EFSA risk assessment methodology - Biological Relevance & 3Rs

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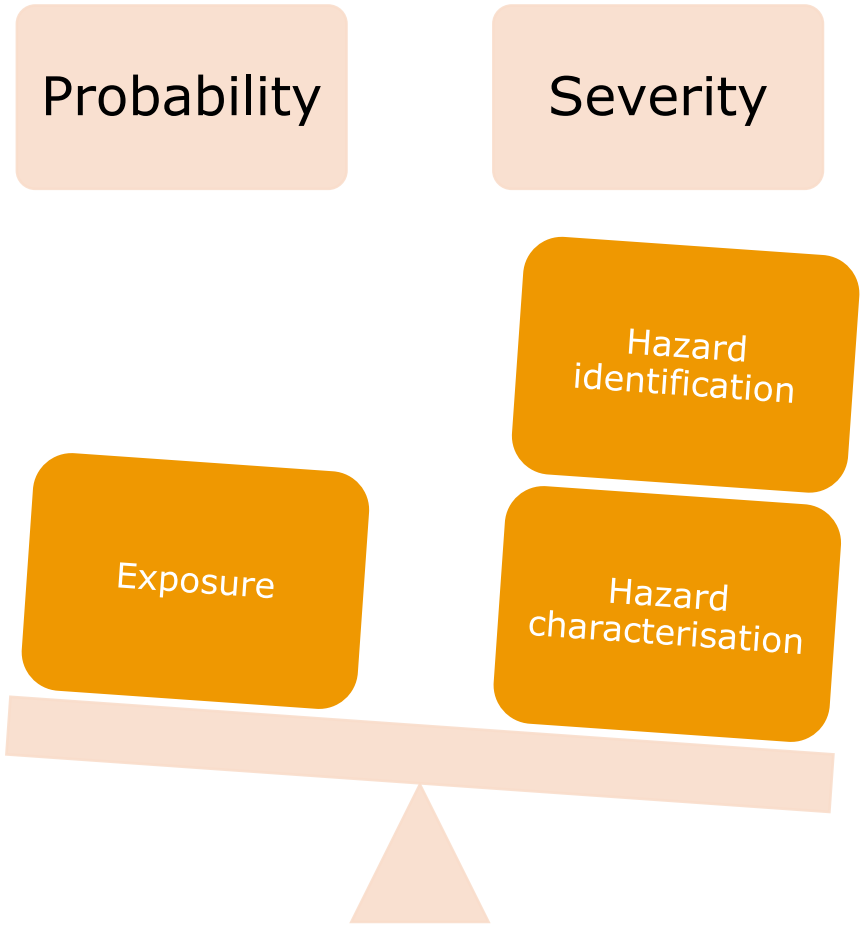
Trusted science for safe food

European Food Safety Authority

Risk

'(Exposure to) the possibility of loss, injury, or other adverse or unwelcome circumstance; a chance or situation involving such a possibility.'

Source: Oxford English Dictionary



Data, data, data

- Exposure data
  - Consumption database
  - Occurrence data

Data, data, data

- Hazard data
  - ADME – absorption, distribution, metabolism and excretion (toxicokinetics)
  - Repeat dose in vivo toxicity studies (sub-chronic & chronic)
  - Gene mutation and chromosome damage studies
  - Carcinogenicity
  - Fertility, pre-natal and post-natal development
  - Special studies
    - Endocrine activity
    - Developmental neurotoxicity
    - Immunotoxicity

Sources of data

- Exposure data
  - EFSA's Comprehensive European Food Consumption Database
  - Occurrence data
- Hazard data
  - Animal bioassay data
  - In vitro data
  - Human data
    - Epidemiological data
    - Clinical trials

Animal bioassay data

- Represent the major source of data relevant to risk assessment of substances in food.
- For regulated substances (intentionally added to food)
  - Type of studies required is specified by legislation (e.g. PPPs, feed additives) or indicated in EFSA Guidance documents (e.g. food additives, food contact materials).
  - For regulatory acceptance, the studies need to be performed
    - According to OECD Test Guidelines
    - Following GLP principles

