



Working together as Industry & Regulatory Communities to make Safety Decisions without Animal Testing

Julia Fentem

Head of Unilever's Safety & Environmental Assurance Centre (SEAC)

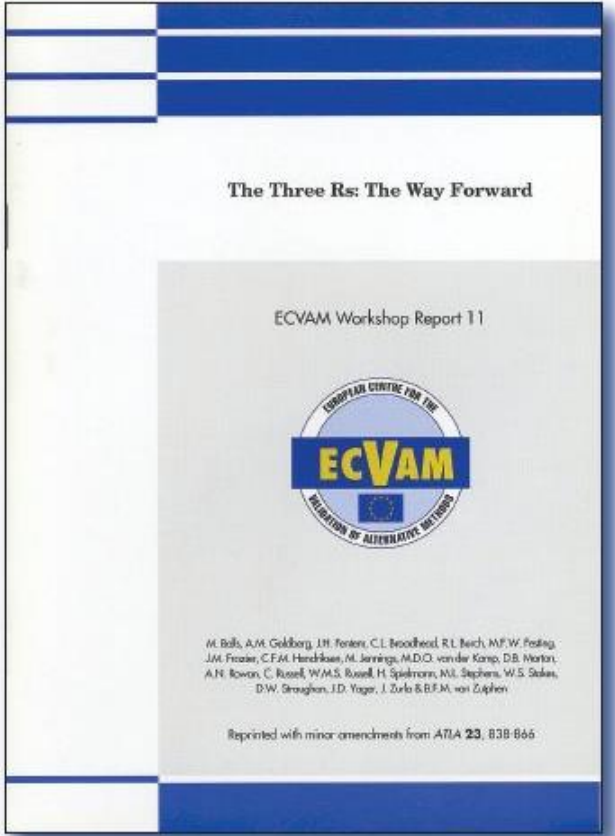
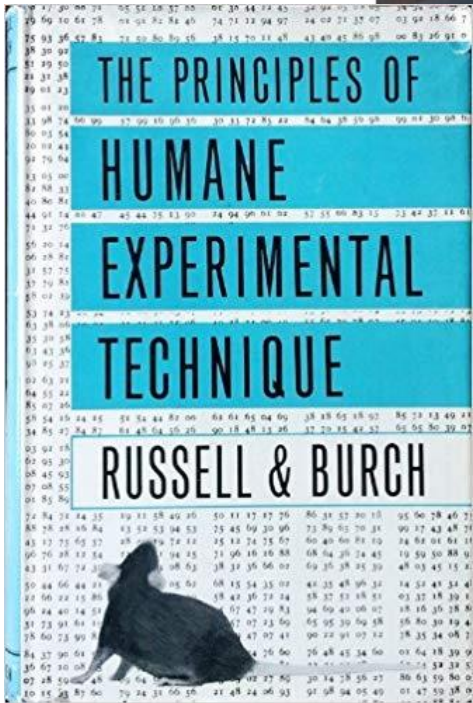
**+ Carl Westmoreland, Gavin Maxwell, Paul Russell, Matthew Dent, Paul Carmichael
and our SEAC colleagues & partners**

29-10-2019 EPAA Annual Conference, Brussels

"Building Confidence for the use of 3Rs"

2019 – celebrating 60 years of the Three Rs, but still building confidence in their application. So, how do we accelerate change?

1959



1995

October 2005 – calling for renewed Commitment & Collaboration ...

Working Together to Respond to the Challenges of EU Policy to Replace Animal Testing

Julia H. Fentem

Unilever Safety & Environmental Assurance Centre (SEAC), Colworth Laboratory, Sharnbrook, Bedfordshire MK44 1LQ, UK

E-mail: Julia.Fentem@unilever.com

Summary — This paper presents a personal perspective on efforts during the past 15 years to replace animal testing for assessing the safety of chemicals and products. It is based on an invited lecture — the FRAME Annual Lecture — given in October 2005, with the theme of “making progress by working together” (government–industry–academia–NGOs). Where we have achieved some successes, these have clearly been due to effective cooperation and collaboration between the relevant stakeholders. In recent times, there has not been this same level of active commitment and coordination. This needs to change, since, if we are to make good progress in the years to come in responding to the new challenges of the EU policy to replace animal testing, this will undoubtedly require us to work together, hopefully facilitated by effective leadership and coordination from the EU policy-makers themselves.

