



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

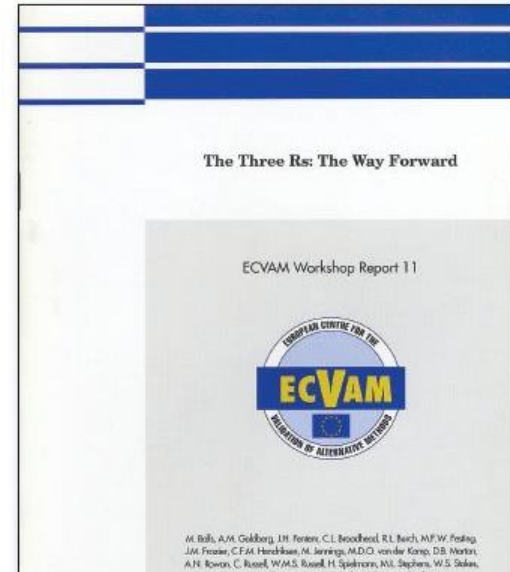
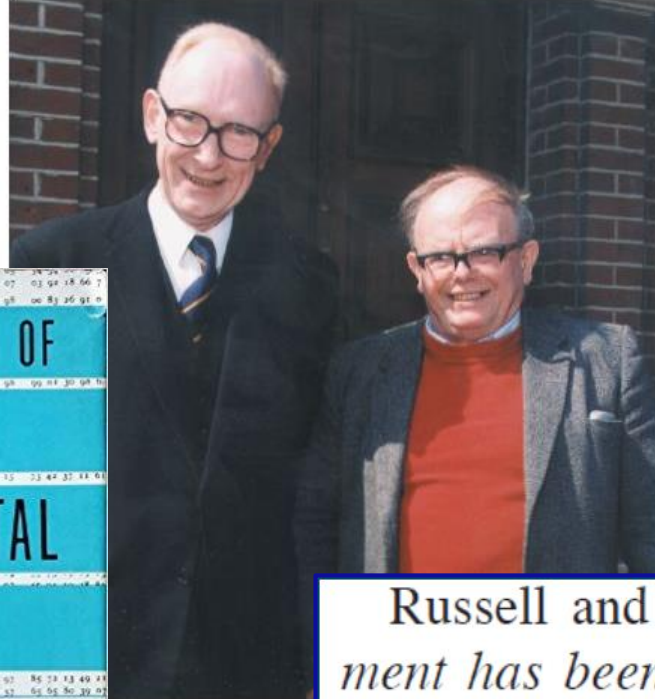
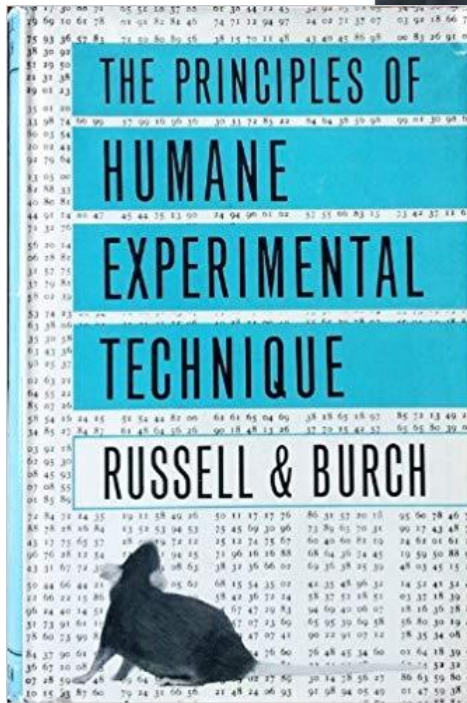
Julia Fentem

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

1959



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.*

HIGHLIGHTS OF WC7

2009 – 50 years of the Three Rs

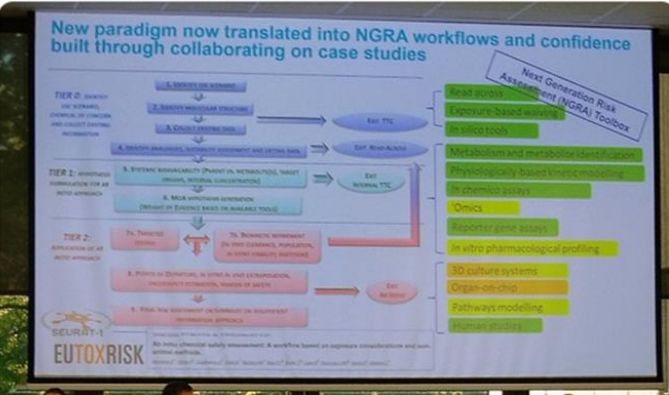
**The Principles of Humane Experimental Technique:
Timeless Insights and Unheeded Warnings**

Michael Balls
FRAME, Nottingham, UK

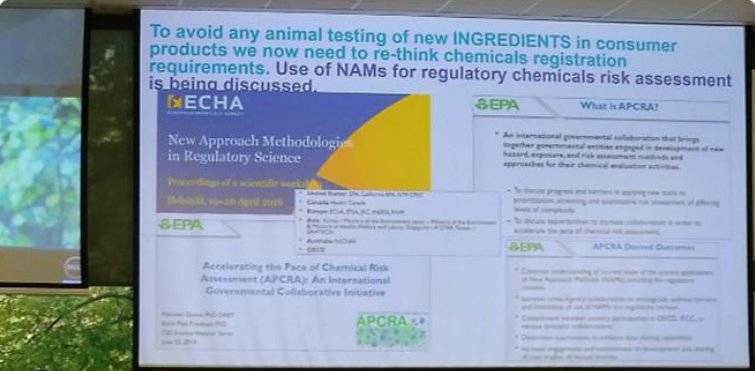
Some personal reflections, insights & future wishes: 1991-2019+

