Safety & Environmental Assurance Centre

Practical application of *in silico* approaches in Next Generation Risk Assessment for consumer products

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Introduction

Use of computational models is commonplace across the consumer product development pipeline. Approaches include Structure-Activity Relationships (SAR), Quantitative Structure-Activity Relationships (QSAR), read-across, as well as mechanistic and pharmacokinetic models. Next Generation Risk Assessment (NGRA) is an exposure-led, hypothesis driven approach that integrates one or more New Approach Methodologies (NAMs), which can be applied to ensure the safety of consumer products without the need for animal testing.

Methods to identify and characterise hazard and risk are applied in a tiered manner starting with exposure-based waiving (e.g. TTC) and building through *in silico*, *in chemico* and *in vitro* assays combined in weight of evidence assessments. The need for robustness, reliability, traceability and transparency of decisions made using computational approaches is paramount to their acceptance and success.

In Silico input to NGRA

There are multiple aspects of NGRA that either rely or are supplemented by *in silico* approaches. Figure 1 shows a graphical framework for NGRA with areas for *in silico* input circled in red.

- Many of the chemical-dependant input parameters for PBK modelling can be predicted *in silico* e.g. metabolic clearance, unbound fraction in plasma, various partition coefficients(2)
- Predictions for many traditional endpoints are available from a variety of free and commercial software
- Models to predict Molecular Initiating Events (MIEs) have recently been developed and expanded to cover many protein targets of toxicological significance
- Models to predict likely *in vivo* metabolites can also be used to investigate detoxification and activation of chemicals
- Read across where information from one chemical is used to infer activity of another "similar" chemical is a common feature in many risk assessments

