# 国际化妆品监管合作组织(ICCR)化妆品安全评估原则：新一代风险评估 & 消费品行业研究案例

**The ICCR principles for cosmetic safety assessment: next generation risk assessment & case studies**

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化妆品国际技术交流峰会(2022.02 22-23 上海)

# 主要内容
# Main content

1. 新原则发展背景
   Background

2. 新一代化妆品安全风险评估
   Next generation risk assessment

3. 香豆素在化妆品案例研究
   Case Studies: Coumarin

Unilever

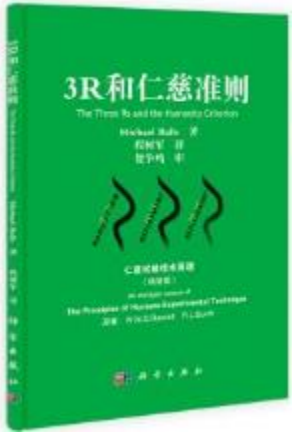
# 1 新原则发展背景

# Background

# 全球动物福利和消费者需求
# 3Rs: worldwide animal welfare and consumers' demand

## 3R理论(替代，减少和优化）诞生60周年
## 2019 – Celebrating 60 years of the 3Rs

1959


## 所有消费者想要安全产品，但许多人不想在动物身上测试

## Consumers want safe products, but many want them Not To Be Tested On Animals

Shop Cruelty-Free

PETA APPROVED
Global Animal Test Policy

NO CRUEL COSMETICS

EUROPEAN VEGETARIAN UNION
V-LABEL.EU
VEGAN

NOT TESTED ON ANIMALS

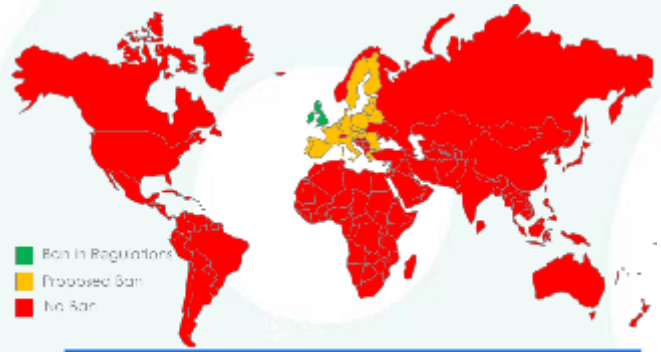
Unilever

# 全球范围内禁止动物测试的化妆品法规越加增多

## A growing number of cosmetic regulations with animal testing (AT) ban worldwide

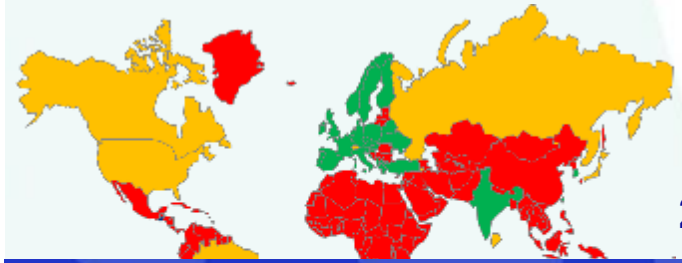
| | |
|---|---|
| 1998 | 英国-测试禁令 |
| 2007 | 以色列-测试禁令 |
| 2009 | 欧盟-测试禁令 |
| 2013 | 欧盟-销售禁令 |
| 2014 | 以色列-销售禁令；挪威-测试禁令及销售禁令；印度-测试禁令及销售禁令；巴西圣保罗州及南马托格罗索州-测试禁令；中国-取消国产非特殊用途化妆品强制性动物实验 |
| 2015 | 韩国-部分的销售禁令；新西兰-测试禁令；土耳其-部分的测试及销售禁令；巴西巴拉那州、亚马逊州-测试禁令；俄罗斯-测试及销售部分禁令的提案；阿根廷-测试及销售禁令的提案；加拿大-测试及销售禁令提案 |
| 2016 | 巴西帕拉州-测试禁令；中国台湾-测试禁令；瑞士-测试及销售禁令；智利-测试及销售禁令提案；澳大利亚-测试及销售禁令 |
| 2017 | 巴西里约热内卢-测试及销售禁令；危地马拉-测试禁令；南非-测试及贸易禁令提案 |
| 2018 | 美国加州、弗吉尼亚州-测试及销售部分禁令 |
| 2019 | 美国伊利诺斯州、内华达-测试及销售部分禁令；Nov 18th, 美国参众两院-《人道主义化妆品议案》 |

AT Ban at 39 countries/areas
39个国家/地区禁止




2013

Testing cosmetic products and their ingredients on animals was banned in the UK in 1998 and across the EU in 2013.



2016

*"Today's memo directs the agency to aggressively reduce animal testing, including reducing mammal study requests and funding 30% by 2025 and completely eliminating them by 2035"*

EPA Administrator, 2019

Unilever

# 科学进步：从TT21C到NGRA
# Scientific Progress: From TT21C to NGRA

**新一代安全评估：一种以暴露为导向、假设驱动的风险评估方法，该方法集成了新技术方法学（NAMs），以确保安全性，无需使用动物试验. Next Generation of Risk Assessment (NGRA) is defined as an exposure-led, hypothesis-driven risk assessment approach that integrates New Approach Methodologies (NAMs) to assure safety without the use of animal testing**


Unilever video on NGRA
https://youtu.be/tJWG3YCXT0Y

# 2. 新一代化妆品安全风险评估

## Next generation risk assessment （NGRA）

# 我们可以安全地使用新成分吗?

## Can we use a new ingredient safely?

**我们可以安全地在产品z中使用x%的成分y吗?**

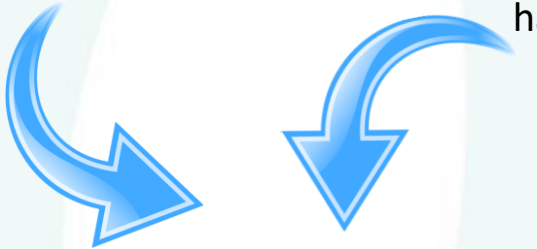
Can we safely use **x**% of ingredient **y** in product **z**?

# 我们可以安全地使用新成分吗?
**Can we use a new ingredient safely?**

## 化妆品的所有安全性评估都是暴露驱动的
**All safety assessments of cosmetic products are exposure-driven**

消费者暴露
Consumer Exposure

理解成分的潜在危害
Understanding the potential hazards of the ingredients



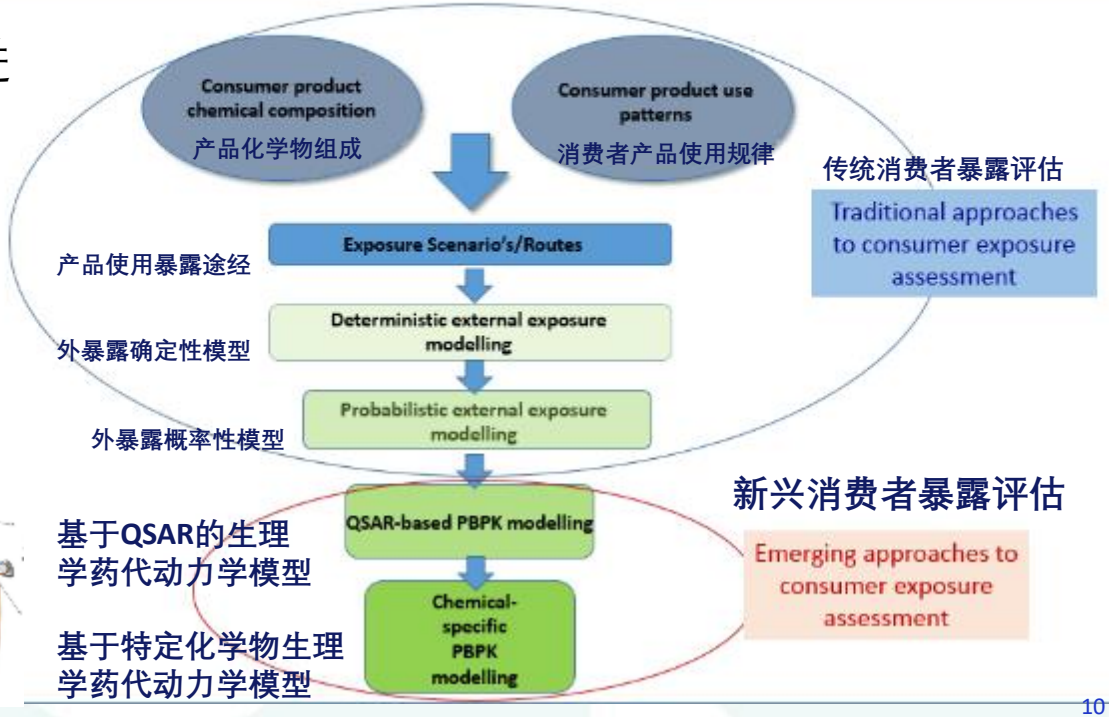
Risk Assessment
风险评估

# 暴露科学概述 Exposure Science overview

**Exposure assessment:** Drives the risk assessment process. This quantifies the dose (amount) of a material that is externally applied during consumer use of the product, which is then compared to the relevant dose at which toxicological effects are expected to establish the safety risk.

**暴露评估**：引导风险评估进程。

量化在消费者使用产品时，某一化学物成分实际外部暴露剂量，然后将其与可导致毒性作用的相关剂量进行比较，以确定安全风险



# 消费者暴露途经

## Routes of Consumer Exposure for different product types

**Skin 皮肤**:

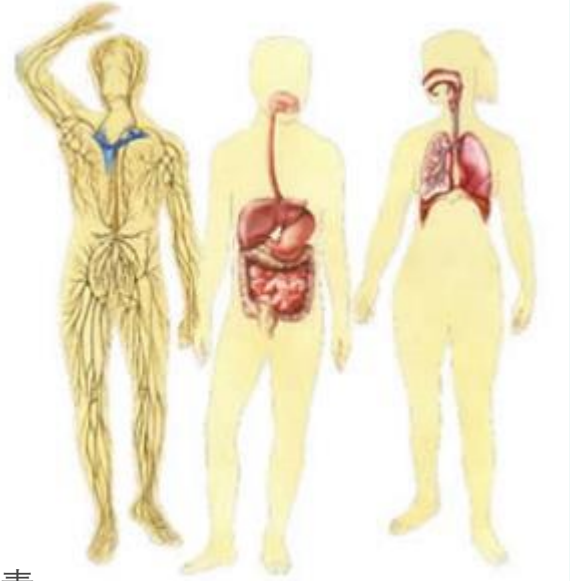
Skin creams 护肤霜

Deodorants/Aps
除臭剂/ 止汗剂

Soap/cleansers
肥皂/清洁剂

Hair shampoo/
conditioner 洗发水/护发素

Shower gel 沐浴露



**Ingestion 食入** :

Toothpaste牙膏/
mouthwash漱口水

Lipsticks唇膏

**Inhalation 吸入**:

Aerosols 气溶胶

Pump sprays喷雾剂

Hair shampoo 洗发水/
conditioner 护发素

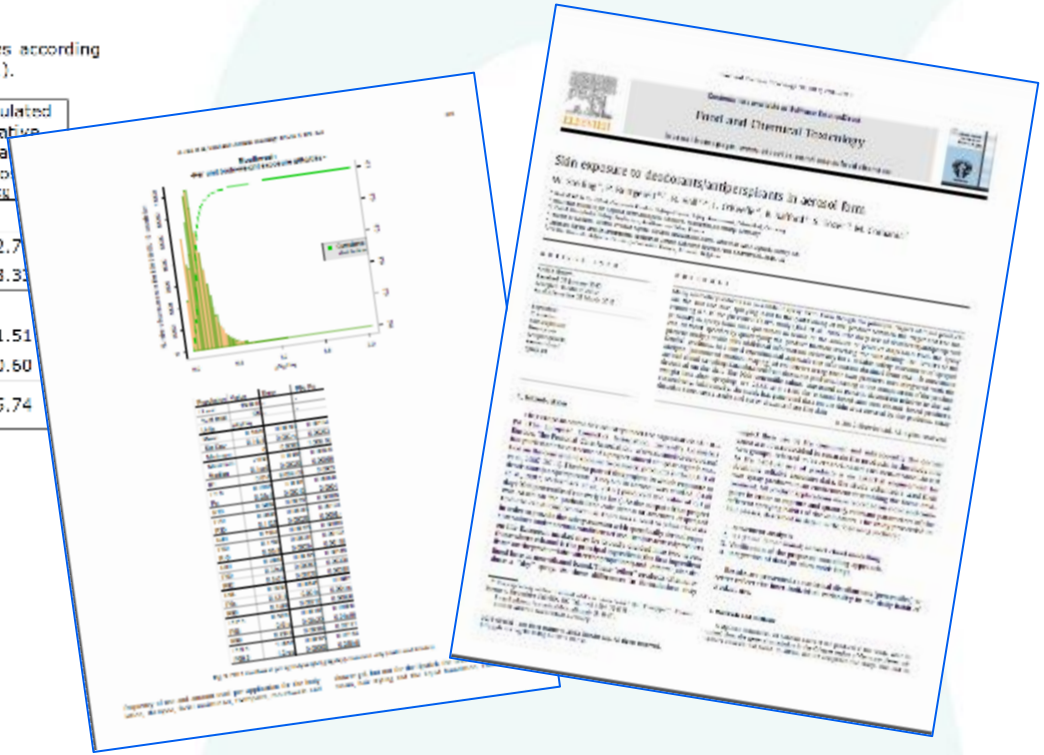
Shower gel 沐浴露

# 习惯和做法 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 (g/d) | Calculated relative da expo (mg/kg |
|---|---|---|---|---|---|
| **Bathing, showering** | | | | | |
| Shower gel | 18.67 g | 279.20 | 0.01 | 0.19 | 2.7 |
| Hand wash soap [2] | 20.00 g | - | 0.01 | 0.20 [3] | 3.3 |
| **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 |

