Removing Blockers to the Acceptance of New Methodology in Regulatory Science

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"The current paradigm for testing agricultural and industrial chemicals for potential human health effects is **inefficient, expensive, and relies heavily on experimental animals**."
(Andersen and Krewski, 2009; Holsapple et al., 2009; NRC, 2007).

Pemberton, MA, Oliver GJA, Pate I, Rhodes C, Barlow A, Doe JE and Botham PA (1989)

Initial validation of an *in vitro* technique for the assessment of skin irritant chemicals.
Toxicologist

→

OECD Test No. 430: In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER)

This Test Guideline was originally adopted in 2004 and updated in 2015

1989 Quarter of a Century! 2005

If it took 25 years to adopt alternative skin corrosivity methods, what do we have to do to get alternative systemic toxicity, carcinogenicity and DART methods adopted before the end of the 21st Century?

ECHA EUROPEAN CHEMICALS AGENCY

Conditions for non-standard data for REACH registration

- Results must be adequate for classification.
- Results must enable adequate risk assessment.
- Key parameters from the standard study are addressed, e.g. adequate exposure duration & route for toxicology data.
- Thoroughly-documented scientific explanation to justify the non-standard methods, e.g. a hypothesis for why the properties of a substance can be 'read across' with supporting evidence.

Are these conditions acting as blockers?

What does society do with the results of toxicological testing?

Decides whether a chemical can be allowed in specified situations (e.g. uses, products, residues or contaminants in food or water)

How does it make the decisions?

Risk Assessments which compare toxicity and exposure

Classification which codifies toxicity.

Is there a difference between the way toxicology study results are used in **risk assessment** and in **classification?**

Same structure:

Hazard Identification -What the substance does

Hazard Characterisation - Degree of hazard

Large amounts of data are distilled down:

Categories & Reference Doses

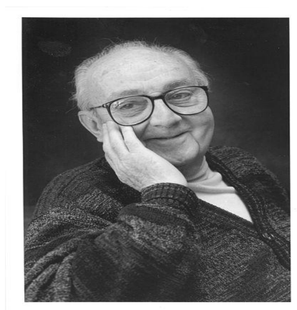
The Codified Output from Toxicology Studies

HAZARD	CLASSIFICATION	RISK ASSESSMENT
Sensitisation	Categories 1A, 1B based on severity in LLNA	Min sensitising dose based on LLNA
Single exposure lethality	Categories 1, 2, 3, 4 based on LD50	Probit from LD50 data
Local irritancy	Categories 1 & 2 based on severity of effect in rabbit or in vitro studies	Min irritating concentrations from rabbit or in vitro studies
Adverse effects	STOT SE and RE categories 1, 2, 3 based on effect levels in toxicity studies Values adjusted for dosing duration	Reference doses derived from NOEL in toxicity studies Reference value for each exposure duration
Carcinogenicity	Category 1 & 2 based on weight of evidence in carc studies SCLs based on potency	Reference dose based on results of carc studies with method depending on MoA
Reproductive toxicity	Category 1 & 2 based on weight of evidence SCLs based on potency	Reference doses derived from NOEL in toxicity studies Reference value for life stage
Mutagenicity	Category 1 & 2 based on weight of evidence	Reference dose based on conservative assumption

CATEGORIES

REFERENCE DOSES

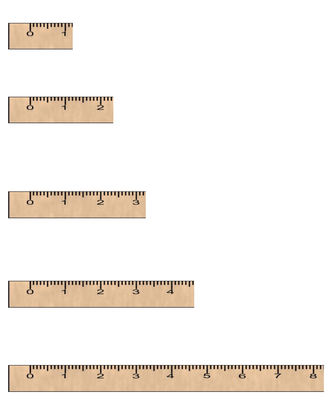
How good are the models?