Fentem 2006 *ATLA* 34, 11-18

EU policy to ban cosmetics testing meant scientists had to re-think how we do PRODUCT safety assessments with new non-animal approaches

Fentem, Chamberlain, Sangster. 2004. *ATLA*. 32. 617-623

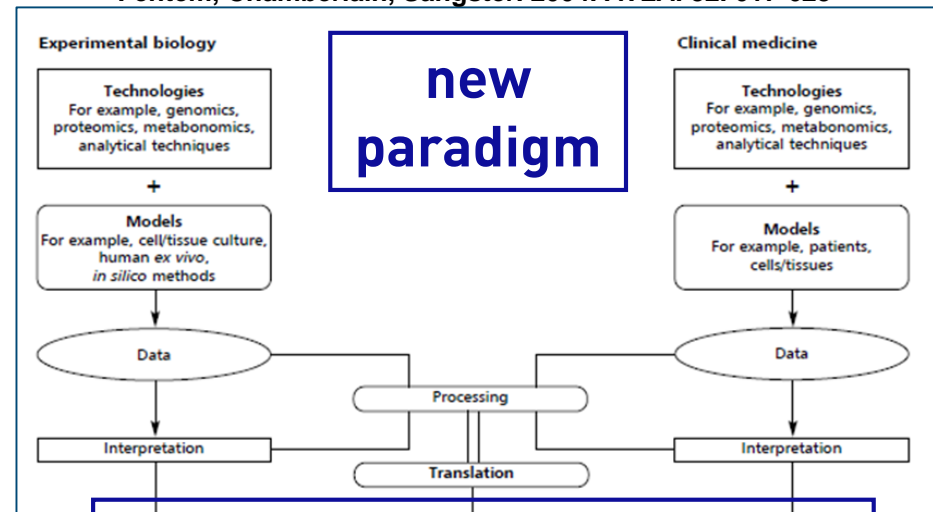
Figure 2: Safety assessment — future needs

exposure-based

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

Tier 1

IN SILICO-FIRST
EXAMPLES:
MIE *in silico* Atlas & QSARs
Skin haptation modelling
In silico receptor screening

In silico-first approaches for identifying pathways of concern, building weight of evidence and formulating hypotheses for testing

Tier 2

PATHWAY IDENTIFICATION
(TARGETS AND OFF-TARGETS)
EXAMPLES:
HT-Transcriptomics
In vitro screening panels
High content imaging
SPME free concentration

Identifying/characterising lead MIEs and pathways through experimental data generation, informatics data mining and computational modelling

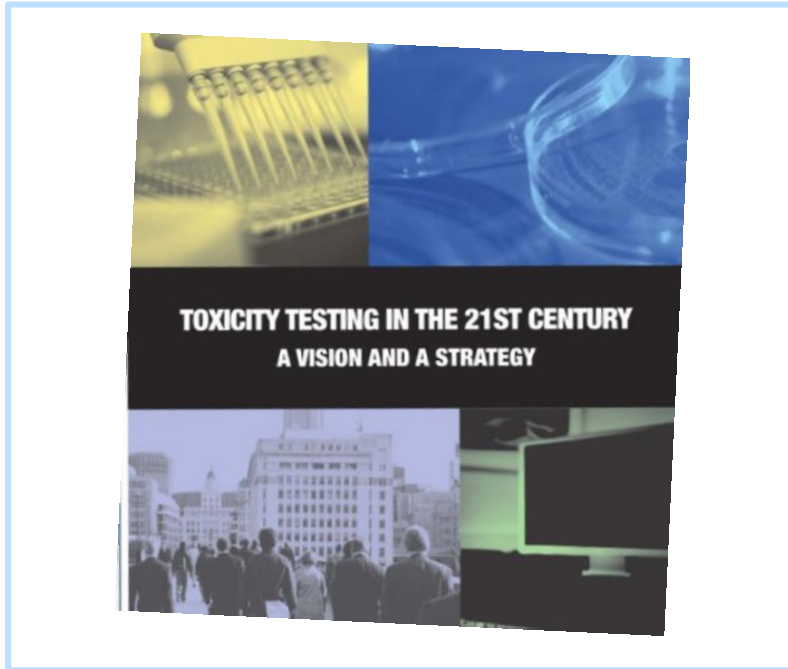
Tier 3

PATHWAY CHARACTERISATION
(TARGETS)
EXAMPLES:
3D and organotypic cell models
Molecular dynamic simulations
Integrated *in vitro* systems