OECD & animal bioassay test guidelines

- **OECD Guidelines for the Testing of Chemicals**
  - a set of internationally accepted specifications for the testing of chemicals decided on by the **Organisation for Economic Co-operation and Development** (OECD)
  - They were first published in 1981
  - They are split into five sections:
    - ✓ Section 1: Physical Chemical Properties
    - ✓ **Section 2: Effects on Biotic Systems**
    - ✓ Section 3: Environmental Fate and Behaviour
    - ✓ **Section 4: Health Effects**
    - ✓ Section 5: Other Test Guidelines
- Animal welfare concerns are dealt with by ensuring that animal tests are only permitted where necessary
- Guidelines under constant review
  - Periodically updated, new guidelines being adopted or withdrawn

Example: OECD TG 408

OECD/OCDE **408**

Adopted:
25 June 2018

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Repeated dose 90-day oral toxicity study in rodents

Example: OECD TG 408

- 90-day oral toxicity study (sub-chronic oral toxicity)
- Provides information on health hazard likely to arise from exposure to test substance via oral administration over a prolonged period (one dose level daily during 90 days)
- Test Guideline is intended primarily for use with rodents (rat preferably).
- At least 20 animals (10 female and 10 male) should be used for each test group.
- Three concentrations, at least, should be used.

Example: OECD TG 408

- The test compound is administered by gavage or via the diet or drinking water.
- The results of this study include:
  - Measurements (weighing at least once a week, food and water consumption)
  - Daily and detailed observations (ophthalmological examination, haematology, clinical biochemistry and urinalysis)
  - Gross necropsy and histopathology.
  - A number of endocrine-related measurements, particularly relevant to thyroid function have been added in 2018.
- A properly conducted 90-day subchronic test should provide a satisfactory estimation of a no-effect level.

Example: OECD TG 408 – Data & Reporting

- **Individual data** should be provided.
- Numerical results should be evaluated by an appropriate and generally acceptable **statistical method**.
- For quality control it is proposed that control data are compared to **historical control values** originating from the same laboratory, species, strain, and collected under similar conditions.

The Principles of Good Laboratory Practice

- OECD Principles of GLP
  - to ensure the generation of high quality and reliable test data
- Addresses the quality of non-clinical health and environmental safety studies upon which hazard assessments are based
- GLP deals with how studies are:
  - Planned
  - Performed
  - Monitored
  - Recorded
  - Reported and archived

The Principles of Good Laboratory Practice

- Why GLP?
  - To make information traceable
  - To be able to reconstruct the work
  - To be able to verify the results

Why do we need OECD test guidelines & GLP?

- **Mutual Acceptance of Data (MAD)** system
  - To avoid conflicting or duplicative safety data requirements
  - Inefficient regulation would have costly implications for the environment, human health, government budgets and industry
- MAD criteria for non-clinical health and safety test study
  1. The study must have been conducted according to OECD TGs and principles of GLP;
  2. The study must have been conducted in a test facility which has been inspected by a national GLP compliance monitoring programme and;
  3. The national GLP compliance monitoring programme must have undergone a successful evaluation by OECD.

What about studies carried out in research laboratories?

