

# International Developments and Collaborations on New Approach Methods (NAMs) for Consumer Safety of Cosmetics

化妆品消费者安全最新技术方法 (NAMs) 的国际发展与合作

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Unilever's Safety & Environmental Assurance Centre (SEAC)

+ Carl Westmoreland, Paul Carmichael, Paul Russell, Charlie Lai, Jie-Bing Zhu, SEAC colleagues and partners



Unilever

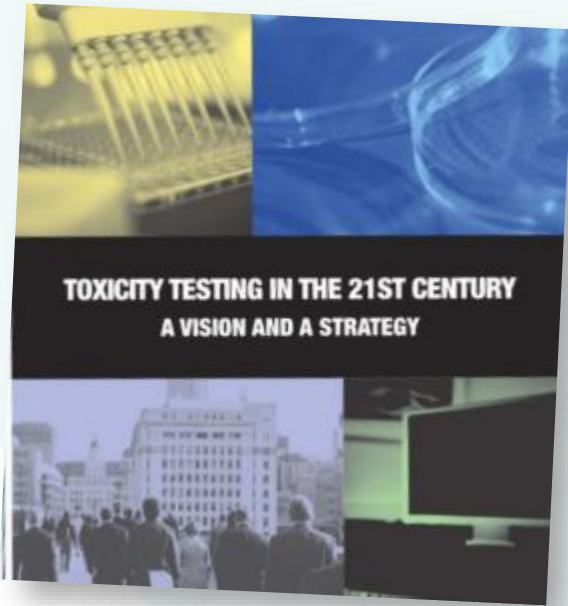
# Main content 主要内容

1. The world is changing fast
2. Non-animal next generation safety sciences:  
New approach methods (NAMs)
  - Introduction to NAMs
  - An example: Coumarin 香豆素在化妆品案例
3. Our global collaborations and partnerships



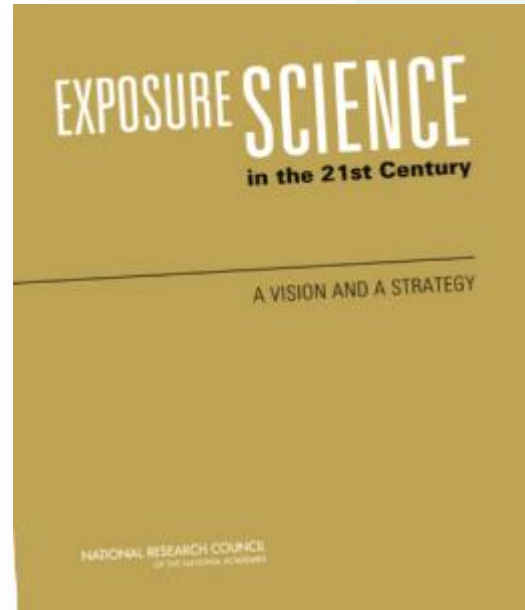
# 21<sup>st</sup> century safety sciences advanced greatly 21世纪安全科学取得了巨大进步

## TT21C



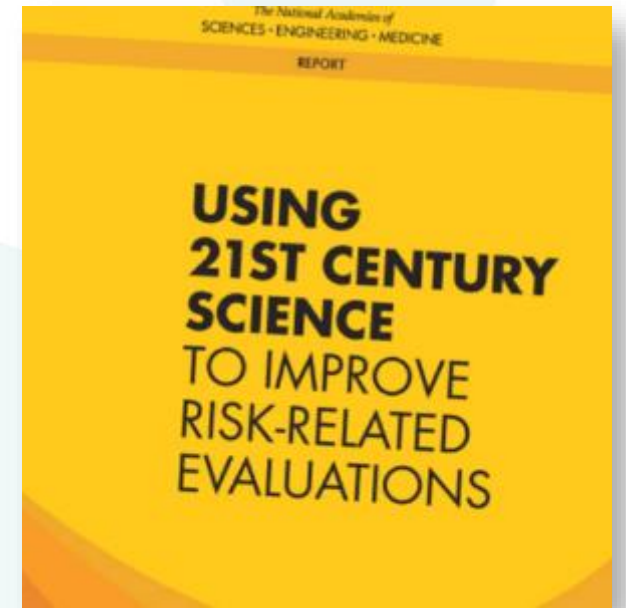
US National Academies of  
Science 2007  
美国国家科学院2007报告

## ES21C



US National Research  
Council 2012  
美国国家研究委员会  
2012报告

## 21C Risk Assessment



US National Academies of  
Science 2017  
美国国家科学院  
2017报告

# 9 principles of NGRA from ICCR for cosmetic risk assessment

国际化妆品监管合作组织 (ICCR): 新一代化妆品风险评估 (NGRA) 的9大原则

4 + 3 + 2 = 9

## Main Overriding Principles

- A human safety risk assessment
- Exposure Led
- Hypothesis Driven
- Prevent Harm

### 4总体原则

- 人体安全风险评估
- 以暴露为引导
- 以假设为驱动的
- 防止危害

## How to conduct an NGRA

- Appraisal of Existing Information
- Tiered and Iterative Approach
- Robust and relevant strategies

### 3实施原则

- 对现有信息进行适当评估
- 使用分层和迭代方法
- 使用可靠而相关的方法和策略

## NGRA Documentation

- Document and characterise sources of uncertainty
- Transparent logic of approach

### 2记录原则

- 对不确定性来源进行表征和记录
- 该方法的逻辑应该透明并记录在案

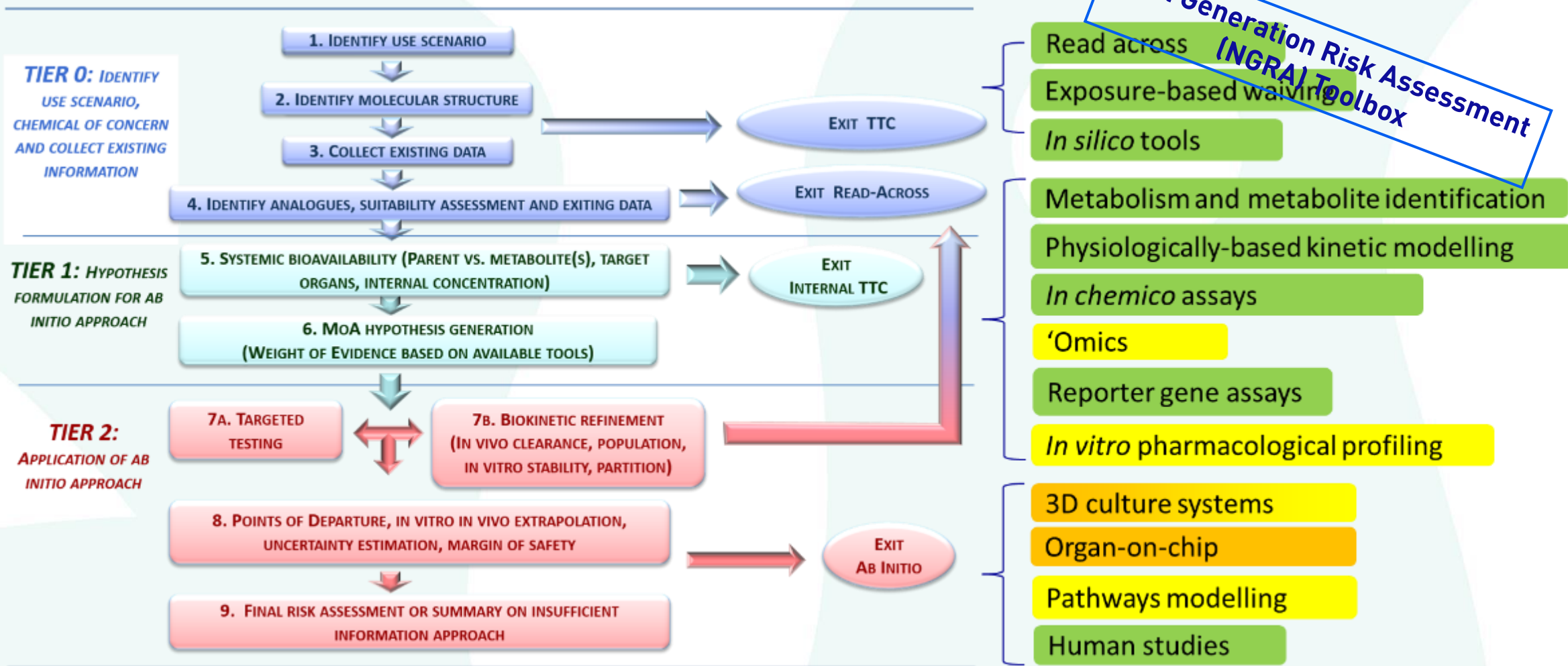


Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

Dent et al., (2018) *Comp Tox* 7:20-26

# New paradigm now translated into NGRA workflows in EU

## 在欧盟，新范式已转换为NGRA新一代风险评估工作流程



Comput Toxicol. 2017 Nov;4:31-44. doi: 10.1016/j.comtox.2017.10.001.

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

Berggren E<sup>1</sup>, White A<sup>2</sup>, Quedroogo G<sup>3</sup>, Paini A<sup>1</sup>, Richarz AN<sup>1</sup>, Bois FY<sup>4</sup>, Exner T<sup>5</sup>, Leite S<sup>6</sup>, Grunsven LAV<sup>6</sup>, Worth A<sup>1</sup>, Mabony C<sup>7</sup>.

# Frameworks of non-animal approaches (NA) to chemical safety in US 在美国，非动物化学安全方法框架，

Tox21/ToxCast

~700 HTS Biological Pathways Assays



<https://www.epa.gov/chemical-research/toxicity-forecasting>

EPA Work Plan Launched June 2020

The screenshot shows the EPA website page for the New Approach Methods Work Plan. The page features a blue header with navigation links for Environmental Topics, Laws & Regulations, and About EPA. Below the header, there is a search bar and social media icons. The main content area is titled "EPA New Approach Methods Work Plan: Reducing Use of Animals in Chemical Testing" and includes five key objectives in blue boxes: Evaluate regulatory flexibility for accommodating NAMs, Develop baselines and metrics for assessing progress, Establish scientific confidence and demonstrate application, Develop NAMs that fill critical information gaps, and Engage and communicate with stakeholders. A "Contact" section provides feedback information, and a "Resources" section lists related documents and a webinar.

**EPA** United States Environmental Protection Agency

Environmental Topics    Laws & Regulations    About EPA    Search EPA.gov

Related Topics: Safer Chemicals Research    CONTACT US    SHARE    f    t    e

## EPA New Approach Methods Work Plan: Reducing Use of Animals in Chemical Testing

- Evaluate regulatory flexibility for accommodating NAMs
- Develop baselines and metrics for assessing progress
- Establish scientific confidence and demonstrate application
- Develop NAMs that fill critical information gaps
- Engage and communicate with stakeholders

**Contact**

If you have feedback about the EPA New Approach Methods Work Plan please contact [NAM@EPA.gov](mailto:NAM@EPA.gov)

**Resources**

- [New Approach Methods Work Plan for Reducing the Use of Animals in Chemical Testing](#)
- [New Approach Methods Work Plan Release Webinar](#)

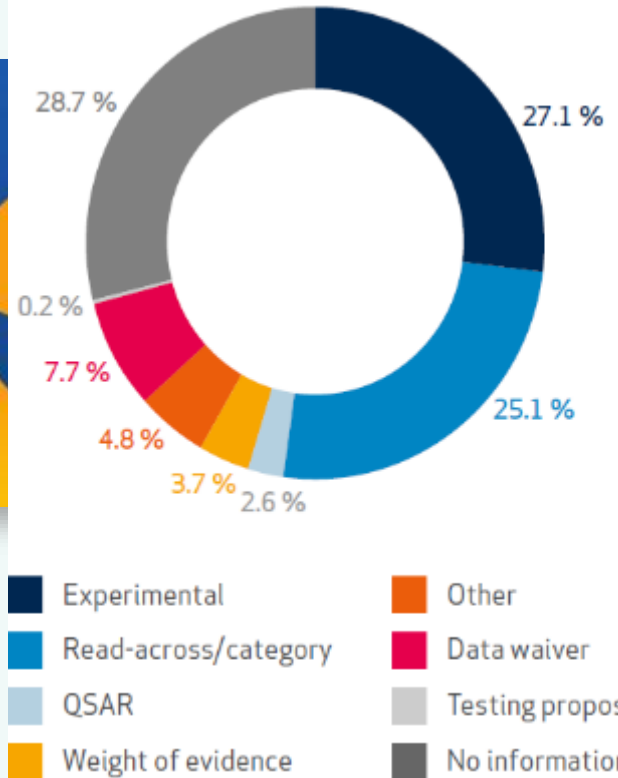
EPA uses information from a broad range of animal tests to evaluate the potential risks of chemicals, assess potential impacts on the environment, and approve chemicals for certain uses. Given the large number of chemicals regulated by EPA, the number of animals used to generate the necessary information is substantial.

