见美,见未来

PCHi Technology Summit

全球个人护理用品化妆品行业领袖峰会

2020年8月26-27日 上海 SHANGHAI

Non-Animal Approaches to Cosmetic Safety Assessments and Applications

基于非动物新科技方法的化妆品安全评估及其应用

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联合利华中国消费者产品安全合作中心

国药励展 Reed Sinopharm Exhibitions

Main content 主要内容

1. **Background 背景**

2. **Risk Assessment with Non-Animal Approaches 非动物新科技方法的化妆品安全评估**

3. **Case Studies: Coumarin**

   香豆素在化妆品案例研究

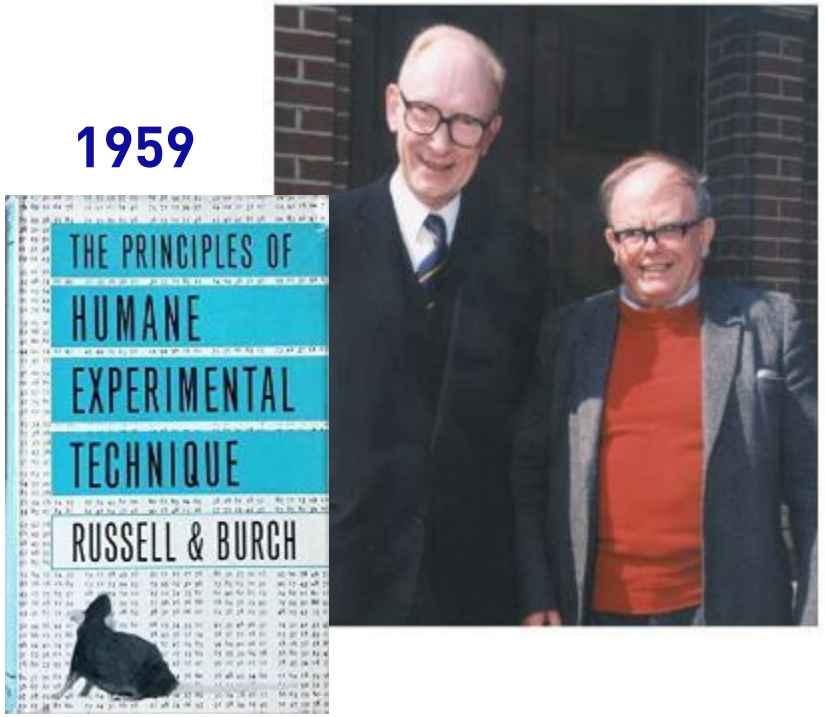
Background
Changes in the world and in China

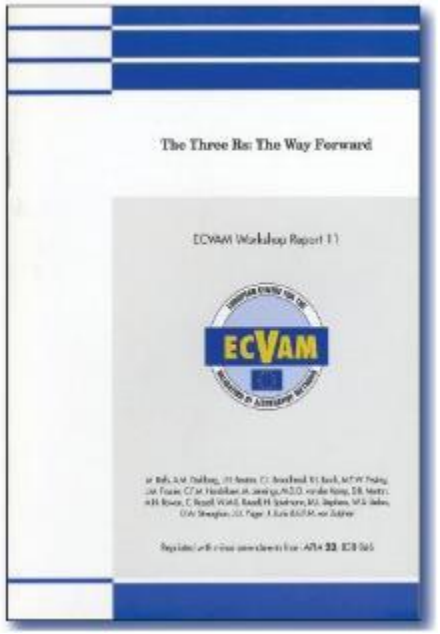
背景-全球和中国的变化

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

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

1959

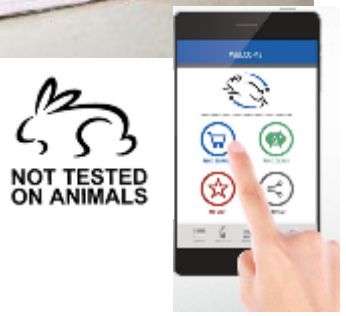




1995

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

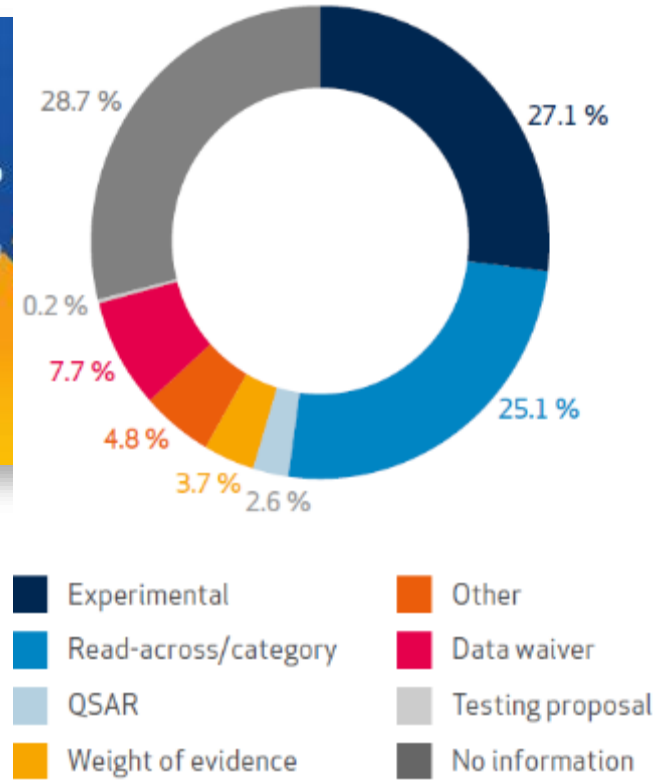
消费者想要安全的产品，
但希望不经过动物测试



Unilever

Non-animal approaches increasingly taken up in regulations
法规越来越多地采用非动物方法

In EU 欧洲



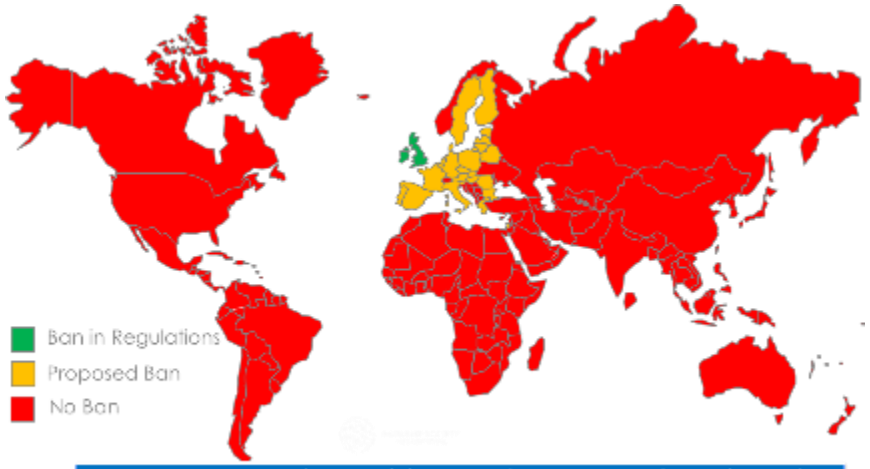
In US 美国

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

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

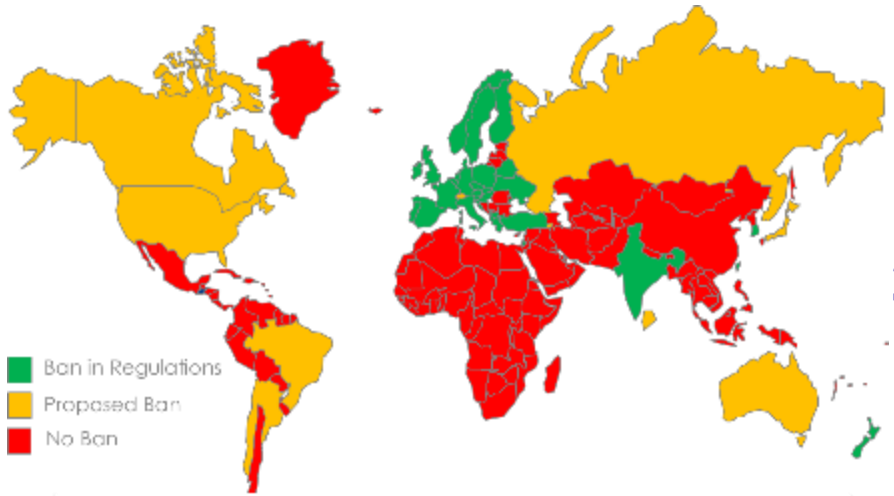
AT Ban at 39 countries/areas
39个国家/地区禁止

- 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》



2013

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

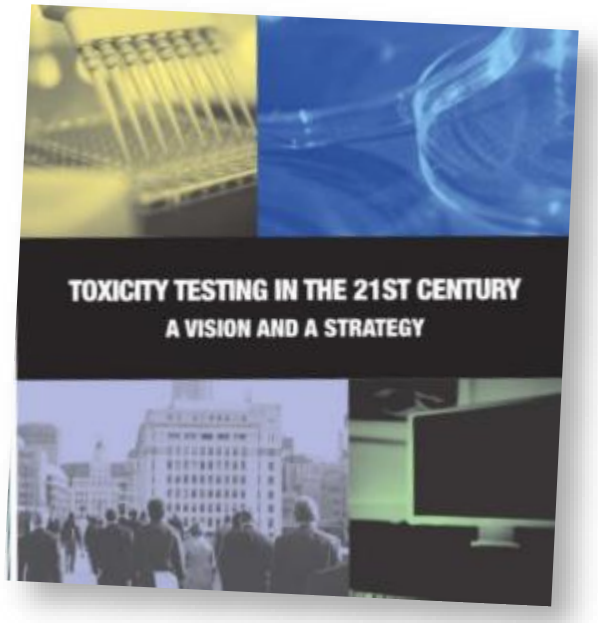


2016

2016 - 39 national testing/trade bans/restriction; 10+ others in development

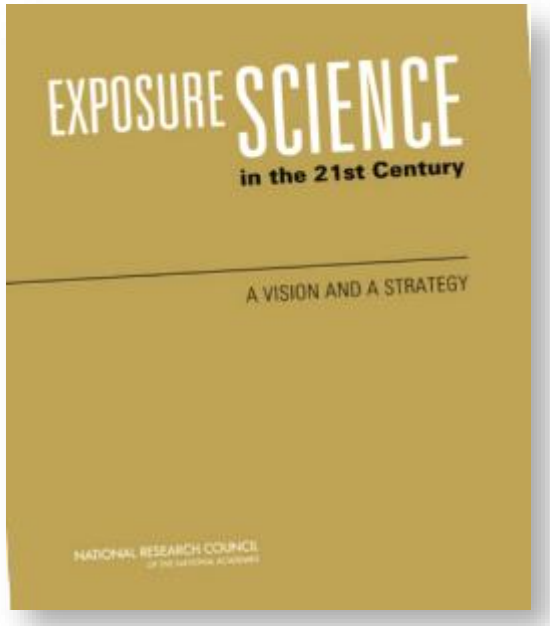
21st century safety sciences advanced greatly
21世纪安全科学取得了巨大进步

TT21C



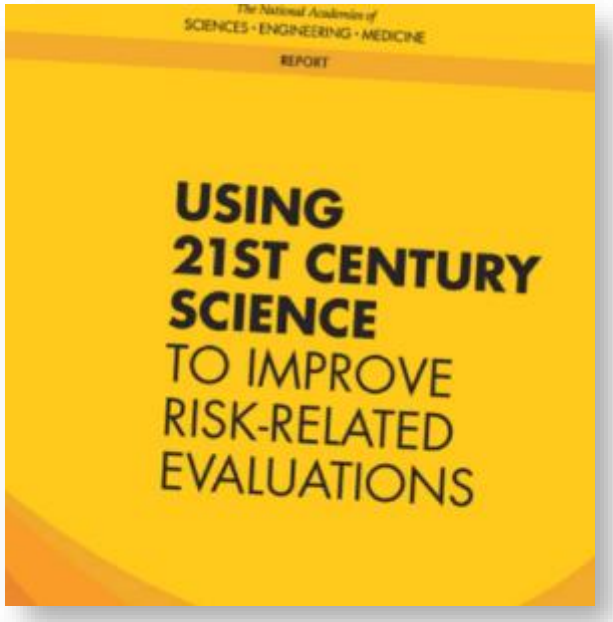
US National Academies of Science 2007
美国国家科学院2007报告

