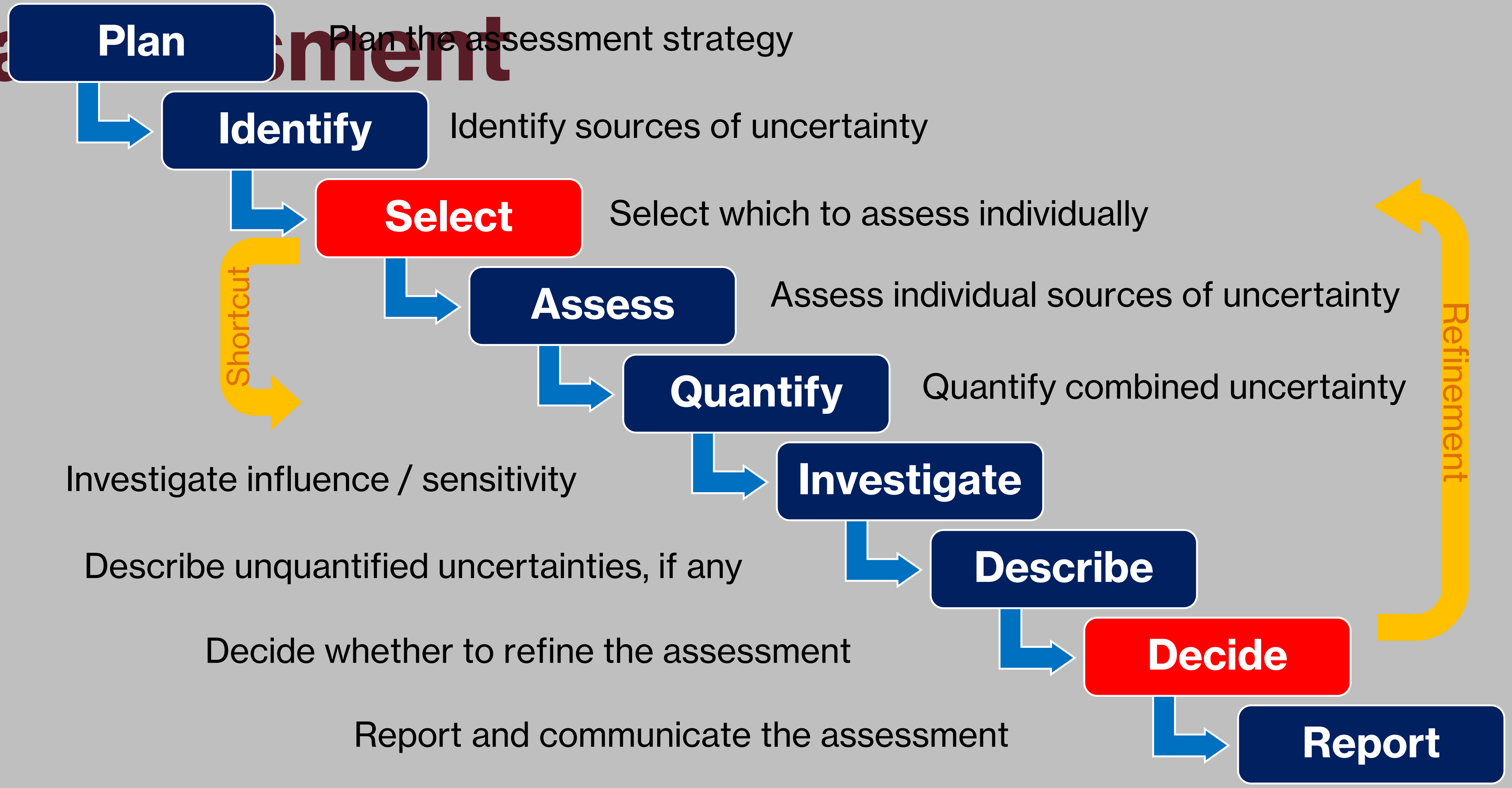
Uncertainty Assessment (EFSA Journal 2018;16:5123)

- Often defined in terms of 'limitations in knowledge'
- EFSA draft Guidance defines uncertainty as:
  - **"A general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question"**
- Available knowledge refers to the evidence, data, etc.
  - available to the assessors
  - at the time the assessment is conducted
  - within the time and resources agreed for the assessment