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

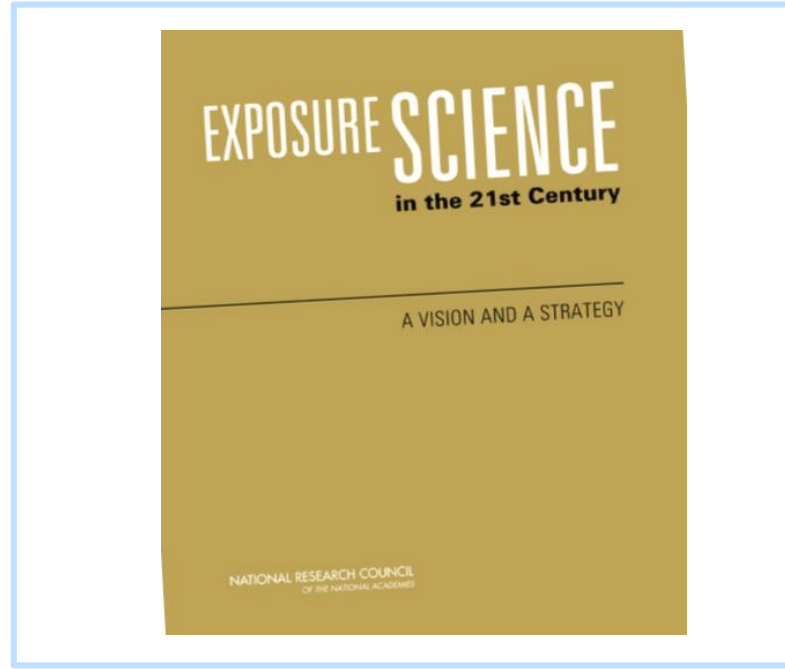
Frameworks for applying 21C Science & Technology for Safety Decisions