Creme GLOBAL



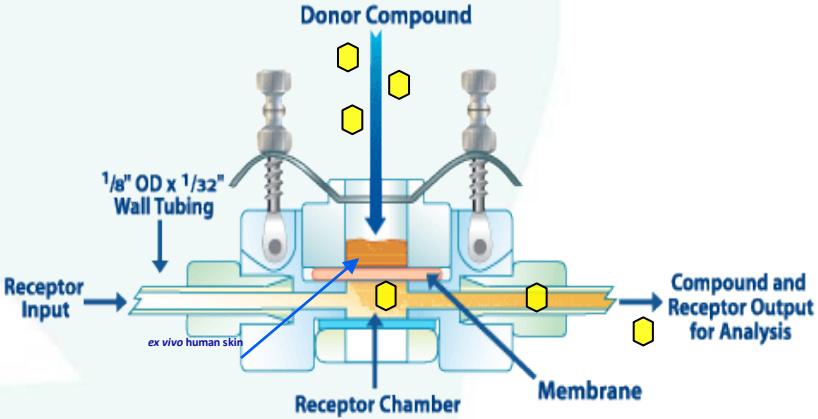
Food and Chemical Toxicology

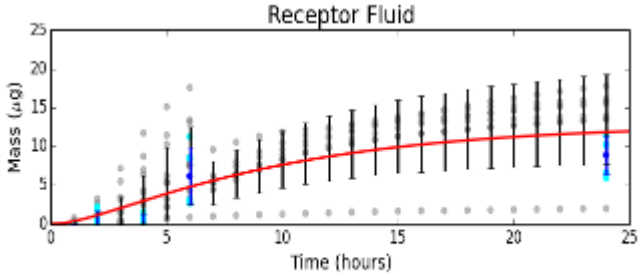
Skin exposure to deodorants/antiperspirants in aerosol form

B. Hall et al. / Food and Chemical Toxicology 49 (2011) 408–422

# 皮肤渗透数据 skin penetration data

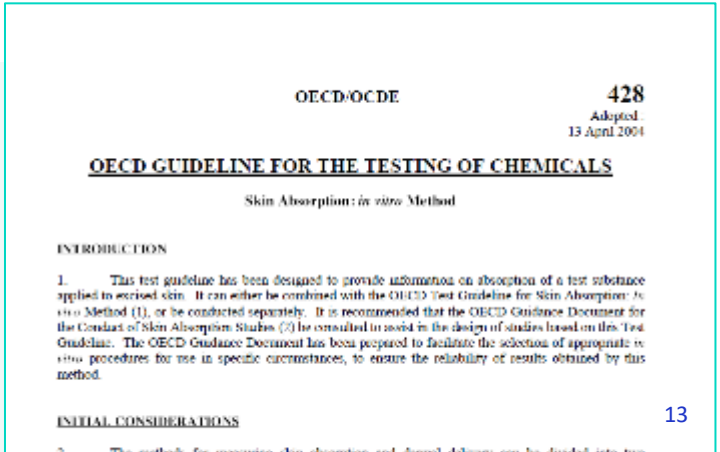
- 皮肤渗透信息细化 Refinement of skin penetration information




**在没有数据的情况下,假设100%皮肤穿透**

Assumption of 100% skin penetration in the absence of data



OECD/OCDE 428

Adopted: 13 April 2004

**OECD GUIDELINE FOR THE TESTING OF CHEMICALS**

Skin Absorption: *in vitro* Method

INTRODUCTION

1. This test guideline has been designed to provide information on absorption of a test substance applied to excised skin. It can either be combined with the OECD Test Guideline for Skin Absorption: *in vivo* Method (1), or be conducted separately. It is recommended that the OECD Guidance Document for the Conduct of Skin Absorption Studies (2) be consulted to assist in the design of studies based on this Test Guideline. The OECD Guidance Document has been prepared to facilitate the selection of appropriate *in vitro* procedures for use in specific circumstances, to ensure the reliability of results obtained by this method.

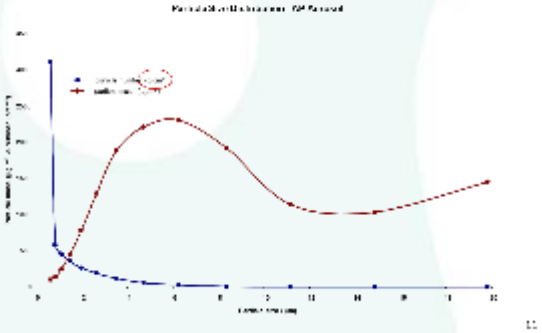
INITIAL CONSIDERATIONS

# 吸入暴露 Inhalation Exposure

- Simulated use studies can be conducted to measure lung exposure
  **模拟使用研究测量肺部暴露**
- Usually concerned with aerosol or pump spray products. Other products can be tested under simulated use conditions **通常与气雾胶或泵喷雾产品相关。 其他产品可在模拟使用条件下进行测试**
- Can measure inhalation of volatile and non-volatile components using aerodynamic particle sizer **可以使用空气动力学粒度分析仪测量挥发性和非挥发性组分的吸入**

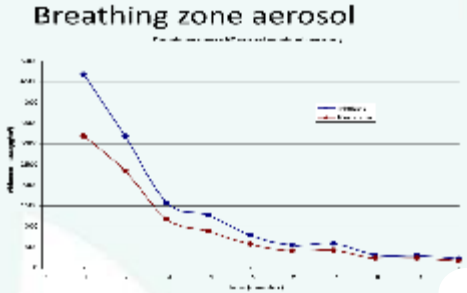
**模拟使用研究输出**

Simulated use study output

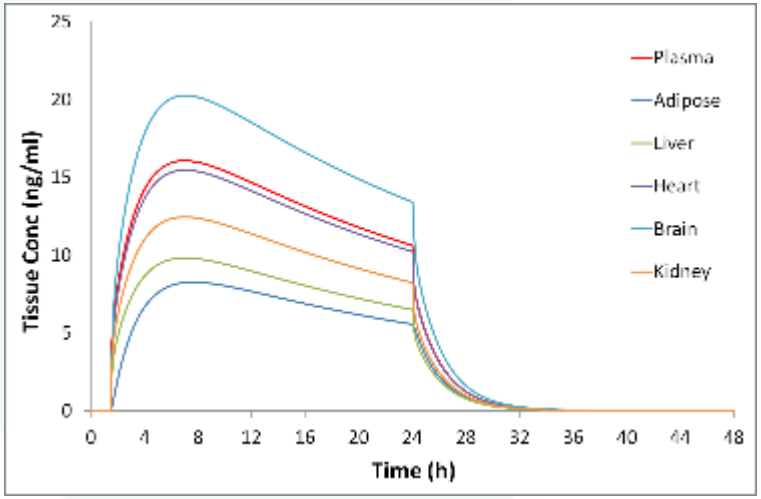


**呼吸区气雾剂**

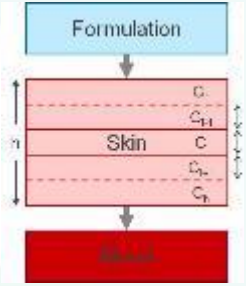
Breathing zone aerosol



# 了解全身暴露量 Understanding systemic exposure




**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

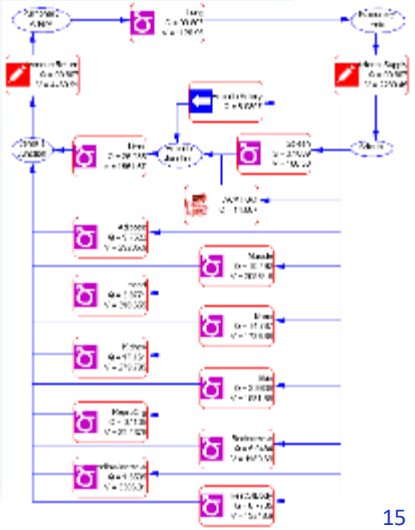



预测全身暴露

使我们能够选择和测试相关剂量

利用临床的数据, 以确认全身暴露水平

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



# 我们可以安全地使用新成分吗?
**Can we use a new ingredient safely?**

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**All safety assessments of cosmetic products are exposure-driven**

**消费者暴露**
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**理解成分的潜在危害**
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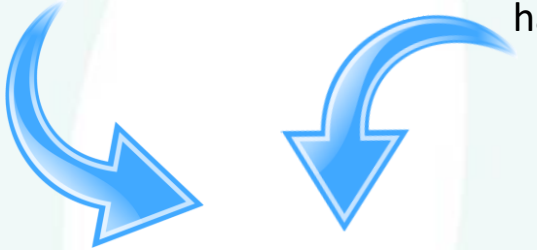


Risk Assessment
风险评估

# 毒性终点(人类健康) Toxicity Endpoints (Human Health)

**2021 根据欧盟消费者安全科学委员会制定的《化妆品成分测试及安全评估指南》确定需要考虑的相关毒性终点**

**Relevant toxicity endpoints based on the Scientific Committee on Consumer Products guidance document "Notes of Guidance for the Testing of Cosmetic Substances and their Safety Evaluation, 11th Revision**

- 急性毒性 Acute toxicity
- 致突变性/遗传毒性 Mutagenicity/genotoxicity
- 刺激性和腐蚀性 Irritation and Corrosivity
- 光诱导毒性 Photo-induced toxicity

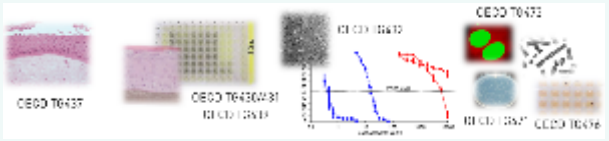
- 皮肤致敏 Skin sensitisation
- 重复剂量毒性 Repeated dose toxicity
- 生殖毒性 Reproductive toxicity
- 致癌性 Carcinogenicity


SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation, 11th Revision" (SCCS/1628/21)

# 最大限度地利用现有信息和非动物方法
# Maximising use of existing information and non-animal approaches

- 挖掘所有可用的安全数据（例:临床,流行病学,以前的动物数据）
- **基于暴露的豁免方法**
- **安全使用史**
- 计算机预测
- 交叉参照
- **使用现有的OECD体外方法**
- **新一代风险评估（NGRA）**

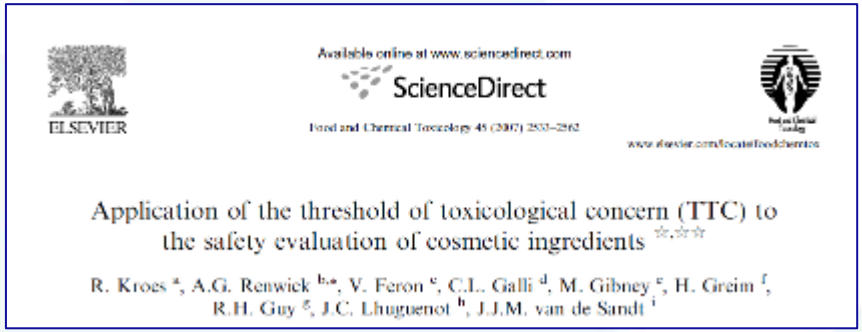
- All available safety data (Clinical, epidemiological, animal (if dates permit), in vitro etc)
- *in silico* predictions
- Exposure-based waiving approaches (e.g. TTC, DST, Inhalation TTC)
- History of safe use
- Read across
- Use of existing OECD *in vitro* approaches
- Next Generation Risk Assessment (NGRA)



# 基于暴露的豁免办法
## Exposure-based waiving approaches

- 如果没有可用的数据，那么在某些情况下，可以采用基于暴露的豁免办法，例如关注毒理学阈值（TTC）
- TTC：一种实用的方法，推导出的对人类健康没有明显风险的暴露水平
- 对于化学物质Cramer类别，都有一个相对应的TTC水平，由此类长期NOAEL的第5百分位应用100倍外推因子来确定。

- If no data are available then in some instances exposure based waiving approaches such as the Toxicological Threshold of Concern (TTC) can be employed
- TTC – a pragmatic approach to derive an exposure level at which there is no appreciable risk to human health
- The TTC levels were determined applying a 100-fold extrapolation factor to the 5th percentile NOAEL for chemicals in each Cramer class derived from chronic studies.


Available online at www.sciencedirect.com
ScienceDirect
Food and Chemical Toxicology 45 (2007) 2551–2562
ELSEVIER
www.elsevier.com/locate/foodchemtox
Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients ☆,☆☆
R. Kroes [a], A.G. Renwick [b,*], V. Feron [c], C.L. Galli [d], M. Gibney [e], H. Greim [f], R.H. Guy [g], J.C. Lhuguenot [h], J.J.M. van de Sandt [i]


Food and Chemical Toxicology 109 (2017) 170–183
Contents lists available at ScienceDirect
Food and Chemical Toxicology
journal homepage: www.elsevier.com/locate/foodchemtox
ELSEVIER
Thresholds of Toxicological Concern for cosmetics-related substances: New database, thresholds, and enrichment of chemical space
Chihae Yang [a,b], Susan M. Barlow [c], Kristi L. Muldoon Jacobs [d,1], Vessela Vitcheva [a,b,e], Alan R. Boobis [f], Susan P. Felter [g], Kirk B. Arvidson [h], Detlef Keller [h], Mark T.D. Cronin [i], Steven Enoch [i], Andrew Worth [j], Heli M. Hollnagel [k,*]

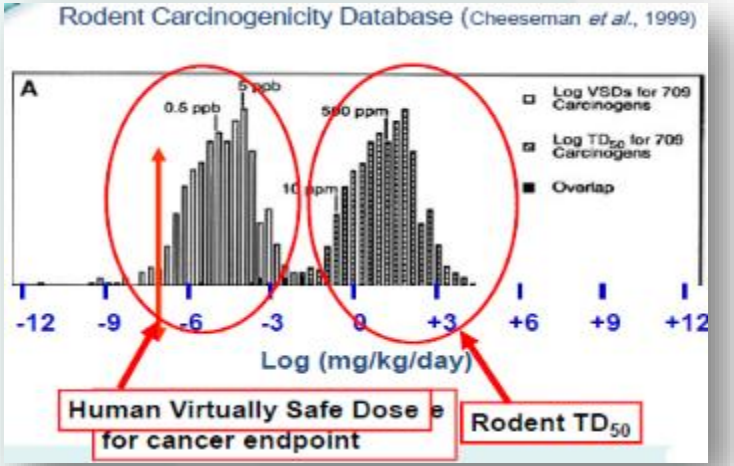
# 一般毒性TTC值的推导

**毒理学关注阈值（TTC）是一种实用的风险评估工具**

**基于为所有化学品建立人体暴露阈值的原则，低于此阈值暴露，对人一生健康风险都非常低**

Threshold of Toxicological Concern (TTC) is a pragmatic risk assessment tool that is based on the principle of establishing a human exposure threshold value for all chemicals, below which there is a very low probability of appreciable risk to human health for a lifetime

| Chemical Types<br>化学物分类 | 5th percentile NOEL<br>第5百分数NOEL<br>(mg/kg/day) | 基于暴露限值的<br>TTC (μg/kg/day) | 基于暴露限值<br>的TTC (μg/天) |
|---|---|---|---|
| Genotoxicity alert<br>遗传毒性警示 | | 0.0025 | 0.15 |
| Organophosphates 有机磷酸盐<br>/Carbamates 氨基甲酸酯 | 0.03 | 0.3 | 18 |
| Cramer I类 （低毒性） | 3 | 30 | 1800 |
| Cramer II 类（中毒性） | 0.91 | 9 | 540 |
| Cramer III 类（高毒性） | 0.15 | 1.5 | 90 |

