Revolutionizing chemical assessment and cumulative health impacts

Chair:

Nicola Crawhall, CEO, Canadian Water Network

Panelists:

Dr. Milou Dingemans, Chief Science Officer, KWR Water Research Institute
Dr. Niladri Basu, Canada Research Chair in Environmental Health Sciences, McGill University

Canadian Water Network
Igniting interest. Inspiring action.

Land acknowledgement

CWN respectfully recognizes and acknowledges the deep connection that First Nations, Inuit and Métis peoples across Canada have with the land that all Canadians call home. We also honour and recognize the significance of the treaties that establish the relationship between Indigenous peoples and settlers on this land.

Our office is located in Waterloo, Ontario, on the traditional territory of the Neutral, Anishinaabeg and Haudenosaunee peoples. More specifically, our office is situated on the Haldimand Tract, the land granted to the Six Nations that extends six miles on each side of the Grand River.

We are grateful for the privilege to work and live on this land.

About us

CWN is a national not-for-profit that is dedicated to protecting and respecting our vital water resources, and ensuring healthy, equitable and resilient water management for all.

CWN works with water managers and other decision makers to tackle complex water-related challenges that affect our communities, health and climate.

Water and communities

Water and health

Water and climate

Panelists

Dr. Niladri Basu
Canada Research Chair in Environmental Health Sciences,
McGill University

Dr. Milou Dingemans
Chief Science Officer,
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Canadian Water Network

Advances in chemical and human exposure assessment – a revolution in the making

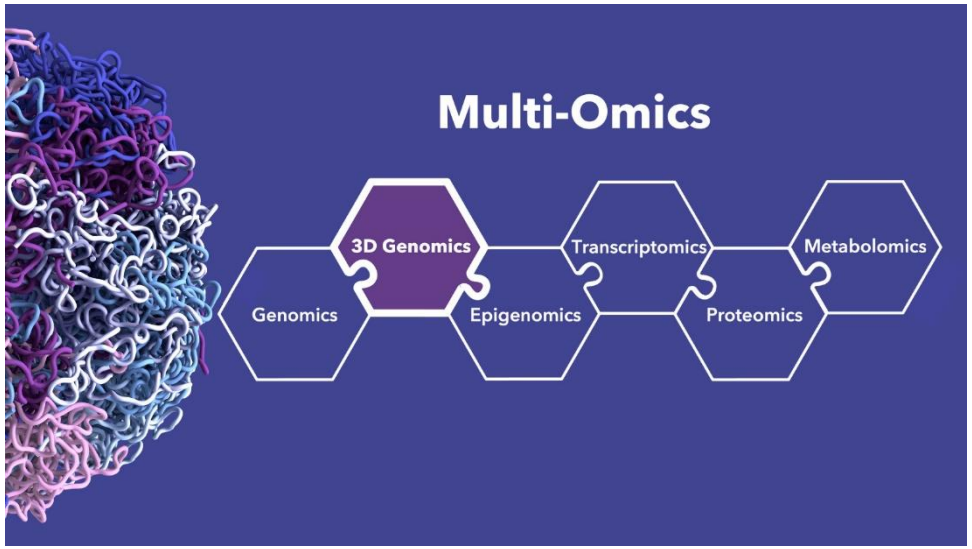
- Technical advances in identifying and assessing chemicals in water and measuring human exposure have the potential to change the way chemicals are regulated and even how products are designed.
- Until recently, regulatory frameworks have not kept pace with these scientific advances, focusing on lengthy, costly chemical-by-chemical assessments.
- Recent changes to Canadian Environmental Protection Act (Bill S-5) and in EU legislation open the way for regulating chemicals based on our ‘real life exposure’, a.k.a. cumulative effects.

Advances in chemical and human exposure assessment – a revolution in the making

Technical and scientific advances over the last ten years are making the regulation of contaminants based on their cumulative impact on humans possible.

Some of these advances include:

- Biomonitoring, the measurement of the body burden of toxic chemicals.
- Effects-based monitoring, capturing the mixture effects of chemicals in water and then applying bioanalytical methods to quantify the effects of these chemicals on us.
- Genomics and other omics technologies and bioinformatics methods.
- The human exposome, your lifetime exposure to contaminants, whether they be environmental, socio-economic, or lifestyle.



August 12, 2024, Toronto

Cumulative effects of chemicals

Developments at the science-to-practice interface

Milou Dingemans

KWR

Bridging Science to Practice

Utrecht University

KWR Water Research institute

- Nieuwegein, The Netherlands
- Shareholders: 10 Dutch and 1 Flemish water utilities
- +/-200 employees: +/- 150 researchers
- Covering the full water cycle

Brief history:

1948: Founded als KIWA

1973: start toxicology research (surface water quality)

2006: KWR founded

KWR's Water Quality and Health research

Chemical Water Quality

Environmental Forensics

Analytical Chemistry

Toxicology

Microbiological Water Quality

Water pathogens and health

Microbial activity and growth

Environmental biotechnology

Methods and tools

Detection&Identification

Data science

Sewage Surveillance

Hazard&Risk Assessment

Lab facilities

EU regulations on cumulative exposures

EU chemical legislations are strongly interconnected (tentative analysis)

Mixture effect (aggregate, synergistic, cumulative) assessment requirements specified in:

- WHO GDWQ annex on mixtures (2017)
- EFSA Guidance on … risk assessment of combined exposures (2019)
- ECHA Guidance on the Biodical Products Regulation (2017)
- ECHA Guidance on the Application of CLP Criteria (2024)

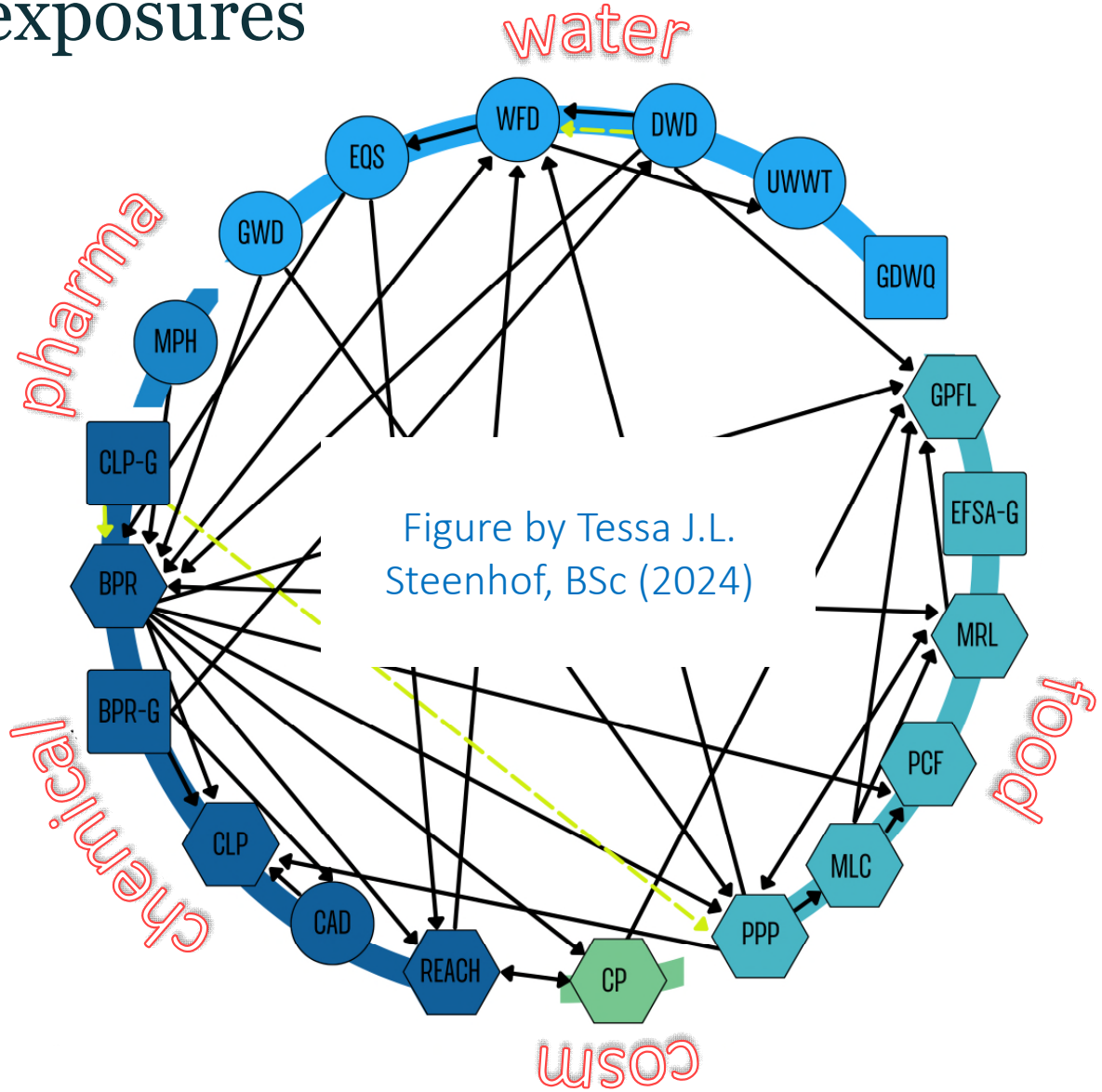


Figure by Tessa J.L. Steenhof, BSc (2024)

