Working Together to Replace Animal Testing for Assessing the Safety of Consumer Products
- pioneering change, building confidence & next steps

Julia Fentem
Head of Unilever’s Safety & Environmental Assurance Centre (SEAC)

11-22-2019   CAAT - 60 Years of the 3Rs
“Lessons Learned and the Road Ahead”
Celebrating 60 years of the 3Rs - still building confidence in their application

Russell and Burch go on to say that Progress in replacement has been restricted by certain plausible, but untenable assumptions about models, which have led to the high-fidelity fallacy.

2009 – 50 years of the Three Rs

The Principles of Humane Experimental Technique: Timeless Insights and Unheeded Warnings
Michael Balls
FRAME, Nottingham, UK
Some personal reflections, insights & future wishes: 1991-2019+

1. Policy and Legislation have stimulated change & scientific progress
2. Working Together across all Stakeholders has been key to making progress
3. Progress would be faster if we weren’t Constrained by traditional Beliefs & Assumptions
4. Case Studies on Application of NGRA / NAMs for Safety Decisions are building Confidence
5. Leverage APCRA initiative to Pioneer Change with NAMs for Regulatory Chemicals Testing
1. EU Policy to ban cosmetics testing meant scientists had to re-think how we do PRODUCT safety assessments with new non-animal approaches

Safety assessment — future needs

- consumer safety decisions without animal testing
  - based on scientific risk assessment
  - improve relevant fundamental biological understanding
- bring experimental biology/toxicology and clinical medicine closer together (in context of human health risk assessment)
- improve in vitro models (tissue engineering)
- apply omics/other new technologies as appropriate
- develop in silico modelling tools
- move to a computational "systems biology" approach

Fentem (2006) ATLA 34, 11-18

Next Generation Risk Assessment (NGRA) Toolbox

Fentem, Chamberlain, Sangster (2004) ATLA 32, 617-623
Frameworks for applying 21C Science & Technology for Safety Decisions
New paradigm now translated into NGRA workflows and Confidence Built through collaborating on Case Studies

TIER 0: IDENTIFY USE SCENARIO, CHEMICAL OF CONCERN AND COLLECT EXISTING INFORMATION
- 1. IDENTIFY USE SCENARIO
- 2. IDENTIFY MOLECULAR STRUCTURE
- 3. COLLECT EXISTING DATA
- 4. IDENTIFY ANALOGUES, SUITABILITY ASSESSMENT AND EXITING DATA

Exit TTC

Exit READ-ACROSS

5. SYSTEMIC BIOAVAILABILITY (PARENT VS. METABOLITE(S), TARGET ORGANS, INTERNAL CONCENTRATION)

6. MOA HYPOTHESIS GENERATION (WEIGHT OF EVIDENCE BASED ON AVAILABLE TOOLS)

Exit INTERNAL TTC

TIER 1: HYPOTHESIS FORMULATION FOR AB INITIO APPROACH

7A. TARGETED TESTING

7B. BIOKINETIC REFINEMENT (IN VIVO CLEARANCE, POPULATION, IN VITRO STABILITY, PARTITION)

8. POINTS OF DEPARTURE, IN VITRO IN VIVO EXTRAPOLATION, UNCERTAINTY ESTIMATION, MARGIN OF SAFETY

9. FINAL RISK ASSESSMENT OR SUMMARY ON INSUFFICIENT INFORMATION APPROACH

Exit Ab Initio

courtesy of Dr Andy White & EUToxRisk team

Next Generation Risk Assessment (NGRA) Toolbox
Read across
Exposure-based waiving
In silico tools

Metabolism and metabolite identification
Physiologically-based kinetic modelling
In chemico assays
‘Omics
Reporter gene assays
In vitro pharmacological profiling
3D culture systems
Organ-on-chip
Pathways modelling
Human studies
2. Working Together across all stakeholders is key to making progress

EUToxRisk

New scientific tools & application

ICCR

Regulatory application

Animal-Free Safety Assessment Collaboration (AFSA)

Building capability globally

CASE STUDIES on chemical ingredients used in cosmetics & other product types
ICCR: international Collaboration with cosmetics regulatory authorities on use of New Approach Methodologies (NAMs) has Built Confidence

ICCR NINE PRINCIPLES OF NEXT GENERATION RISK ASSESSMENT (NGRA)