EPA's New Approach Methods (NAMs) Work Plan was created in response to EPA Administrator Andrew

新方式方法工作计划

# Non-animal approaches increasingly taken up in regulations 法规越来越多地采用非动物方法, 禁止用动物实验数据

## In EU 欧洲



**For 70% of substances registered, at least one non-animal approach used.**

## In US 美国



## 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

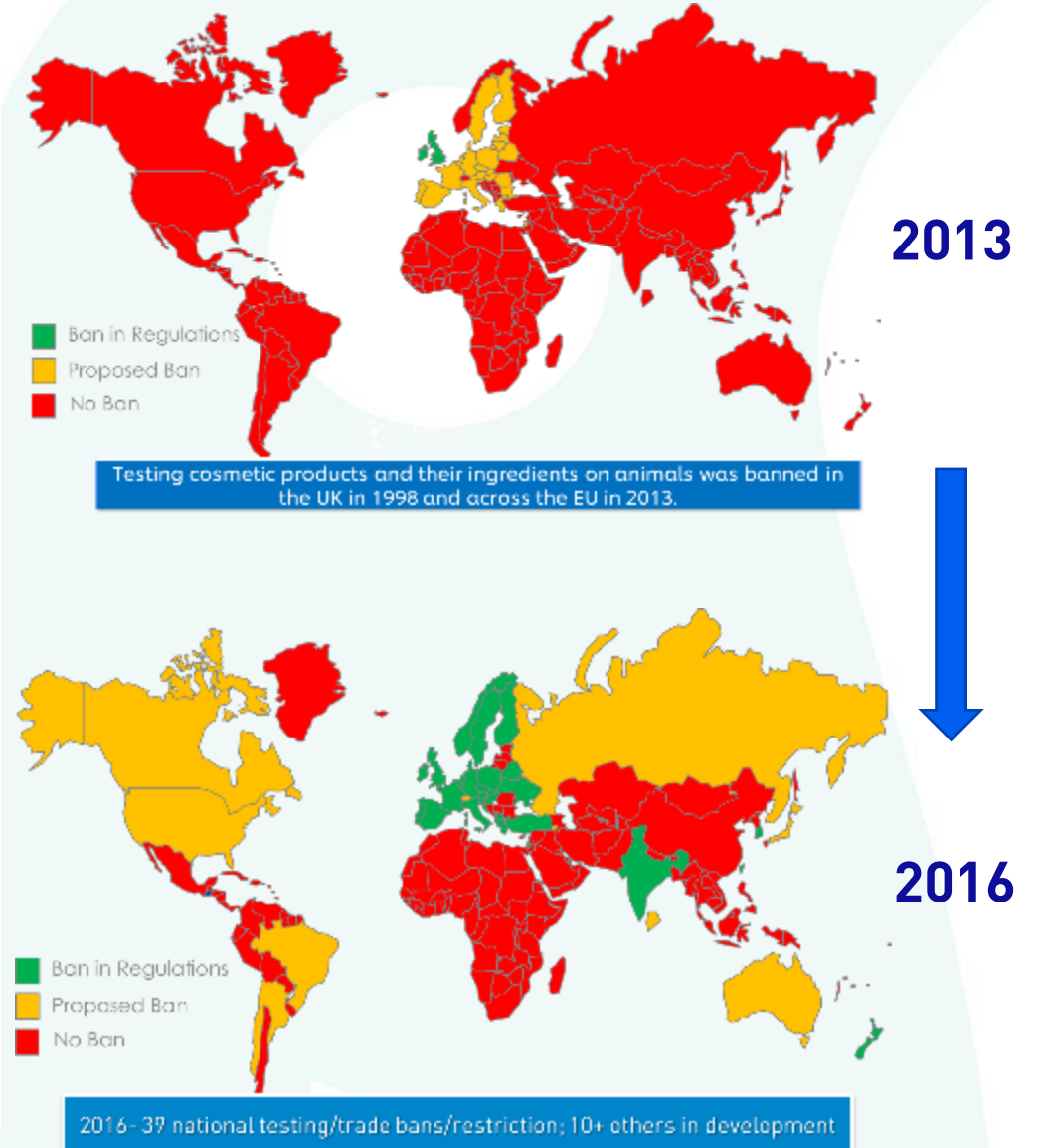
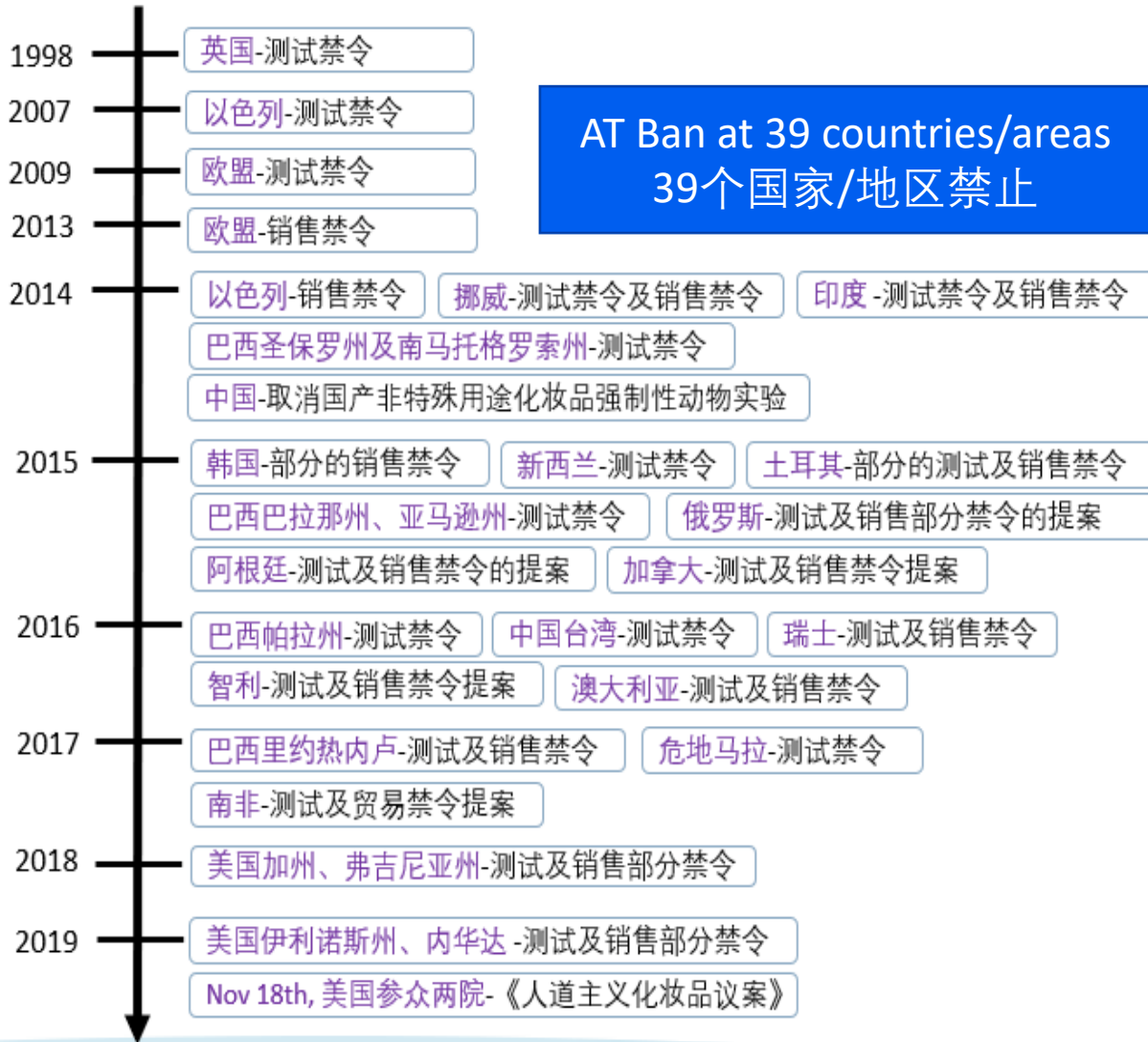
US EPA Administrator Andrew Wheeler has signed a memo directing the agency to eliminate all requests and funding for mammal studies by 2035, and reduce both requests and funding by 30% by 2025. Exceptions will have to be approved by the administrator on a case-by-case basis.

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



**ChemicalWatch**  
GLOBAL RISK & REGULATION NEWS

# A growing number of cosmetic regulations with animal testing (AT) ban worldwide 全球范围内禁止动物测试的化妆品法规越加增多





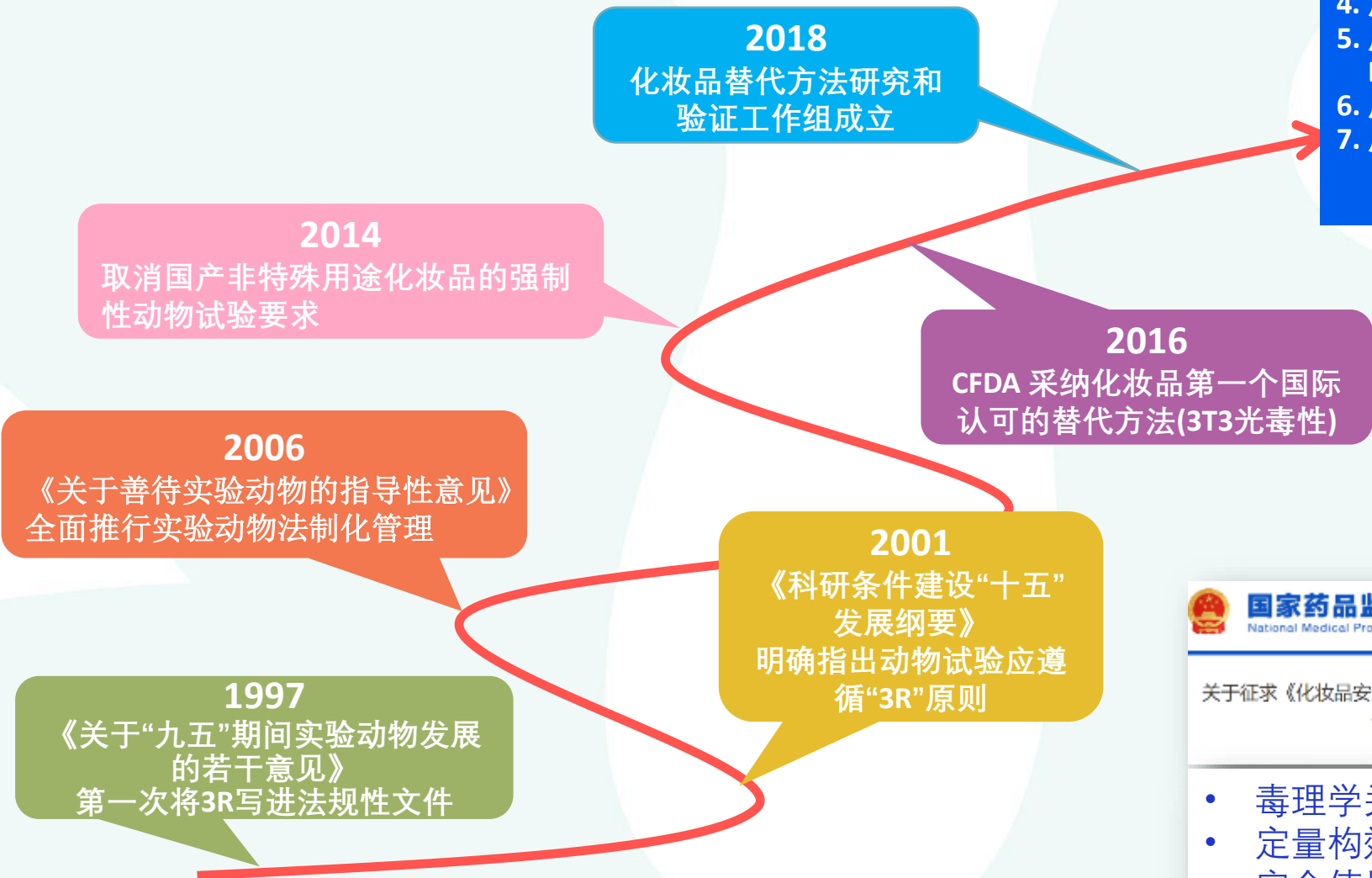
# Increasing numbers of global consumers want their consumer products not tested on animals+ transparency