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

Susanna Louhimies @SLouhimies · Oct 29
"These collaborative studies are really starting to deliver on new #NonAnimal approaches" by @juliafentem quoting @EU_ToxRisk at @EPA3Rs annual conference #3Rs



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"The key to making a difference and building confidence in #NonAnimal approaches is to show how they work, case studies" concluded by @juliafentem from @Unilever at the end of an active panel session at @EPA3Rs annual conference #3Rs



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

Figure 2: Safety assessment — future needs

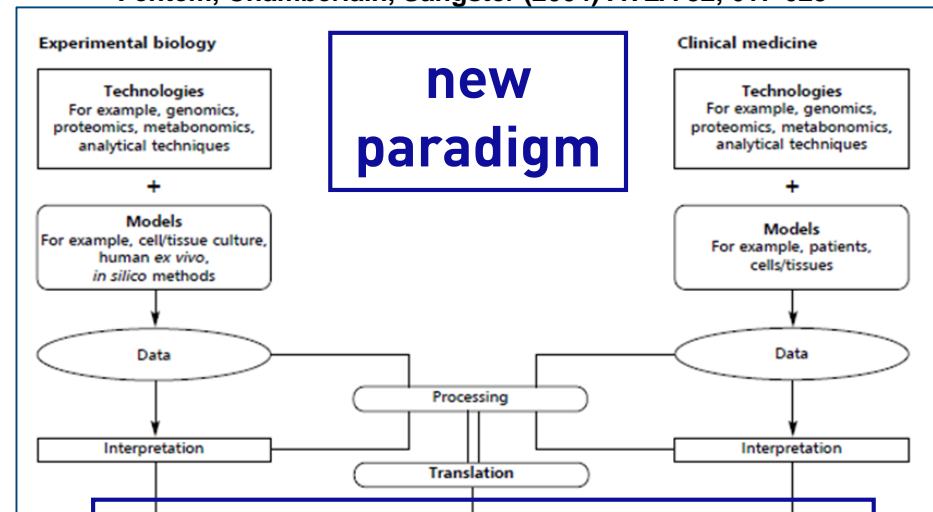
exposure-based

Safety assessment — future needs

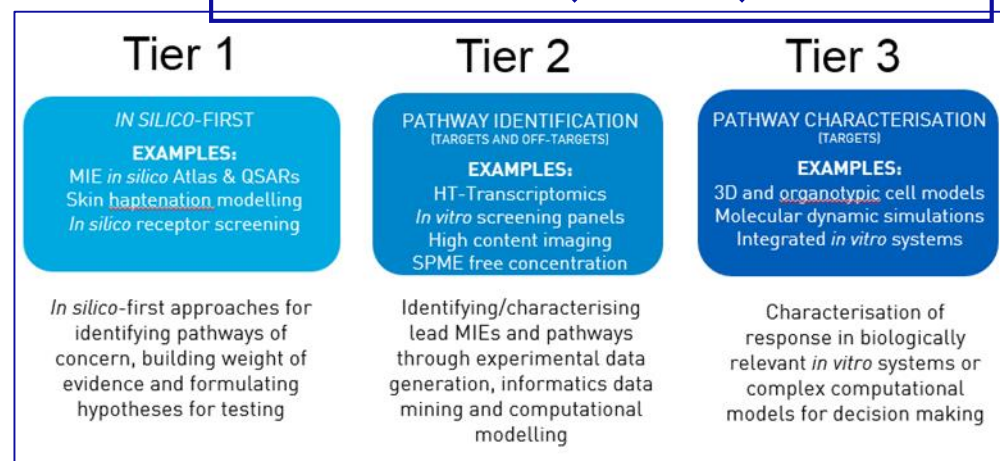
- consumer safety decisions without animal testing
- based on scientific risk assessment
- improve relevant fundamental biological understanding
- bring experimental biology/toxicology and clinical medicine closer together (in context of human health risk assessment)
- improve *in vitro* models (tissue 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

