3rd June 2019

# Investigating the Causality of Adverse Effects: Mechanistic Toxicology Meets Epidemiology

**Jean Lou Dorne and Marios Georgiadis**

European Food Safety Authority

Trusted science for safe food

efsa
European Food Safety Authority

# EU FOOD SAFETY SYSTEM

efsa
European Food Safety Authority

## SCIENTIFIC ADVICE

efsa
European Food Safety Authority

Member states

## STAKEHOLDERS


## FOOD SAFETY LEGISLATION

Member states

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(SANTE)

European Parliament

European Commission

## RESEARCH

European Commission
(RTD, JRC, AGRI)

Member states

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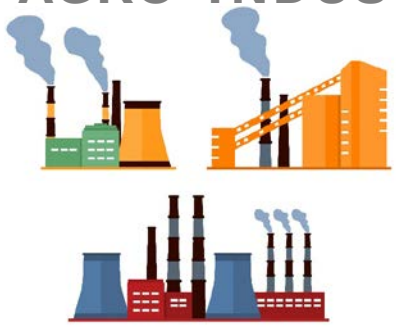
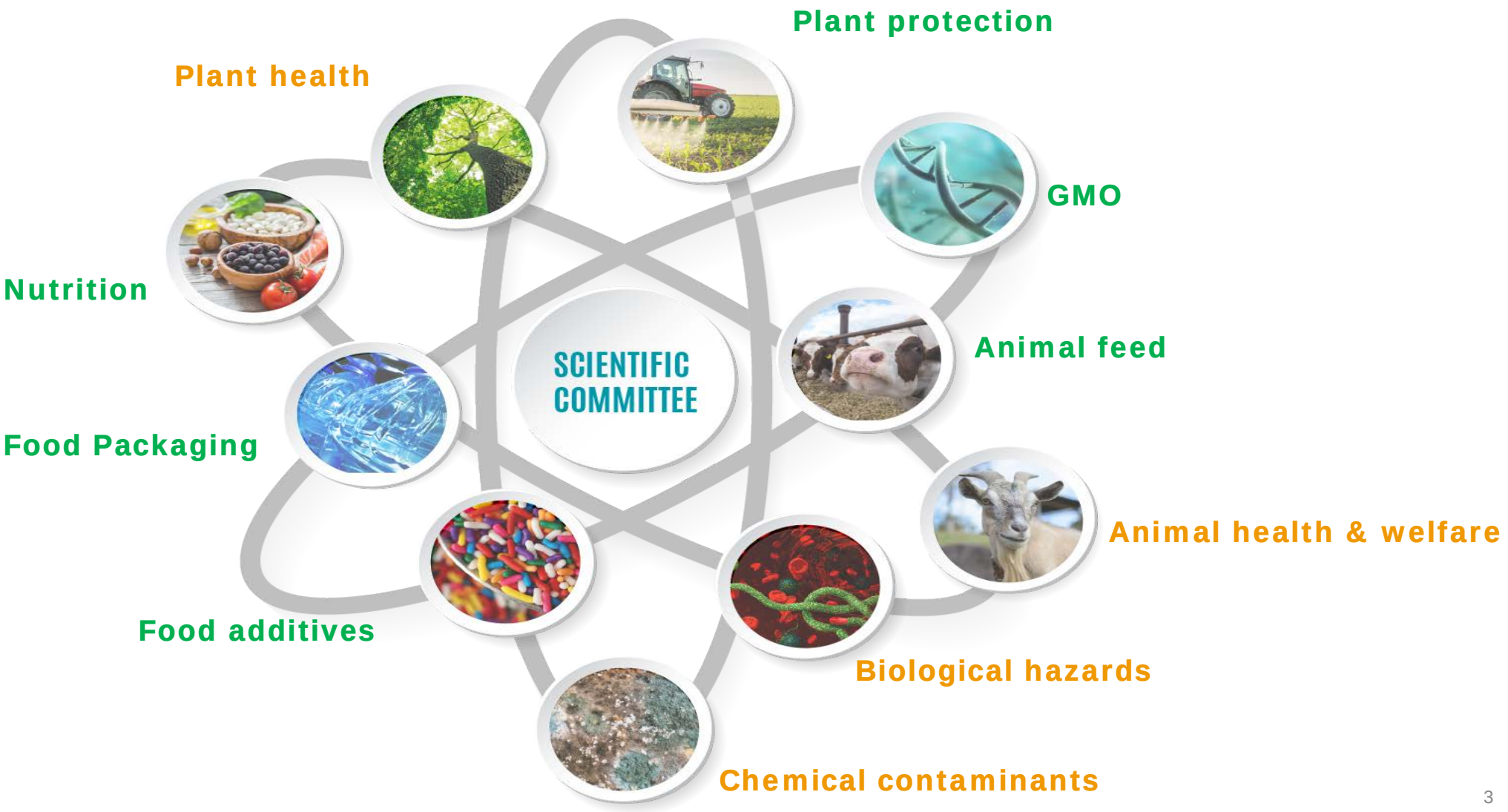


## CONTROL & ENFORCEMENT

Member states

European Commission
(FVO)