EU's chemicals strategy for sustainability towards a toxic-free environment

The EU's chemicals strategy aims to:

- better protect citizens and the environment
- boost innovation for safe and sustainable chemicals

Proposed actions include mixture effects of chemicals when assessing risks (for the others, see Chemicals strategy - European Commission (europa.eu))

Partnership for the Assessment of Risks from Chemicals | Parc (eu-parc.eu):

- Universities and research institutes
- National Authorities
- ECHA, EFSA, EEA

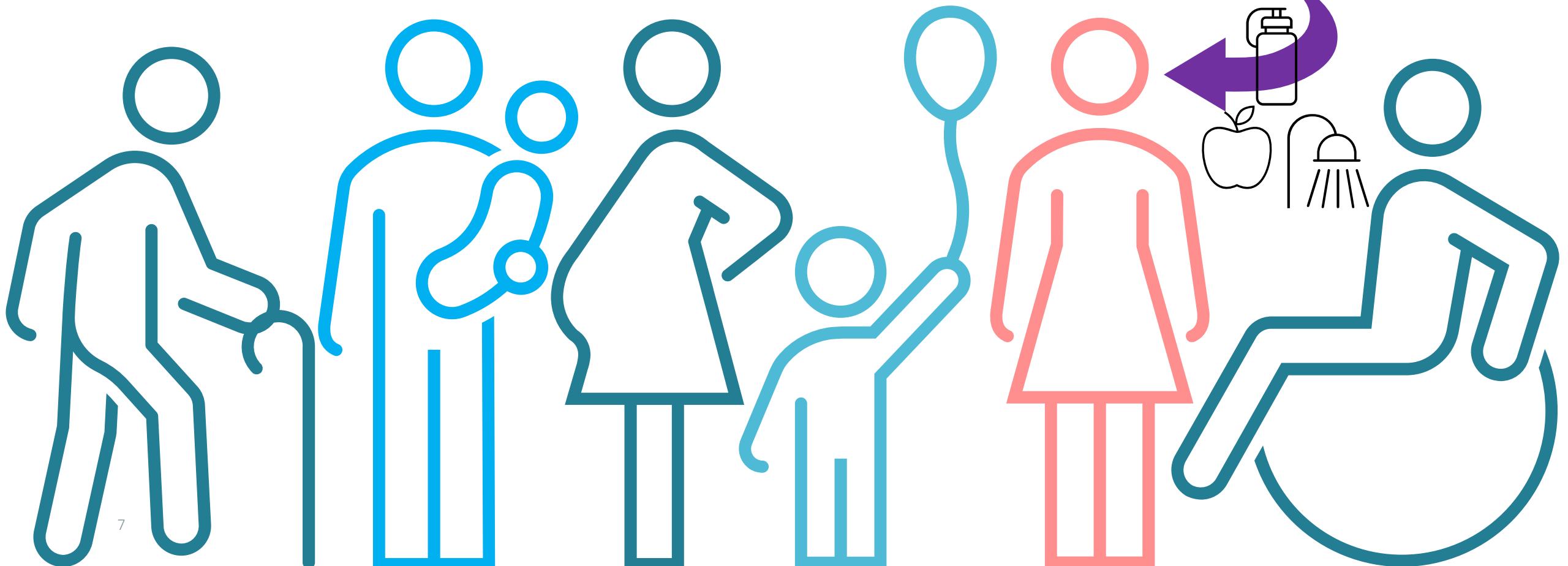
The ambitions of Bill S-5

Can be supported by developments in toxicological risk assessment

A right to a healthy environment	Protecting vulnerable populations	Assessing real-life exposures	a new Plan of Chemicals Management Priorities	Supporting the shift to safer chemicals	Increased transparency in decision-making	A stronger regime for toxic substances that pose the highest risk
environmental justice, intergenerational equity, and non-regression	*research, studies, and (bio)monitoring activities*	*consider …the cumulative effects on the environment and health ….when conducting and interpreting the results of risk assessments*	*reduce animal testing, cavoiding regrettable substitutions, better information to the public*	*maintain a Watch List*	*communicate anticipated timelines for completing risk assessments and for proposing subsequent risk management actions*	*persistence, bioaccumulation, carcinogenicity, mutagenicity, and reproductive toxicity*

Risk = hazard x exposure

Individual substances (route-specific/aggregated)



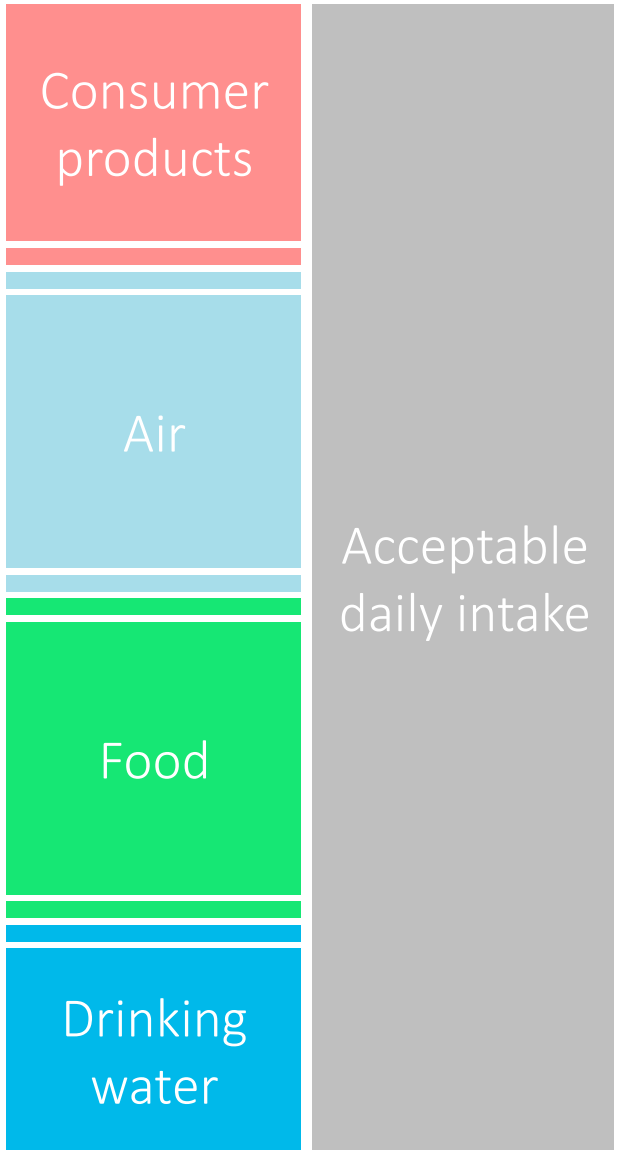
Science-to-practice developments

Individual substances (route-specific/aggregated)

Human exposure to chemicals involves multiple sources from the general and occupational environments and takes place via different routes.