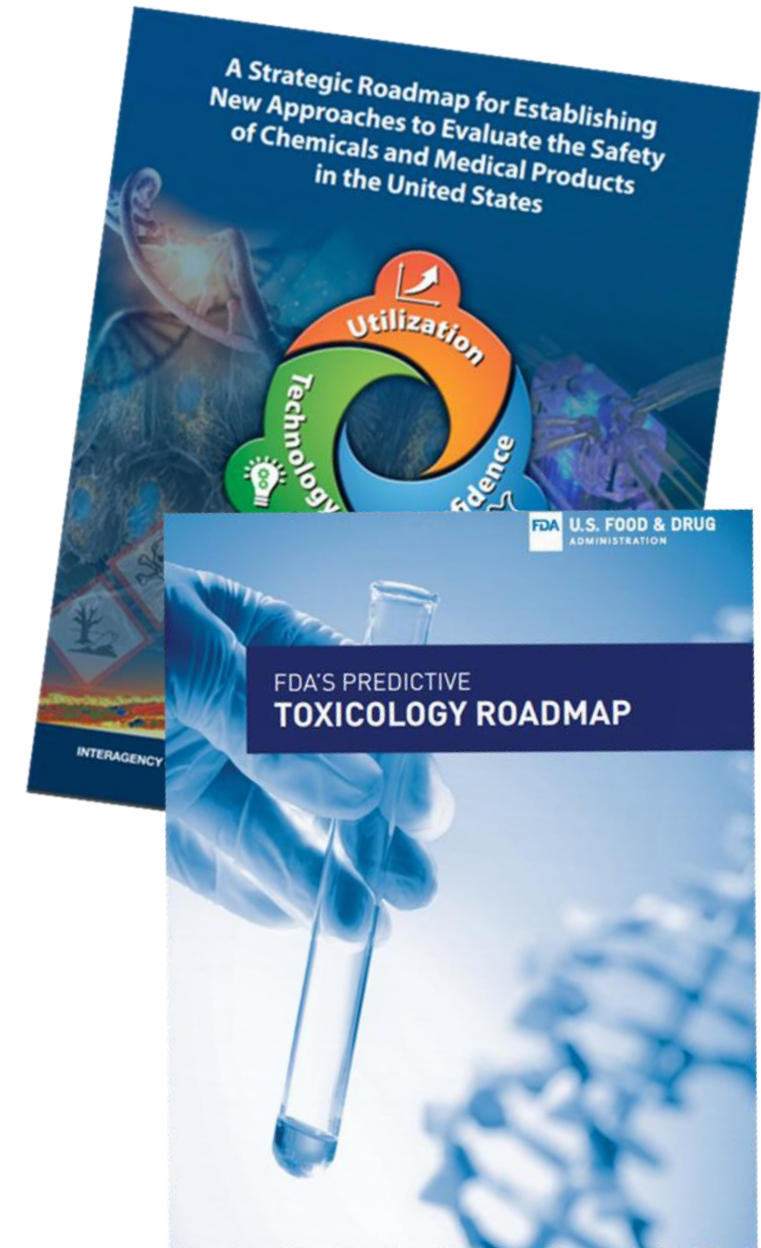
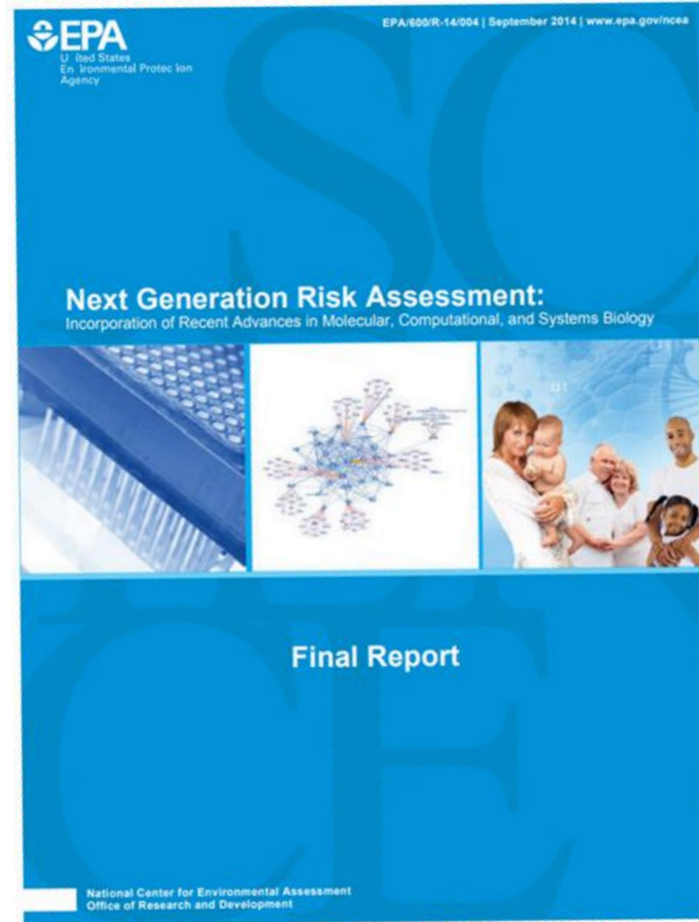
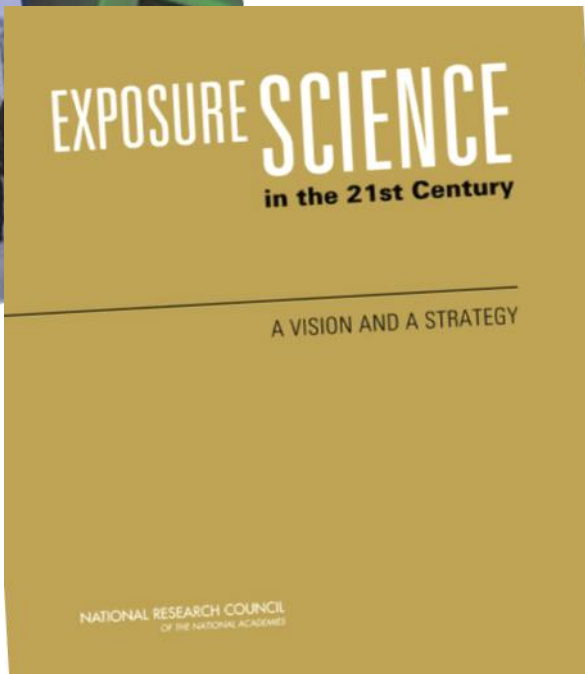
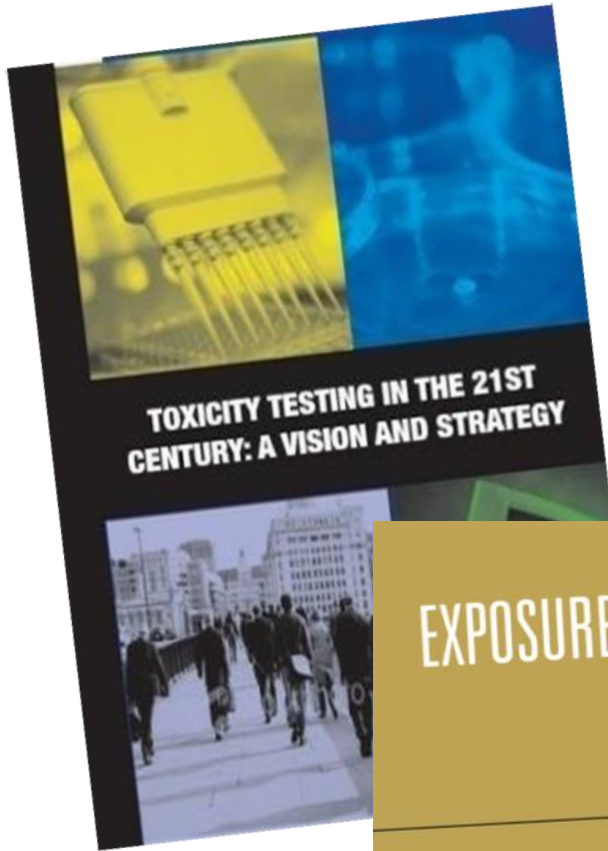
Fentem, Chamberlain, Sangster (2004) *ATLA* 32, 617-623