Uncertainty and variability

* Uncertainty refers to our state of knowledge
* Variability is a property of the real world
* Uncertainty may be altered (either increased or decreased) by further research, but variability cannot
* Some types of variability can be altered by risk management actions (e.g. to change exposures)

Main steps of uncertainty assessment



Toolbox for assessing uncertainty

Flexibility: use what suits your assessment

- **Qualitative** methods include:

  Descriptive, ordinal scales, matrices,
  NUSAP, uncertainty tables

- **Quantitative** methods include:

  Confidence intervals, bootstrap, Bayesian inference, probability bound analysis,
  Monte Carlo simulation,
  approximate calculations, deterministic calculations with conservative assumptions

- **Expert judgement methods include**:

  Semi-formal and formal Expert Knowledge Elicitations

Uncertainty: Role of expert judgement

* **Expert judgement is...**
  * a vital component of all assessments
  * essential and unavoidable for assessing uncertainty
  * not guesswork!
  * careful, reasoned, evidence-based, transparent
  * subjective, and subject to psychological biases
* **Formal methods (e.g. EKE) have been developed to...**
  * mitigate the impact of the psychological biases
  * take account of the available evidence
  * help experts reach well-founded judgements
  * make the process as objective & transparent as possible

Adverse Outcome Pathways (AOP)

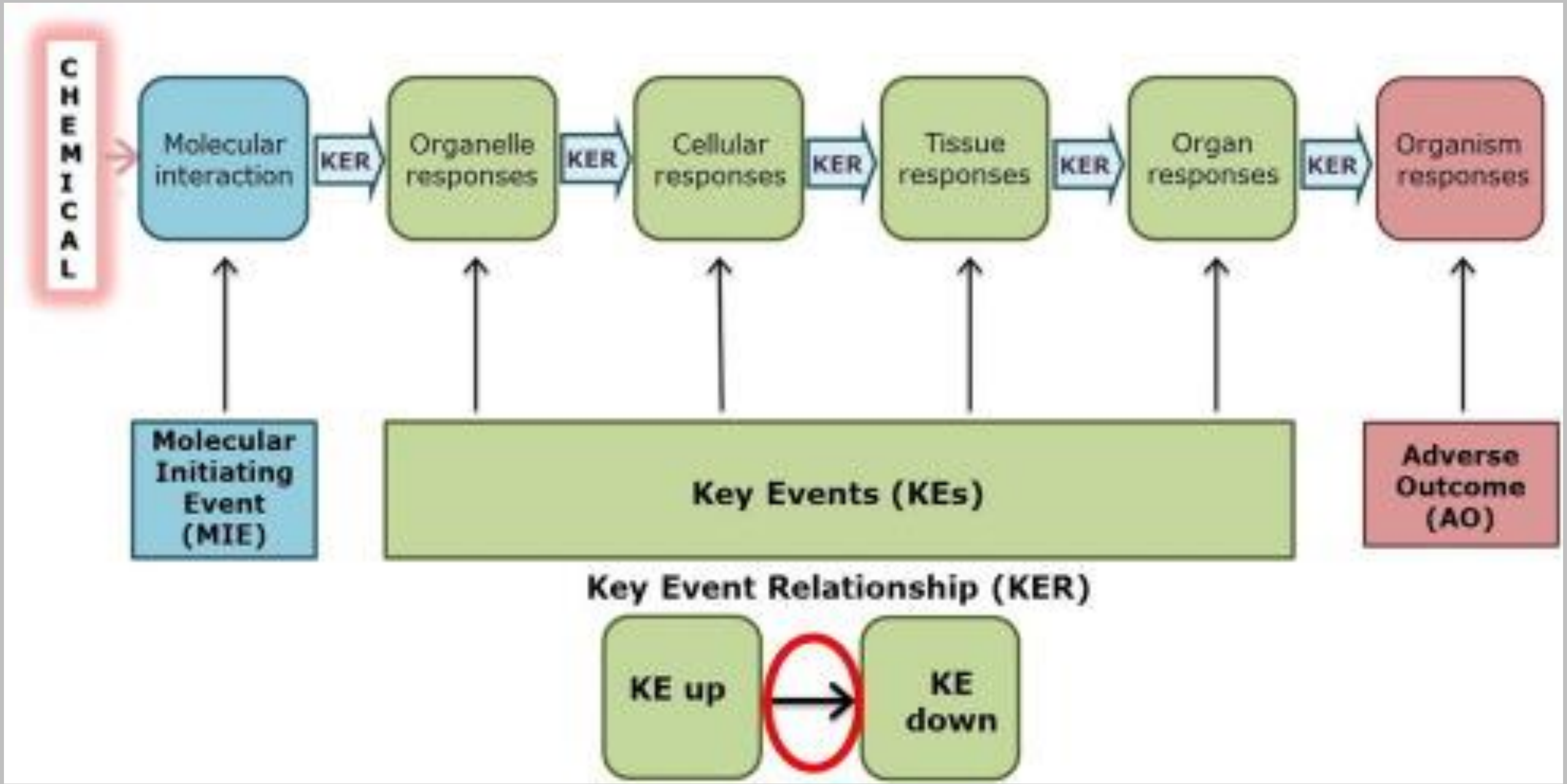
- Systematic application of mechanistic information and biomarkers data leading from exposure to anapical adverse outcome
- A sequence of molecular/cellular events that are causally related leading to an (adverse) health (or environmental) outcome
- Organizes “key events” along a chain of events
- Further development of the IPCS Mode of Action framework

