Risk Assessment of multiple chemicals

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MIXTURE = any combination of two or more chemicals that may jointly contribute to real or potential effects, regardless of source and spatial or temporal proximity

REGULATED MIXTURES

- Plant Protection Products
- (Food Additives)
- Nutraceuticals
- Biocide Products
- Drugs
- Cosmetics
- Detergents

CLP – Regulation 1272/2008
Hazard Assessment - Classification of mixtures

BASED ON CALCULATION

- Acute Toxicity
- Skin irritation
- Eye irritation
- Environmental Acute Toxicity
- Environmental Chronic Toxicity

CONCENTRATION THRESHOLD

- Skin/Respiratory sensitisation
- Mutagenicity
- Carcinogenicity
- STOT SE / STOT RE
- Reproductive Toxicity

$$\frac{100}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i}$$

where:

C_i	=	*concentration of ingredient i (% w/w or % v/v)*
i	=	*the individual ingredient from 1 to n*
n	=	*the number of ingredients*
ATE_i	=	*Acute Toxicity Estimate of ingredient i.*

Acute Toxicity

1. Test on the mixture itself
2. Test on similar tested mixtures
3. Classification of ingredient substances and their concentrations in the mixture.

Challenges for testing of chemical mixtures

- Very little information exist for toxicity of mixtures
- Chemicals in mixtures may affect each others uptake, metabolism, excretion and toxicodynamics either leading to additive, synergistic or antagonistic effects
- Low exposure may lead to high body concentration if substance accumulates
- For single chemicals Mechanism of Action (MoA) is often missing
- Animal tests practically possible in rare cases because of costs (high number of tests would be needed), material need, biological relevance, ethics
- Mixtures are never tested *in vivo* at the moment
- NAMs (New Approach Methodologies) are relevant opportunity

Potential use of NAMs to support the hazard and risk assessment of chemical mixtures

***In vitro* methods**

- predict the hazard of individual compounds and their combinations
- assess many compounds in a fast and cost-efficient manner, without testing on animals
- test whole mixtures and support effect-based monitoring
- investigate MoA and for MoA based grouping
- evaluate the Concentration Additivity assumption at low doses

***Omics* (transcriptomics, proteomics, metabolomics)**

- investigate affected pathways for unraveling MoAs
- investigate possible interactions (antagonisms or synergisms)

QSAR (Quantitative Structure Activity Relationship)

- predict (missing) information on individual compounds (physico-chemical properties, toxicological effects)
- predict the combined effects and interactions of chemicals in a mixture
- support the grouping of chemicals and assess whether they will act in a similar or dissimilar way

TTC (Threshold of Toxicological Concern) or ecoTTC

- establish conservative values (safe exposure levels) for use in the absence of chemical-specific toxicity data

Read-across

- predict missing information for untested constituents of a mixture in a component based approach
- read-across the effects of similar mixtures in a whole mixture approach

TK models

- model internal exposure assess the potential/probability for internal co-exposure
- predict potential TK interactions between mixture components
- facilitate the use of HBM data in toxicological risk assessment

Critical Reviews in Toxicology, 49:2, 174-189, DOI: 10.1080/10408444.2019.1579169