Next Generation Risk Assessment (NGRA) Toolbox

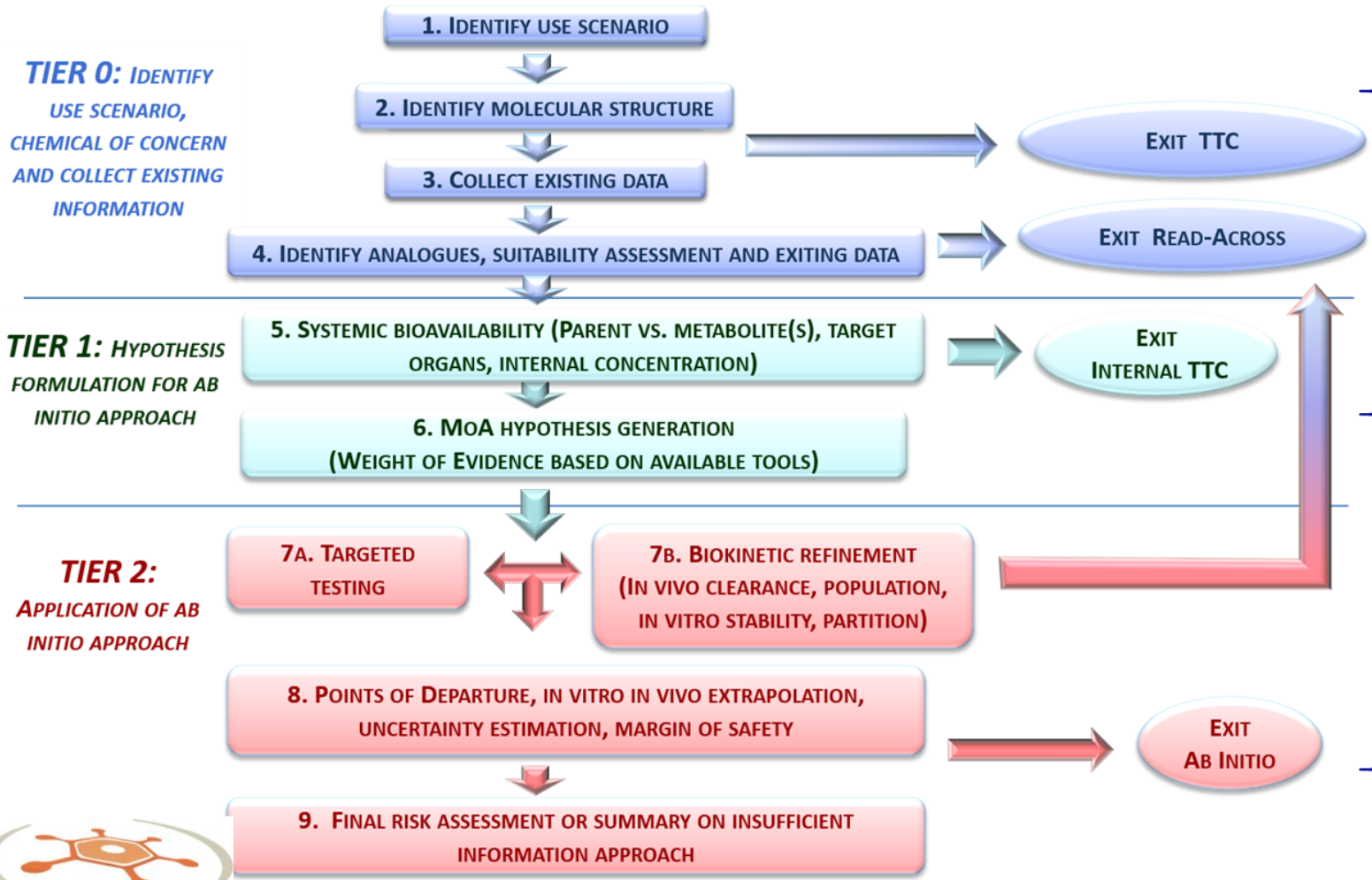


Frameworks for applying 21C Science & Technology for Safety Decisions



New paradigm now translated into NGRA workflows and Confidence Built through collaborating on Case Studies

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



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.