4 Main overriding principles:
The overall goal is a human safety risk assessment
The assessment is exposure led
The assessment is hypothesis driven
The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:
Following an appropriate appraisal of existing information
Using a tiered and iterative approach
Using robust and relevant methods and strategies

2 Principles for documenting NGRA:
Sources of uncertainty should be characterized and documented
The logic of the approach should be transparently and documented

Application of principles via a tiered framework

Calculate Exposure

"The assessment is exposure-led"

Literature search

"Using all available information"

Next Generation Risk Assessment

"Exposure-led, human-relevant, hypothesis driven, designed to prevent harm"

Can a decision be made? If so STOP

"Using a tiered and iterative approach"

courtesy of Dr Matt Dent & ICCR team
"THE ASSESSMENT IS EXPOSURE LED" - HABITS AND PRACTICES

Table 2: Estimated daily exposure levels for different cosmetic product types according to Cosmetic Europe data (ECOCOPHY/2011/LVRE. Mair et al., 2007, 2011).

<table>
<thead>
<tr>
<th>Product type</th>
<th>Estimated daily exposure level</th>
<th>Remaining amount applied (mg/kg)</th>
<th>Remaining factor</th>
<th>Calculated daily exposure level</th>
<th>Calculated relative daily exposure level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bathing, cleansing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shower gel</td>
<td>18.67 g</td>
<td>279.20</td>
<td>0.01</td>
<td>0.19</td>
<td>2.79</td>
</tr>
<tr>
<td>Hand wash soap</td>
<td>2.00 g</td>
<td>-</td>
<td>0.01</td>
<td>0.20</td>
<td>3.23</td>
</tr>
<tr>
<td>Personal care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shampoo</td>
<td>10.46 g</td>
<td>150.49</td>
<td>0.01</td>
<td>0.11</td>
<td>1.51</td>
</tr>
<tr>
<td>Hair conditioner</td>
<td>3.92 g</td>
<td>57.49</td>
<td>0.01</td>
<td>0.06</td>
<td>0.83</td>
</tr>
<tr>
<td>Hair styling products</td>
<td>4.50 g</td>
<td>67.49</td>
<td>0.01</td>
<td>0.05</td>
<td>0.74</td>
</tr>
</tbody>
</table>

CHARACTERISE THE PHYSICOCHEMICAL PROPERTIES

- **In Silico determinations:**
  - OSAR, ToxTree, OECD Toolbox, DEREK alerts, MIE Atlas, Drugbank, Metacore
- **Chemistry determinations:**
  - Partition coefficient logP
  - Peptide binding potential
- **In vitro determined:**
  - Kinetic solubility
  - Thermodynamic solubility
  - Metabolic & chemical stability
  - Stability in human plasma
  - Plasma protein binding
  - Partitioning in blood
  - Free concentration determinations

**In Vitro Assays:**
- Keratin Solubility
- Thermodynamic Solubility
- Metabolic Stability
- Human Hepatic Microsomes
- Human Hepatic Mitochondria
- Stability in Human Plasma
- Plasma Protein Binding
- Partitioning in Human Blood

"THE ASSESSMENT IS EXPOSURE LED" - PBK

- Predicting systemic exposure
- Enabling us to select and test relevant doses
- Increased role for clinical work to confirm systemic exposure levels

courtesy of Prof. Paul Carmichael & SEAC team
In silico-first approaches for identifying pathways of concern and formulating hypotheses for testing

Tier 0

Hazard Identification
- Literature
- Databases
- Dashboard
- In silico alerts
- MIE atlas
- AOP wiki

Tier I/II

Pathway determination
- Transcriptomics
- Proteomics
- Receptor screens
- Stress panels
- PBK

Tier II

Pathway characterisation
- Live cell imaging
- Systems toxicology models
- Repeat dose models
- Organotypic models

Characterisation of response in biologically relevant in vitro systems and complex computational models for decision making

Uncertainty

Mechanistic understanding

“USING A TIERED AND ITERATIVE APPROACH” - NAMS
Collaborating with Chinese government & academics to implement AAT

UCCPSCC established in June 2017

MoU with Shanghai FDA for training

courtesy of Dr. Carl Westmoreland & Dr. Jin Li
3. Building Confidence to accelerate change in making product & chemical safety decisions without animal testing. So, what’s really stopping us?

