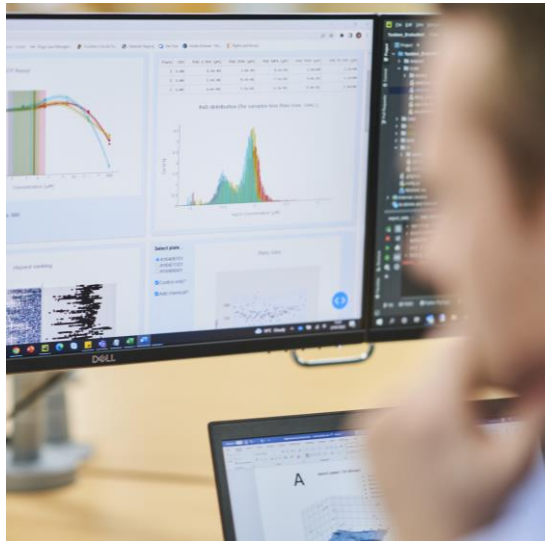
Progress with NAMs in Next Generation Risk Assessment

新技术方法在下一代风险评估当中的进展

Carl Westmoreland



One of the world's largest consumer goods companies with a portfolio of leading purposeful brands, an unrivalled presence in future growth markets, and a determinedly commercial focus as a sustainable business.

全球最大的消费品公司之一，拥有一系列领先的具有行善致美使命的品牌，在未来增长市场中拥有无与伦比的影响力，并坚定地将可持续性最为商业重点放在业务中。

A large global business 大型全球企业

2022 turnover 年营业额

€60.1 billion

9.0%
underlying sales growth in 2022
基本销售额增长

Available in over
销售在
190
Countries 国家

59%
of turnover from emerging markets
新兴市场营业额

3.4bn
people use our products every day
每天使用我们的产品人数

Second
largest advertiser globally
第二
全球最大的广告商

We make many of the world's favourite brands 生产许多世界上最受欢迎的品牌

Over 超过

400

Brands 品牌

14

brands with turnover over €1bn 品牌销售超过十亿欧元

13 of the top **50**

consumer goods brands

13品牌在前50名内

Unilever's Safety & Environmental Assurance Centre (SEAC)
联合利华安全与环境保障中心（SEAC）

SEAC is Unilever's global centre of excellence in Safety & Sustainability Sciences.

Diverse, multi-disciplinary team of ~150 scientists based at Colworth, UK; ~70 miles north of London

Highly collaborative, working with over 70 academic, industry, government & NGO partners worldwide

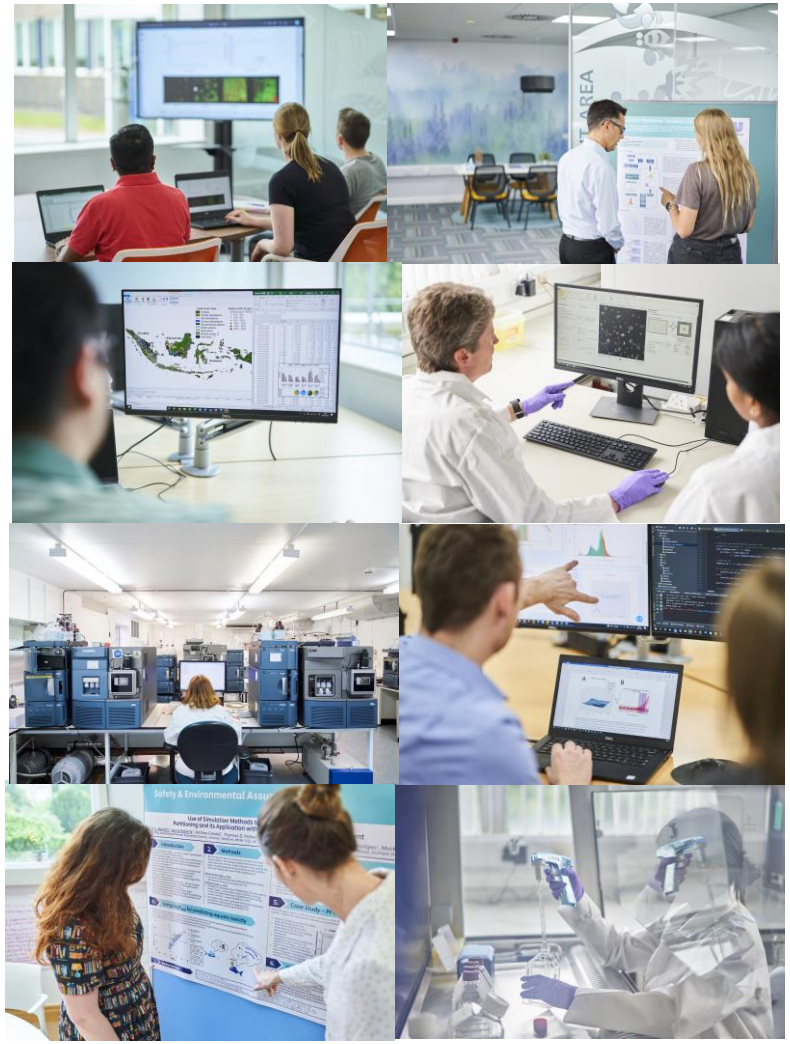
SEAC 是联合利华全球安全与可持续发展科学卓越中心

多元化、多学科团队，由约 150 名科学家组成；
位于英国伦敦以北，约 70 英里科尔沃斯

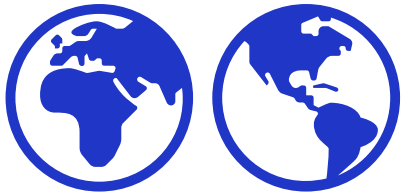
高度协作，
与全球 70 多个学术、行业、政府和非政府组织合作伙伴合作

Unilever

SEAC's purpose is to protect people & the environment
SEAC 的宗旨是保护人类和环境



SEAC is a diverse, multi-disciplinary team of ~150 scientists
SEAC 是一个由约 150 名科学家组成的多元化、多学科团队



20+ Nationalities 国籍
15+ Languages 语言

- Cell Biology 细胞生物学
- Chemistry 化学
- Computational Modelling 计算建模
- Environmental Safety 环境安全
- Environmental Sustainability 环境可持续性
- Exposure Science 暴露科学
- Informatics & Data Science 信息学与数据科学
- Mathematics 数学
- Microbiology 微生物学
- Molecular Biology 分子生物学
- Process Safety 工艺安全
- Statistics 统计学
- Toxicology 毒理学

Unilever

SEAC's purpose is to protect people & the environment
SEAC 的宗旨是保护人类和环境

Around the world, 3.4 billion people use a Unilever product every day. **We want our consumers to be confident that our products are safe**.

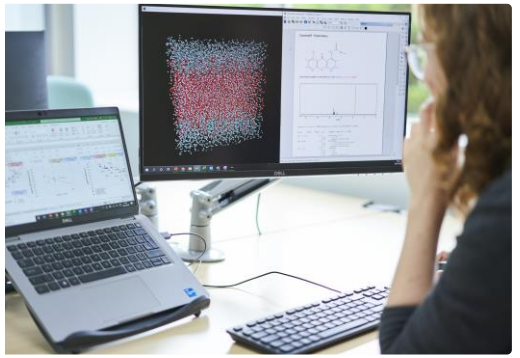
In collaboration with our partners, SEAC scientists help ensure **Unilever's innovations are safe & sustainable without animal testing**.

We engage with all stakeholders to build shared understanding and promote trust in **our scientific evidence-based approach to decision-making**.

全球有 34 亿人每天使用联合利华的产品。我们希望消费者相信我们的产品是安全的。

SEAC 科学家与我们的合作伙伴合作，帮助确保联合利华的创新在无需动物测试的情况下安全且可持续。

我们与所有利益相关者合作，建立共识，并增进基于科学证据的决策方法的信任。



https://seac.unilever.com/our-science/safety-without-animal-testing/

All Unilever products must be safe for humans and the environment

联合利华确保所有产品对人类和环境是安全的



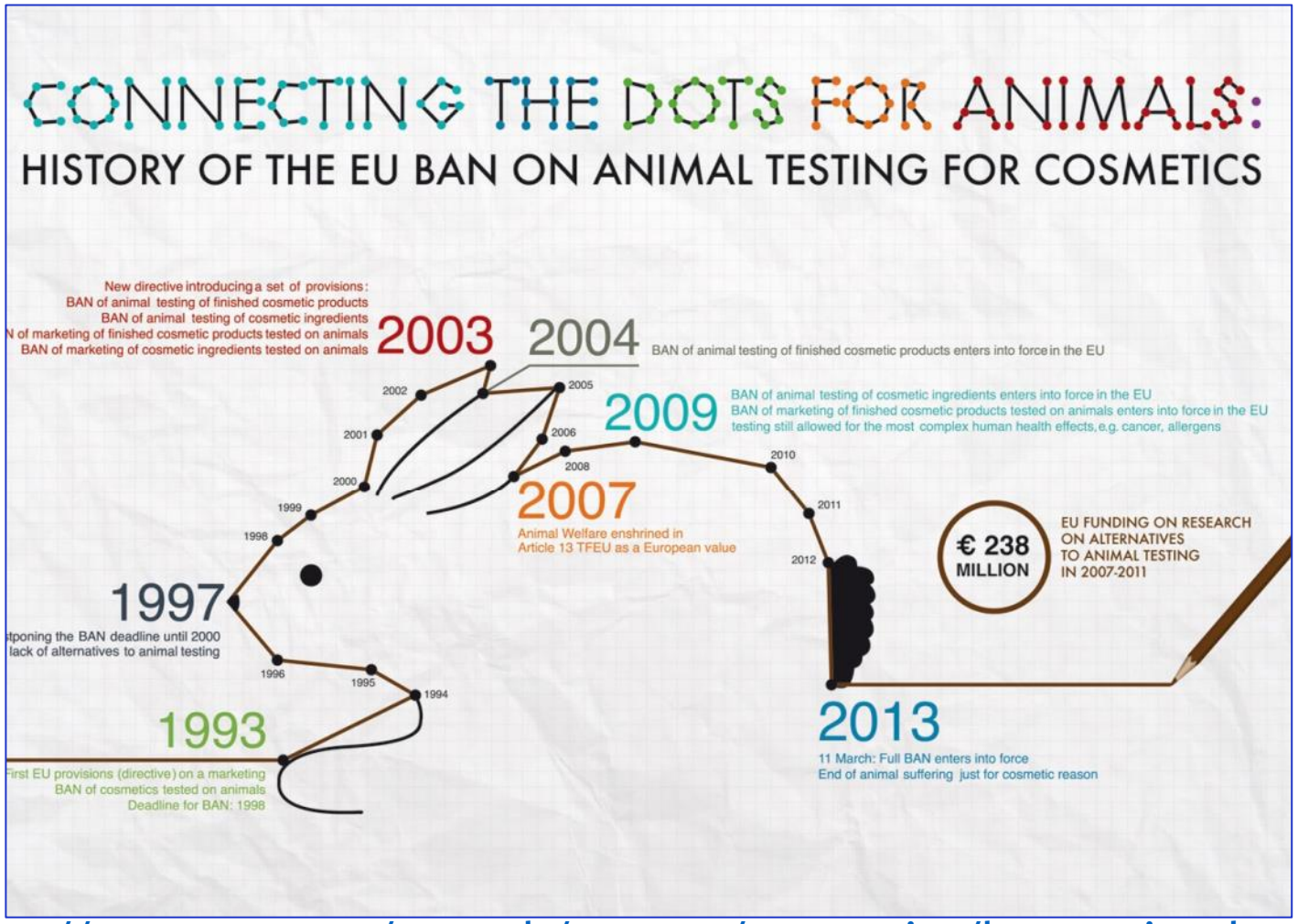



Unilever

The history of bans on animal testing for cosmetic products and ingredients in the EU
欧盟禁止对化妆品和成分进行动物测试的历史

