化妆品安全与功效评价的整合策略

For a safer world

Integrated Test Strategy for Cosmetics Safety and Efficacy Assessment

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提纲 outline

一、整合测试策略概念和背景

Conception and background of Integrated Testing Strategy

二、安全评价的整合测试策略

ITS for safety

三、功效评价的整合测试策略

ITS for efficacy

四、应用前景展望

Prospect of application

一、整合测试策略的概念

ITS：系列测试的组合，覆盖相关机制的步骤，并以合乎逻辑和假说驱动的决策程序组合，以有效利用产成的数据和获得用于全面危害或风险决策的信息。ITS can be described as combinations of test batteries covering relevant mechanistic steps and organized in a logical, hypothesis-driven decision scheme, which is required to make efficient use of generated data and to gain a comprehensive information basis for making decisions regarding hazard or risk.

不同于分层方法tiered approach

---决策是在最后一步，如皮肤刺激（0ECD 2002）；

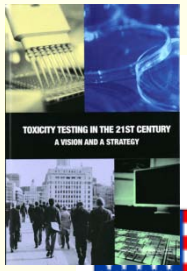
---测试方法的排序是基于平均的生物这相关性；

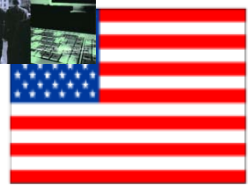
大背景

科学驱动 **science driven**

Toxicity pathway ⟶ New strategies

实用主义的替代法
Pragmatism





The Transatlantic Divide

Top-down development
of new toxicological tools

Tox-21c

3Rs=Alternative

Bottom-up support to
alternative methods and
legislative pressure

政策/法规驱动 **policy driven**

Cosmetics/chemicals ⟶ EU/OECD individual methods

3R替代与TT21C

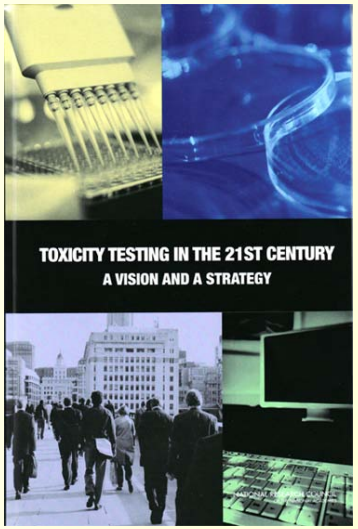
美国科学院报告（NAS Report）

---21世纪毒性试验：观念和策略

Toxicity Testing in the 21st Century: A Vision and Strategy

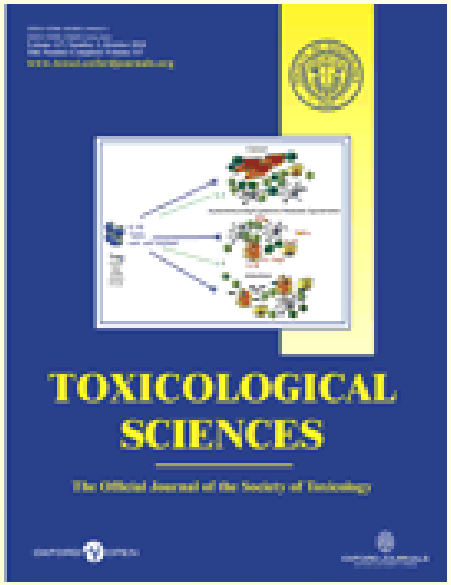
---科学与决策：推进风险评估

Science and Decisions: Advancing Risk Assessment

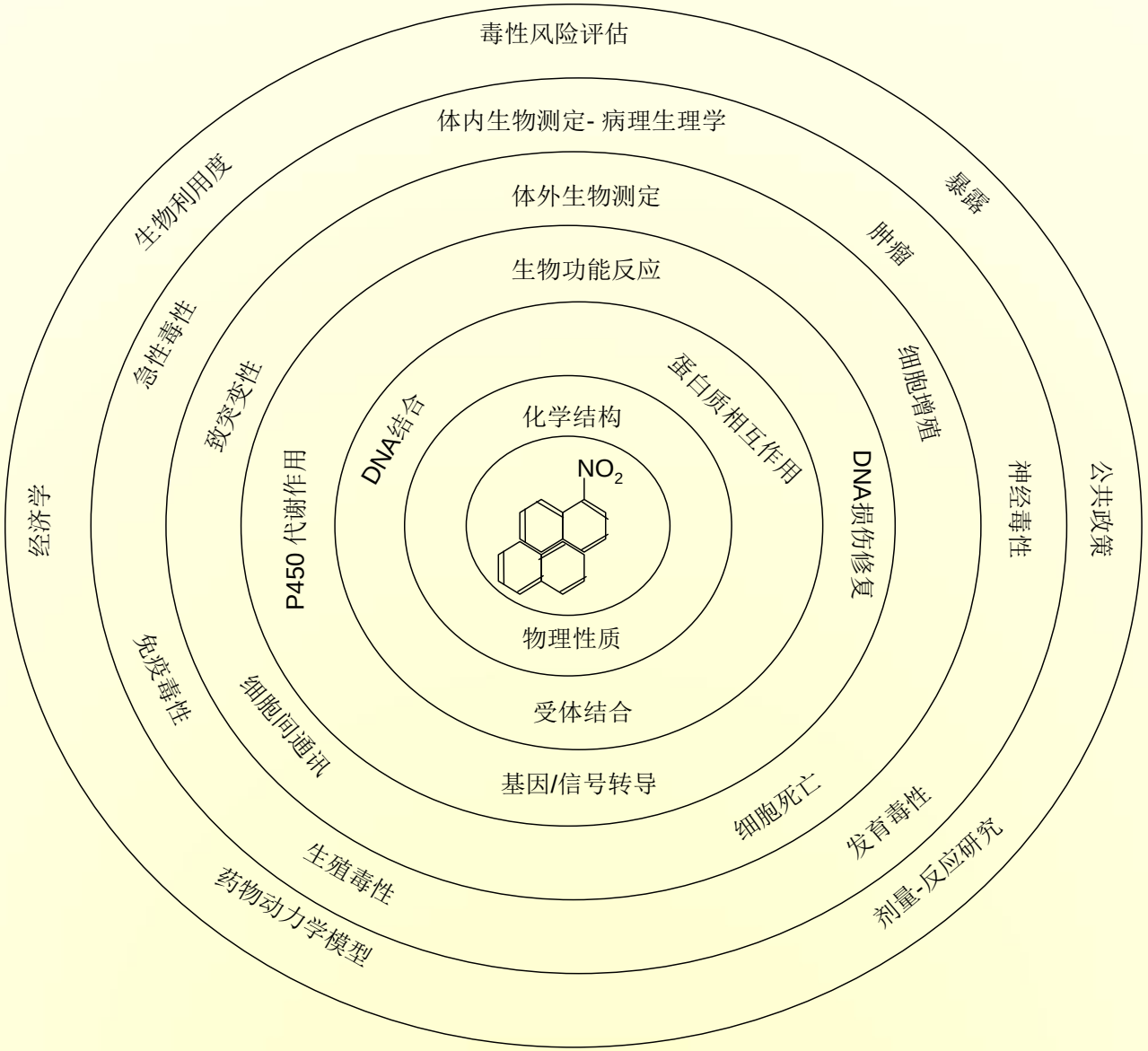


- 传统毒理学方法从1930建立
- 低通量，高成本
- 很少使用现代生物学技术
- 很少关注毒物作用模式
- 外推不确定性
- 与人群实际风险的相关性受质疑
- 大量使用动物