# EFSA'S SCOPE OF ACTIVITY



# MANDATE DRIVEN PROCESS

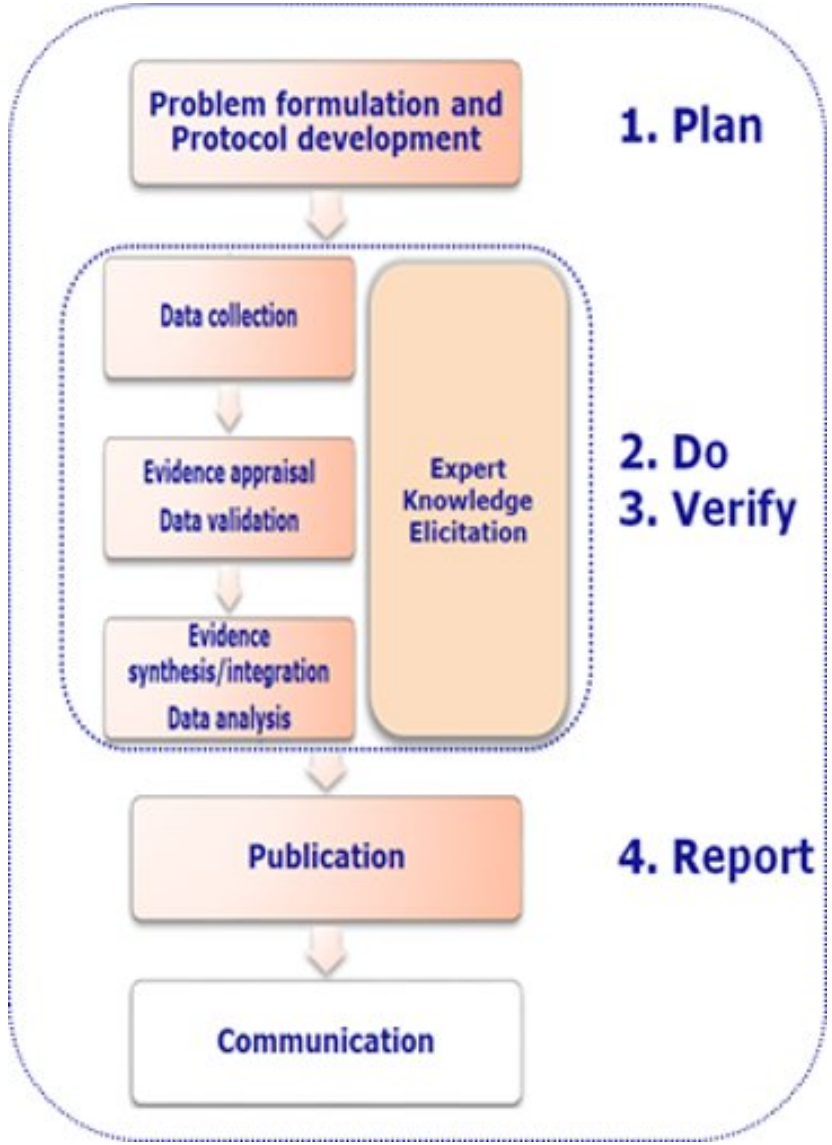
EU Commission

EU Parliament

Member States

EFSA self mandate

EFSA receives a mandate



# STEPS IN CHEMICAL RISK ASSESSMENT

Step 1
**Hazard Identification**

Step 2
**Hazard Characterisation**

Step 3
**Exposure Assessment**

Step 4
**Risk Characterisation**

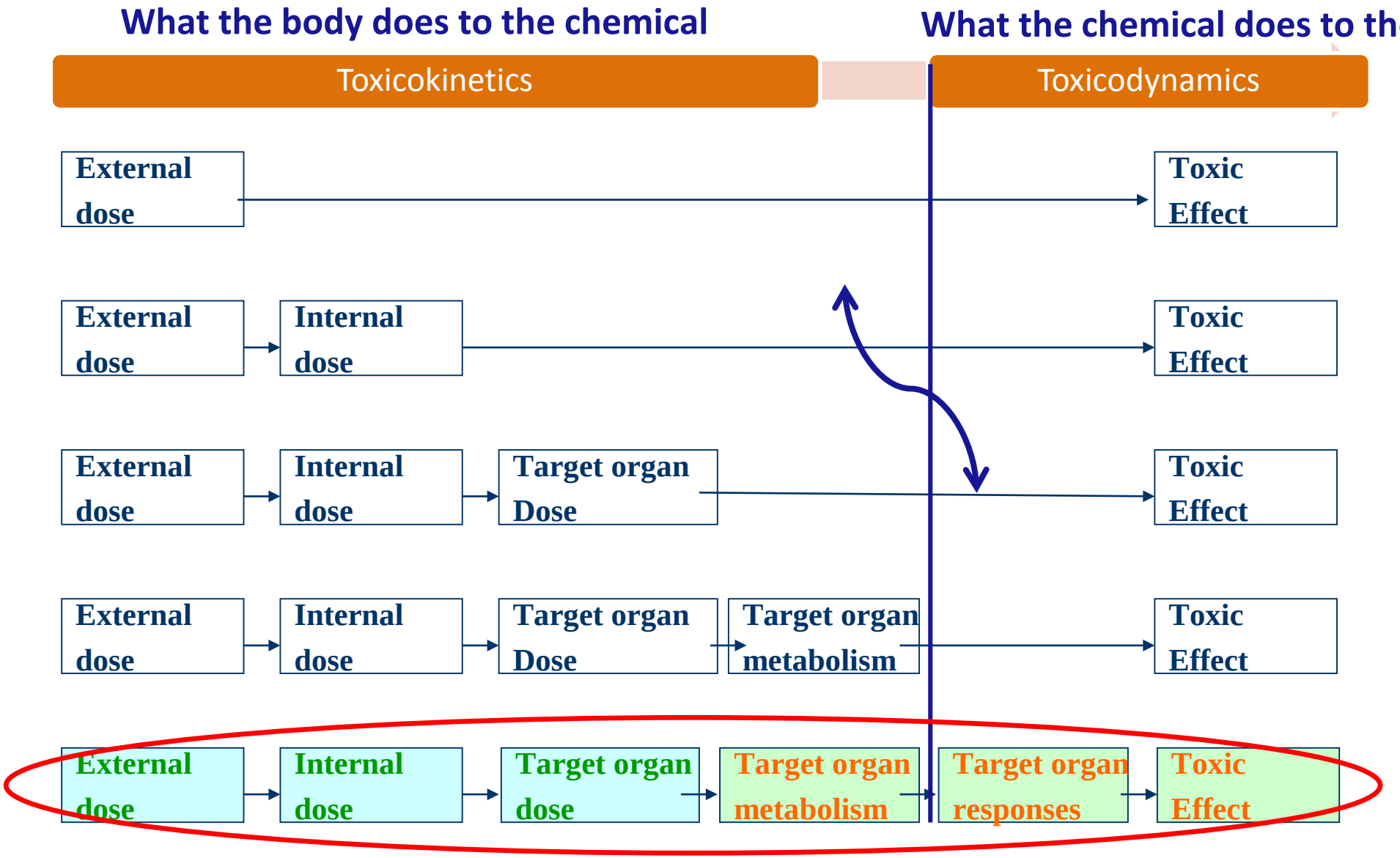
**Identify toxic effects**

**Quantify toxic effects:**
- Dose response
- Reference Point
- Reference value

**Occurrence**
**x Consumption**

**Hazard vs Exposure: Risk**

# Connecting Exposure, Dosimetry and Effects



# EFSA Weight of Evidence Framework I

EFSA Journal

EDITORIAL

APPROVED: 26 March 2015

PUBLISHED: 27 March 2015

doi:10.2903/j.efsa.2015.e13031

## Increasing robustness, transparency and openness of scientific assessments

Hardy A, Dorne JLCM, Aiassa E, Alexander J, Bottex B, Chaudhry Q, Germini A, Nørrung B, Schlatter J, Verloo D, Robinson T

EFSA Journal

SPECIAL ISSUE

doi: 10.2903/j.efsa.2016.s0511

## Weighing evidence and assessing uncertainties

Jean Lou C. M. Dorne[1], Bernard Bottex[1], Caroline Merten[1], Andrea Germini[1], Nikolaos Georgiadis[1], Elisa Aiassa[1], Laura Martino[1], Lorenz Rhomberg[2], Harvey J. Clewell[3], Matthias Greiner[4], Glenn W. Suter[5], Maurice Whelan[6], Andrew D. M. Hart[7], Derek Knight[8], Prabhat Agarwal[9], Maged Younes[10], Jan Alexander[11] and Anthony R. Hardy[1]

**Abstract**

Methodologies for integrating (weighing) evidence and assessing uncertainties are of utmost importance to ensure that scientific assessments are transparent, robust and fit for purpose to support decision-makers. One of the key challenges remains the development of harmonised methodologies for both weighing scientific evidence and assessing uncertainties in the food safety area mainly because of the multidisciplinary and complex nature of the topics involved. The breakout session 'Weighing evidence and assessing uncertainties' was held at the EFSA 2nd Scientific Conference 'Shaping the Future of Food Safety, Together'. This paper aims at summarising the contributions of this breakout session and formulates recommendations to further support the development of harmonised methodologies and practical applications for weighing evidence and analysing uncertainty in key areas of food safety, including chemical risk assessment, microbiological risk assessment and environmental risk assessment.