A better understanding of the main exposure sources and routes and an integrated and harmonised methodology are being developed to support European agencies in proposing effective risk assessment of the aggregate human exposures that will lead to efficient risk management measures PARC

Roadmap for action for advancing aggregate exposure to chemicals in the EU | EFSA (europa.eu)



Science-to-practice developments

Individual substances (route-specific/aggregated)

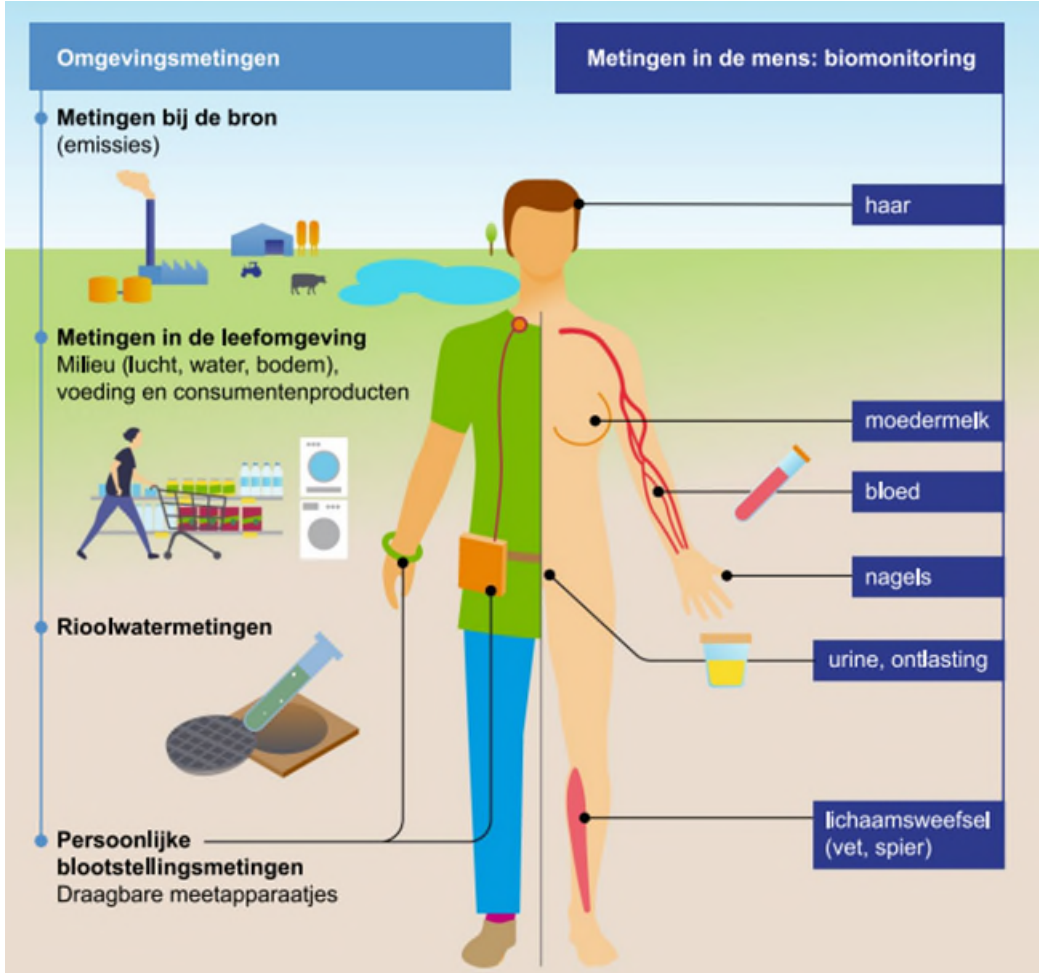
Premarket:policy, production and risk assessment

Postmarket: inspection, environmental monitoring, biomonitoring

Biomonitoring programs identify

- Internal concentrations resulting from aggregate exposure
- Internal cumulative exposure
- Vulnerable populations

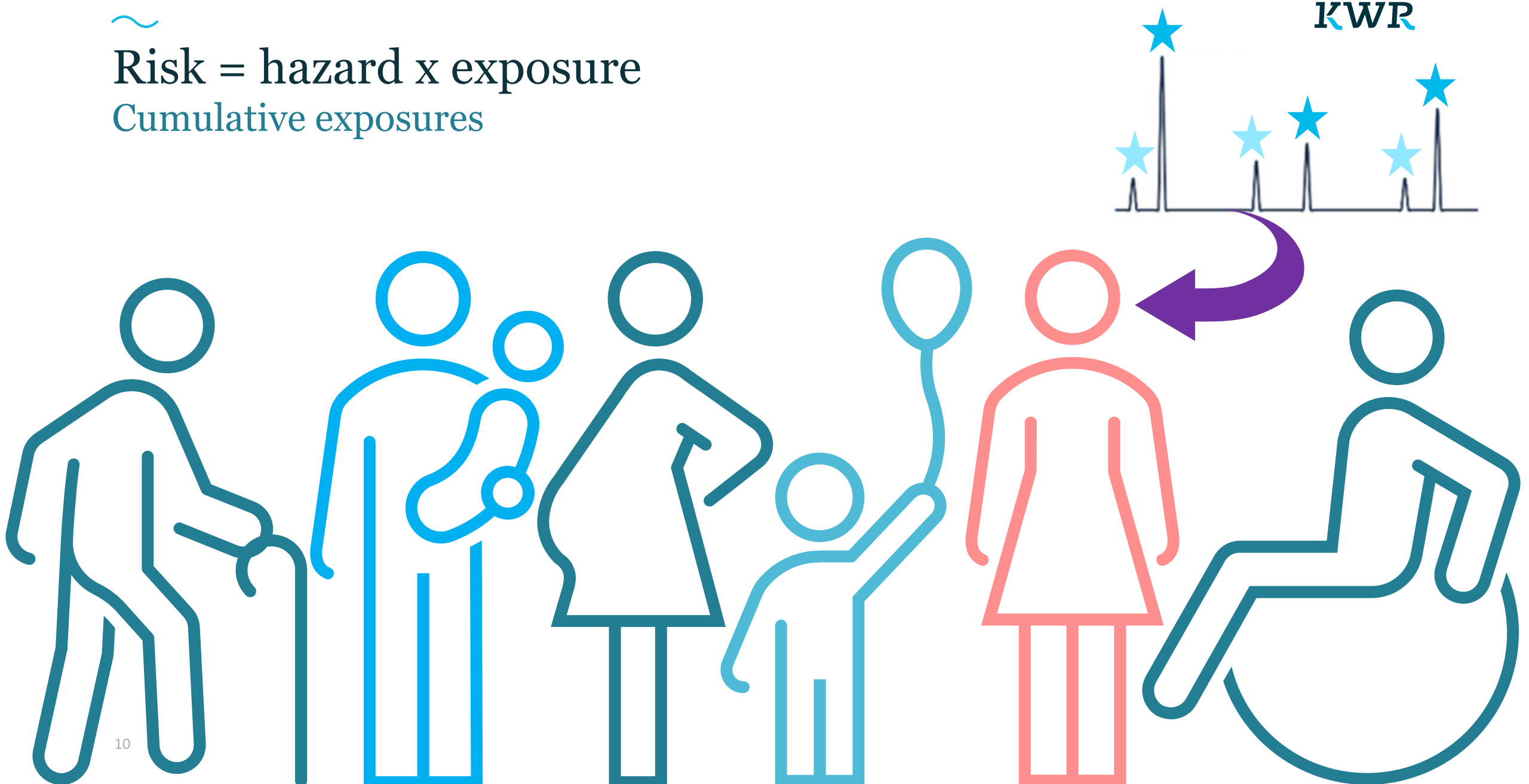
Surveys and statistical programs - Canadian Health Measures Survey (CHMS) (statcan.gc.ca)



Dutch Health Council (2024)

~ Risk = hazard x exposure

Cumulative exposures



Science-to-practice/policy developments

Cumulative exposures

Hazard assessment	WHO	EFSA
Tier 0	• HI approach (default dose addition) TTC concept can be used when values are unavailable	• HI approach (default dose addition). If reference values are not available, the lowest available reference value can be used.
Tier 1	• Point of Departure Index (PODI), similar to HI but uses each chemicals POD instead of a reference value.	• PODI • Target Organ Toxicity Dose (TTD)
Tier 2	• Relative Potency Factor (RPF), and refinement of grouping based on mode of action	• RPF of each component and refinement of grouping based on mode of action
Tier 3	• Probabilistic estimate of risk and PBPK modelling	• Derivation of reference points from studies and probabilistic PB-TK/PB-TK-TD modelling.