1.使用人源细胞培养物
系统生物学和通路的机制研究

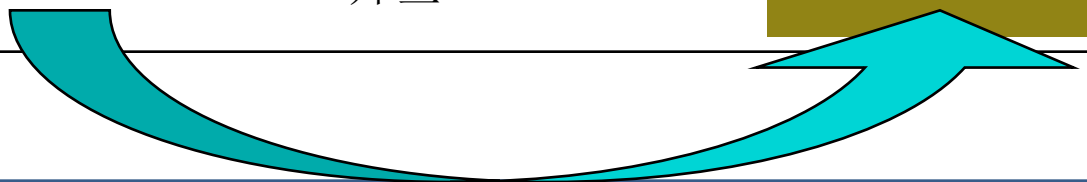


毒性预测的复杂性---单一 测试系统 局限性



化妆品整合测试策略的现状和未来

选择 I 体内实验	选择 II 分层体内实验	选择 III 体外/体内	选择 IV 体外
基于动物生物学	基于动物生物学	人体生物学为主	人体生物学为主
高剂量	高剂量	剂量范围广	剂量范围广
低通量	通量提高	高和中通量	高通量
高成本	低成本	低成本	低成本
耗时	少耗时	少耗时	少耗时
大量使用动物	较少动物	更少动物	几乎不用动物
单一终点	单一终点	毒性通路紊乱	毒性通路紊乱
	少量计算机或体外筛查	使用计算机筛查	计算机筛查



二、化妆品安全与功效的整合测试策略

Integrated testing strategy for cosmetics safety and efficacy

安全毒性实验

safety/toxicity test

Eye irritation 眼刺激：HET-CAM+BCOP+RBC+Epiocular
Skin irritation皮肤刺激：TER+皮肤模型
phototoxicity光毒性：3T3 NRU
Skin Sensitization皮肤过敏：LLNA-BRDU
Percutaneous absorption皮肤吸收：**in vitro**扩散池
Genotoxicity testing遗传试验：
Oral toxicity经口毒性：
cytoxicity screen细胞筛选试验
embryotoxicity胚胎和发育毒性：**EST**
Endocrine distrupt 内分泌干扰作用
……

功能功效实验

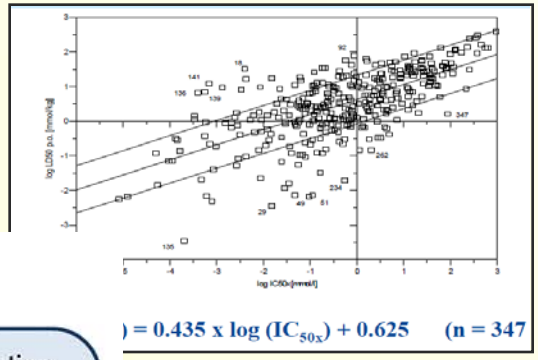
Efficacy test

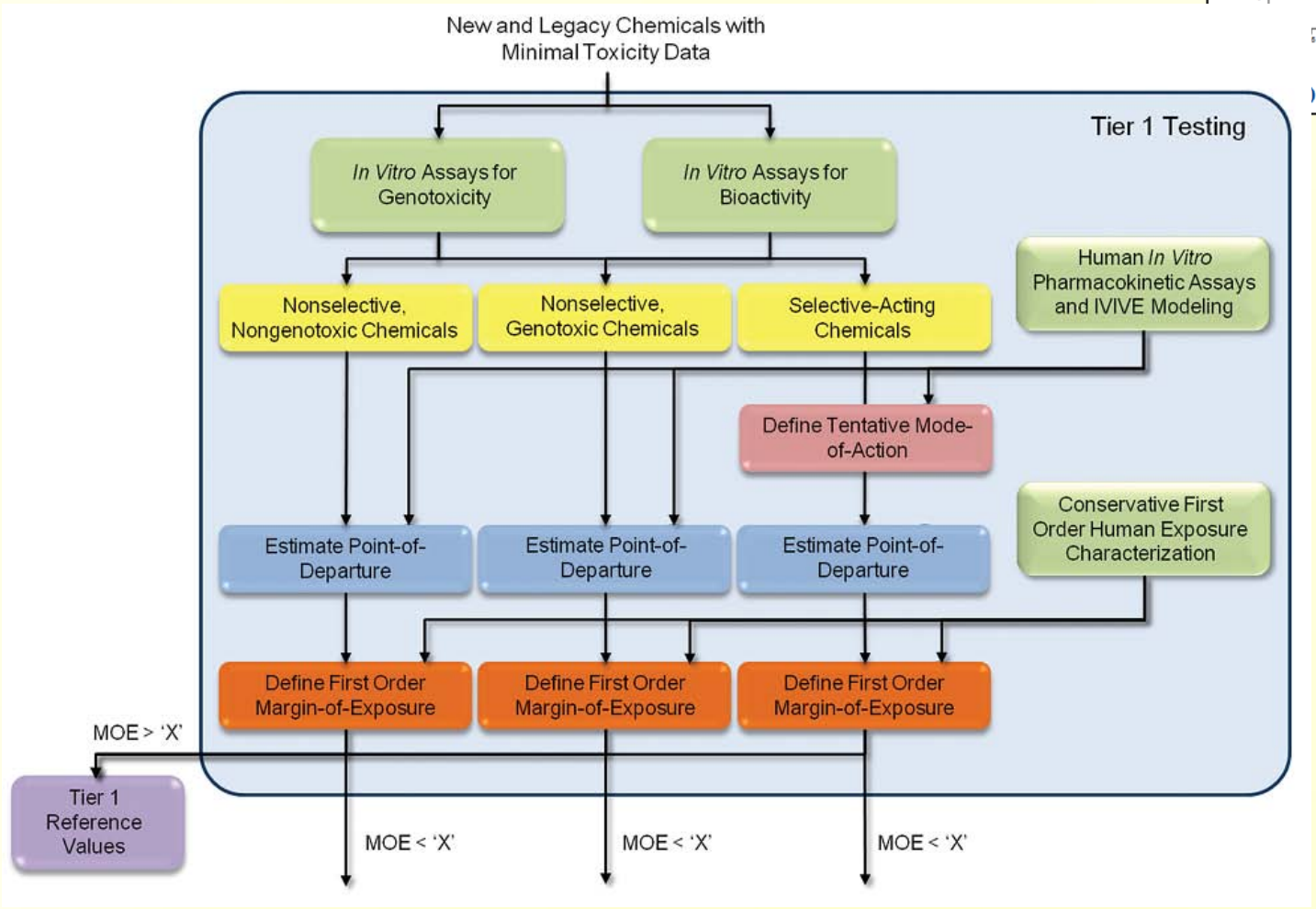
Whitening 美白作用
Nutrition 营养细胞作用
Anti-oxidant 抗氧化作用
Anti-ageing 抗衰老作用
Anti-inflammation抗炎作用
angiogenesis 促进血管生成
Hair growing 生发育发作用
Anti adipose 减肥作用
Basic cytomics基本细胞作用
Repair in vitro 体外修复作用
Patch test斑贴试验
Photo patch test光斑贴测试
SPF test instrument assay and human test 防晒指数测试（体外和人体测试）