>10 years of assuring safety without animal testing

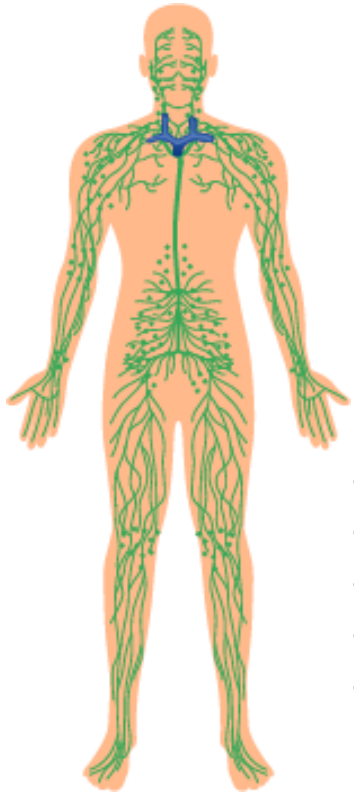
>10 年无需动物测试即可确保安全



Source: https://ec.europa.eu/growth/sectors/cosmetics/ban-animal-testing_en

Assuring consumer safety of cosmetic ingredients is exposure-led
确保化妆品成分的消费者安全以暴露为引导

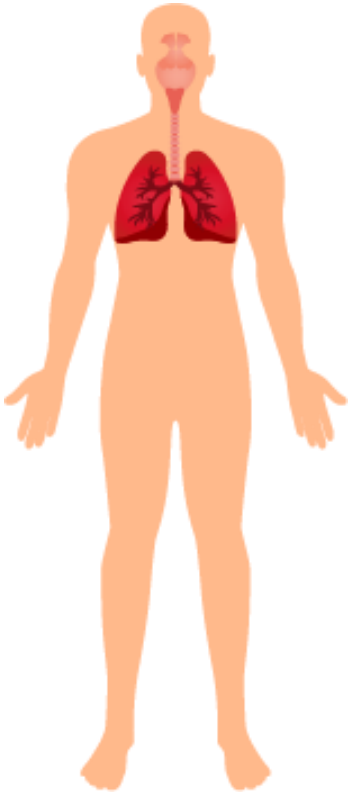
Skin经皮



- Skin creams
- Deodorants
- Soap/cleansers
- Shampoo/ conditioner
- Shower gel

- 护肤霜
- 除臭剂
- 肥皂/清洁剂
- 洗发水/护发素
- 沐浴露

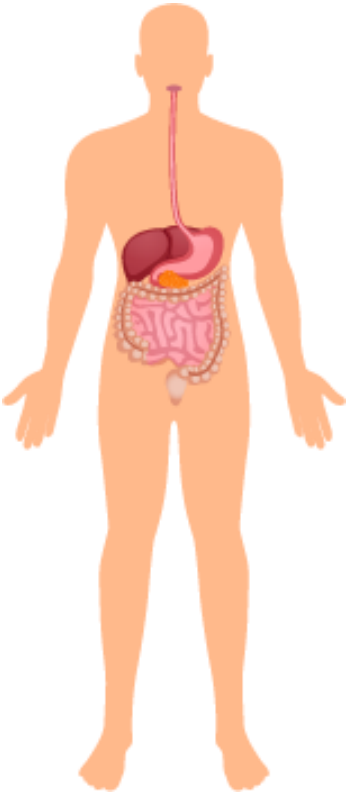
Inhalation* 吸入



- Aerosols
- Pump sprays

- 气溶胶
- 泵喷雾剂

Oral 经口



- Toothpaste
- Lipsticks

- 牙膏
- 口红

Images from: AFSA training module 'Consumer Exposure', 2022

* Generally, depends on delivery system rather than product type.

* 通常，取决于输送系统而不是产品类型

Assuring consumer safety of cosmetic ingredients is exposure-led 确保化妆品成分的消费者安全以暴露为引导

Product type	Estimated daily amount applied q_x (g/d)	Relative daily amount applied[1] q_x /bw (mg/kg bw/d)	Retention factor[2] f_{ret}	Calculated daily exposure $E_{product}$ (g/d)	Calculated relative daily exposure[1] $E_{product}$ /bw (mg/kg bw/d)
Bathing, showering					
Shower gel	18.67	279.20	0.01	**0.19**	**2.79**
Hair care					
Shampoo	10.46	150.49	0.01	**0.11**	**1.51**
Hair styling products	4.00	57.40	0.10	**0.40**	**5.74**
Skin care					
Body lotion	7.82	123.20	1.00	**7.82**	**123.20**
Face cream	1.54	24.14	1.00	**1.54**	**24.14**
Hand cream	2.16	32.70	1.00	**2.16**	**32.70**

SCCS Notes of Guidance (2023) sccs_o_273.pdf (europa.eu)

Data on consumer habits and practices
有关消费者习惯和实际使用的数据

Food and Chemical Toxicology 50 (2012) 2206–2215

Contents lists available at SciVerse ScienceDirect

Food and Chemical Toxicology

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

Skin exposure to deodorants/antiperspirants in aerosol form

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Aerosol cloud
Spray jet

ABSTRACT

Many cosmetic products are available in spray form. Even though the principal targets of these products are the skin and hair, spraying leads to the partitioning of the product between the target and the surrounding air. In the previous COLIPA study (Hall et al., 2007) the daily use of deodorant/antiperspirant (Deo/AP) in spray form was quantified in terms of the amount of product dispensed from the spray can, without specifically quantifying the product fraction reaching the skin during use. Results of the present study provide this additional information, necessary for a reliable safety assessment of sprayed Deo/AP products. In a novel experimental approach the information obtained from real-life movement analysis (automated motion imaging) of volunteers using their own products was integrated with the aerosol cloud sampling data obtained from the same products, leading to the computation of the product deposited on the skin. The 90th percentile values, expressed as percent deposition relative to the can weight loss after spraying, are 23.5% and 11.4% for ethanol-based and non-ethanol-based products, respectively. Additionally, the study has generated data on the skin area covered by the products, spray duration time, spray angle and spray distance from the skin.

1. Introduction

The European cosmetics industry under the organisation of COLIPA (The European Cosmetics Association, currently Cosmetics Europe, The Personal Care Association, www.cosmeticseurope.eu) has published the outcome of a project aimed at updating information on the consumer exposure to cosmetic products in the EU (Hall et al., 2007, 2011). The first part of this project, in which exposure to deodorants/antiperspirants (Deo/AP) in aerosol was studied, (Hall et al., 2007; McNamara et al., 2007) produced the value of 6.1 g/day (90th percentile of can weight-loss). As the output of that project was based on the probabilistic calculation of amounts dispensed from the can during product use, there was a need to refine the data in order to provide the safety assessor with specifically dermal exposure values under normal conditions of use. Deo/AP aerosol products on the European market may be broadly divided into two types: those where ethanol is the principal ingredient (the first ingredient listed on the product label after the propellant) and "others", also defined here as non-ethanol based. These "other" products often produce a "dry" spray. As these differences in formulations may impact their use by the consumer and subsequently the dermal exposure, it was decided to separate the products in the study into two groups, referred to as ethanol-based and non-ethanol-based. As the habitual use of products is an essential requirement for obtaining reliable exposure data, the study volunteers used their own spray products in an environment resembling the home environment. All product applications were recorded on video and computer in order to capture and quantify relevant parameters of the different spraying habits of the volunteers. The study proceeded in four phases, described in detail in the following sections:

1. Movement analysis.
2. 3D (three dimensional) aerosol cloud modelling.
3. Verification of the proposed modelling approach.
4. Integration of data (*in silico* modelling).

Results are presented as statistical distributions (percentiles) to better reflect the inter-individual variability in the daily habit of product use.