Table by Tessa J.L. Steenhof, BSc (2024)

Science-to-practice/policy developments

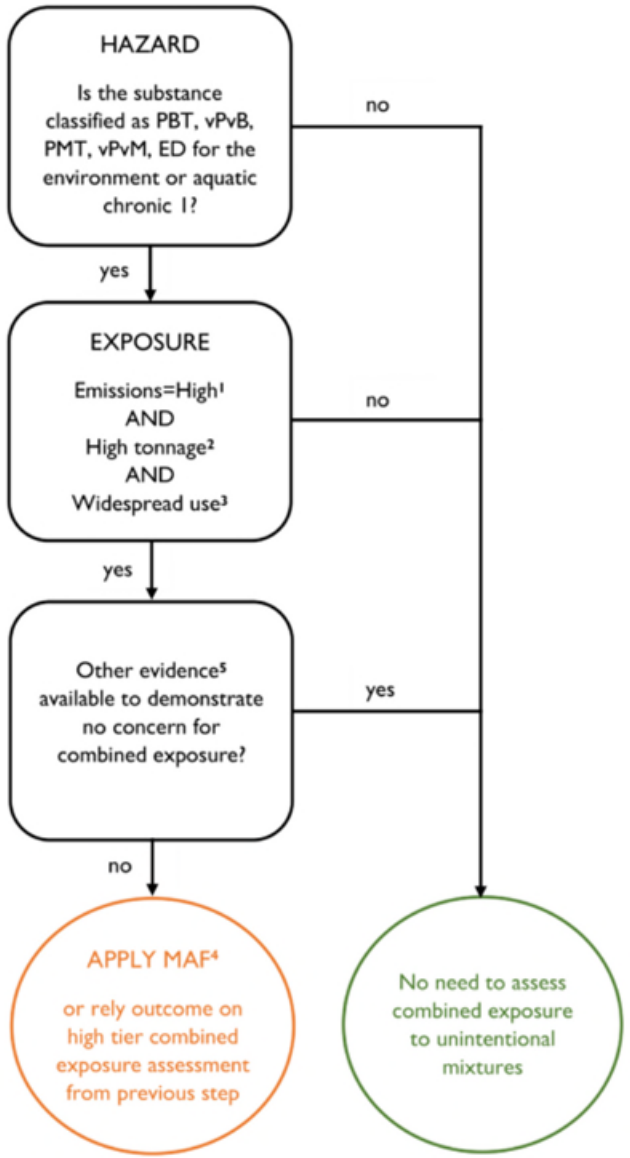
Cumulative exposures

Discussions are ongoing on a “Mixture Assessment Factor” (MAF)

This MAF would be applied in risk assessments for specific substances that are likely to end up in (various) unintended (environmental) mixtures

Concerns are disproportional overestimation of risks and difficulties in risk communication

A recent proposal is an approach that allocates maximum percentages of a substance to unintended mixtures (Backhaus, 2023)



Science-to-practice/policy developments

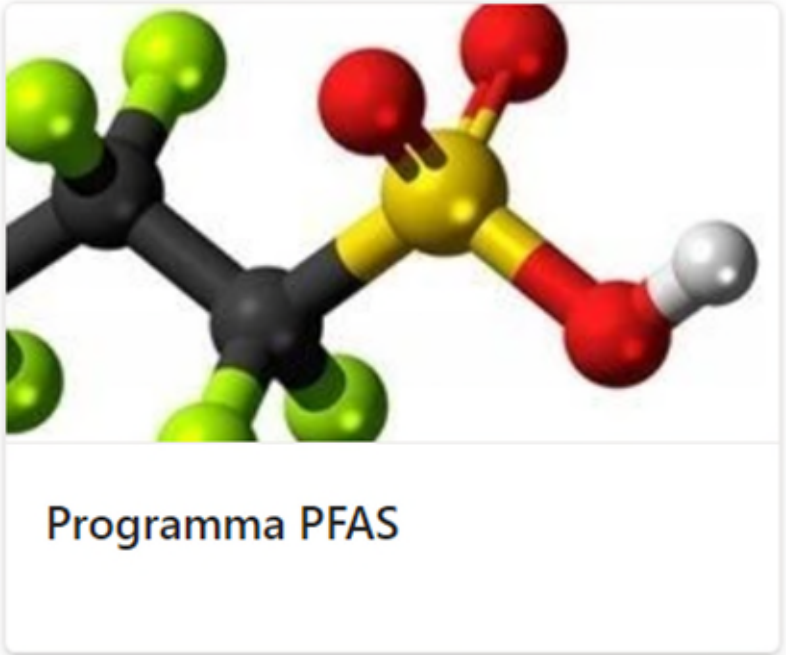
Cumulative exposures

Thousands of different PFAS are found virtually everywhere

In 2020, EFSA advised that a safe intake of PFAS should be much lower than advised before based on effects on the immune system (4 PFAS were grouped in a tolerable weekly intake).

The Dutch health authority developed a health-based guidance value for ~20 grouped PFAS based on the EFSA TWI and a relative-potency factor approach: 4,4 ng PFOA equivalents/L.

The recast of the EU Drinking Water Directive (2021), includes a limit of 0.5 µg/l for 20 *or* all PFAS



Discussions on grouping criteria are ongoing worldwide (toxicity, occurrance, structure, analysis..)

Science-to-practice/policy developments

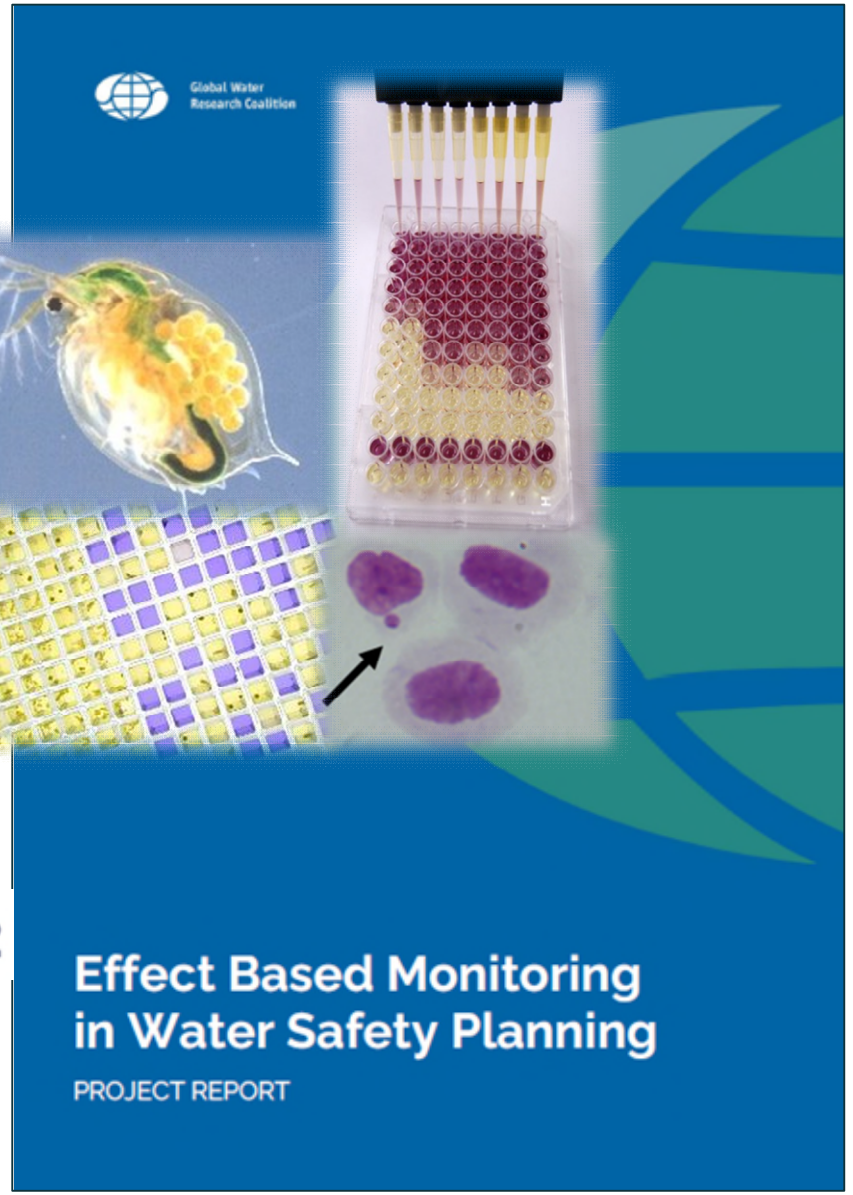
Cumulative exposures

Application of Effect Based Methods – detecting responses of all contaminants in a sample if active in the applied bioassays

Integrated evaluation of water quality, using environmental and drinking water sets for effect-based monitoring and effect-based trigger values - detect specific toxic mechanisms (mutagenicity, endocrine disruption, ..)