ES21C



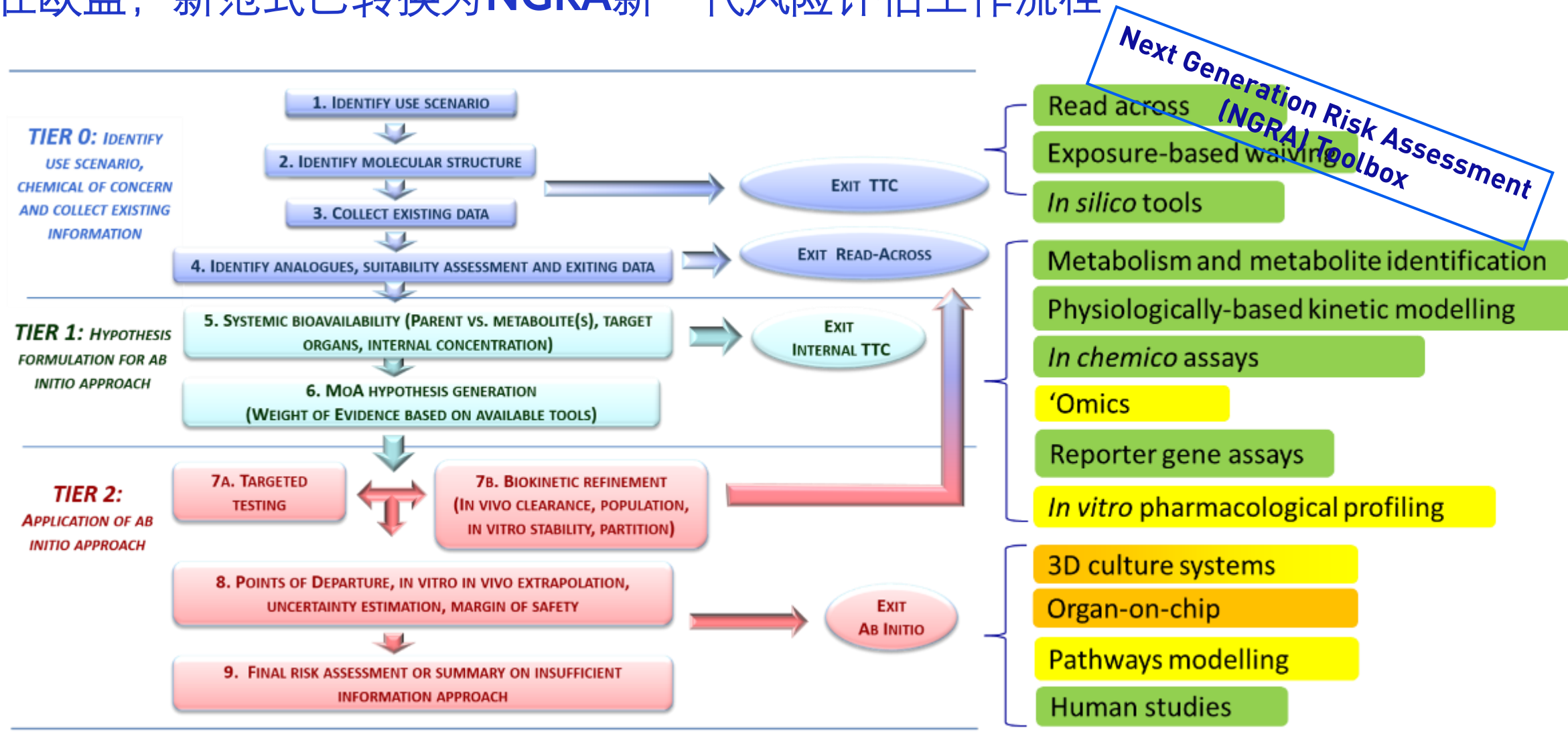
US National Research Council 2012
美国国家研究委员会
2012报告

21C Risk Assessment



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

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[1], White A[2], Ouedraogo G[3], Paini A[1], Richarz AN[1], Bois FY[4], Exner T[5], Leite S[6], Grunsven LAV[6], Worth A[1], Mahony C[7].

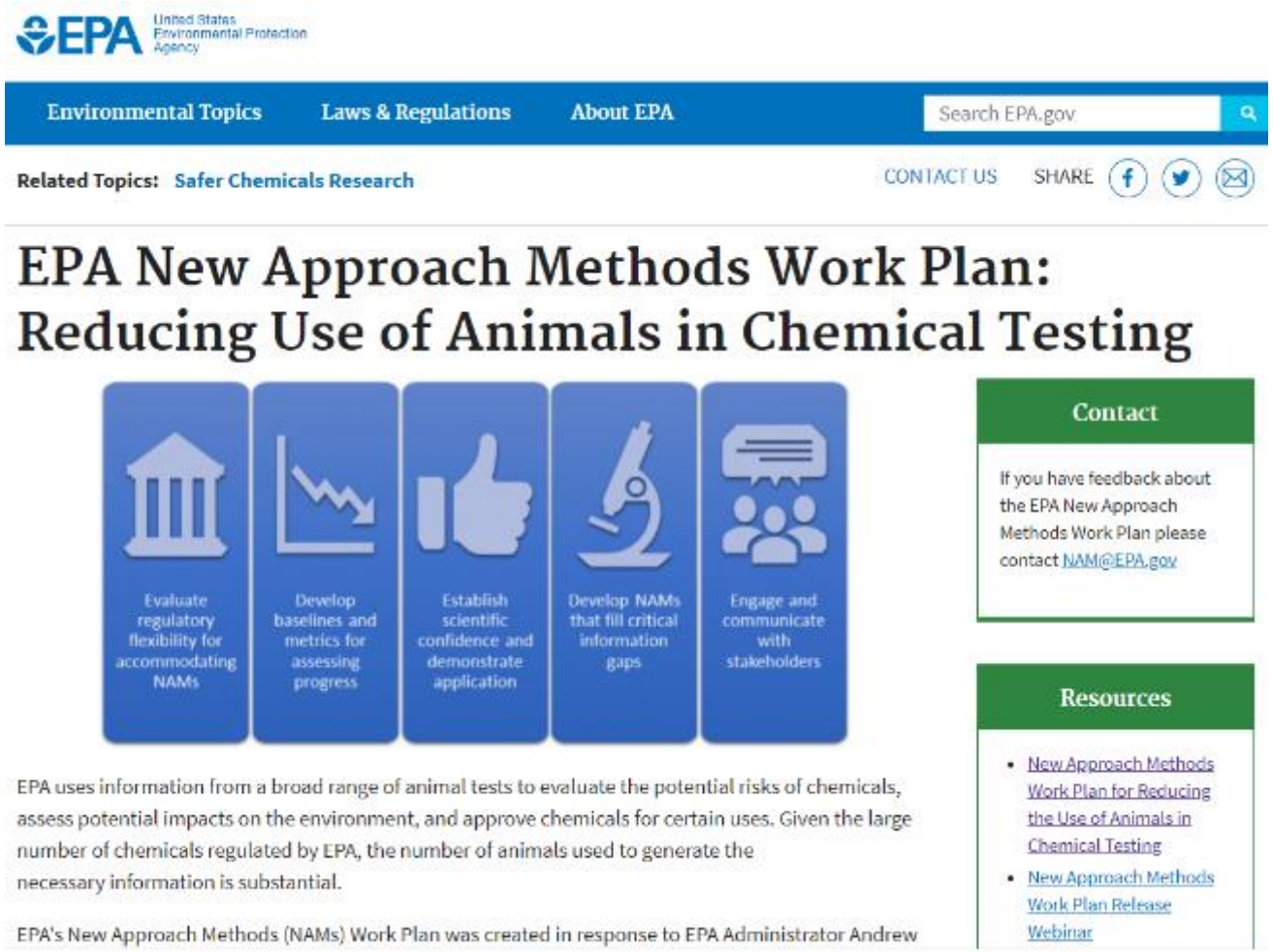
SEURAT-1 EUTOXRISK

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



新方式方法工作计划

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

2018
化妆品替代方法研究和验证工作组成立

2014
取消国产非特殊用途化妆品的强制性动物试验要求

2016
CFDA 采纳化妆品第一个国际认可的替代方法(3T3光毒性)

2006
《关于善待实验动物的指导性意见》全面推行实验动物法制化管理

2001
《科研条件建设“十五”发展纲要》明确指出动物试验应遵循“3R”原则

1997
《关于“九五”期间实验动物发展的若干意见》第一次将3R写进法规性文件

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

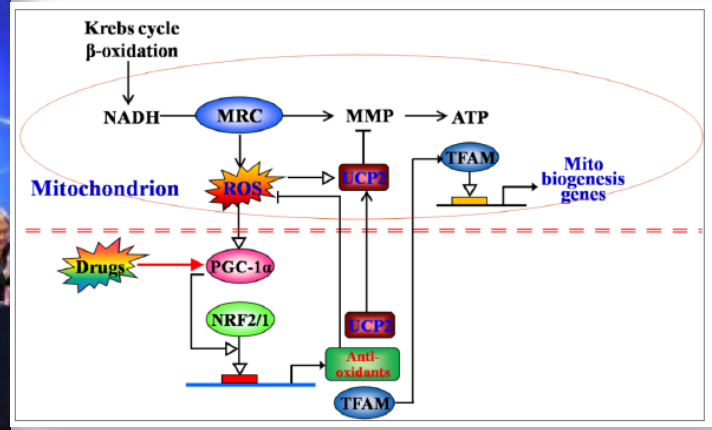
关于征求《化妆品安全评估技术导则（征求意见稿）》和《化妆品分类规则和分类目录（征求意见稿）》意见的函

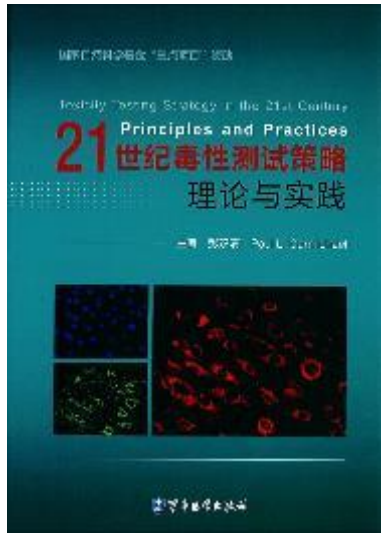
药监化函〔2020〕82号

- 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**





Cosmetic Safety Assessment：Next Generation Risk Assessment (NGRA)

化妆品安全评估：下一代风险评估

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**

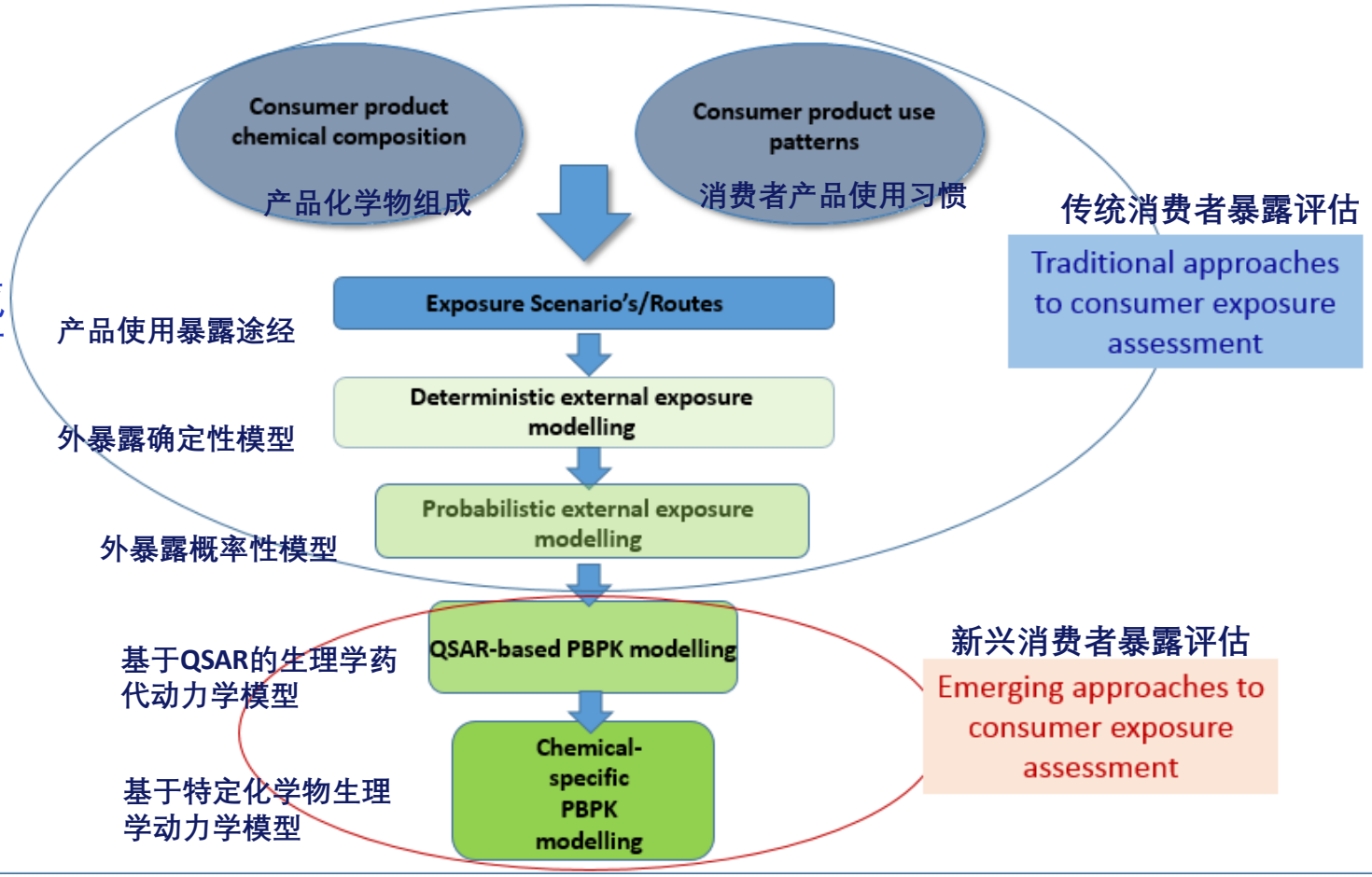
Risk Assessment
风险评估

Exposure Science overview 暴露科学

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

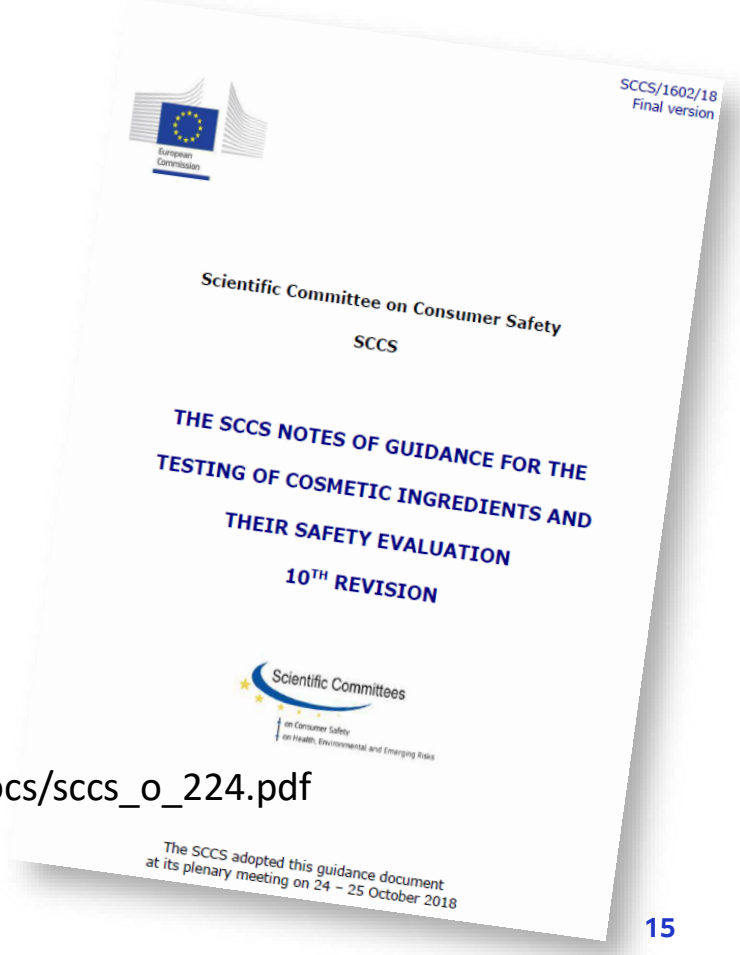


Toxicity Endpoints (Human Health) 毒性终点(人类健康)

e.g. 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, 10th Revision, 2018" 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

