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

Carl Westmoreland, Andy Scott – Unilever

James Sidaway - AstraZeneca

Kim Travis - Syngenta

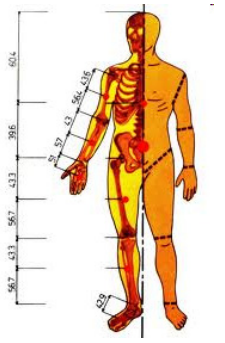
How do we ensure that a new ingredient will not pose a safety risk for humans (patients, workers, consumers) who are exposed to it at the concentration it will be used?

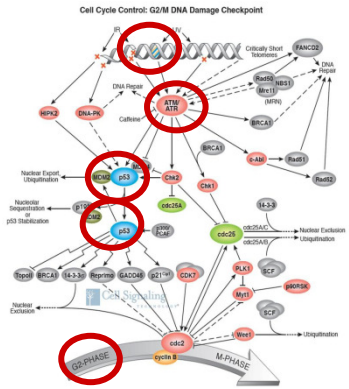
At present, systemic toxicity information data generated in animals plays a large part in these decisions

Could we ever make such decisions without toxicology data in animals?

A long-term research investment

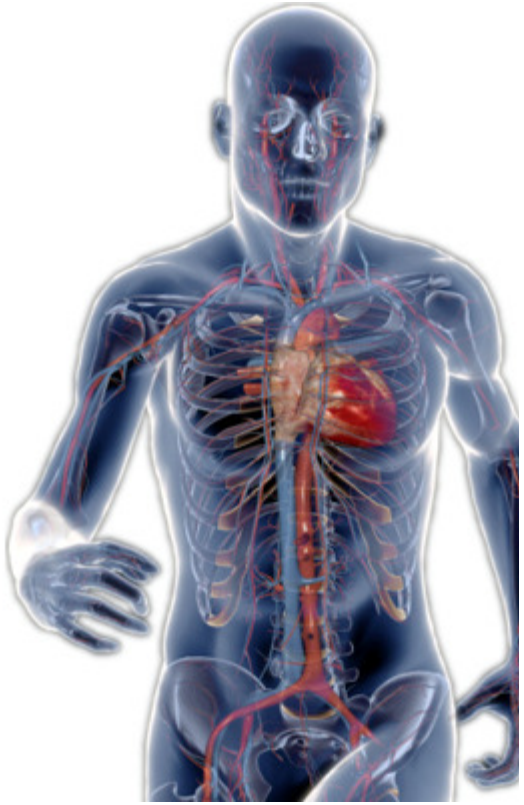
CRACK-IT will bring (we hope!) … new eyes, new ideas and creativity to this challenge



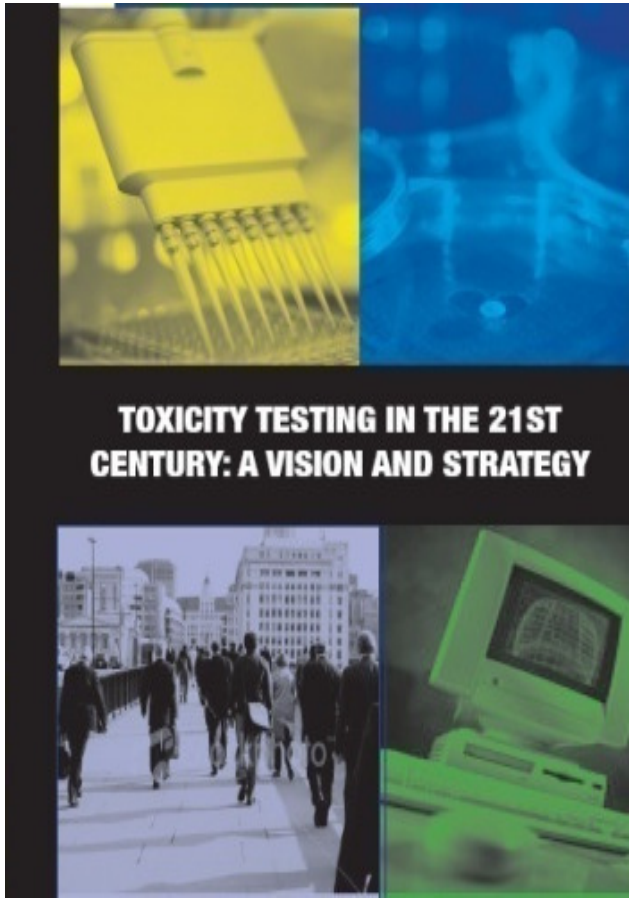


Systemic exposure

- Exposure to the systemic circulation
  - We are exposed to products/formulations, but ultimately it is ingredients and their metabolites that may get into the bloodstream
- Routes into the body
  - Oral
  - Inhaled
  - Dermal
  - Intravenous
  - Etc
- Intended route of exposure vs unintended
- How much gets in?
  - Dose
  - Habits and practices of use