TT21C



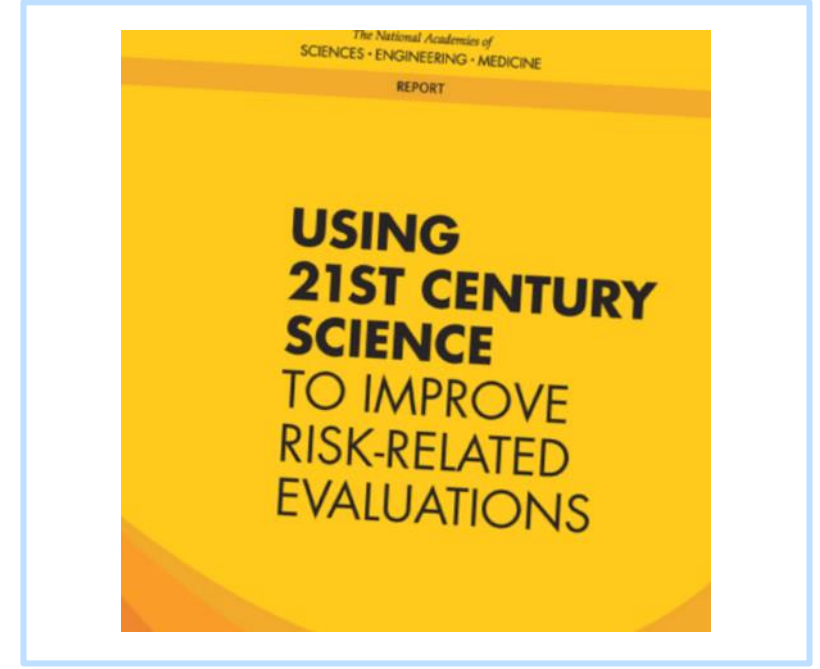
US National Academies of Science 2007

ES21C



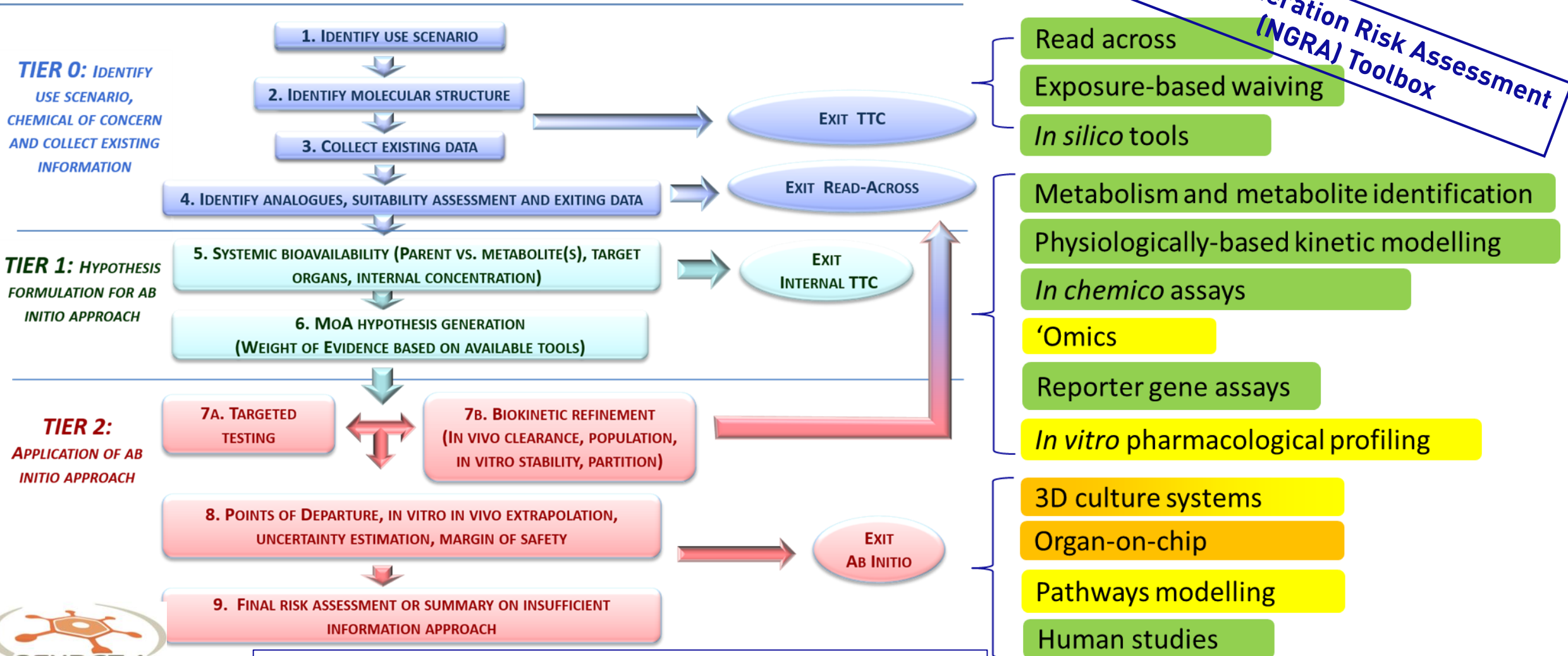
US National Research Council 2012

21C Risk Assessment



US National Academies of Science 2017

New paradigm now translated into NGRA workflows and confidence built through collaborating on case studies



EUTOXRISK

[Comput.Toxicol. 2017 Nov;4:31-44. doi: 10.1016/j.comtox.2017.10.001.](https://doi.org/10.1016/j.comtox.2017.10.001)

Ab initio chemical safety assessment: A workflow based on exposure considerations and non-animal methods.

Berggren E¹, White A², Ouedraogo G³, Paini A¹, Richarz AN¹, Bois FY⁴, Exner T⁵, Leite S⁶, Grunsven LAV⁶, Worth A¹, Mahony C⁷.