Scientific, regulatory societal, and ethical reasons are demanding change; calls for Non-animal next generation safety sciences



# Chinese cosmetic regulations: Non-animal approaches 中国替代法化妆品法规的发展近况



## 2020-化妆品安全技术规范3R方法:

1. 原料体外3T3中性红摄取光毒性试验
2. 原料离体皮肤腐蚀性大鼠经皮电阻试验
3. 原料体外兔角膜上皮细胞短时暴露试验
4. 原料皮肤变态反应: 局部淋巴结试验:DA
5. 原料皮肤变态反应: 局部淋巴结试验:BrdU-ELISA
6. 原料体外皮肤变态反应: 直接多肽反应试验
7. 原料/产品:细菌回复突变试验

## 正在开展的替代方法验证

1. 皮肤致敏性氨基酸衍生物反应法
2. 皮肤致敏性荧光素酶报告基因LuSens试验
3. 皮肤致敏性U937细胞系活化试验、
4. 眼刺激/腐蚀性荧光素渗漏试验
5. 皮肤致敏性人细胞系活化试验
6. 遗传毒性哺乳动物细胞体外微核试验

国家药品监督管理局  
National Medical Products Administration

关于征求《化妆品安全评估技术导则(征求意见稿)》和《化妆品分类规则和分类目录(征求意见稿)》意见的函

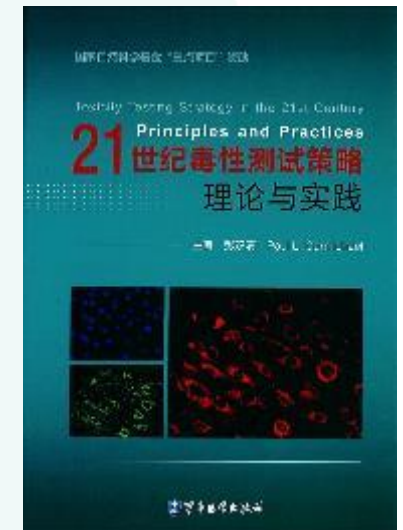
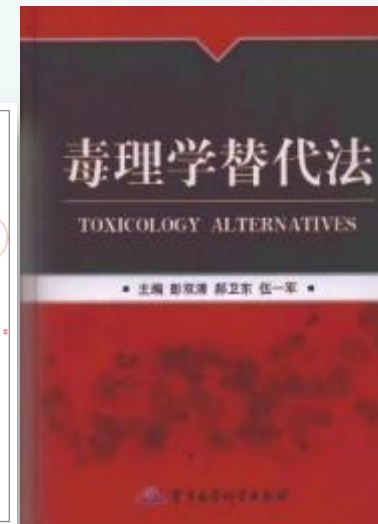
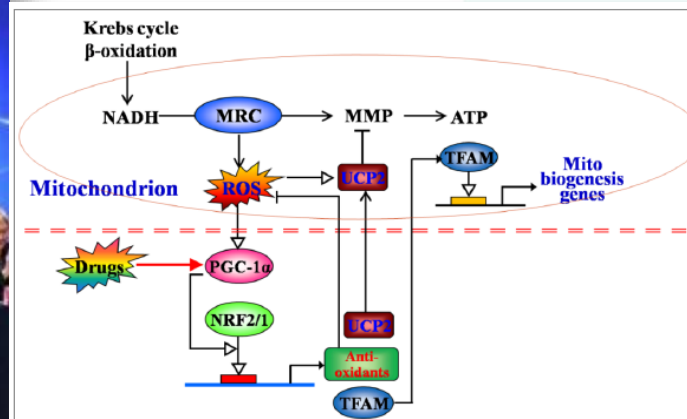
药监发函〔2020〕82号

- 毒理学关注阈值 (TTC)
- 定量构效关系 (QSAR) 交叉参照
- 安全使用历史 (HoSU)

# Chinese scientific advances: Non-animal approaches (NA)

## 中国科学进步：非动物方法 (NA)

- **Two NA scientific societies established from 2015**  
二个替代科学专委会建立
  1. The Society of Toxicological Alternative and Translational Toxicology (TATT), CSOT
  2. The Society of Toxicity Testing and Alternatives (TTA), CEMS
- **Sciences development with rising national funding and more national NA programmes** 大量基金和国家项目
- **Annual NA national conferences from 2014** 每年替代大会



## 2. Non-animal next generation safety sciences: New approach methods (NAMs)



Unilever

# Can we use a new ingredient safely?

我们可以安全地使用新成分吗？

Can we safely use **X%** of ingredient **Y** in product **Z**?

我们可以安全地使用**X%**的成分**Y**, 在产品**Z**中吗？



**All safety assessments of product ingredient are exposure-driven**

所有产品原料的安全性评估都是暴露驱动的



Consumer Exposure  
消费者暴露

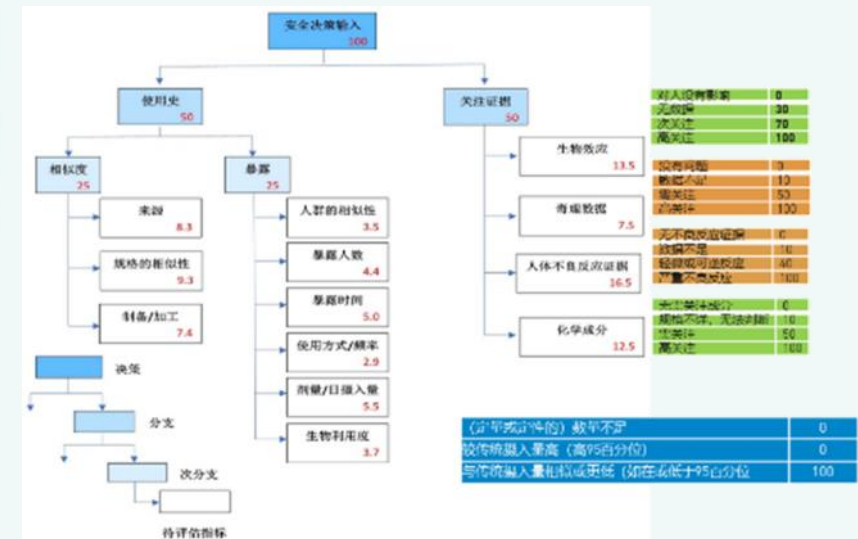
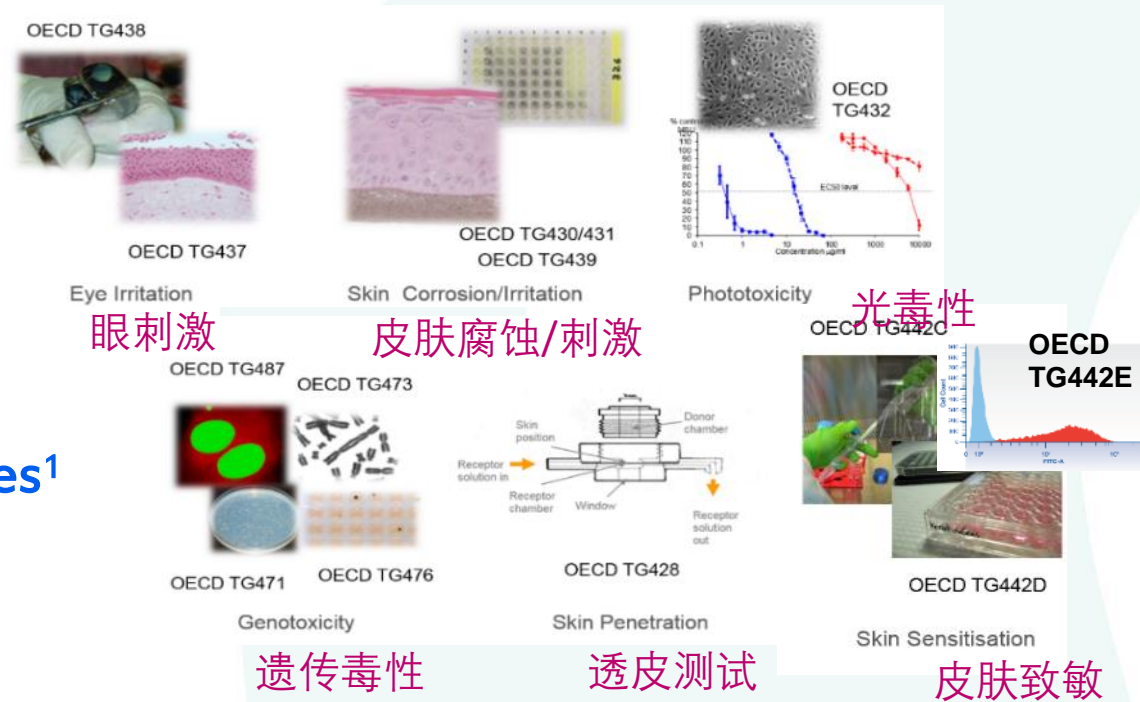
Understanding the potential hazards of the ingredients  
了解成分的潜在**危害**

Risk Assessment  
风险评估

# Maximising use of existing information and non-animal approaches

1. All available safety data
2. *In silico* predictions
3. Exposure-based waiving approaches<sup>1</sup>
4. History of safe use<sup>2</sup>
5. Read across
6. Use of existing OECD *in vitro* approaches

(Skin and eye irritation; skin sensitization; phototoxicity; mutagenicity)



<sup>1</sup> Yang C, Barlow SM, Muldoon Jacobs KL, et al. Thresholds of Toxicological Concern for cosmetics-related substances: New database, thresholds, and enrichment of chemical space. *Food Chem Toxicol.* 2017;109(Pt 1):170-193. doi:10.1016/j.fct.2017.08.043