EFSA Journal

SCIENTIFIC OPINION

ADOPTED: 12 July 2017

doi: 10.2903/j.efsa.2017.4971

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

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Emilio Benfenati, Qasim Mohammad Chaudhry, Peter Craig, Geoff Frampton, Matthias Greiner, Andrew Hart, Christer Hogstrand, Claude Lambre, Robert Luttik, David Makowski, Alfonso Siani, Helene Wahlstroem, Jaime Aguilera, Jean-Lou Dorne, Antonio Fernandez Dumont, Michaela Hempen, Silvia Valtueña Martínez, Laura Martino, Camilla Smeraldi, Andrea Terron, Nikolaos Georgiadis and Maged Younes

**Abstract**

# EFSA Weight of Evidence Framework II

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**

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Emilio Benfenati, Qasim Mohammad Chaudhry, Peter Craig, Geoff Frampton, Matthias Greiner, Andrew Hart, Christer Hogstrand, Claude Lambre, Robert Luttik, David Makowski, Alfonso Siani, Helene Wahlstroem, Jaime Aguilera, Jean-Lou Dorne, Antonio Fernandez Dumont, Michaela Hempen, Silvia Valtueña Martínez, Laura Martino, Camilla Smeraldi, Andrea Terron, Nikolaos Georgiadis and Maged Younes

**Abstract**

The toolbox to combine evidence:
-Assemble
-Weigh
-Integrate

## WoE assessment as 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**

# Reporting a Weight of Evidence Analysis

| | | |
|---|---|---|
| **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).* |

**Range of methods from qualitative to quantitative methods depending on problem formulation, data available, time and resources**

# Epidemiology and Toxicology: Contributions to causality assessment

- Causation of an adverse outcome is multifactorial
- Association between exposure and adverse outcome does not automatically imply causation
- Investigation of causality requires assessment of information from many different sources and lines of evidence
- '*The Environment and Disease: Association or Causation?*', A.B. Hill, 1965, *Proceedings of the Royal Society of Medicine* 58:295-300.
- A.B. Hill's criteria including subsequent modifications from WHO/IPCS[1] and others applied to Mode Of Action/AOP can assist in transparent WoE analysis.