# 基于暴露豁免的其他类型

## Other types of exposure-based waving

Regulatory Toxicology and Pharmacology 51 (2008) 195–200

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The Dermal Sensitisation Threshold—A TTC approach for allergic contact dermatitis

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ARTICLE INFO

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Available online 18 March 2008

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Threshold
Threshold of toxicological concern
TTC
Contact sensitisation
Allergic contact dermatitis

ABSTRACT

The Threshold of Toxicological Concern (TTC) is a useful concept that is becoming of increasing interest as an addition to the arsenal of tools used for characterising the toxicological risk of human exposure to chemicals. Traditionally used for low level indirect additives, flavours and contaminants in foods, the TTC obviates the need for toxicological testing of chemicals where human exposure is low. Proposals have recently been made for the use of the TTC for low level ingredients in cosmetic and personal care products. However, use of the TTC is only protective for systemic toxicity endpoints, and cannot be used for local endpoints such as contact sensitisation. In this paper a probabilistic analysis of available sensitisation data, similar to that used in the development of the TTC, is presented. The incidence of sensitisers in the world of chemicals was estimated using the ELINCS (European List of Notified Chemical Substances) data set, and a distribution for sensitisation potency was established using a recently published compilation of Local Lymph Node Assay data. From the analysis of these data sets it is concluded that a Dermal Sensitisation Threshold (DST) can be established below which there is no appreciable risk of sensitisation, even for an untested ingredient. Use of a DST would preclude the need for sensitisation testing of ingredients where dermal exposure is sufficiently low.

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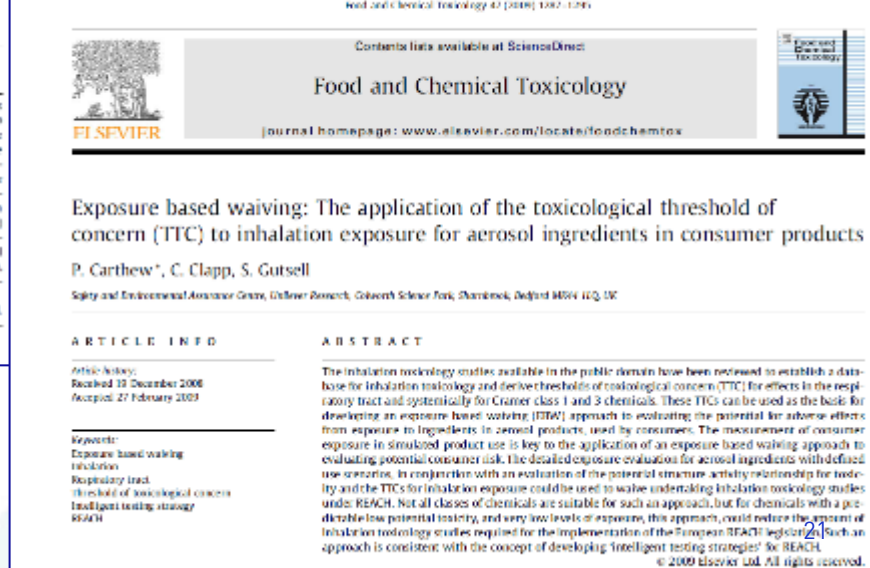
皮肤致敏豁免阈值

气雾成分吸入豁免阈值



Food and Chemical Toxicology

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/foodchemtox

Exposure based waiving: The application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products

P. Carthew*, C. Clapp, S. Gutsell

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Inhalation
Respiratory tract
Threshold of toxicological concern
Intelligent testing strategy
REACH

ABSTRACT

The inhalation toxicology studies available in the public domain have been reviewed to establish a database for inhalation toxicology and derive thresholds of toxicological concern (TTC) for effects in the respiratory tract and systemically for Cramer class 1 and 3 chemicals. These TTCs can be used as the basis for developing an exposure based waiving (EBW) approach to evaluating the potential for adverse effects from exposure to ingredients in aerosol products, used by consumers. The measurement of consumer exposure in simulated product use is key to the application of an exposure based waiving approach to evaluating potential consumer risk. The detailed exposure evaluation for aerosol ingredients with defined use scenarios, in conjunction with an evaluation of the potential structure–activity relationships for toxicity and the TTCs for inhalation exposure could be used to waive undertaking inhalation toxicology studies under REACH. Not all classes of chemicals are suitable for such an approach, but for chemicals with a predictable low potential toxicity, and very low levels of exposure, this approach could reduce the amount of inhalation toxicology studies required for the implementation of the European REACH legislation. Such an approach is consistent with the concept of developing 'intelligent testing strategies' for REACH.

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# 安全使用史
## History of Safe' Use In risk assessment

- 风险评估的植物材料（草药，中药，阿育吠陀等）在世界某些地区有长期使用历史
  Risk assessment of botanical materials (herbals, traditional Chinese medicines, Ayurvedics etc) which have a long history of use in certain parts of world.

- "安全使用史"（HoSU）广泛用于食品成分的安全性评估（例如新型食品和转基因生物食品）
  'History of Safe Use' (HoSU) is widely used for safety assessment of food ingredients (e.g. novel foods and foods derived from genetically modified organisms) *

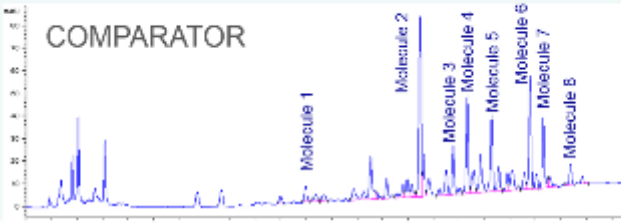
- 基于该物质与适合比较物的相似性，该比较物具有安全使用史（使用量等于或大于该物质）
  Based on similarity of the substance to appropriate comparator for which there is a history of safe use *(at levels equal to or greater than the substance)*

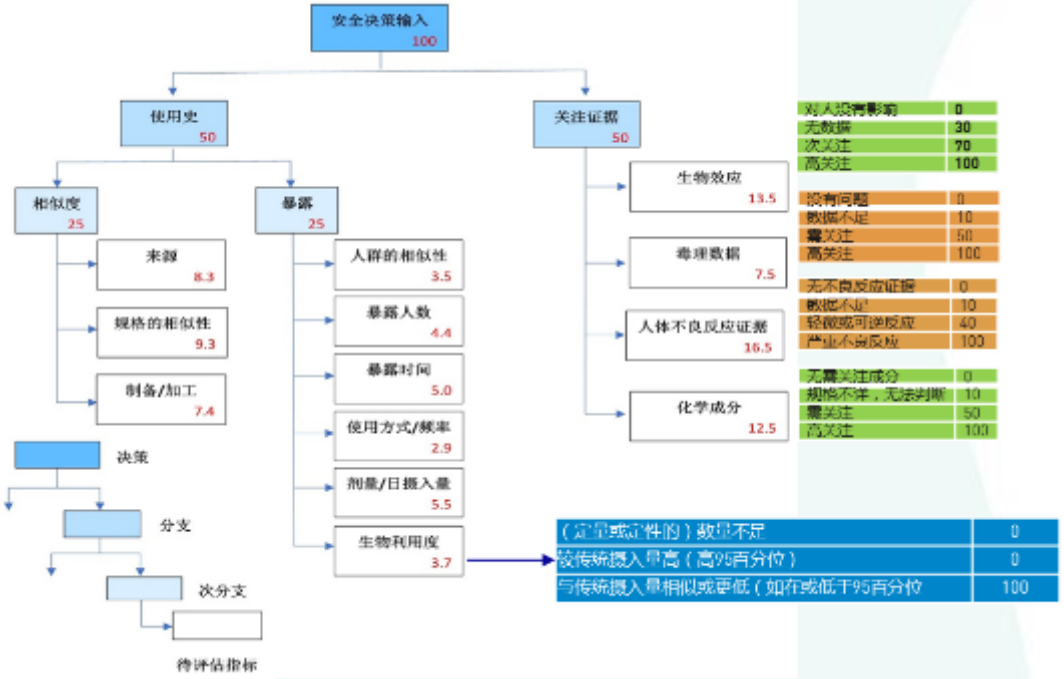
*Constable A et al (2007). Food and Chemical Toxicology, 45(12): 2513-25

# 安全使用史多指标决策分析模型

## HoSU multicriteria decision-making

### EXAMPLE OF $^1$H NMR FINGERPRINT



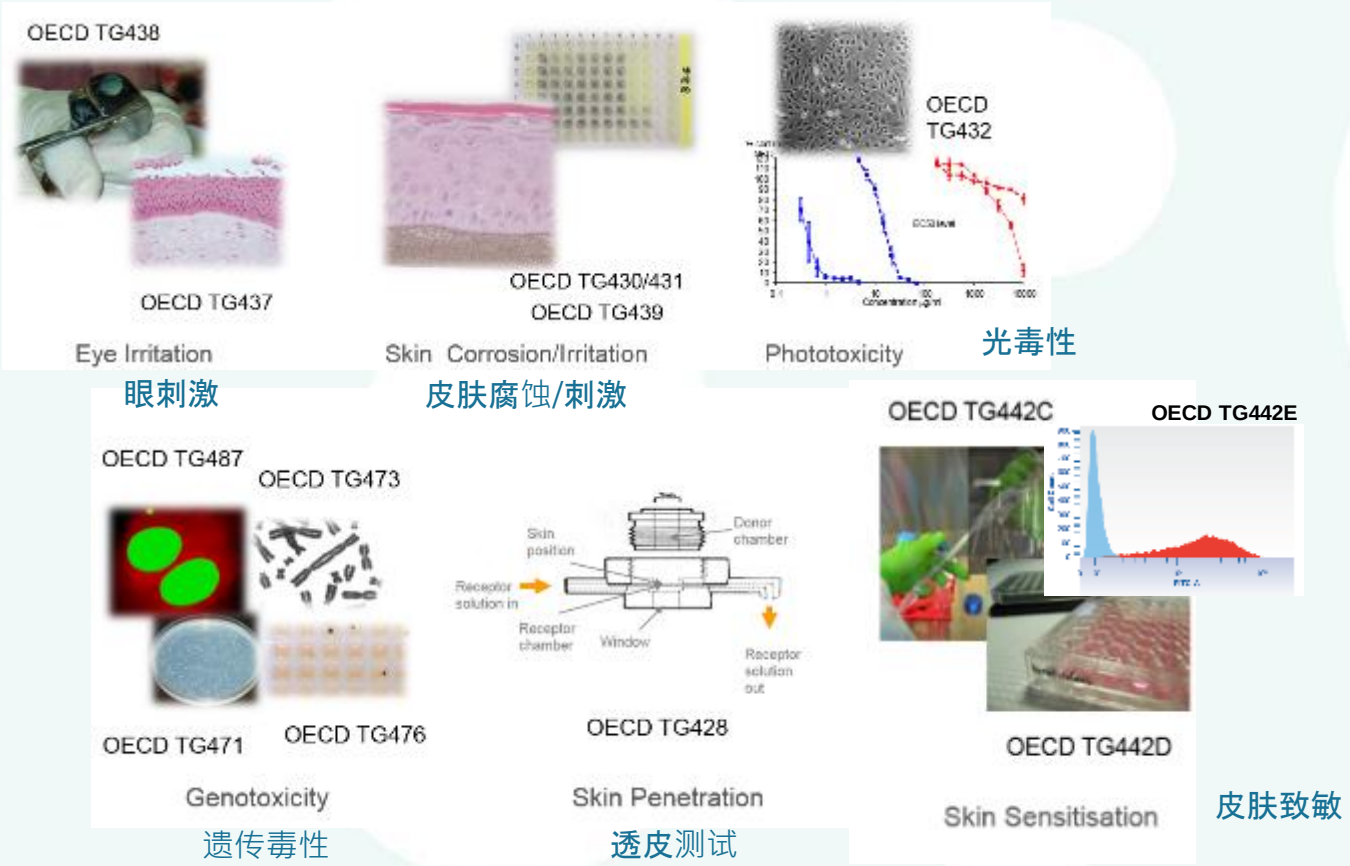

Toxicol Int. 2011 Aug; 18(Suppl1): S20–S29.
doi: 10.4103/0971-6580.85082; 10.4103/0971-6580.85082
PMCID: PMC3199690
PMID: 22025816

**A Multi-Criteria Decision Analysis Model to Assess the Safety of Botanicals Utilizing Data on History of Use**

T. Neely, B. Walsh-Mason, P. Russell, A. Van Der Horst, S. O'Hagan, and P. Lahorkar[1]

# 无动物的经济合作与发展组织（ OECD）测试

# OECD tests that do not use animals



# 新一代风险评估（NGRA）：国际化妆品监管合作组织（ICCR）无动物试验原则

## ICCR principles of risk assessment without animal testing

European Commission: Scientific Committee on Consumer Safety (2021)


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

**PART 2:** https://www.iccr-cosmetics.org/files/8315/4322/3079/ICCR_Integrated_Strategies_for_Safety_Assessment_of_Cosmetic_Ingredients_Part_2.pdf