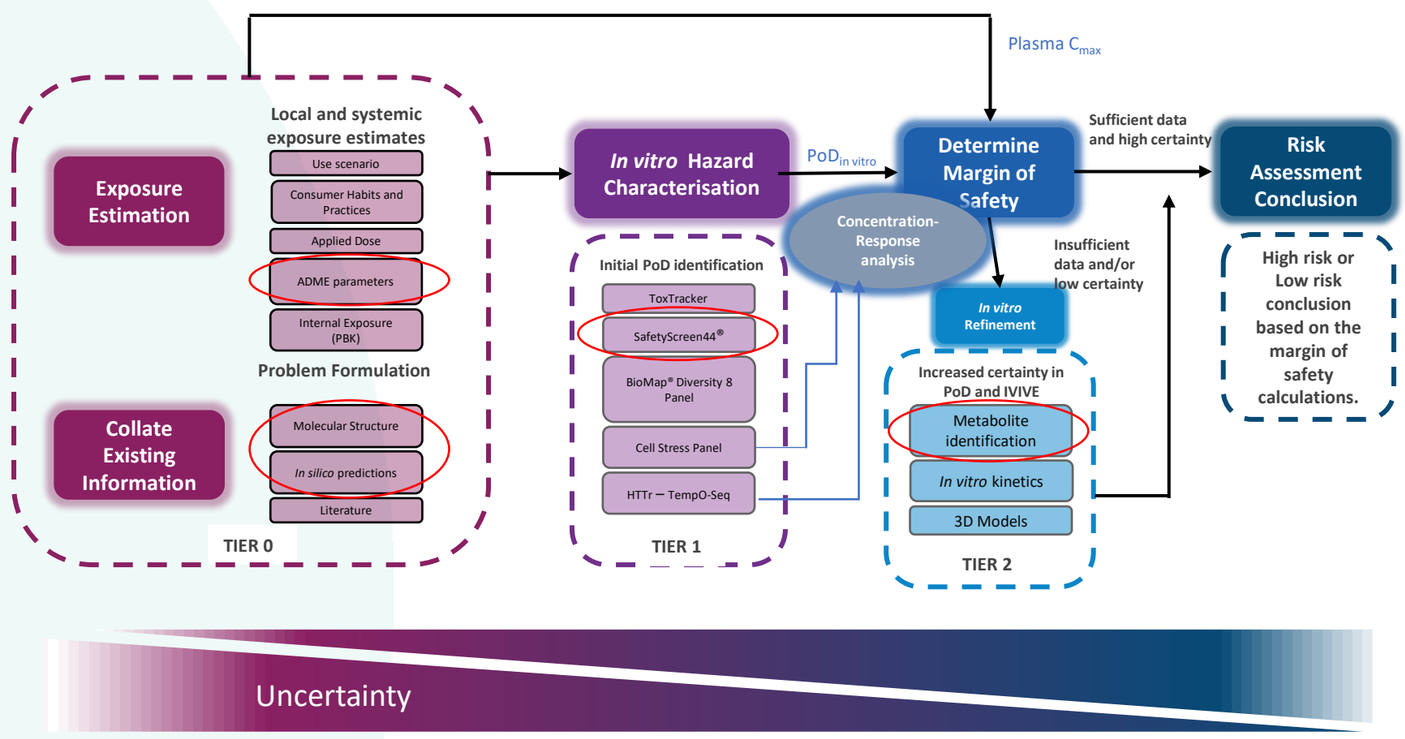


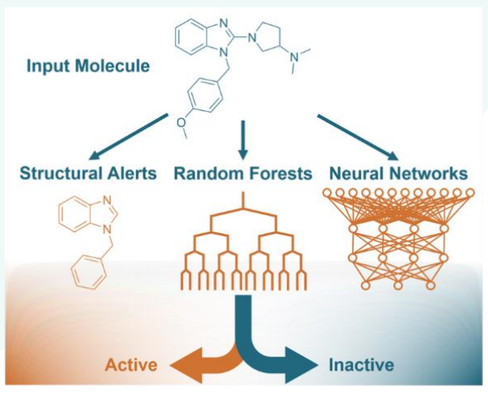
Fig.1 Framework for ab initio next generation risk assessment(1)

Example 1 – MIE Atlas

An MIE is part of the Adverse Outcome Pathway (AOP) framework. It is the initial interaction between a molecule and a biomolecule or biosystem that can be linked to an outcome via a pathway.(3) *In silico* models are available using a variety of methods for >100 protein targets. Predicted MIEs can be followed up with focused *in vitro* studies.(4)

Bioactivity (MIE, key event level) represents protective estimate of point of departure (even when the pathway is not fully characterised).(5)

Understanding interactions at the MIE and key event level allows reliable predictions which have less variability from subsequent complex biological networks.



Current work is focusing on expanding the MIE Atlas concept to quantitative MIE prediction and MIEs associated with mitochondrial toxicity.

Example 2 – Read Across

Read-across can often help to define a hypothesis that leads to further testing e.g. *in vitro* point of departure characterisation, or metabolism investigation. In this way computational approaches help to structure an assessment.

Figure 2 shows a typical workflow used to introduce consistency and rigour to the read across approach. *In silico* models underpin the target profiling, source identification and source evaluation steps.

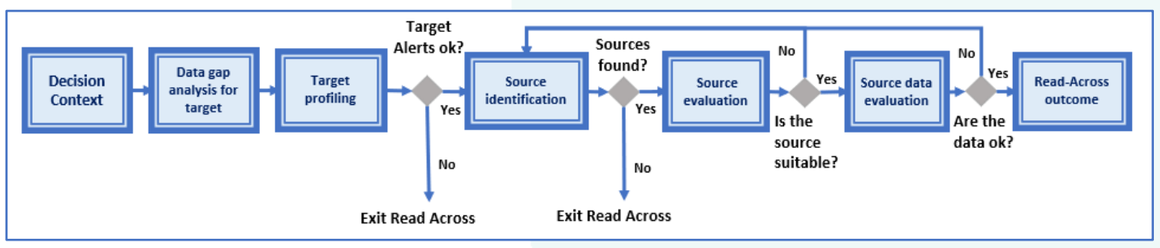


Fig 2 Typical Read Across workflow

When attempting to complete a risk assessment including computational approaches it is often necessary to generate additional data using NAMs to build confidence in the underlying hypothesis.

Conclusions

In silico approaches are used by many regulators for prioritisation and screening of chemical inventories and there are some limited examples of use in final safety decisions. Regulatory uptake of *in silico* approaches remains a challenge in some areas (e.g. chemical registration), though they are often listed as potential alternative approaches. Some chemical regulations are hazard-focussed and do not include adequate consideration of exposure and risk. More flexibility regarding the inclusion of non-traditional data and alternative means of demonstrating safety for chemicals registrations together with sharing examples of scientifically robust assessments will help to increase the acceptance of read-across and *in silico* approaches to allow them to fulfil their potential to drastically reduce the reliance on animal testing.

References

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