courtesy of Dr Andy White & EUToxRisk team

2. 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

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

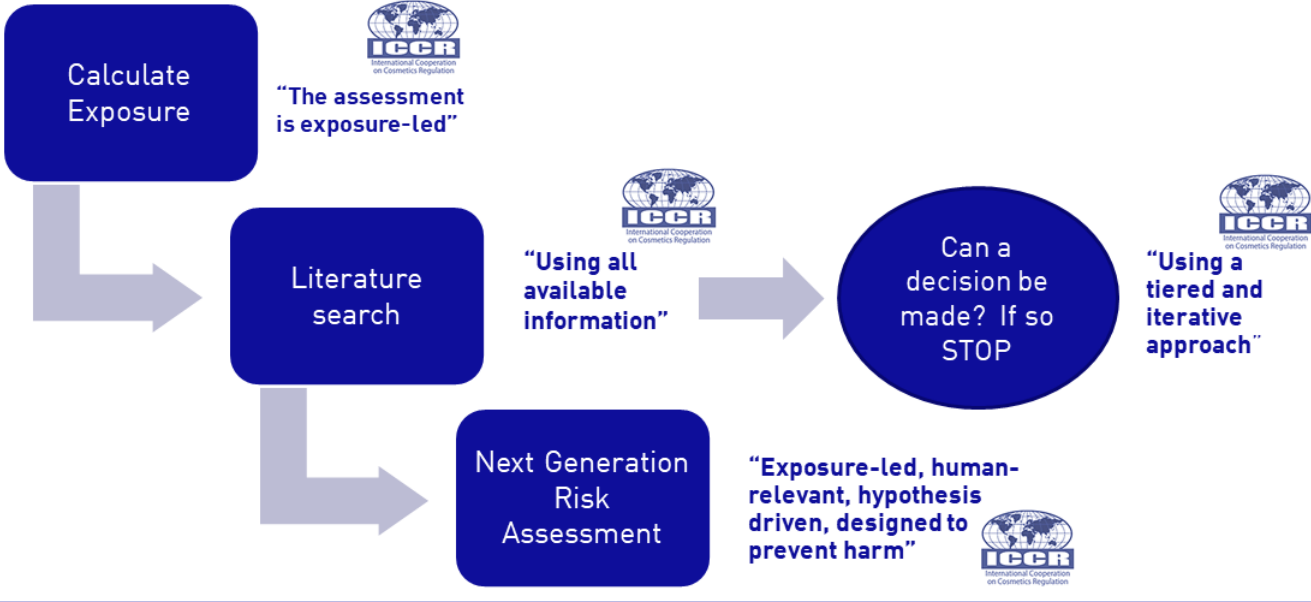
3 Principles describe how a NGRA should be conducted:

- 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 Safety and Health, Sharnbrook, Bedfordshire MK44 1LQ, UK
^b Instituto de Química de São Carlos, Caixa Postal 1356-970, São Carlos, SP 01311-000, Brazil

courtesy of Dr Matt Dent & ICCR team

“THE ASSESSMENT IS EXPOSURE LED” – HABITS AND PRACTICES

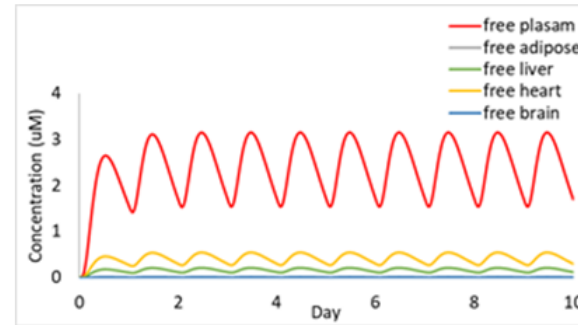


Table 2: Estimated daily exposure levels for different cosmetic product types according to Cosmetics Europe data (SCCNFP/0321/00; Hall et al., 2007, 2011).

Product type	Estimated daily amount applied	Relative amount applied (mg/kg bw/d)	Retention factor ¹	Calculated daily exposure (µg/d)	Calculated relative daily exposure (mg/kg bw/d)
Bathing, showering					
Shower gel	18.67 g	279.20	0.01	0.19	2.79
Hand wash soap ²	20.00 g	-	0.01	0.20 ³	3.33
Hair care					
Shampoo	10.46 g	150.49	0.01	0.11	1.51
Hair conditioner ²	3.92 g	-	0.01	0.04	0.60
Hair styling products	4.00 g	57.40	0.1	0.40	5.74



“THE ASSESSMENT IS EXPOSURE LED” - PBK



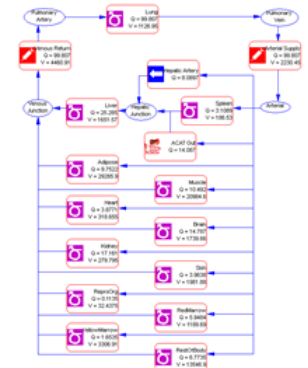
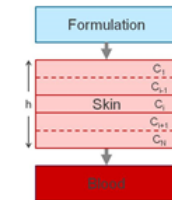
In Vitro Assays:
 Kinetic Solubility
 Thermodynamic Solubility
 Metabolic Stability
 -Human Hepatocytes
 -Human CYP450 Isoforms
 -Human Hepatic Microsomes
 Stability in Human Plasma
 Plasma Protein Binding
 Partitioning in Human Blood

CHARACTERISE THE PHYSICOCHEMICAL PROPERTIES

Name	Curcumin
CAS	458-37-7 -Sigma 8024-37-1 (Keto) 115851-80-4 (enol) - ChempSpider
MW	368.380 Da (Phys chem prop database)
Log P	3.36 (Phys chem prop database)
Solubility	122 µM [45 mg/L] (Phys chem prop database)
Log S	-3.91 (Phys chem prop database)
Log K _{AW}	-19.541 (EpiSuite)
Log K _{BSA}	2.94 (Exposure tool)
Form	odourless yellow solid

