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"New Approach Methodologies"- Requirements for setting OELs

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New Approach Methodologies – Why?

Growing concern on the value and use of animal experiments

- Societal reasons
  - Animal welfare

- Scientific reasons
  - Predictive capacity and power for detecting human health effects
  - Coverage of human endpoints
    - Mild effects such as headache, psyco-somatic effects
    - Prediction of specific human diseases such as Parkinson, Alzheimer, ADHD

New Approach Methodologies – What?

New Approach Methodologies (NAMs)

- Indicate a complex system that joins together many different techniques to support a decision on the effect of a substance on the human health, thereby avoiding the use of vertebrate animals.
- Any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals.

Next-Generation Risk Assessment

- New risk assessment paradigm
- But what does it look like?

New Approach Methodologies

- Started with *in vitro*, *in silico*, *in chemico* as part of 3R's
  - in vitro irritation tests, in vitro sensitization tests
  - qualitative tests: yes/no answers

- NAMs are being developed for the Next-Generation Risk Assessment
  - bottom-up or top-down

- Top-down (revolution): but what is the view at the 'top'?
- Bottom-up (evolution): developing tools within present frameworks aimed at
  - replacement of animal experiments
  - fulfilment of present regulatory requirements

New Approach Methodologies: aim

- Basic question:
  - are there potential risks, and if so, what kind of effects can be expected?
    - Production/manufacturing
    - Application/use
    - Disposal

- Present toxicological data requirements limited by
  - proportionality
  - costs in terms of time, money

- Limited or no data on e.g., effects on reproduction, kinetics

New Approach Methodologies: aim

- New risk assessment paradigm: what does it look like?
  - should be aimed at regulatory needs, not focused on meeting present requirements

- NAMs are not just about replacement of animal experiments
  - not just generate the same data as with animal experiments

- NAMs should be:
  - aimed at the (bigger) questions behind the requirements
  - compatible with developments in exposure assessment
    - exposome
    - smart air monitoring sensors
    - real exposure scenarios

New Approach Methodologies: regulatory needs

1. What are the hazardous properties of the chemical? Is it a sensitizer, does it cause cancer etc.?
   - Qualitative: yes/no

2. What is a safe level of exposure, so safe production and use of the chemical can be assured?
   - Human limit value, *e.g.*, an OEL