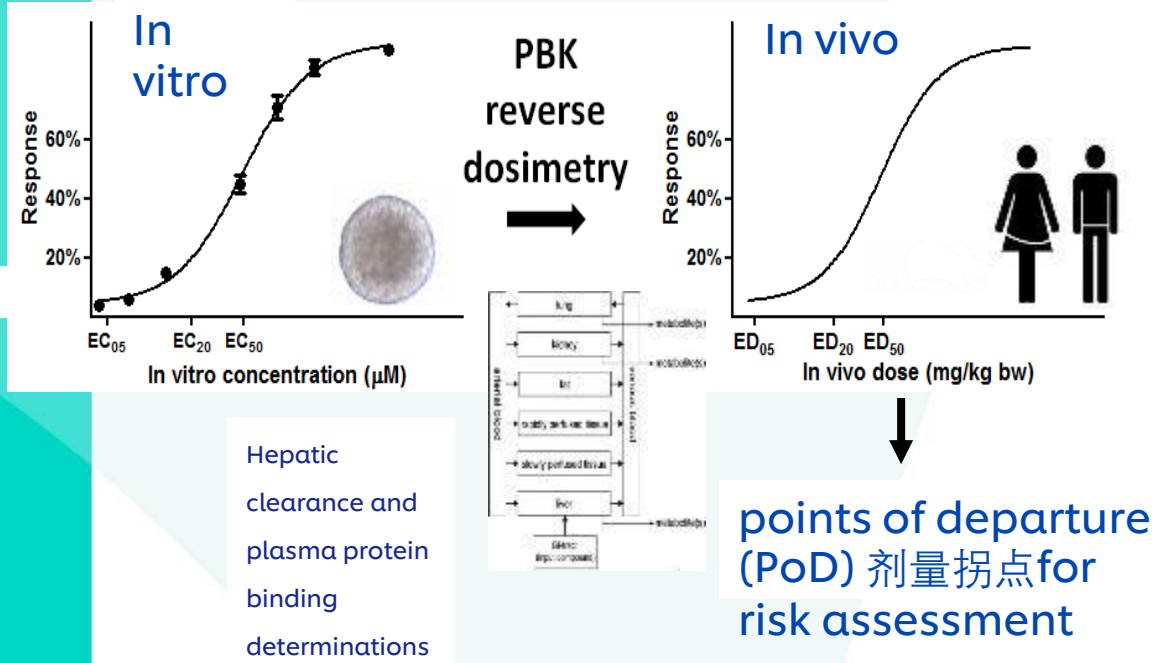
<sup>2</sup> Neely, T et al. "A multi-criteria decision analysis model to assess the safety of botanicals utilizing data on history of use." *Toxicology international* vol. 18, Suppl 1 (2011): S20-9. doi:10.4103/0971-6580.85882

# Quantitative in vitro to in vivo extrapolation

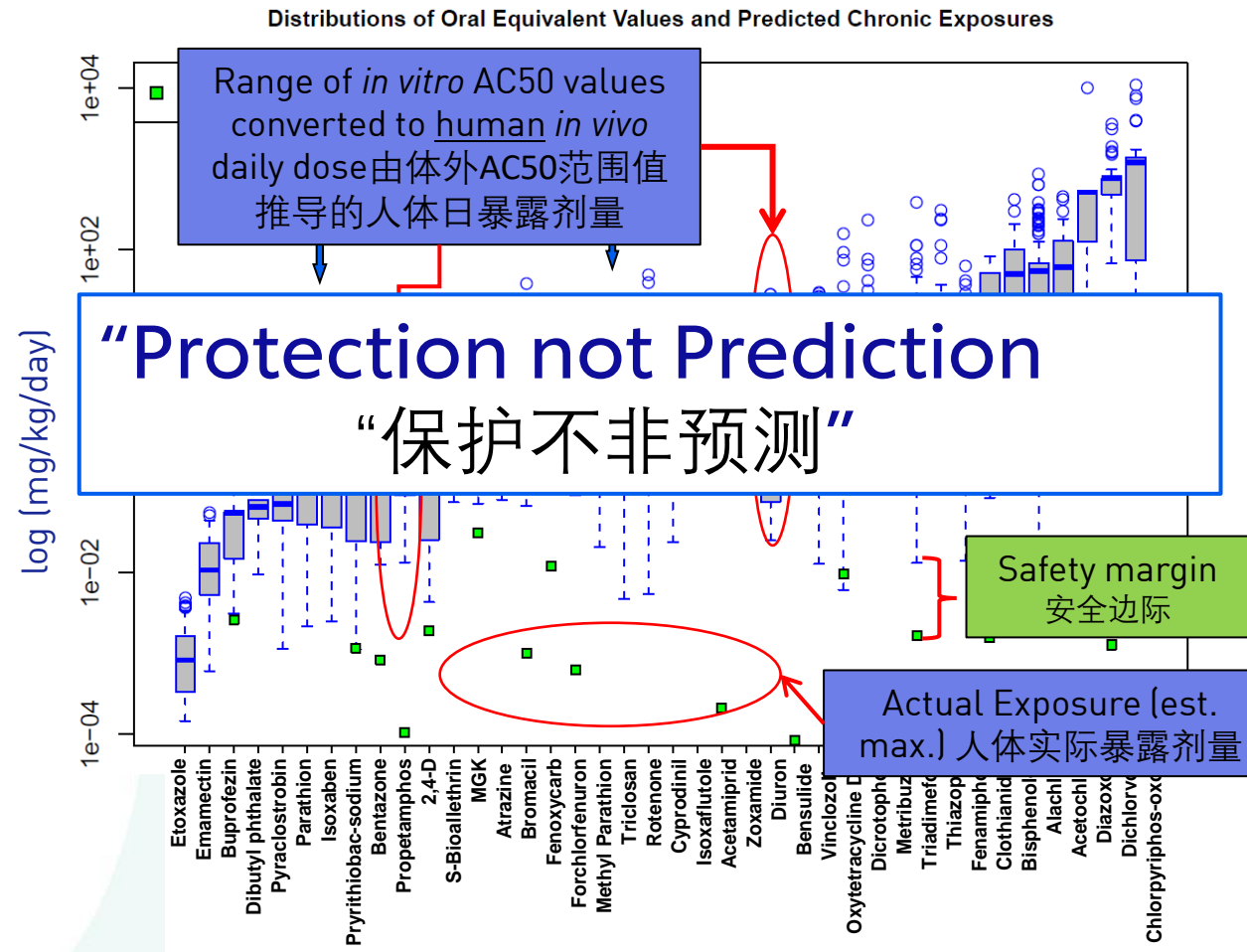
## 体外到体内定量外推



背后的理念是基于“保护不是预测”的前提。



由体外AC50范围值推导的人体日暴露剂量

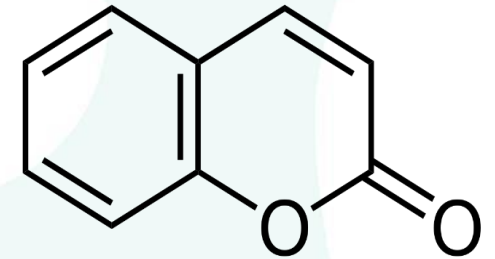


if there is no bioactivity observed at consumer-relevant concentrations, there can be no adverse health effects.  
 如果在与消费者相关的剂量下未观察到生物活性，则不会对健康造成不利影响



# A case study approach – human health safety assessment required for...

## 0.1% COUMARIN IN FACE CREAM FOR EU MARKET (NEW FRAGRANCE)

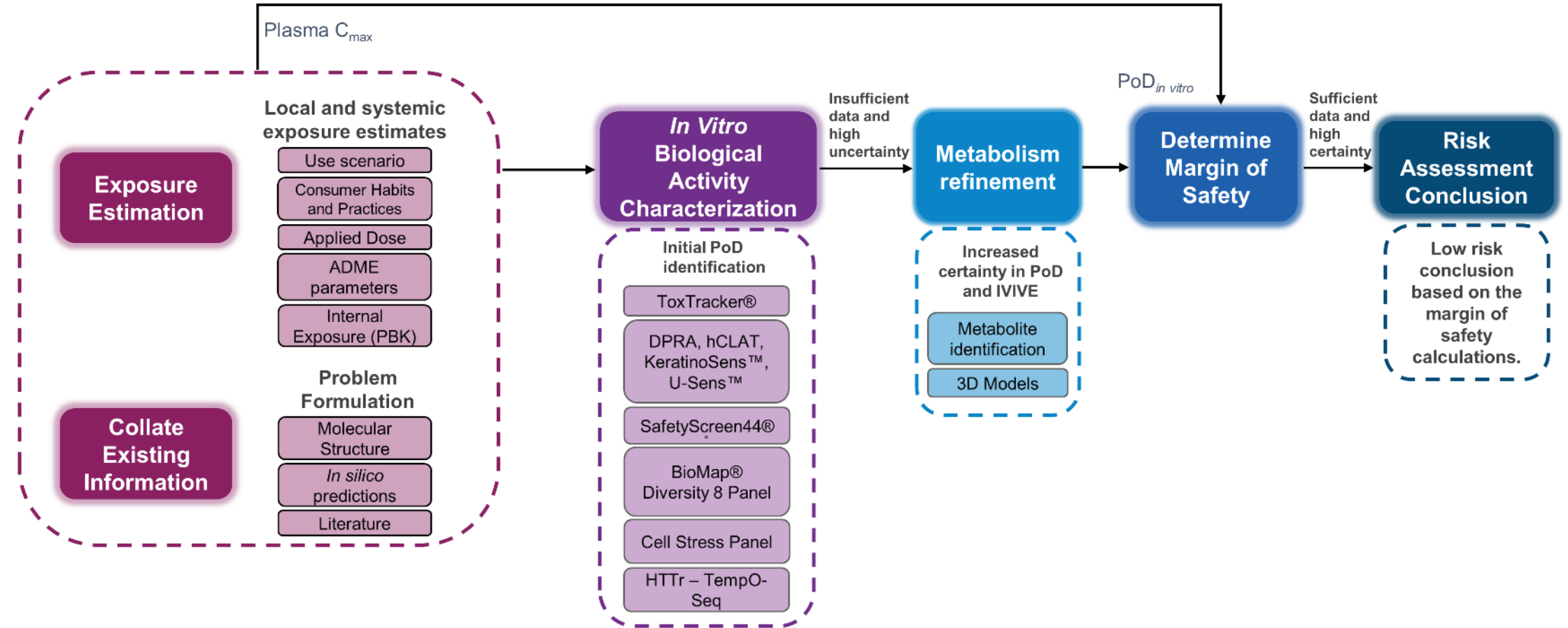


Assumed that:

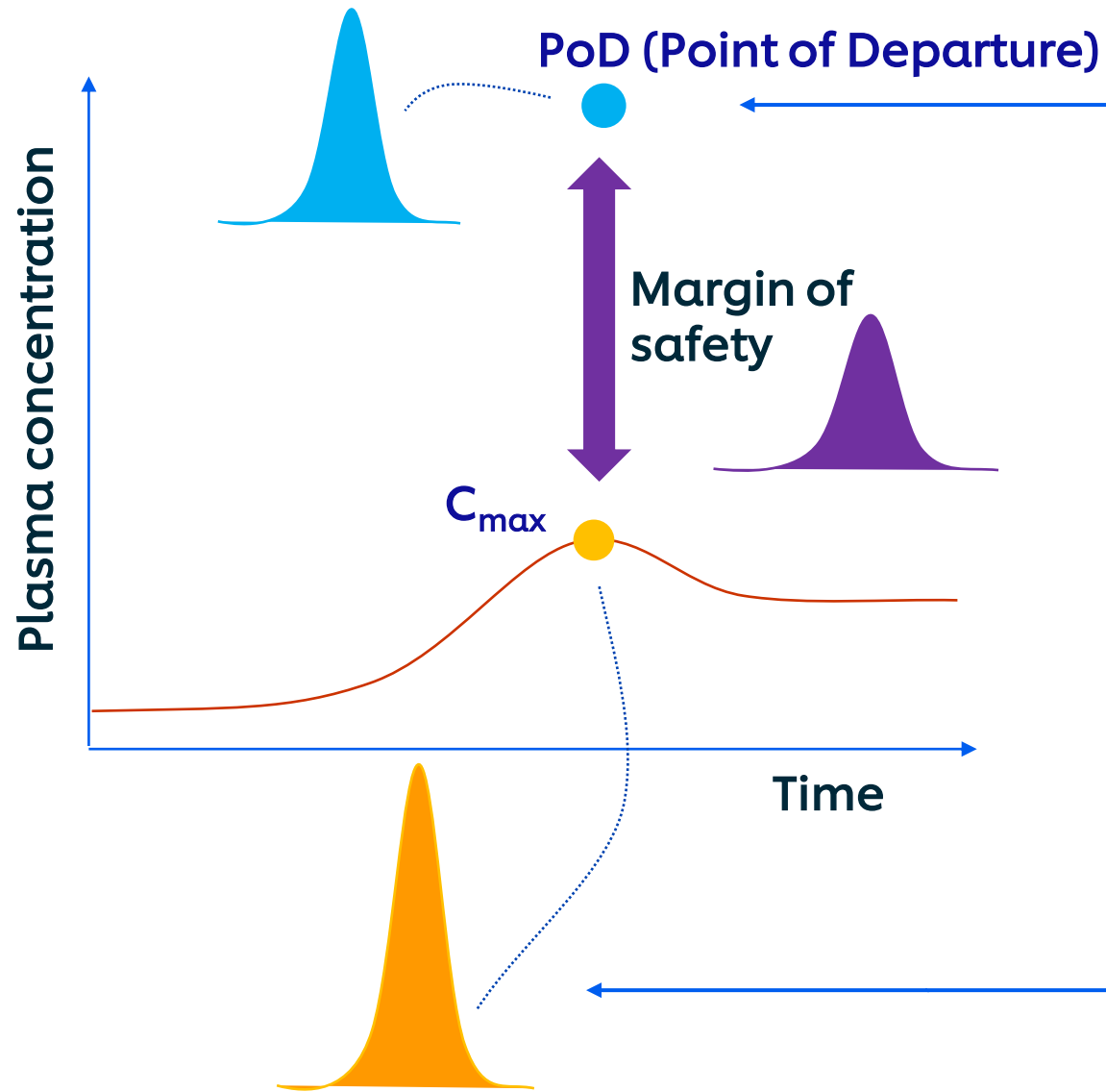
- Coumarin was 100% pure
- no *in vivo* data was available such as animal data, History of Safe Use (HoSU) info. or Clinical data
- no use of animal data in Read Across
- *In silico* alerts known to be based on animal or *in vivo* data or on the structure of Coumarin itself were excluded



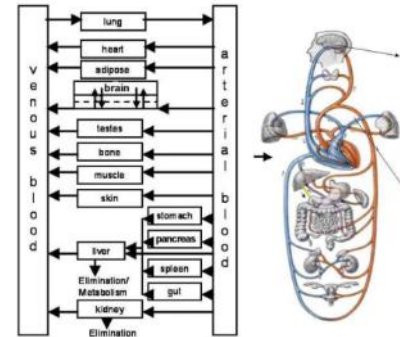
# Next-Generation Risk Assessment case study workflow for 0.1% coumarin in face cream



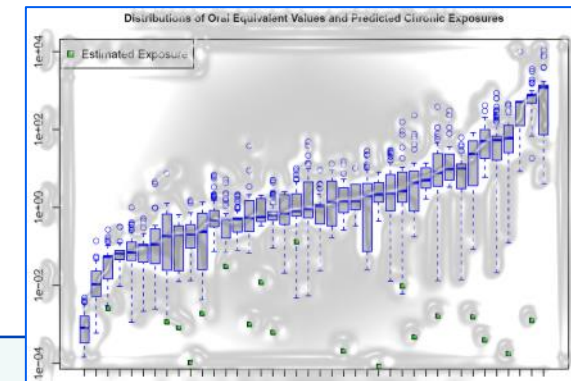
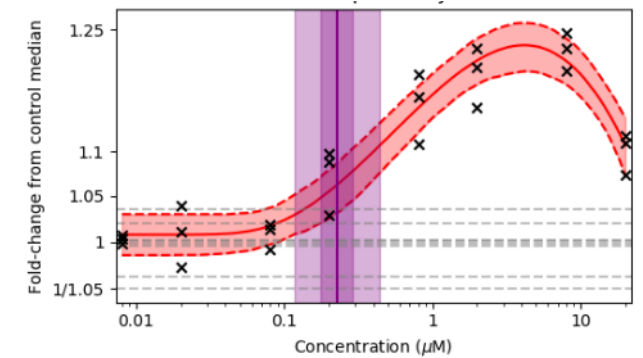
# The Margin of Safety Approach



Exposure models  
(PBK, free/total  
concentration)



NAM Point of departure  
derived from *in vitro*  
concentration-response



# NAMS used to predict biological activity based on chemical structure

**Collate Existing Information**

**Problem Formulation**

- Molecular Structure
- In silico predictions**
- Literature

**ToxTree**

The screenshot shows the ToxTree interface with a chemical structure on the left and a list of rules on the right. The rules are categorized into 'Low (Class I)', 'Intermediate (Class II)', and 'High (Class III)'. The 'High (Class III)' rule is highlighted in red.

**Derek nex**

The screenshot shows the Derek nex interface with a chemical structure on the left and a table of hazard predictions on the right. The table has columns for 'ID', 'Endpoint', 'Species', 'Assay', and 'Result'. The 'Chromosome damage mouse' endpoint is highlighted in red.

**OECD**

**QSAR TOOLBOX**

The screenshot shows the OECD QSAR Toolbox interface, which is a complex web-based tool for hazard assessment.

**In silico models to predict Molecular initiating events (MIEs)**

**Meteor nex**

OXFORD

**SOT** Society of Toxicology  
www.toxsci.oxfordjournals.org

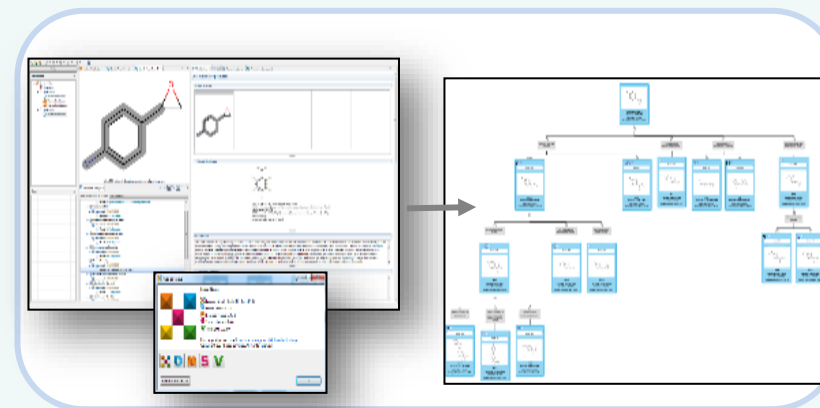
**ToxSci** 20 Years

TOXICOLOGICAL SCIENCES, 165(1), 2018, 213–223

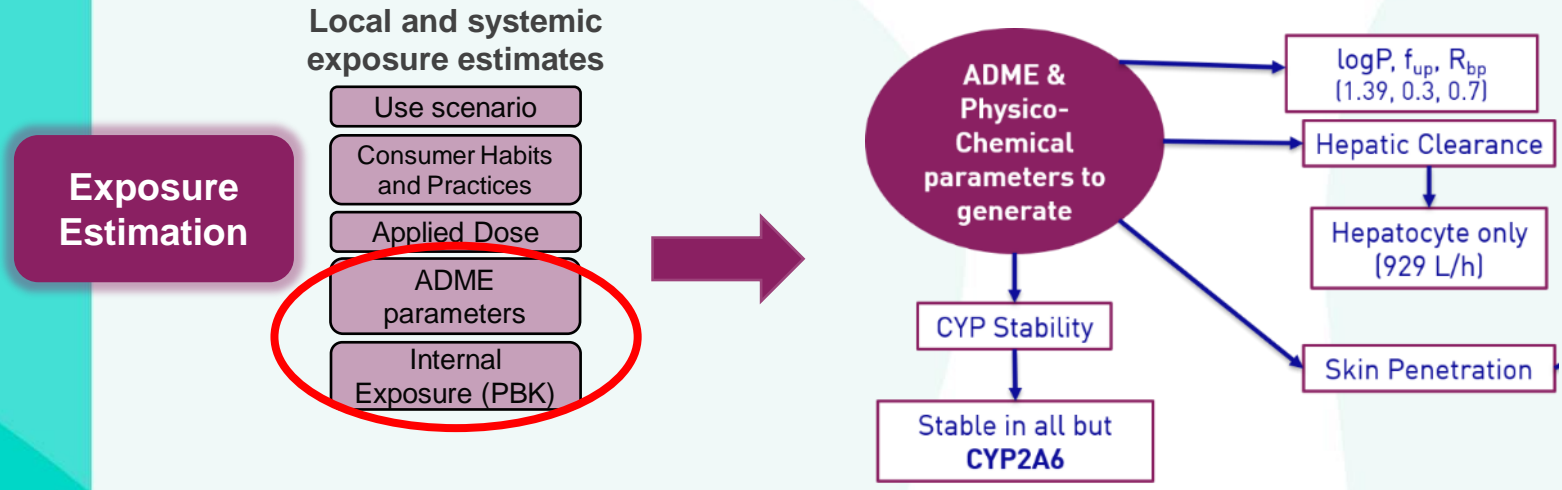
doi: 10.1093/toxsci/kfy144  
Advance Access Publication Date: July 18, 2018  
Research Article

## Using 2D Structural Alerts to Define Chemical Categories for Molecular Initiating Events

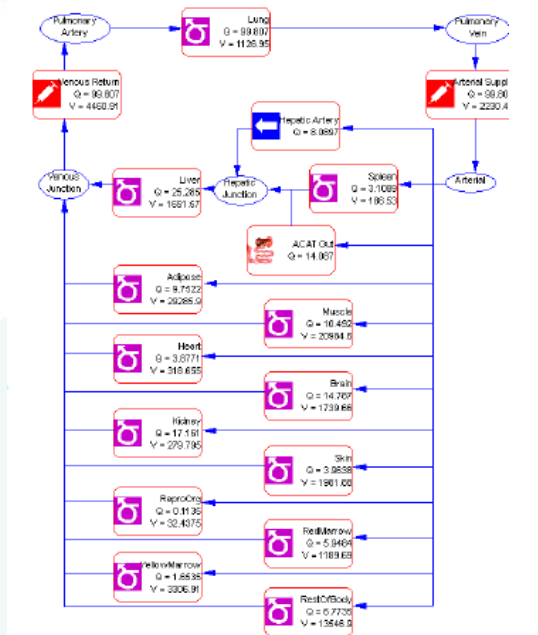
Timothy E. H. Allen,\* Jonathan M. Goodman,\*<sup>1</sup> Steve Gutsell,<sup>†</sup> and Paul J. Russell<sup>†</sup>



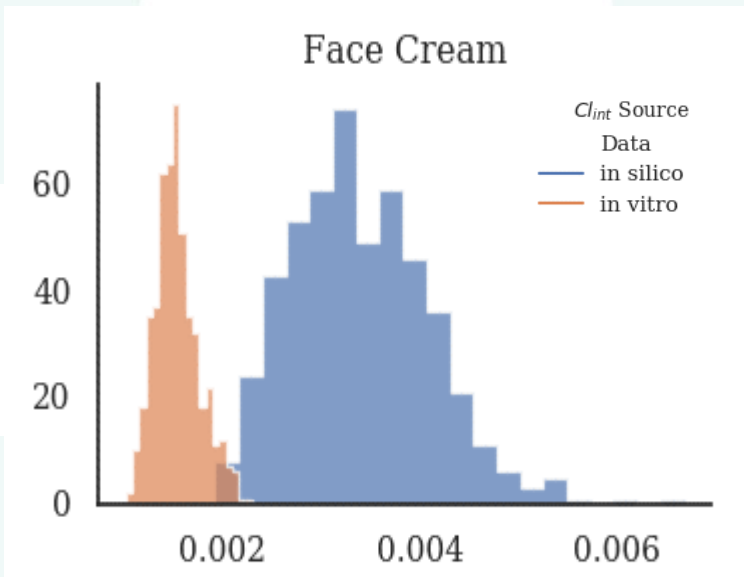
# NAMS used to estimate internal concentration



## GastroPlus® (Simulations Plus)



Simulated plasma concentration of coumarin after dermal exposure.