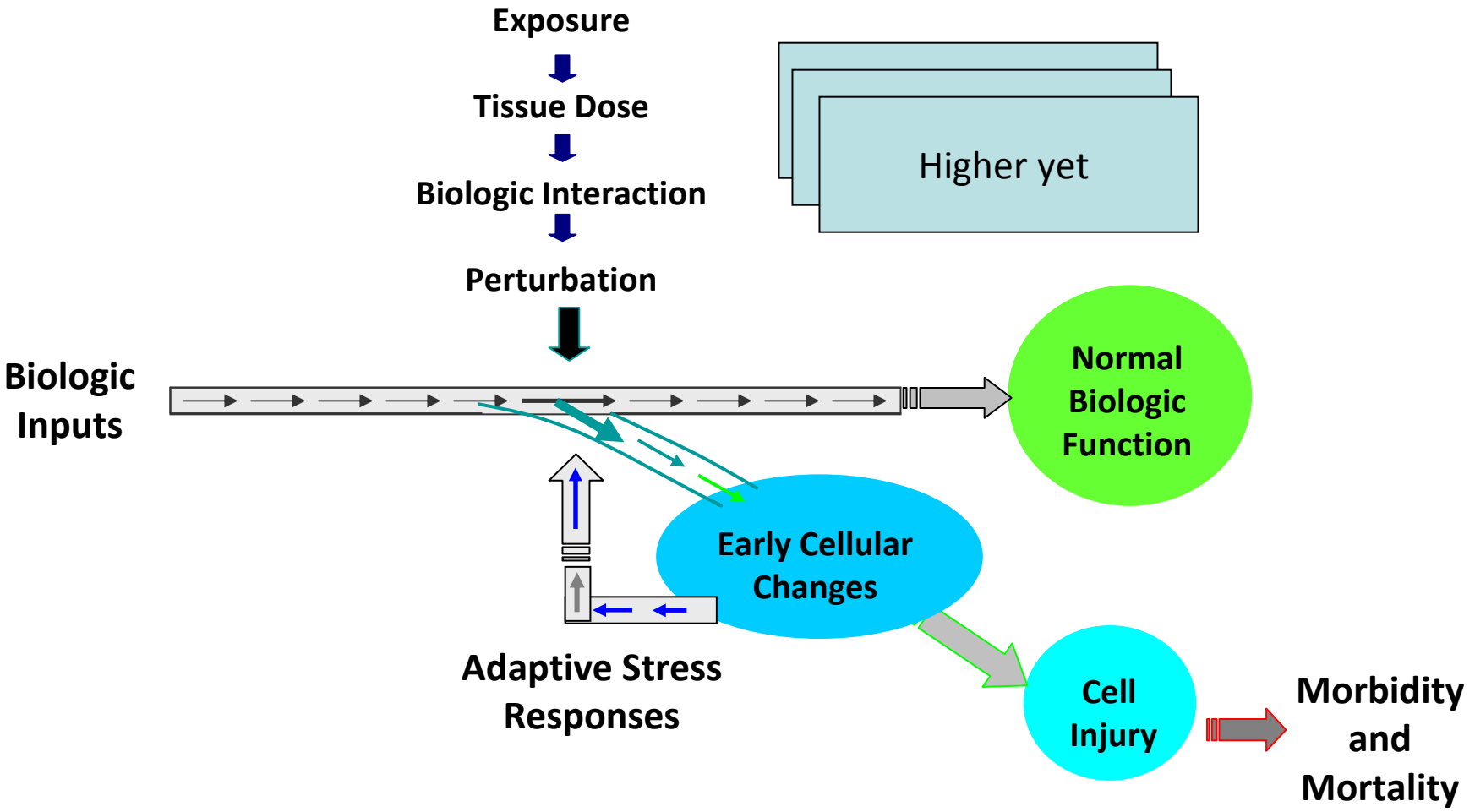
USA: NRC Report June 2007*



"Advances in toxicogenomics, bioinformatics, systems biology and computational toxicology could transform toxicity testing from a system based on whole-animal testing to one founded primarily on *in vitro* methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin."