An example: inhalation toxicity

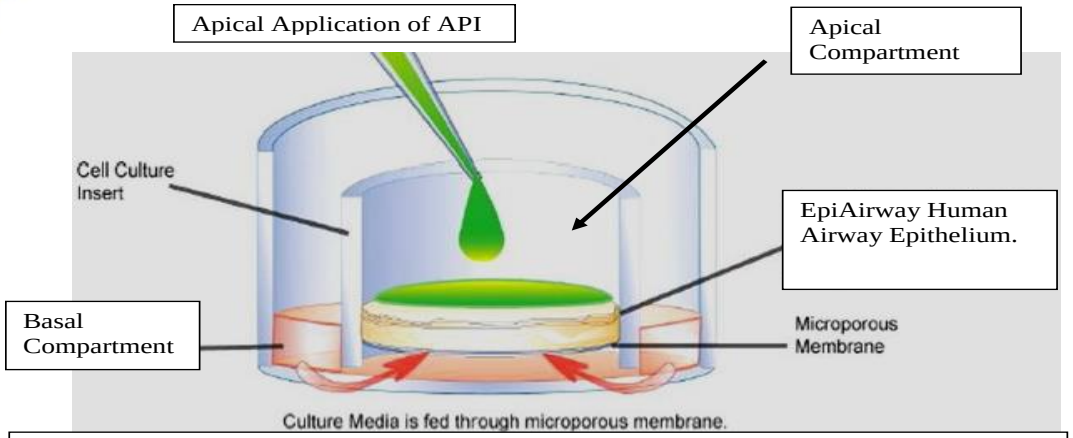


Figure 1. The EpiAirway Model System showing apical compartment, epithelial tissue, microporous membrane and basal (receiver) compartment.

in vitro EpiAirway™ Tissue Model

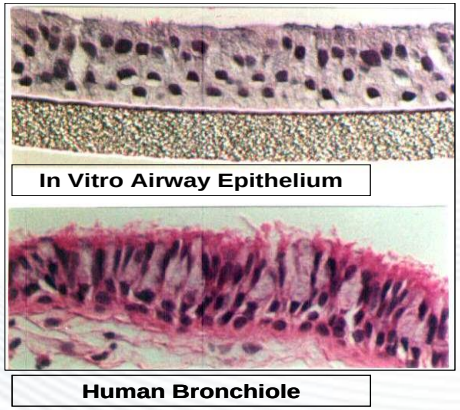


Figure 2. Pseudostratified muco-ciliary morphology of the EpiAirway tissue compared to excised human bronchial epithelium.

