Title of Challenge

Improved *in vitro* to *in vivo* extrapolation in chemical safety risk assessment of human systemic toxicity

Background

The safety assessment of new chemicals across the industrial chemical, agrochemical, pharmaceutical and consumer product sectors has long relied on high dose treatments in animals with default methods for extrapolating observed results to low level exposures in human populations. These traditional 'whole-animal' methods are expensive, can use many animals, and can sometimes be misleading with respect to human safety risk. As a result, increasing emphasis has centred on the development of predictive *in vitro* models for endpoints of toxicity, and their use to provide mode-of-action understanding within the risk assessment process. Although progress has been made in developing *in vitro* models to predict some chemical toxicities such as skin irritation and corrosion, models to detect systemic toxicity across multiple organs are not currently available. Recently published opinions by the EU Scientific Committee on Consumer Safety (1) and a review by experts selected by the European Commission (2) indicate that, in the future, greater priority needs to be given to developing non-animal approaches which provide biological and chemical concentration-response data that can be integrated into consumer exposure and safety risk assessments.

In 2007 the US National Research Council (NRC) issued its landmark report on "Toxicity Testing in the 21st Century: A Vision and a Strategy" (TT21C; (3)). The report sees a future in which routine toxicity testing would be conducted in human cells, human tissue surrogates, or human cell lines *in vitro* by evaluating cellular responses in a suite of toxicity pathway assays. These tools would enable risk assessors to predict regions of exposure that are expected to be without adverse consequences, rather than making predictions on the incidence of specific adverse responses in human populations. A key element to the realisation of this vision is the development of systems to understand exposure parameters *in vitro* and their extrapolation to inform safe *in vivo* exposure/in use scenarios. This will be the focus for this challenge.

3Rs benefits

Historically, 'alternative' methods in toxicology have aimed to reproduce data generated using animal-based models. The aim of this challenge is not to predict animal toxicity data but rather focus on safety risk assessment based on data relevant to human use as outlined in the TT21C vision (3). As such, if successful long term, the challenge will ultimately provide tools and a means to address safety without use of animals.

Need for collaboration

As outlined in (3) a pathways approach to safety risk assessment will require a truly multi-disciplinary collaborative effort. Modelling approaches have been used with success in the pharmaceutical industry (e.g. 4) to predict human-drug kinetics (predominantly via oral routes of exposure). There are opportunities to broaden the applicability of these approaches to other areas of chemical space and to bridge the gap between *in vitro* concentration responses (toxicity pathways) and the relevance of these concentrations to human safety. There is already considerable on-going effort in this area (e.g. 5). However, this is predominantly led by traditional toxicology expertise. We would welcome the

opportunity to work with scientists able to bring new perspectives to the challenge (e.g. partnerships with SMEs and academic groups with expertise in cell biology, physiology, mathematical modelling, chemical analyses etc).

Overall objectives

- Develop a model that provides understanding of the relevance of toxicity concentration response data from human *in vitro* systems to predictions of safety following relevant *in vivo* human exposure. This should focus on assessment of systemic toxicity rather than localised endpoints such as skin or eye irritation.

- This challenge should deliver new understanding of exposure parameters *in vitro* and how these relate to safe human doses.

Key deliverables

- For a defined toxicity pathway (applicants choice[*]), establish concentration response information in human *in vitro* system(s) relevant to that pathway.

- Based on the above, establish a model(s) to predict the concentration effect and dose response in the human *in vivo* for the chosen pathway.

- Application of the above to safety decision making (e.g. would the predicted changes in the identified pathway result in an adverse health effect?).

- To provide proof of concept, consideration should be given to the validation of the proposed approach.

Industry sponsors

Unilever, Syngenta and AstraZeneca.

In-kind contributions

AstraZeneca, Syngenta and Unilever would be happy to provide relevant human, animal and *in vitro* data to which they have access, to aid access to specialised technologies, and to share expertise in modelling, risk assessment and toxicology.

Industry sponsor access to foreground Intellectual Property

Applicants free to publish or commercialise where appropriate. Access to IP will be through a non-exclusive licence to the sponsors for R&D purposes.

Duration

Up to three years

[*] Clearly, many different toxicity pathways exist associated with a large variety of adverse health outcomes. The selection of 'case study' pathways to explore the 'Toxicity Testing in the 21st Century' concept is currently the subject of much discussion (e.g. 6). For example Bhattacharya et al. (7) are currently exploring a case study (DNA-damage-induced carcinogenicity) to evaluate the potential application of a toxicity pathways-based approach within a risk assessment context for repeat dose toxicity. Some examples of toxicity pathways are listed in (8); applicants may select from this list or focus on a different pathway of their own selection.

Budget

Up to £1 million in total, inclusive of VAT where applicable

Funding model

Although success in this project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is possible that an applicant from a single organisation with departments covering a wide range of disciplines would be able to access all the required expertise. However, applications would also be welcomed from consortia of smaller more focused enterprises but this would require a strong scientific lead and vision. More than one such consortium could be funded, particularly if the proposed approaches take substantially different routes. Under such circumstances, the budget will be divided between the successful applicants who will need to identify shorter term milestones appropriate to the budget available.

References

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4. Jones HM *et al*. (2009) Modelling and PBPK simulation in drug discovery. *AAPS J* 11(1):155-66.
5. Blaauboer BJ (2010) Biokinetic modeling and *in vitro-in vivo* extrapolations. *J Toxicol Environ Health B Crit Rev* 13(2-4): 242-52.
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Keywords

Toxicity pathways, *in vitro in vivo* extrapolation, PBPK modelling, concentration response, human safety, risk assessment.