BIOMARKERS OF NEUROACTIVE COMPOUNDS IN THE AQUATIC ENVIRONMENT: INTEGRATION INTO ADVERSE OUTCOME PATHWAY FRAMEWORK

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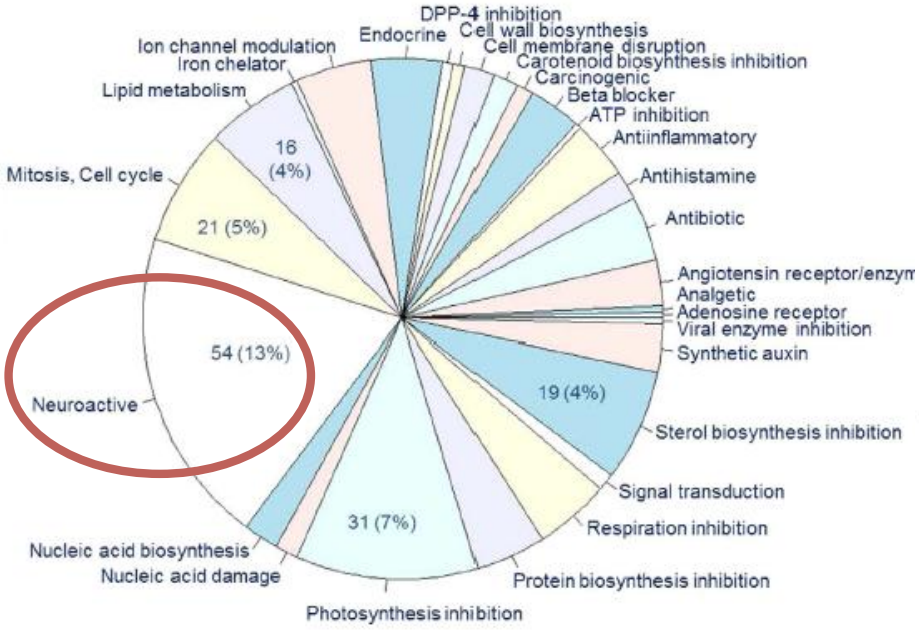
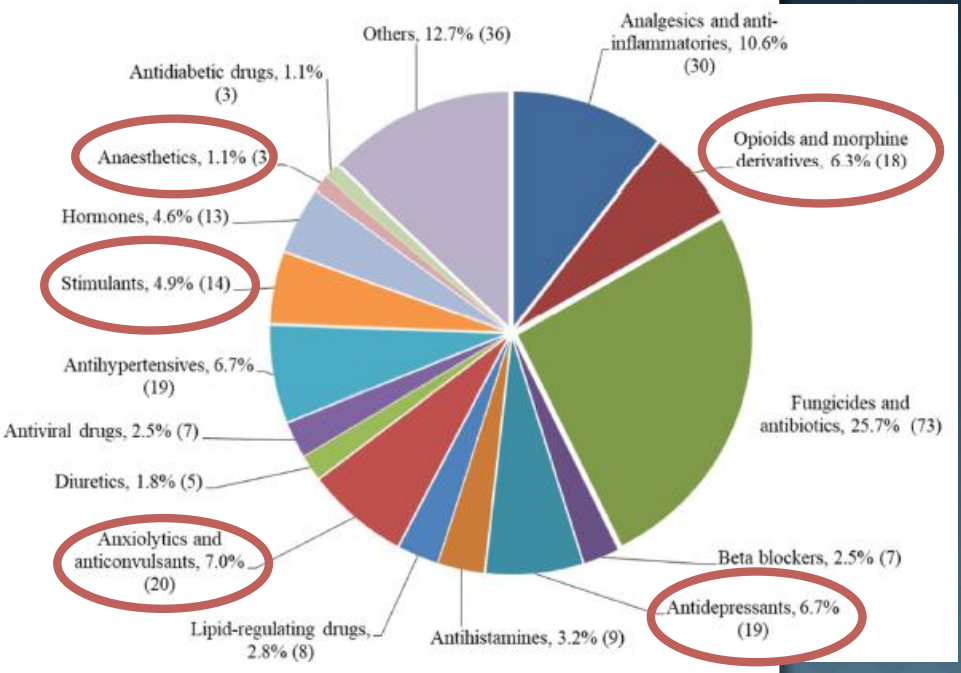
WHY A STUDY ON NEUROACTIVE COMPOUNDS (NCs)?