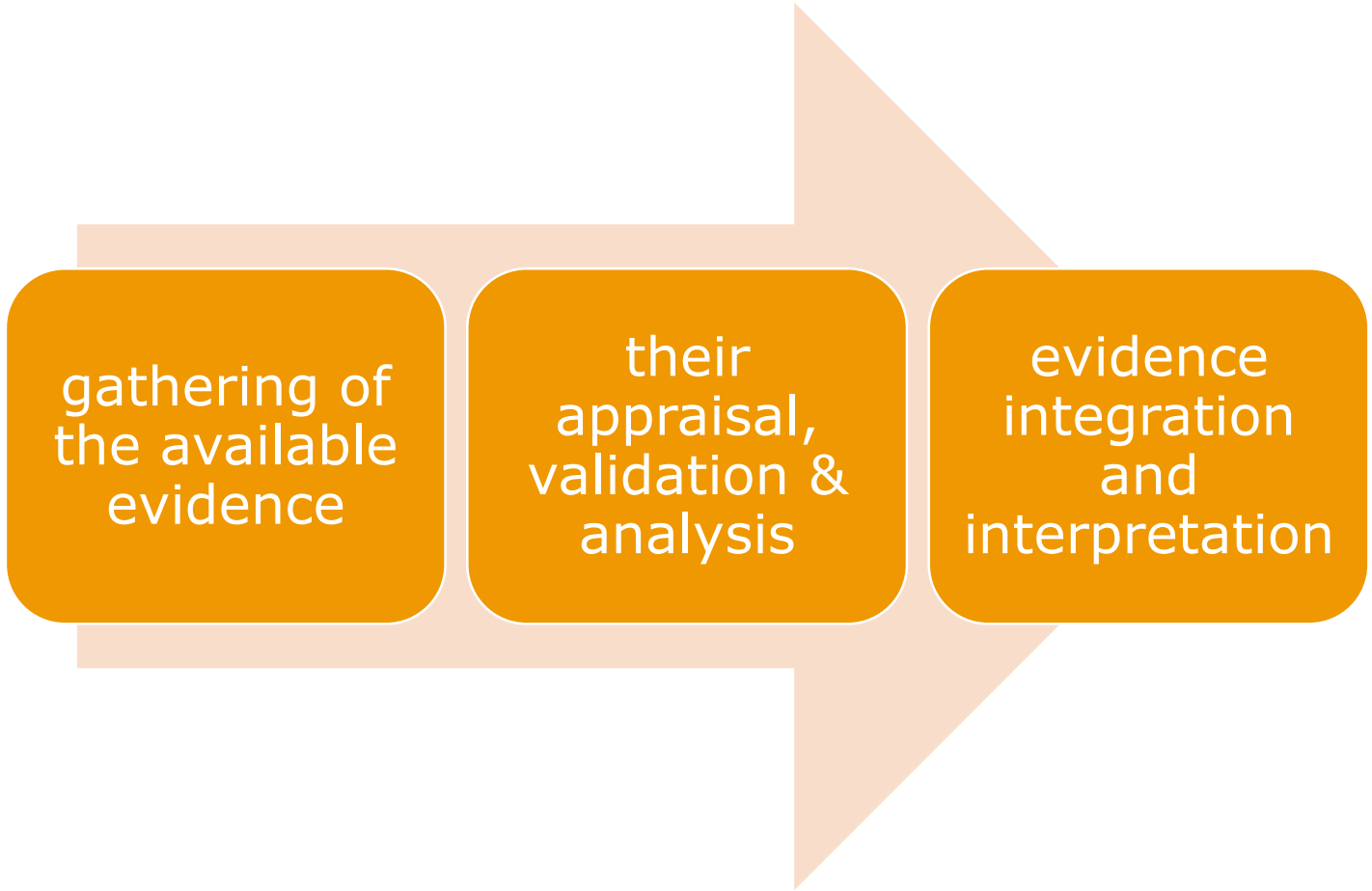
- University laboratories and other research centres are generally not GLP accredited
  - This does **not** diminish the scientific value of the studies produced in these laboratories
  - Some **specialised studies** will not be performed by GLP accredited contract research organisations (CRO)
  - Studies are reported as **scientific papers**
    - Results rather than data
    - The manuscript may or may not have been peer-reviewed

- EFSA has the obligation to evaluate **all available data.**
- The relevance of the data for the risk assessment depends on the **context**.
  - Regulatory studies
  - Confirmatory studies

    versus
  - Hypothesis-generating studies
  - Exploratory studies
- The **use and value** of research publications depends on their purpose and their quality