2. Materials and methods

Sixty-nine volunteers, all habitual users of the products in the study, were recruited from the general population in the Cologne region of Germany. Seven volunteers enrolled but failed to attend and 62 completed the study. This had no

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Assuring consumer safety of cosmetic ingredients is exposure-led 确保化妆品成分的消费者安全以暴露为引导

Generate specific data on exposure 生成有关暴露的具体数据

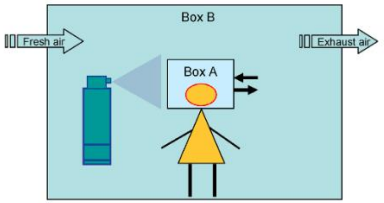
Photo: Ruth Pendlington

OECD TG 428

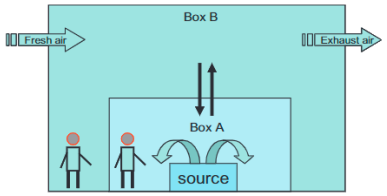
Exposure Modelling

暴露模型

Near-field
Products sprayed directly at the body



Far-field
Spray directed away from the body



Steiling et al (2014) *Toxicology Letters*, **227**, 41-49

Simulated consumer exposure methods

消费者模拟暴露方法

Skin Penetration 皮肤渗透

Inhalation Exposure 吸入暴露

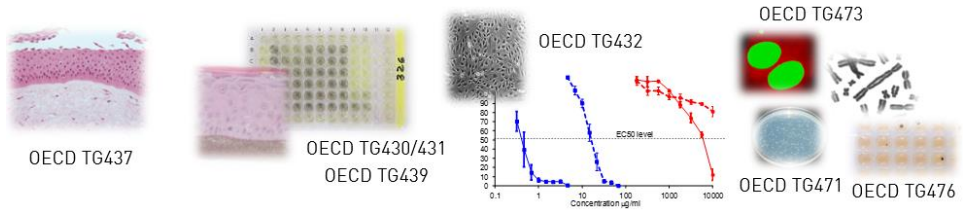
Assuring safety without animal testing: Maximising use of existing information and non-animal approaches
无需动物测试即可确保安全：最大限度地利用现有信息和非动物方法

- Use all available safety data on the ingredient 使用该成分的所有可用安全数据
  - Clinical, epidemiological, animal (if dates permit), *in vitro* etc （临床、流行病学、动物（如果日期允许）、体外等
- Exposure-based waiving approaches (e.g. Threshold of Toxicological Concern, TTC)
  基于暴露的豁免方法 （例如 毒理学关注阈值，TTC）

- *in silico* predictions 计算机预测

(Neely et al (2011) Tox Int ,18, (Suppl 1):S20-9)

- History of safe use 安全使用史



- Read across 交叉参照
- Use of existing OECD *in vitro* approaches
  使用现有的OECD体外方法
- Next Generation Risk Assessment (NGRA) 下一代风险评估（NGRA）

Unilever

What is next generation risk assessment (NGRA)?
什么是下一代风险评估？

"An exposure-led, hypothesis driven risk assessment approach that incorporates one or more NAMs to ensure that chemical exposures do not cause harm to consumers"

"一种以暴露为引导、以假设为驱动的风险评估方法，包含一种或多种新技术方法，以确保化学品暴露不会对消费者造成伤害"

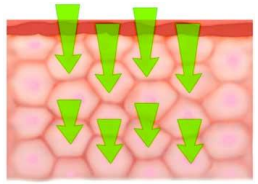
Dent *et al* ., (2018) *Comp Tox* 7:20-26

Unilever

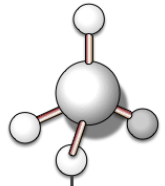
What is next generation risk assessment (NGRA)?
什么是下一代风险评估(NGRA)?

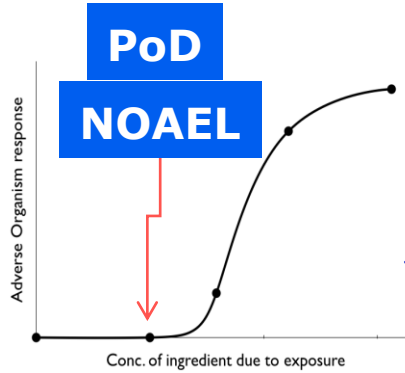
Unilever

Why is NGRA important? The Systemic Challenge
为什么 NGRA 很重要？系统毒性挑战

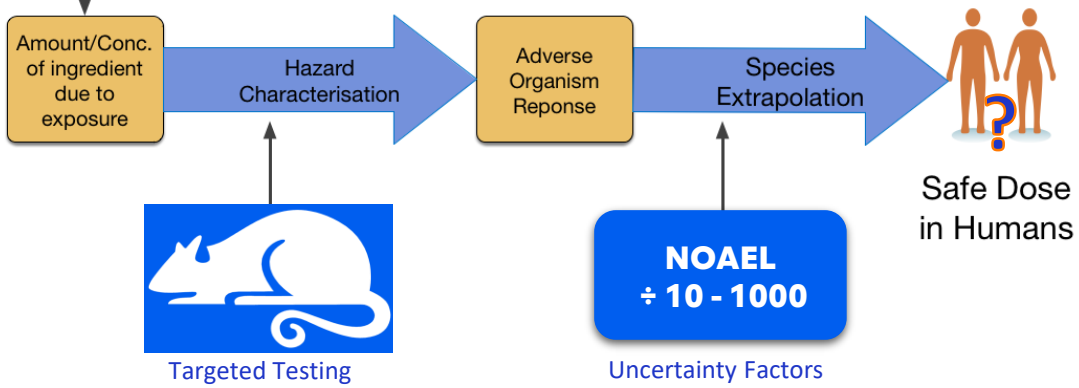


Is it safe?
安全吗？





e.g. 90 Day Repeat Dose Study
例如：90 天重复剂量实验



A new non-animal paradigm is needed...需要一个新的非动物范例

...but replacement of animal test data is not the answer
但用动物试验数据来取代并不是解决问题的办法

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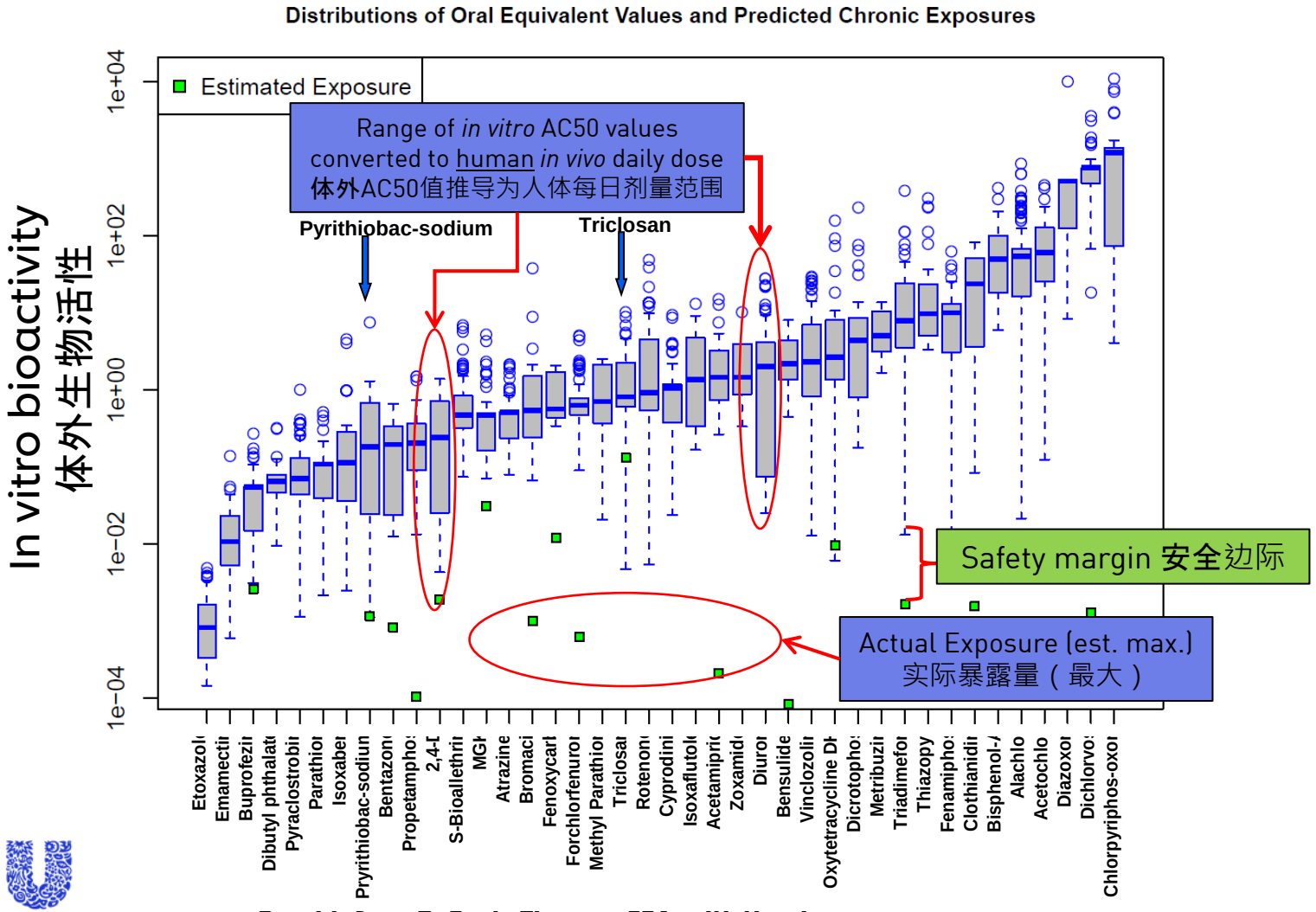
Paradigm shift for systemic safety - Protection not Prediction
系统毒性安全的范式转变—保护而非预测



Graphic from Dr Rusty Thomas, EPA, with thanks
图片由美国环保局 **Rusty Thomas** 博士提供，并致谢

Rotroff, *et al.* Tox.Sci 2010

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

支持此类 NGRA 的假设是，如果在与消费者相关的浓度下没有观察到生物活性，则不会对健康产生不利影响。

Tiered, exposure-led NGRA means we can make robust safety decisions
分层、以暴露为导向的 NGRA 意味着我们可以做出可靠的安全决策

- Increasing recognition that *in vitro* bioactivity can inform decision making (e.g. Health Canada, EU SCCS)
  越来越认识到体外生物活性可以为决策提供信息（例如加拿大卫生部、欧盟 SCCS）


Computational Toxicology 7 (2018) 20–26

Contents lists available at ScienceDirect

Computational Toxicology

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

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

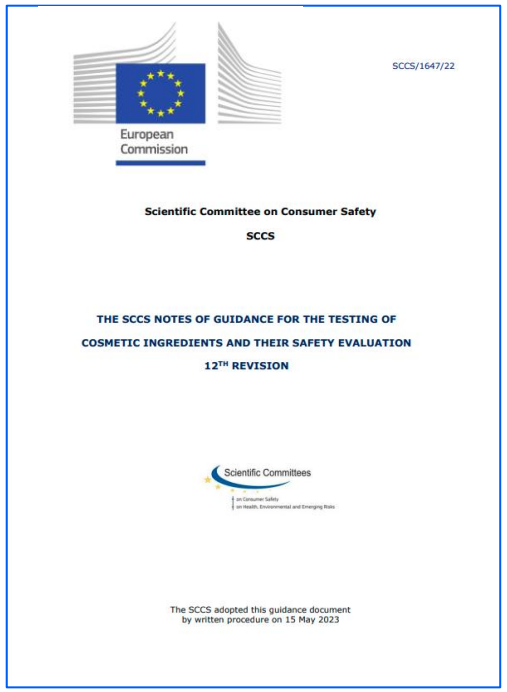
Matthew Dent[a,*], Renata Teixeira Amaral[b], Pedro Amores Da Silva[b], Jay Ansell[c], Fanny Boisleve[d], Masato Hatao[e], Akihiko Hirose[f], Yutaka Kasai[g], Petra Kern[h], Reinhard Kreiling[i], Stanley Milstein[j], Beta Montemayor[k], Julcemara Oliveira[l], Andrea Richarz[m], Rob Taalman[n], Eric Vaillancourt[o],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

