Safety & Environmental Assurance Centre

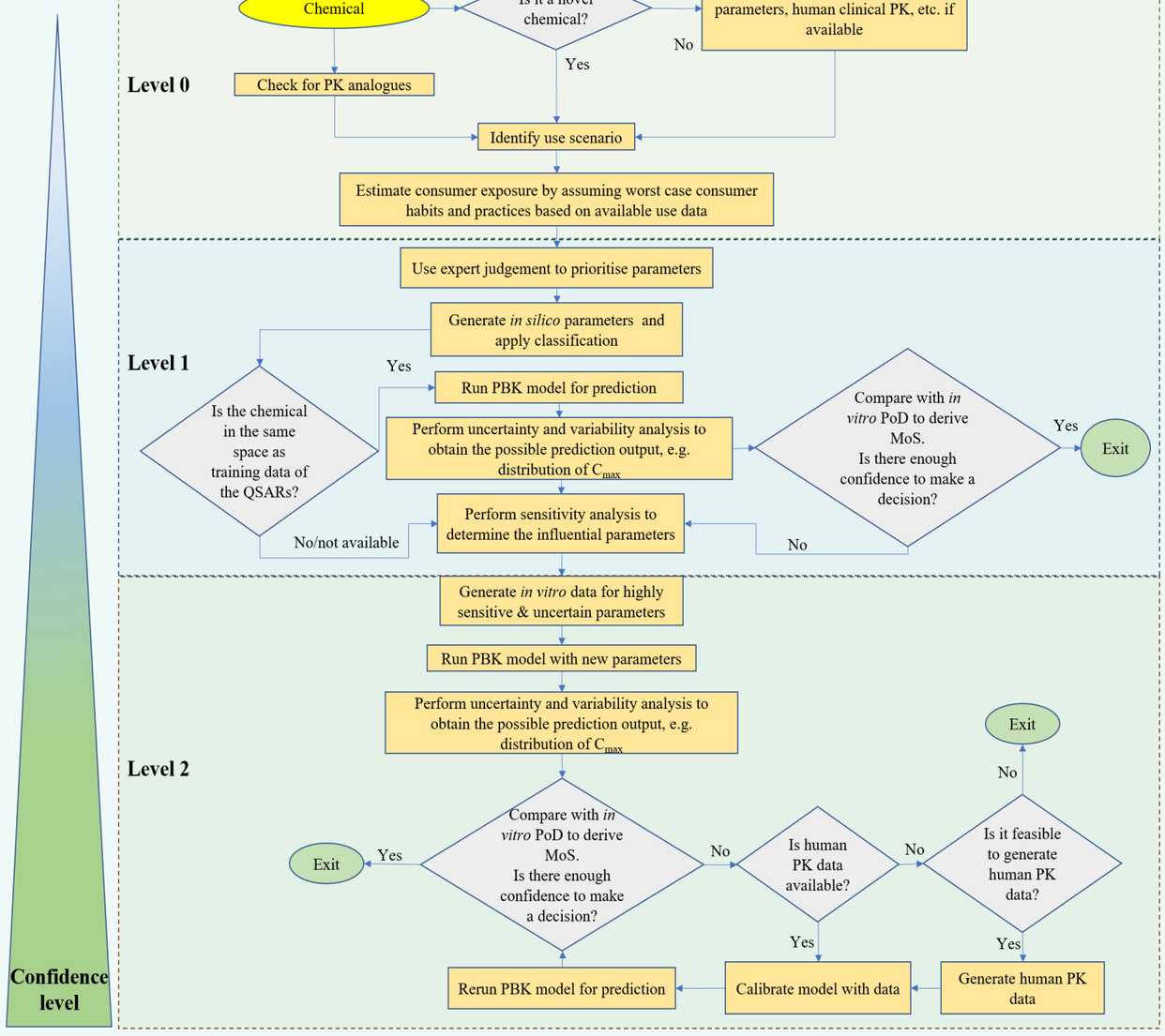
Framework for Physiologically-Based Kinetics (PBK) modelling in the Next Generation Risk Assessment (NGRA) of Consumer Goods.

Thomas E Moxon, Dawei Tang, Beate Nicol, Joe Reynolds, Georgia Reynolds, Alistair Middleton, Hequn Li
[1]*Unilever, Sharnbrook, United Kingdom;*

Introduction

Physiologically-Based Kinetics (PBK) modelling is an integral part of the tool set used in Next Generation Risk Assessment (NGRA) of ingredients in consumer products (Moxon, *et al.*, 2020, Baltazar, *et al.* 2020). Accurate predictions of the exposure allow for comparison to biological effects, and an understanding of the risk to consumers. However, providing confidence in these exposure predictions without the use of *in vivo* data for validation can prove difficult. This work proposes and outlines the use of a PBK framework, with application to a number of case study chemicals (coumarin presented here) in hypothetical products, and further sets out a vision for future development of the framework towards a future goal of a fully probabilistic PBK framework.