3. What effects can be expected when people have been exposed to a higher level than the safe level?

4. Does a certain chemical cause a certain disease, such as *e.g.*, Alzheimer's?

New Approach Methodologies: Health-based Guidance Values

- Define the strategy and develop the tools in coherence

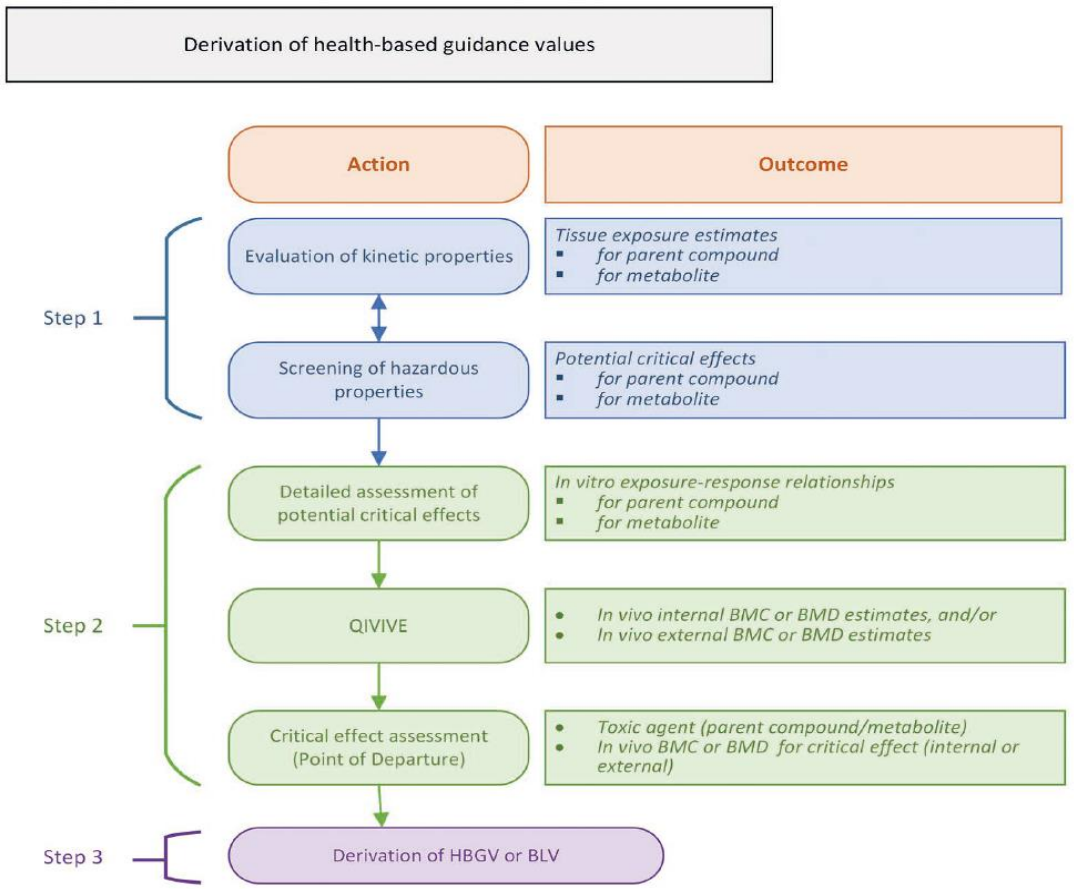


Fig. 2: Stepwise approach for generating data to meet the information needs for derivation of health-based guidance values (HGBV)

Bos et al (2018). *Towards an Animal-Free Human Health Assessment: Starting from the Current Regulatory Needs.* ALTEX 2020; 37:395-408. doi:10.14573/altex.1912041

New Approach Methodologies: QIVIVE

- In vitro EC50/EC10

- Steady-state plasma concentration

- External exposure estimate

NAMs: QIVIVE

- **In vitro EC50/EC10**
  - **Concentration over time?**

- Steady-state plasma concentration

- External exposure estimate

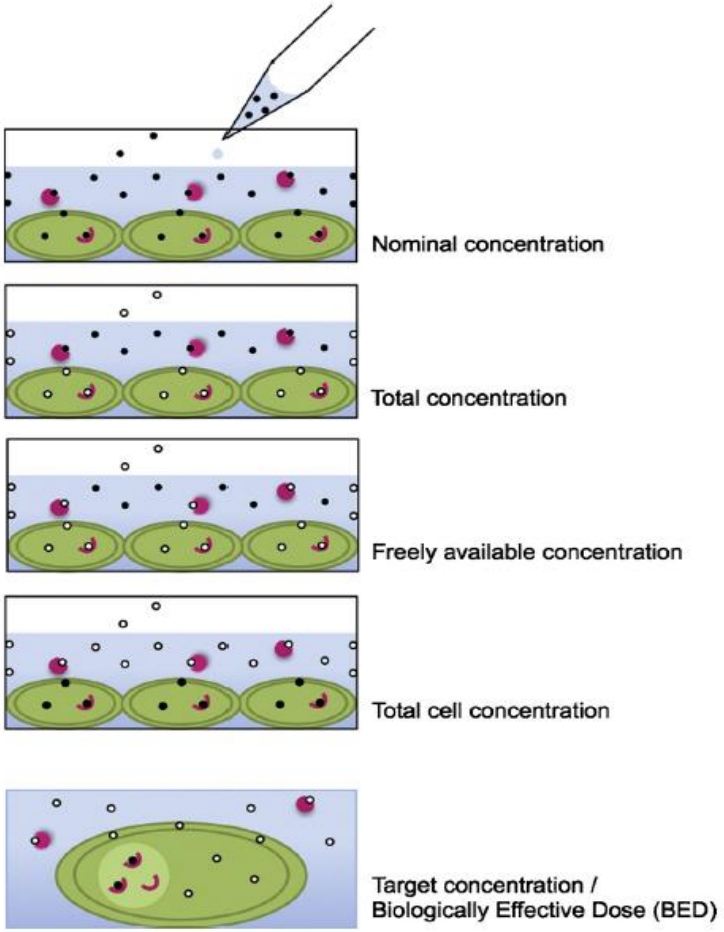


Fig. 2. Illustrations of different (surrogate) dose metrics in a typical *in vitro* assay. At the bottom, the theoretical target dose, also termed biologically effective dose (BED) is shown. Towards the top, surrogate dose metrics further away from the target site are shown. Solid black circles represent the chemical fraction included in the depicted measure of dose, while the open black circles represent the fraction not determined by the depicted dose metric.