[1]M. E. Meek, A. Boobis, I. Cote, V. Dellarco, G. Fotakis, S. Munn, J. Seed and C. Vickers (2014) New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol.34(1):1-18

# Epidemiology and Toxicology: Contributions to causality assessment

- For environmental contaminants, epidemiological and toxicological studies can both provide different lines of evidence to evaluate Hill's criteria.

- Examples include :

-Strength of association between exposure and adverse outcome in human populations can be assessed using information from epidemiological studies.

- Biological plausibility can be assessed using information from mechanistic toxicology

- Risk factors add complexity to causality assessment (e.g. age, genetic polymorphisms)

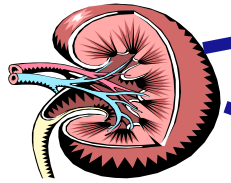
- Evidence from both types of epi/tox studies should be subjected to rigorous appraisal

- All evidence should be considered in the framework of a weight of evidence approach

# Cadmium : Mechanistic TOX Meets Epidemiology


Exposure (External dose)

**Accumulates Over years**



Kidney

Internal dose biomarker

**Urinary Cadmium** Reflects this accumulation

Effect biomarker

Kidney damages: **β2-microglobulin**

**EFSA (2009) Risk Assessment cadmium in food**

**-Internal Dose Biomarker:**

Physiologically-based toxicokinetic model (One –compartment model)

-Population variability in human absorption rates and half life of cadmium

**-Effect Biomarker:**

Meta-analysis and Benchmark dose modelling of Human data (group averages) using urinary levels/β2-microglobulin excretion for nephrotoxicity.

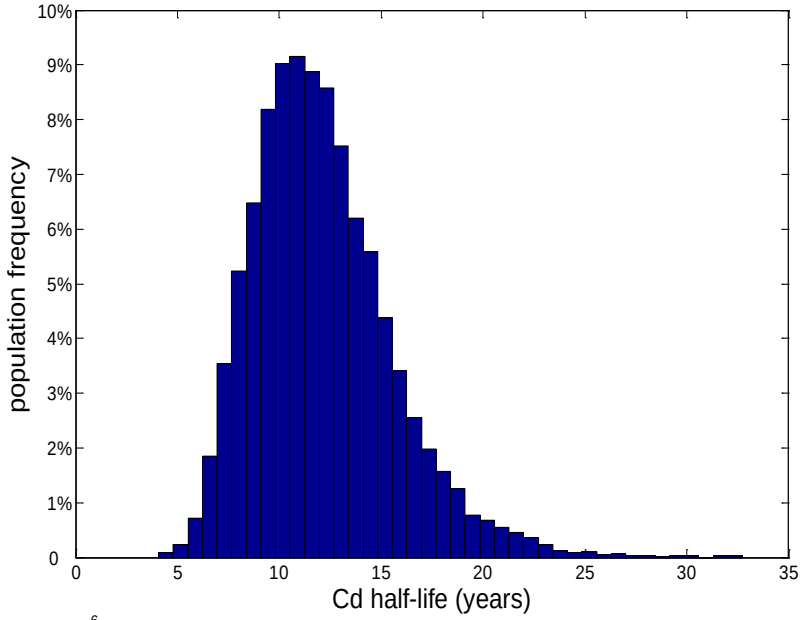
# Cadmium : Mechanistic TOX Meets Epidemiology II

-Population variability and uncertainty in Toxicokinetics And Toxicodynamics of cadmium.