# 国际化妆品监管合作组织(ICCR): 新一代化妆品风险评估(NGRA)9大原则
# 9 principles of NGRA from ICCR for cosmetic risk assessment

**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

**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

**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

4 + 3 + 2 = 9

**Main Overriding Principles**
- A human safety risk assessment
- Exposure Led
- Hypothesis Driven
- Prevent Harm

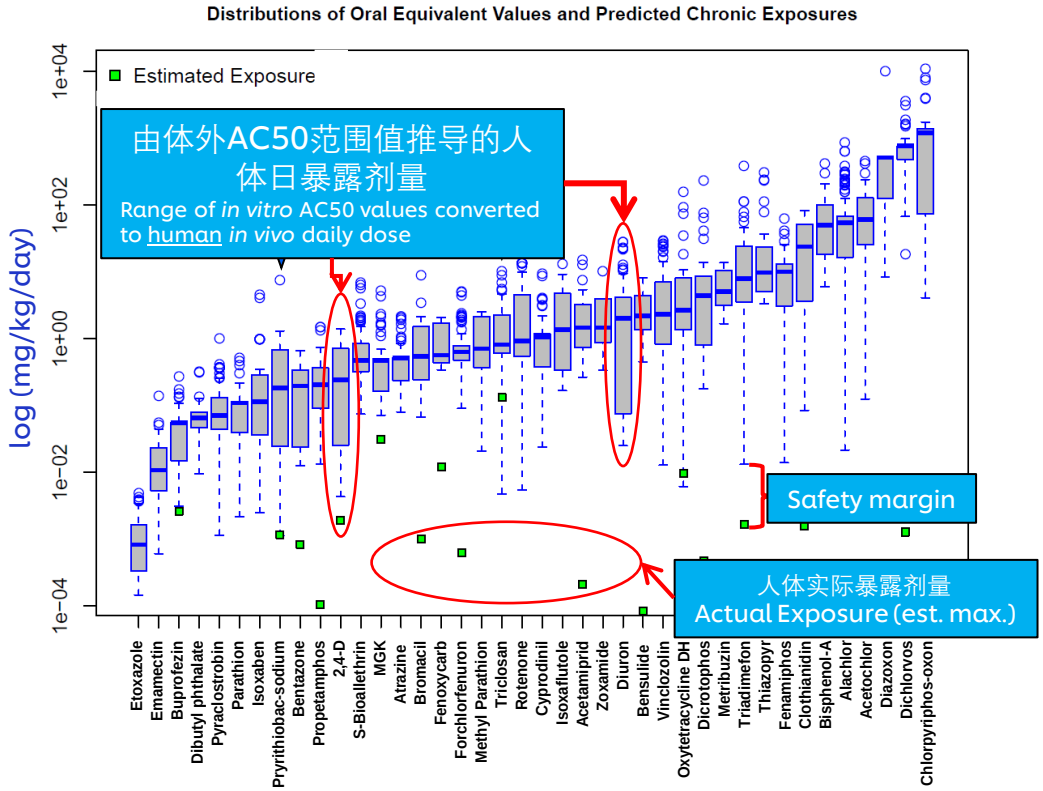
**How to conduct an NGRA**
- Appraisal of Existing Information
- Tiered and Iterative Approach
- Robust and relevant strategies

**NGRA Documentation**
- Document and characterise sources of uncertainty
- Transparent logic of approach

ICCR
International Cooperation on Cosmetics Regulation

# NGRA 的特点：保护而非预测

## NGRA: Protection not prediction




支持NGRA的假设: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

The hypothesis underpinning this NGRA is that if no bioactivity is observed at consumer-relevant concentrations, there can be no adverse health effects.

**NGRA无论如何都不试图预测高剂量下动物毒理学实验的结果**

At no point does NGRA attempt to predict the results of high dose toxicology studies in animals

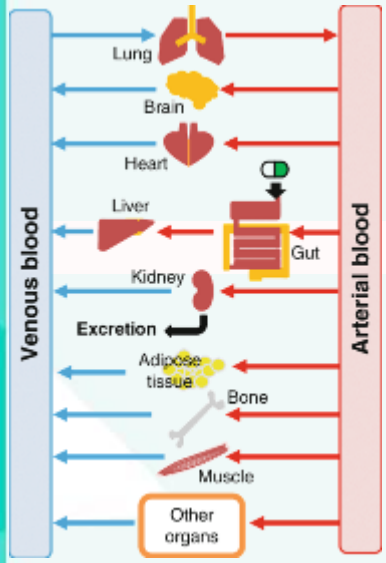
**NGRA利用暴露科学和对人类生物学的理解**

NGRA uses new exposure science and understanding of human biology

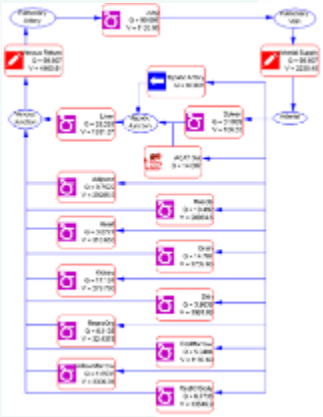
Graph from Rusty Thomas EPA, with thanks. Rotroff*et al* (2010) Toxicological Sciences , **117**, 348-358

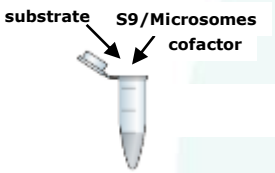
# NGRA中的关键技术：PBK（基于生理的动力学）模型

## One key tool in NGRA: PBK (Physiologically Based Kinetic) Modelling




模型输入：
生理参数
分配系数
动力学常数（体外）



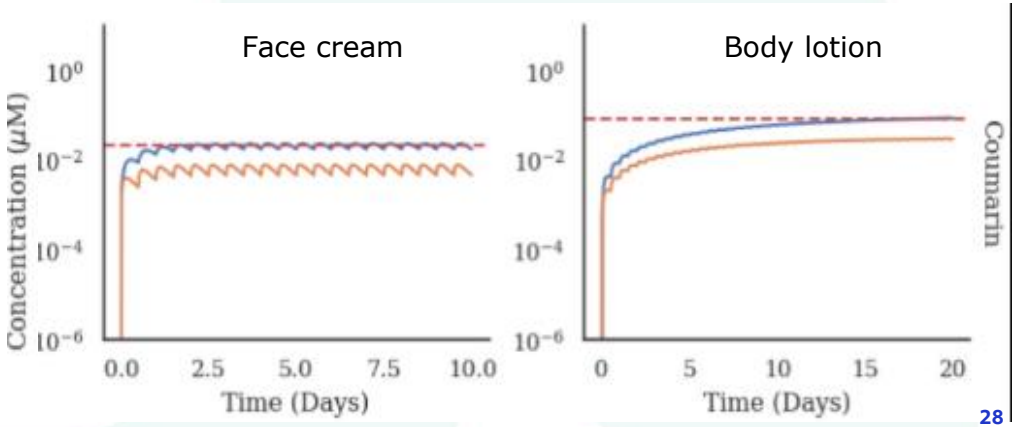



吸收 Uptake

动脉至静脉血转运
Transport from arterial to venous blood

代谢Metabolism

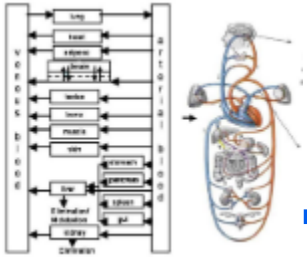
$$dA/dt = + K_A * A_{GI} + QL * (CA - CV) - V_{max} * CL / (K_m + CL)$$




Moxon *et al.*, (2020) *TIV* 63

# The Margin of Safety Approach 计算安全边际的方法

暴露模型（PBK、游离/总浓度）
**Exposure models (PBK, free/total concentration)**



肝脏清除率及血浆蛋白结合测定
Hepatic clearance & plasma protein binding determinations

体外生物活性拐点值
**Point of Departure (PoD)**

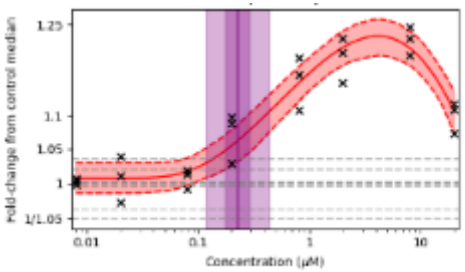
安全边际
**Margin of safety (MoS)**

血液中化学物的最高浓度
$C_{max}$

Plasma concentration

Time

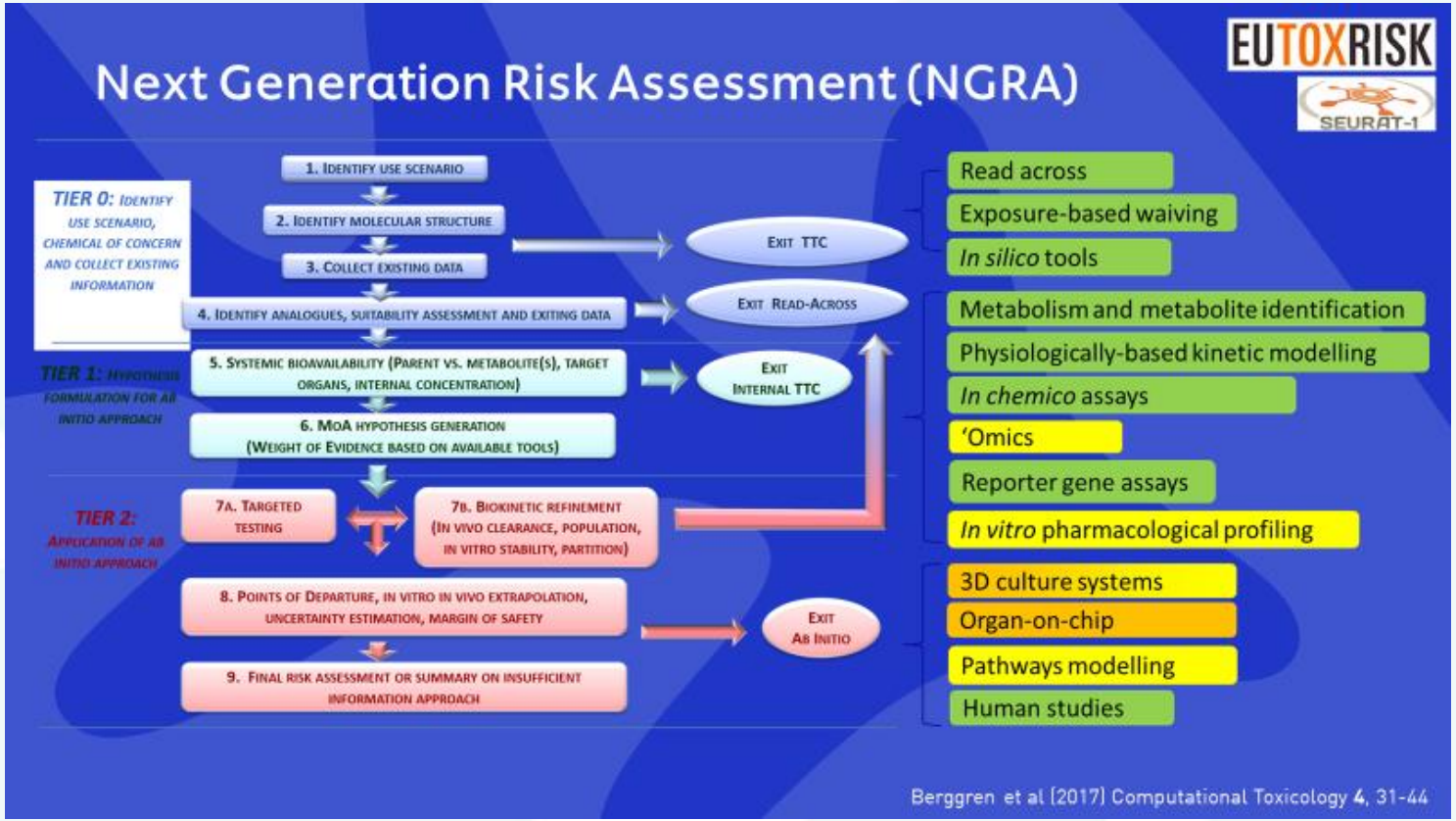
从体外浓度反应得出的生物活性拐点值
**Point of departure derived from *in vitro* concentration-response**




$$\text{MoS(安全边际)} = \frac{\text{PoD}}{\text{Exposure}} = \frac{\text{PoD}}{C_{max}} = \frac{\text{体外生物活性拐点值}}{\text{血液中化学物的最高浓度}}$$