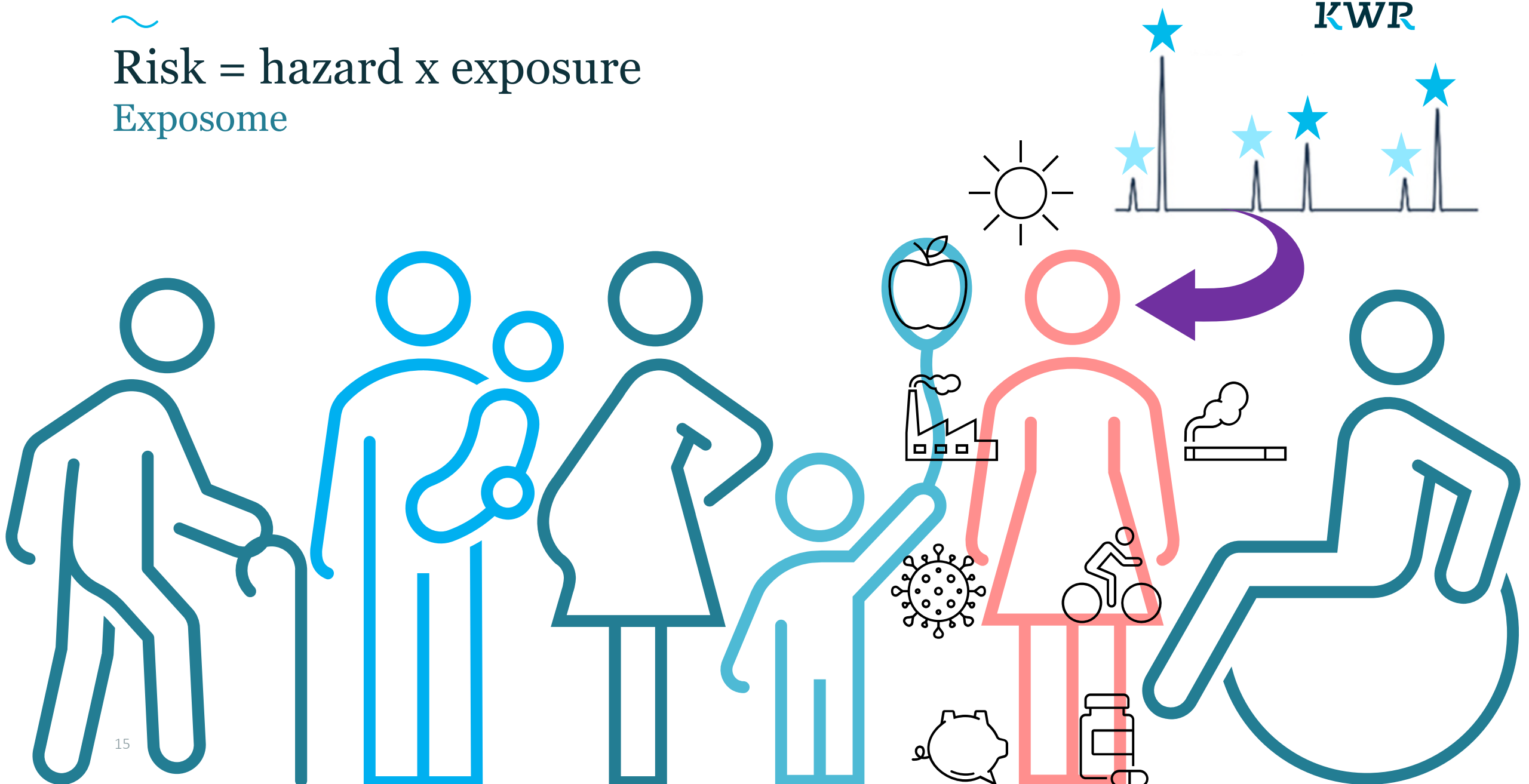
Resources (reports, factsheets, scientific papers) are available via Effect Based Monitoring (EBM) Archives - Global Water Research Coalition (GWRC)

(Other recent initiatives: OECD, Dutch water sector, CIS)



Risk = hazard x exposure

Exposome



Science-to-practice/policy developments

Exposome

Discovering the non-genetic drivers of health and disease

Lifetime exposures (environment, lifestyle, physico-chemical, social)

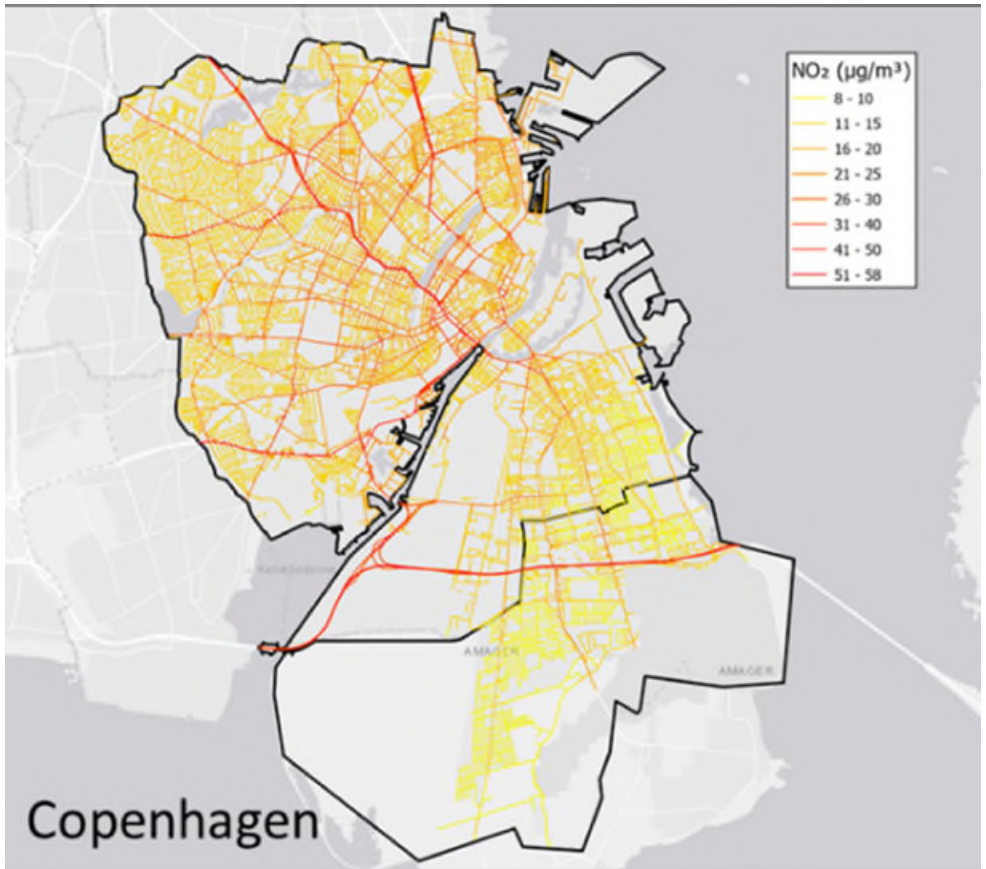
Exposure studies

- Environmental/air/water contamination (including WBE)

Cohort studies

- Biomonitoring (NTA, omics)
- Health outcomes

Efforts to implement new approaches (wearables, GIS, metabolomics) and combine different data types



Kerckhoff et al. 2022

Home - The European Human Exposome Network (EHEN)

Conclusion

The proposed amendment in the *Canadian Environmental Protection Act* (Bill S-5) can benefit from recent international research and current developments in the EU science-to-policy interface

Combine (refined) chemical grouping approaches with (advanced) effect based methods