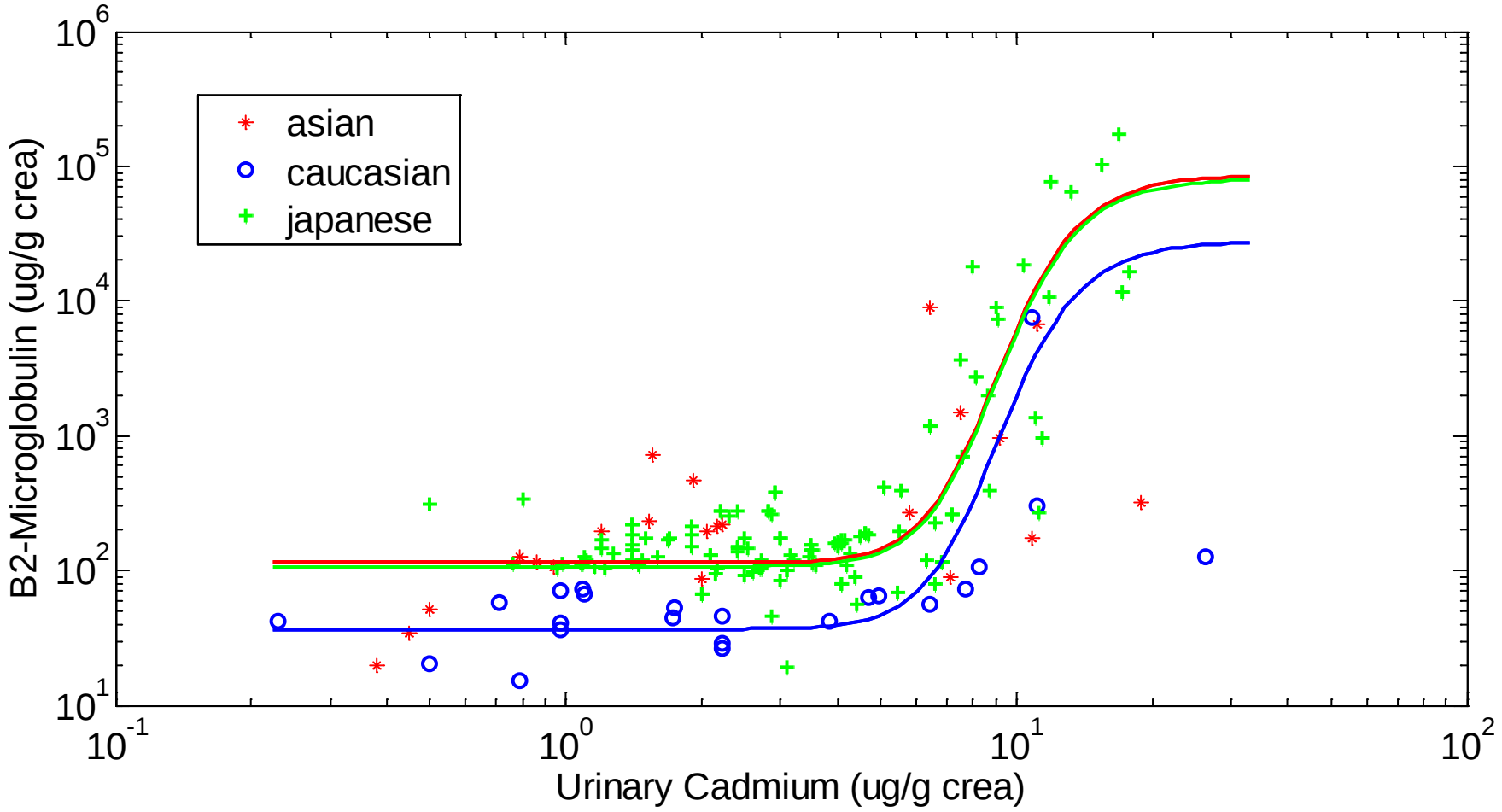
-Data from a population of non smoking swedish wormen (58-70 years old) provided TK variability (distribution of half life).

- BMDL modelling between $\beta_2$Microglobulin biomarker excretion and urinary cadmium provided TD variability.

-Linking internal dose (TK model) and effect biomarker (BMD model) allowed to derive a Tolerable weekly Intake for Cadmium of 2.5 µg/ kg b.w.



# Risk Factors: Cadmium Model Fit with Adjustment for Ethnicity



# Arsenic: Epidemiology meets Mechanistic Toxicology

## Animal Toxicokinetics and Metabolism differ from humans

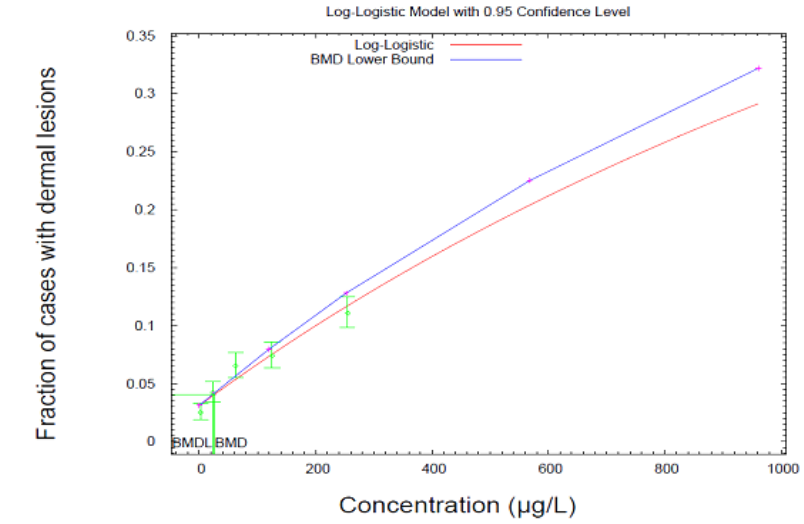
## Toxicity studies in animals not suitable for risk characterisation