局部毒性
- Acute toxicity 急性毒性
- Mutagenicity/genotoxicity 致突变性/遗传毒性
- Irritation and Corrosivity 刺激性和腐蚀性
- Photo-induced toxicity 光诱导毒性
- Dermal/percutaneous absorption 真皮/经皮吸收

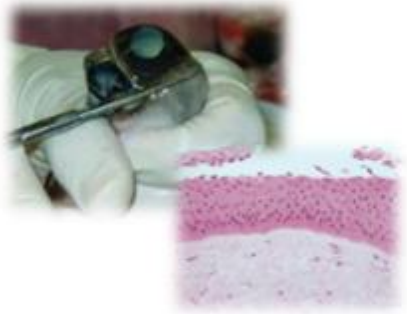
全身毒性
- Skin sensitisation 皮肤致敏
- Repeated dose toxicity 重复剂量毒性
- Reproductive toxicity 生殖毒性
- Carcinogenicity 致癌性
- Toxicokinetic studies 毒代动力学研究



https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_224.pdf

OECD tests that do not use animals
不使用动物的经济合作与发展组织（OECD）测试标准

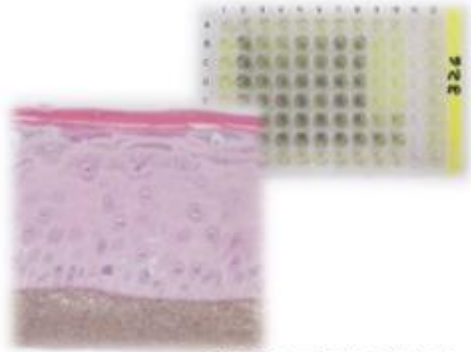
OECD TG438



OECD TG437

Eye Irritation

眼刺激

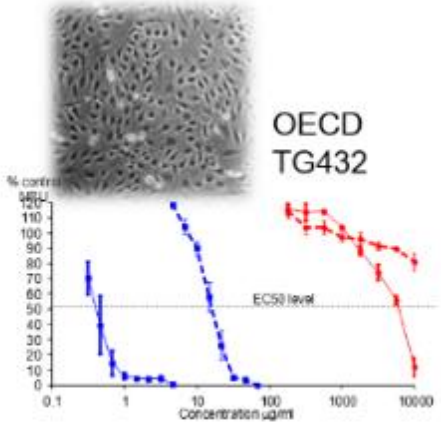


OECD TG430/431

OECD TG439

Skin Corrosion/Irritation

皮肤腐蚀/刺激

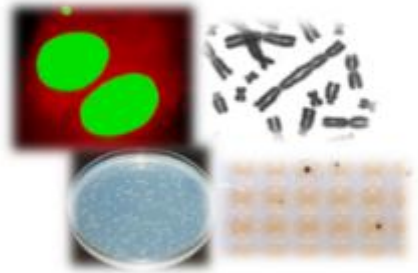


OECD TG432

Phototoxicity 光毒性

OECD TG487

OECD TG473

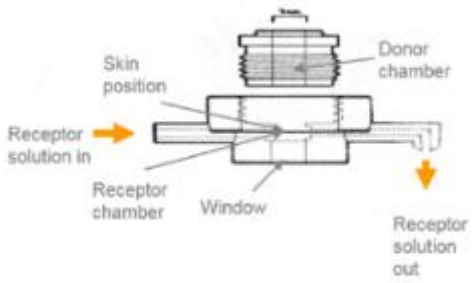


OECD TG471

OECD TG476

Genotoxicity

遗传毒性



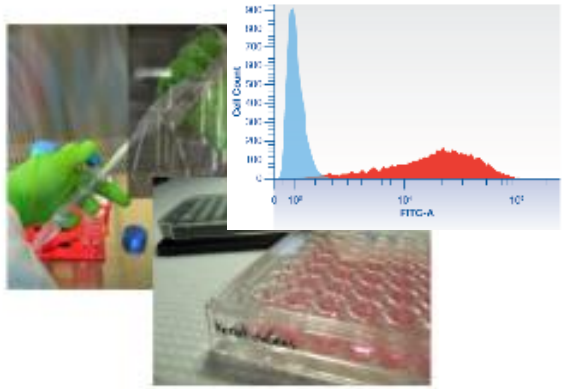
OECD TG428

Skin Penetration

透皮测试

OECD TG442C

OECD TG442E

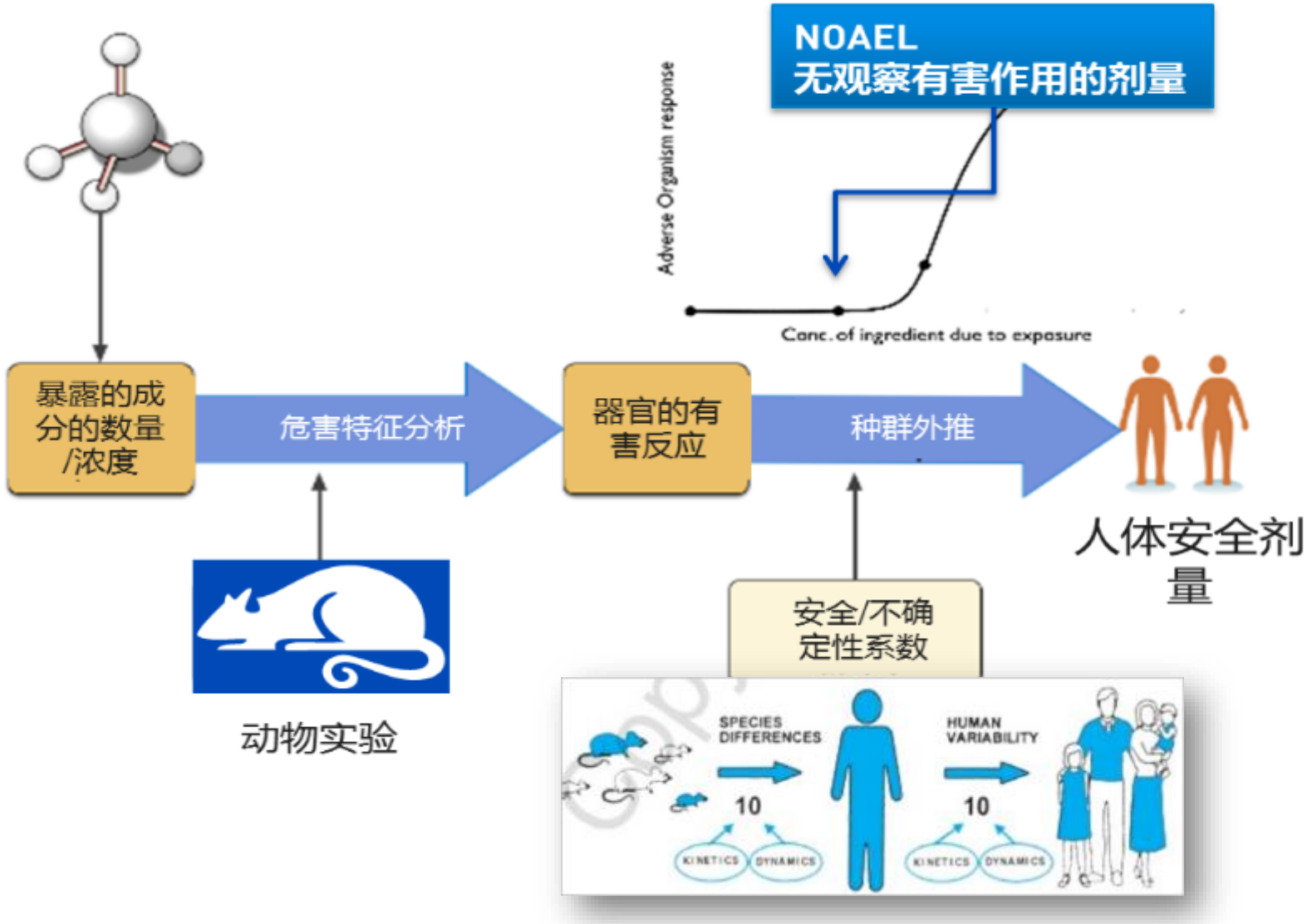


OECD TG442D

Skin Sensitisation

皮肤致敏

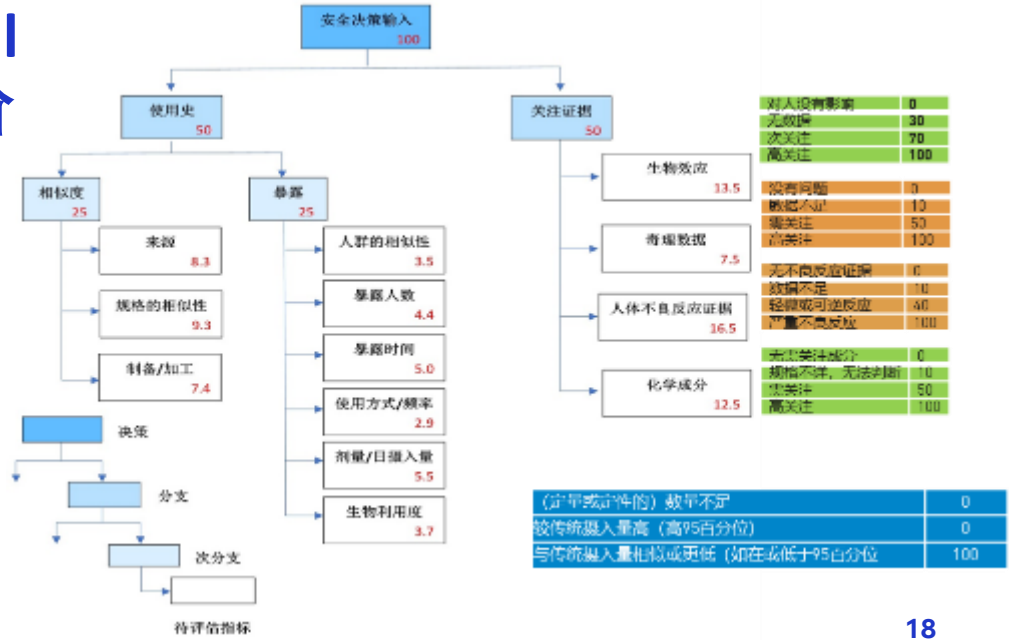
Challenges with systemic toxicity 挑战：不用动物评估全身毒性



Non-testing approaches may help 非测试方法是一种解决方案

1. **Threshold of Toxicological Concern (TTC) - Exposure based waiving approaches**
   毒理学关注阈值（TTC）- 基于暴露的免除方法
2. **(Quantitative) Structure Activity Relationships [(Q)SAR] & Read-across: grouping and category approaches;**
   (定量)构效关系[(Q)SAR] 交叉参照：分组和分类方法;
3. **History of Safe Use (HoSU) 安全使用历史**
   widely used for safety assessment of natural ingredients 广泛用于天然原料的安全性评价

Constable A et al (2007). Food and Chemical Toxicology, 45(12): 2513-2525

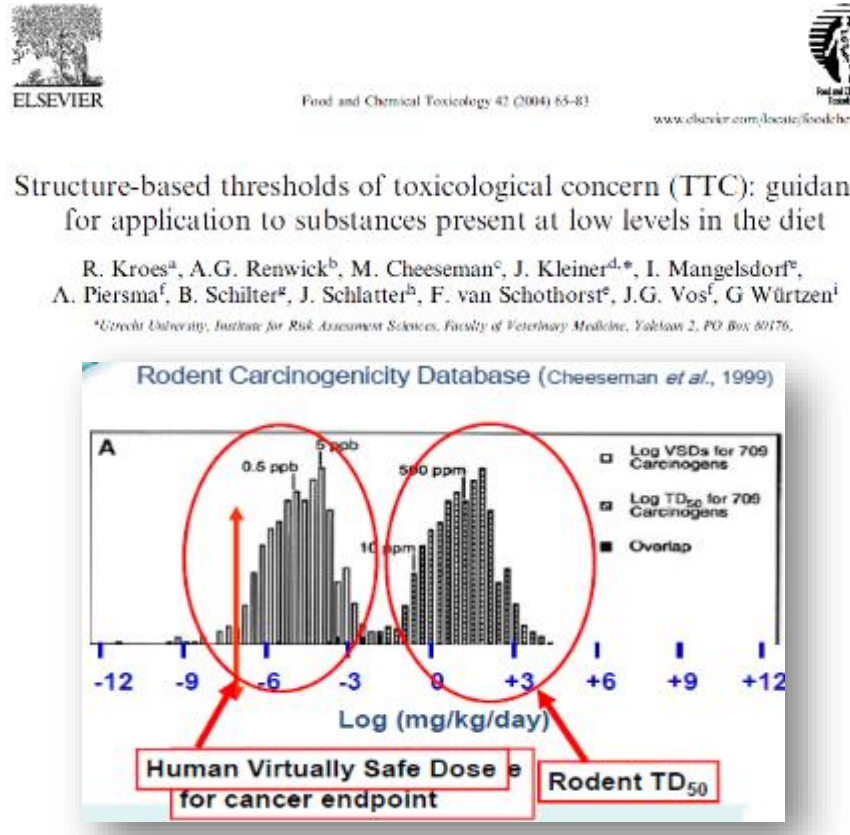


Threshold of Toxicological Concern (TTC) - Exposure based waiving approaches 毒理学关注阈值（TTC）- 基于暴露的免除方法