Current Framework & Case Study



The framework breaks the modelling down into 3 levels for a novel chemical:

Level 0: Checking for PK analogues, existing data, and understanding the consumer usage of the exposure scenario

Level 1: Modelling with *in silico* parameters:

- Checking applicability domain of parameter
- Run PBK models, and perform uncertainty & population analysis
- Perform sensitivity analysis to highlight parameters which could warrant further study & understanding

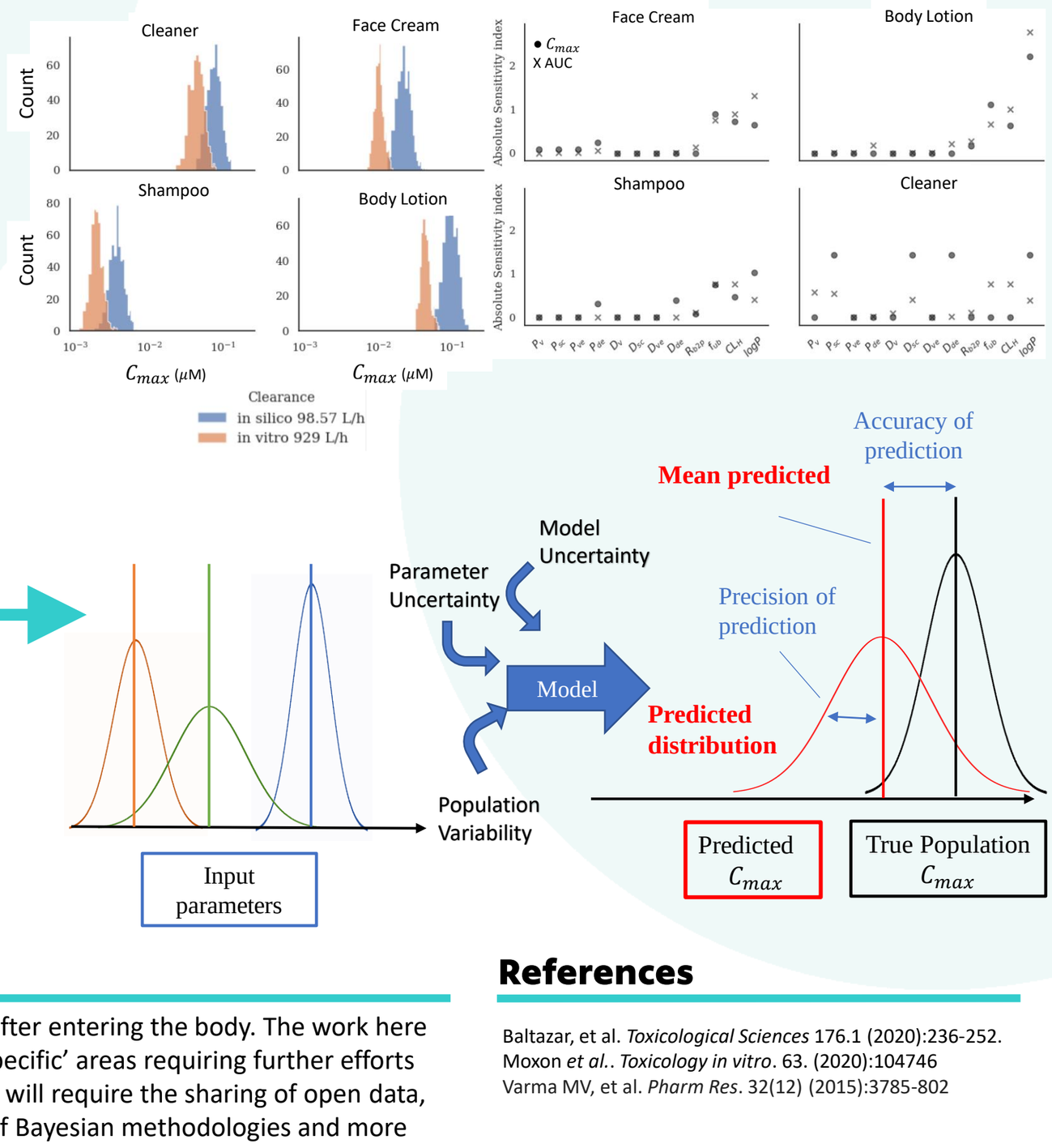
Level 2: Generate *in vitro* data for sensitive/uncertainty parameters

- Re-run PBK models & uncertainty/population analysis with new parameterisation
- Generate distribution of C_{max} values to compare with in vitro bioactivity data for the derivation of margin of exposure

The framework was applied to 3 chemicals in 4 different consumer use scenarios (At 0.1% inclusion), with the Coumarin results presented here.

The sensitivity plots show how the effect of different parameters on the output can differ between different exposure scenarios for the same chemical, and for the different output metrics (C_{max}: ●, AUC: x).

The final output for Coumarin shows possible distributions at two different clearance rates (*in silico & in vitro*), and how the exposure scenario can affect both the mean predicted C_{max} and the standard deviation.



Future Vision – Moving towards Probabilistic PBK

Current Approach

- Local Sensitivity Analysis
- Use of default values for parameter uncertainty / variability based on expert judgements
- Simple classifiers, e.g., ECCS (Varma et al.) etc.
- Default protective uncertainty factors based on expert judgement (e.g., 10x)

Future Vision

- Global Sensitivity Analysis
- Mechanistically and empirically / statistically informed parameter uncertainty & variability
- Classifiers to consider additional potentially important processes, e.g., biliary clearance, lymphatic circulation, active secretion/reabsorption etc.
- Data-driven additional uncertainty factors

Conclusion and Next Steps

PBK modelling offers an intuitive insight into understanding how chemicals may behave after entering the body. The work here presents a framework for building confidence in the results, and highlighting 'chemical-specific' areas requiring further efforts to allow confident usage. There are still challenges to face in the area, and many of these will require the sharing of open data, to build models and better understand uncertainty in predictions (e.g., through the use of Bayesian methodologies and more complex processes (e.g., transport mediated processes)

References

Baltazar, et al. *Toxicological Sciences* 176.1 (2020):236-252.
Moxon *et al.*. *Toxicology in vitro*. 63. (2020):104746
Varma MV, et al. *Pharm Res*. 32(12) (2015):3785-802