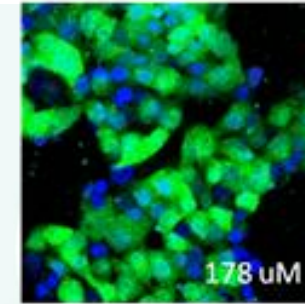


Moxon et al., (2020). Application of physiologically based kinetic (PBK) modelling in the next generation risk assessment of dermally applied consumer products. Toxicology in Vitro Volume 63

# In vitro Bioactivity Characterisation to Estimate PoD

1) *In vitro* bioactivity: cell stress panel  
体外生物活性：细胞应激小组

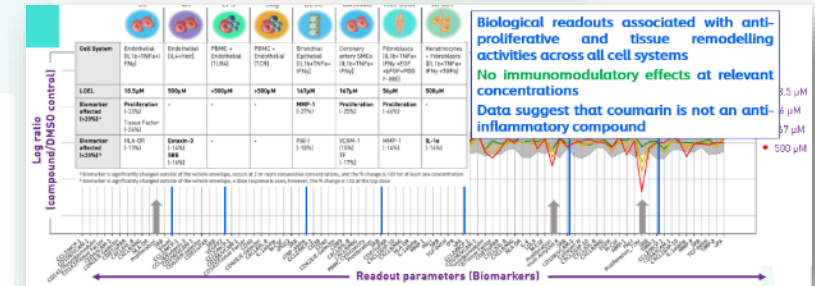
~40 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways  
Hatherall et al., 2020 *Toxicol Sci.* 2020;176(1):11-33.



Stress pathways

- Mitochondrial Toxicity
- Oxidative Stress
- DNA damage
- Inflammation
- ER Stress
- Metal Stress
- Osmotic Stress
- Heat Shock
- Hypoxia
- Cell Health

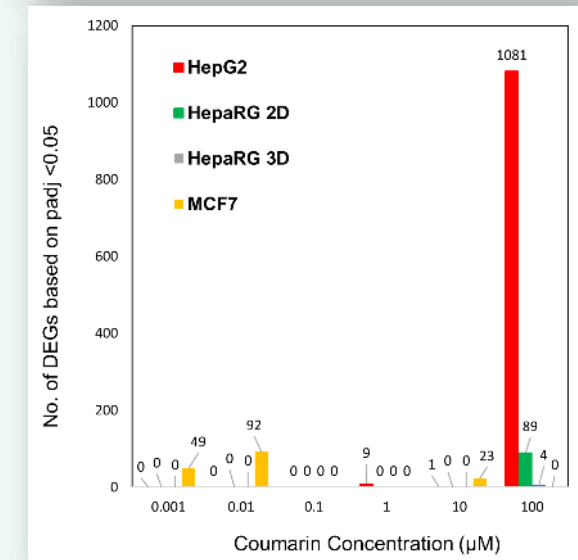
2) Immunomodulatory bioactivity: BioMap® Diversity 8 panel  
免疫调节生物活性：BioMap® Diversity 8 面板



3) High-Throughput Transcriptomics (HTTr) using TempO-SEQ technology

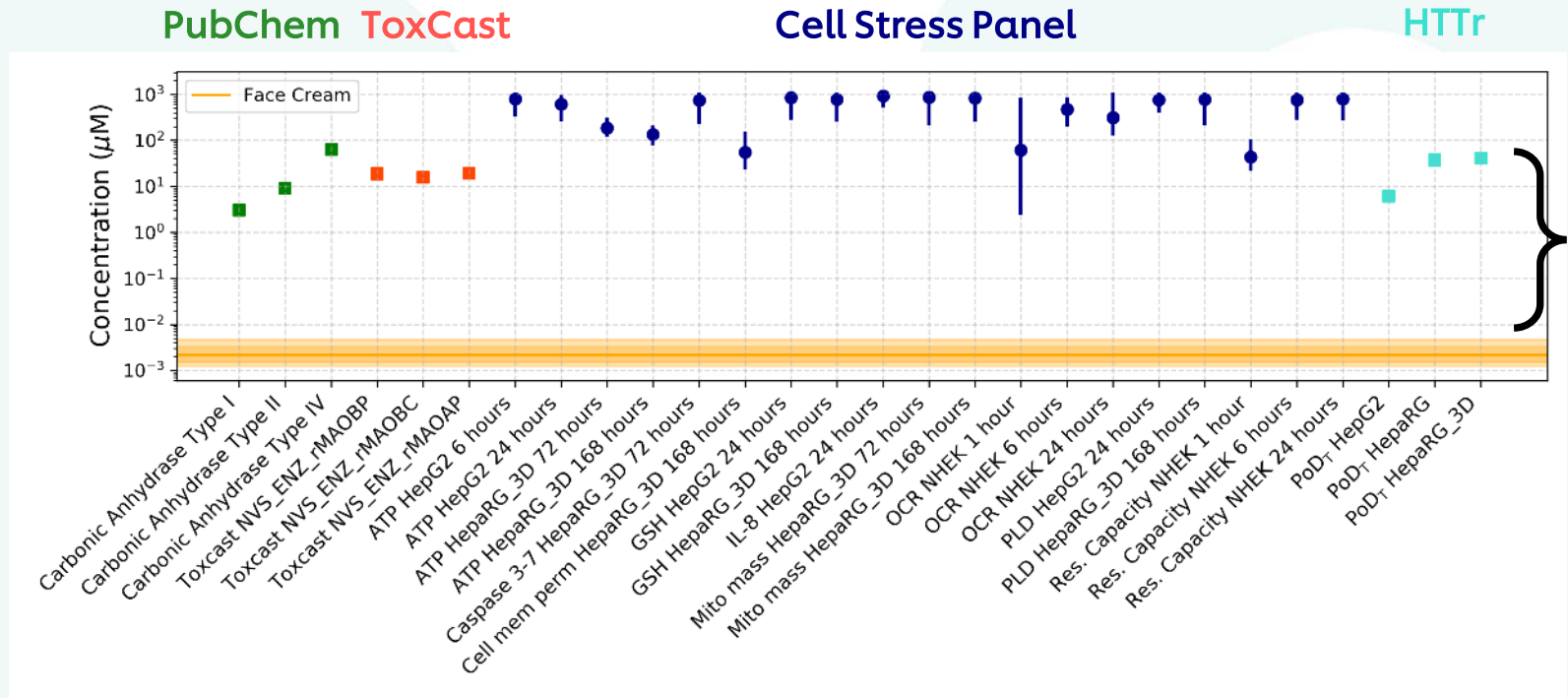
高通量转录组学基因表达谱分析 (HTTr)

Across the cell lines, coumarin resulted in limited gene-expression changes at concentrations below 100  $\mu\text{M}$ ,



# Determination of MoS using NAMs and risk assessment conclusion

Determine Margin of Safety

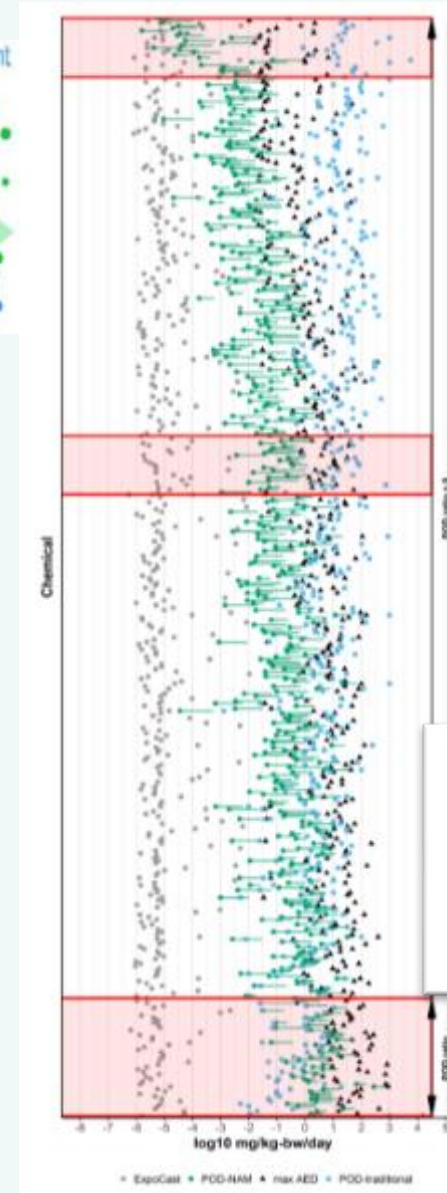
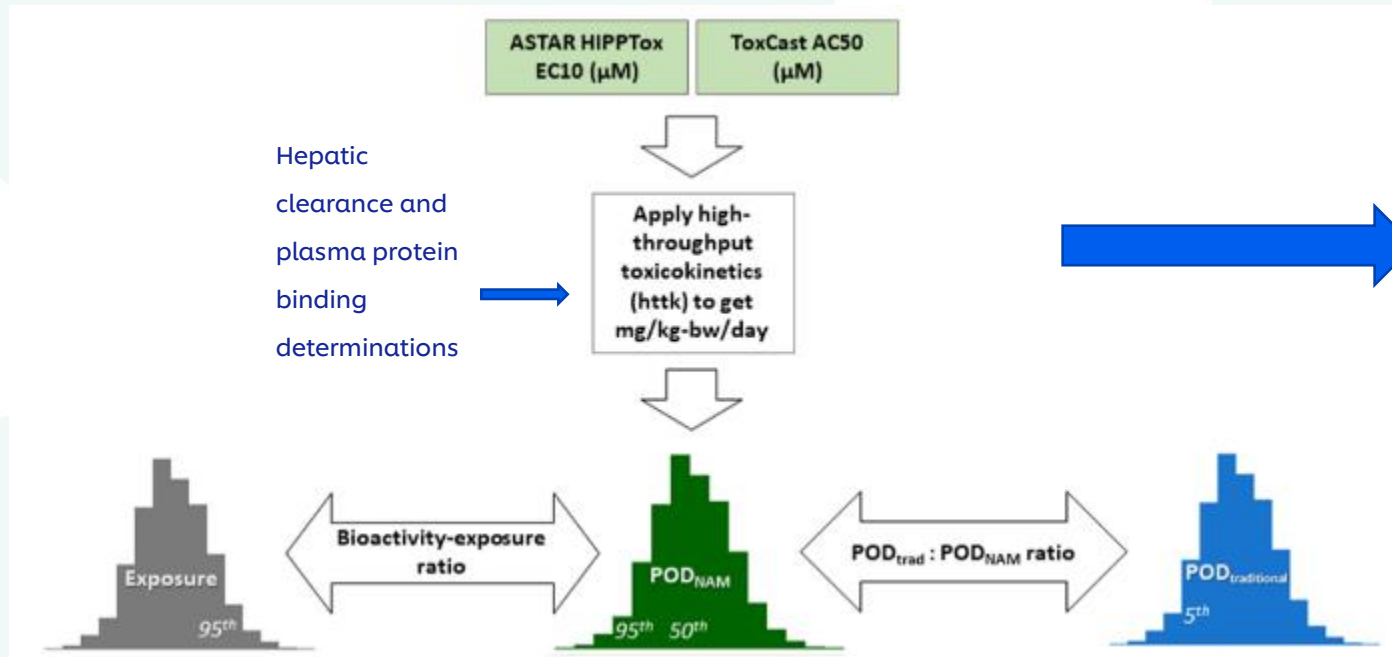


The 5<sup>th</sup> percentile of the MoS distribution ranged between 706 and 96738

- In this case study:
- Weight of evidence suggested that the inclusion of 0.1% coumarin in face cream is safe for the consumer

# Recent research has shown that for 417 out of 448 chemicals tested the point of departure derived (PoD) from NAMS was more conservative than the *in vivo* PoD (新一代方法，相对于动物实验方法更加保守, 更多保护消费者)

- **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**



Katie Paul-Friedman *et al.* 2019 *Tox Sci* 173(1): 202-225

# Our global collaborations and partnerships



Unilever



# Unilever, SEAC HISTORY 我们的历史



SEAC is formed, bringing together all Unilever's safety resources across consumer, occupational, environmental safety and sustainability.