适应性和功效测试

Adaptability and Efficacy test

细胞毒性及预测急性毒性





皮肤刺激的替代方法
Alternatives for skin irritation tests

Transcutaneous Electrical Resistance Assay (TER) （OECD430）

Positive threshold level (5kΩ)

Skin model testing 皮肤模型 OECD 431,439

EpiSkin, Epiderm

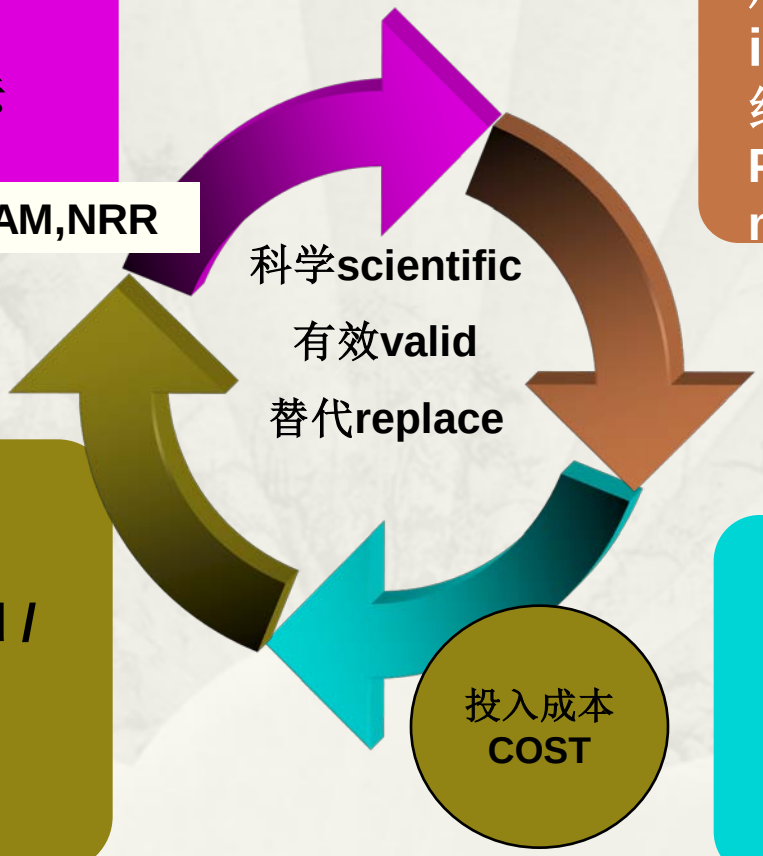
眼刺激的整合测试策略

BCOP-437,ICE-438,FL-460

法规认可方法
regulatory accept

有效未完成验证方法
valid methods

IRE,RBC,CAMVA,HET-CAM,NRR



产品配方研发
ingredients/formula
终产品安全监控
Products safety monitoring

化学品chemicals
日化产品household /
化妆品cosmetics
药品/农药
medicine/pesticide

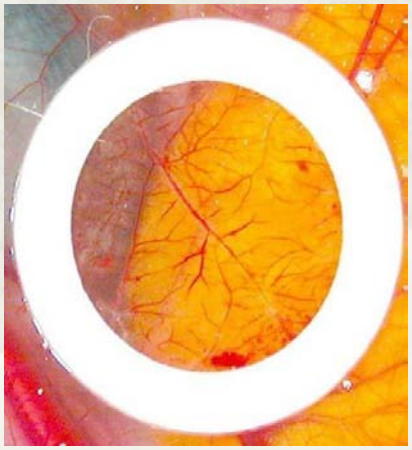
剂型form
溶解性solubility
颜色color
固体/液体Solid/liquid

眼刺激的鸡胚方法

绒毛尿囊膜　　Chorio-allantois membrane (CAM)

Hen’s Egg Test Chorioallantoic Membrane (HET-CAM)
鸡胚绒毛尿囊膜检测

Chorioallantoic Membrane Vascular Assay (CAMVA)
绒毛尿囊膜血管检测



应用举例

鸡胚绒毛尿囊膜血管试验（CAMVA）

CAMVA法计算RC50值，判定区间如下：

RC50 > 3.0%　　=　无刺激性

RC50≥1.0%≤3.0%　=　中度刺激性

RC50<1.0%　　=　轻刺激性

如果试验物质明显含有酒精，刺激性/非刺激性的阈值最大可达30%-40%

CAMVA方法的科学使用：

-- 用于轻度到中度眼刺激性的评估，

--适用于原料和配方间的研究和比较，

--产品眼刺激性预测，

--损伤作用机制的研究。

---可与其它替代方法组合提供产品全面信息。

特别用于：配方及工艺优化，

原料和产品的质控，

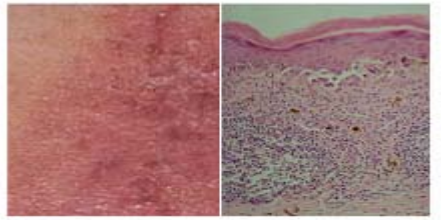
原料筛查和安全浓度，

Bovine Cornea Opacity and Permeability
牛角膜混浊和渗透性试验 (BCOP)

- **特殊试验规程Specialized Protocols:**
  - 含表面活性剂：10%稀释，20或60分钟暴露，60分钟后暴露（重点关注渗透性分数）
  - 多重暴露：原样，3和10分钟暴露，120分钟后暴露（适用于溶于有机溶剂的样品）
  - 延长后暴露：10分钟暴露，4和20小时后暴露（适用于如 H_2O_2 的活性化学物）
  - 组织学检查：可在任意试验后增加

应用举例

皮肤致敏实验替代方法
skin sensitization AAT methods



AOP

Chemical (hapten) penetrates skin and reacts with protein(s)

皮肤渗透Skin penetration
体外方法

蛋白结合Protein binding

DC activation
In vitro ?

T reaction
in vitro?