ICCR International Cooperation on Cosmetics Regulation

ABSTRACT

Consumer safety is a prerequisite for any cosmetic product. Worldwide, there is an ever-increasing desire to bring safe products to market without animal testing, which requires a new approach to consumer safety. 'Next Generation Risk Assessment' (NGRA), defined as an exposure-led, hypothesis-driven risk assessment approach that integrates *in silico*, *in chemico* and *in vitro* approaches, provides such an opportunity. The customized nature of each NGRA means that the development of a prescriptive list of tests to assure safety is not possible, or appropriate. The International Cooperation on Cosmetics Regulation (ICCR) therefore tasked a group of scientists from regulatory authorities and the Cosmetic Industry to agree on and outline the principles for incorporating these new approaches into risk assessments for cosmetic ingredients. This ICCR group determined the overall goals of NGRA (to be human-relevant, exposure-led, hypothesis-driven and designed to prevent harm); how an NGRA should be conducted (using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies); and how the assessment should be documented (transparent and explicit about the logic of the approach and sources of uncertainty). Those working on the risk assessment of cosmetics have a unique opportunity to lead progress in the application of novel approaches, and cosmetic risk assessors are encouraged to consider these key principles

International Cooperation on Cosmetics Regulation (2018)
化妆品监管国际合作（2018）


European Commission

SCCS/1647/22

Scientific Committee on Consumer Safety

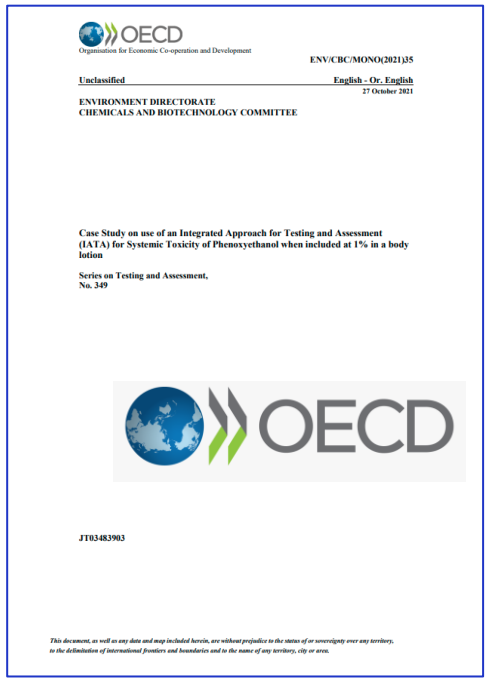
SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION 12TH REVISION

Scientific Committees on Consumer Safety on Health, Environmental and Emerging Risks

The SCCS adopted this guidance document by written procedure on 15 May 2023

European Commission: Scientific Committee on Consumer Safety (2021, 2023)
欧盟委员会：消费者安全科学委员会（2021 年、2023 年）


OECD
Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)35

Unclassified — English - Or. English

27 October 2021

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Case Study on use of an Integrated Approach for Testing and Assessment (IATA) for Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion

Series on Testing and Assessment, No. 349

OECD

JT03483903

This document, as well as any data and map included herein, are without prejudice to the status of or sovereignty over any territory, to the delimitation of international frontiers and boundaries and to the name of any territory, city or area.

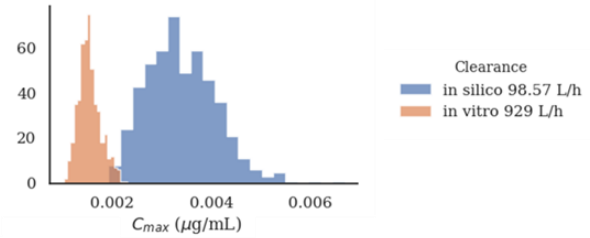
OECD (2021)
经合组织 (2021)

Unilever

Key tools in our NGRA approaches for Systemic Toxicity: Bioactivity
NGRA 系统毒性方法中的关键工具：生物活性

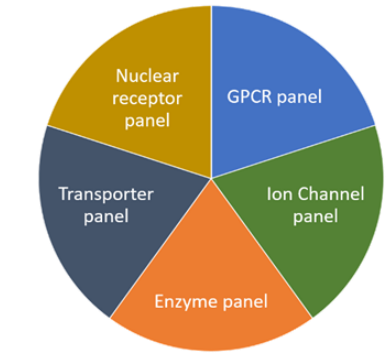
基于生理的动力（**PBK**）模型

PBK Modelling



Toxicology in Vitro (2020), **63**, 104746

In vitro pharmacological profiling



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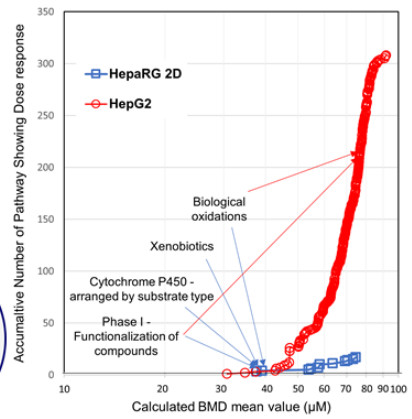
体外药理学分析

高通量转录组学

Transcriptomics

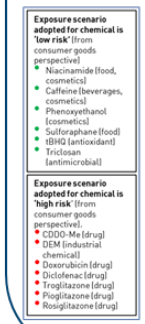
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

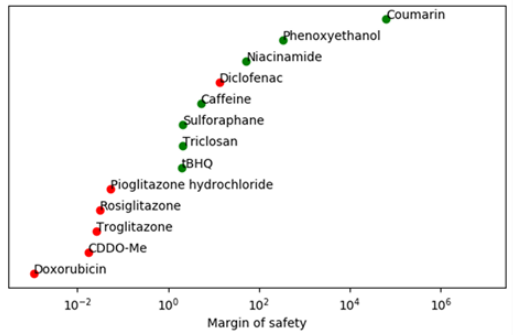
BMDexpress 2



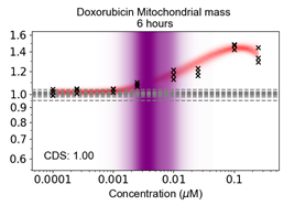
Cellular Stress Pathways

13 chemicals, 36 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways





cyprotex AN EVOTEC COMPANY



Toxicol Sci (2020), **176**, 11-33

细胞应激通路

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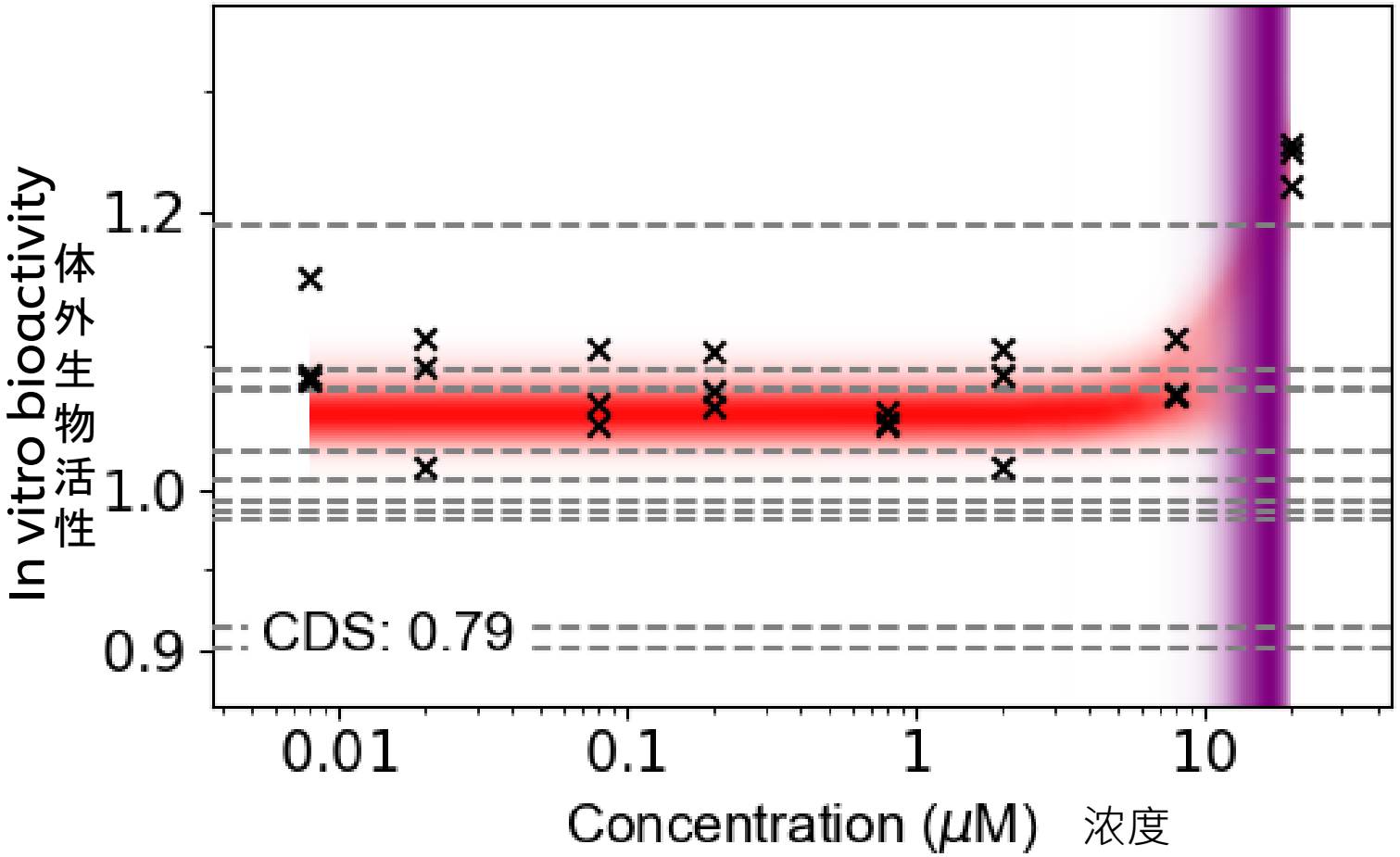
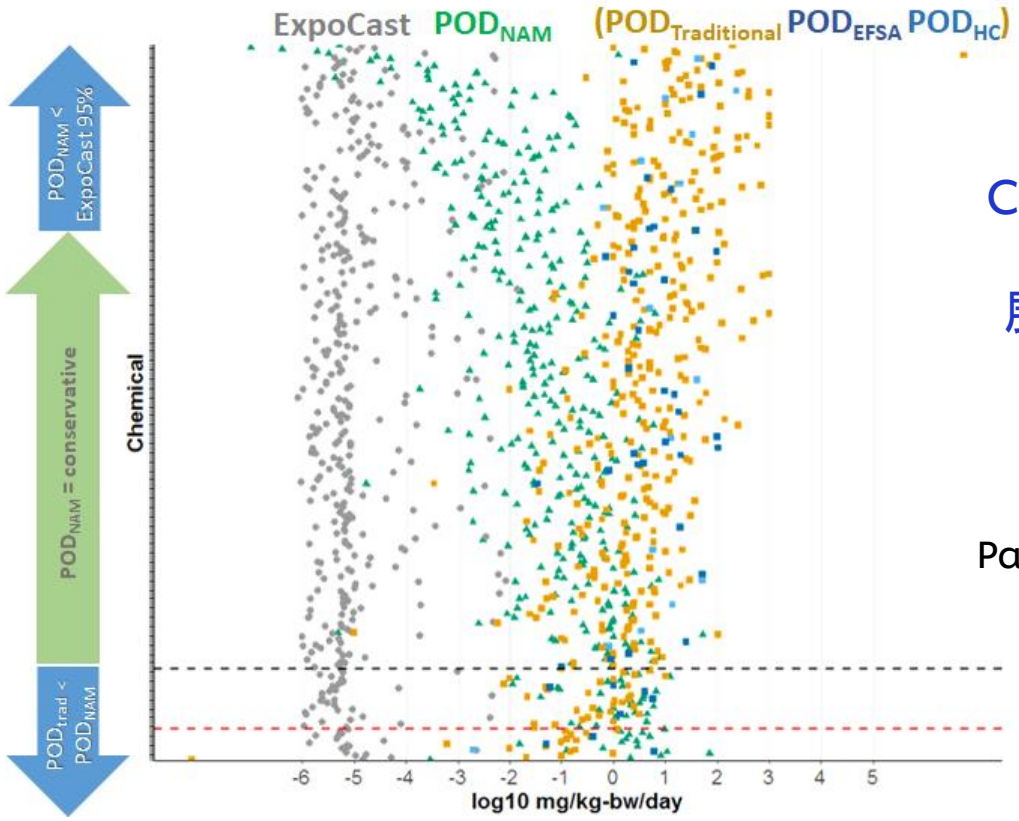
Point of Departure (POD) 生物活性剂量拐点