- 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

  例如 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，人类健康可能性风险非常低

- TTC is a robust scientific tool based on the probabilistic analysis of extensive toxicity databases TTC是基于广泛毒性数据库的概率分析的强大科学工具
- Initially developed in the context of food safety (leakage materials, US FDA) but turned into a scientific approach by Kroes et al (2004) 最初是在食品安全的背景下开发的（泄漏材料，美国FDA），但后来由Kroes等人(2004年)转变为科学方法
- The TTC methodology was adapted in recent years for other endpoints (e.g., Skin sensitisation (Safford, 2011); Inhalation toxicity (Carthew et al, 2009)) 近年来，对TTC方法进行了调整，使其适用于其他指标（例如，皮肤致敏（Safford，2011); 吸入毒性(Carthew等，2009))。

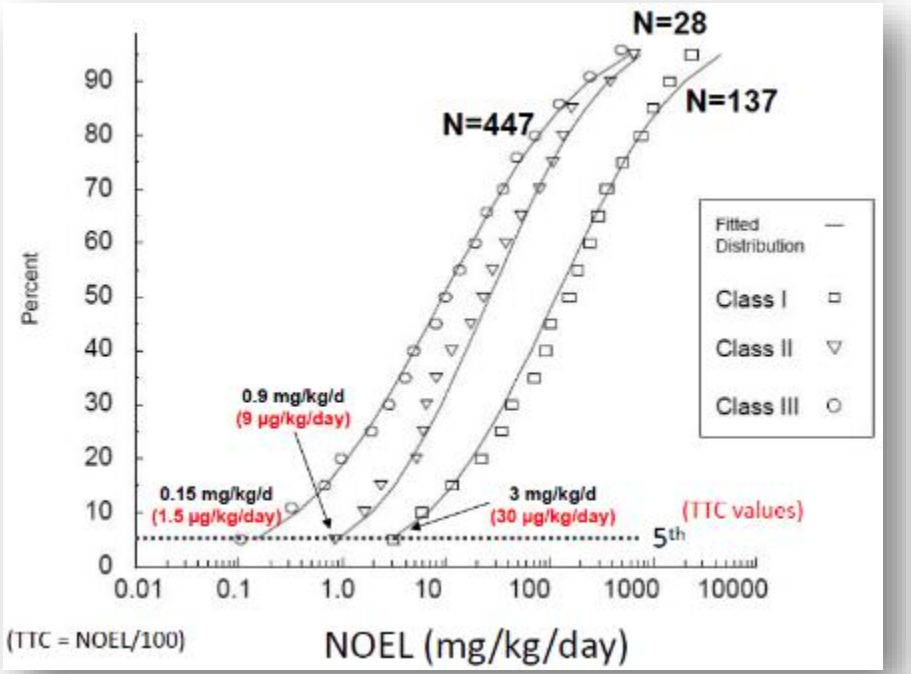


Kroes et al (2004, Systemic tox), Safford (2011, Skin sensitisation), Carthew et al, (2009, Inhalation)

TTC in a nutshell: general toxicity-derivation of TTC values
简而言之: 一般毒性TTC值的推导

- Derivation of the 5th percentile of NOAELs distributions for each Cramer class
- Application of 100-fold uncertainty factor/ MoS
- TTC NOT used for some exceptional compounds (metal, high potent carcinogens, proteins, etc)

Chemical Types 化学物分类	5th percentile NOEL 第5百分数NOEL (mg/kg/day)	基于暴露限值的 TTC (µg/kg/day)	基于暴露限值 的TTC (µg/天)
Genotoxicity alert 遗传毒性警示		0.0025	0.15
Organophosphates 有机磷酸盐 /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

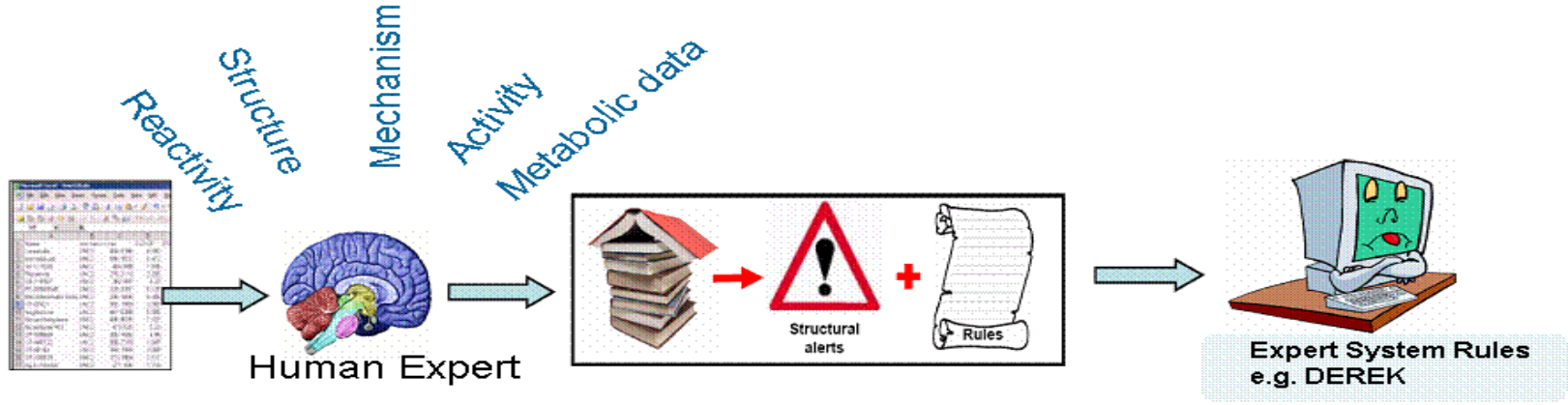


Structure-activity relationships /Alerts (SAR) and Quantitative Structure-activity relationships (QSAR)

构效关系/警示（SAR）和定量构效关系（QSAR）：基于毒理数据计算机方法

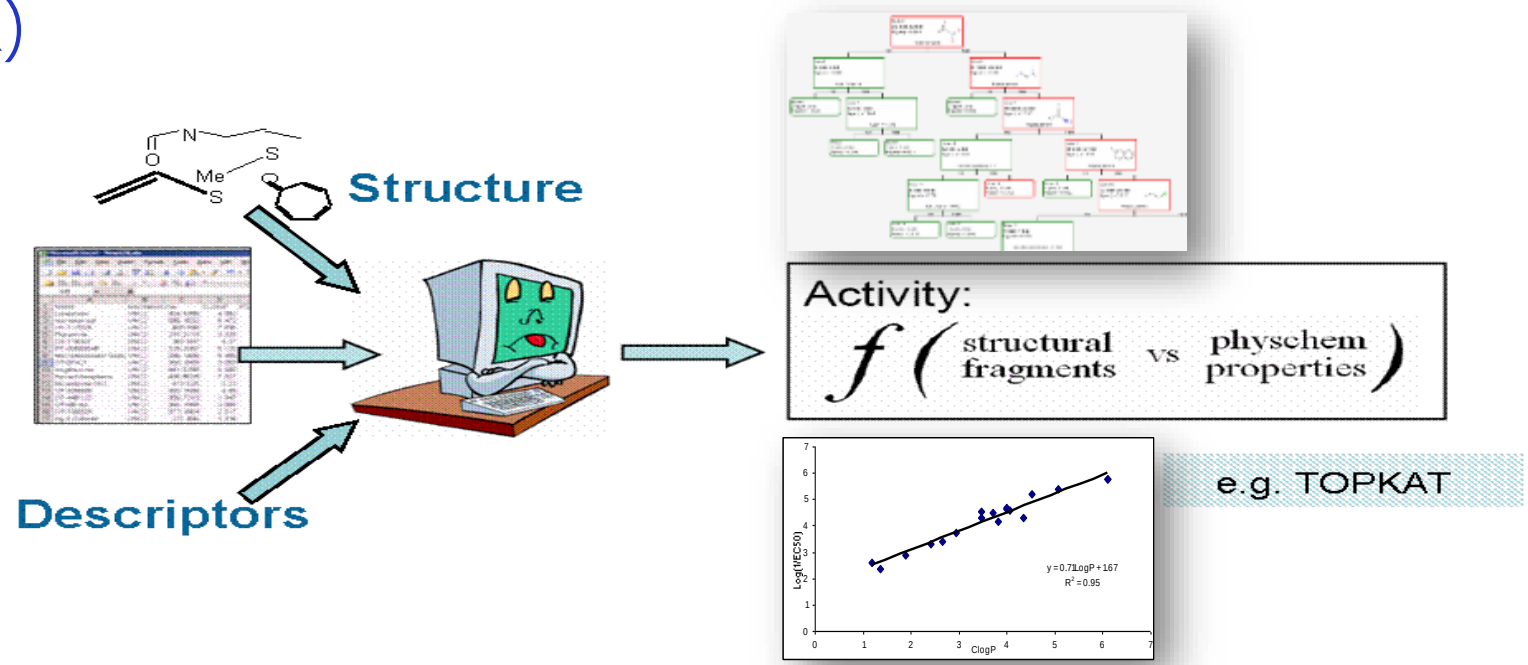
构效关系/警示 （SAR）

预测结果：警示- 有害或无害



定量构效关系（QSAR）

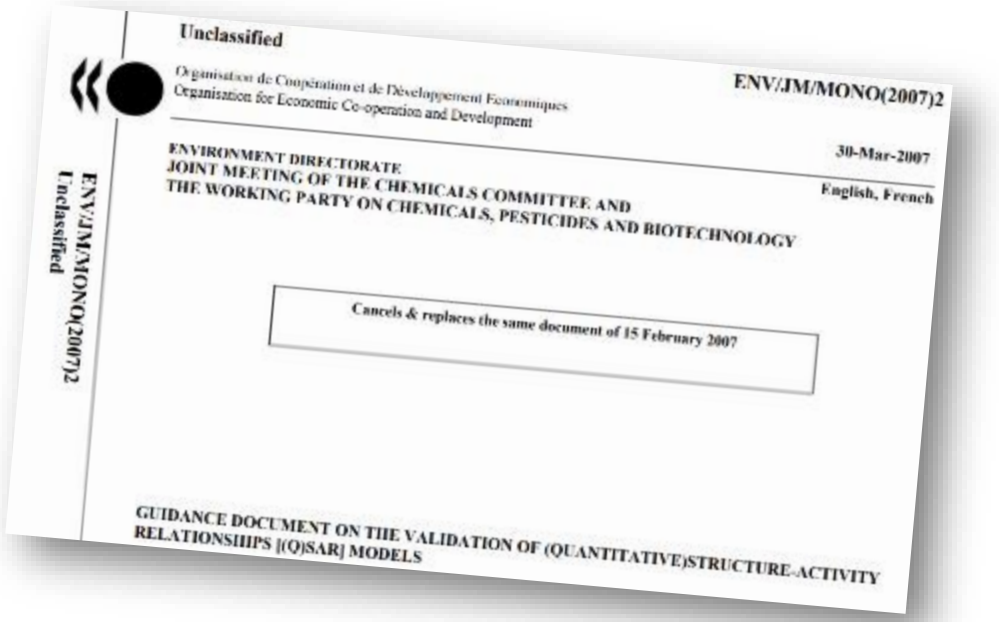
预测结果：
1） 警示- 有害或无害
2） 毒性强弱程度



OECD guidance on (Q)SAR 经合组织(Q)SA模型指导原则

- **A (Q)SAR should be associated with the following Info: (Q)SAR**
  - a defined endpoint 明确的毒理学终点
  - an unambiguous algorithm 清晰的算法
  - a defined applicability domain 应用适合范围
  - appropriate measures of goodness-of-fit, robustness and predictivity 合适的预测拟合度，可靠性和准确性
  - a mechanistic interpretation, if possible 可能的机理解释

- **Many (Q)SAR tools available 很多软件**
  - Toxtree, Derek, Meteor, Leadscope, Times
  - OCED QSAR Toolbox – serving REACH regulation for filling-in data gaps


Unclassified

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

ENV/JM/MONO(2007)2

30-Mar-2007

English, French

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

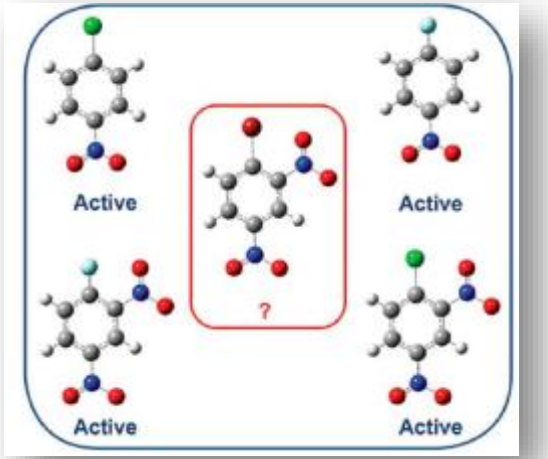
Cancels & replaces the same document of 15 February 2007