Groothuis et al (2015). *Dose metric considerations in* in vitro *assays to improve quantitative* in vitro-in vivo *dose extrapolations.* Toxicology 332:30-40.

New Approach Methodologies: QIVIVE

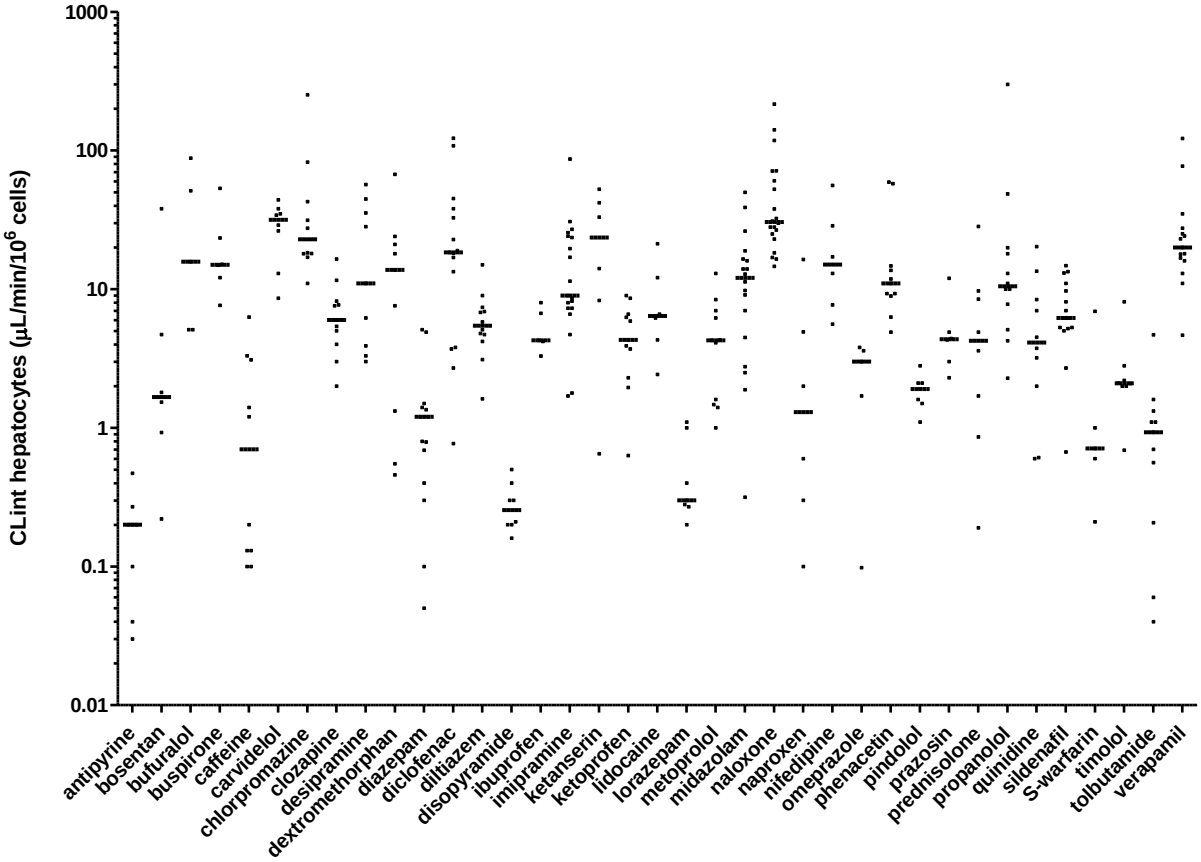
- "Ideally an in vitro approach requires the right types of cells or organoids for assays that can closely mimic the physiological environments in vivo, including the native extracellular milieu and cell-to-cell interactions normally encountered in a tissue. This is hardly the case as the tissue culturing technology stands today."