(pharmaceuticals, illicit drugs, neuroactive pesticides)





Busch et al. (2016) Micropollutants in European Rivers: A Mode of Action Survey to Support the Development of Effect-Based Tools for Water Monitoring. *Environ. Toxicol. Chem*. 35, 1877-1879.

Zhou et al. (2019) Optimization of screening-level risk assessment and **priority selection of emerging pollutants** – The case of pharmaceuticals in **European surface waters.** *Environ. Int.* 128, 1-10.

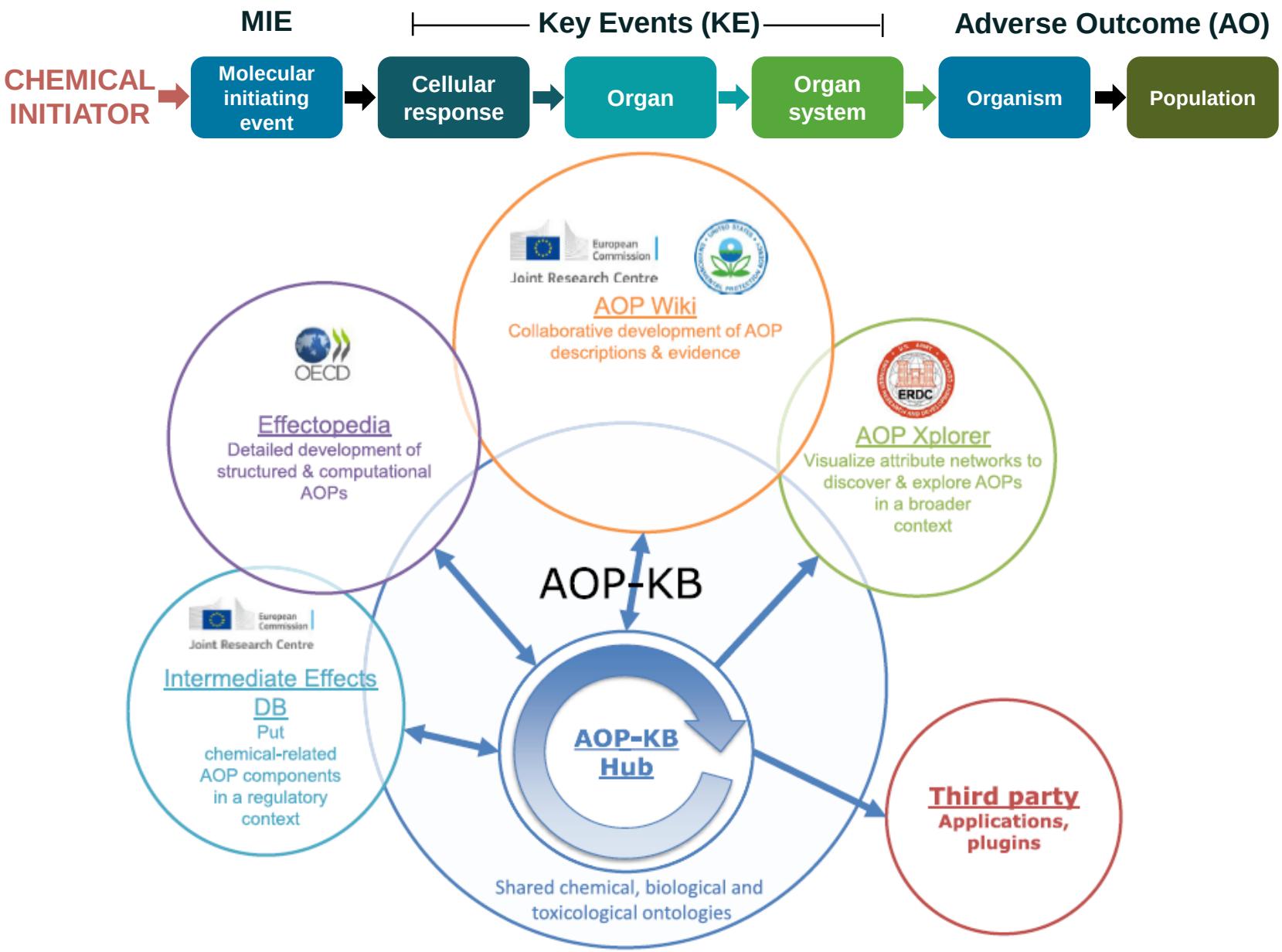
Emerging environmental problem in European surface waters posing a great risk for wildlife and human!