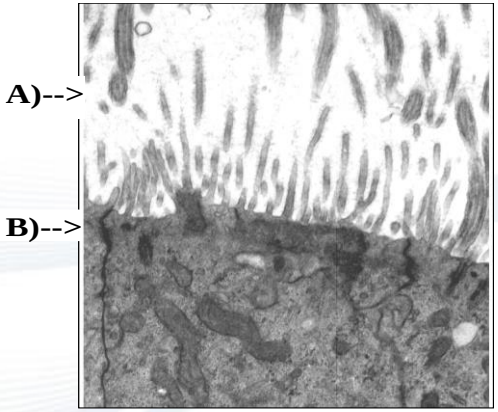
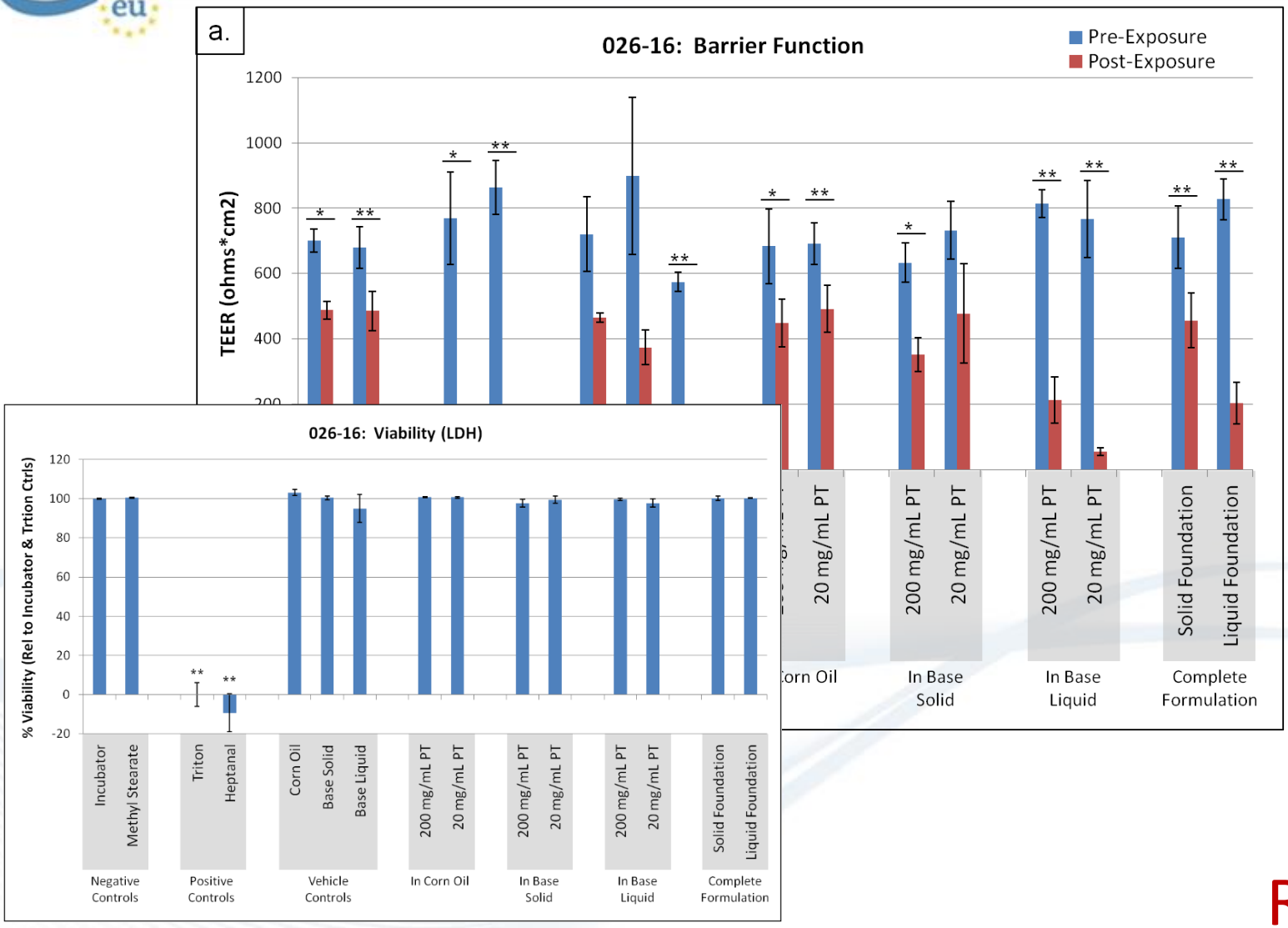
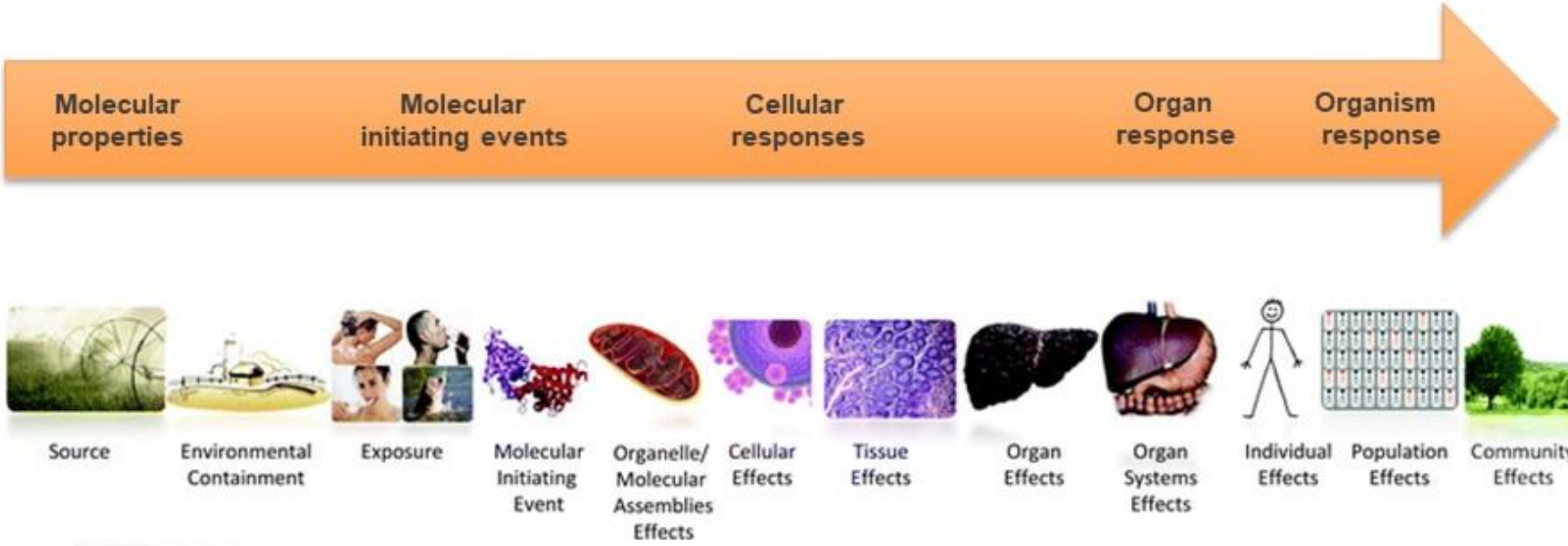