DC

Chemical is recognised by Langerhans cells which then migrate from the skin to the draining lymph node

Mature LC presents chemical to T cells

临床症状

GP Tests, HRIPT

细胞增生水平

LLNA

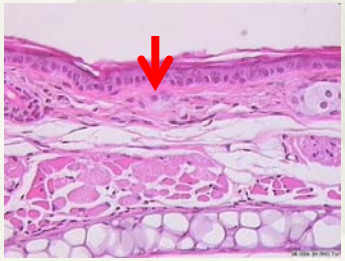
Increased number of chemical-specific T-cells released into the systemic circulation

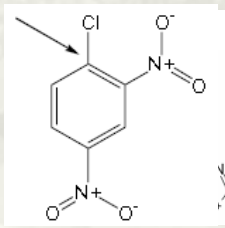
皮肤致敏的有害结局通路

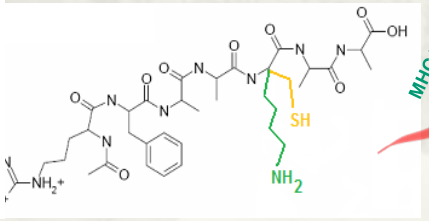
Adverse Outcome Pathway (AOP) for Skin Sensitization

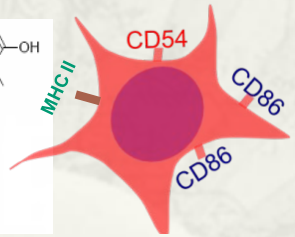
分子特性Molecular properties	分子启动事件 Molecular Initiating Event	细胞水平反应 Cellular Response	组织水平反应 Organ Response	机体反应 Organism Response

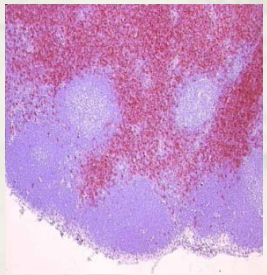
Penetration into the viable epidermis → Electrophilic reactivity → Covalent interaction with proteins → Expression of cell surface markers and cytokines → Proliferation of T-cells in lymph nodes → Dermal inflammation (after challenge)











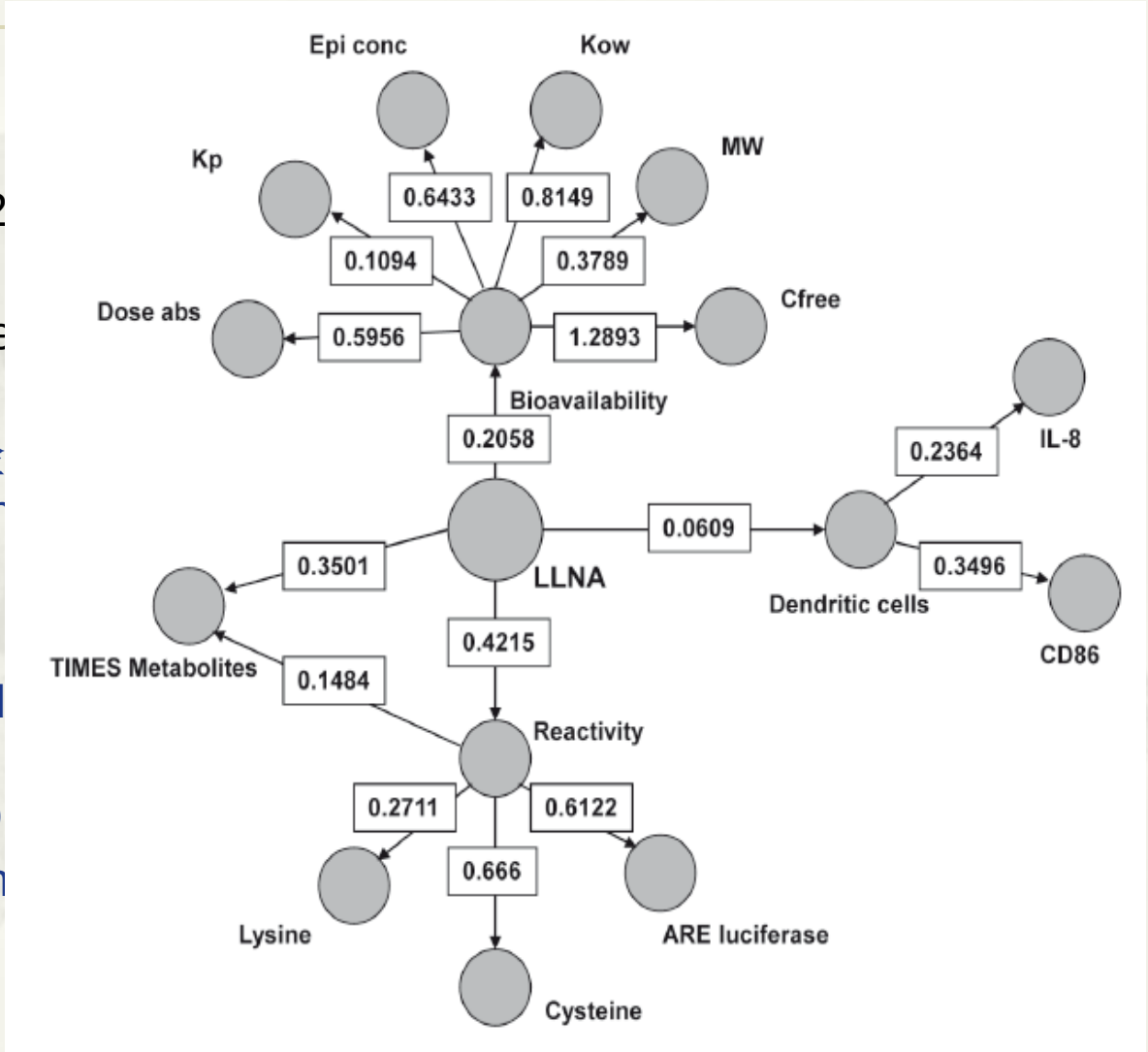
DPRA OECD 442C + KeratinoSens OECD442D + h-CLAT