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

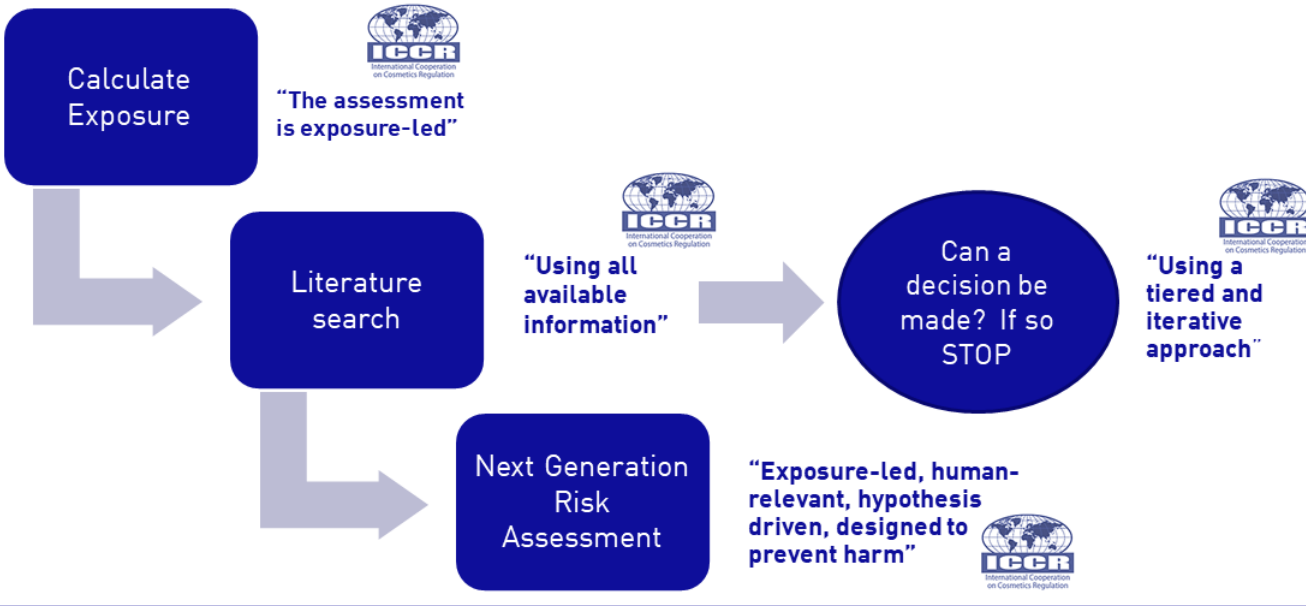
3 Principles describe how a NGRA should be conducted:

- 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



ELSEVIER
 Computational Toxicology
 journal homepage: www.elsevier.com/locate/comtox

Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

Matthew Dent^{a,*}, Renata Teixeira Amaral^b, Pedro Amores Da Silva^b, Jay Ansell^c, Fanny Boisleve^d, Masato Hatao^e, Akihiko Hirose^f, Yutaka Kasai^g, Petra Kern^h, Reinhard Kreilingⁱ, Stanley Milstein^j, Beta Montemayor^k, Julcemara Oliveira^l, Andrea Richarz^m, Rob Taalmanⁿ, Eric Vaillancourt^o, Rajeshwar Vermaⁱ, Nashira Vieira O'Reilly Cabral Posada^l, Craig Weiss^p, Hajime Kojima^f

^a Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^b Instituto de Química de São Carlos, São Carlos, Brazil
^c Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^d Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^e Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^f Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^g Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^h Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
ⁱ Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^j Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^k Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^l Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^m Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
ⁿ Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^o Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK
^p Centre for Computational Toxicology, School of Chemistry, University of Southampton, Southampton, UK

NGRA consumer safety case studies & new products in market where NAMs provide data for safety decisions – no reliance on new animal data

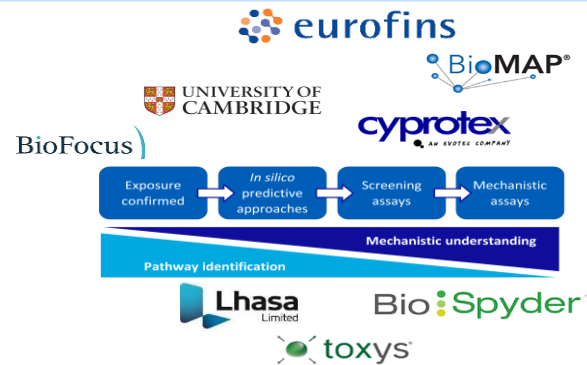
imagine we had no animal data – coumarin case study