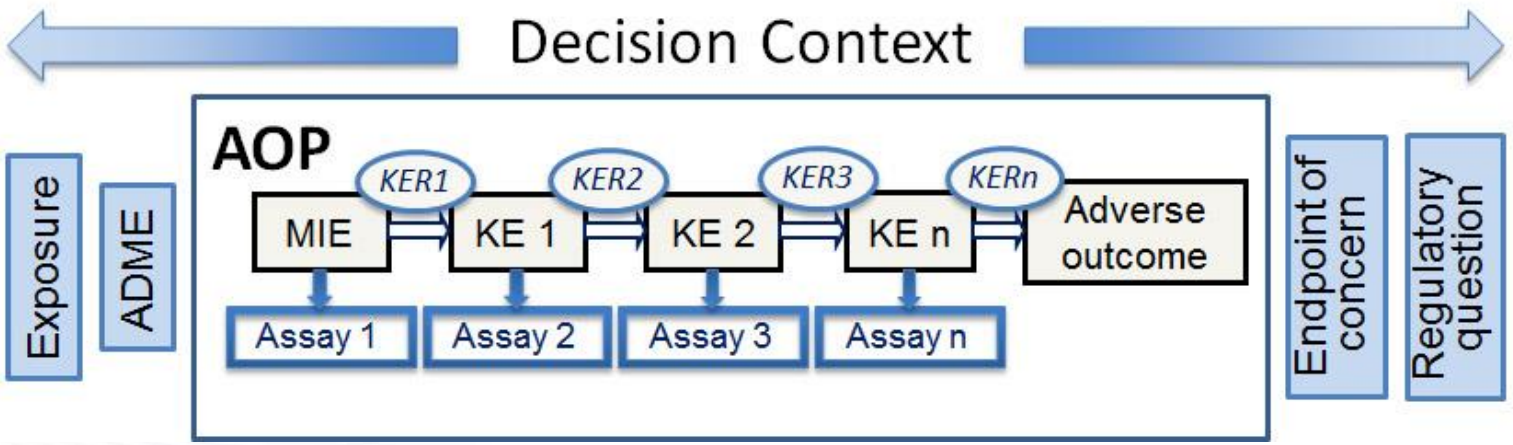
Figure 3. Transmission electron micrograph of EpiAirway showing cilia (A) and tight junctions (B).