EU FP7 Collaborative Project SOLUTIONS (www.solutions-project.eu) - NCs detected in serum and muscle of caged fish after *in situ* exposure, and in water samples at Danube River hot spot in Novi Sad.

→ **BIANCO as a follow-up**

Adverse Outcome Pathway (AOP)

(framework proposed by Ankley et al. (2010) *Environ.Toxicol.Chem.* 29, 730-741.

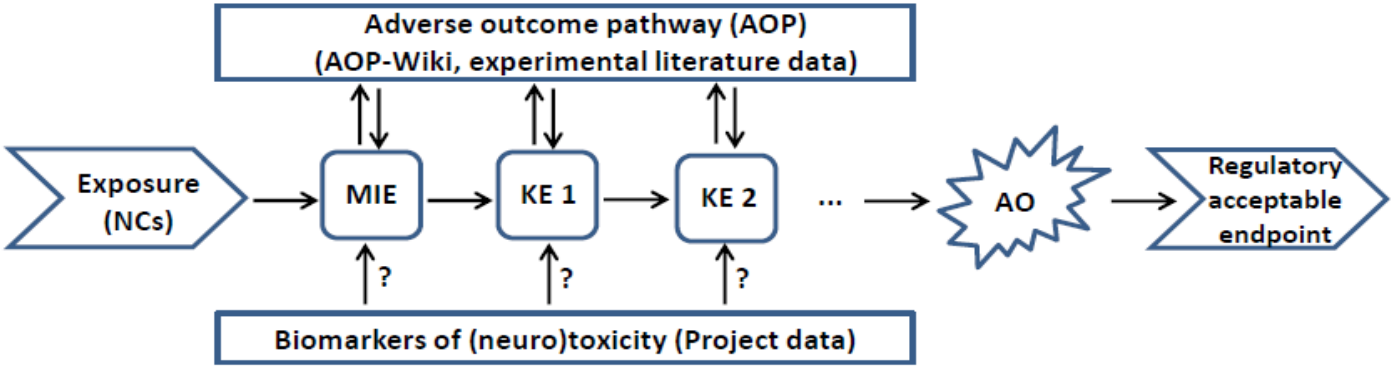


Kleinstreuer et al. (2016) Adverse outcome pathways: From research to regulation Scientific workshop report. *Regul. Toxicol. Pharmacol.* 76, 39-50

Specific objectives of the Project :

(a) To identify molecular targets and define biomarker patterns of NCs frequently occurring in the aquatic environment, integrate them into existing AOP frameworks, and provide new lines of evidence for key events relationship (KERs) between NCs exposure and Adverse Outcomes (AOs).

(b) To contribute to the new strategies in development of AOPs for NCs in aquatic environment by combining experimental and data mining approach i.e. by linking observed specific biomarker responses with the Molecular Initiating Events (MIEs) and/or Key Events (KEs) reported in the accessible AOPs, and give input to database supporting safety evaluation of chemicals and regulatory decision-making.



(c) To move forward the research of our group, from the traditional (eco)toxicity testing to the novel field of development of AOP signatures and networks, boost research and project management capacities of the PI and participating young scientists, and prepare the research group for the upcoming EU-funded programs for research and innovations.