Data, results and evidence

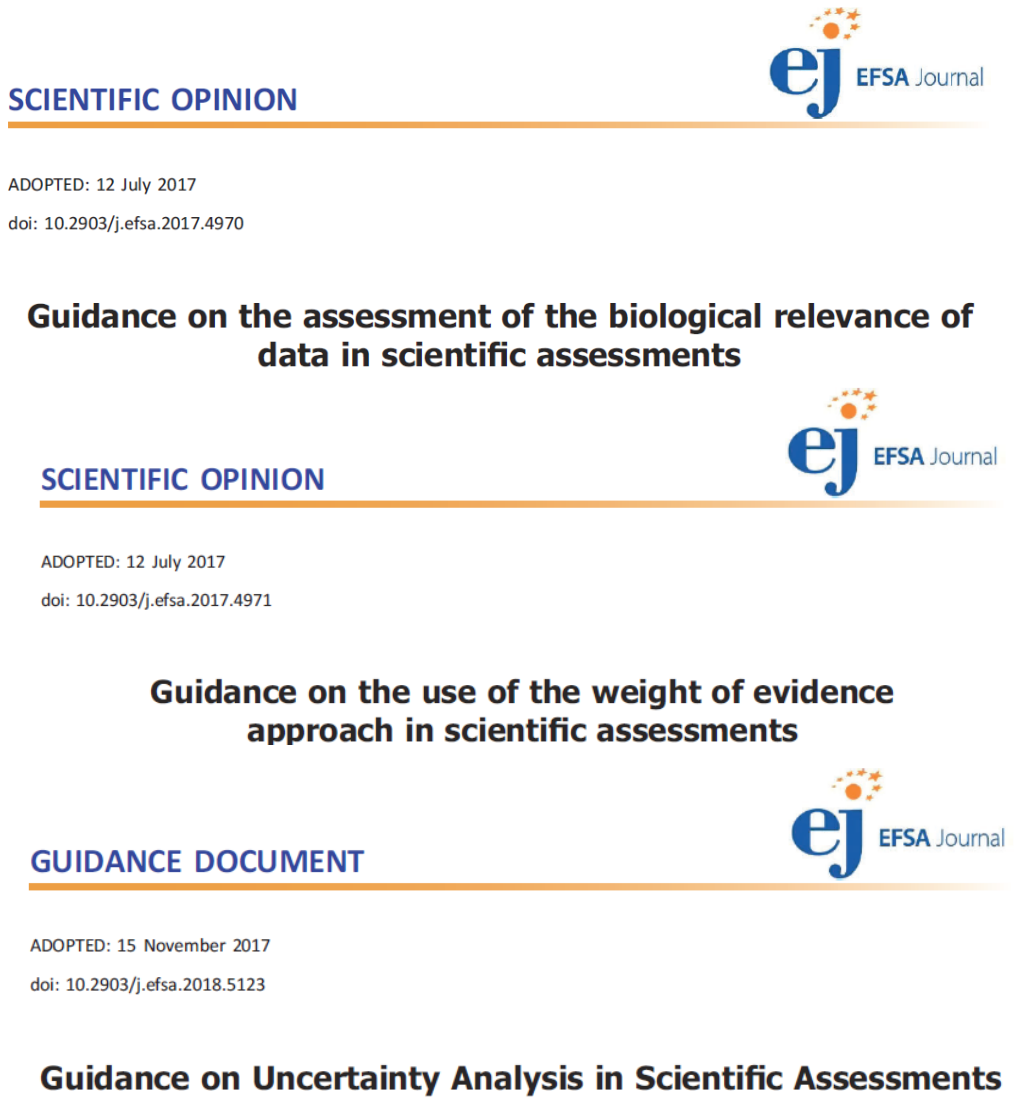
Steps in the risk assessment procedure



These key steps are supported by EFSAs cross-cutting guidance documents

Cross-cutting guidance documents for evidence evaluation

1. Biological relevance
2. Weight of evidence
3. Uncertainty



SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 12 July 2017

doi: 10.2903/j.efsa.2017.4970

Guidance on the assessment of the biological relevance of data in scientific assessments