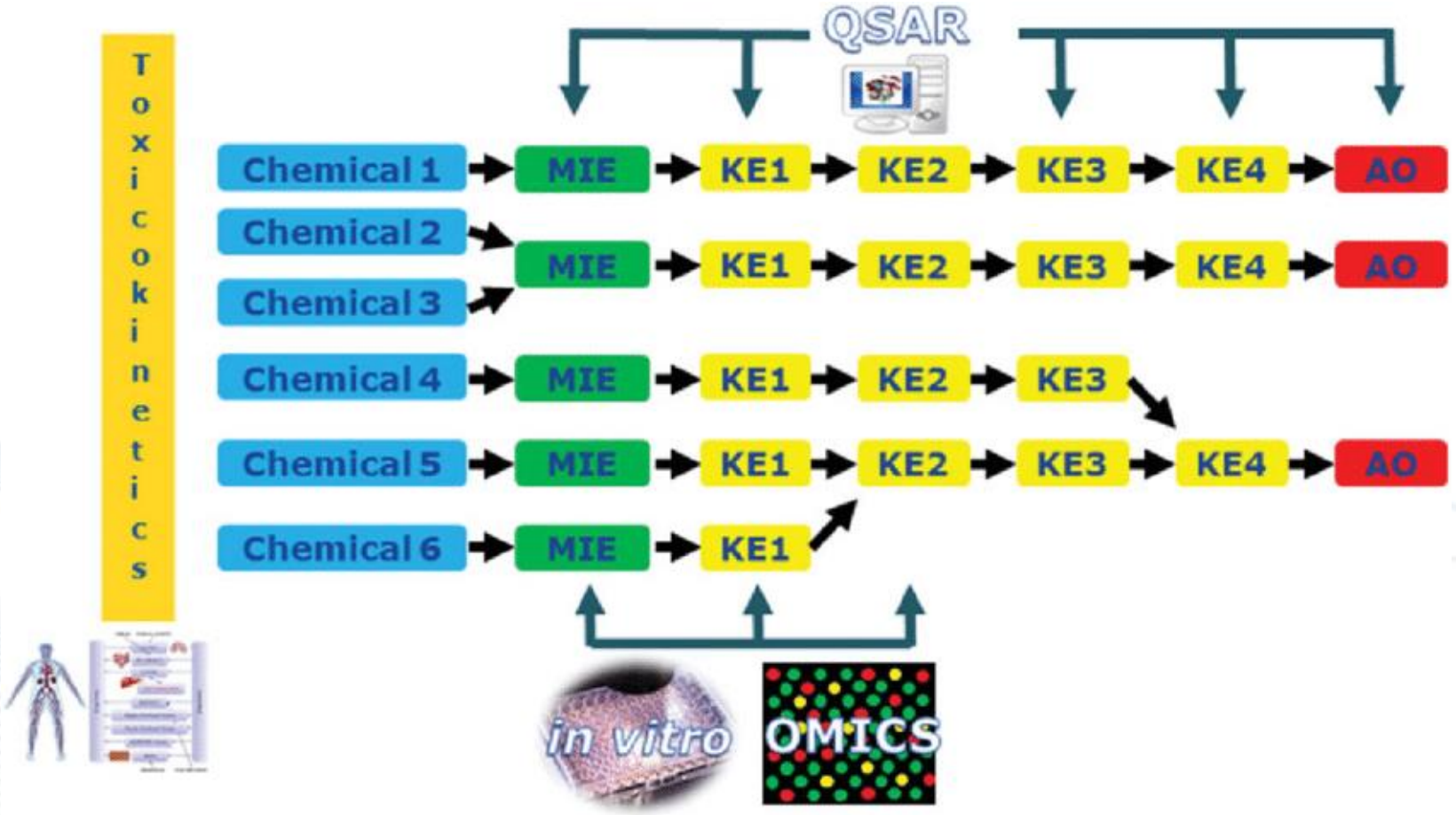
Results

AOP: Adverse Outcome Pathway





Organisation of information in AOP for the risk assessment of mixtures



Ecosystems

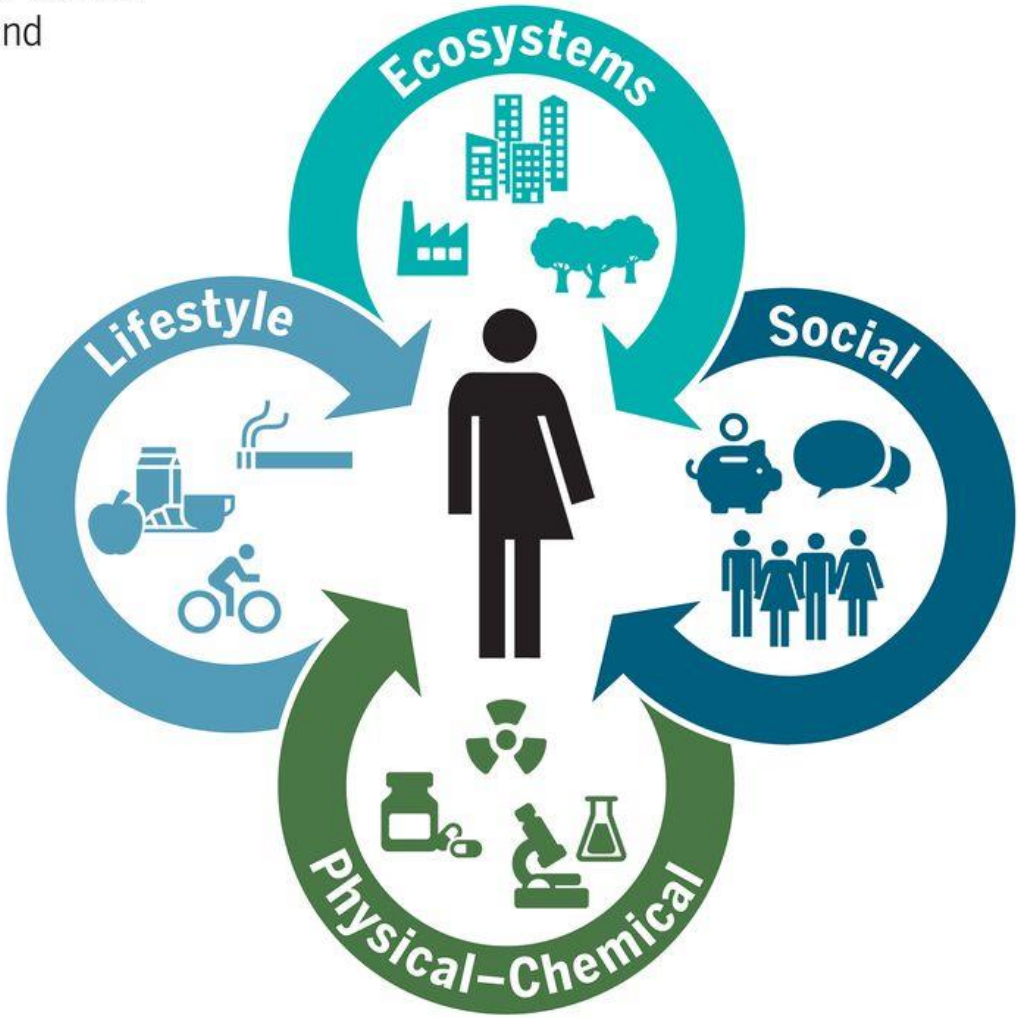
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

Lifestyle

Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

Social

Household income
Inequality
Social capital
Social networks
Cultural norms
Cultural capital
Psychological and mental stress