LLNA 442AB

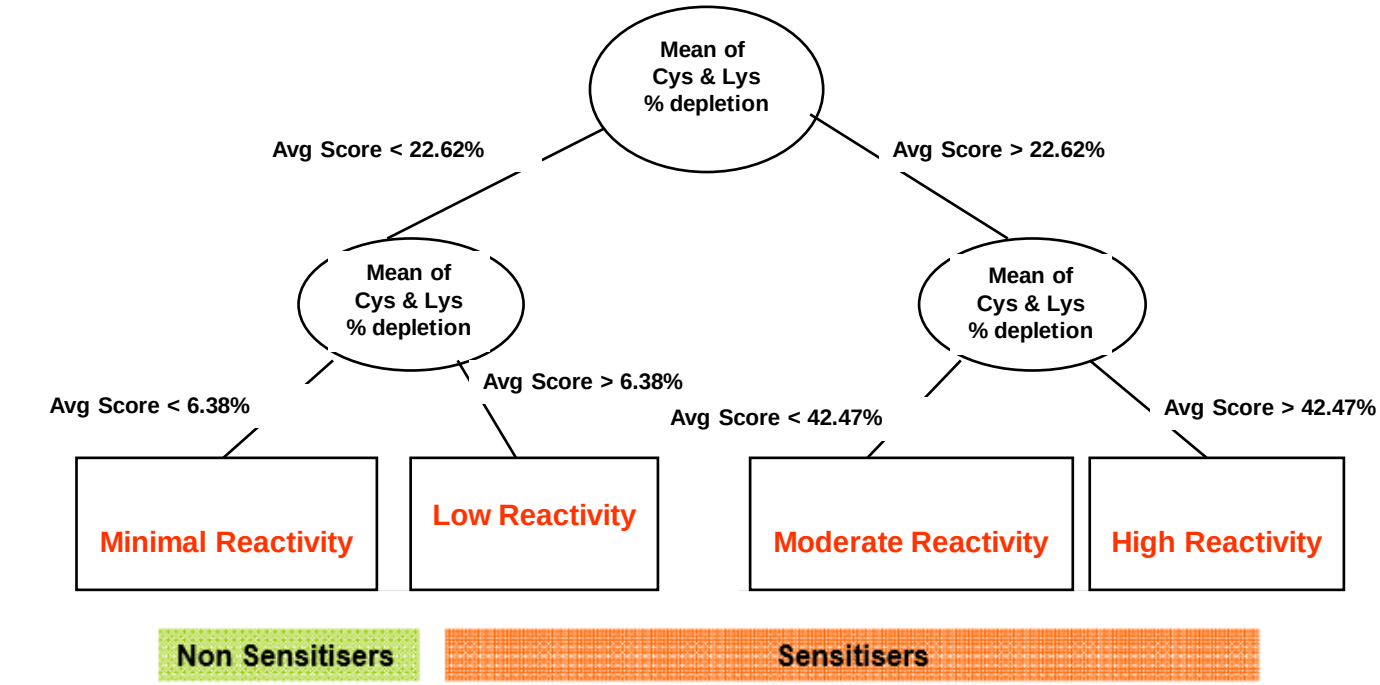
In Vitro Test Strategy

- Direct Peptide Reactivity Assay (DPRA)OECD442C,2015
- KeratinoSens,OECD442D,2015
- 人细胞系激活试验Human cell line activation test (h-CLAT)
- 骨髓U937细胞皮肤致敏试验MUSST - Myeloid U937 skin sensitization test

- Development of AOP-based Integrated testing Strategy (ITS) for hazard identificatio
- OECD Test Guidelines on th 3 methods



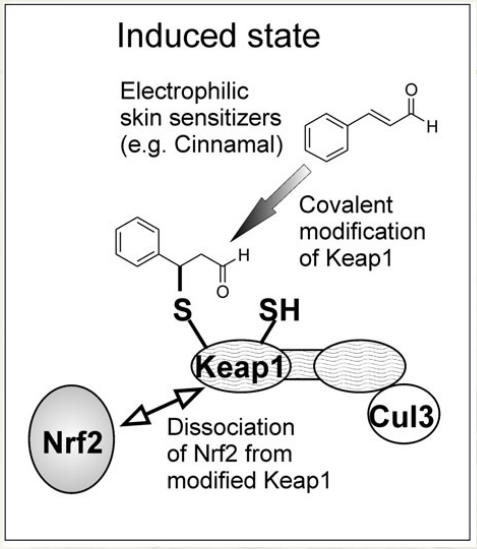
直接多肽结合反应DPRA: 预测模型



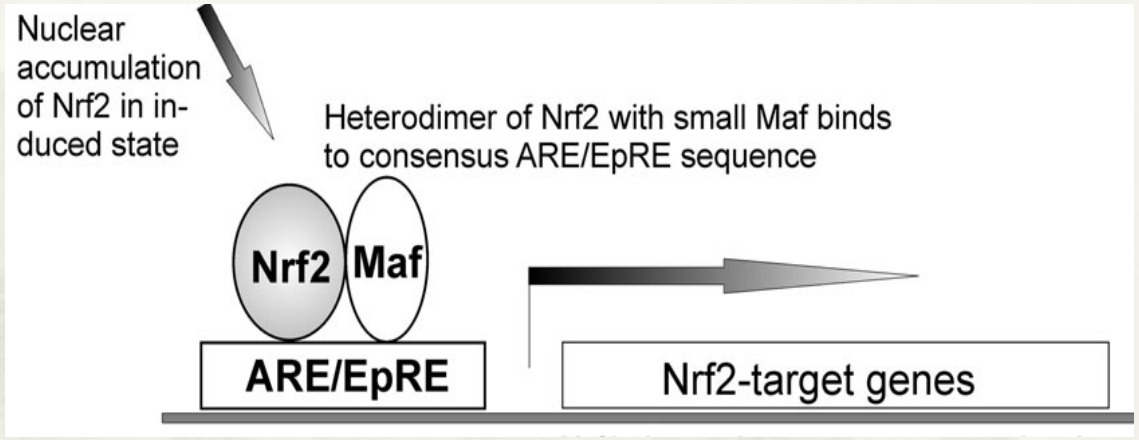
Joint Research Centre

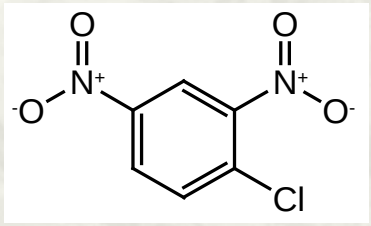
Casati, S. Non-animal Tests and their Validation Status, The EURL-ECVAM Strategy for Skin Sensitisation. European Commission Joint Research Center. Skin Sensitization Training Workshop, February 2013

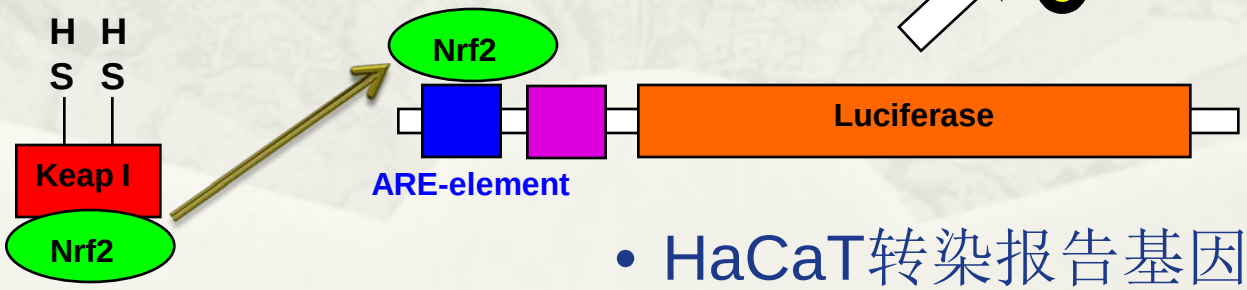
角质细胞致敏试验
KeratinoSens Assay



- 原理：Nrf-2-亲电通路：Keap1蛋白+转录因子Nrf2+抗氧化反应元件 (ARE)