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 12 July 2017

doi: 10.2903/j.efsa.2017.4971

Guidance on the use of the weight of evidence approach in scientific assessments

GUIDANCE DOCUMENT

EFSA Journal

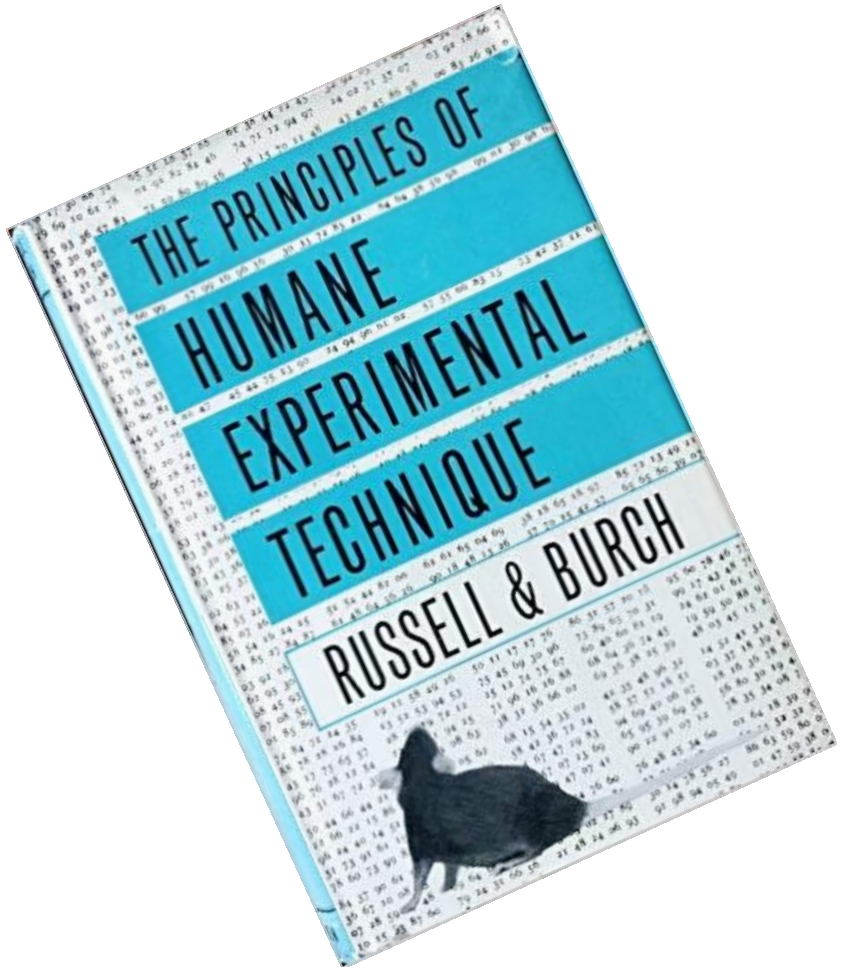
ADOPTED: 15 November 2017

doi: 10.2903/j.efsa.2018.5123

Guidance on Uncertainty Analysis in Scientific Assessments

Future developments in risk assessment

The 3 Rs principles: Replacement, Reduction and Refinement



- The principle of the '3Rs' in the EU legislation in spirit since 1986.
- Directive 2010/63/EU on the protection of animals used for scientific purposes makes the 3Rs a firm legal requirement.