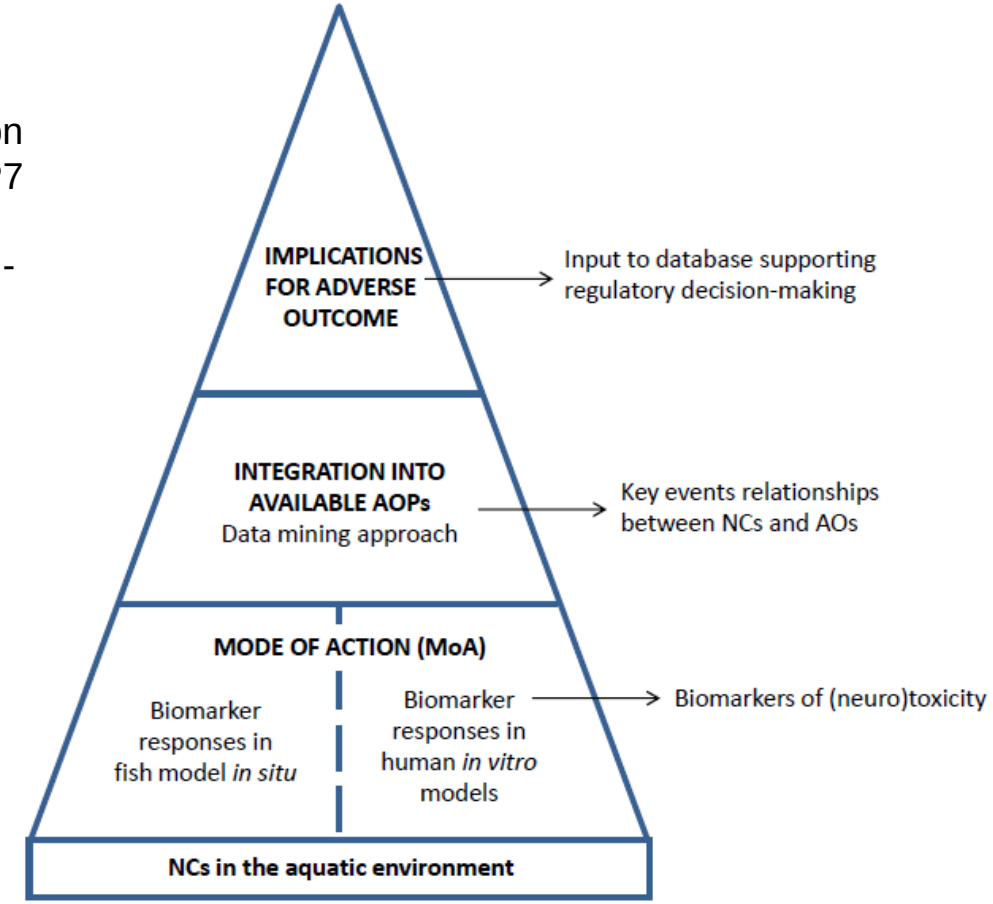
***Real-life scenario*:**
Caging experiment with common carp (already conducted within FP7 SOLUTIONS) at:

- Danube River pollution hot spot - confirmed presence of NCs
- Sava River – poorly chemically characterized