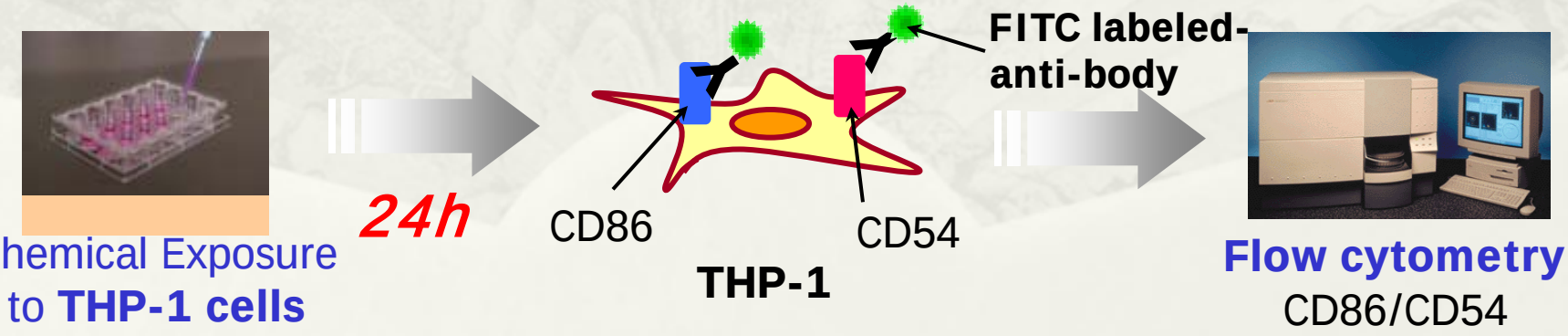


- HaCaT转染报告基因（ARE-元件+荧光素酶基因）

人细胞系活化实验
human Cell Line Activation Test (h-CLAT)

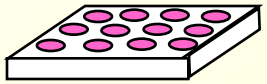
- **Prediction Model**

Viability ≥ 50% by Propidium Iodide (PI)
Positive criteria: CD86 RFI ≥ 150% and/or CD54 RFI ≥ 200%
Positive: 2 of 3 independent data at any dose should exceed the positive criteria



Slide courtesy of Kao Corporation

Overview of h-CLAT



THP-1
1x10^6 cells /mL

Culture with chemicals,
8 doses based on CV75

Flow cytometric analysis

Cell staining (CD86 & CD54)

FcR blocking

Relative Fluorescence Intensity (RFI)

$$RFI = \frac{\text{MFI of chemical treated cells - MFI of chemical treated Isotype control cells}}{\text{MFI of vehicle control cells - MFI of vehicle Isotype control cells}} \times 100$$

***MFI = geometric mean fluorescence intensity**

Prediction Model

Viability ≥ 50% by Propidium Iodide (PI)
Positive criteria: CD86 RFI ≥ 150% and/or CD54 RFI ≥ 200%
Positive: 2 of 3 independent data at any dose should exceed the positive criteria

*: Ashikaga et al., 2006 Toxicol In Vitro 767-73., Sakaguchi et al., 2006 Toxicol In Vitro 774-84.

Slide courtesy of Kao Corporation

神经毒素体外替代方法

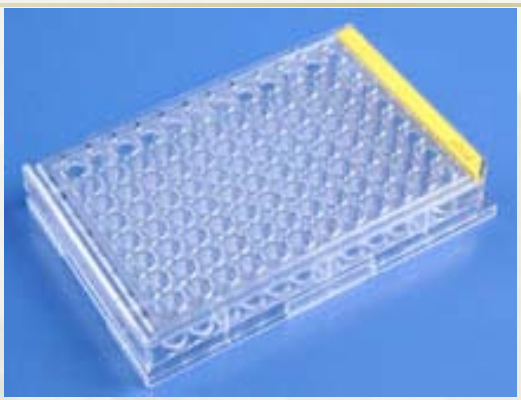
方法名称	试验系统	标准化	检测样品
促离子谷氨酸受体检测神经毒性	大鼠和小鼠脑膜；转染细胞和爪蟾卵；原代神经元培养	检测软骨藻素的方法已标准化	所有化学物、神经毒性、海洋生物样品
$GABA_A$受体检测神经毒性	大鼠和小鼠脑组织和神经原代培养，表达$GABA_A$受体的工程细胞系和爪蟾卵	优化中，积累数据以应用于组合筛查	有机氯杀虫剂、惊厥药、驱虫药阿维菌素、毒蝇鹅膏菌毒等。苯环类、巴比妥类药物和麻醉剂等
电压敏感钠离子通道检测神经毒性	脑组织；原代培养大鼠或小鼠神经和肌管；人或啮齿类神经细胞系；表达神经钠离子通道亚单位的爪蟾卵	正进行室间转移，美国FDA已批准用于确证雪卡毒素，正在等待AOAC认可为替代小鼠生物试验的方法	化学物、农药、神经毒素、贝类毒素、蝎毒素，杀虫剂
神经细胞突起生长形态学测定和生化试验检测轴突病变神经毒性	外植体培养、源于成神经细胞瘤和神经胶质瘤的细胞系，神经元	开发和优化中，需要积累基础数据	有机磷酸酯类化合物、工业化学物、有机磷酸酯类药物、抗肿瘤药物
神经酯酶试验体外筛查有机磷化合物神经毒性	大脑细胞重聚团；大脑匀浆；人、大鼠和小鼠神经细胞系	已在多个实验室使用，实验室间一致性较好。	有机磷类和氨基甲酸酯类杀虫剂、农药和工业化学品、有机磷类药物制剂
神经细胞乳酸脱氢酶（LDH）释放试验	原代培养细胞（神经元和星形胶质细胞）	常规试验方法	工业化学物，神经毒素
神经毒性试验的脑细胞聚集培养高内涵方法	大鼠脑细胞聚集培养	已开发和用于研究实验室/ACuteTox项目开发	急性神经毒性评价，