SEAC成立，汇集了联合利华在消费者，职业，环境安全和可持续发展方面的所有安全资源。

Unilever invests in a novel long-term research programme to apply modelling and informatics approaches for safety and sustainability.

联合利华投资一项新的长期研究计划，将建模和信息学方法应用于安全性和可持续性评估。

1961

The Unilever Board establishes a mandatory toxicological safety clearance system for all company products.

联合利华董事会为所有公司产品建立了强制性毒理学安全检查系统。

1990

SEAC is formed, bringing together all Unilever's safety resources across consumer, occupational, environmental safety and sustainability.

SEAC成立，汇集了联合利华在消费者，职业，环境安全和可持续发展方面的所有安全资源。

1994

SEAC publishes its 100th research paper on non-animal approaches for assessing consumer safety.

SEAC发布了第100份关于评估消费者安全的非动物方法的研究论文

2004

Unilever invests in a novel long-term research programme to apply modelling and informatics approaches for safety and sustainability.

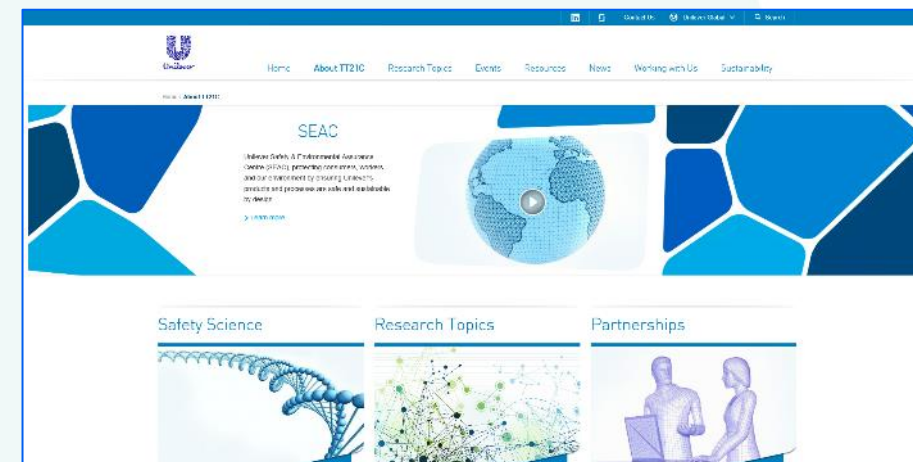
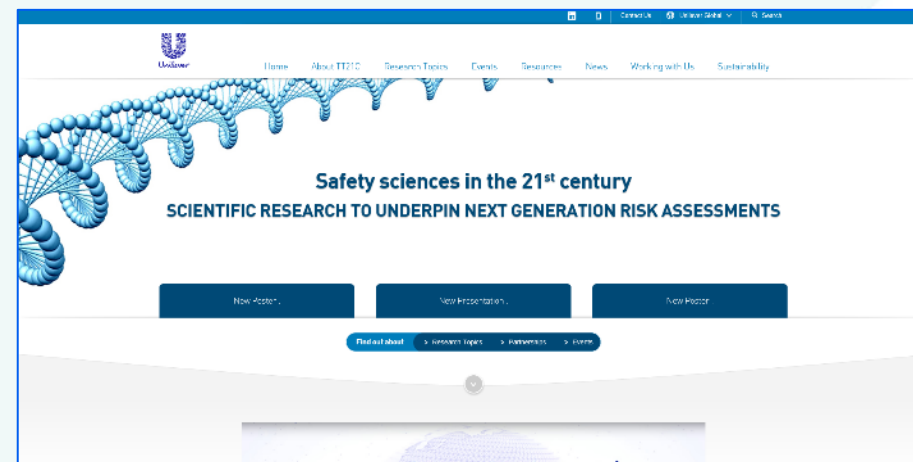
联合利华投资一项新的长期研究计划，将建模和信息学方法应用于安全性和可持续性评估。

2016

In the last 10 years SEAC scientists have published more than 550 articles in peer-reviewed journals, some articles have been cited over 200 times in literature.

在过去10年中，SEAC科学家在同行评审的期刊上发表了550多篇文章，有些文章在文献中被引用了200多次。

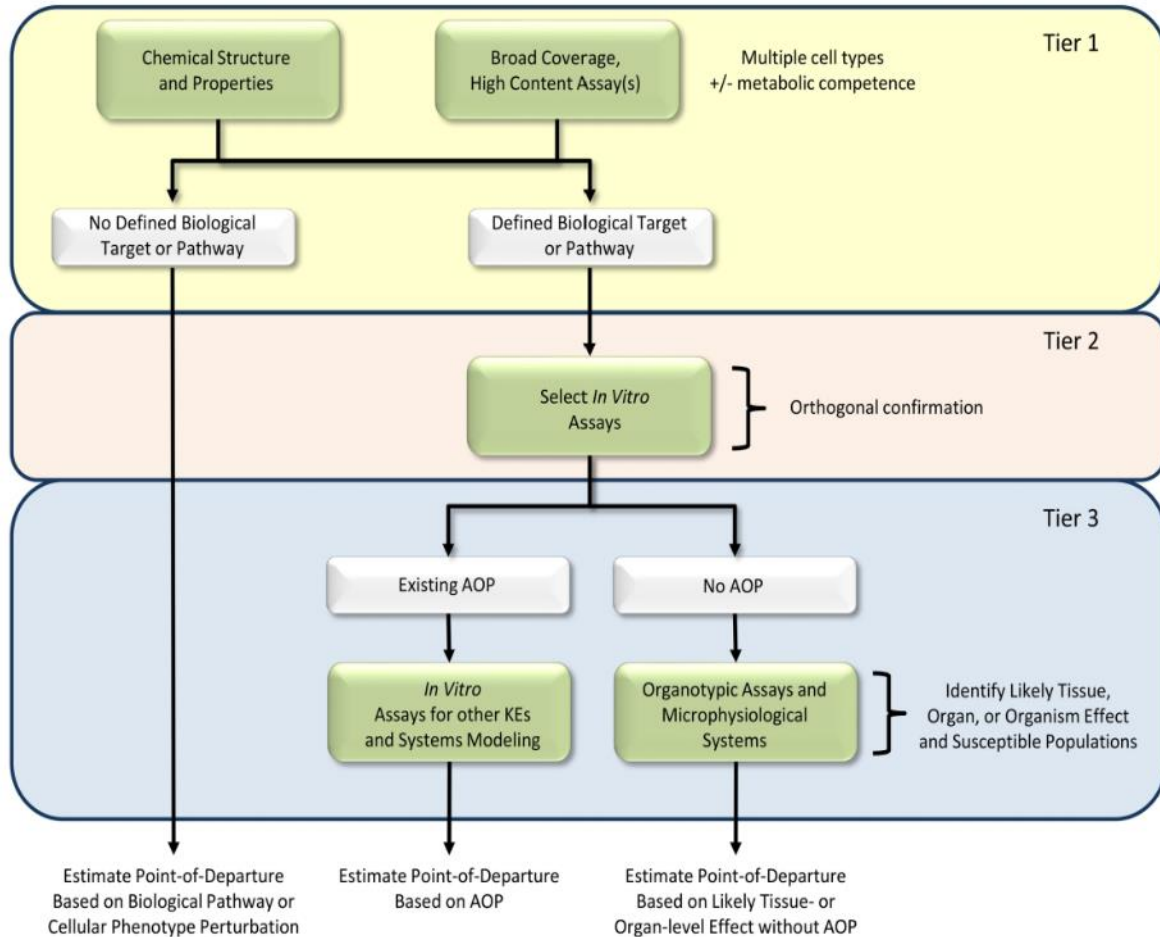
# Scientific partnership 科学合作



More Unilever Collaborations can be found on <https://tt21c.org/safety/>

# The Unilever Partnership with EPA

## The EPA Blueprint



FORUM  
**The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency**  
 Russell S. Thomas,<sup>\*,1</sup> Tina Bahadori,<sup>†</sup> Timothy J. Buckley,<sup>‡</sup> John Cowden,<sup>\*</sup> Chad Deisenroth,<sup>\*</sup> Kathie L. Dionisio,<sup>‡</sup> Jeffrey B. Frithsen,<sup>‡</sup> Christopher M.

The posters shown are:

- SEAC:** Progress on the Unilever and EPA Collaboration Developing *In Vitro* and *In Silico* Methods for Toxicological Risk Assessment. Authors: Russell S. Thomas, Tina Bahadori, Timothy J. Buckley, John Cowden, Chad Deisenroth, Kathie L. Dionisio, Jeffrey B. Frithsen, Christopher M. Frithsen.
- SEPA:** Chemical Screening for Broadened Phenotypic Mechanisms Using High-Throughput of Metabolic Enzymes (HME). Authors: Russell S. Thomas, Tina Bahadori, Timothy J. Buckley, John Cowden, Chad Deisenroth, Kathie L. Dionisio, Jeffrey B. Frithsen, Christopher M. Frithsen.
- EPA:** OPTIMIZATION OF A HIGH-THROUGHPUT TRANSCRIPTOMIC (HTT) BIOACTIVITY SCREEN IN MCF7 CELLS USING TARGETED RNA-SEQ. Authors: Russell S. Thomas, Tina Bahadori, Timothy J. Buckley, John Cowden, Chad Deisenroth, Kathie L. Dionisio, Jeffrey B. Frithsen, Christopher M. Frithsen.
- EPA:** Combining *In Silico* and Toxicological Data to Refine a Case Study Using Cellfex. Authors: Russell S. Thomas, Tina Bahadori, Timothy J. Buckley, John Cowden, Chad Deisenroth, Kathie L. Dionisio, Jeffrey B. Frithsen, Christopher M. Frithsen.