- Our next generation of safety assessors are not constrained by traditional beliefs & assumptions that only animal tests can provide the data needed to protect consumers, workers & our environment from hazardous chemicals.
- They are readily embracing new science & technology and applying it for evidence-based decision making.
- They are more open to “having a go” with NAMs and seeing how far we can get ...
4. NGRA consumer safety Case Studies & new products in market where NAMs provide data for safety decisions – no reliance on new animal data

“imagine we had no animal data” – coumarin case study

- can we actually make safety decisions about our products with NGRA?
- non-animal safety risk assessment by integrating kinetic modelling & data from NAMs
- discussions with external experts, publication in progress

sharing how we apply our safety science via case study non-animal risk assessments

“novel ingredient” – applying NAMs for safety assessment

- novel oral care active in very early development
- use network of our NAMs partners to generate bespoke data package

embedding NGRA from the earliest stages of innovation

“new product” – hand dishwash with novel biosurfactant

- bespoke consumer safety assessment
- new assays developed
- consumer exposure data modelled
- no systemic exposure
- novel non-animal assays confirmed no immunotoxicity (potential key risk from research studies)

consumer safety assessment for new ingredient based on non-animal approaches

Coumarin Body Lotion

- novel oral care active in very early development
- use network of our NAMs partners to generate bespoke data package

embedding NGRA from the earliest stages of innovation

consumer safety assessment for new ingredient based on non-animal approaches
NGRA Framework used in Coumarin Case Study

courtesy of Dr Alistair Middleton, Dr Maria Baltazar & SEAC team
5. To avoid any animal testing of new INGREDIENTS in consumer products we now need to re-think chemicals registration requirements. Use of NAMs for regulatory chemicals risk assessment is being discussed.
Recent US EPA Policy changes start to tackle replacing animal testing for CHEMICAL Safety with New Approach Methodologies (NAMs)

**US EPA to ‘eliminate all mammal study funding’ by 2035**

Agency to award $4.25m in grants for alternatives testing research

10 September 2019 / Animal testing, TSCA, United States

US EPA Administrator Andrew Wheeler has signed a memo directing the agency to eliminate all requests and funding for mammal studies by 2035, and reduce both requests and funding by 30% by 2025. Exceptions will have to be approved by the administrator on a case-by-case basis.

In support of this, the EPA will award $4.25m in grants to five universities to advance research on new approach methodologies (NAMs). And Mr Wheeler has directed the Office of Chemical Safety and Pollution Prevention (OCBPP) and the Office of Research and Development (ORD) to host a joint conference on NAMs before the end of the year.

"Oftentimes we find that the animal tests themselves have perhaps misled us on the science," he said at a press conference at the EPA's HQ in Washington, DC, today announcing the directive. "Sometimes the information we learn from rats is not directly applicable to human beings.

"I really do think that in the long term, we need to rely more on *in-vitro* testing, we need to rely more on computer modelling."
To accelerate change & build confidence with NAMs for assessing new CHEMICALS, EU policy makers & regulators should strengthen their commitments, drive transparency and broaden stakeholder involvement.

Take learnings from cosmetics sector successes: key roles in implementing non-animal approaches for consumer safety assessment were played by:

1. **EU policy makers** - set clear direction & timings based on EU citizens’ views
2. **Regulators** - ICCR collaboration (with industry)
3. **Global NGOs** – now coordinating policy changes & scientific capability development activities in parallel at global level

**Future Opportunities:**

- Increase transparency & broaden stakeholder involvement with APCRA to build capability & confidence
- Establish “NAM User Forum” to build confidence in their use for safety decision making
- Accelerate follow-up on 2016 ECHA NAM workshop conclusions

All Working Together with Companies & Trade Associations committed to building the new Capability and to Cooperation & Change

29-10-2019 EPAA Annual Conference, Brussels
“Building Confidence for the use of 3Rs”
Personal Reflections – Lessons Learned

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Pioneering Change – Thought Leadership & Inspiring Others ... 

with many thanks to all of my SEAC colleagues & our collaborators across the globe
11th World Congress on Alternatives and Animal Use in the Life Sciences

23-27 August 2020
MECC Maastricht – The Netherlands

More information on: http://wc11maastricht.org/