Join us at our 'KWR & Friends' booth

Here, we showcase our collective research, innovative technologies, and solutions for a water-wise world, all centered around and inspired by collaboration.

kwr_water

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KWR

the international water association

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BTO Collective Research Programme

Global Water Research Coalition

PARC Partnership FOR THE Assessment OF Risks FROM Chemicals

eu-parc.eu

DESIGNING NEW APPROACH METHODS (NAMS) FOR REGULATORY DECISION MAKING OF WATER QUALITY

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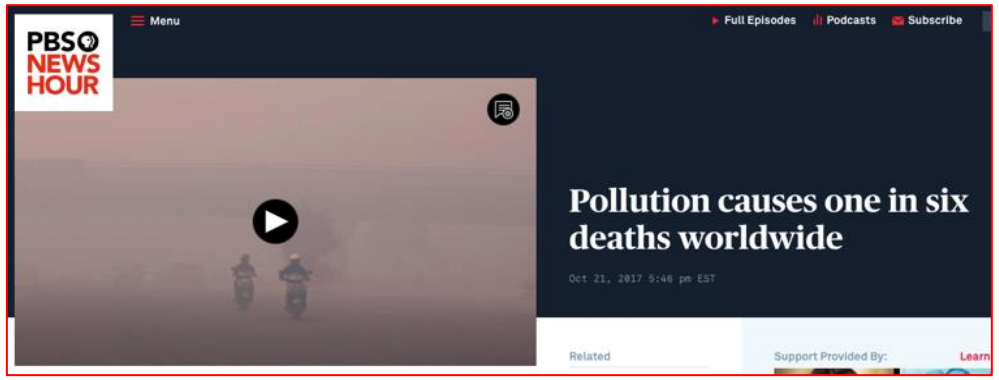
ecotoxchip



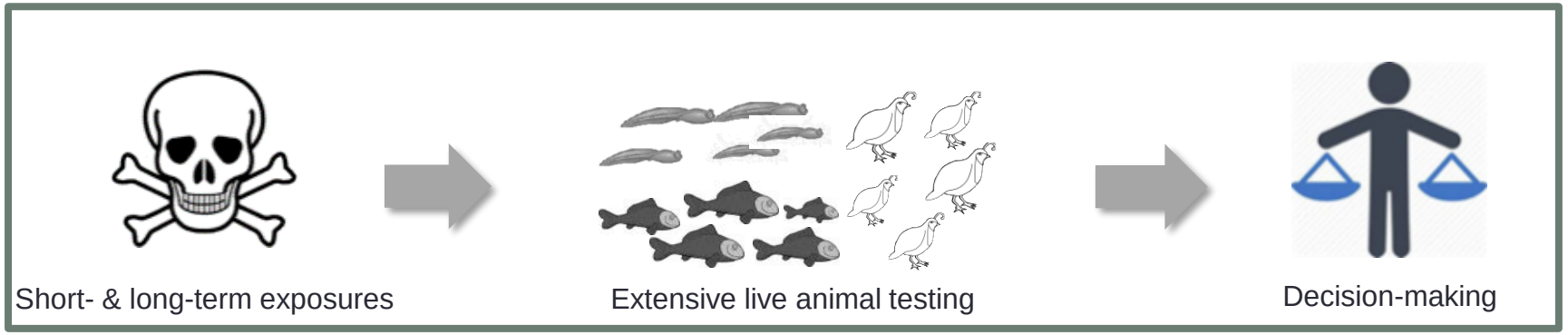
Landrigan et al. 2018
The Lancet
391(10119):462-512

Key Challenge

- Pollution is a significant threat globally, and in Canada
- Chemicals released into aquatic environments are eroding ecosystem health and economic potential[1]
- Only a small fraction of the >350,000 chemicals identified for use have ecotoxicological data[2,3]
- Most exist in complex environmental samples
  - Sediment, water, and effluents for compliance monitoring (section 36 of *Fisheries Act*)
  - $6.2B/yr for pollution control/prevention

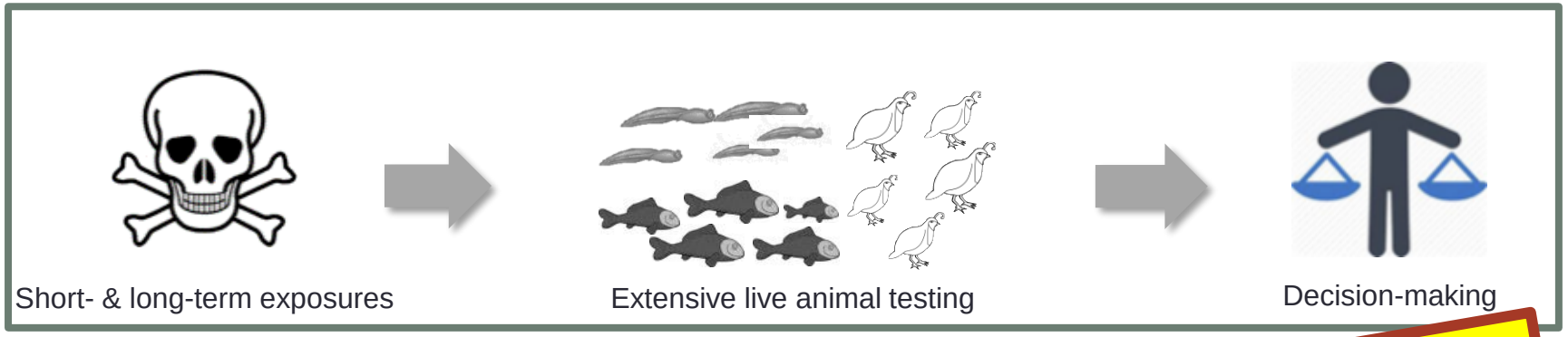
1. Lancet. 2018. 391(10119):462-512; 2. J Toxicol Environ Health B Crit Rev. 2010. 13(2-4):51-138; 3. Environ Sci Technol. 54(5):2575-2584

Change is needed



- Testing is costly (money, time, animals)
  - Cost per chemical: $0.4-25M; 4 yrs; >1,000 animals
  - Single chronic ecotoxicity test: $150K; 8 wks; 135 animals
- Example: European Union REACH estimates
  - Chemical testing between 2011 and 2021:
    - 54.3 million vertebrate animals used
    - Total cost of 9.5 billion euros
- In Canada, modelling approaches are often needed due to a lack of experimental data

Change is needed



- Testing is costly (money, time, animals)
  - Cost per chemical: $0.4-3[illegible]
  - Single-[illegible]
  - [illegible]billion euros
- In Canada, modelling approaches are often needed due to a lack of experimental data

Urgent worldwide demand for improved testing tools that are more efficient, affordable, accessible, flexible and less dependent on animal studies + trusted by users

Regulatory Change

2007: NRC Toxicity Testing in the 21st Century – a Vision and Strategy

2016: New Approach Methodologies (NAMs)

- 2022: Current Canadian government introduced legislation to refine/reduce/replace animal testing, promote environmental justice, incorporate alterative methods, assess cumulative risks
- 2021: US EPA New Approach Methods (NAMs) Work Plan created… lots of activity!
- 2016: Workshop on New Approach Methodologies in Regulatory Science… lots of activity!

Barriers to change: The "If you build it, they will come" fallacy

Expectation:

- If scientists develop NAMs, they will be rapidly integrated into risk assessment, thereby reducing the number of animals used and the time and cost of testing.