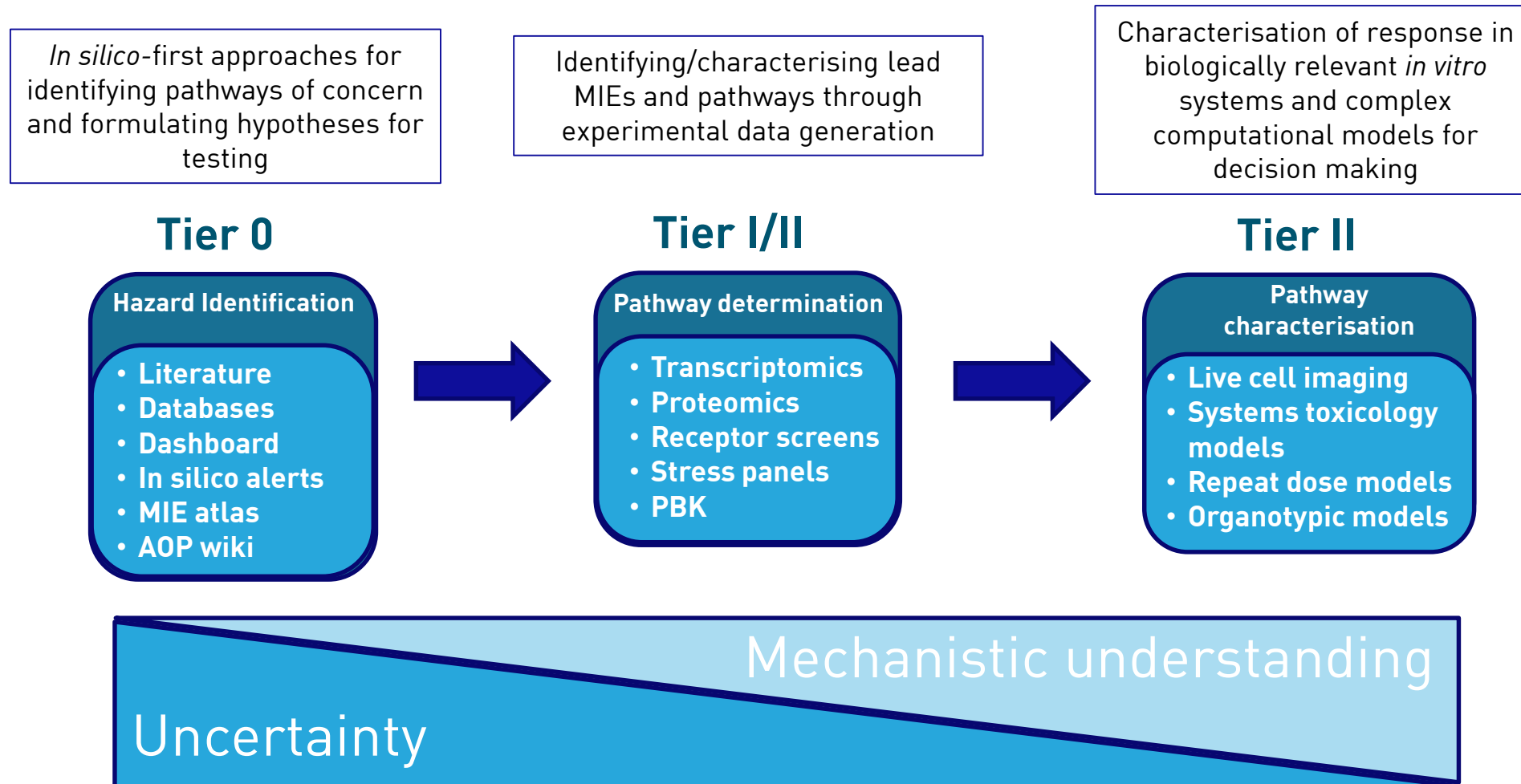
- In Silico determinations:
 - QSAR; ToxTree; OECD Toolbox; DEREK alerts; MIE Atlas; Drugbank; Metacore
- Chemistry determinations:
 - Partition coefficient logP
 - Peptide binding potential
- In vitro determined:
 - Kinetic solubility
 - Thermodynamic solubility
 - Metabolic & chemical stability
 -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