- can we actually make safety decisions about our products with NGRA?
- non-animal safety risk assessment by integrating kinetic modelling & data from NAMs
- sharing at conferences, publication in progress; feedback welcome

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
- importance of partnering across R&D

embedding NGRA from the earliest stages of innovation

hand dishwash - 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

Working together across all stakeholders is key to making progress

EUToxRisk



ICCR



Animal-Free Safety Assessment Collaboration (AFSA)




New scientific tools & application

Regulatory application

Building capability globally

CASE STUDIES on chemical ingredients used in cosmetics & other product types

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.




ECHA
EUROPEAN CHEMICALS AGENCY

New Approach Methodologies in Regulatory Science


Proceedings of a scientific workshop
Helsinki, 19–20 April 2016

- **United States:** EPA, California EPA, NTP, CPSC
- **Canada:** Health Canada
- **Europe:** ECHA, EFSA, JRC, INERIS, RIVM
- **Asia:** Korea – Ministry of the Environment, Japan – Ministry of the Environment & Ministry of Health, Welfare and Labour, Singapore – A*STAR, Taiwan – SAHTECH
- **Australia:** NICNAS
- **OECD**




Accelerating the Pace of Chemical Risk Assessment (APCRA): An International Governmental Collaborative Initiative

Maureen Gwinn PhD DABT
Katie Paul Friedman PhD
CSS Science Webinar Series
June 25, 2019




Accelerating the Pace of Chemical Risk Assessment
APCRA



What is APCRA?

- **An international governmental collaboration that brings together governmental entities engaged in development of new hazard, exposure, and risk assessment methods and approaches for their chemical evaluation activities.**
 - To discuss progress and barriers in applying new tools to prioritization, screening, and quantitative risk assessment of differing levels of complexity.
 - To discuss opportunities to increase collaboration in order to accelerate the pace of chemical risk assessment.



APCRA Desired Outcomes

- Common understanding of current state of the science applications of New Approach Methods (NAMs), including the regulatory context.
- Increase cross-Agency collaboration to strategically address barriers and limitations of use of NAMs in a regulatory context.
- Complement member country participation in OECD, RCC, or various bi-lateral collaborations.
- Determine mechanisms to enhance data sharing capabilities.
- Increase engagement and commitment to development and sharing of case studies of mutual interest.

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 (OCSPP) 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."

ChemicalWatch
GLOBAL RISK & REGULATION NEWS



Lisa Martine Jenkins
Americas reporter

EPAA 2019: “Building Confidence for the use of 3Rs” – multi-stakeholder Cooperation & Collaboration is essential for progress. Still a key role for EPAA for another 15 years?



Fentem 2006 *ATLA* 34, 11-18

If new approaches for establishing safety without animal testing are to be delivered, then we need: a) strong Commission leadership and *coordination*; b) funding via EU and national research programmes; c) cross-sector company *commitment* and *collaboration*; d) stakeholder *cooperation*; and e) better *communication*, i.e. we probably need to focus as much on the “5 Cs” as on the “3 Rs”. Given we have some history of wasted opportunities, it is important not to miss the boat this time around.

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

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



Future Opportunities:

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



Building confidence to accelerate change in making product & chemical safety decisions without animal testing. So, what's really stopping us?

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*. The major premise is that *the highest possible fidelity is always desired in medical research and testing*, and that, *for man, a member of another placental mammal species would be a model of higher fidelity than a bird or a microbe*. This assumption can have disastrous consequences in terms of the data produced, and can also lead to unnecessary, and therefore unacceptable, animal suffering.

HIGHLIGHTS OF WC7

2009 – 50 years of the Three Rs



The Principles of Humane Experimental Technique: Timeless Insights and Unheeded Warnings

Michael Balls

FRAME, Nottingham, UK

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 ...

We must not hold them back, but work together to ensure much faster progress in implementing the Three Rs than that made in the past 60 years.