Reality:

- Uptake of NAMs into regulatory risk assessment has been slow and formal adoption is marginal[1,2]
- Driven by insufficient validation, complexity of interpretation, and lack of standardization[1,2]

1. Environ Health Perspect. 2020. 128(10):105002; 2. Environ. Advances. 2021. 4: 100061.

Barriers to change: The "If you build it, they will come" fallacy

Expectation:

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Partnerships between academic scientists and regulatory users are needed to overcome these barriers

Rea

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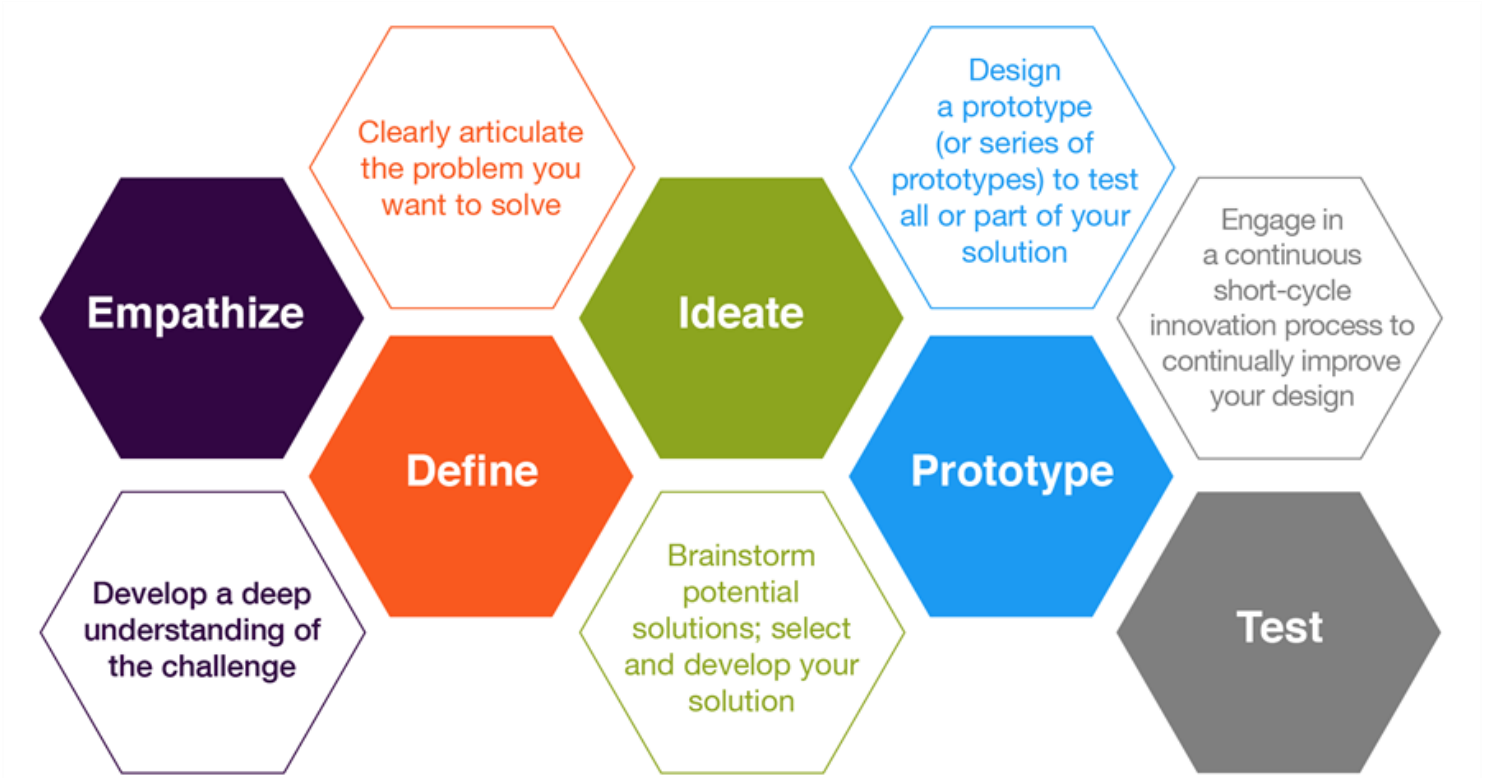
1. Environ Health Perspect. 2020. 128(10):105002; 2. Environ. Advances. 2021. 4: 100061.

Lessons: EcoToxChip Test System

- 2016-2022 Genome Canada LSARP
- 2023-2026 Genome Canada GAPP

- Develop, test, validate and commercialize quantitative PCR arrays (**EcoToxChips**) and a data evaluation tool (**EcoToxXplorer.ca**) for the characterization, prioritization and management of environmental chemicals and complex mixtures of regulatory concern