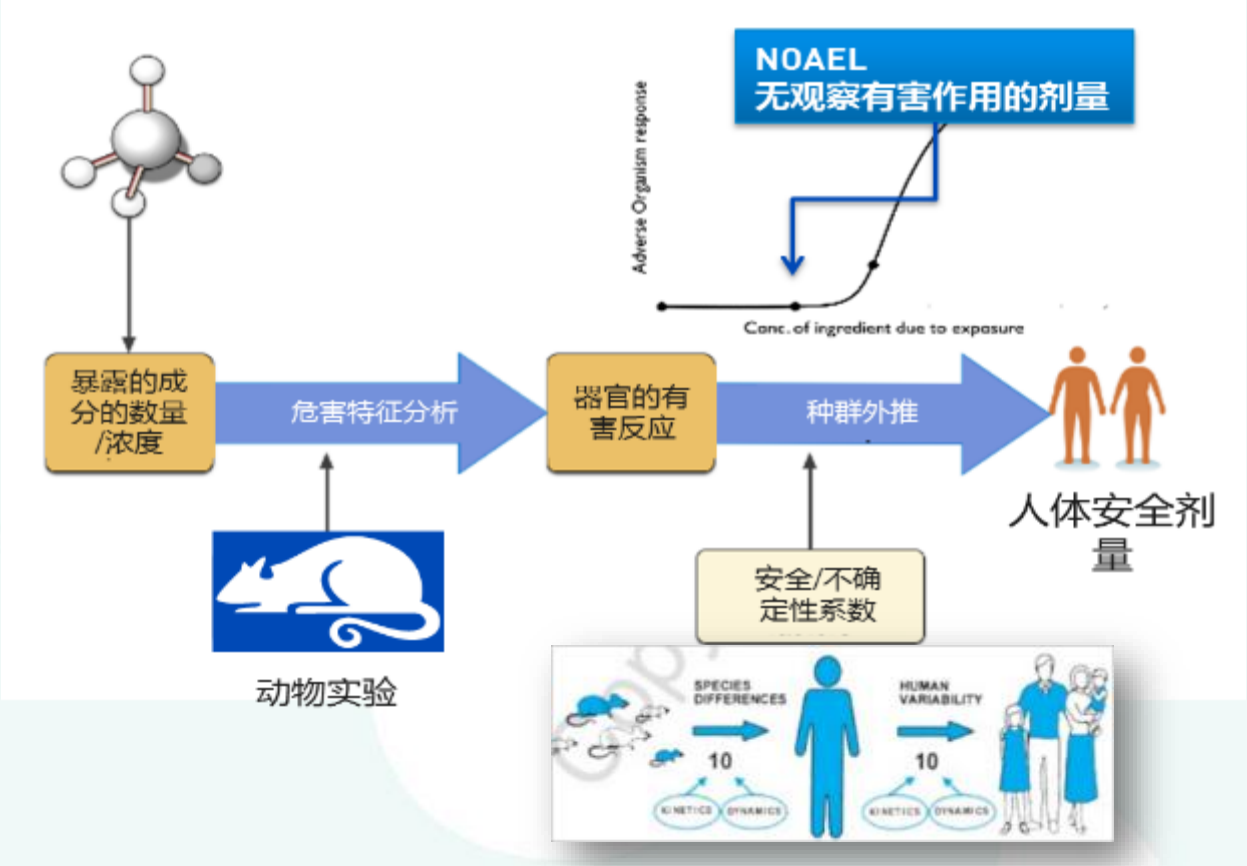
# 基于新技术方法的分层迭代方法

## One NGRA framework: A tiered and iterative approach using NAMs



# 传统的动物动物实验方法：对于全身毒性的风险评估

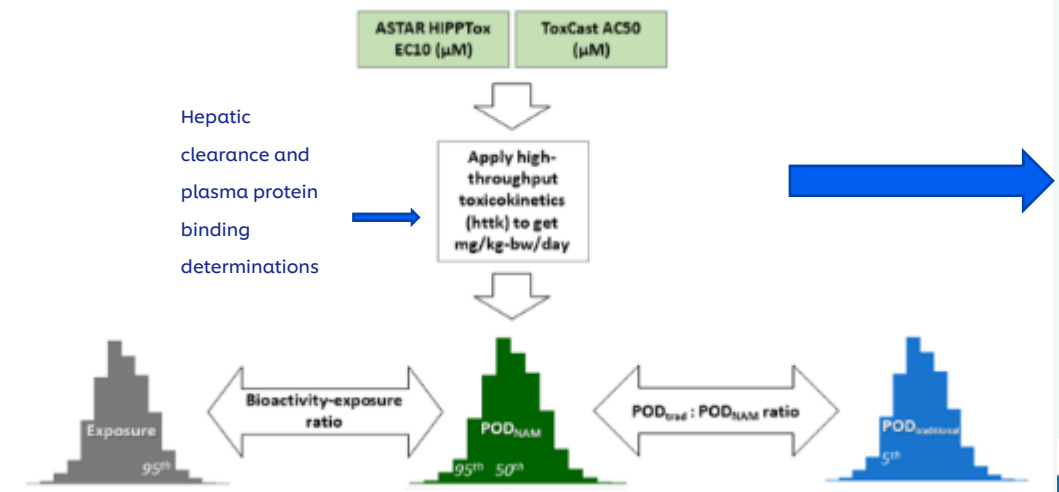
## Risk assessment for systemic toxicity: the traditional approach

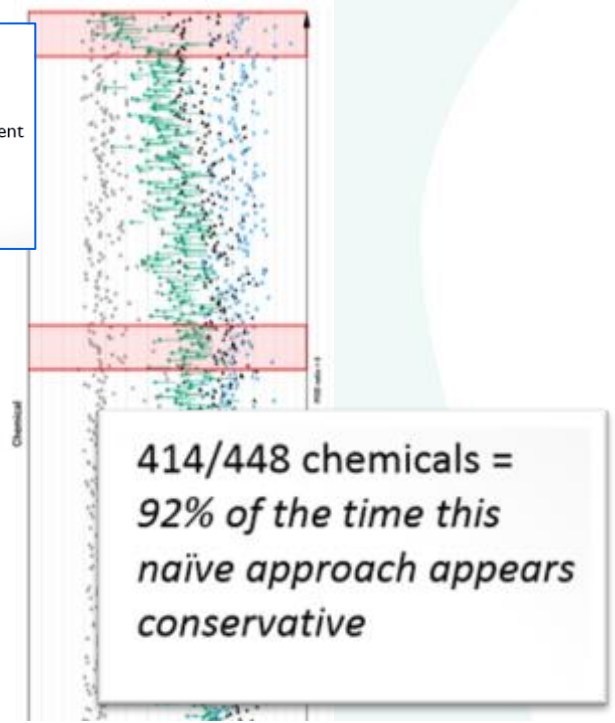


# Recent research has shown that for 417 out of 448 chemicals tested the point of departure derived (PoD) from NAMs was more conservative than the in vivo PoD (新一代方法，相对于动物实验方法更加保守)

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

- **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

# 3. Case Studies: Coumarin

香豆素在化妆品案例研究

Unilever

# 案例研究方法……假设我们没有以下数据：香豆素

## Case study approach… imagine we have no data for: Coumarin


Safety assessment required for **0.1% coumarin in Face Cream**

**面霜中0.1%香豆素需要进行安全评估**

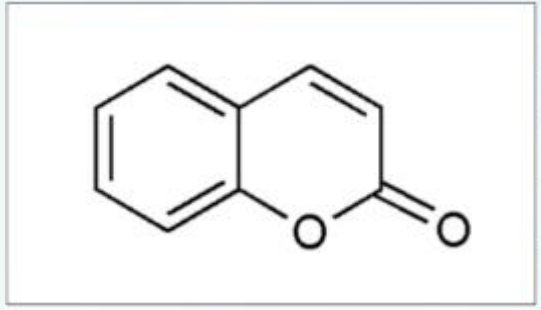
设立的案例安全评估的假设：

- 香豆素是100%纯的
- 没有体内数据 （例如动物数据，安全使用历史（HoSU）信息 或临床数据）
- 已知基于动物或体内数据或基于香豆素自身结构的计算机警示已被排除

# Coumarin (香豆素)

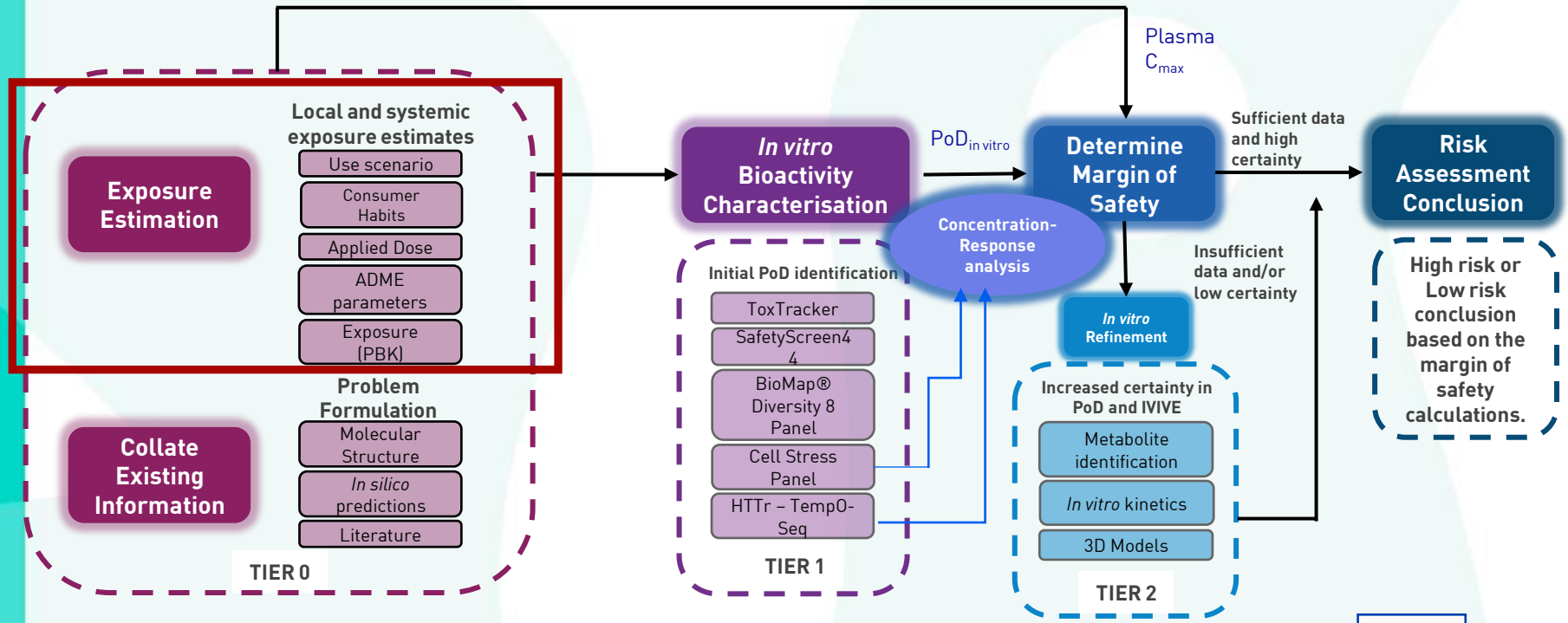
香豆素是一种调味物质，其在肉桂品种中含量相对较高。 它也被用作化妆品中的香料

Coumarin is a flavouring substance which is contained in relatively high concentrations in cinnamon varieties collectively known as "Cassia cinnamon". It’s also used as a fragrance in cosmetic products



| | |
|---|---|
| 化學名稱 | 香豆素 |
| 外觀 | 無色或白色晶體 |
| 化學物質登錄號 | 91-64-5 |
| 分子式 | $C_9H_6O_2$ |
| 分子量 | 146.14 |

# *Ab Initio* NGRA Framework 从零开始NGRA框架

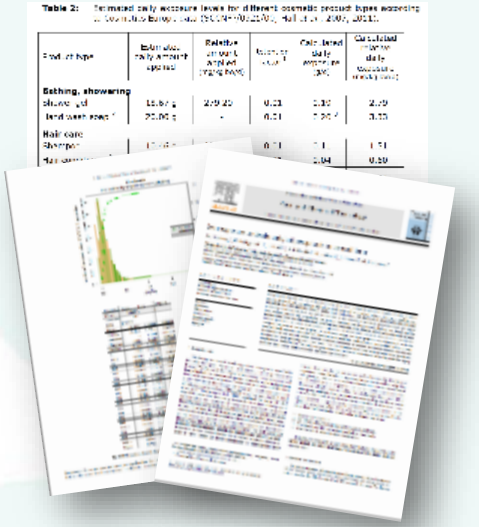


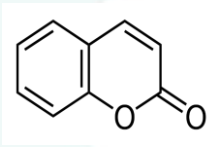

Baltazar *et al.*, (2020) *Tox Sci* Vol 176, Issue 1, July 2020, p236–252

# 0.1%香豆素产品的暴露估计

## Exposure estimation for 0.1% coumarin products

Creme GLOBAL





| Parameter | Face cream |
|---|---|
| Amount of product used per day (g/day) using 90th percentile | 1.54 |
| Frequency of use | 2 times/day |
| Amount of product in contact with skin per occasion (mg) | 770 |
| Ingredient inclusion level | 0.1% |
| Skin surface area (cm2) | 565 |
| Exposure duration per occasion | 12 hours |
| Amount of ingredient in contact with skin per occasion (mg) | 0.77 |
| Local dermal exposure per occasion (µg/cm2) | 1.36 |
| Systemic exposure per day (mg/kg) | **0.02** |

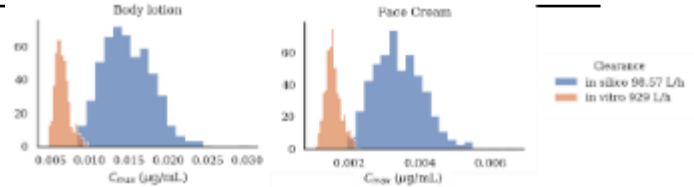
**Assessment is exposure-led and uses available habits and practices data**

Unilever

# Systemic bioavailability using PBK modelling
# 使用基于生理的动力学(PBK)建模的系统生物利用度

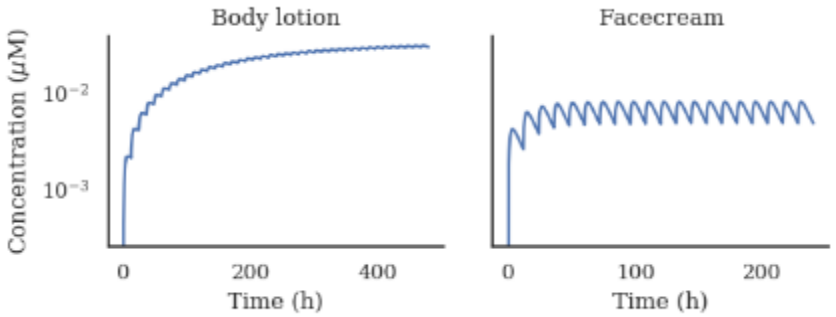
**Key output parameters from uncertainty analysis:**

| Parameter | Face cream (applied 2x/day) | Body lotion (applied 2x/day) |
|---|---|---|
| Plasma Cmax total (µM) | 0.023 | 0.10 |
| 95th percentile Cmax (µM) | 0.032 | 0.14 |




**Uncertainty & Population Variability**

**0.1% Face cream & body lotion in Europe**

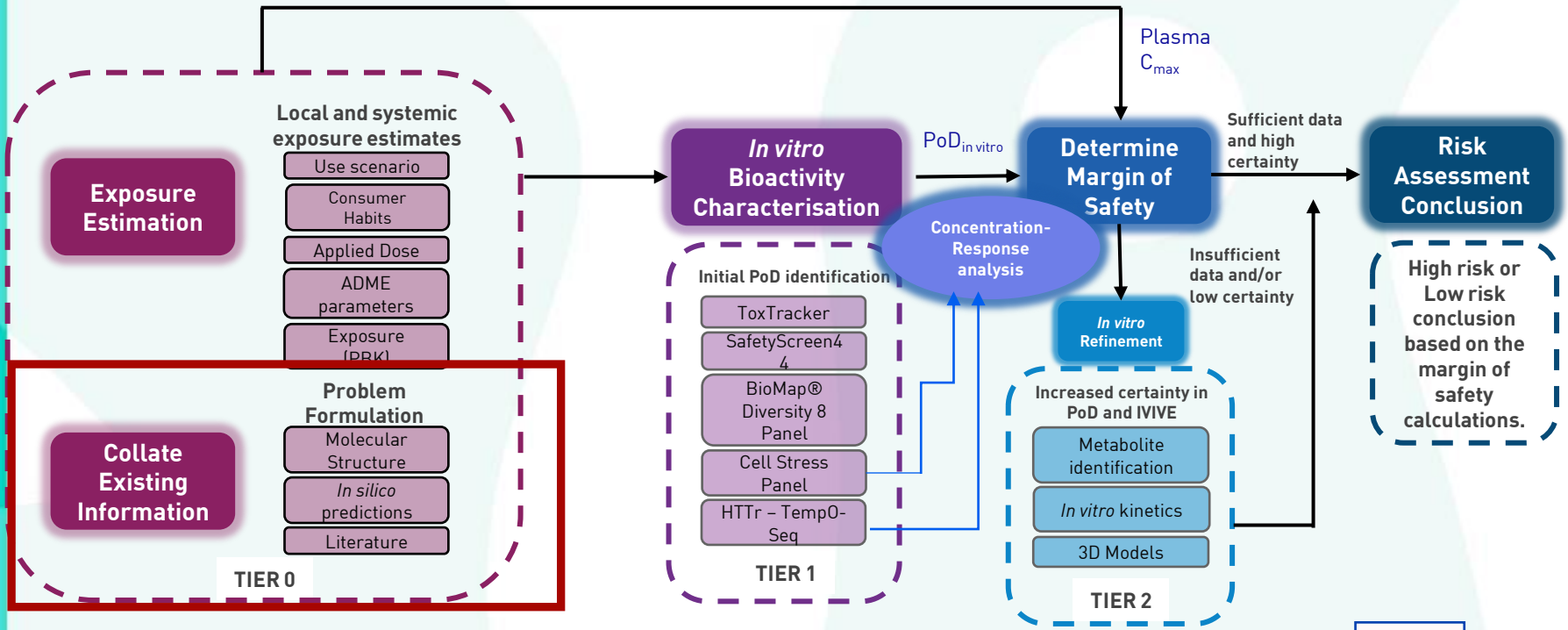



Physiologically-based kinetic modelling using GastroPlus® v9.5. Estimations based on experimental data (Clint, fup, bpr, solubility, LogP). Skin penetration parameters were fitted against skin penetration data.