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

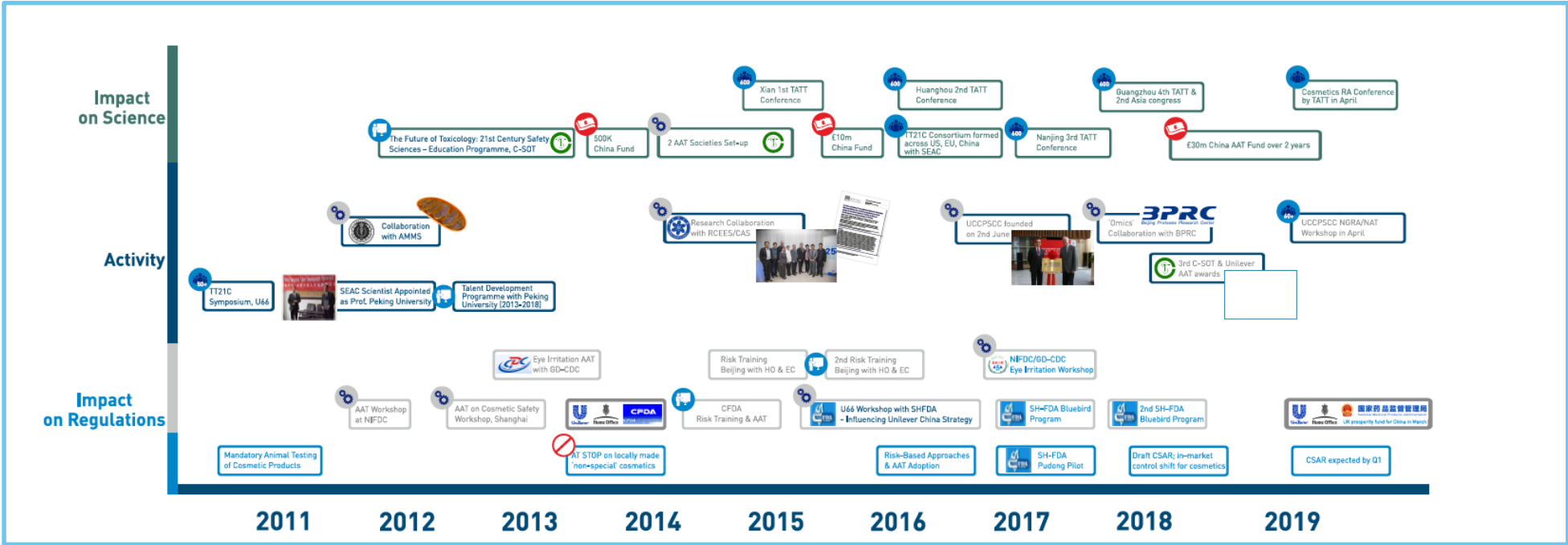


courtesy of Prof. Paul Carmichael & SEAC team

“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



SEAC



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

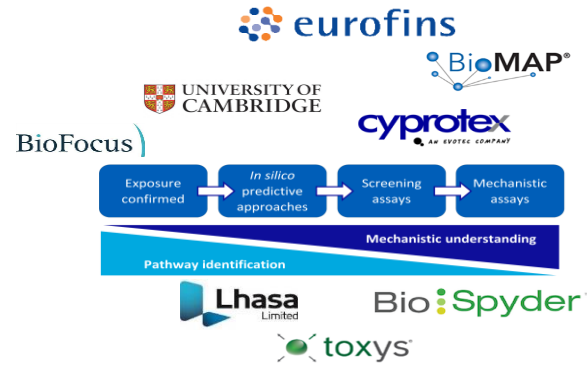
“imagine we had no animal data” – coumarin case study



- 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


NGRA Framework used in Coumarin Case Study




Hypothetical products containing coumarin



Safety assessment required for 0.1% coumarin in Shampoo




Safety assessment required for 0.1% coumarin in Face Cream

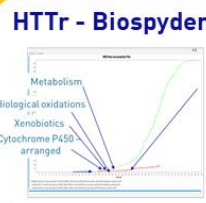


Safety assessment required for 0.1% coumarin in Body Lotion

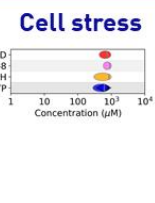
PBK models




HTTr - Biospyder

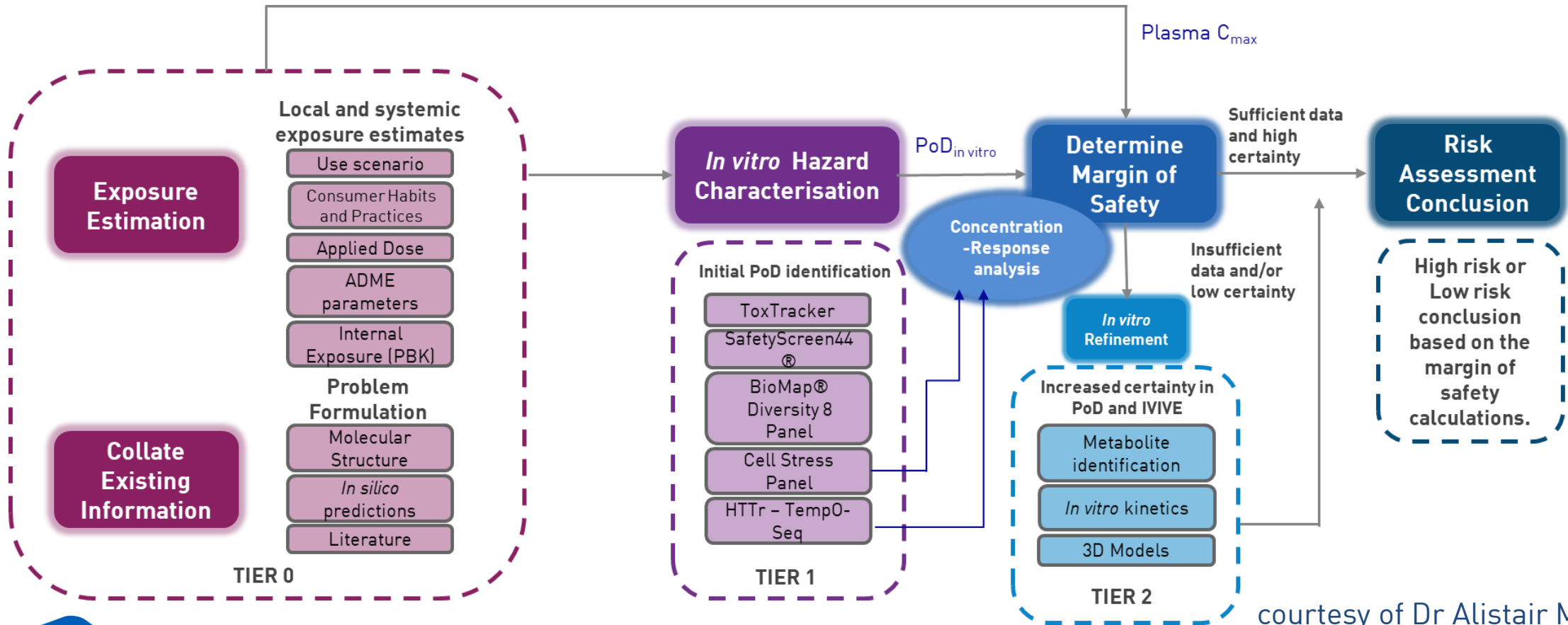


Cell stress




CEREP 44





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.