***High throughput lab study*:**
Human neuroblasoma SH-SY5Y cell line:

- Treatment by environmentally relevant NCs, single and in mixtures

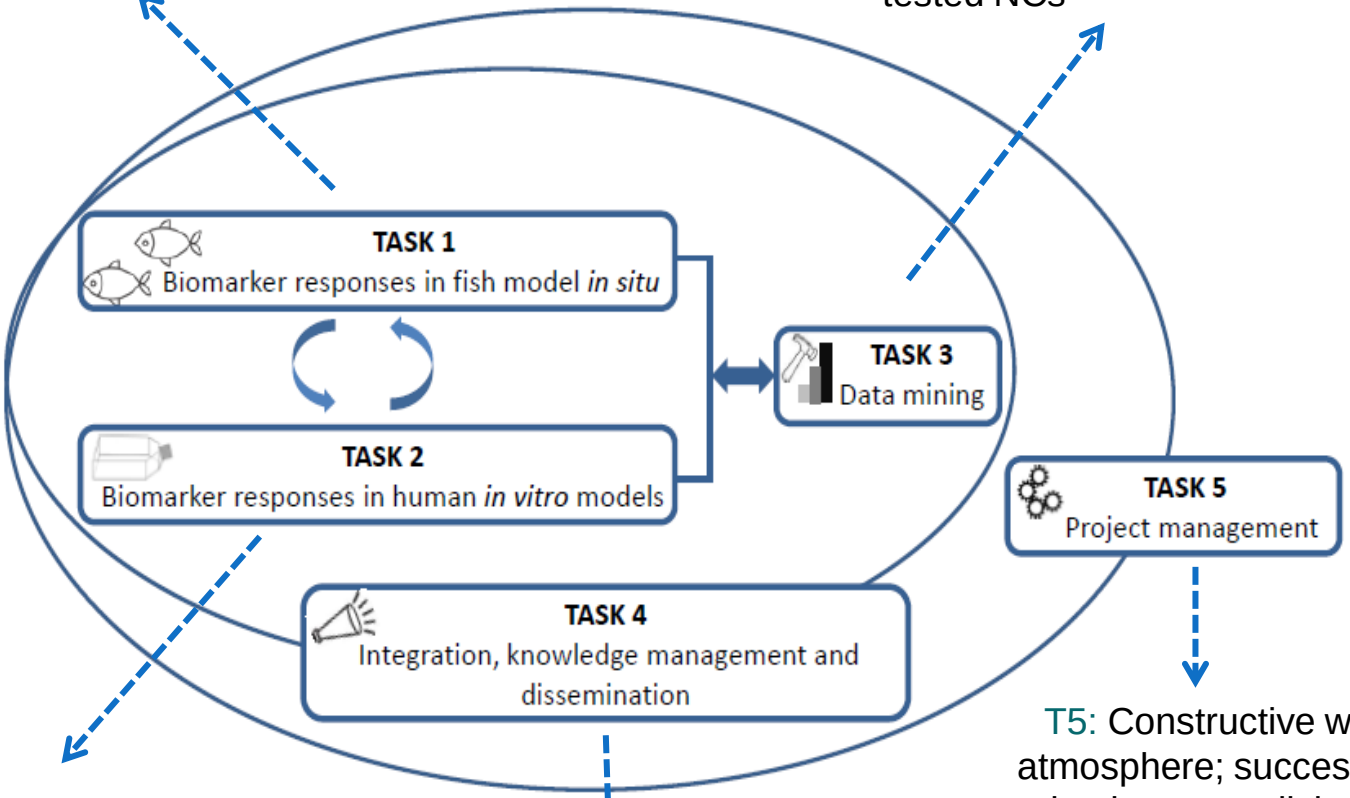
***Data mining*:**
Literature and AOP-Wiki search;
Extracting of AOPs for NCs



Biomarkers of neurotoxicity	Tissue/cell line	Methods
Key neurotransmiter pathways (corresponding enzyme or receptor activity)	fish brain tissue; SH-SY5Y cell line	enzyme activity assays; gene expression analyses (RQ-PCR)
Disturbance of exocytosis of neurotransmiters		gene expression analyses (RQ-PCR)
Myelination of axones and neuroprotection		gene expression analyses (RQ-PCR)
Neuroendocrine regulation of reproduction		gene expression analyses (RQ-PCR)
Disturbance of membrane resting potential		enzyme activity assays

T1: Biomarker response patterns for real-life mixtures of NCs;
their applicability;
responsive biomarkers as potential KEs

T3: Biomarker responses (T1 and T2) as MIEs and KEs defined within the existing AOPs;
implication to KERs and AOs for tested NCs