Moxon *et al* (2020) Toxicology in Vitro, 63 104746

# 从零开始NGRA框架：已知信息

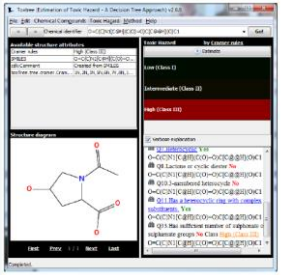
## *Ab Initio* NGRA Framework: existing info




Baltazar *et al.*, (2020) *Tox Sci* Vol 176, Issue 1, July 2020, p236–252

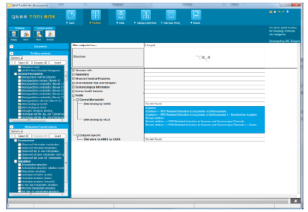
# 计算机模拟工具预测香豆素毒性
# *In silico* tools used for predict toxicity of coumarin

**ToxTree**



Derek nexus

OECD QSAR TOOLBOX

EPA iCSS ToxCast Dashboard

- Genotoxicity and skin sensitisation alerts for parent compound
- Hydroxylation predicted as main route of biotransformation
- Reactive metabolites (e.g. epoxides) predicted.
- Low bioactivity in ToxCast and Pubchem: binding to Carbonic Anhydrases and MAO-A/B reported
- Lowest PoD was 3 µM for carbonic anhydrase I

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

Meteor nexus

OXFORD SOT Society of Toxicology www.toxsci.oxfordjournals.org ToxSci 20 Years

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

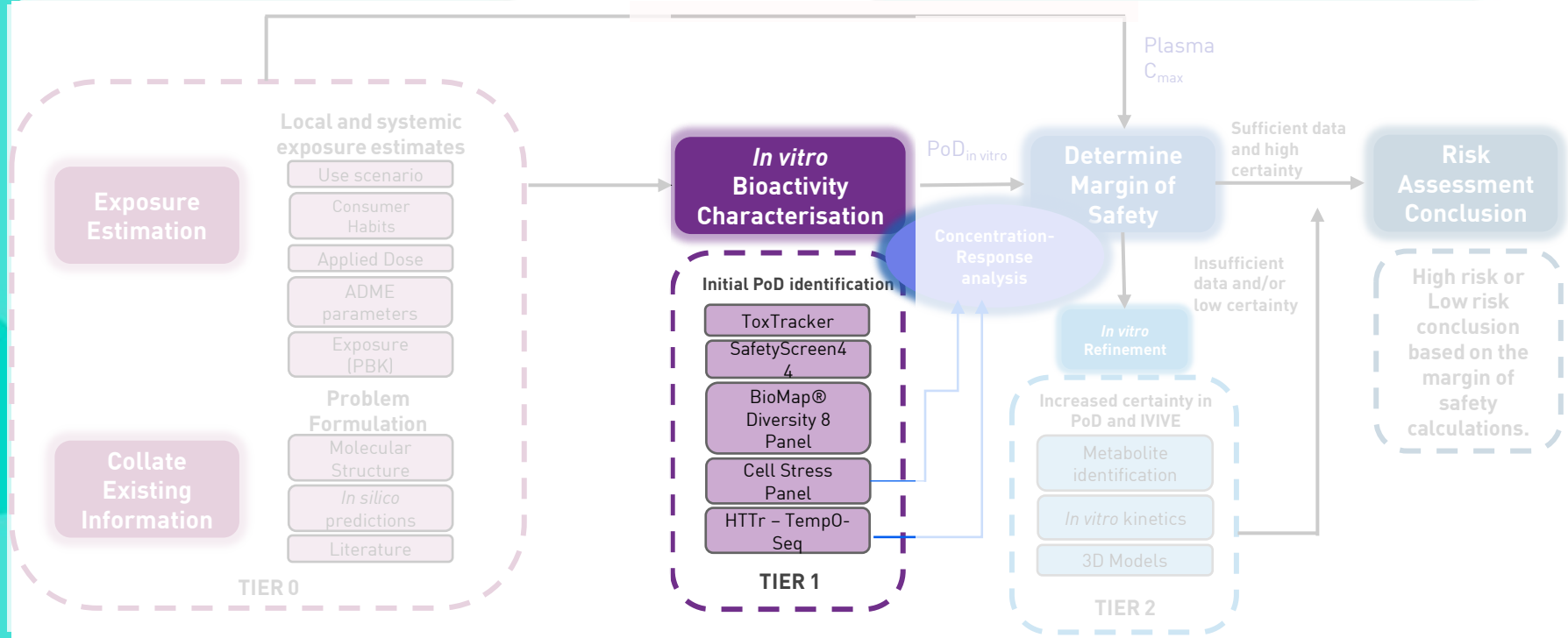
Timothy E. H. Allen,* Jonathan M. Goodman,*,† Steve Gutsell,† and Paul J. Russell†

**Metabolic fate predictions**

*Allen THE et al., 2018. Toxicol Sci. 2018 Sep 1;165(1):213-223

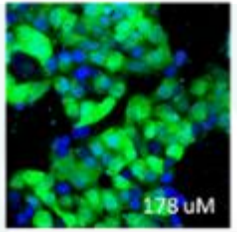
Unilever

# *Ab Initio* NGRA framework 从零开始NGRA框架



# *In vitro* Bioactivity Characterisation

cyprotex AN EVOTEC COMPANY

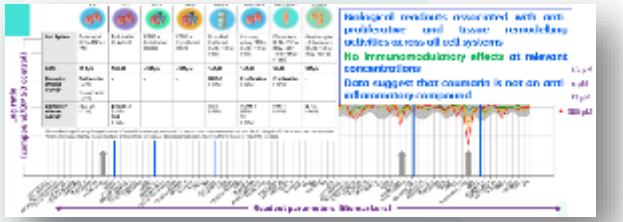



Stress pathways

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

**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.*

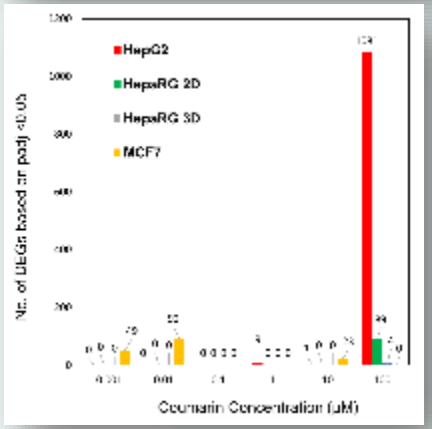


**2) Immunomodulatory bioactivity: BioMap® Diversity 8 panel**
免疫调节生物活性：BioMap®Diversity 8 面板

**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 µM,



# Margin of Safety considering PoDs and Exposure
# 结合生物拐点和暴露量的安全边际值

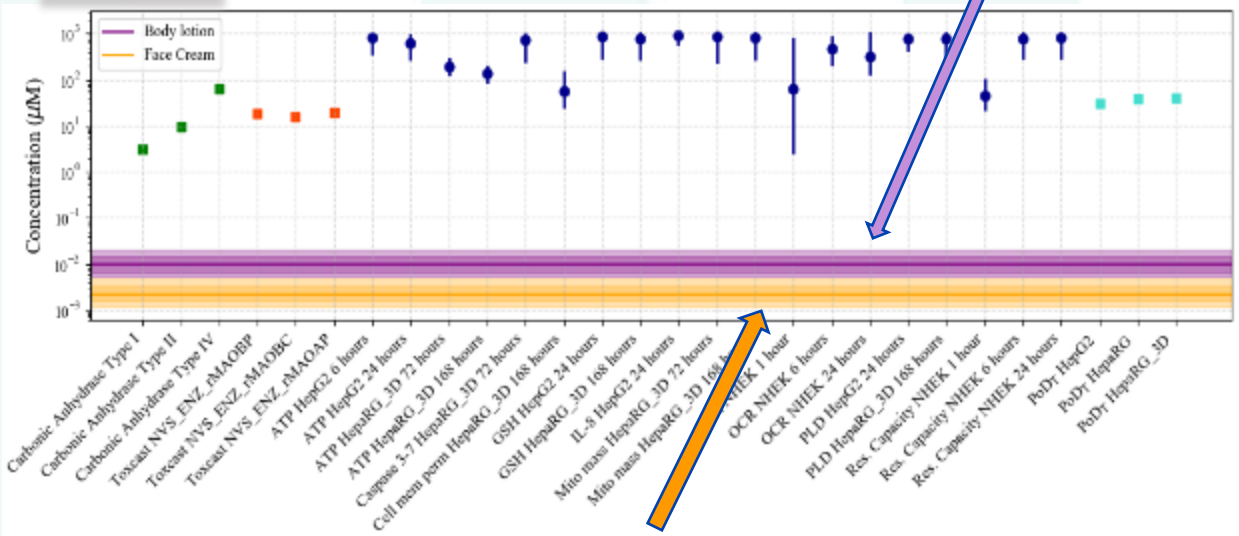
**PoDs and plasma $C_{max}$ (µM) are expressed as total concentration**

**$C_{max}$ expressed as a distribution:**

- Line = median (50th percentile)
- Inner band = 25th-75th percentile
- Outer band = 2.5th-97.5th percentile (95th credible interval)

Body Lotion
身体乳液（人体血液暴露量）

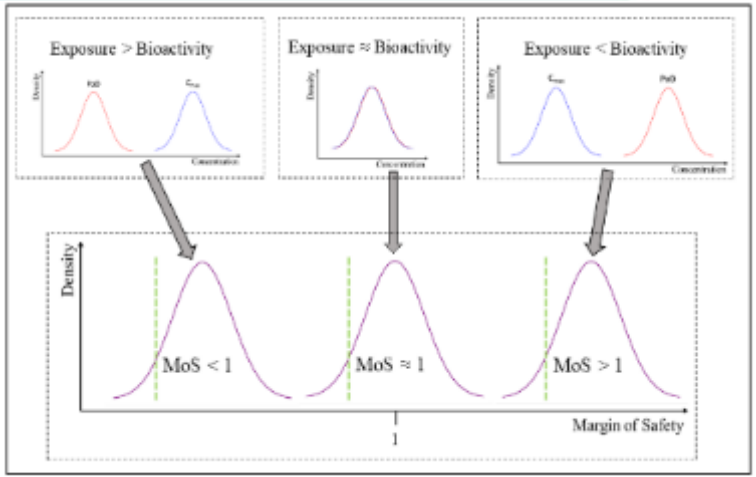
PubChem ToxCast | Cell Stress Panel | HTTr




Face cream
面霜（人体血液暴露量）

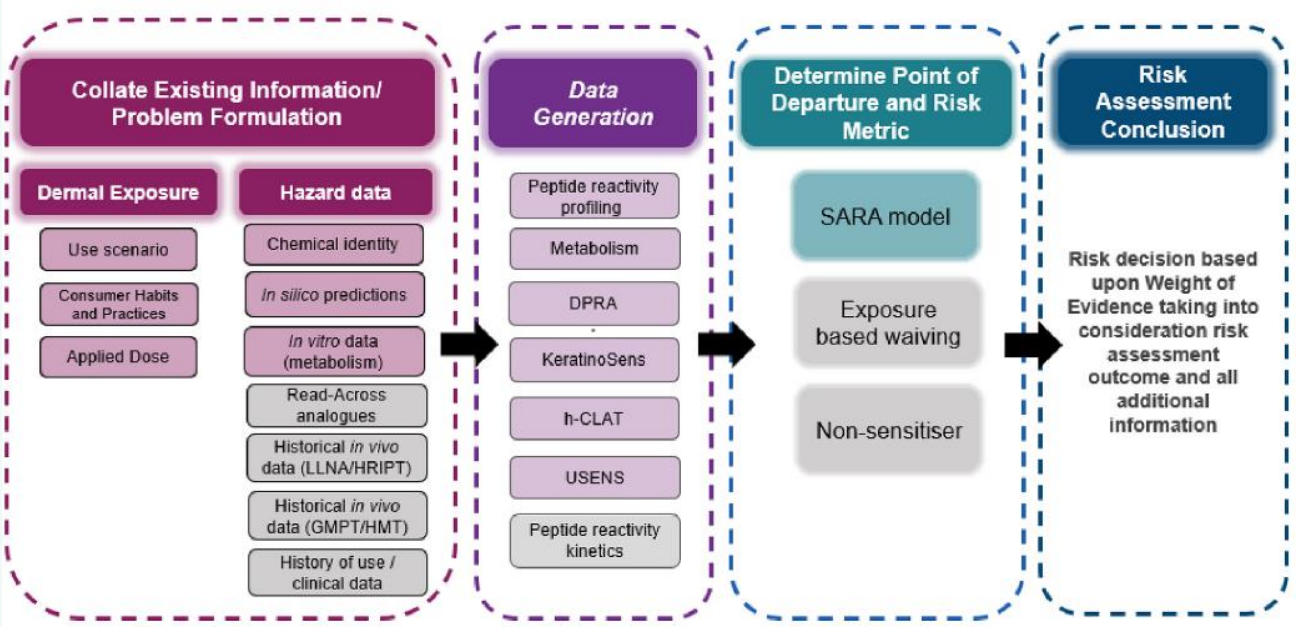
# Application of *Ab Initio* Approach: Risk Assessment (NGRA)
# 从零开始方法的应用：新一代风险评估（NGRA）的结论