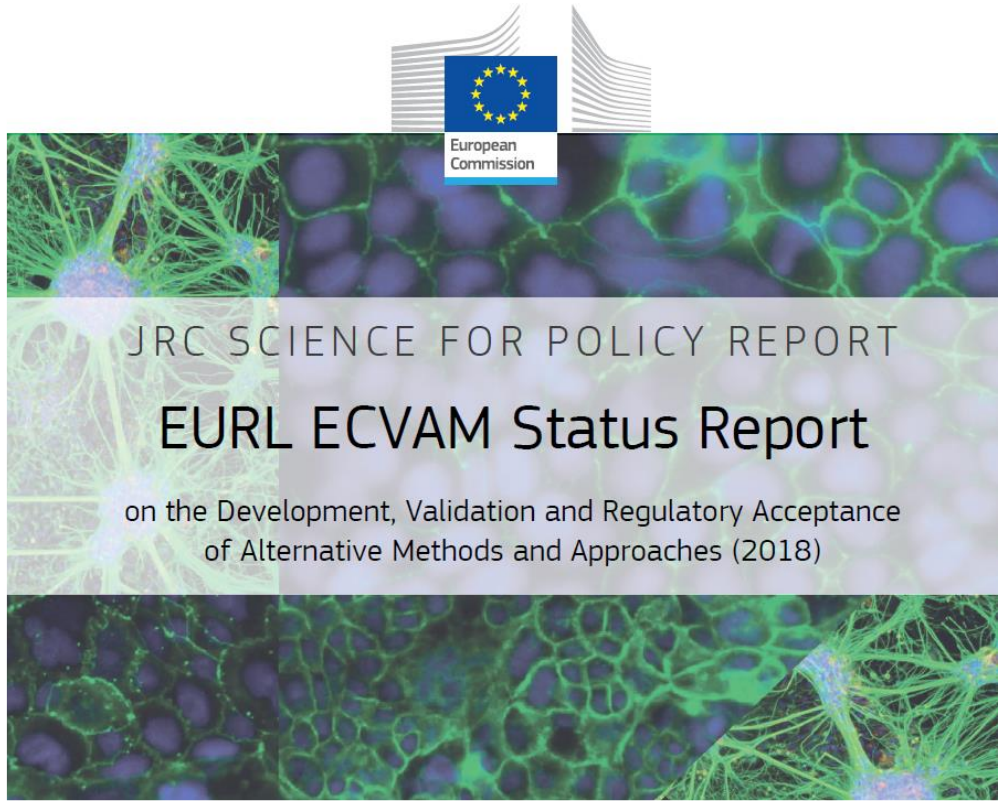
EUROPEAN
COMMISSION

Brussels, 11.3.2013
COM(2013) 135 final

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics

Alternatives to animal testing



- Domains
  - Non-testing approaches
    - In silico (Q)SAR tools
    - Read-across
    - TTC
  - In vitro testing approaches
    - Mutagenicity
    - Chromosomal aberrations
    - Acute toxicity
    - Skin and eye irritation/corrosion
    - Skin sensitisation
    - Mechanistic studies

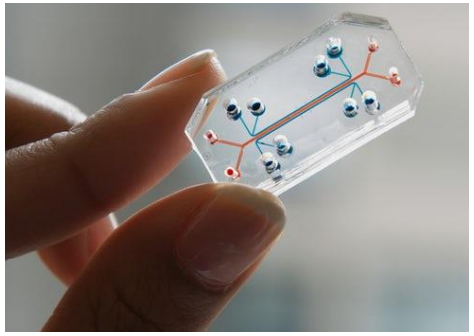
NAMs – New Approach Methodologies

NAMs – New Approach Methodologies

- In silico approaches, in chemico and in vitro assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard assessment.
- They also include a variety of new testing tools, such as ‘high-throughput screening’ and ‘high-content methods’ e.g. genomics, proteomics, metabolomics (ECHA, 2016)