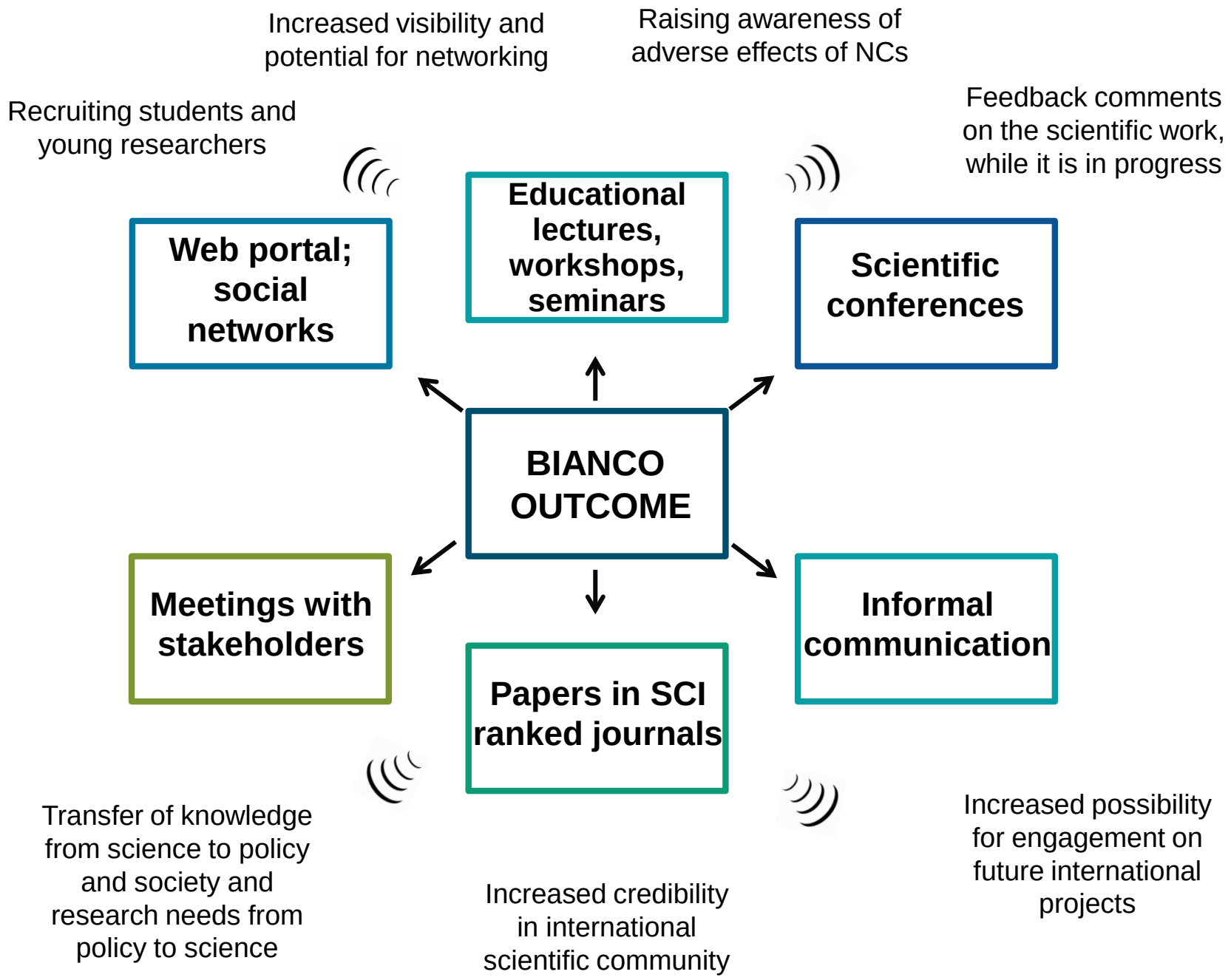
T2: Biomarker response patterns for specific NCs;
common biomarkers regardless primary MoA of NCs;
responsive biomarkers as potential KEs

