Animal Welfare Perspective on Pathway-based Approaches to Chemical Safety Assessment

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Outline

• Scientific need for a new approach to chemical assessment
• Animal cost, in terms of numbers, suffering
• Precedents for a pathway-base approach
• Current programs and projects in pathway development
• What’s needed for the future?
• Conclusions
The need for a new approach

Pharmaceuticals:
- 92% of drug candidates fail in clinical studies
- “The average drug developed by a major pharmaceutical company costs at least $4 billion, and it can be as much as $11 billion” (Forbes 2012)
- Need to assess novel chemistries (i.e. nanomaterials)

Industrial chemicals:
- Growing concern over lack of data (>10K chemicals worldwide)
- Large-scale regulatory programs: REACH (EU, China, S.Korea)

Pesticides:
- Registration requires the use of approximately 10,000 animals, millions of USD, and many years (decades)
- Need to identify “greener” chemistries

Cosmetics:
- European Cosmetics Directives ban on animal testing
- Consumer concern over safety and animal testing worldwide
The argument for a new approach

Regulatory cost in animal use: gross approximation*

Annual animal use in research world-wide 115 million/year
15% used for regulatory testing 17 million/year

*Estimates based on:
UK numbers extrapolated to other countries
Few reported numbers
Most countries don’t require reporting
US AWA does not cover
• fish, amphibians, reptiles, birds
• purpose bred mice and rats
• (these are covered by OLAW and AAALAC but not required reporting)

→ Likely underestimated
The argument for a new approach

Animal suffering

Lifetime captivity
- “purpose-bred” mammal maintain instincts
- demonstrate signs of depression
- clinical signs of stress

Toxicological testing
- By definition is “purposeful poisoning”
- MTD required in most guideline studies
- Acute studies can involve high levels of pain
- Lifetime studies → lifetime of suffering

The “3Rs” approach:
- Refinement (better cages, enrichment, lower doses)
- Reduction (fewer numbers)
- Replacement
The argument for a new approach

A pathway-based system for chemical evaluation will:

- Provide support for biological hypothesis-based testing
- Allow development better decision-making tools
- Result in less uncertainty in risk determinations

AND

- toward measuring upstream biological events
  - assessed in cells and reconstructed tissues
- toward computer assisted predictive modeling
- away from animal testing (reduce, replace)

→ Win, Win, Win situation
Precedents for pathway-based toxicology

1. Dose-response modeling
   • Using pharmacokinetic and mechanistic information

2. IPCS/WHO mode of action frameworks
   • Human relevance of rodent cancer findings
   • Extrapolated to non-cancer endpoints

3. Mode of action pathways in drug and product development
   • Drug and target-specific

   “envisions a new toxicity-testing system that evaluates biologically significant perturbations in key toxicity pathways by using new methods in computational biology and a comprehensive array of in vitro tests based on human biology”
Pathway-related projects

**US Government**

**EPA: ToxCast**
- High-throughput data generation
- With industry partners
- ~ 800 in vitro assays, thousands of endpoints
- ~300 pathways
- ~3000 chemicals at ~10 concentrations
- All data publically available
- Application to US EDSP: E, A and T pathways

**Tox21: NIH/EPA/FDA**
- Screening 10,000 chemicals, including drugs
- At the NIH Center for Advancing Translational Science using innovative robotic technology

**“Human on a Chip”: DARPA/NIH/FDA**
- $132 million over 5 years to universities
- Wyss/Harvard/MIT: lung, liver, intestine
- Goal is 10 organs in 5 years
Pathway-related projects

US Government, cont.

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
- Endocrine and developmental pathway development
- Assay development and evaluation

EPA: Mid-Atlantic division
- QSARs, AOPs for aquatic toxicity
- Estrogen receptor-mediated reproductive impairment

EPA Office of Research and Development
- Virtual liver
- Virtual embryo

US Army Corps of Engineers
- AOPs for ecotoxicology
- Aromatase inhibition
- Androgen agonism
- HTG axis
- Chemical-specific case studies
Pathway-related projects

**The Hamner Institutes**

- **“Tier 1 and done”**
  - Complete estrogen receptor pathways
- **PPAR\(\alpha\) network**
  - Systems biology approach to complex network interactions
- **DiliSym:**
  - Computer model for drug-induced liver injury

**Johns Hopkins School for Public Health Center for Alternatives to Animal Testing**

- **Pathways of Toxicity**
  - “omics” approaches to mapping all pathways
  - Goal of establishing the “Human Toxome”
- **Evidence-based toxicology**
Pathway-related projects

EU: European Commission Joint Research Centre (JRC)

• Safety Evaluation Ultimately Replacing Animal Testing (SEURAT)
  – 25€ million from FP7 and 25 € million from Cosmetics Europe
  – Repeat dose toxicity
  – AOPs for liver toxicity
  – Database
  – Predictive models

• European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM)
  – Development and assessment of low and high-throughput methods
  – EU-NETVAL (European Union Network of Laboratories for the Validation of Alternative Methods)
  – QSAR Model Database

• JRC/OECD/US EPA
  – AOP knowledgebase
Pathway-related projects

Organization for Economic Cooperation and Development
Advisory Group on Molecular Screening and Toxicogenomics

- Template for building AOPs, organizing information
- Guidance document on developing and assessing AOP (2013), No. 184 Series Testing and Assessment
- AOP-KB:
  - AOPwiki was publically released Sept 25, 2014,
  - Intermediate effects DB, Effectopedia
  - AOPwiki Handbook (in preparation)
- Current workplan: 25 AOPs, 7 case studies

OECD QSAR toolbox
  - Large collection of QSAR and SAR models, databases, guidance
What’s needed for the future?

- A series of prototype pathways
- Quantification of relationships between pathway events
- Assessment systems for querying key events including complex endpoints
- Integration of absorption, metabolism and distribution information
- Quantitative *in vitro-in vivo* extrapolation
- Improved predictive tools
- Integrated databases
- Relational “knowledge bases”
Conclusions

The application of pathway, or system biology approaches to chemical and product safety assessment has many benefits, including:

• Systematic biology-based integration of all types of information
• Hypothesis-based testing and assessment
• Improved understanding, and therefore predictivity, of adverse effects
• Faster, more effective assessment, therefore decreased assessment time and resource commitment

There are a large number of projects in development
And a lot of information needs to be developed

For the systems biology approach to work, a global and cross-sector effort is necessary, is already happening, and momentum is building.
Thank You

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Supporting the Science:

Presentations · Workshops · Papers · Sponsorship

Articulating the Vision:

Website · Articles · Videos

Lobbying/Funding:

Bill language · Appropriations · Horizon 2020
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