Harnessing mathematical models and uncertainty in toxicological risk assessments

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Why do we need mathematical models?

There has been increasing pressure to end the overreliance on animal experiments and to consider non-animal approaches when making decisions about human safety. Mathematical models are becoming a viable alternative.

The costs of running mathematical models are considerably less than the costs of laboratory experimentation. However, just as mice and rats are not humans, a mathematical model is not a human, but a mathematical model can be thought to be representative of a human response to chemical exposure (Gosling, 2014).

There is yet to be a general acceptance of the value of mathematical models in the context of safety assessment. The difficulty is in bringing the results from complicated mathematical models into safety assessments that have been historically driven by animal data.

In the NC3Rs-funded project, “Uncertainty and confidence in applying mathematical models and in vitro data in toxicological safety assessments”, modellers and risk assessors are working together to build mathematical models into the risk assessment process.

Bringing mathematical models into risk assessment: A statistical approach

We consider our mathematical model(s) to be a function of inputs that produce an output that is relevant to our risk assessment.

We would like to know if a new product with a certain chemical has the potential to cause an adverse human effect.

\[ f(\text{biology, chemistry, exposure}) \]

\[ \neq \]

adverse human effect

The flow chart in this box highlights the stages from a conceptual model of adverse human effect to risk assessment relevant predictions. Each stage requires effort on the part of the biology, chemistry and toxicology experts and the mathematical and statistical modellers. Note that the end point is not just a prediction: it is quantified uncertainty, which is far more valuable than a conservative point estimate.

Identification of models and data sources

Screening for important model inputs

Linking models, data and reality

Quantified outcome uncertainty

Uncertainty modelling and calibration

Uncertainty

The key to using mathematical models in toxicological safety assessments is to acknowledge that models are imperfect representations of reality. Uncertainty appears in many guises:

- Model settings
- Experiment errors
- Human variability
- Model-to-reality gap
- Missing scientific understanding

Using Bayesian statistics, we can characterise these uncertainties and help focus future research on areas where reduction of uncertainty will help safety assessors through sensitivity analyses. Sensitivity analysis is used to identify the inputs of mathematical models that contribute most to our uncertainty about adverse human effects.

A forthcoming case study

Chemical and biological events driving induction of human skin sensitisation have been investigated for many years and are now relatively well understood at a qualitative level. A mathematical model of human CD8+ T cell responses following topical exposure to a sensitising chemical is being developed for use in human risk assessment. Given the years of study, there are many data sources available for calibration and model checking (Maxwell et al., 2014).

We view experimental data as being observations of the modelled process (like in Gosling et al., 2013). We can characterise the links between the mathematical model and the data using Bayesian hierarchical modelling, which provides a framework for expert judgement.

We plan to model individuals by setting appropriate input parameters based on exposure scenarios and experimental data. We will ultimately use clinical data and human T-cell response information to reduce the uncertainty about these parameters. We will propagate the uncertainty through the Bayesian framework to produce estimates of potential skin sensitisation prevalence in the population and, most importantly, to quantify the uncertainty.


Maxwell et al. (2014). Applying the skin sensitisation adverse outcome pathway (AOP) to quantitative risk assessment. Tox in Vitro.