*Text also published in Krewski D et al (2010), J Toxicol Environ Health B Crit Rev, **13**, 51-138

Based on Perturbation of Toxicity Pathways



(From Andersen & Krewski, 2009, Tox Sci, **107**, 324)

Selecting Case Studies

- Proof of principle case studies*
  - Generating data on a specific pathway to demonstrate
    - How this new approach may work
    - Where the real challenges / data gaps are for future research in this area
- Test system(s)
  - Your choice
  - 'Cells, cell lines, or cellular components, preferably of human origin'
    - Ensuring the relevance of the models chosen
- Toxicity pathway(s)
  - Your choice
    - e.g. oxidative stress, mitochondrial toxicity, inflammation, DNA damage, PPAR activation etc.
  - concentration-related effects
  - effects on multiple pathways?
  - defining adverse changes …

*Ref: Andersen et al (2011) ALTEX, 28, 175-182
Can case study approaches speed implementation of the NRC report?

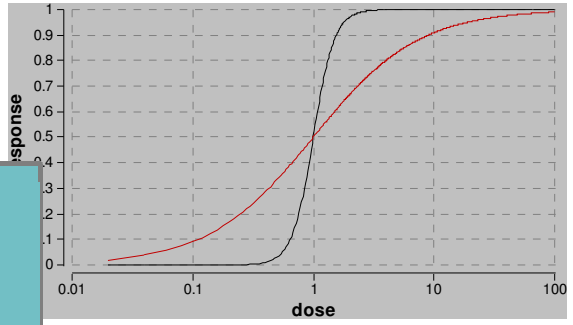
Toxicity Pathway Results and Quantitative Risk Assessments

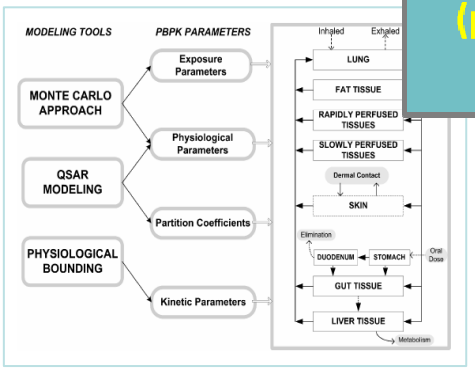
i. in vitro rapidly performed toxicity pathway test battery for *n*-assays in human cells , cell lines, or tissue aggregates

ii. Computational systems biology description of pathway circuitry for creating biologically realistic dose response models

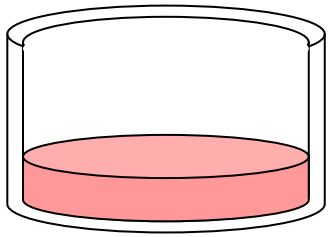
iii. Dose dependent transition studies for sequential pathway activation to understand linkage to cell and tissue level responses (perturbations to adversity)

iv. PBPK Modules – Compound specific or QSAR-based models for *reverse dosimetry* based on adverse concentration defined in the in vitro studies



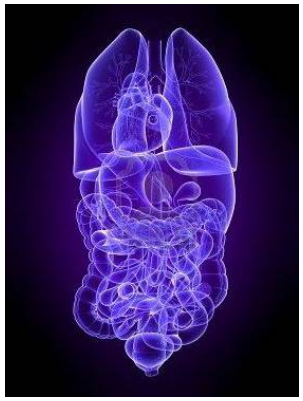


In Vitro to In Vivo (human exposure) Extrapolation



In vitro **adaptive/adverse threshold concentration (µM)**

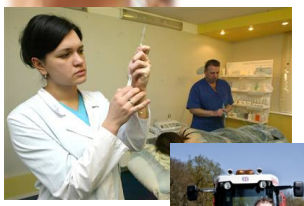
In vitro to in vivo extrapolation



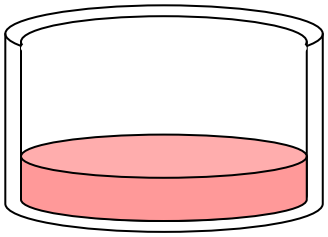
Target site concentration (µM)

Systemic/Organ Levels

Exposure mg/kg/day



Developing confidence in predictions

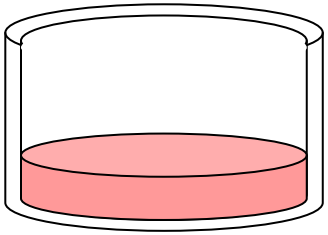


Validation

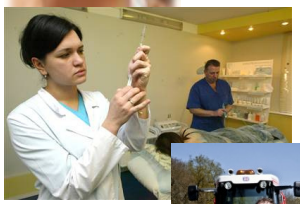
Animal *in vitro*

Existing animal *in vivo* data

Confidence



Prediction



Human *in vitro*

Human *in vivo*

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 defined toxicity pathway(s) (applicants choice), establish concentration response information in human *in vitro* system(s) relevant to that pathway.
- Based on the above, establish 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

- In-kind contributions
- AstraZeneca, Syngenta and Unilever are 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

syngenta AstraZeneca Unilever

Looking forward to your creative ideas!!