Benefits of AOPs (modified from NTP)

- A model that identifies the sequence of molecular and cellular events required to produce a toxic effect when an organism is exposed to a substance.
- Construction of an AOP can:
  - Organize information about biological interactions and toxicity mechanisms into models that describe how exposure to a substance might cause adverse effects
  - Suggest cell- or biochemical-based tests for pathway elements that could be used to develop testing strategies for targeted toxicity
  - Identify steps in a toxicity mechanism that need improved characterization
- Could provide a conceptual basis for non-animal testing strategies

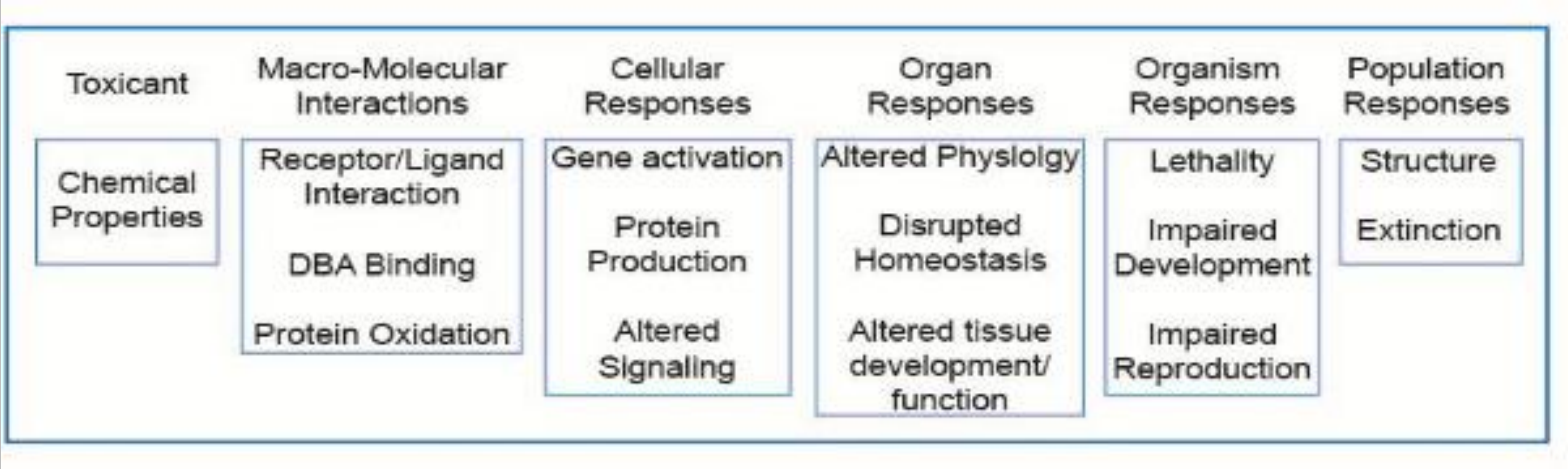
https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-aop/aop.html

AOP: General scheme



AOP: Potential key events

Schematic representation of the AOP illustrated with reference to a number of pathways (OECD 2012)



New Approach Methodologies (NAMs)

* In silico, in vitro, OMICs, cellular, micro-arrays and more complex system data
* Research ongoing to reduce/replace animal testing
* Test batteries developed to cover various enpoints (e.g. neurotoxicity)
* Need to be combined with toxicokinetic/toxicodynamic data
* Together with AOPs and kinetic modelling, would serve as a logical tool for risk assessment