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

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:

- **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**




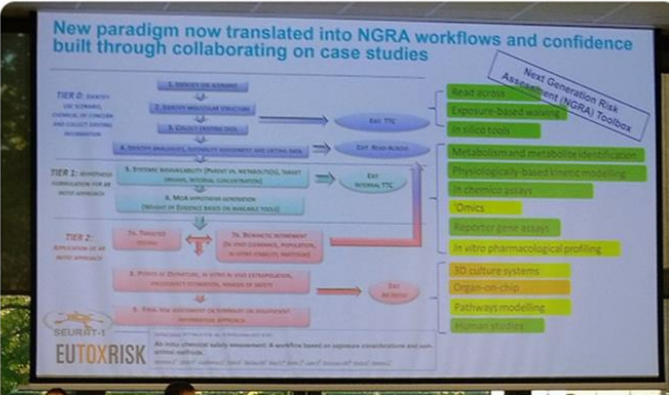
29-10-2019 EPAA Annual Conference, Brussels


“Building Confidence for the use of 3Rs”

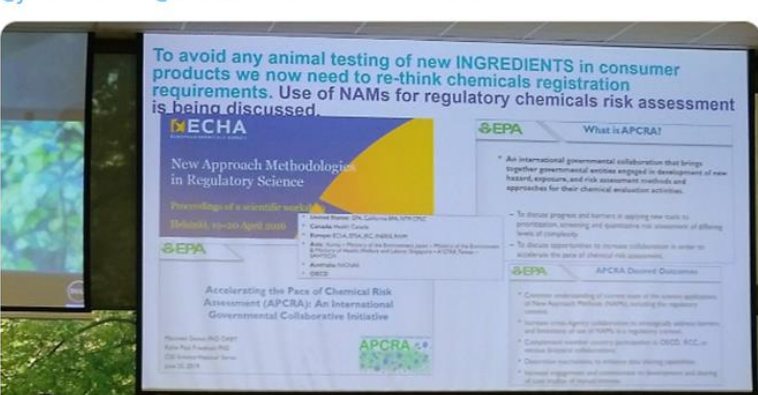
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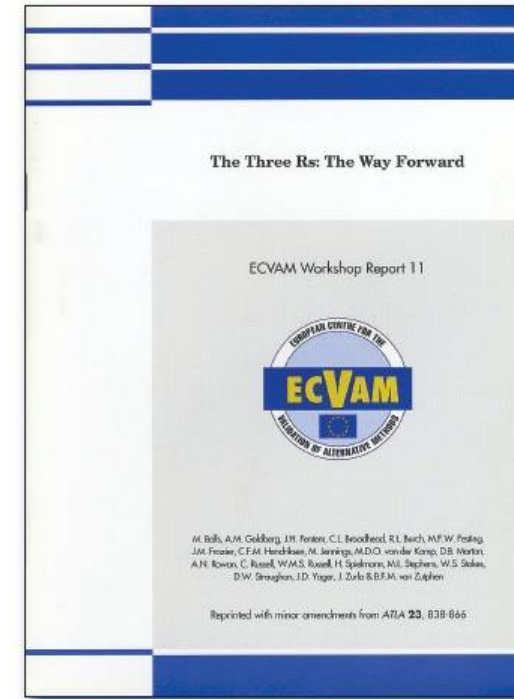
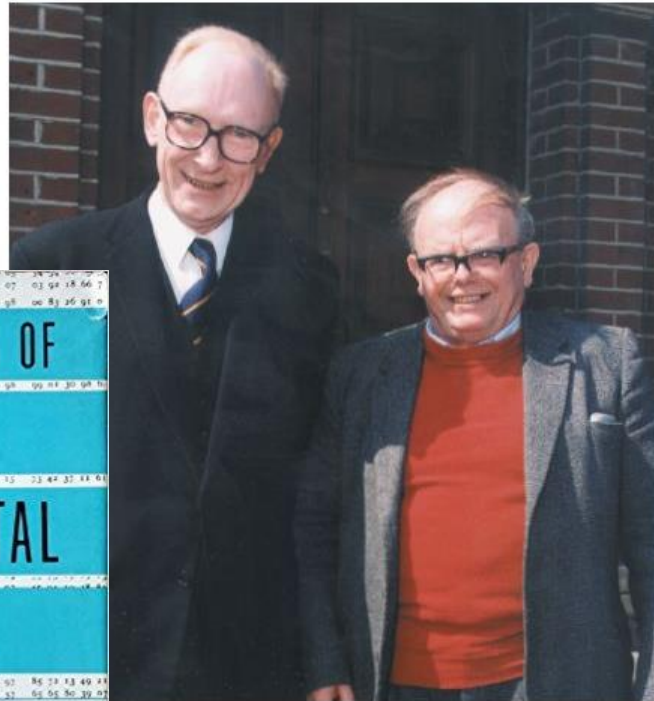
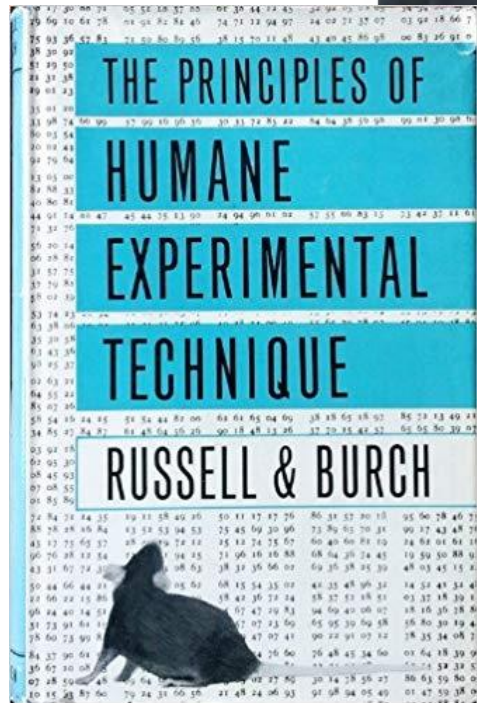


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Pioneering Change – Thought Leadership & Inspiring Others ...

1959



with many thanks to all of my SEAC colleagues
& our collaborators across the globe



3Rs in transition From development to application

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/>