Points of Departure (PODs) from NAMs can be protective
从新技术方法产生的生物活性拐点起到保护作用。

Human Exposure 人体暴露 | NAMs 新技术方法 | PODs 拐点 Animal 动物



Case Studies Demonstrating Application of Bioactivity as a Protective POD
展示生物活性作为保护性 POD 的应用案例研究

Paul-Friedman et al., 2020. Toxicol. Sci **173**, 202-225

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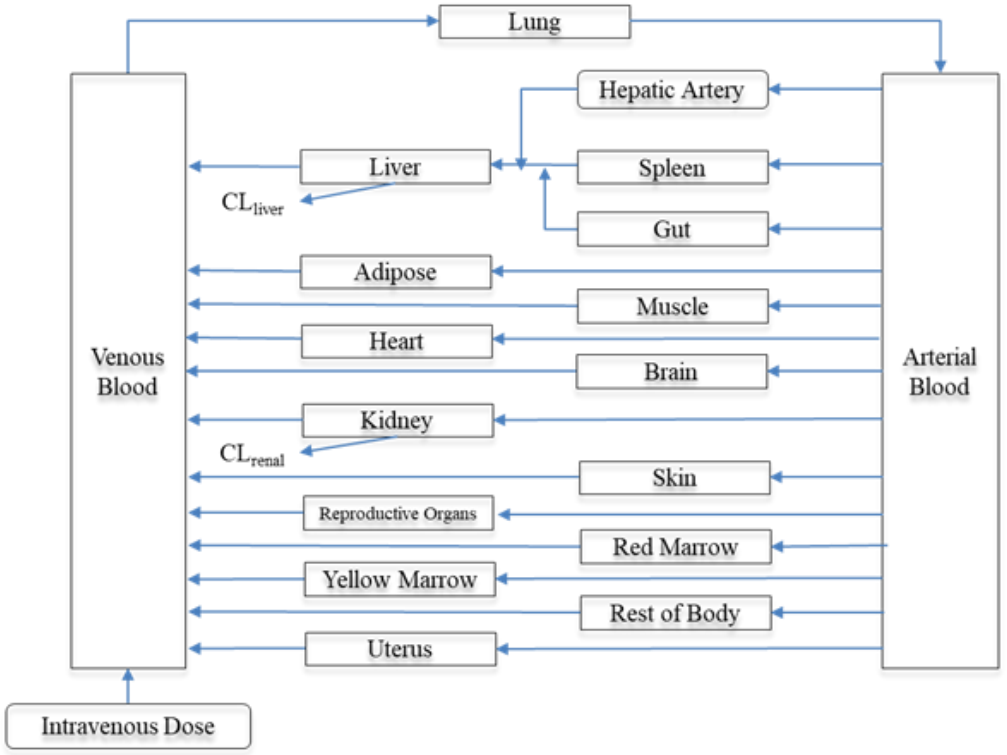
APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

Key tools in our NGRA approaches for Systemic Toxicity: Exposure
我们的 NGRA 系统毒性方法中的关键工具：暴露

Physiologically-based Kinetic Modelling (PBK Modelling)
基于生理的动力模型 （PBK模型）



Input 输入参数

- Physiological parameters (e.g. body weight, blood flow rates, tissue volume)
- Physico-chemical parameters (e.g. LogP, Fup, tissue/plasma partition coefficients)
- Kinetic parameters (e.g. dermal absorption, hepatic metabolism, renal excretion)
- Product use information (e.g. dose, frequency, site area, formulation)

- **生理参数**（**例如体重、血流量**、组织体积）
- **物理化学参数**（**例如 LogP、Fup**、组织**/血**浆分配系数）
- 动力学参数（例如皮肤吸收、肝脏代谢、肾脏排泄）
- 产品使用信息（例如剂量、频率、**作用面**积、配方）

Output 输出参数

- Cmax prediction in tissue of interest or plasma
- Sensitivity analysis can be performed to identify the parameter(s) contributing the most to the result

- **相关**组织或血浆中的 **Cmax** 预测
- **可以**进行敏感性分析来识别对结果影响最大的参数

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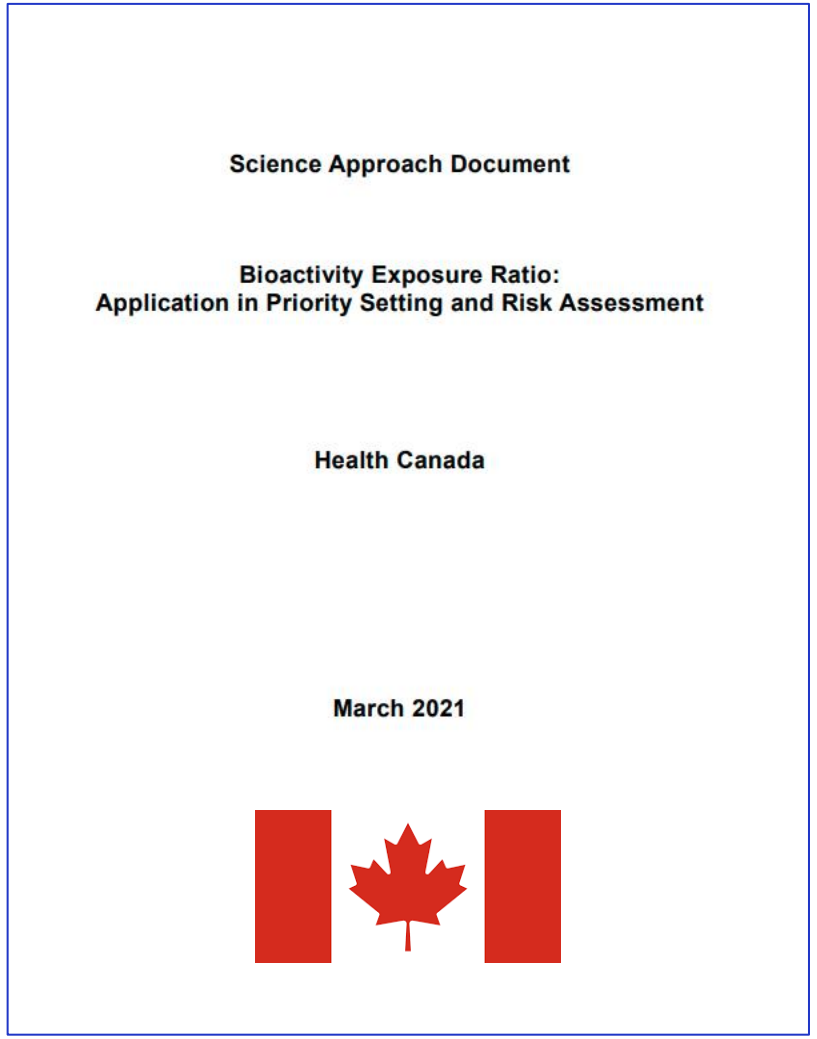
Bioactivity: Exposure Ratio (BER)
生物活性：暴露 比率(BER)

POD from *in vitro* Bioactivity Assays
体外生物活性测定中的 POD

Systemic exposure in humans (from PBK)
人体全身暴露（来自 PBK模型）

'Bioactivity exposure ratios (BERs). BERs are analogous to the traditional margin of exposure used in risk assessment in that chemicals with a lower BER possess a higher potential for risk'
生物活性：暴露 比率 BERs 类似于风险评估中使用的传统暴露边际，BER 较低的化学品具有较高的潜在风险

Kuo *et al* (2022)

