The European Commission’s science and knowledge service

Joint Research Centre

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The Joint Research Centre (JRC)

As the science and knowledge service of the Commission our mission is to support EU policies with independent evidence throughout the whole policy cycle.

~ 3000 staff

Almost 75% are scientists.

Headquarters in Brussels.

Research facilities located in 5 Member States.
Experiences with Paradigm Change in European Union Science and Regulatory Decisions

Understanding Pathways to a Paradigm Shift in Toxicity Testing and Decision Making

A workshop of the National Academies of Sciences, Engineering, and Medicine, Washington DC, November 20–21, 2017
Directive 2010/63/EU on the protection of animals used for scientific purposes

"... an important step towards achieving the final goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so."
The European Union Reference Laboratory for Alternatives to Animal Testing

- Research
- Validation
- Dissemination
- Promotion
Risk management depends on **generic risk considerations** and **specific risk assessment**.
Chemicals legislation

- Protection of human health and environment
- Innovation, competitiveness, sustainability
- Functioning of markets and trade
Regulatory science leading the way

Addressing the New Challenges for Risk Assessment

SCHER  SCENIHR  SCCS
2013
Progress through collaboration

- In vitro Test Guidelines
- QSAR Toolbox
- AOP Development Programme
- Integrated Approaches to Testing and Assessment (IATA) and Defined Approaches (DA)
- IATA case studies project
- Guidance
8.3.1. Skin sensitisation, in vitro/in chemico

Information from in vitro/in chemico test method(s) recognised according to Article 13(3), addressing each of the following key events of skin sensitisation:

(a) molecular interaction with skin proteins;
(b) inflammatory response in keratinocytes;
(c) activation of dendritic cells.
Uncertainty of current approaches

Extrapolating from early to late effect
Extrapolating across dosing duration
Extrapolating across dosing patterns

Determination of a PoD
Extrapolating to low-effect levels
Estimating Intra-species variability

Conventional Toxicology

Sources of 'familiar' uncertainty
Inter-species extrapolation
Estimating the impact of missing studies

Extrapolating across exposure metrics
Extrapolating across agents
Extrapolating from in vitro or in chemico to in vivo data

Uncertainty of new approaches

**Inputs**
- Organ-on-a-chip
- EOMICS
- Cell cultures
- 3D tissues
- Cheminformatics & Comp. chemistry
- Exposure modeling

**Combining inputs**

**Mathematical expressions**

\[ f(x|x) = \binom{n}{x} p^x q^{n-x}, \quad 0 \leq x \leq n \]

\[ f(x,n) = \binom{n}{x} p^x q^{n-x} a_n, \quad 0 \leq x \leq n \]

\[ m(x) = \sum_{n=x}^{\infty} \binom{n}{x} p^x q^{n-x} a_n = p^x \sum_{n=x}^{\infty} \binom{n}{x} q^{n-x} a_n = p^x \sum_{k=0}^{\infty} \binom{x+k}{x} q^{x+k} a_{k+x} \]

\[ f(n|x) = \frac{f(x,n)}{m(x)} = \frac{\binom{n}{x} p^x q^{n-x} a_n}{p^x \sum_{k=0}^{\infty} \binom{x+k}{x} q^{x+k} a_{k+x}} = \sum_{k=0}^{\infty} \binom{x+k}{x} q^{x+k} a_{k+x} \]

**Categorisation / Read-across**

**Testing Strategies (ITS / STS)**

**Weight of Evidence**
Scientific Credibility

The willingness of others to use predictions to inform their decisions*

Established through a process of social epistemology to develop a shared knowledge and understanding between developers, users, and decision-makers.

Credibility Matrix

**Knowledge:** Acquaintance with facts, truths and principles

**Strength:** Availability, applicability and dependability

Patterson, Worth, & Whelan; "Establishing the credibility of predictive toxicology approaches intended for regulatory purposes" *Submitted.*

Social Epistemology

Establishing Scientific Credibility
- process as important as the result!
A true paradigm shift for toxicology

What should we really be trying to predict?

What predictions provide adequate protection?

Is it time to redefine toxicological hazard?
Replacing or displacing?
Win

Win

Win
Thank you

Any questions?

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