ENV/JM/MONO(2007)2
Unclassified

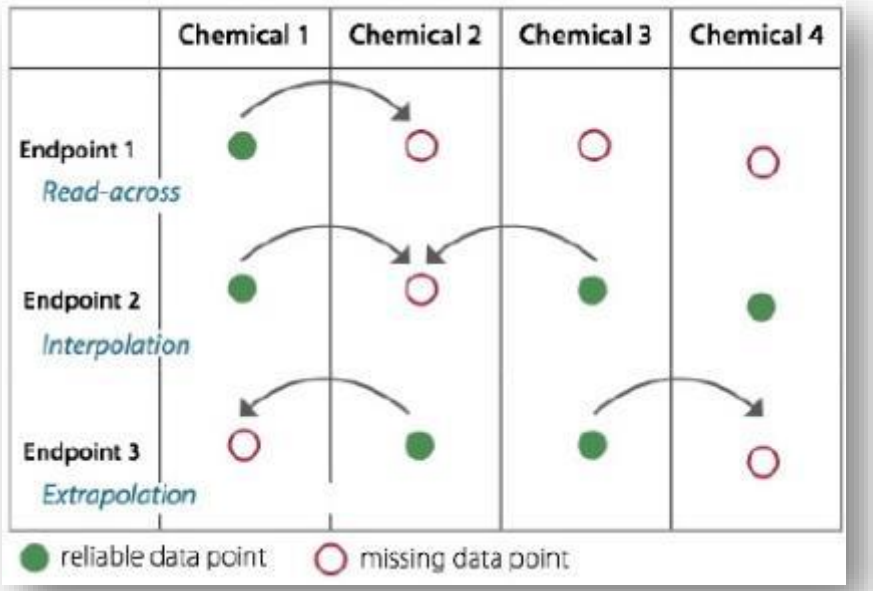
GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE)STRUCTURE-ACTIVITY RELATIONSHIPS [(Q)SAR] MODELS

OECD guidance aims to assist the regulatory acceptance of a (Q)SAR prediction, and provide a usable framework to interpret and assess computational models for toxicity

Read-across (RA): grouping and category approaches
交叉参照：化学分组方法



- Endpoint information (from a study) for one or several substances (i.e. the source analogue) are used to predict the same endpoint for a "similar" untested substance (i.e. the target analogue)
- Types of RA 交叉参照的类型
  1. Analogue approach 类似物方法
     - Based on a limited number of chemicals, cannot study trends in properties
  2. Category approach 分组方法
     - Based on more chemicals, can study trends in properties
- Guiding Principles for Acceptance 接受的指导原则
  - Mechanistic justification
  - Statistical justification
  - Relevant in vitro and in chemico endpoints
- RA is the most used alternative method in REACH



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

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

International Cooperation on Cosmetics Regulation

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

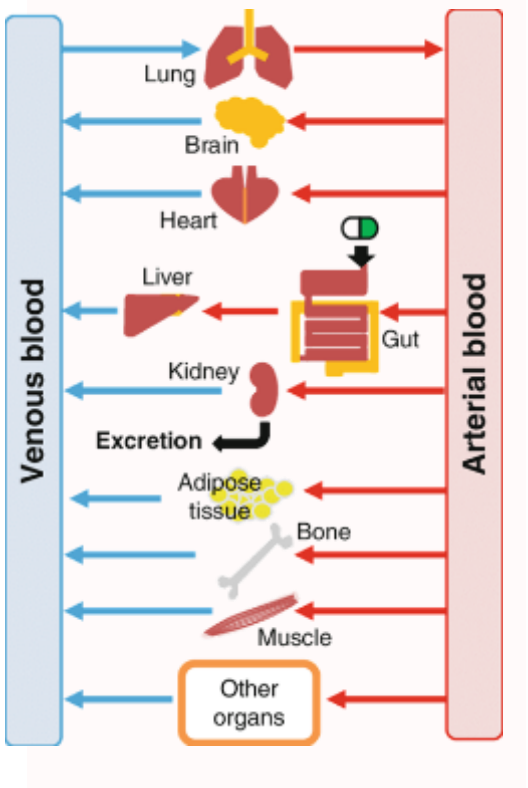

Computational Toxicology

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

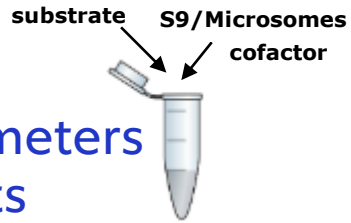
Dent *et al* ., (2018) *Comp Tox* 7:20-26

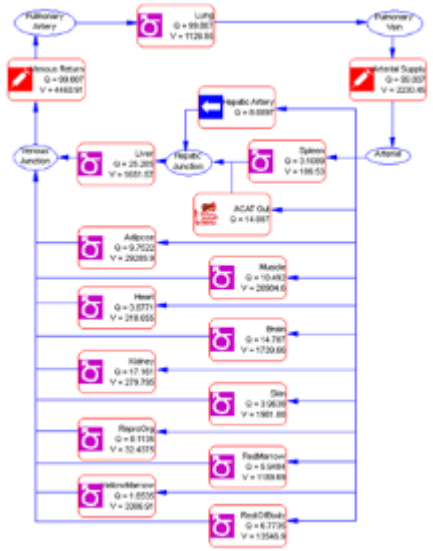
Unilever

One key tool in NGRA: PBK (Physiologically Based Kinetic) Modelling
NGRA中的关键技术：PBK（基于生理的动力学）模型



Model Input:
Physiological parameters
Partition coefficients
Kinetic constants (in vitro)



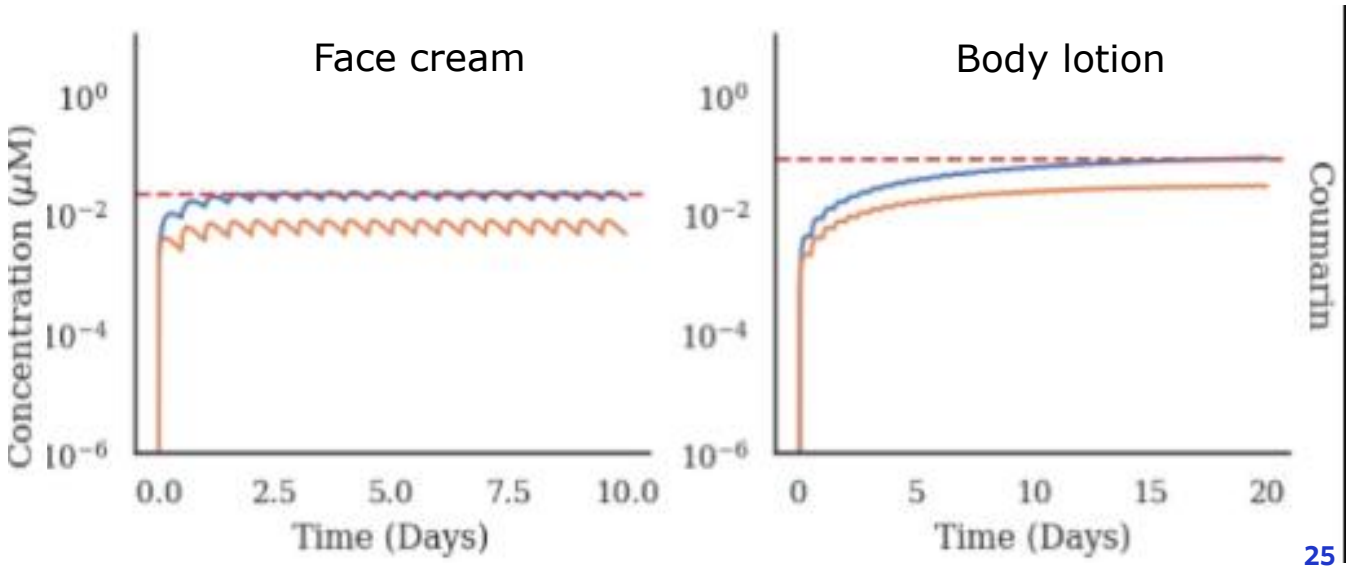


Uptake

Transport from arterial to venous blood

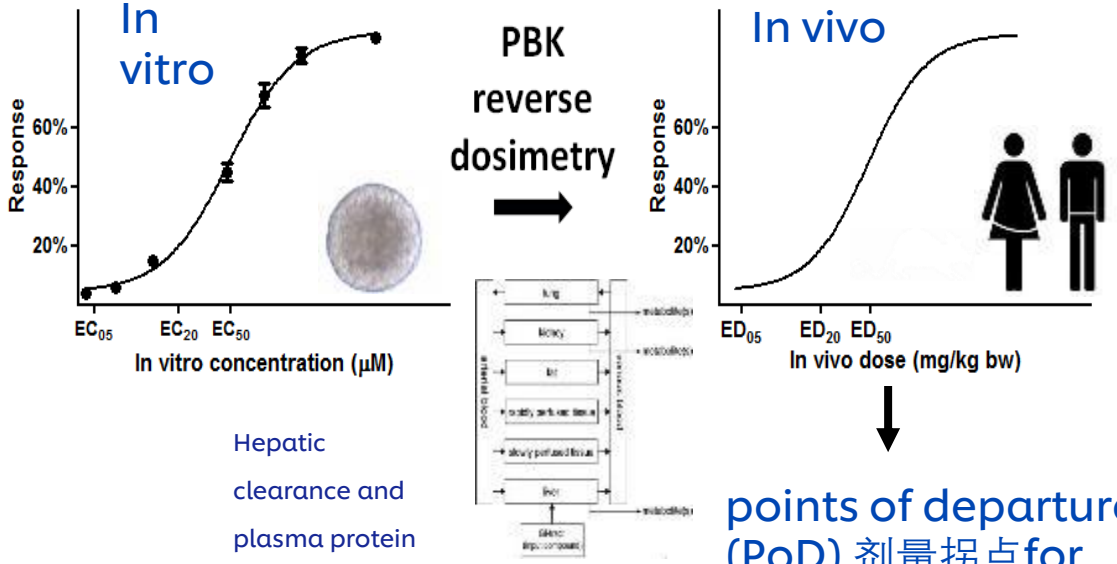
Metabolism

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



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

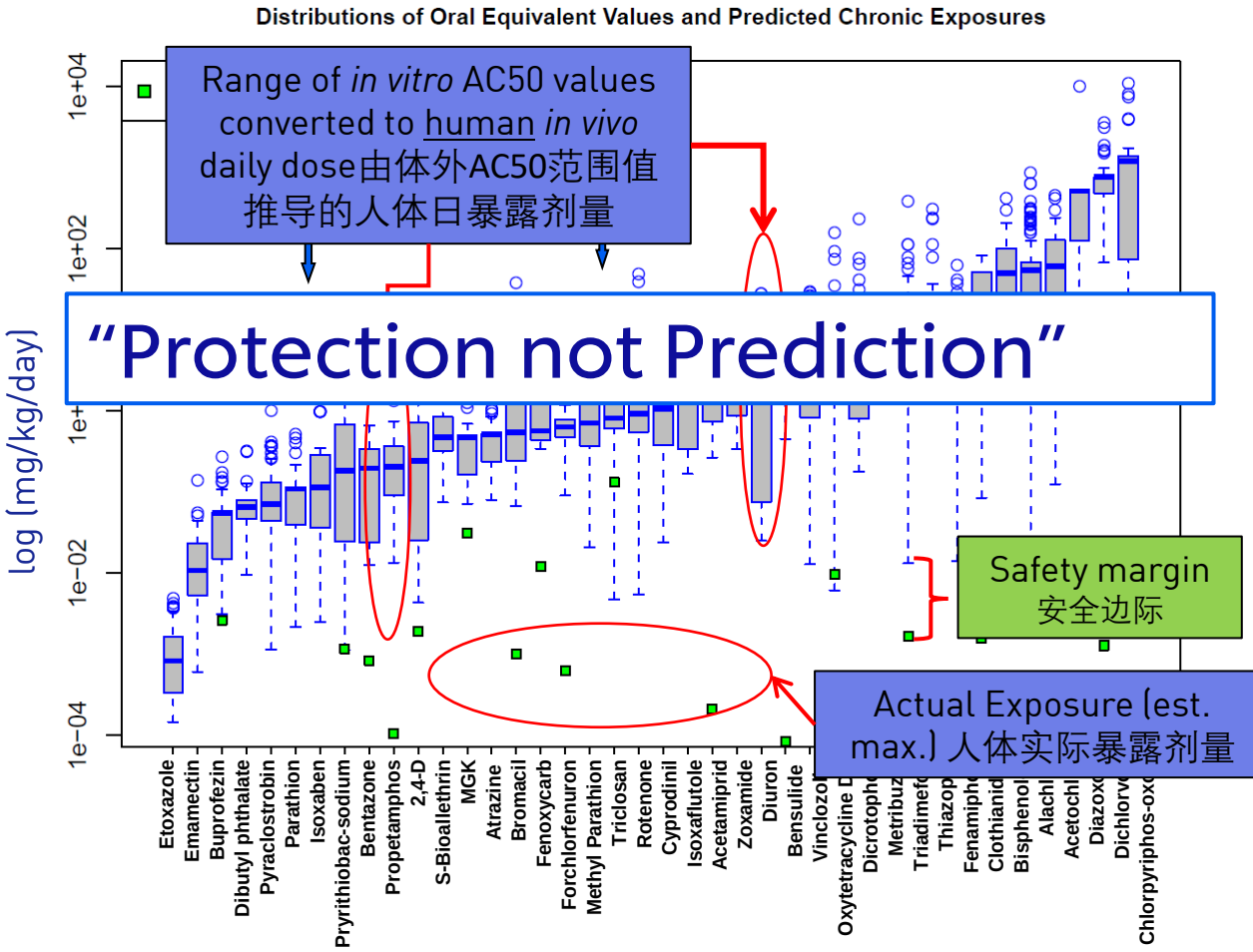
Quantitative in vitro to in vivo extrapolation
体外到体内定量外推