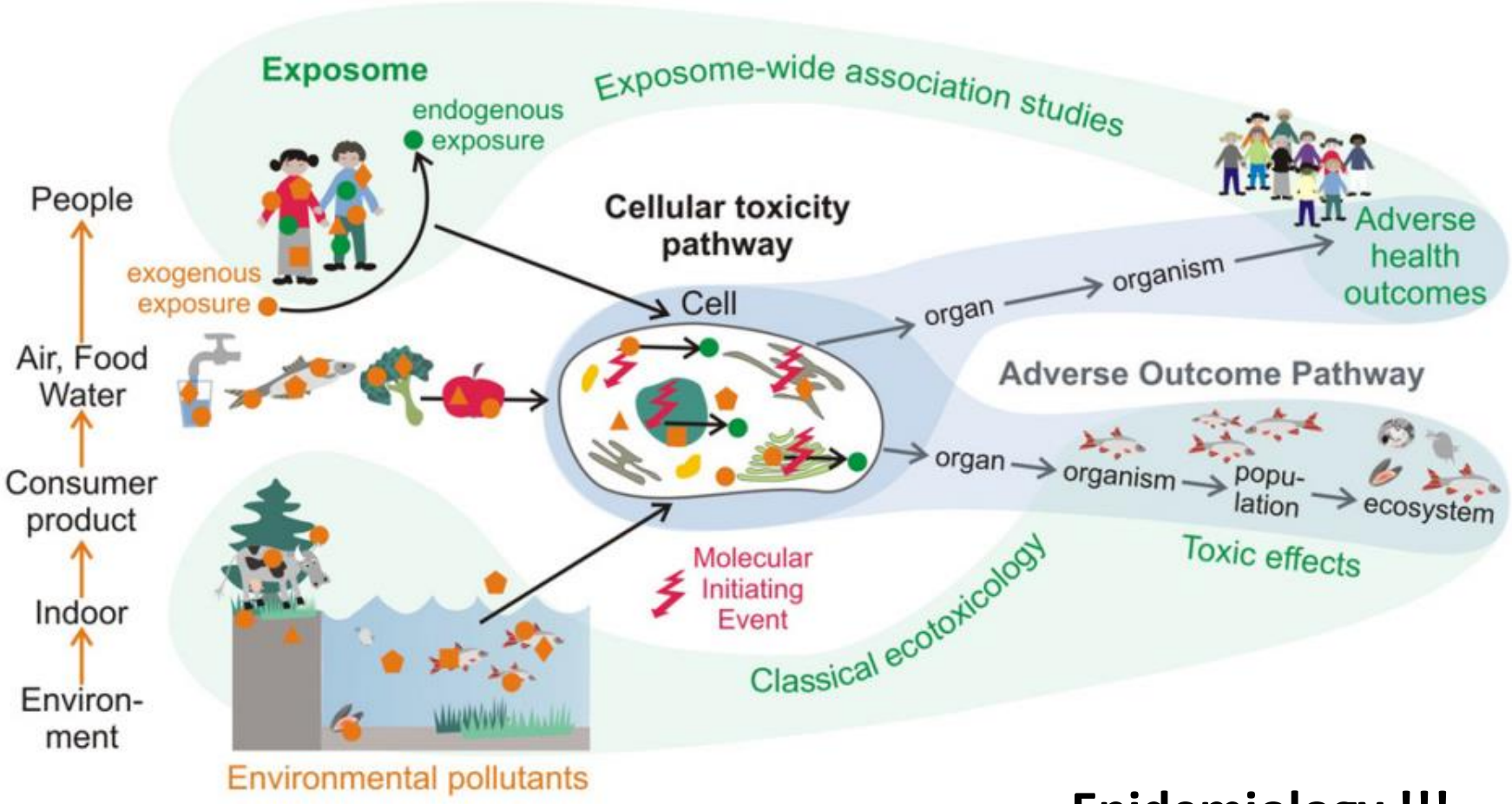


Physical–Chemical

Temperature/humidity
Electromagnetic fields
Ambient light
Odor and noise
Point, line sources, e.g, factories, ports
Outdoor and indoor air pollution
Agricultural activities, livestock
Pollen/mold/fungus
Pesticides
Fragrance products
Flame retardants (PBDEs)
Persistent organic pollutants
Plastic and plasticizers
Food contaminants
Soil contaminants
Drinking water contamination
Groundwater contamination
Surface water contamination
Occupational exposures

Science 24 Jan 2020: Vol. 367, Issue 6476, pp. 392-396 DOI: 10.1126/science.aay3164

The exposome



Epidemiology !!!

.Environment International Volume 99, February 2017

Conclusions

We leave in a safer world

European Union is the most regulated country

That's not enough!

More *in vivo* tests are not the solution

Integrated approach with team of experts

More advance *in vitro* testing, big data, epidemiology

Paradigm shift to face the problem