- "With respect to dosimetry, there are challenges in describing the in vitro kinetics in the culture medium, where the stability of the test chemicals would affect the cellular responses, and challenges in mimicking the actual chemical kinetics cells in the target tissues experience under real-world exposure scenarios."

- "Defining the proper in vitro point-of-departure (PoD) at the cellular level and extrapolating it to in vivo apical endpoint alterations, often occurring on a different time scale, is a challenging task."

Zhang et al (2018). *Bridging the Data Gap From in vitro Toxicity Testing to Chemical Safety Assessment Through Computational Modeling.* Front. Public Health 6:261. doi: 10.3389/fpubh.2018.00261

New Approach Methodologies: QIVIVE



Louisse et al (2020). *Towards harmonization of test methods for* in vitro *hepatic clearance studies.* Toxicology in vitro 63:104722. doi.org/10.1016/j.tiv.2019.104722

New Approach Methodologies: QIVIVE

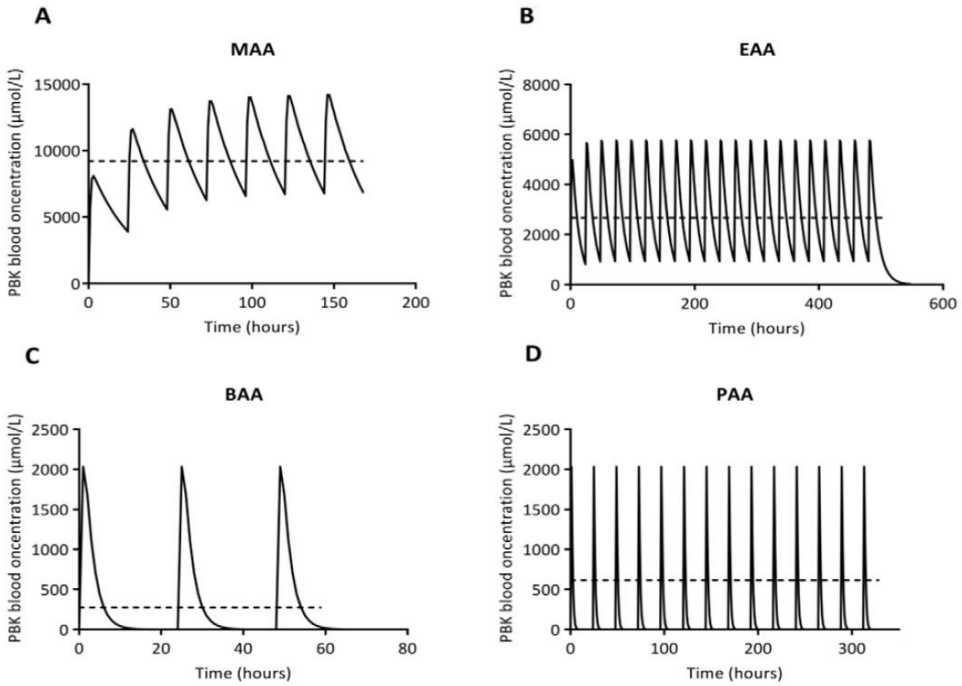
- In vitro EC50/EC10

- **Steady-state plasma concentration**
  - **often average plasma concentration**

- External exposure estimate

New Approach Methodologies: QIVIVE

- **Steady-state plasma concentration: example glycol ethers**



Fragki et al. (2017) In vitro *to* in vivo *extrapolation of effective dosimetry in developmental toxicity testing: Application of a generic PBK modelling approach. Toxicol. Appl. Pharmacol. 332:109-120.* http://dx.doi.org/10.1016/j.taap.2017.07.021

Fig. 4. (A) Time-course PBK model simulation of MAA in venous blood, after oral administration of eight consecutive daily doses of the parent EGME (dose: 620 mg/kg bw/day). The average venous blood terminal half-life of MAA was 20 h. (B) Time-course model simulation of EAA in venous blood, after oral administration of 21 consecutive daily doses of the parent EGEE (dose: 372 mg/kg bw/day). The venous blood terminal half-life of EAA was 8 h. (C) Time-course model simulation of BAA in venous blood, after oral administration of three consecutive daily doses of the parent EGBE (dose: 200 mg/kg bw/day). The venous blood terminal half-life of BAA was 1.5 h. (D) Time-course model simulation of PAA in venous blood, after oral administration of 14 consecutive daily doses of the parent EGPE (dose: 300 mg/kg bw/day). The venous blood terminal half-life of PAA was 0.7 h.