**Margin of safety** is the **fold difference** between the **Cmax** and the ***in vitro*** **POD**




| Technology | Cell line/ Enzyme/Biomarker | Face cream Min. 5th percentile MoS | Body Lotion Min. 5th percentile MoS |
|---|---|---|---|
| **Cell stress panel** | HepG2 (ATP, 24h) | 96738 | 22048 |
| **Cell stress panel** | NHEK (OCR 1h) | 1330 | **295** |
| **HTTr** | HepG2 (24h) | 7223 | 1618 |
| **HTTr** | HepaRG (24h) | 8864 | 1986 |
| **Toxcast** | MAO B (rat bain) | 3711 | 831 |
| **PubChem** | Carbonic Anhydrase Type I | **706** | **158** |
| **PubChem** | Carbonic Anhydrase Type II | 2140 | 479 |
| **PubChem** | Carbonic Anhydrase Type VI | 14652 | 3282 |
| **Cell stress panel** | HepaRG_3D (cell mem perm 168h) | 9601 | 2197 |
| **HTTr** | HepaRG_3D_24h | 9538 | 2137 |

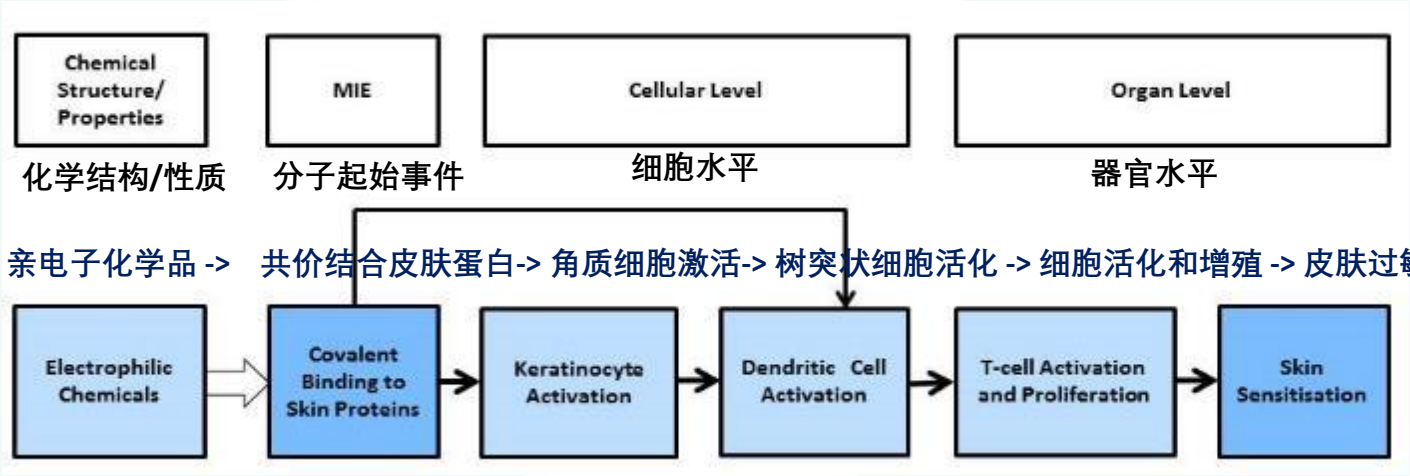
# Skin Allergy: Next Generation Risk Assessment (NGRA) Framework




- Our NGRA framework for skin allergy is based upon the ICCR principles and the previously published NGRA frameworks for systemic tox and skin allergy (Gilmour *et al* 2020).
- Designed to use a WoE based upon all available information, accommodate range of consumer product exposure scenarios and provide a quantitative point of departure and risk metric → SARA Model.

*Gilmour et al, (2020),Regulatory Toxicology and Pharmacology,* ***116***

# 新一代风险评估:皮肤致敏 AOP Skin Sensitisation AOP




Key Event 1 (KE1) | KE2 | KE3 | KE4 | Adverse Outcome (AO)

**Predictive Chemistry**

**For example:**
- DEREK-NEXUS
- OECD QSAR Toolbox
- TIMES
- ToxTree

**Protein Reactivity**

OECD TG 442C
**Includes:**
- ADRA
- DPRA

**Keratinocyte Activation**

OECD TG 442D
**Includes:**
- KeratinoSens™
- LuSens

**DC Activation**

OECD TG 442E
**Includes:**
- h-CLAT
- IL-8 Luc Assay
- U-Sens™

**T Cell Proliferation**

**For Example:**
- Human T cell proliferation assays (hTCPA)

**Skin Sensitisation**

OECD TG 429: mouse local lymph node assay (LLNA) & variants TG442A & 442B

OECD TG 406: Buehler & Guinea Pig Maximisation Test (GPMT)

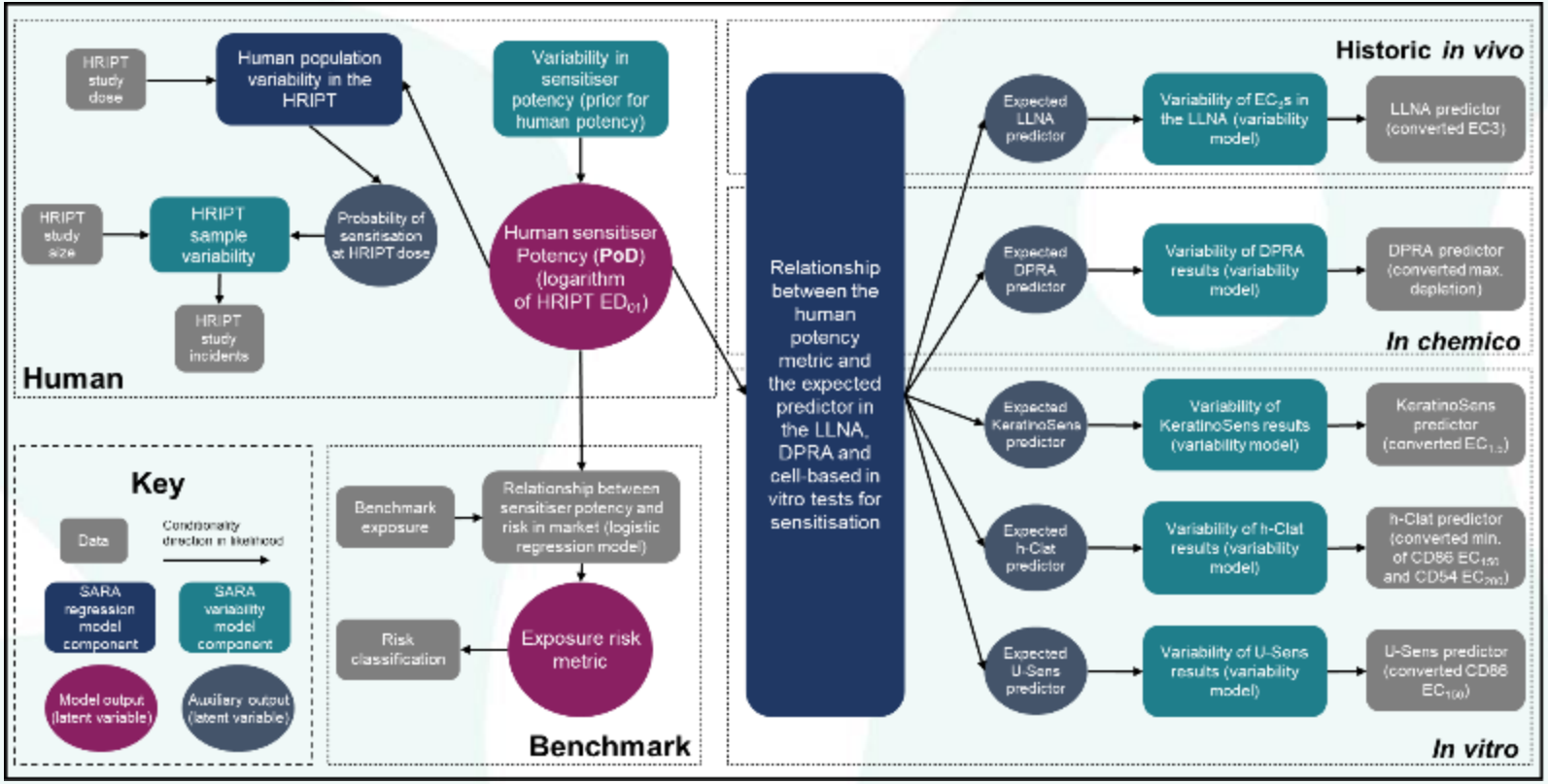
Human evidence
e.g. Human Repeat Insult Patch Test (HRIPT)

*in silico* NAM | *in chemico/vitro* NAM | *in vivo* evidence

*Reynold G. et. at (2021) RTAP, 127*

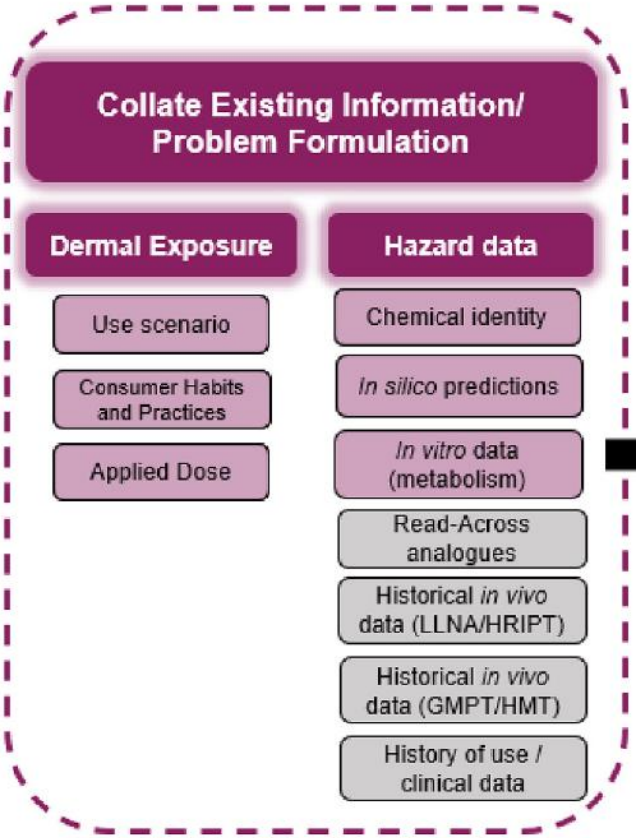
# SARA Model

SARA证据权重（WoE）人群致敏强度模型*是描述来自以下多维数据来源的概率分布：



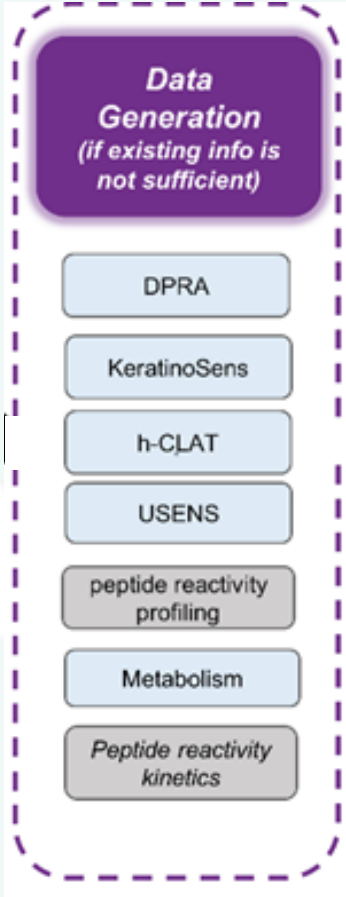

- The SARA model uses Bayesian statistics to infer a probability that a consumer exposure to some chemical can be considered low risk, to inform risk assessment decisions.
- The SARA Model uses a database of public NAM data covering AOP KEs 1-3, and historic LLNA and HRIPT data for the AOP AO.

# Local exposure + Collate Existing Information/ Problem Formulation




- *In silico* chemistry predictions for the sensitiser potential of coumarin: TIMES-SS predicts coumarin and metabolites non-sensitisers; Derek Nexus, ToxTree and OECD QSAR Toolbox all predict sensitiser potential. ToxTree and OECD QSAR Toolbox predicted a Michael Acceptor mechanism. Both direct and indirect (pro-hapten) mechanisms were indicated.
- Meteor Nexus identified hydroxylation as the main route of biotransformation. Most metabolites were predicted to bind to protein, a flag for skin sensitization. 7-OH coumarin was identified as one of the main metabolites in an investigation in human hepatocytes.