**Use Epidemiological data**

**Skin lesions**

**Cancer (bladder, lung, skin)**

**Developmental, Neurotoxicity**
**Cardiovascular, diabetes**

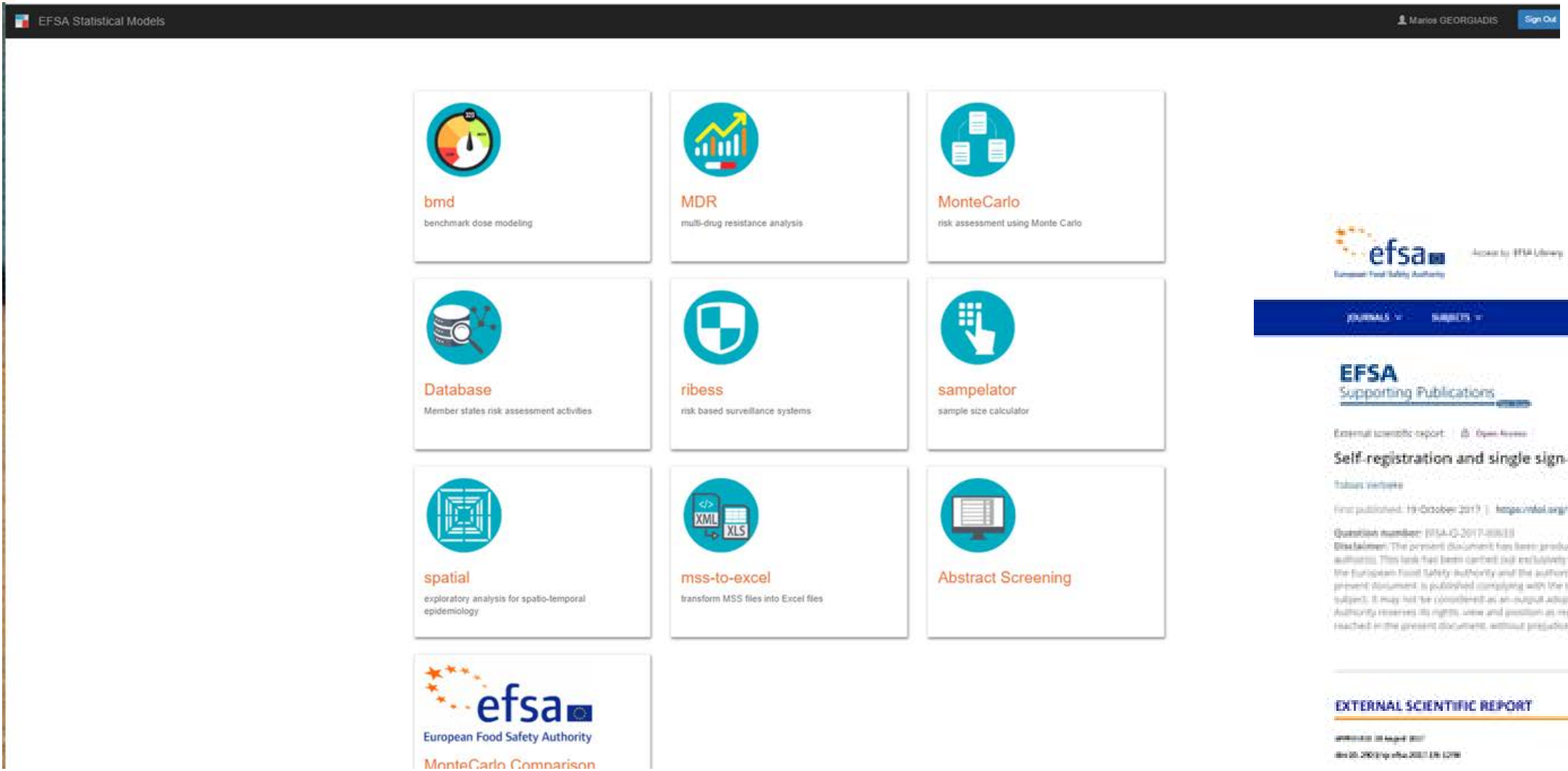



# Arsenic: Summary of Endpoints for Hazard Characterisation

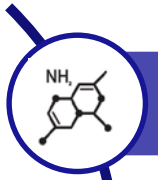
## Summary of Endpoints

| Endpoint | Population | Reference point µg/L water | Reference point µg/kg b.w. per day |
|---|---|---|---|
| Dermal lesions | Bangladesh (Ahsan et al., 2006) | $BMCL_{01}$: 23[(a)] | $BMDL_{01}$: 2.2-5.7[(b)] |
| Dermal lesions | Bangladesh (Rahman et al., 2006a) | $BMCL_{01}$: 5[(a)] | $BMDL_{01}$: 1.2-4.1[(b)] |
| Dermal lesions | Mongolia (Xia et al., 2009) | $BMCL_{01}$: 0.3[(a)] | $BMDL_{01}$: 0.93-3.7[(b)] |
| Lung cancer | Chile (Ferreccio et al., 2000) | $BMCL_{01}$: 14 (NRC, 2001) | $BMDL_{01}$: 0.34-0.69[(c)] |
| Bladder cancer | North East Taiwan (Chiou et al., 2001) | $BMCL_{01}$: 42 (NRC, 2001) | $BMDL_{01}$: 3.2-7.5[(b)] |
| Skin cancer | USA (New Hampshire) (Karagas et al., 2002) | Change point[(d)]: 1-2 | Change point: 0.16-0.31[(c)] |
| Bladder cancer | USA (New Hampshire) (Karagas et al., 2004) | Change point: *ca.* 50 | Change point: 0.9-1.7[(c)] |