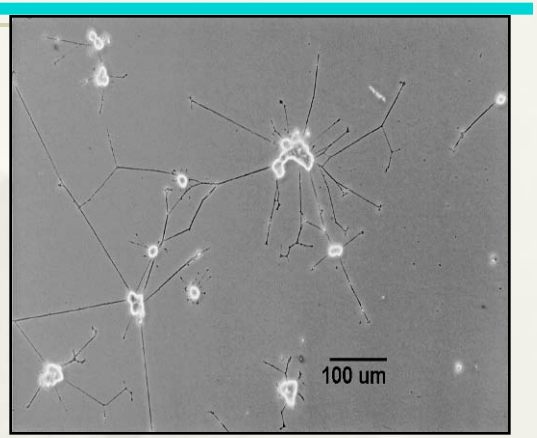
神经毒性的体外方法

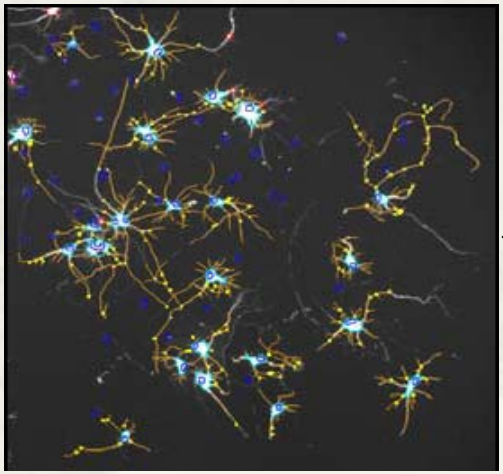
* 体外方法依据脑发育过程中的关键事件
  * 增殖、分化、生长、突触形成、髓鞘形成、凋亡
* 检测终点可以应用高通量/高内涵技术
  * 细胞水平的检测点，生物标志物，分子信号
* 便于从已知的神经毒物建立训练集，提高检测方法预测未知毒性的能力

–为进入下一步测试的先后顺序提供数据

基于高内涵的神经毒性检测技术
High Throughput Cell-Based Assays







High Content Analysis

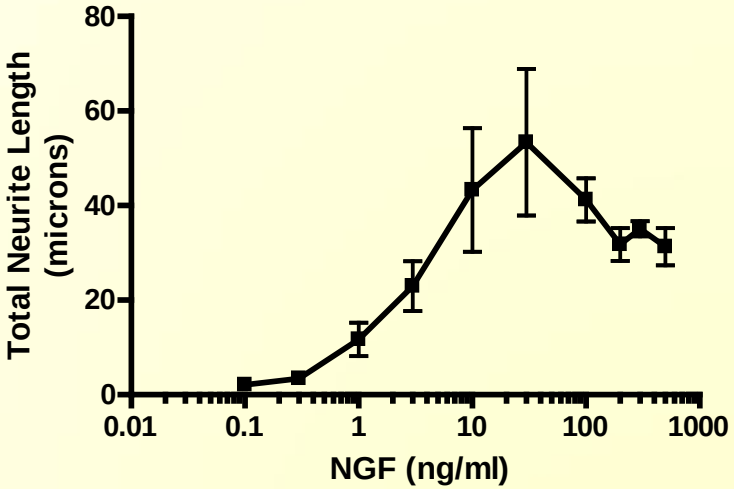
- 高通量成像
- 细胞水平数据
- 非常适合神经毒性的研究和检测

输出: 自动分析96孔板，耗时20-30 min
(200 细胞 x 96 孔 x 10 终点/细胞 = 192,000 数据)

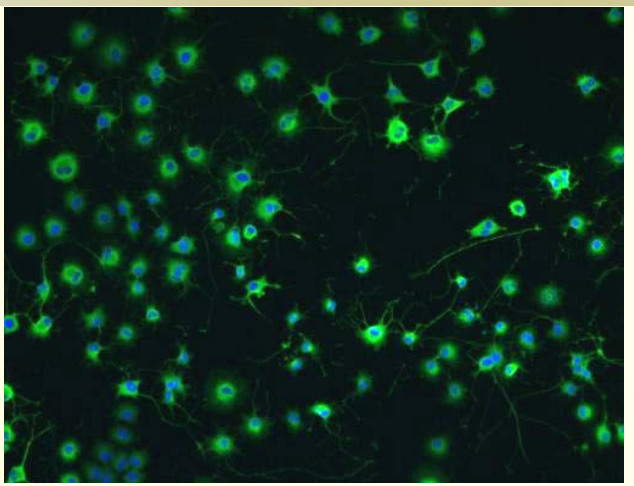
原代神经细胞或细胞系的检测：轴突生长

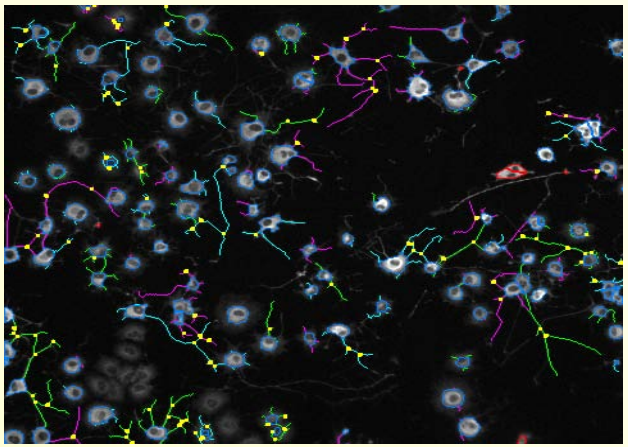
NS-1 Cells (Clonal PC12 cells)

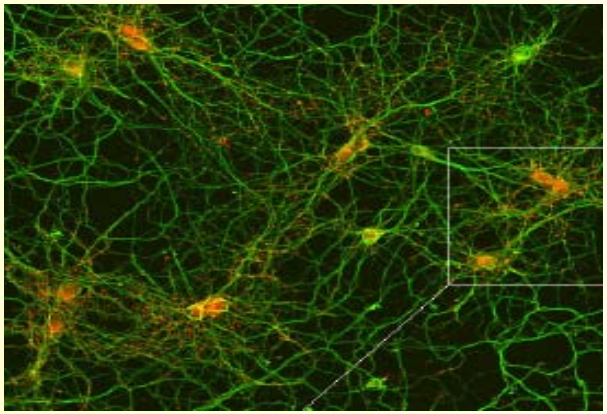
- 检测化合物刺激/抑制轴突生长作用（如NGF）
- 4天后固定和染色
- 30 min自动检测
- 多种靶标的荧光标记：CY3突触素，FITCβ-微管蛋白，DAPI