Hepatic clearance and plasma protein binding determinations

points of departure (PoD) 剂量拐点for risk assessment

由体外AC50范围值推导的人体日暴露剂量

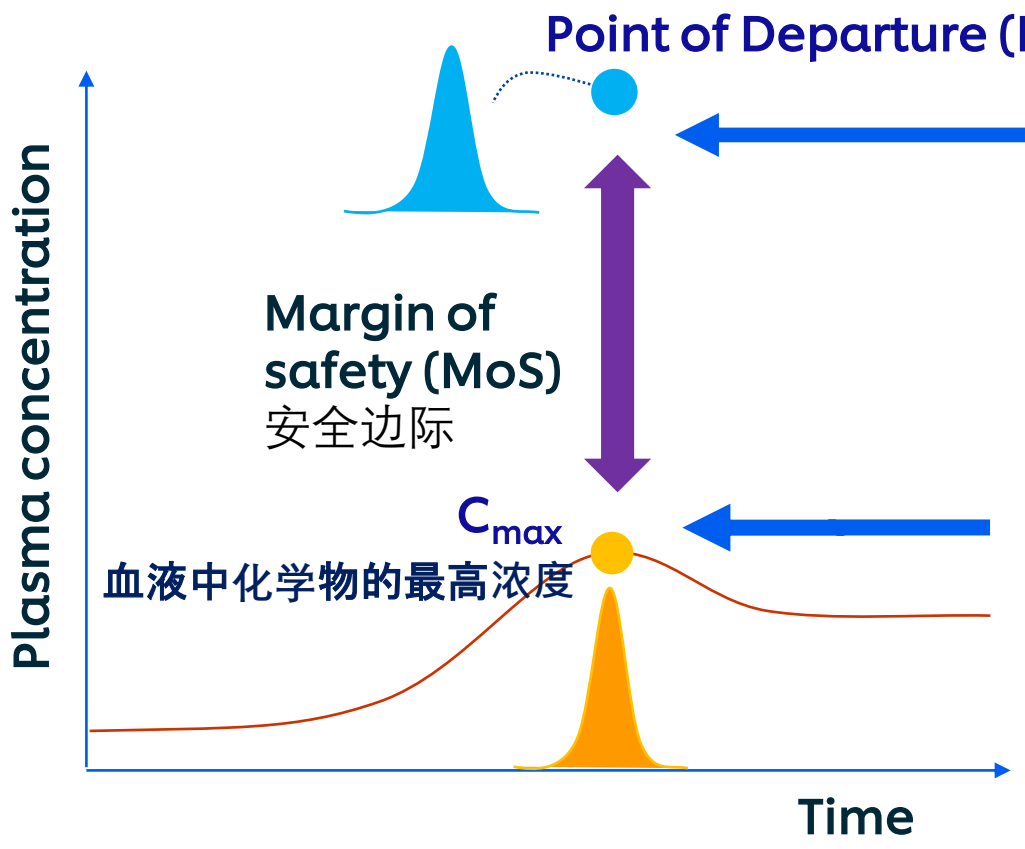


Rotroff, *et al.* Tox.Sci 2010

Slide from Dr Rusty Thomas, EPA, with thanks

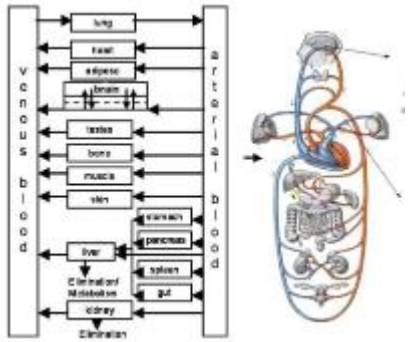
if there is no bioactivity observed at consumer-relevant concentrations, there can be no adverse health effects.
如果在与消费者相关的剂量下未观察到生物活性，则不会对健康造成不利影响

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



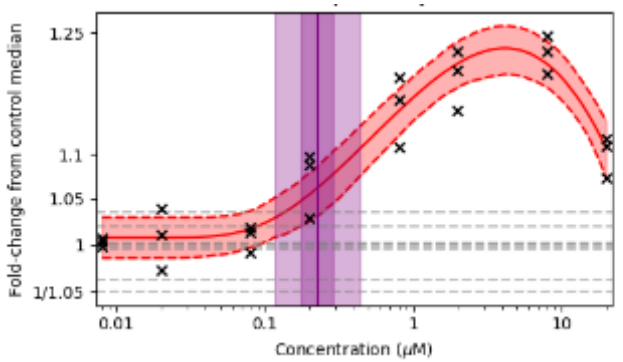
Exposure models (PBK, free/total concentration)

=



Hepatic clearance and plasma protein binding determinations

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



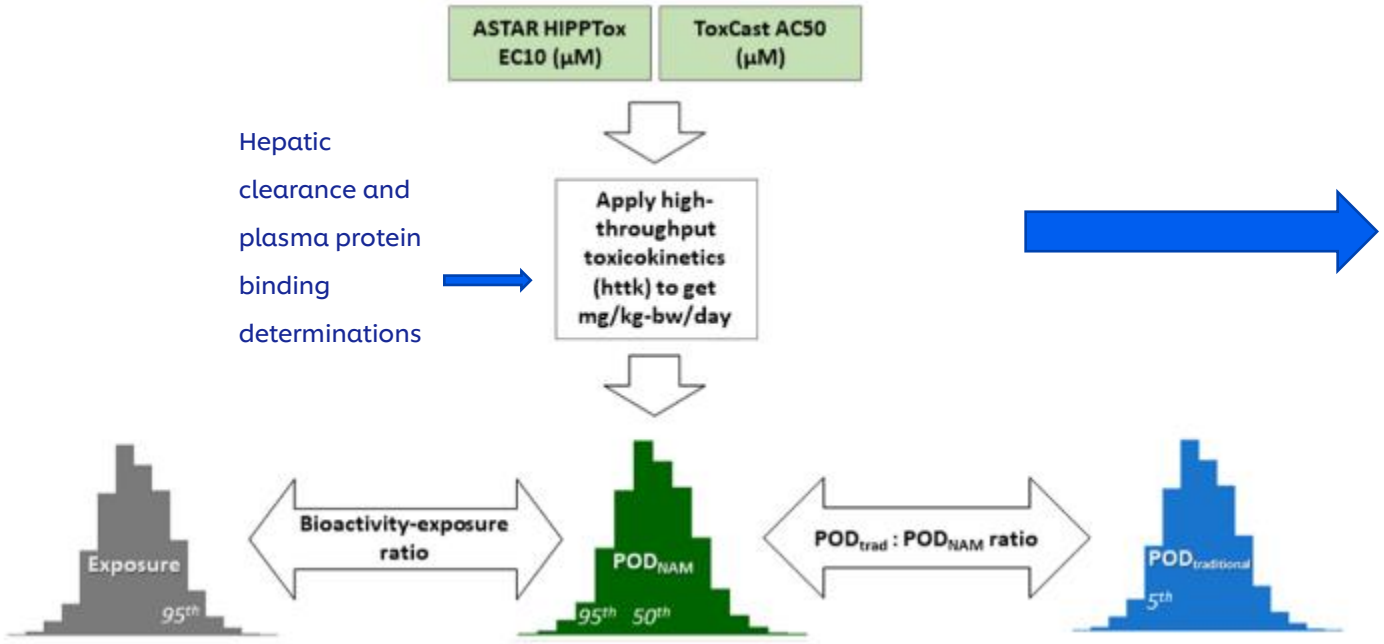
$$\text{MoS} = \frac{\text{PoD}}{\text{Exposure*}} = \frac{\text{PoD}}{C_{max}} = \frac{\text{体外生物拐点值}}{\text{血液中化学物的最高浓度}}$$

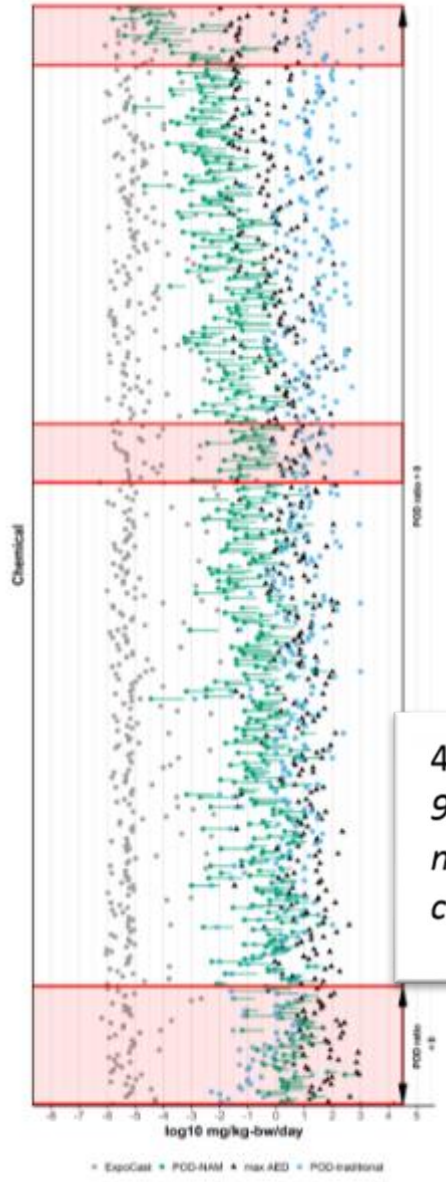
Recent research has shown that for 417 out of 448 chemicals tested the point of departure derived (PoD) from NAMS was more conservative than the in vivo PoD (新一代方法，相对于动物实验方法更加保守)

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

Accelerating the Pace of Chemical Risk Assessment

APCRA





414/448 chemicals = *92% of the time this naïve approach appears conservative*

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

Case studies: Coumarin

香豆素在化妆品案例研究

Case study approach… imagine we have no data for: Coumarin
案例研究方法……假设我们没有以下数据：香豆素

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

Safety assessment required for **0.1% coumarin in Body lotion**

身体乳液中0.1%香豆素需要进行安全评估

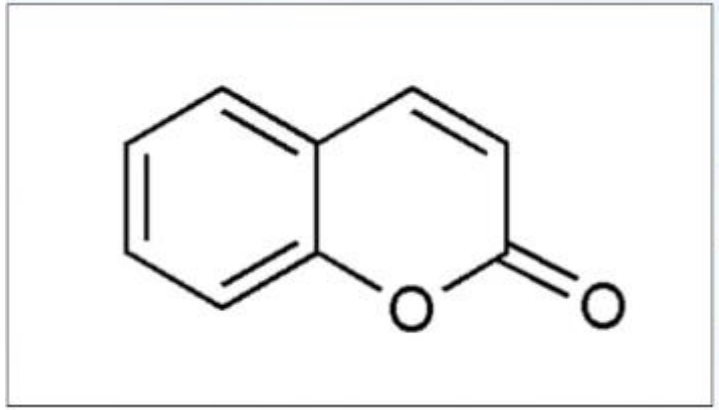
设立的案例安全评估的假设：

- 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)

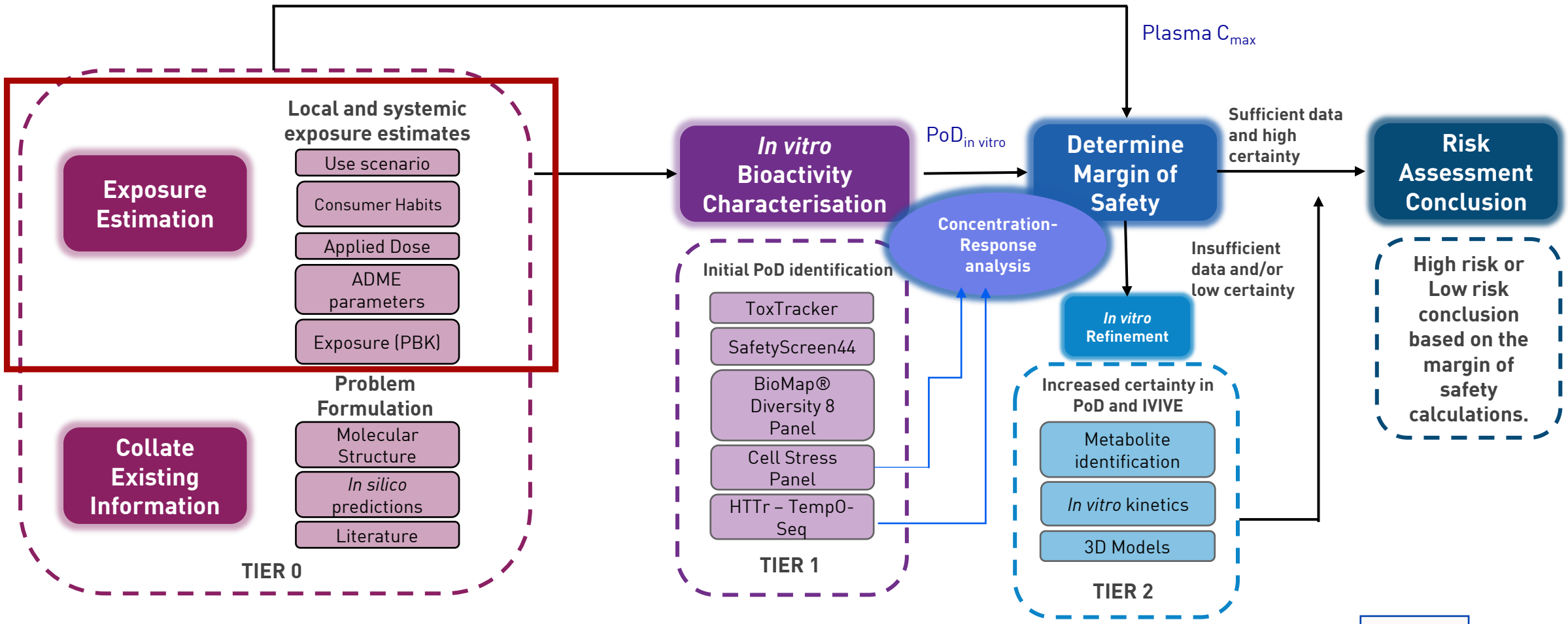
Coumarin is a flavouring substance which is contained in relatively high concentrations in cinnamon varieties collectively known as "Cassia cinnamon". It’s also used as a fragrance in cosmetic products