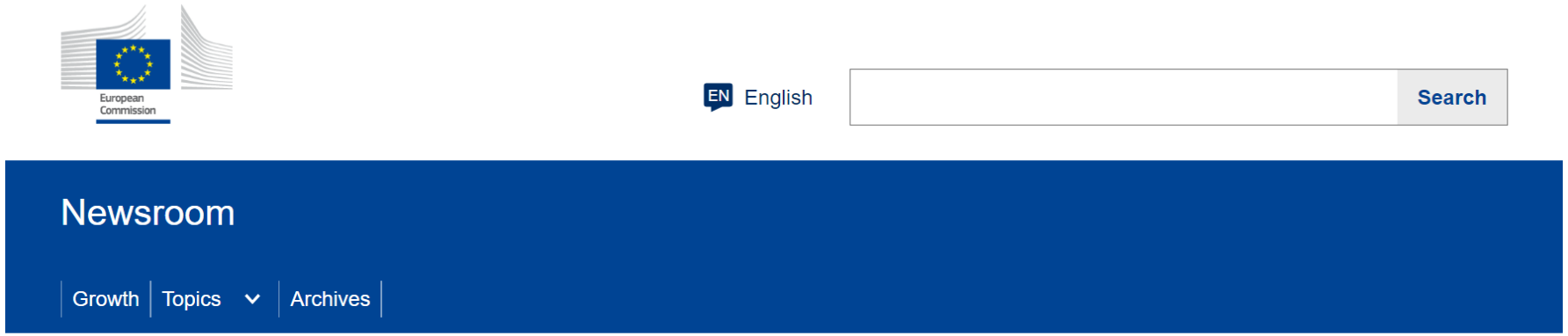


Science approach document - Bioactivity exposure ratio: Application in priority setting and risk assessment - Canada.ca

科学方法文献 - 生物活性暴露比：在优先级设定和风险评估中的应用 - Canada.ca

An example of using NGRA – Benzophenone-4 (BP4)
使用 NGRA 的案例 – 二苯酮-4 (BP4)

Benzophenone-4 (BP4) case study 二苯酮-4 (BP4) 案例分析。



Is a tiered NGRA approach is sufficiently protective and useful to answer a real-life question?

分层 NGRA 方法是否具有足够的保护性且解答现实中的疑问吗？

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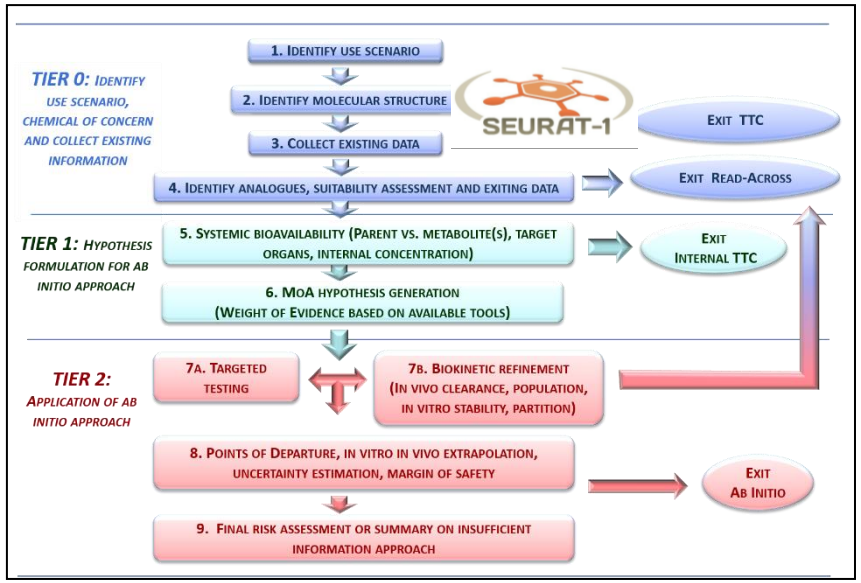
Guiding principles for the *ab initio* NGRA applied to the BP4 case study 适用于 BP4 案例研究的从零开始 NGRA 的指导原则



OXFORD SOT Society of Toxicology
academic.oup.com/toxsci
TOXICOLOGICAL SCIENCES, 176(1), 2020, 236–252
doi: 10.1093/toxsci/kfaa048
Advance Access Publication Date: April 10, 2020
Research article

A Next-Generation Risk Assessment Case Study for Coumarin in Cosmetic Products

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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 Kreiling[i], Stanley Milstein[j], Beta Montemayor[k], Julcemara Oliveira[l], Andrea Richarz[m], Rob Taalman[n], Eric Vaillancourt[o], Rajeshwar Verma[j], Nashira Vieira O'Reilly Cabral Posada[l], Craig Weiss[p], Hajime Kojima[f]

OECD
Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)35

Unclassified English - Or. English
27 October 2021

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Case Study on use of an Integrated Approach for Testing and Assessment (IATA) for Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion

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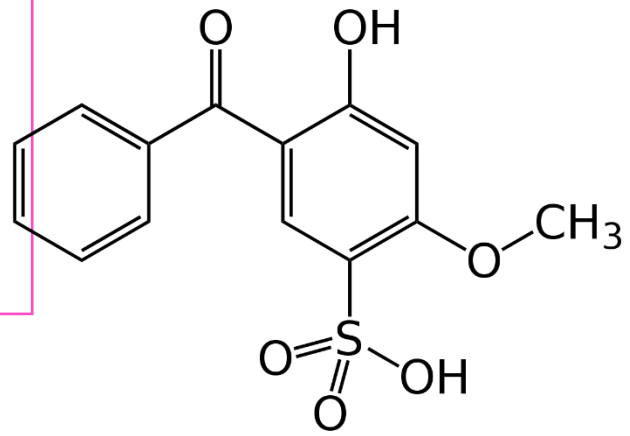
Tiered approach for Exposure estimation
暴露量估计的分层方法

Level 0: Characterise exposure scenario 第0级：描述暴露场景的特征

- 5% in Sunscreen product, 防晒产品含5%,
- 18g/day, two times, 9g/application, 18克/天，两次，9克/次,
- On body and face 17500cm2 (total body area)
  身体和面部17500cm2（身体总面积）



Level 1: PBK model built with in silico parameters only & sensitivity analysis 第1级：仅用计算机模型参数构建 PBK 模型及参数灵敏度分析

- Predicted sensitive parameters 预测敏感参数
  - Fup (Fraction unbound in plasma) Fup 血浆中未结合的部分
  - Liver CL_{int} (intrinsic clearance) 肝脏 CLint（内在清除率）
  - Dermis water partition coefficient 真皮水分配系数
  - Dermis diffusivity 真皮扩散率

Level 2: PBK model built with vitro parameters
第2级：用体外参数构建PBK模型

Moxon et al. 2020. Toxicology in Vitro, Volume 63, 104746.

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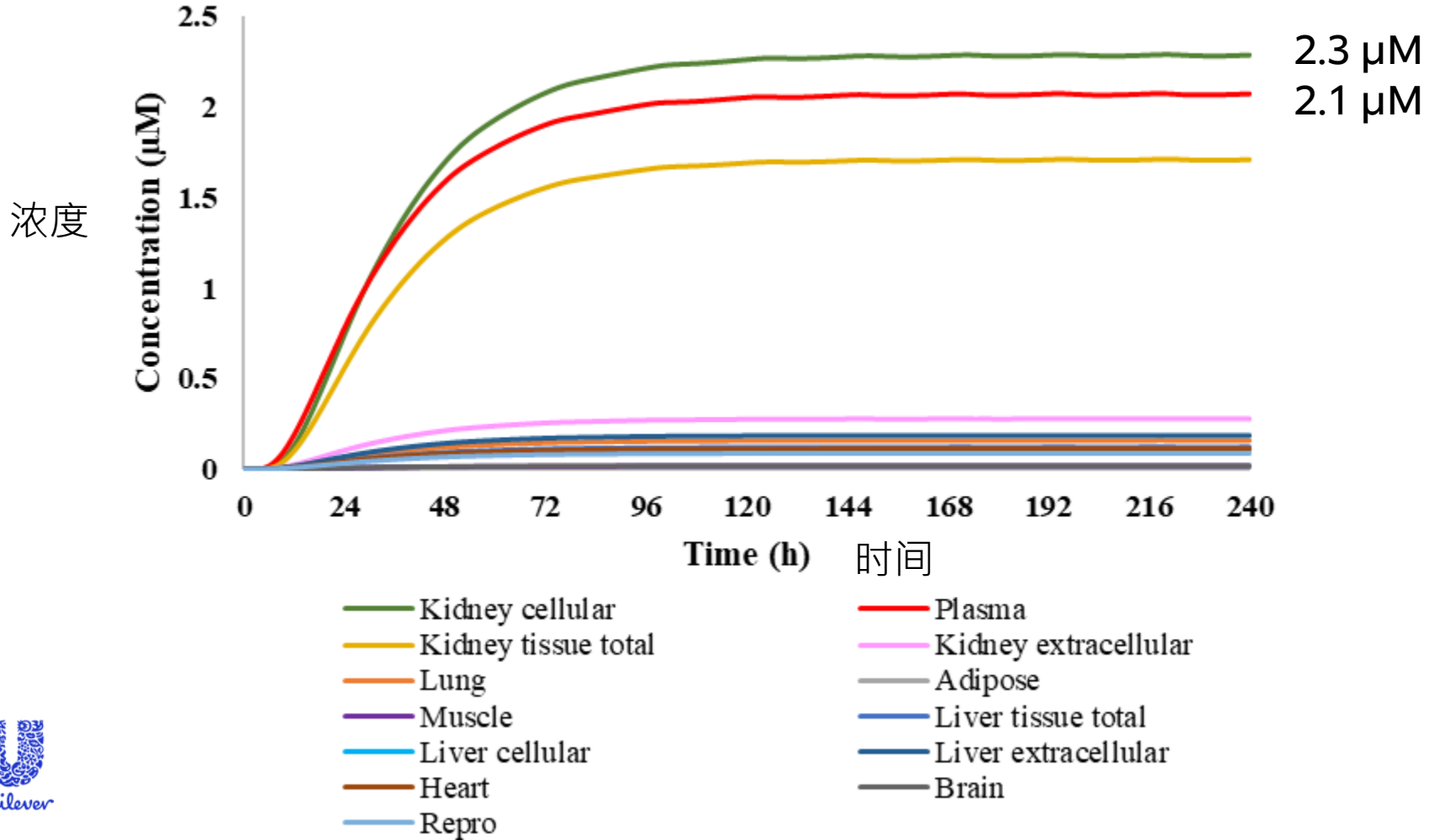
PBK model simulation of C_{max} PBK模型模拟C_{max}