# Open Source Data, Models and Tools: R4EU platform




# OpenSource Tools : OpenFoodTox 2.0




**Chemical Information**

**Exposure**

**Structure**

**Physico-chemical properties**

**Summary Exposure**

**EFSA Outputs**

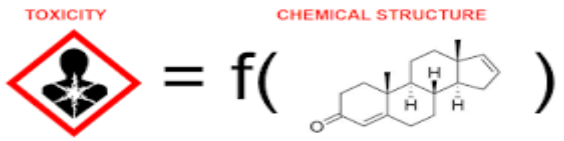
**Hazard Information**

**Genotoxicity**

**TK *vitro vivo human animals***

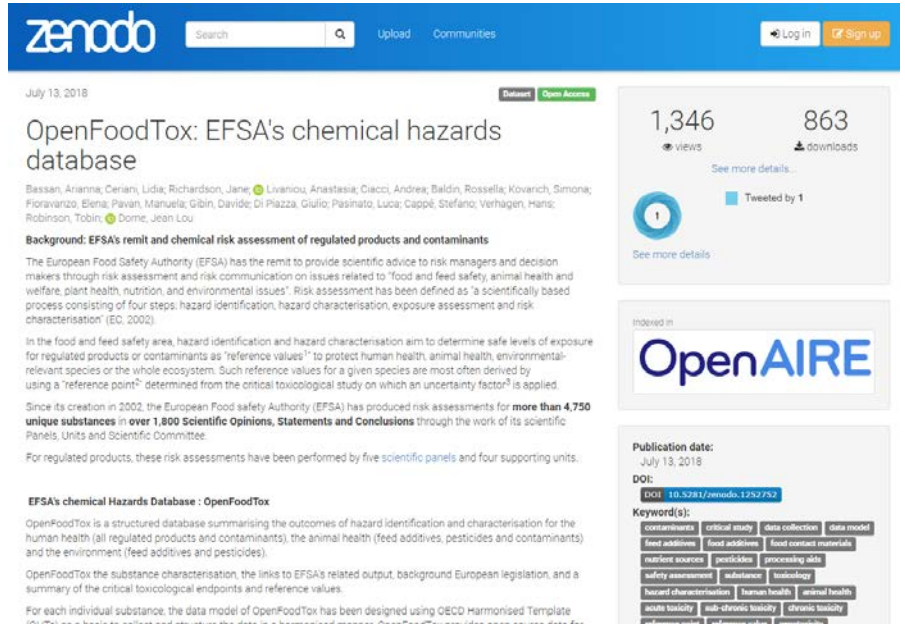
**Toxicodynamics *vitro vivo Epi***

**Modelling Platform**



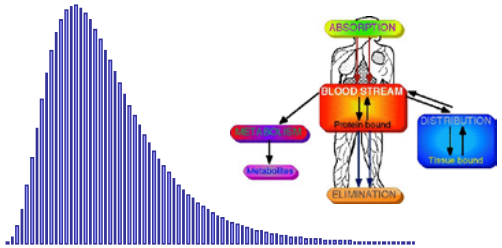

## How to get the data ?

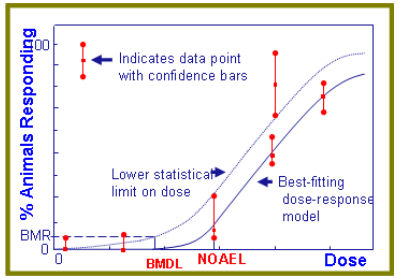
https://doi.org/10.5281/zenodo.780543



# QIVIVE MODELLING

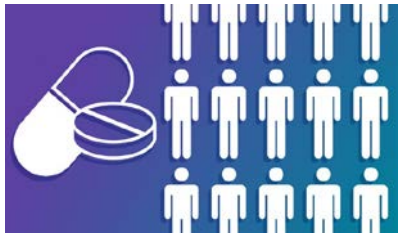
- **Quantitative in vitro in vivo extrapolation at the individual level to quantify effects in populations.**




TK

TD



***TK Variability Distributions***

*Phase I, Phase II enzymes*

*Transporters*

*Renal Excretion*

***TD Variability Distributions***

*Meta-analysis TD/PD studies*

*(Human data, in vitro, in vivo)*

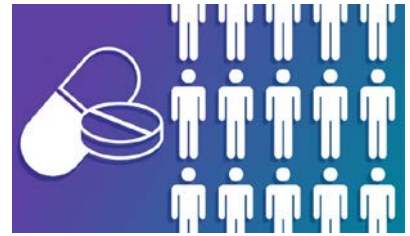
*PD endpoints,* in vivo in vitro *molecular markers of effect, intoxication, OMICs etc…*

Exposure → Dosimetry → Reference Point → Risk

# CONCLUSIONS

- **Progress** in **mechanistic toxicology** within **MoA and AOP frameworks** supports integration of **epidemiological** data using WoE for environmental contaminants
- **Guidance Document** under development on **appraising and integrating** evidence from **epidemiological studies** in EFSA's scientific assessments