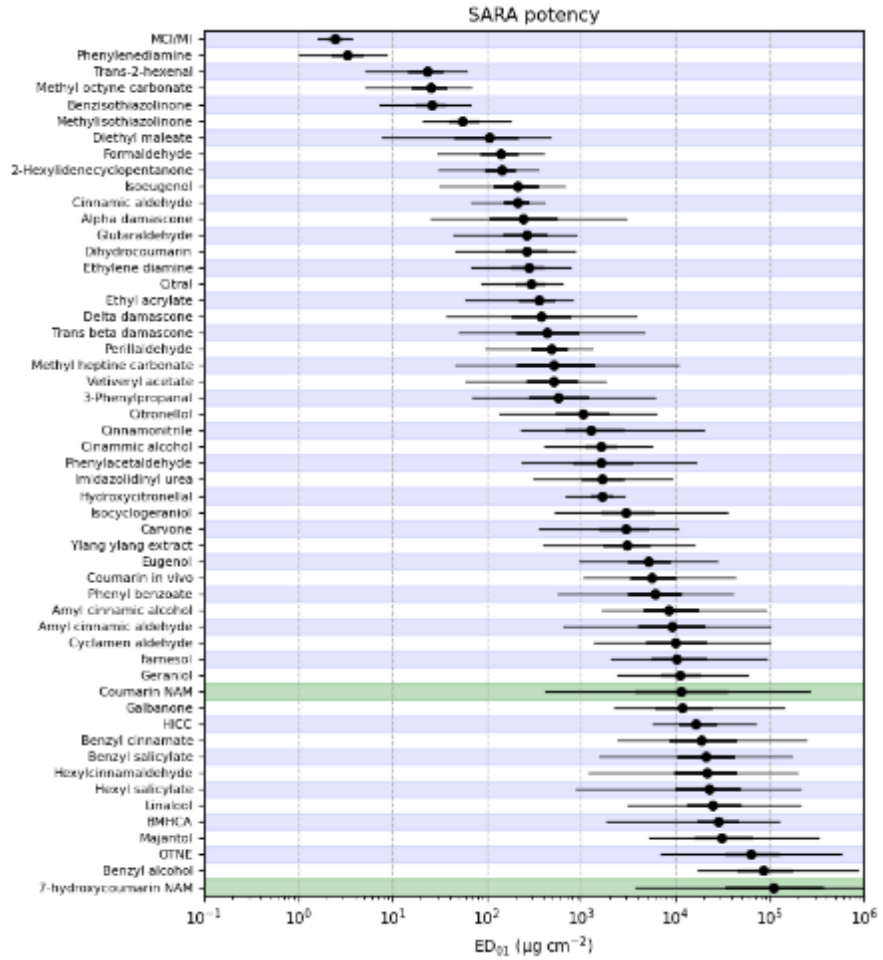
# Data Generation




| | DPRA (TG442C) | | KeratinoSens™ (TG 442D) | h-CLAT (TG 442E) | | U-SENS™ (TG 442E) |
|---|---|---|---|---|---|---|
| | %cys depl. | %lys depl. | EC1.5 (µM) | CD86 (EC200 µg/mL) | CD54 (EC150 µg/mL) | CD86 (EC150 µg/mL) |
| Coumarin | 1.3 | 0 | 187.5 | <178 | >637 | 95.5 |
| 7-OH Coumarin | 0* | 0 | >2000 | >566 | >566 | 182 |

- Coumarin was positive in all tests, except for DPRA where peptide depletion was too low to meet positive threshold.
- 7-OH coumarin was negative in KeratinoSens™ & h-CLAT, positive in USENS™, inconclusive in DPRA. *Peptide profiling was completed which identified cysteine depletion to be caused by dimerization and therefore the DPRA value was adjusted.

# Determine Point of Departure (PoD) using SARA Model

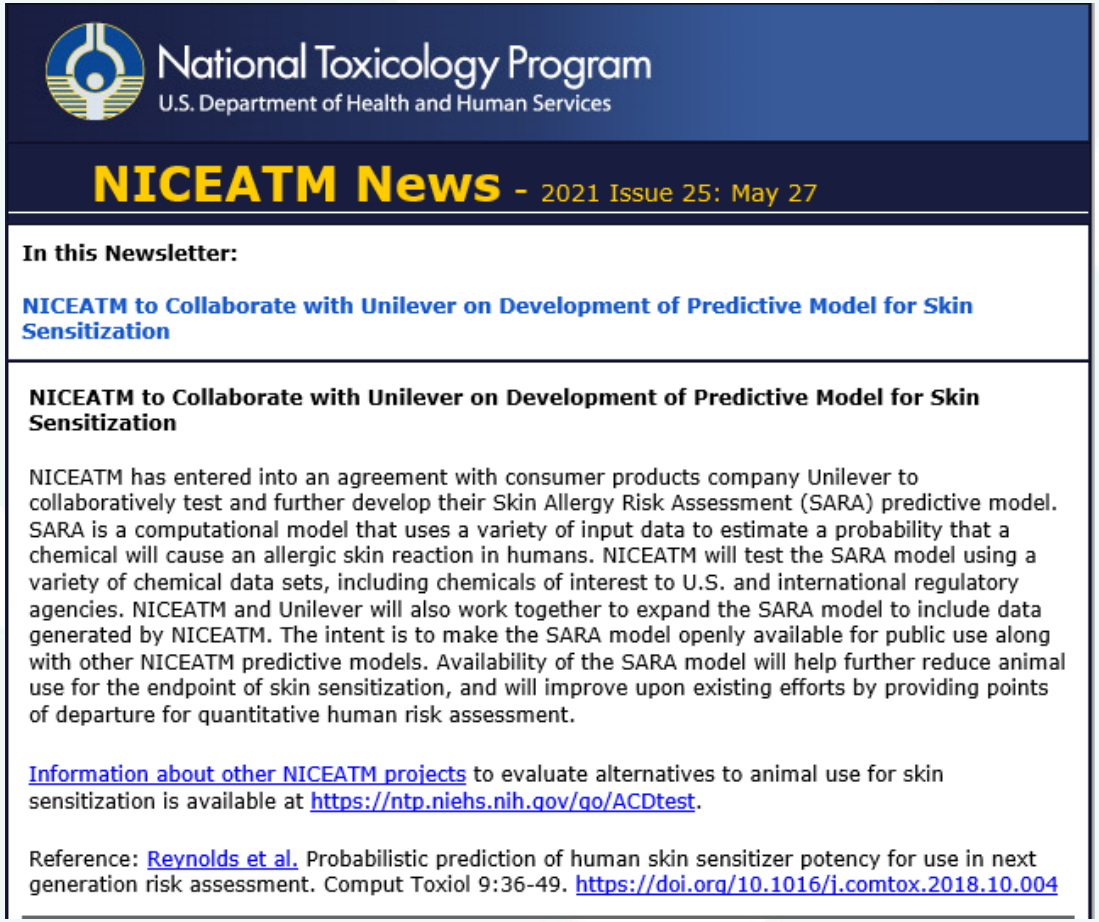



- The generated DPRA, KeratinoSens™, hCLAT and USens™ data were used as inputs into the SARA Model to define a human relevant PoD ($ED_{01}$ i.e the 1% sensitising dose for a HRIPT population).

- For coumarin, the expected SARA Model derived $ED_{01}$ is 11,000µgcm$^{-2}$, whilst for 7-OH coumarin the expected $ED_{01}$ is 110,000µgcm$^{-2}$ i.e. 7-OH coumarin is estimated to be 10-fold less potent than coumarin).

- Therefore, a risk assessment based on coumarin potency data only would be conservative.

# NICEATM-Unilever CRADA



National Toxicology Program
U.S. Department of Health and Human Services

**NICEATM News** - 2021 Issue 25: May 27

**In this Newsletter:**

**NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization**

**NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization**

NICEATM has entered into an agreement with consumer products company Unilever to collaboratively test and further develop their Skin Allergy Risk Assessment (SARA) predictive model. SARA is a computational model that uses a variety of input data to estimate a probability that a chemical will cause an allergic skin reaction in humans. NICEATM will test the SARA model using a variety of chemical data sets, including chemicals of interest to U.S. and international regulatory agencies. NICEATM and Unilever will also work together to expand the SARA model to include data generated by NICEATM. The intent is to make the SARA model openly available for public use along with other NICEATM predictive models. Availability of the SARA model will help further reduce animal use for the endpoint of skin sensitization, and will improve upon existing efforts by providing points of departure for quantitative human risk assessment.

Information about other NICEATM projects to evaluate alternatives to animal use for skin sensitization is available at https://ntp.niehs.nih.gov/go/ACDtest.

Reference: Reynolds et al. Probabilistic prediction of human skin sensitizer potency for use in next generation risk assessment. Comput Toxiol 9:36-49. https://doi.org/10.1016/j.comtox.2018.10.004

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**Unilever Team**
Georgia Reynolds
Nicola Gilmour
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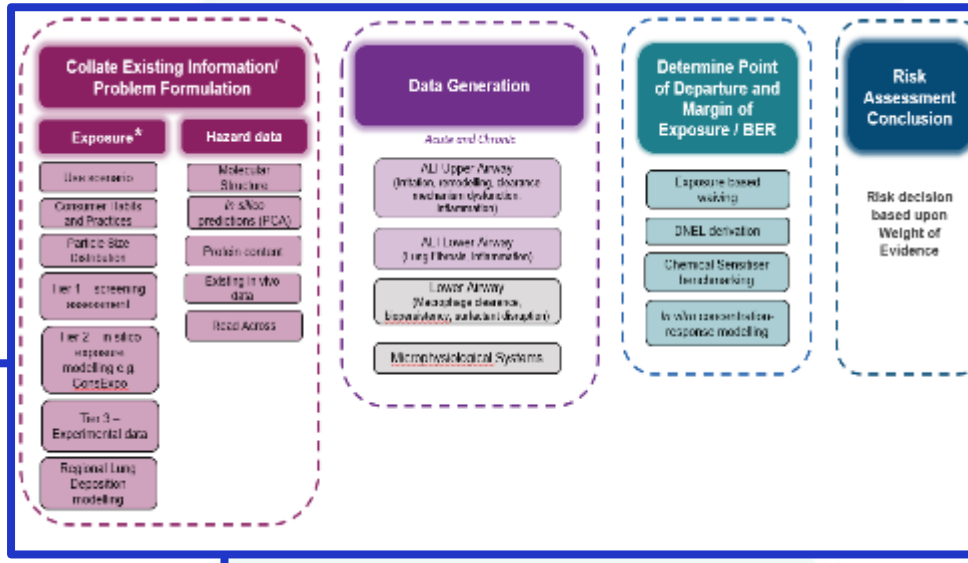
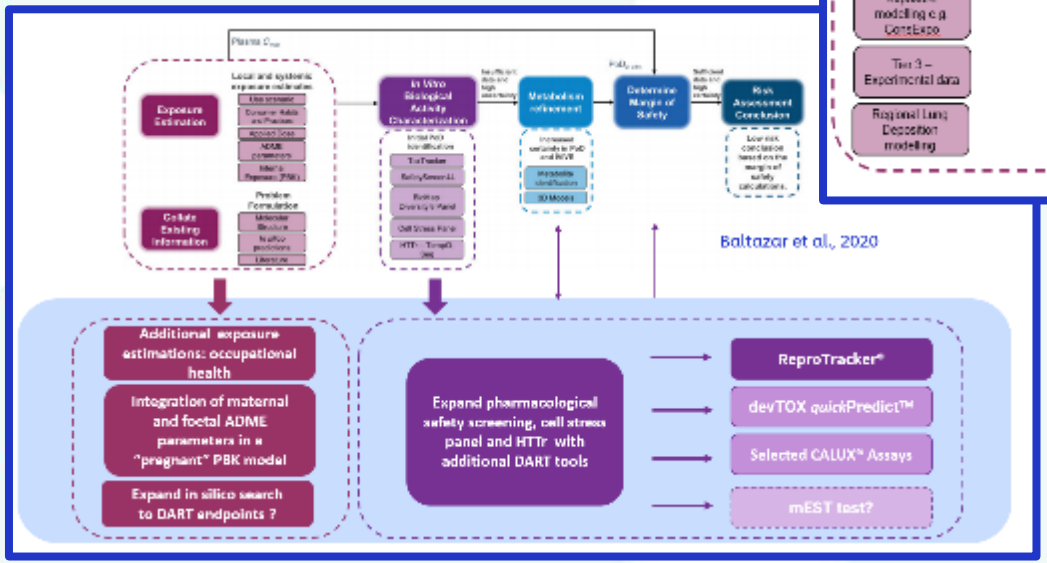
Gavin Maxwell

# Other NGRA approaches for human health

## Inhalation




## DART



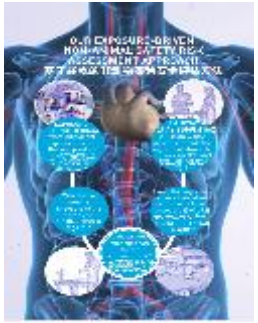

Webinar: https://www.thepsci.eu/wp-content/uploads/2021/06/Presentation-2_Unilever_Inhala Webinar-Day-3.pdf

# 总结 Summary

- 了解消费者暴露的重要性，包括新陈代谢的相关性 Importance of understanding consumer exposure
- 由风险评估问题驱动的非标准，定制数据生成 Non-standard, bespoke data generation driven by the risk assessment question
- 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Many non-animal approaches available: TTC, (Q)SAR/RA, HoSU and NGRA
- 确保非标准化（非技术指南）数据的质量及可靠性。 计算机模拟方法和定制的体外解决方案Ensuring quality, robustness of non-standard (non-TG) work. *In silico* modelling approaches and bespoke *in vitro* solutions
- 定义毒理拐点（POD）和分辨不良反应vs.适应性反应的重要性 Importance of defining points-of-departure and understanding adverse vs. adaptive responses
- 了解风险评估中的不确定因素，以便做出明智的决策Understanding uncertainty in risk assessments to allow informed decision-making
- 未来更多的案例研究和科学技术进步将攻克不足之处Shortcomings will be addressed by current and future research and more case studies


53

# 全球产品安全合作 GLOBAL PRODUCT SAFETY COLLABORATION



SEAC SAFETY & ENVIRONMENTAL ASSURANCE CENTRE

Scientific Excellence And Collaboration

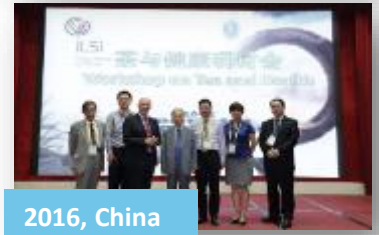
联合利华安全及环境保障中心 - 英国

Unilever CPSC Centre

中国消费者产品安全合作中心 - 上海

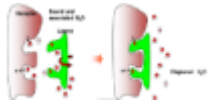
# 在中国的安全科学合作
# Scientific activities in china

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


Working with CAS
与中国科学院的合作

中国科学院
CHINESE ACADEMY OF SCIENCES
中国科学院生态环境研究中心

Molecular Simulation Investigation
on Molecular Initiating Events

Working with AMMS
与军事医学科学院的合作

Academy of Military
Medical Sciences


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

# 全球合作与文章发表 GLOBAL COLLABORATIONS AND PUBLICATION



19 Aug 2021


epaa The European Partnership for Alternative Approaches to Animal Testing

RISK HUNT3R

NICEATM ICCVAM Advancing Public Health and Animal Welfare

SEAC对外演讲和发表的科学文章的详细信息
Details of SEAC's presentations and publications on www.tt21c.org

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**Thank you!**
谢谢!


Unilever