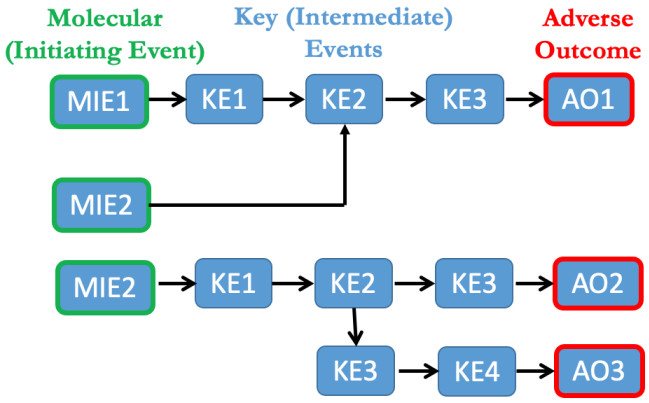
# Nanomaterial-relevant Adverse Outcome Pathways

**Background**

The concept of the adverse outcome pathway (AOP) is a useful tool to develop and understand mechanism-based hazard identification relying on non-animal methods. Nanomaterial-relevant AOPs have been developed and promoted by PATROLS.

The AOP concept was initially introduced in the context of ecotoxicology, but has recently been used extensively in human toxicology. It is endorsed by the Organisation for Economic Cooperation and Development (OECD) as suitable for risk assessment. Specifically, the OECD AOP programme aims at developing AOPs and it provides guidance for their uptake for hazard identification of compounds.

AOPs describe the key events (KEs) leading from a molecular initiating event (MIE) to an adverse outcome (AO), thereby addressing different levels of biological organization from molecules and cells to organs and organisms. The causal relationship between the change of an upstream KE to a downstream KE is described as a key event relationship (KER). The mechanistic evidence identified in the context of AOPs can be used to guide the identification and development of *in vitro* methods that target defined key events of the pathway (Da Silva et al. 2021) (Halappanavar et al. 2021).




Multiple MIEs may induce a single AO and a single MIE may induce multiple AOs. KEs may be shared by different AOPs. Shared or individual KEs can be targeted in intelligent testing strategies.

Figure 1: Schematic representation of an AOP. The arrows between the 'Molecular initiating event' and 'key events' and between 'key events' and 'Adverse outcome' represent key event relationships. There can be more than one key event



This project has received €12.7M in funding from the European Union's Horizon 2020 research and innovation programme under grant agreement 760813

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**Outcomes**

PATROLS has contributed to the development and/or description for:

- Nanoparticle-induced lung carcinogenicity (described in Nymark et al., 2021)
- AOP173: Substance interaction with the lung resident cell membrane components leading to lung fibrosis (https://aopwiki.org/aops/173) (described in Halappanavar et al., 2020)
- AOP303: Frustrated phagocytosis-induced lung cancer (https://aopwiki.org/aops/ 303) (described in Halappanavar et al., 2020)
- In addition, PATROLS members have described how to develop strategies that help identify and prioritize alternative schemes involving individual test models, toxicity endpoints, and assays for the assessment of adverse outcomes, as well as strategies that enable validation and refinement of these schemes for the regulatory acceptance non-animal testing strategies (Halappanavar et al., 2021)
- PATROLS members have co-authored a policy paper describing how to implement AOPs in decision making for nanomaterials (Ede et al, 2020).

**References**

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