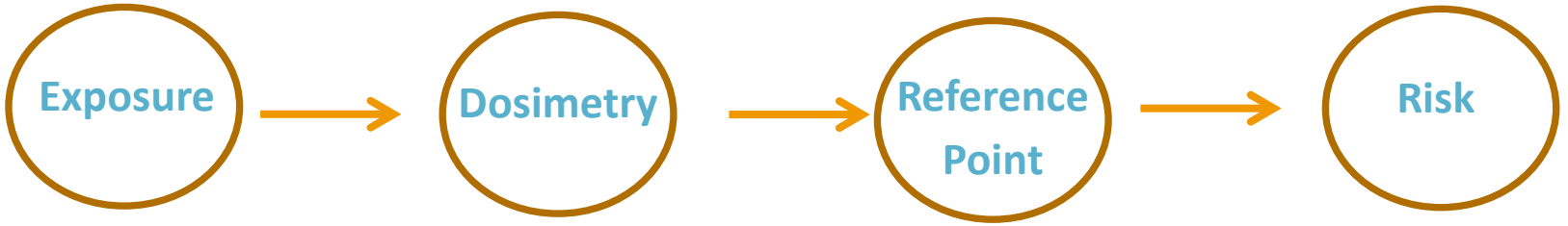
- **QIVIVE models** have the potential to integrate ***in vitro***, ***in vivo*** and **epidemiological** evidence from the **individual** level to **population** level



- **Integrating inter-individual differences** is a **challenge** from a mechanistic and epidemiological perspective i.e. risk factors. Subgroups of the populations e.g. **polymorphisms** in **key enzymes** and **target receptors**

- Future of **Open source databases and tools** to provide data on hazard incl. MoA and AOPs, exposure, epidemiological information to **further refine understanding causality** and the **likelihood of adverse effects**.

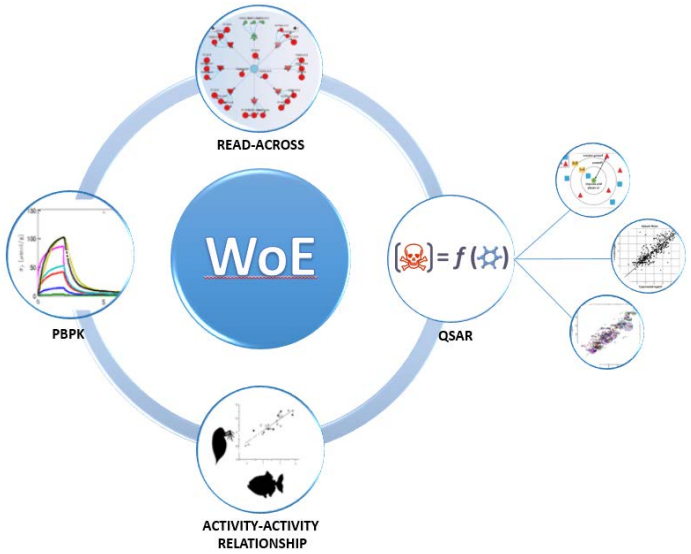
# Open Source databases and Tools : State of the Art Methods and Data Streams



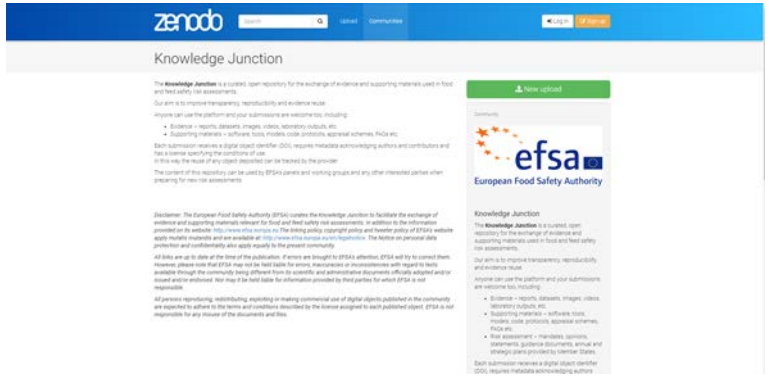

*OpenFoodTox*

*Structured data*

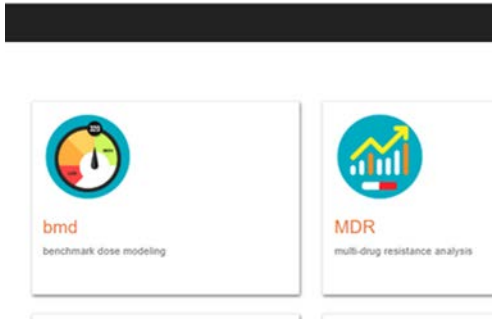
*Epidemiologic al Data*

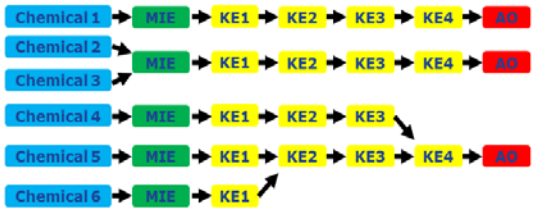



## Open Data and Models: EFSA Knowledge junction

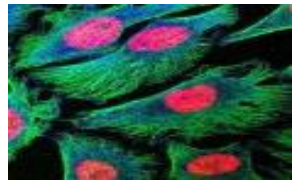



**R4EU**

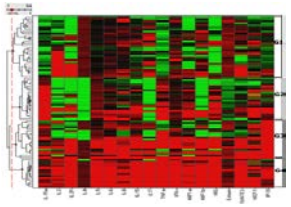


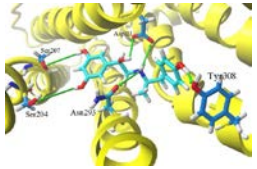

*AOP/MoA*



*In vitro*



*OMICs*



*In Silico*

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