BP4 Systemic Exposure – Repeat BP4 全身暴露 – 重复

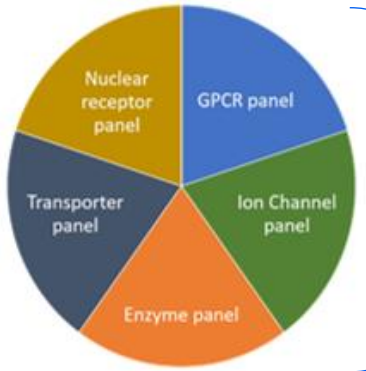


BP-4 concentrations in plasma and tissues after exposure of body lotion 18g/day, (9g twice per day) for a 10 days, with 5% BP4

接触润肤乳 10 天后血浆和组织中 BP-4 浓度（含 5% BP4）

Key bioactivity NAMs 关键的检测生物活性的新技术方法

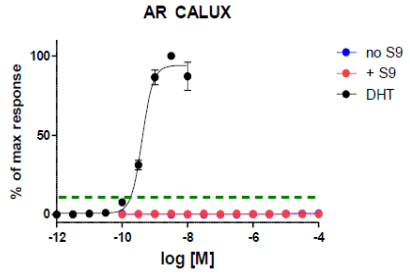
In vitro pharmacological profiling
体外药理学分析



eurofins | Cerep

~83 targets
目标指标

CALUX bioassays and binding assays: TTR-TRß- and hTPO

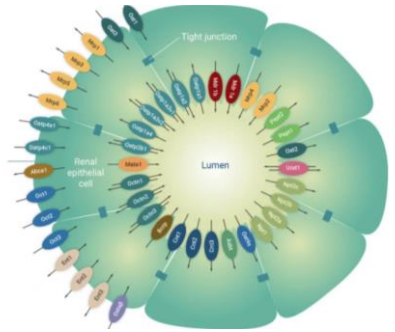


Bowes et al. 2012. Nat Rev Drug Discov 11(12): 909-22
Sonneveld et al. 2005. Toxciol Sci 83(1): 136-48

Renal Toxicity肾毒性

Nephrotoxicity (3 donors, duplicate per donor), 8 concentrations, 24h and 72h timepoints:

- KIM-1
- NGAL
- Clusterin
- TEER (Day 0 and Day 3)
- ATP
- LDH

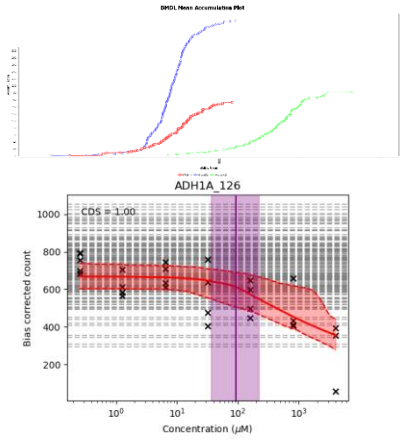


Newcells aProximate™ platform

Piyush Bajaj et al. 2020. Toxicology. 442, 152535

High-Throughput transcriptomics
高通量转录组学

- TempO-seek technology – full gene panel
- 24hr exposure
- 7 concentrations
- 4 cell models: HepG2, MCF7, HepaRG and aProximate cells
- Dose-response analysis using BMDExpress2 and BIFROST model



Reynolds et al. 2020. Comp Tox 16: 100138
Baltazar et al. 2020. Toxicol Sci 176(1): 236–252

Cell stress panel (CSP) 细胞应激测板 (CSP)

- 36 biomarkers covering 10 cell stress pathways
- HepG2
- 24hr exposure
- 8 concentrations
- Dose-response analysis using BIFROST model

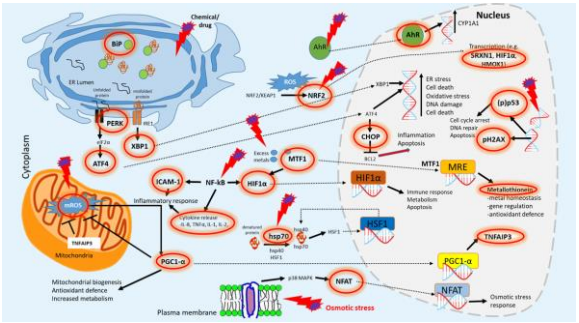


Image kindly provided by Paul Walker (Cyprotex)

Hatherell et al. 2020. Toxicol Sci 176(1): 11-33

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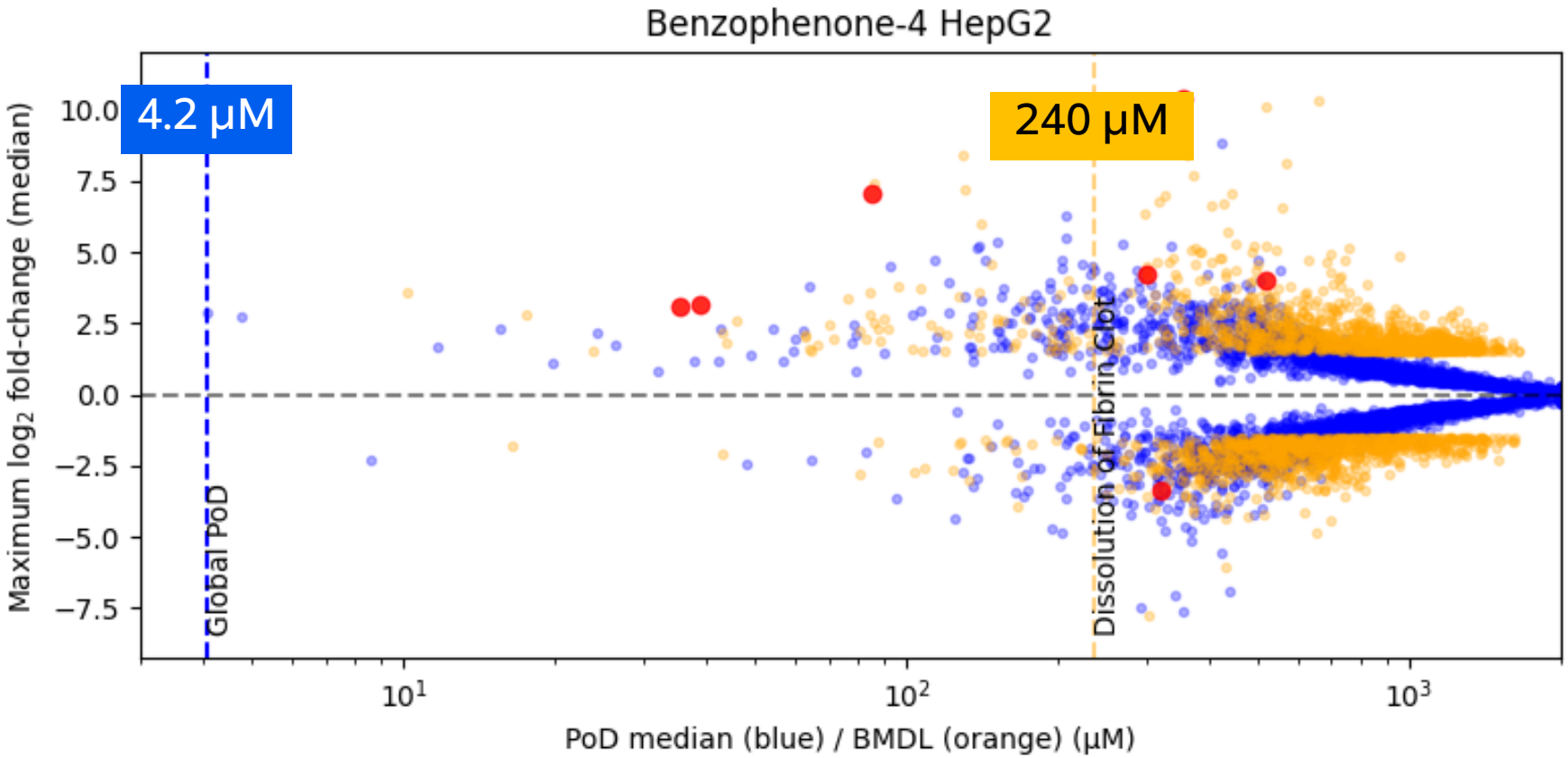
Results from the key NAMs- Deriving Points of Departure (PODs) 关键 NAMs 的结果 - 导出生物活性拐点 (POD)

Very little bioactivity: high throughput transcriptomics in HepG2 cells gave the lowest POD
生物活性非常低：HepG2 细胞中的高通量转录组学给出了最低的 POD



Bioactivity:Exposure Ratios

Gene level = $\frac{4.2}{2.3}$ = 2

Pathway = $\frac{240}{2.3}$ = 114

Acceptable BER? 生物活性：暴露 比率（BER） 可以接纳吗？

Conceptually, with the following assumptions a BER>1 indicates a low risk of adverse effects in consumers following use of the product:

从概念上讲，在以下假设下，BER>1 表明消费者在使用该产品后产生不良影响的风险较低：

a) The in vitro measures of bioactivity provide appropriate biological coverage

生物活性的体外测量提供了适当的生物覆盖

a) There is confidence that the test systems are at least as sensitive to perturbation as human cells *in vivo*