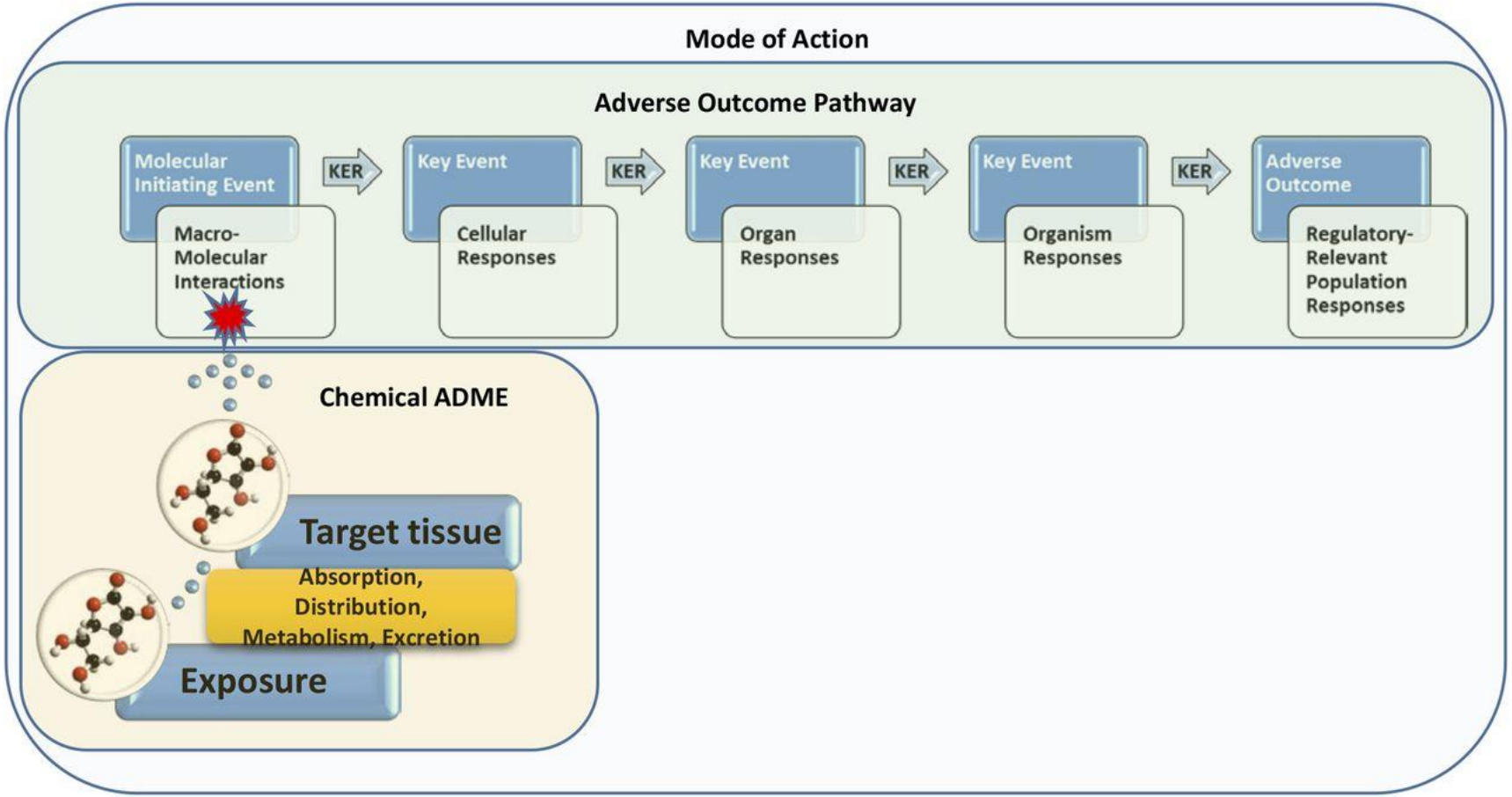
Opportunities

- Human relevant in vitro cell and tissue models
- Complex multi-dimensional and multi-organ systems (e.g. organ on chip)
- Panel of cell models engineered to produce alerts for human pathologies (e.g. cancer) or particular mechanisms of action (e.g. stress responses, endocrine activity)
- High throughput and high content platforms
- Quantitative in vitro to in vivo extrapolation (QIVIVE)



Integrating mechanistic aspects for Risk Assessment

- Adverse Outcome Pathways (AOPs)
- Mode of Action (MoA)



Thank you very much!