George Box

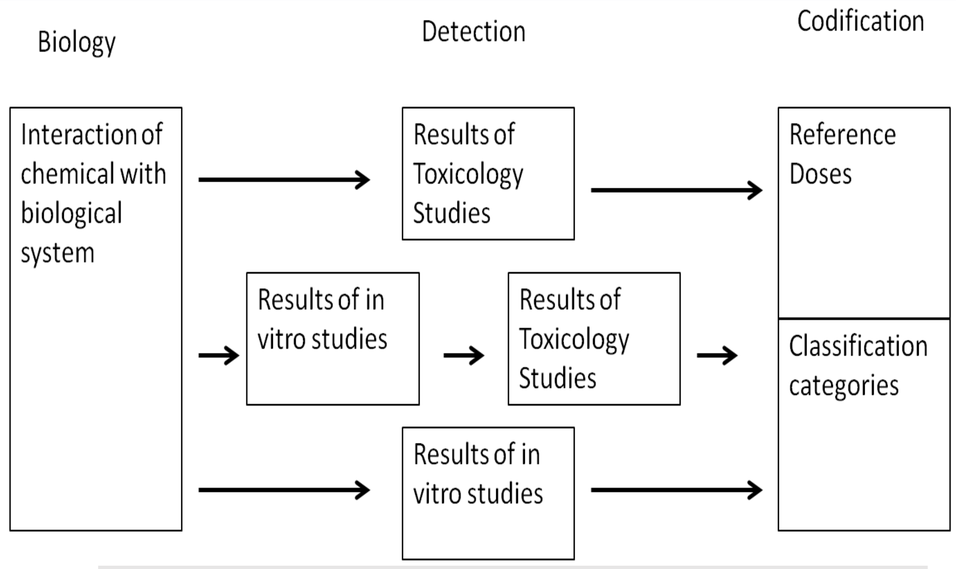
"Remember that all models are wrong;
the practical question is how wrong do they have to be to not be useful?"

Quantitative Hum Rel Frame
Regulatory lab animal studies
Data Driven Tox Testing Framework
ToxCast reverse dosimetry
TTC



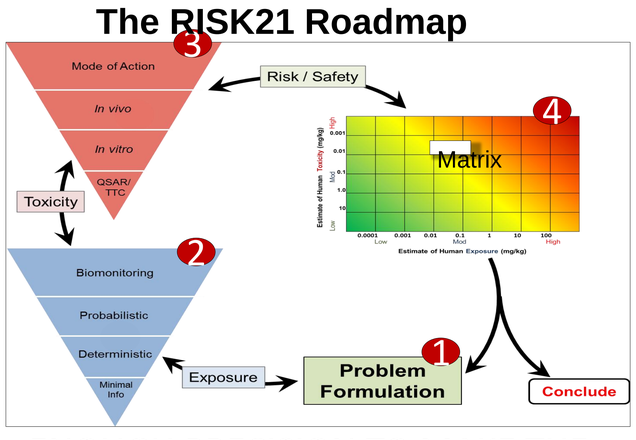
Quantifying "wrongness" or precision (orders of magnitude of imprecision)

We have a range of methods now and we know their "wrongness". Even our standard models have "wrongness".



Assess new methods by how they predict reference doses and categories not how they predict the results of standard tox tests

The RISK21 Roadmap



ENOUGH PRECISION TO MAKE THE DECISION

RISK21 allows methods with defined precision to be used in exposure based risk assessment

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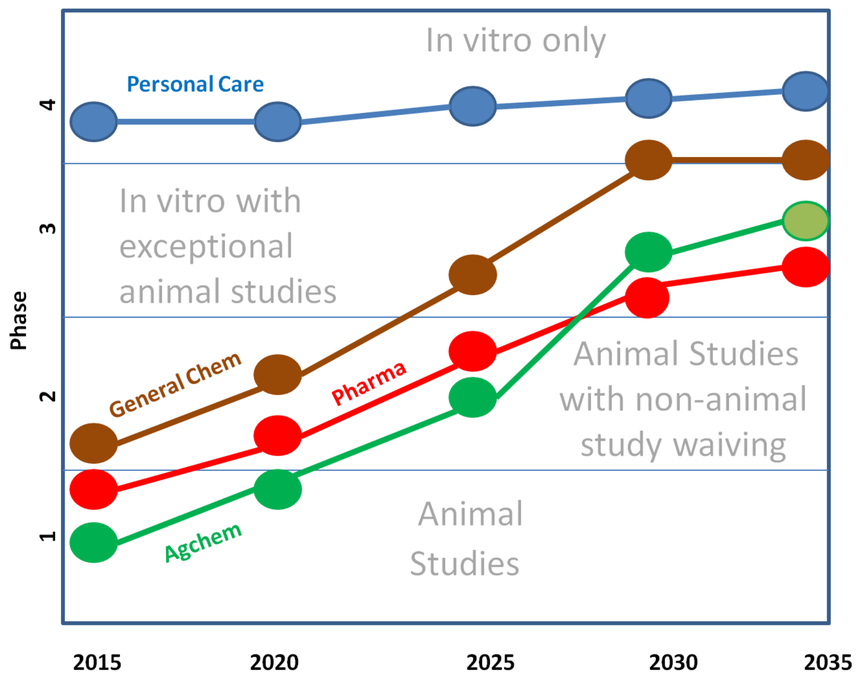
Results must be adequate for classification and risk assessment –forget the rest



Can we speed this up?