New Approach Methodologies (NAMs)-2

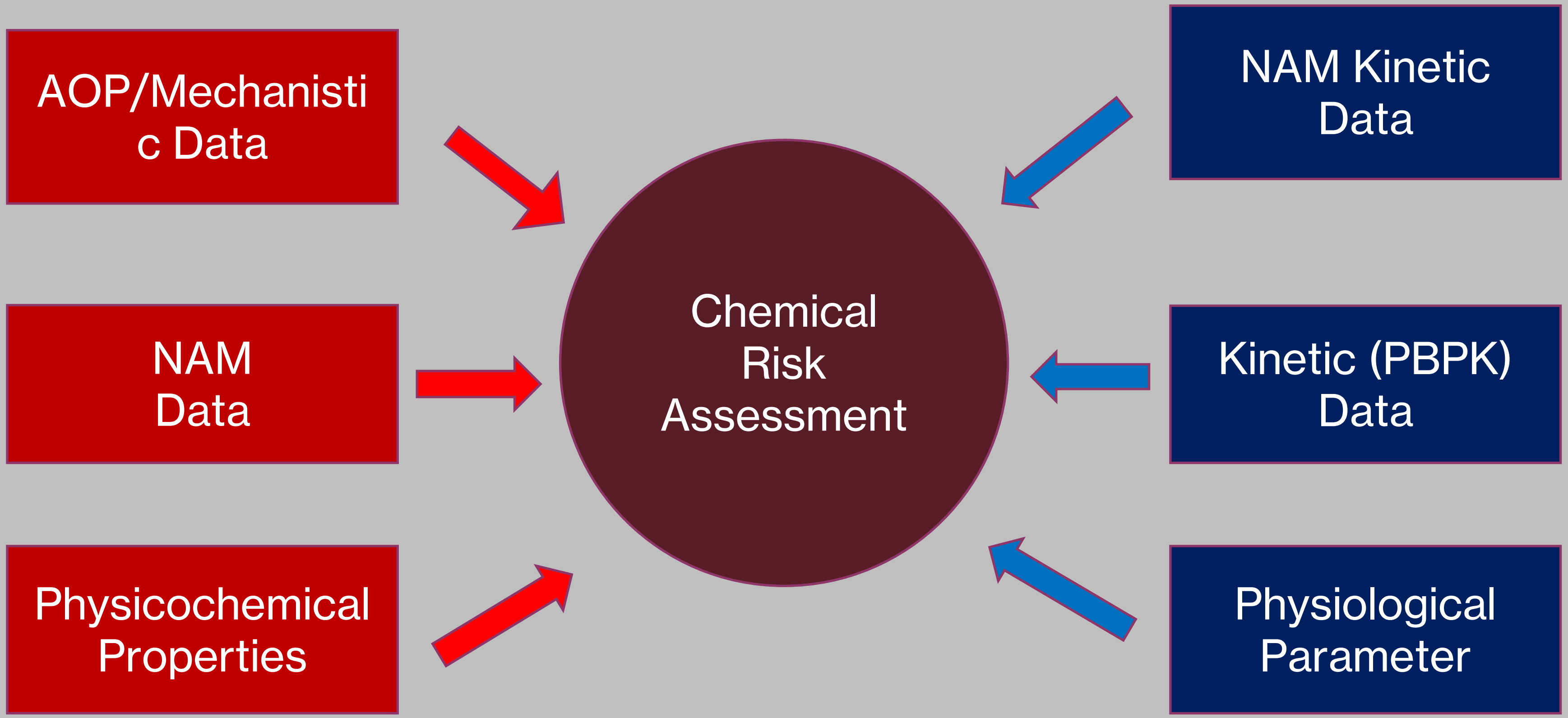
NEEDS:

* Representativeness of complex biological systems
* Reproducibility
* Validation

BUT:

* Future of risk assessment

New Approach Methodologies (NAMs)-3



Outlook

* While the basic principles to chemical risk assessment remain, there are new scientific developments that will accelerate assessments, increase transparency, and provide clear understanding of mechanisms
* Work on biomarkers (in the general and the occupational environment) will enhance the use of novel approaches
* Risk managers will have a clearer picture of risks and uncertainties for the translation of risk assessment results to environmental and occupational standards

Life without chemicals?

“Life is a self-sustained CHEMICAL system capable of undergoing Darwinian evolution”

NASA definition