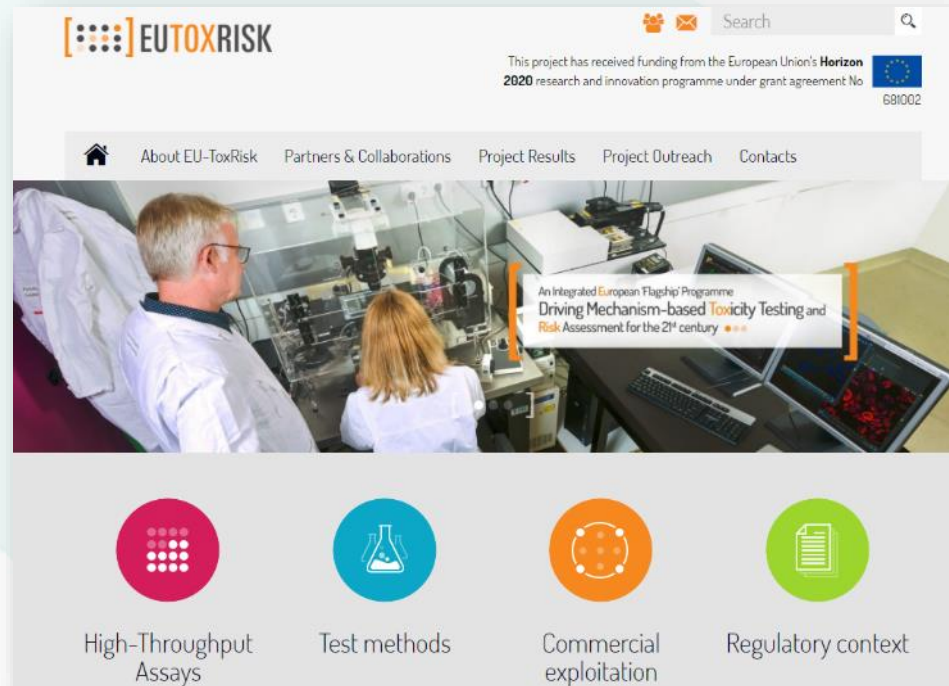
Highlights of Ongoing Research Between EPA & Unilever  
 Society of Toxicology  
**SOT 2016**  
 New Orleans, Louisiana, USA  
 March 13-17, 2016

Highlights of Ongoing Research Between EPA & Unilever  
 Society of Toxicology  
**SOT 2018**  
 San Antonio, Texas, USA  
 March 11-15, 2018

**New Approach Methods Work Plan**  
 Reducing Use of Animals in Chemical Testing  
 U.S. Environmental Protection Agency  
 Office of Research and Development  
 Office of Chemical Safety and Hazard Investigation  
 June 2018

# Participated in EU TEAMS of Safety Sciences

EUToxRisk €30m (2016 – 2021)



EPAA – Industry/European Commission Partnership since 2005



The European Partnership for Alternative Approaches to Animal Testing

RiskHunt3R €24m (2021 – 2026)



## ADVANCING SAFETY ASSESSMENT OF CHEMICALS WITHOUT USE OF ANIMAL TESTING (BHC-11) - EU funding: € 59.4 m

<b>ONTOX</b>	Ontology-driven and artificial intelligence-based repeated dose toxicity testing of chemicals for next generation risk assessment	Vrije Universiteit Brussel (BE)	18
<b>RISK-HUNT3R</b>	RISK assessment of chemicals integrating HUMAN centric Next generation Testing strategies promoting the 3Rs	Universiteit Leiden (NL)	37
<b>PrecisionTox</b>	Toward Precision Toxicology: New Approach Methodologies for Chemical Safety	The University of Birmingham (UK)	16



**An MIE Atlas**  
The roads not taken: avoiding adverse outcome pathways

Compound → Molecular Initiating Event → Adverse Outcome Pathway

Timothy E H Allen  
Jonathan M Goodman, Steve Gutsell, Paul J Russell

3<sup>rd</sup> April 2016

Making predictions of toxicology at the MIE level

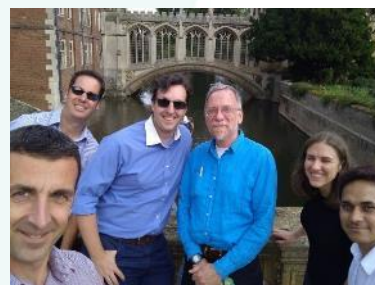
- Structural Activity Relationships
- Transition state modelling
- Neural Networks
- Confidence in predictions

Multiple PhDs, MSc projects and a Post Doc

16 Journal Publications (to date)



International  
Conferences



**In Silico Guidance for In Vitro Androgen and Glucocorticoid Receptor ToxCast Assays**

Timothy E. H. Allen, Mark D. Nelms, Stephen W. Edwards, Jonathan M. Goodman\*, Steve Gutsell, and Paul J. Russell



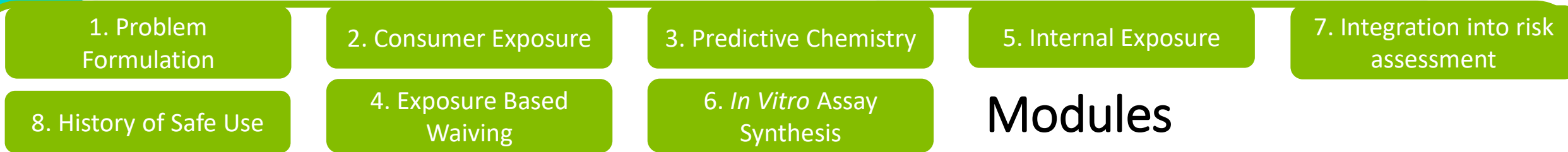
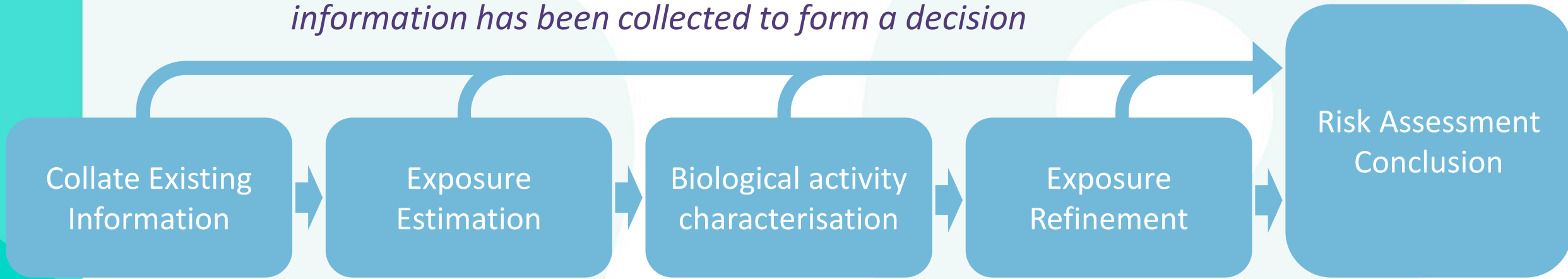
Secondment to US EPA and joint publications



2020 LUSH Science Prize

# Work with AFSA to develop NAMS education module on Risk assessment process

*A tiered and iterative approach is needed until sufficient information has been collected to form a decision*



## Partner Organisations



# Unilever Collaborations in China 已开展的活动内容

Working with CFSA & ILSI  
与国家食品安全风险评估中心和  
国际生命科学学会的合作



2015, Beijing



2016, China

Working with CAS  
与中国科学院的合作




2015, UK



Molecular Simulation Investigation  
on Molecular Initiating Events

Working with AMMS  
与军事医学科学院&BPRC  
的合作




2015, Beijing



PGC-1α & Nrf2 Pathways

Partnering with scientists on risk-based approaches to food and cosmetic safety  
与科研组织及机构关于食品及化妆品安全方面的协作

# Communications with Chinese Regulatory Scientists in China 已开展的活动内容

Working with CFDA  
国家食品药品监督管理总局的合作



Working with SH-FDA  
与上海食品药品监督管理局的合作



Working with Guangdong CDC  
/ NIFDC 与广东省疾病预防控制中心和中国食品药品检定研究院的合作



Partnering with regulators on risk-based approaches to food and cosmetic safety  
和监管部门在食品及化妆品风险评估方面的协作



# Working with China's future scientists 鼓励培训中国新一代科学家合作

China-SOT/Unilever AAT Awards 中国毒理学会联合利华替代法奖



5 awards per year on non-animal approaches

2016 - 2018

2019 - 2022

Talent Development Programme with Peking University 联合利华与北京大学人才培养计划



2013 - 2018

Poster prize winners at the 2019 non-animal safety risk assessment workshop 最佳海报奖得主:非动物安全风险评估研讨会



April 2019 Shanghai, China

## Summary 总结

- The safety sciences move towards NAMs without animals
  - Many non-animal approaches available: TTC, (Q)SAR/RA, HoSU and NGRA  
使用许多非动物方法：TTC, (Q)SAR / RA，安全使用历史，新一代风险评估等
  - Need to ensure quality/robustness of the non-standard (non-TG) work and to characterise uncertainty to allow informed decision-making
  - Interdisciplinary team needed! Available tools can be integrated to make a safety decision;
  - Shortcomings will be addressed by current and future research and more case studies 未来的研究以及更多的案例研究将攻克不足
- Regulations follow scientific advancement - increasing regulatory animal testing ban, especially on cosmetics。
- Working together across all international stakeholders (including Chinese regulatory scientists) is key to making progress

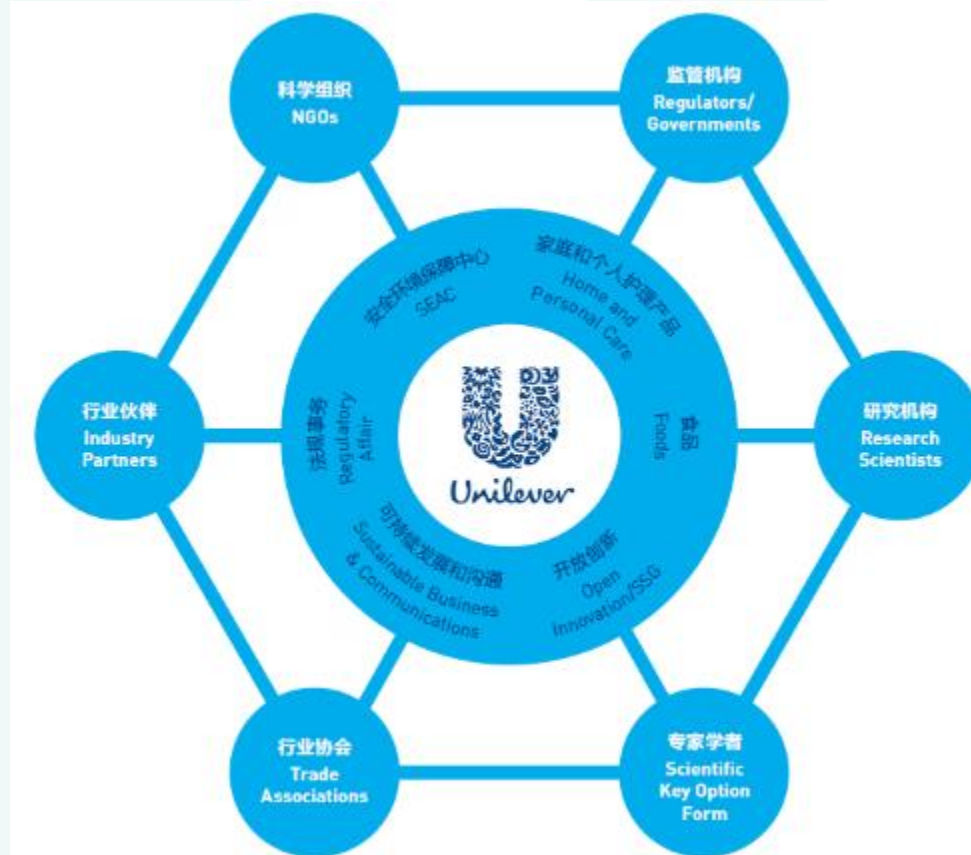
# Unilever China Consumer Product Safety Collaboration Center

## 联合利华中国消费者产品安全合作中心

Unilever R&D Shanghai, China  
Opening Ceremony: Friday 2<sup>nd</sup> June 2017



- **Consumer product safety**  
消费者产品安全
- **Multi-stakeholder partnerships in China**  
与外部的多方伙伴合作
- **Sharing expertise and scientific developments**  
分享专业知识,交流科学进步及开展科研合作



<https://www.unilever.com.cn/about/uccpscc/>

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