有信心显示测试系统对扰动敏感程度与体内人体细胞敏感度至少一样

a) The exposure estimate is conservative for the exposed population

对于人群暴露量而言，暴露量的估计是保守的

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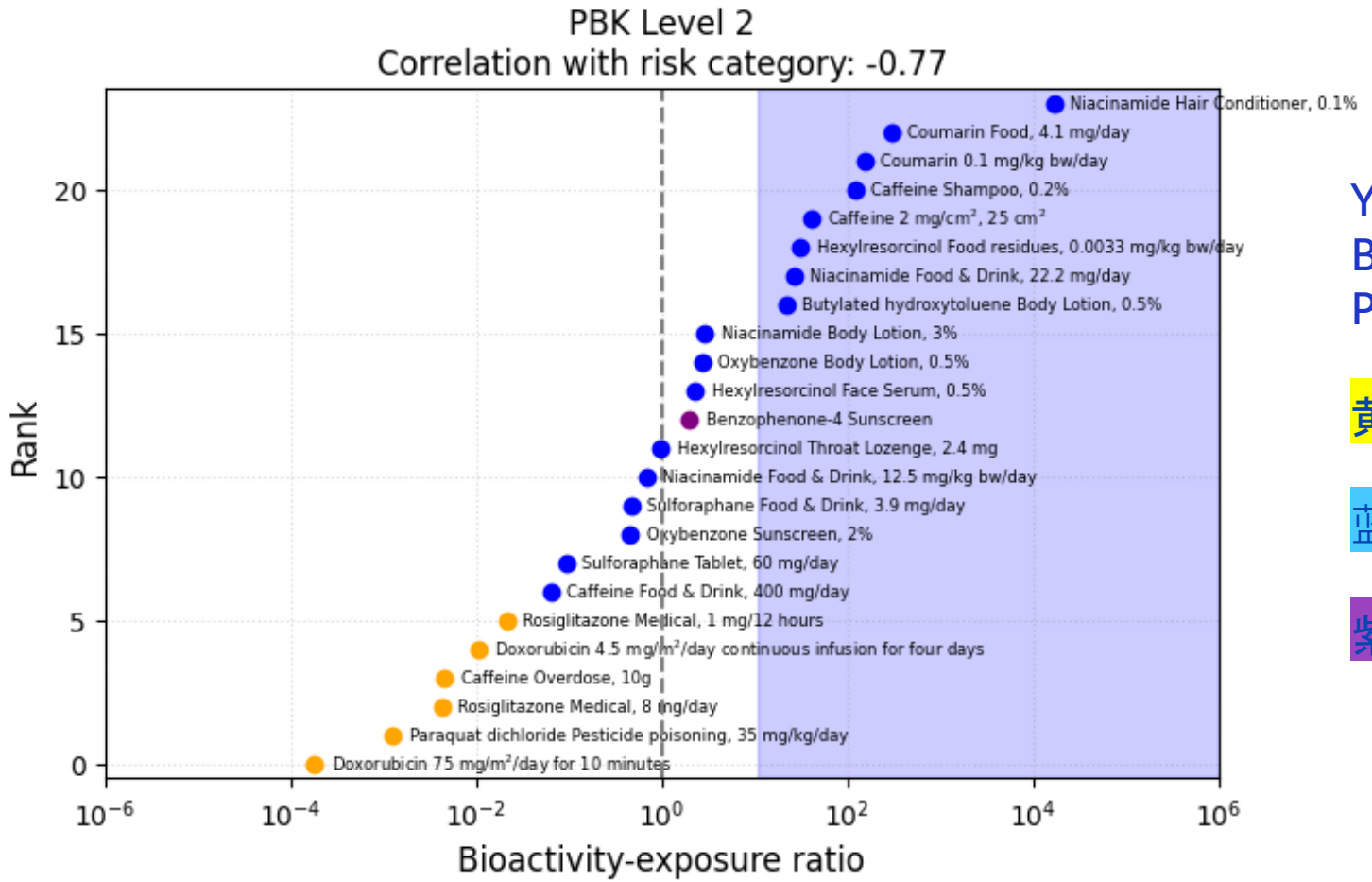
Benchmarking to determine a low-risk BER
通过基准测试来确定低风险 BER



Yellow dots: high risk benchmarks
Blue dots: low risk benchmarks
Purple dot: BP4

黄点：高风险基准

蓝点：低风险基准

紫点：BP4

Middleton et al., (2022) Toxicol Sci, 189, 124-147

BP4 Example: Conclusion BP4 案例结论

- Use of tiered, exposure-led approaches allows safety decisions to be made for systemic effects without animal test data
  使用分层的、暴露为引导的方法可以在没有动物测试数据的情况下针对全身毒性效应做出安全决策

- The ICCR Principles help to formulate the problem and direct the assessment.
  化妆品监管国际合作 原则有助于明确针对问题并指导评估。

- 'Early tier' *in vitro* screening tools show promise for use in a protective rather than predictive capacity.
  "早期层次"体外筛查工具显示出"保护"而非"预测"能力的前景。

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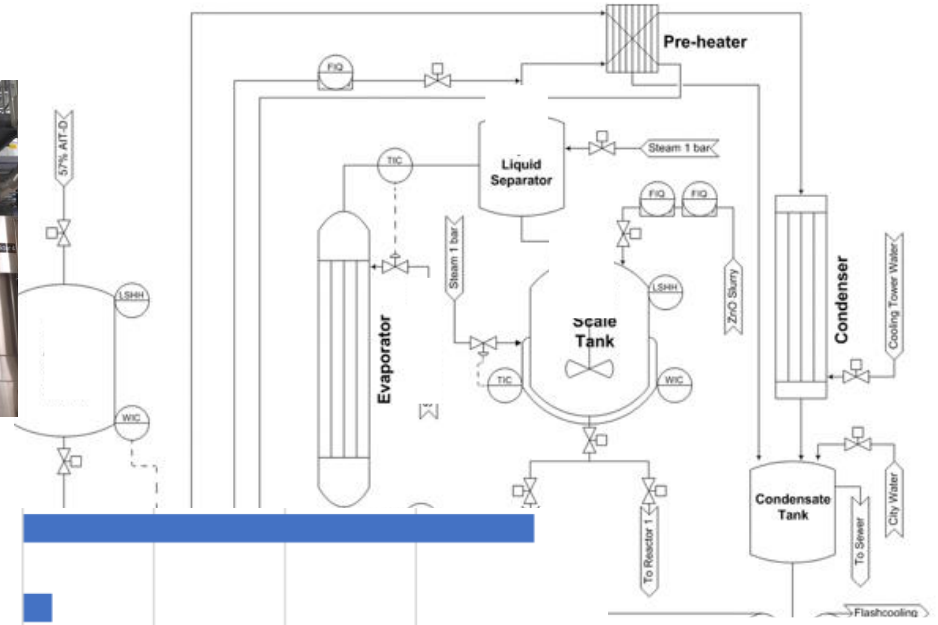
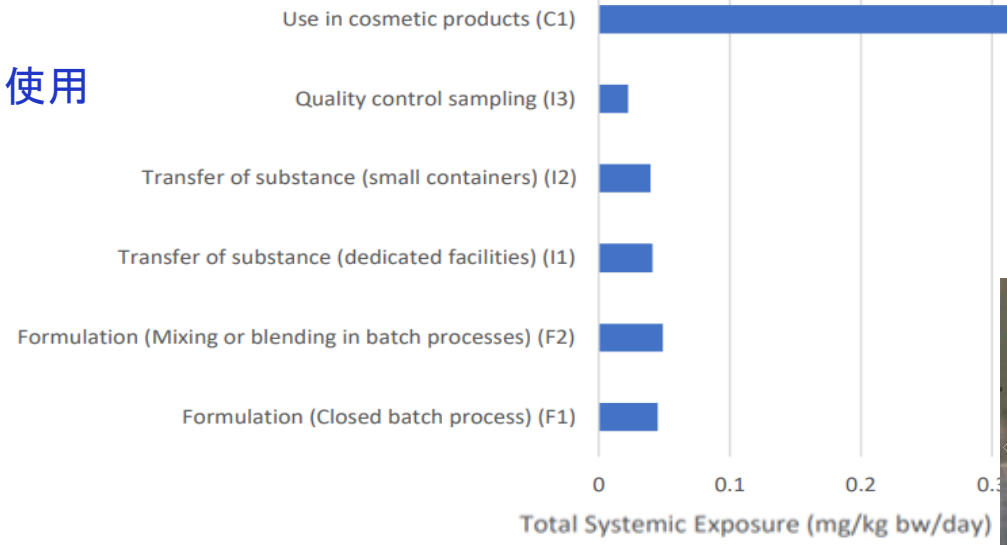
Beyond consumer safety: NGRA for worker safety
超出消费者安全：应用NGRA来保障工人安全

- Understanding worker exposure
  了解工人的暴露情况
  - Different routes of exposure 不同的暴露途径
  - Levels of exposure 暴露水平
  - Engineering controls 工程控制
  - Use of personal protective equipment 使用个人防护装备

- NGRA 下一代风险评估
  - BER approach for worker exposure
    使用针对工人的生物活性：暴露 比率





Conclusions 结论

- The Next Generation Risk Assessment (NGRA) toolbox is increasingly being used as part of decisions on consumer safety that do not involve animal testing
- NGRA and the use of NAMs (New Approach Methodologies) is being mentioned in some regulatory guidelines
- Working on examples of decision-making using NGRA is one of the best ways to build familiarity and confidence with the tools e.g. Baltazar *et al* (2020), *Toxicol Sci*, **176**, 236-252
- There is still work to do e.g. working on a framework for establishing scientific confidence in new approach methodologies (Zalm *et al*, *Archives of Toxicology*, **96**, 2865-2879)

- 下一代风险评估 (NGRA) 技术手段越来越多地被用作不涉及动物测试消费者安全决策的一部分
- 一些监管指南中涉及 NGRA 和 NAMs（新技术方法）的使用
- 使用 NGRA 研究决策案例是建立对技术手段的熟悉度和增强信心的最佳方法之一，例如 Baltazar et al (2020)，Toxicol Sci, 176, 236-252
- 仍有工作要开展，例如 致力于建立一个框架，以增强对新技术方法的科学信心(Zalm *et al*, *Archives of Toxicology*, **96**, 2865-2879)

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Eurofins
BioClavis
Cyprotex
SOLVO
BioDetection Systems
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EPA and Unilever Announce Major Research Collaboration to Advance Non-animal Approaches for Chemical Risk Assessment

August 19, 2021

Contact Information
EPA Press Office (press@epa.gov)

WASHINGTON – Today, the U.S. Environmental Protection Agency (EPA) and Unilever announced a collaborative agreement to explore better ways to assess chemical risks associated with consumer products. This agreement builds on prior cooperation between EPA and Unilever regarding New Approach Methods (NAMs), which are a promising alternative to conventional toxicity testing that are intended to reduce reliance on the use of animals.

EPA and Unilever have been jointly evaluating and using NAMs since 2015. This collaboration is helping EPA implement its New Approach Methods Work Plan and is the foundation for new efforts to demonstrate that these novel approaches can help decision makers better protect consumers, workers and the environment.

"EPA is a pioneer in developing and applying NAMs to identify and quantify risks to human health, while reducing the use of animals in chemical toxicity testing," said **H. Christopher Frey, Deputy Assistant Administrator for Science Policy in EPA's Office of Research and Development**. "We are excited to continue the collaboration with Unilever, which enhances the robustness of our mutual research to demonstrate the use of NAMs."

19 Aug 2021

RISK HUNT3R

epaa The European Partnership for Alternative Approaches to Animal Testing

NICEATM ICCVAM
Advancing Public Health and Animal Welfare

Unilever

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- Wendy Simpson

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