ecotoxchip Driven by Design Thinking



1. Registry of users and their needs

2. 3x Prioritized users & their needs

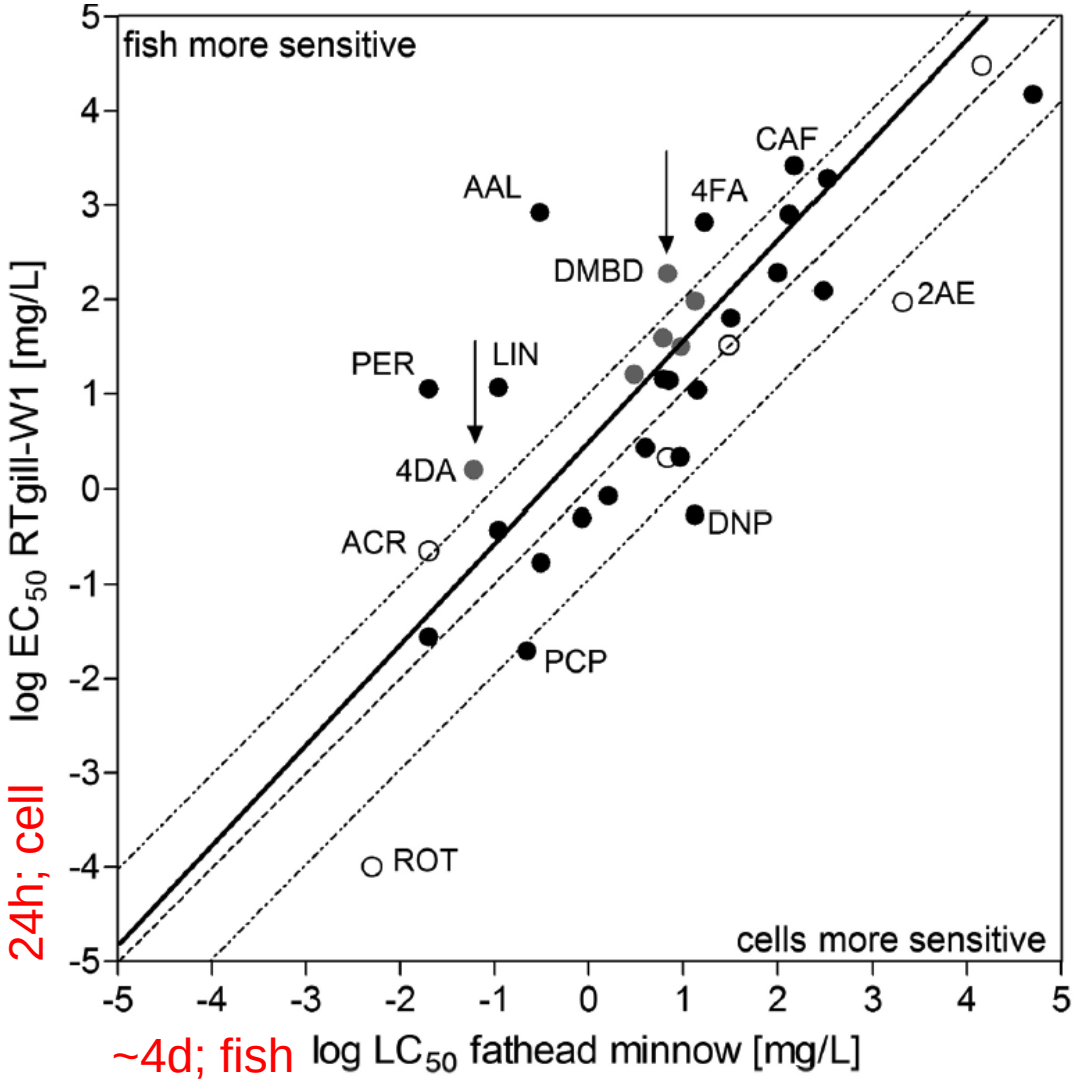
3. EcoToxChip features identified

4. Mock-ups in our conferences & workshops

5. Fall SETAC 2019 tests & results →

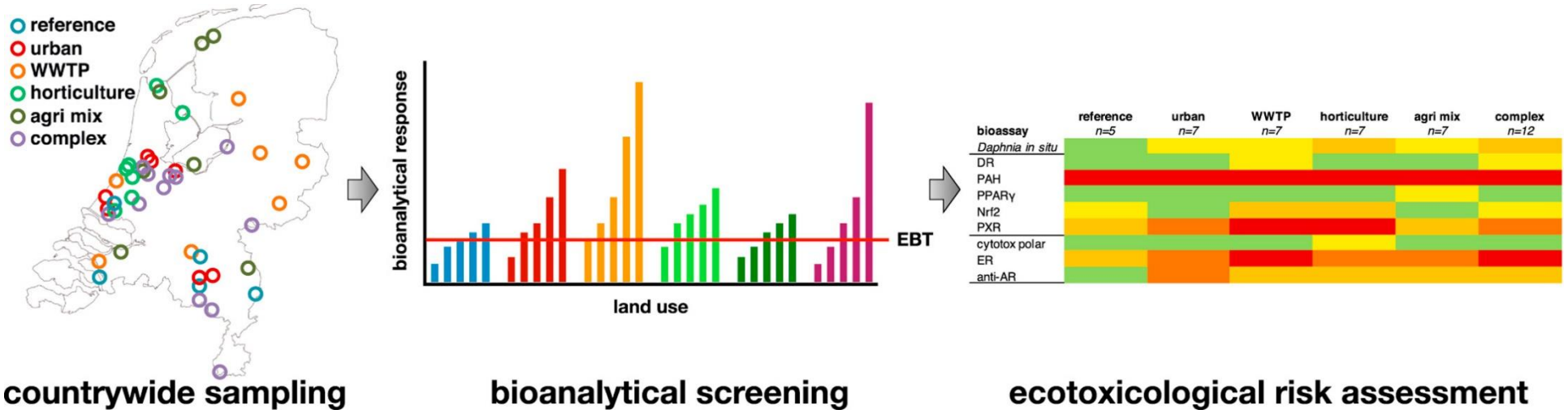
1. Rainbow trout gill cells (RTgill-W1)

- Tanneberger et al.[1] study of 35 organic chemicals (to right), plus dozens more
- 2x faster, 6x cheaper, no animals used[2]
- OECD 249 (Chemical Testing) & ISO2115 (Water Quality)
- ~50-80K trout/yr in Canada?



1. dx.doi.org/10.1021/es303505z
2. https://www.biorxiv.org/content/10.1101/2022.02.24.481630v1

2. Effect-driven bioassays



- De Baat et al. 2019 (Water Research 159: 434-443)
- 45 surface water samples from different land uses
- Passive samplers 6 weeks → 21 bioassays
- Screening and prioritization tool given costly chemical analysis

3. Transcriptomic Point of Departure

- Dose-response analysis most familiar to the regulatory community
- Apical Point of Departure (aPOD): concentration that a chemical starts to have an effect on an organism (e.g., survival, growth)
- Transcriptomic Point of Departure (tPOD): concentration that a chemical starts to cause significant change in gene expression

- Human health studies are showing concordance between aPOD (from chronic animal test) and tPOD (from short-term studies), while being 28x faster and 4x cheaper
- What about for fish?

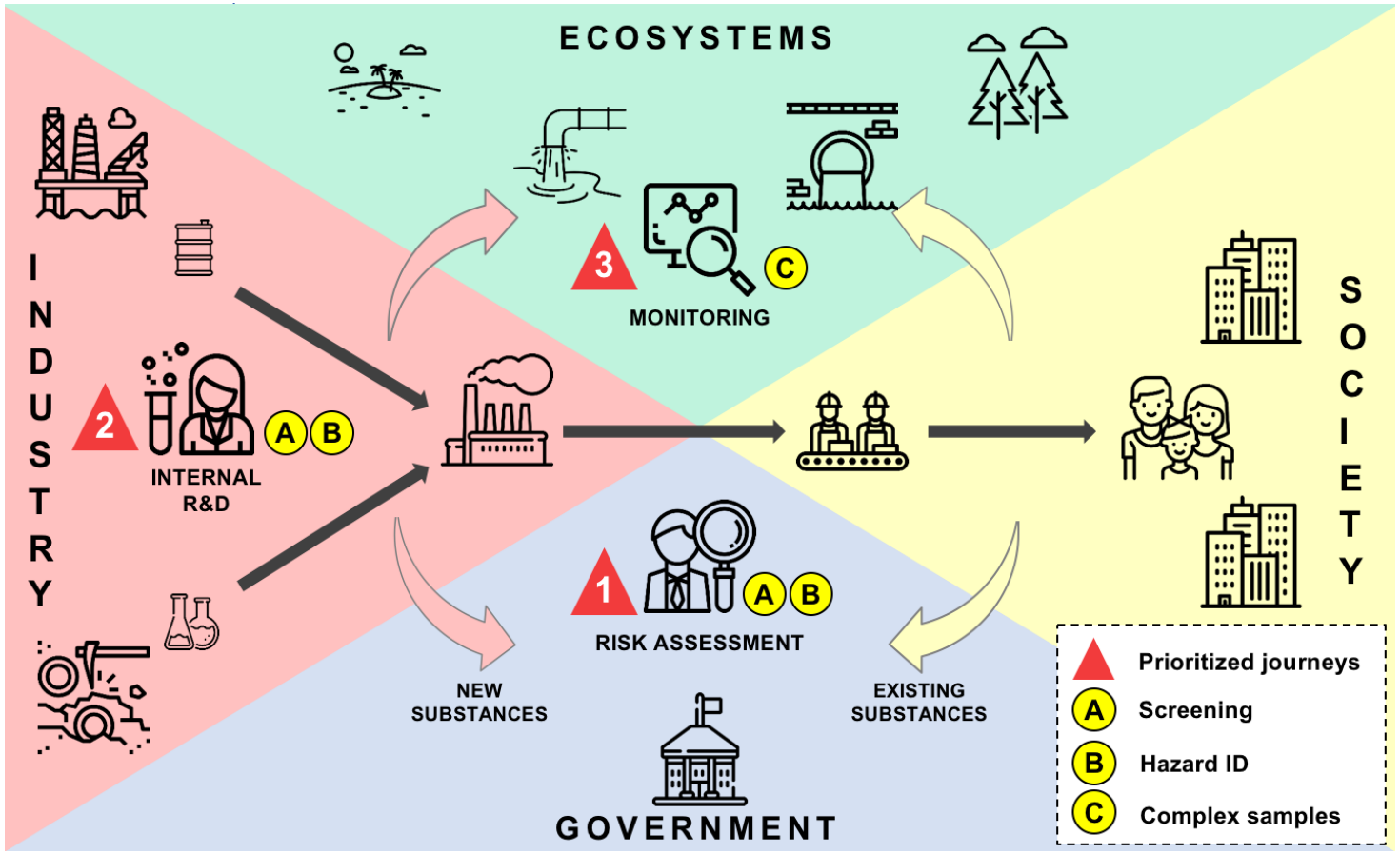
24hr microplate test with trout embryos

	EE2	Copper	SDS	Caffeine	Aniline
# of genes fitted	107	637	189	339	464
# of gene BMDs	865	575	115	276	374
tPOD mode	**9.4 ng/L**	**0.08 mg/L**	**0.68 mg/L**	**12 mg/L**	**20 mg/L**
Chronic measure (LC50)	100ng/L LC50, 28d ZF	1.3mg/ LC50, 14d RBT	~5.5mg/L LC50, 8d FHM	307mg/L LC50, 6d ZF	39mg/L LC50, 28d ZF
Chronic measure (sub-lethal)	**20ng/L developmental, 21d RBT**	**0.03 mg/L, EC10 growth, 28d RBT**	**4.6mg/L LOEC mortality, 8d FHM**	**100mg/L LOEC mortality, 7d FHM**	**159mg/L NOEC mortality, 56d RBT**
Is tPOD "protective" of chronic?	**YES**	**maybe**	**YES**	**YES**	**YES**

~30 diverse chemicals being tested in 3 fish species in partnership with Environment and Climate Change Canada to determine if a short-term alternative to animal test method can be derived that is predictive/protective of chronic fish toxicity.

Designing NAMs “in use”

Projects built around 3 prioritized users and their journeys



Socio-Economic Benefits of NAMs

- Faster, ethical and more economical and informative testing strategies
- Helps modernize risk assessment, which is essential to protect Canadians (especially vulnerable sub-groups) and their environment from chemical pollution
- Contributes to the Canadian (and global) objective of reducing, refining and replacing animal testing

Change is NOW