# QSAR modeling to support regulatory purposes

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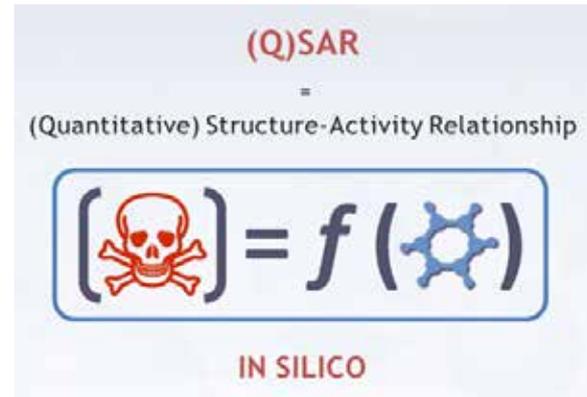
# Problem statement and motivation

Too many chemicals to test with standard animal-based methods
– Cost, time, animal welfare

Alternative

(Q)SAR
=
(Quantitative) Structure-Activity Relationship

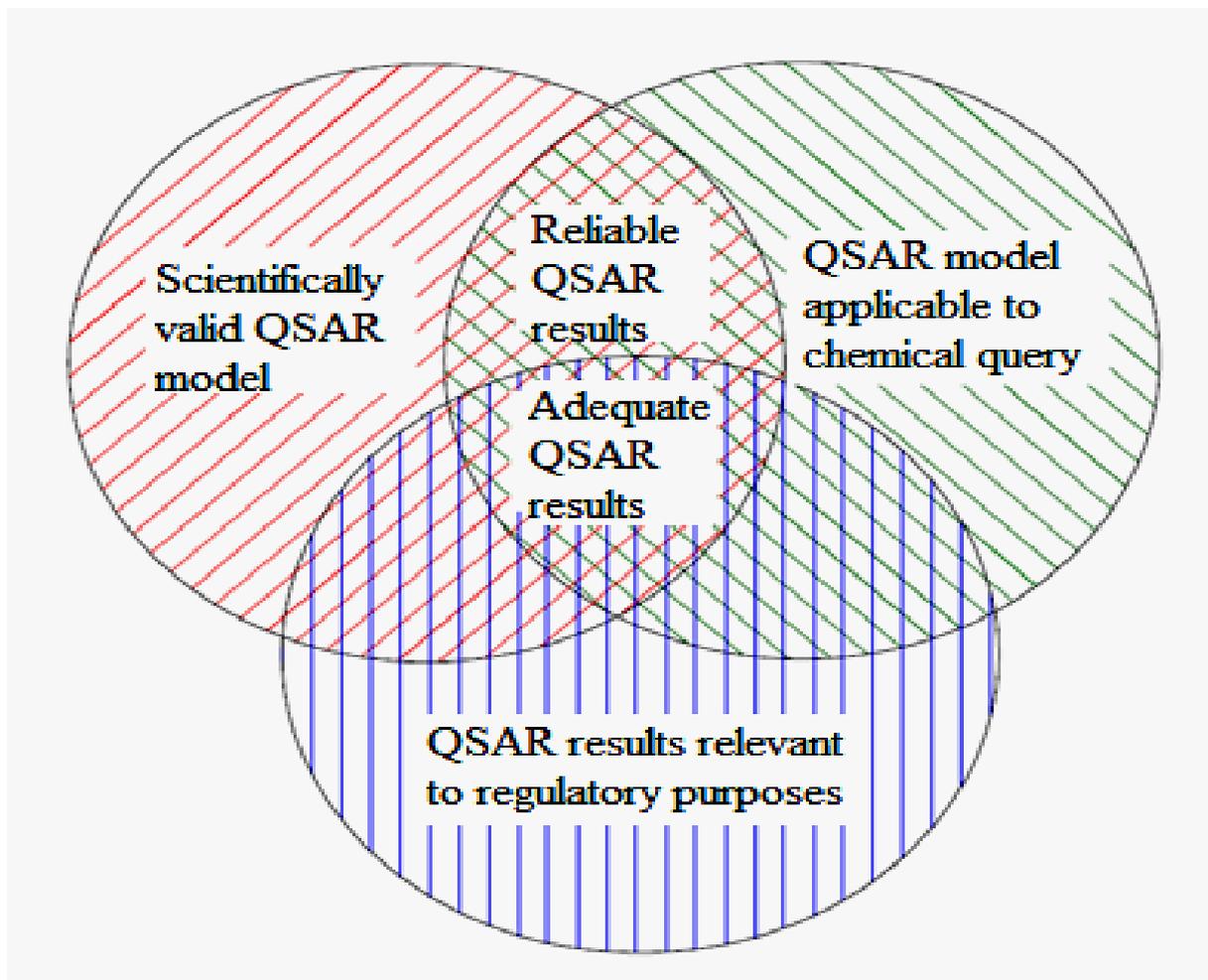IN SILICO

- Organic **pollutants** with exposure potential **accumulate** in body tissues
  - Ø Cause **intoxications** to wild life and humans
- Existence of **gaps in the experimental data** for environmental endpoints
  - Ø Need to fill the data gaps and bridge the **lack of knowledge**
- **Regulatory** requirements:
  - Ø Reduce **animal** testing, **time** and **costs**
- Ø **Methodology:** use of QSAR/QSPR to **predict** the **endpoints** of interest.

# QSARs for regulatory purposes

# The conditions for the validity of QSARs

## The 5 OECD Principles:

| Principle | Description |
|---|---|
| 1) A defined endpoint | Any **physicochemical, biological or environmental** effect that can be measured and therefore modelled. |
| 2) An unambiguous algorithm | **Ensure transparency** in the description of the model algorithm. |
| 3) A defined domain of applicability | **Define limitations** in terms of the types of **chemical structures**, physicochemical properties and mechanisms of action for which the models can generate **reliable predictions**. |
| 4) Appropriate measures of goodness-of-fit, robustness and predictivity | a) The internal **fitting** performance of a model<br>b) the **predictivity** of a model, determined by using an appropriate **external test set**. |
| 5) Mechanistic interpretation, if possible | Mechanistic **associations** between the **descriptors** used in a model and the **endpoint being predicted**. |

# OPERA approach

- Curated **open** access datasets (https://doi.org/10.1186/s13321-018-0263-1)

- **Open-source** code (github.com/NIEHS/OPERA)

- **Transparent** unambiguous algorithms (https://qsardb.jrc.ec.europa.eu/qmrf/)

- **Transparent** validated performances (https://doi.org/10.1080/1062936X.2016.1253611)

- **Defined** applicability domain and limitations of the models

- Predictions **available** through:

    - The EPA's CompTox Dashboard (https://comptox.epa.gov/dashboard)

    - Free and open-source standalone application (github.com/NIEHS/OPERA)