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



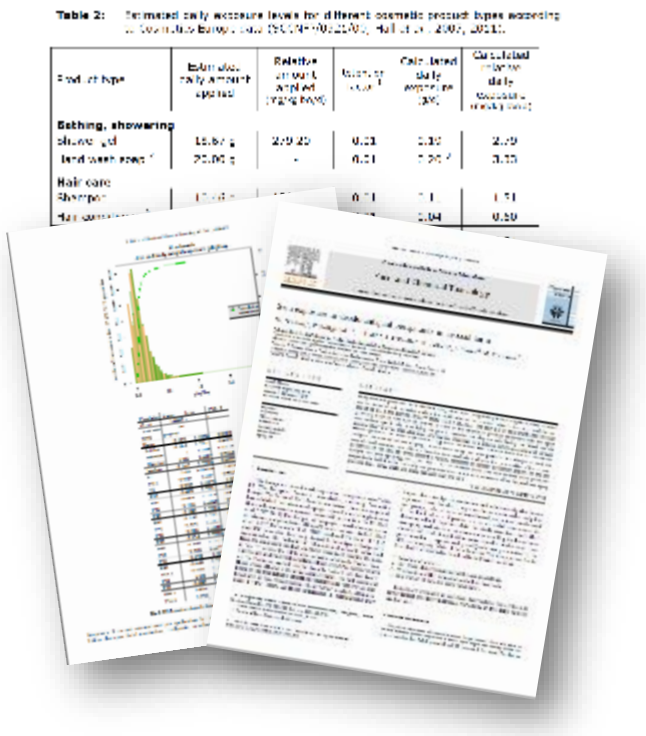
化學名稱	香豆素
外觀	無色或白色晶體
化學物質登錄號	91-64-5
分子式	$C_9H_6O_2$
分子量	146.14

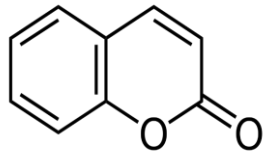
Ab Initio NGRA Framework 从零开始NGRA框架



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

Exposure estimation for 0.1% coumarin products
0.1%香豆素产品的暴露估计





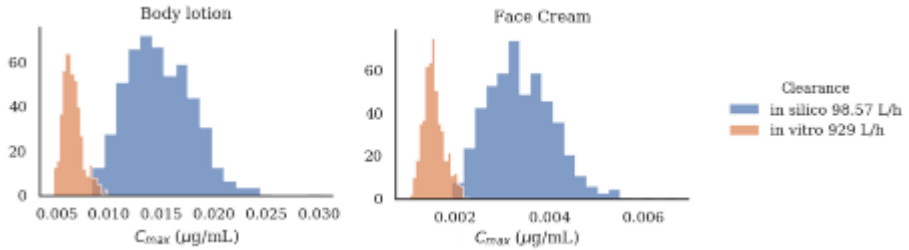
Parameter	Face cream
Amount of product used per day (g/day) using 90th percentile	1.54
Frequency of use	2 times/day
Amount of product in contact with skin per occasion (mg)	770
Ingredient inclusion level	0.1%
Skin surface area (cm2)	565
Exposure duration per occasion	12 hours
Amount of ingredient in 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

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

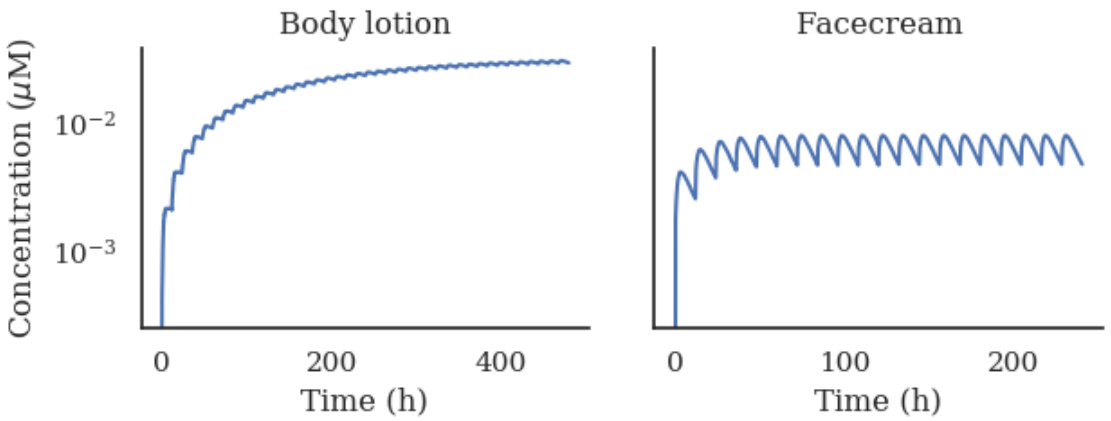
Key output parameters from uncertainty analysis:

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

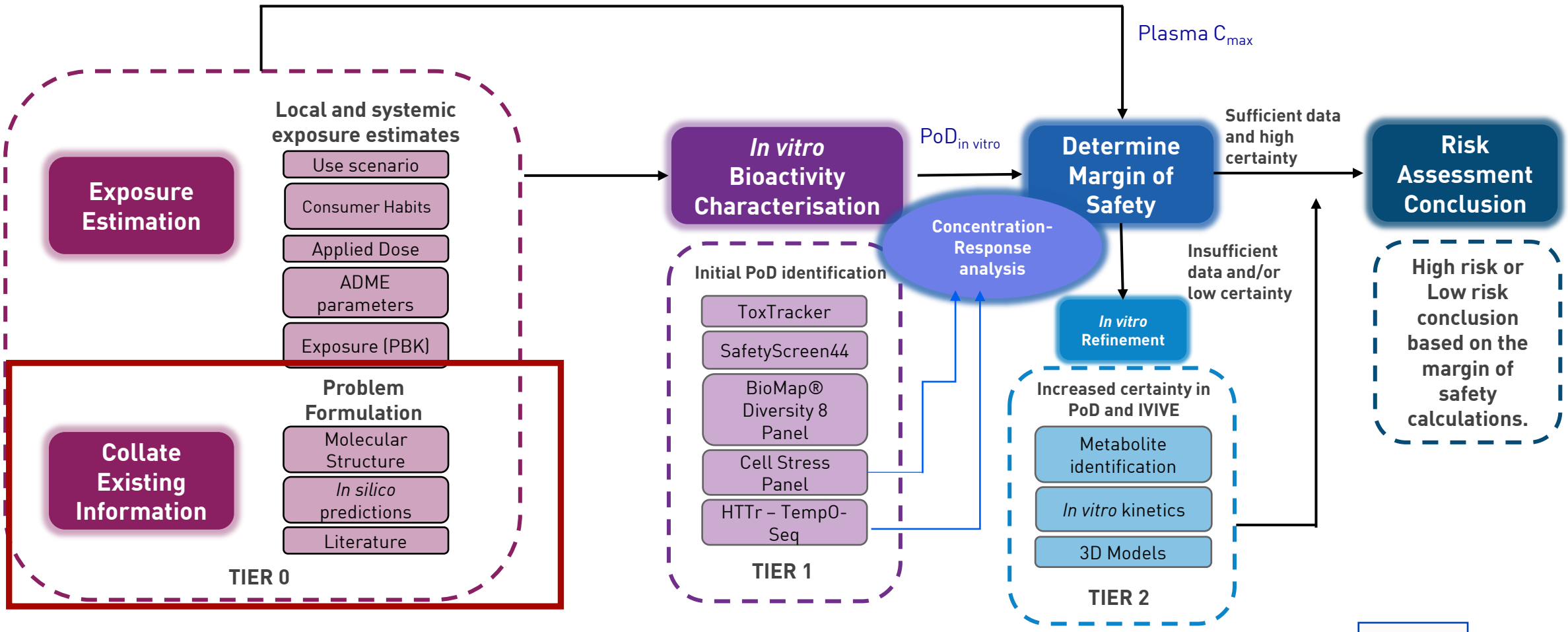
0.1% Face cream & body lotion in Europe



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

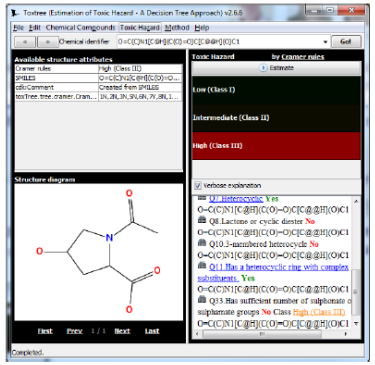
Ab Initio NGRA Framework: existing info 从零开始NGRA框架: 已知信息



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

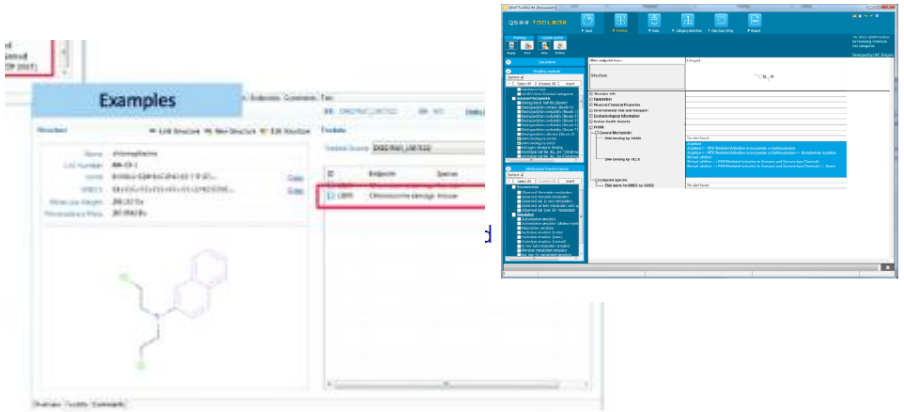
In silico tools used for predict toxicity of coumarin 计算机模拟工具预测香豆素毒性

ToxTree



Derek nexus

OECD QSAR TOOLBOX



In silico models to predict Molecular initiating events (MIEs)

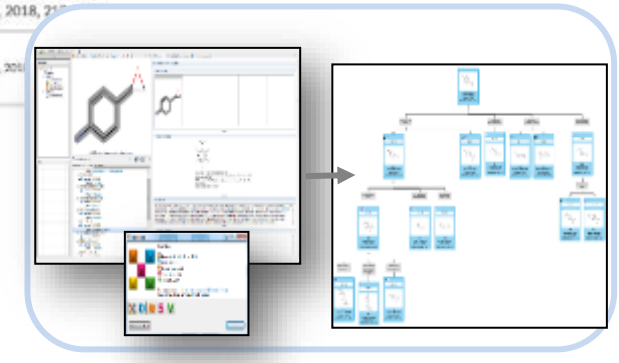
Meteor nexus

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

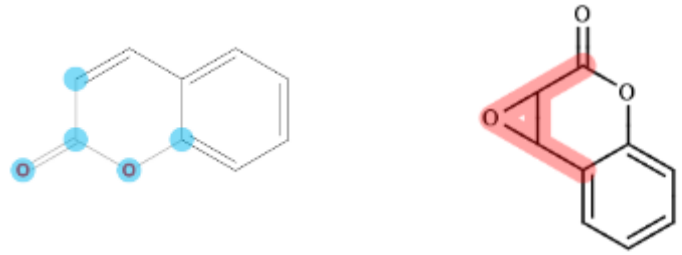
TOXICOLOGICAL SCIENCES, 165(1), 2018,

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

Timothy E. H. Allen,* Jonathan M. Goodman,*,1 Steve Gutsell,† and Paul J. Russell†



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

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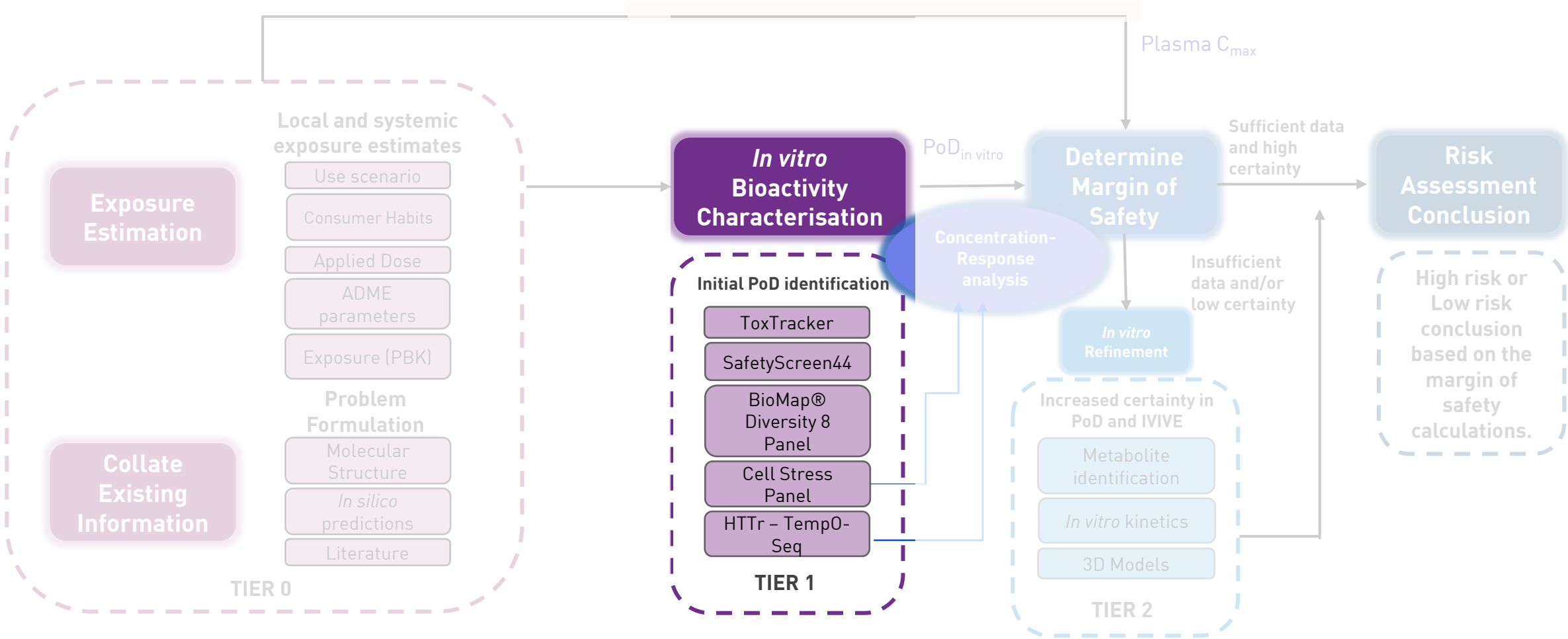
*Allen THE et al., 2018. Toxicol Sci. 2018 Sep 1;165(1):213-223