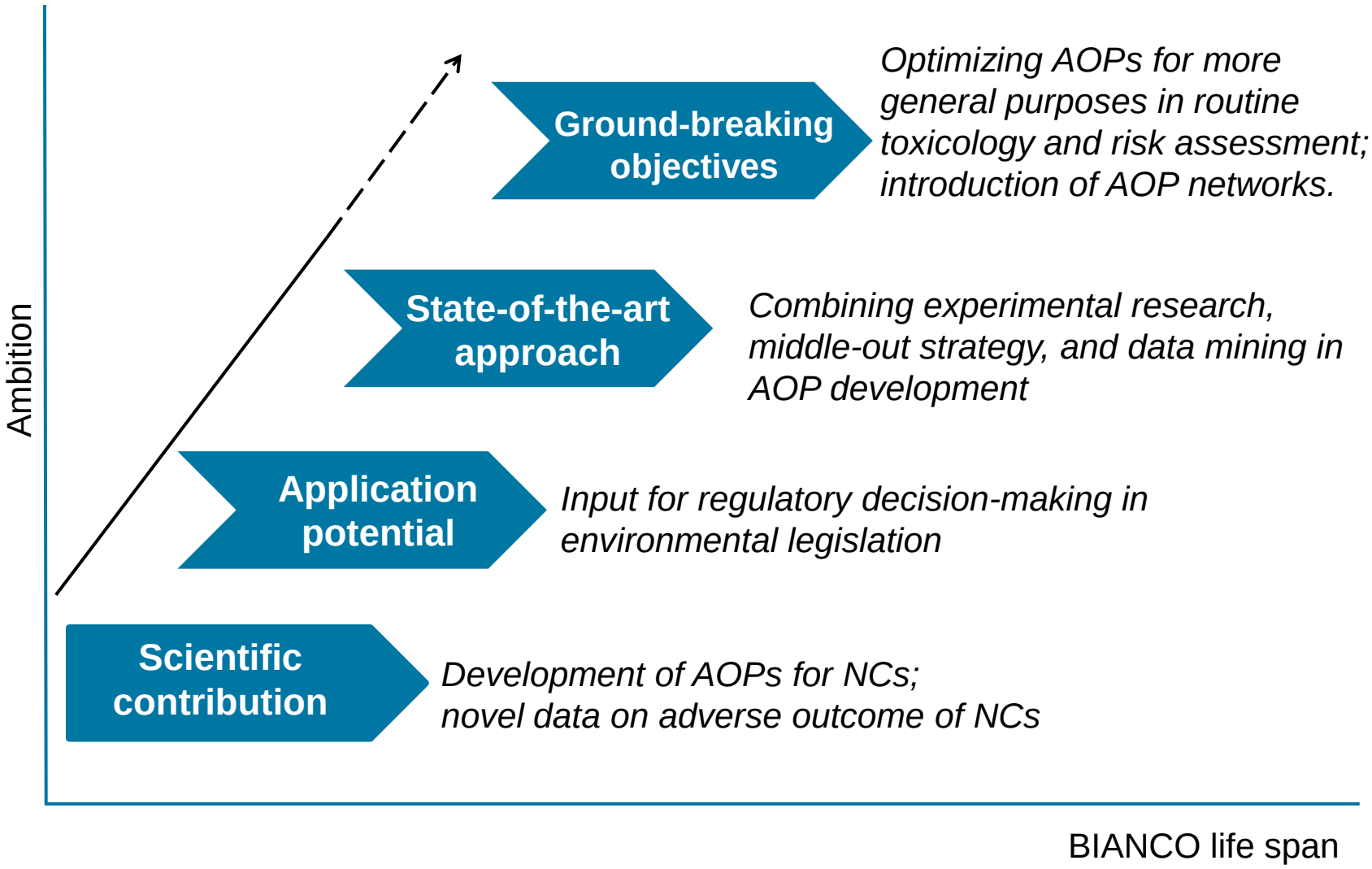
T4: Laboratory knowledge repository; dissemination; transfer of knowledge from science to society

T5: Constructive working atmosphere; successful and timely accomplishment of project tasks and goals

IMPLEMENTATION

IMPACT AND DISSEMINATION





AMBITION

„Some things you don't have to PROMISe. You just do."
Rick Yancey, sci. fiction writer