New Approach Methodologies: QIVIVE

- In vitro EC50/EC10

- Steady-state plasma concentration

- **External exposure estimate**

New Approach Methodologies: QIVIVE

Jarabek (1995) *Consideration of temporal toxicity challenges current default assumptions.* Inhal. Toxicol. 7:927-946. doi:10.3109/08958379509012801

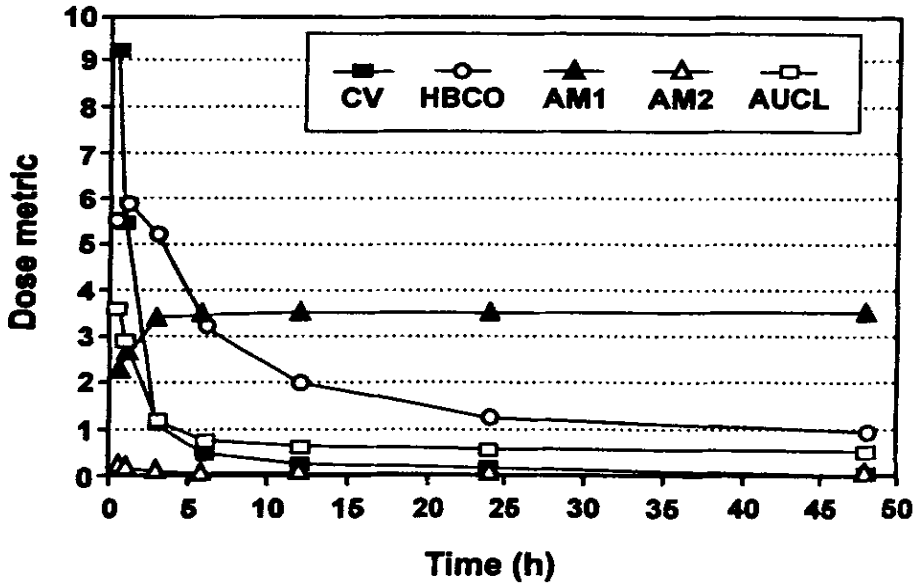


FIGURE 8. Model simulations of different dose metrics in the rat of inhaled DCM at equivalent C x *t* exposure products of 200 ppm-h. The PBPK model used was that published by Andersen et al. (1991). Parameter values used are available elsewhere (Jarabek & McDougal, 1993). CV, venous parent concentration (mg/L); HbCO, percent of carbon monoxide bound to hemoglobin (%); AM1, amount of metabolite formed per gram liver tissue via the mixed-function oxygenase system (mg-h/g); AM2, amount of metabolite formed per gram liver tissue via the glutathione system (mg-h/g); and AUCL, area under the curve for parent compound concentration in the liver (mg/L-h).

NAMs - opportunities

Next-Generation Risk-Assessment/New Risk Assessment Paradigm

- Just new tools (NAMs) but same concept?

- Or start from new concept ("Virtual human")
  - Aimed at actual exposure scenarios
    - temporal characteristics
    - combined exposures

  - What does this mean for development of NAMs?
  - If animal models were not a good model for humans than how do we assure that NAMs will be…

NAMs - Considerations

- Developing NAMs
  - What is the question to be answered?
    - Validation of single tools or combination of tools?
    - Validation with animal data (but animals are not a good model and then back at and limited to all the old endpoints)
  - What is the appropriate *in vitro* dose metric (in relation to mode of action)?
  - How to extrapolate *in vitro* exposure-response relationship to *in vivo* (QIVIVE is a two-way road)?
  - How to relate *in vitro* endpoints of one tool or a combination of tools (with different temporal characteristics) to *in vivo* physiological outcome (including subtle effects and human diseases)?

Thank you

for your attention

Virtual Human Platform project: VHP4Safety
(https://vhp4safety.sites.uu.nl)