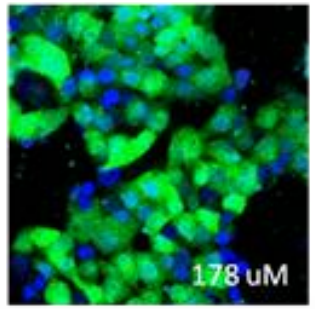
Metabolic fate predictions

Ab Initio NGRA framework 从零开始NGRA框架



In vitro Bioactivity Characterisation
体外生物活性表征

cyprotex AN EVOTEC COMPANY

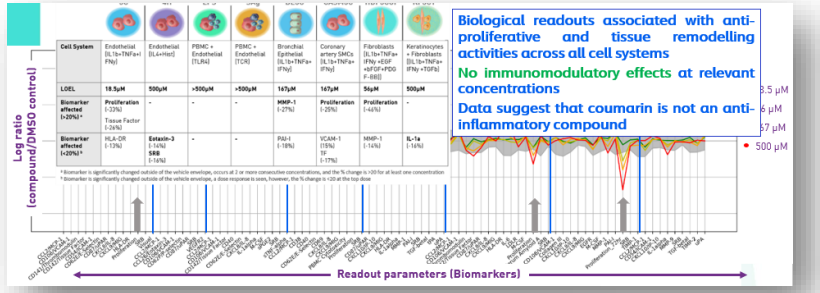


Stress pathways

- 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

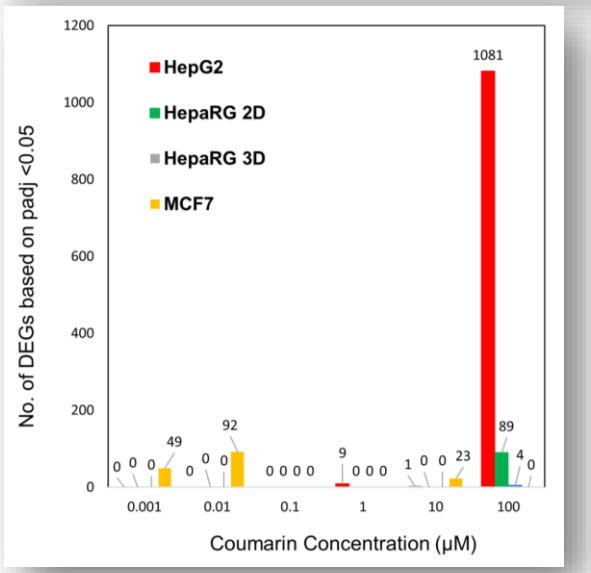
~40 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways Hatherall et al., 2020 *Toxicol Sci. 2020;176(1):11-33.*



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,



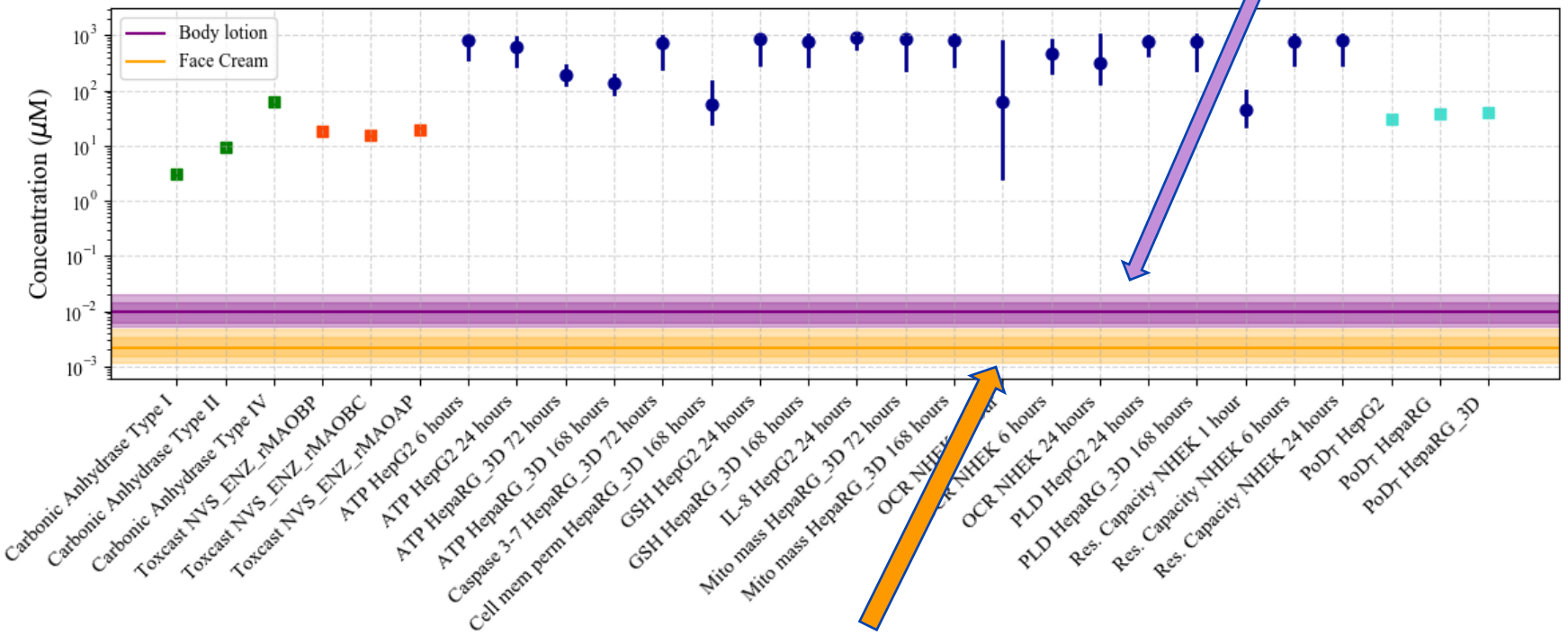
Unilever

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

Body Lotion
身体乳液（人体血液暴露量）

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

PubChem ToxCast Cell Stress Panel HTTr



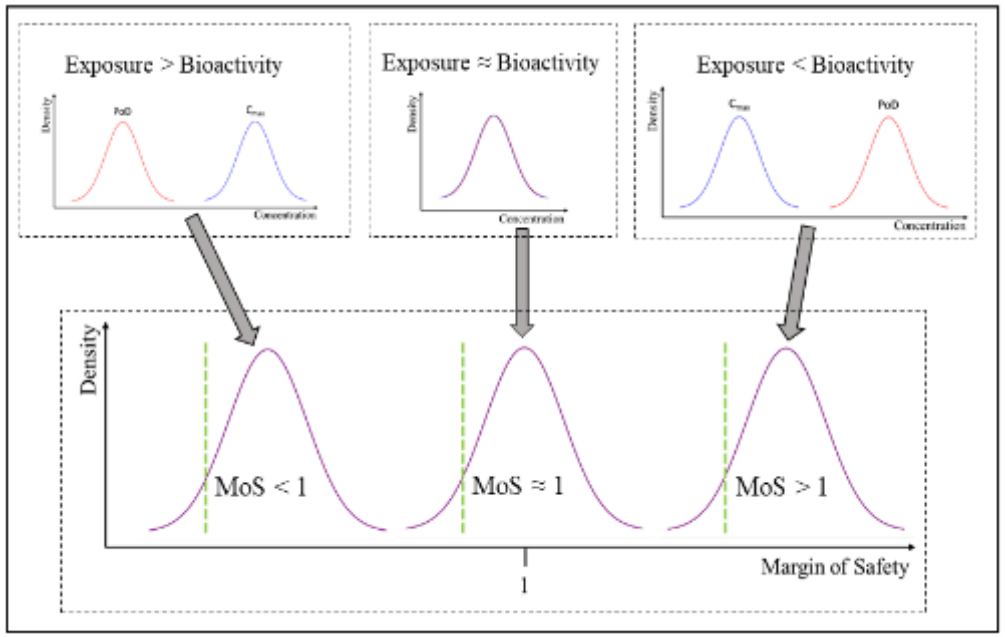
C_{max} expressed as a distribution:

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

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

Summary 总结

- Importance of understanding consumer exposure
  了解消费者暴露的重要性，包括新陈代谢的相关性
- Non-standard, bespoke data generation driven by the risk assessment question
  由风险评估问题驱动的非标准，定制数据生成
- 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
- Ensuring quality, robustness of non-standard (non-TG) work. *In silico* modelling approaches and bespoke *in vitro* solutions
  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
- Importance of defining points-of-departure and understanding adverse vs. adaptive responses 定义毒理拐点（POD）和分辨不良反应vs.适应性反应的重要性
- Understanding uncertainty in risk assessments to allow informed decision-making
  了解风险评估中的不确定因素，以便做出明智的决策
- 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

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Scientific partnership 科学合作

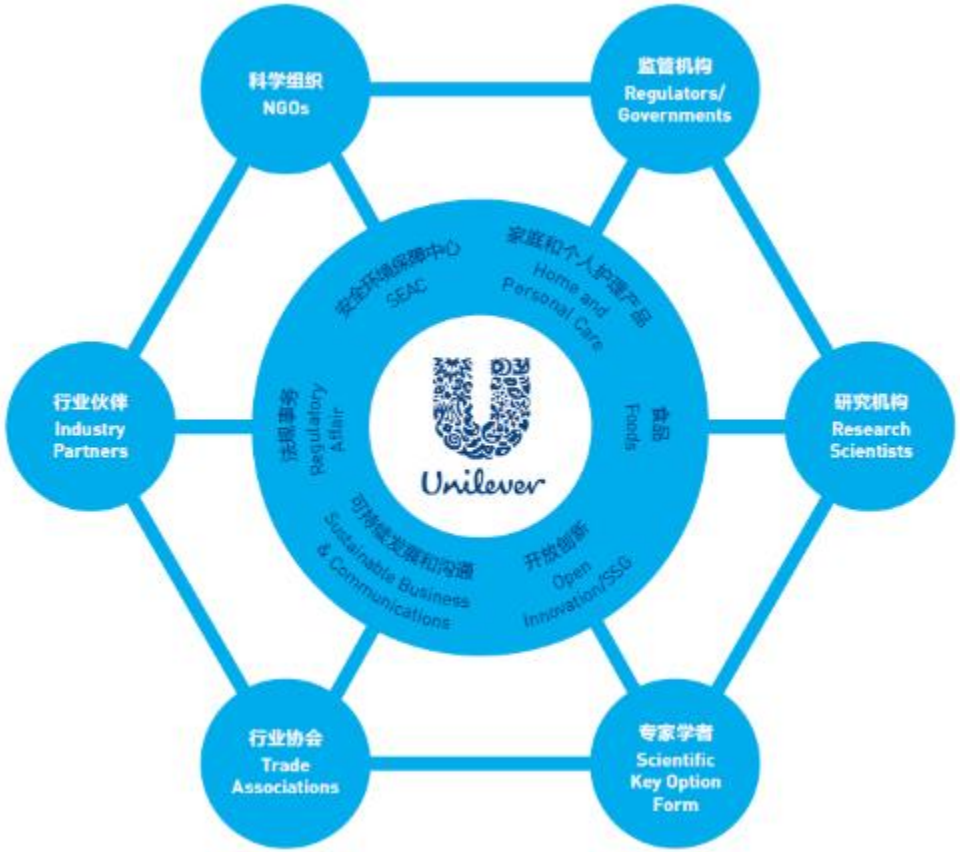
tt21c.org

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 2nd 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



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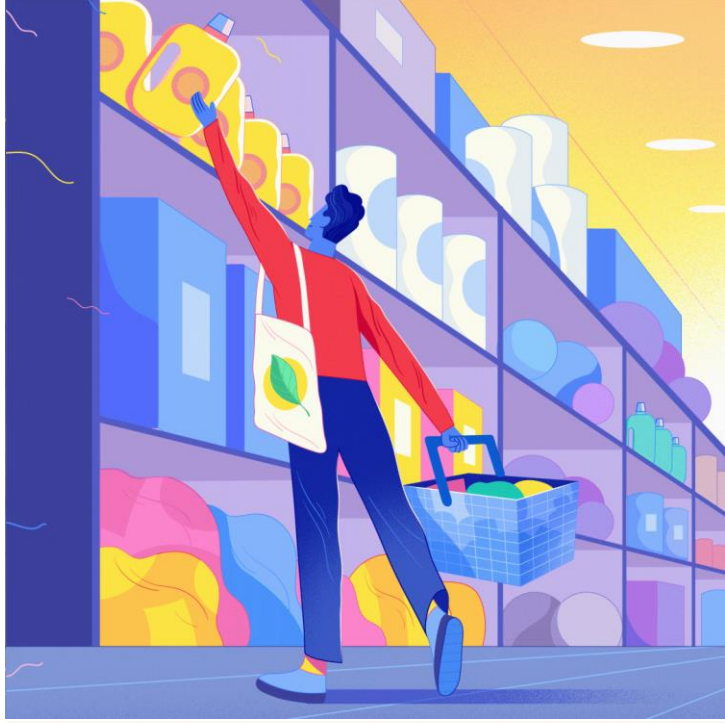

Thank you!

谢谢!

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