NGF Concentration Response







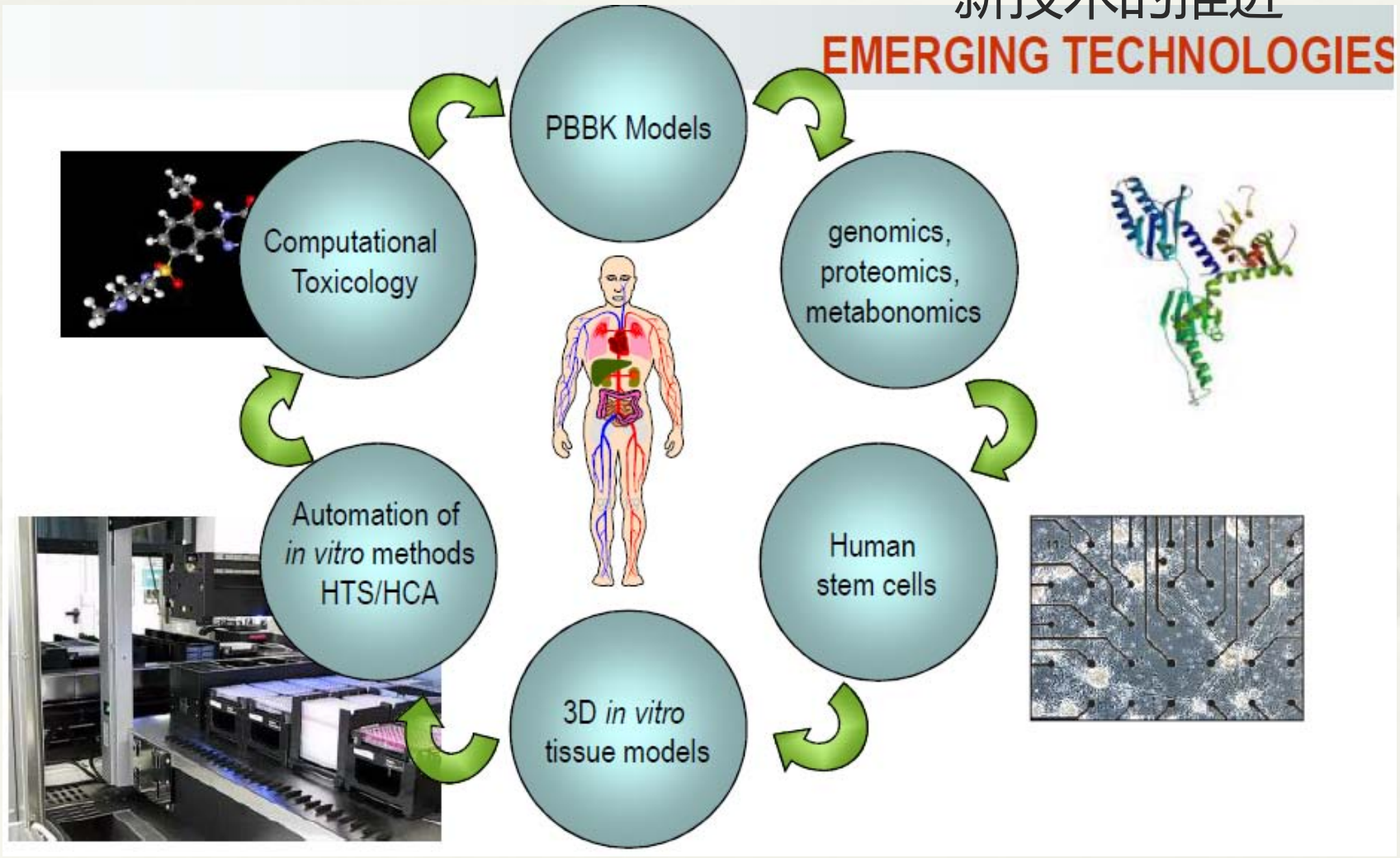
神经毒性检测方法的验证

- 建立神经毒性参考物质库神经毒性？
  发育神经毒性？
  相同机制？
  复合机制？
  种属差异？
- 验证的模式
  传统验证？
  模块验证
  证据权重？
  组合策略？

Human and Animal Data	Only Animal Data
amphetamine	acrylamide
chlordiazepoxide	benzene
cocaine	cadmium
diphenylhydantion	chlorpyrifos (oxon)
hexachlorophene	dieldrin
ethanol	ketamine
lead	methadone
methylmercury	methamidazole
PCBs	methanol
terbutaline	methylazoxymethanol
thalidomide	propylthiouracil
trans-retinoic acid	trichloroethylene
	triethyltin
	trimethyltin
	valproic acid

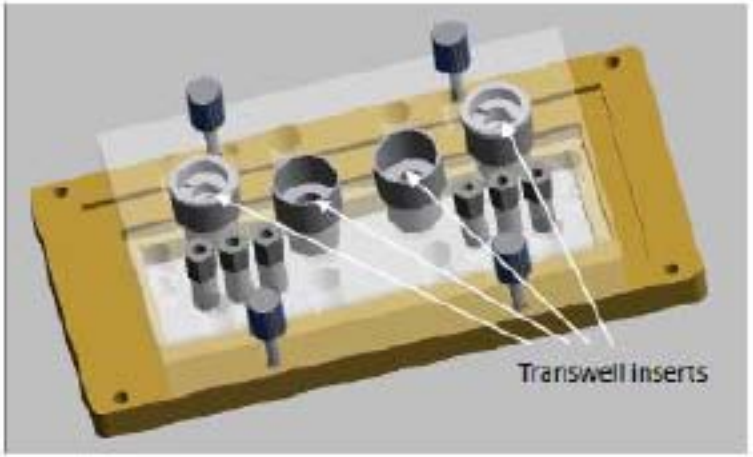
技术创新无止境

新技术的推进



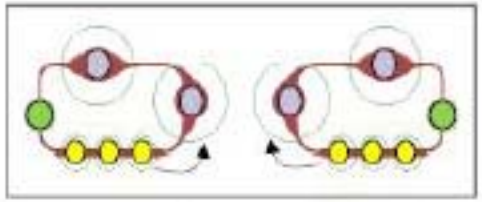
Pathway Testing – toxicogenomics, etc.

The Multi-Organ-Chip (MOC) technology



Laboratory bioreactor

- two peristaltic micro-pumps per chip
- two media perfusion circuits per chip
- adopted to use of Transwell-inserts
- two MOC's (4 circiuts) per bioreactor



MOC's of microscopic slide-format

- peristaltic micro-pump
- Transwell inserts
- injection port

Innovation alternatives methods

2015-2016

1. Integrated testing strategy for skin and ocular irritation
2. AAT for children skin care products

   --more rigorous evaluation and classification standard

   --more specific testing endpoint and time

   IL-1ra/IL-1a, TRPV1（VR-1）+Ca 2^{+}

3. AAT anti eczema of health care products

   -- CD4+ T Th-2

   --sensory neuron Ca2+ mobilization and CGRP release

4. Oral Irritation and Anti-inflammation predictive

   -- related to BCOP model

   --K3/K67,P63 biomarker

   --imagine fluorescence

……

Standardization

• OECD TG 431,432,437,439,442A,442B,442C, 460
ISO 10993.5-10,
SN/T 2285, 2328, 2329, 2330, 3898, 3899
GB/T 21769, 21757,21804,21826,
ECVAM DB-ALM:INVITTOX n 3,47,54,78,96,100,109,108,113,127 ,139,…
ICCVAM/ NIH: No 02-4502,04-4510,07-4618

+

Customization

•Ocular: CAMVA, CAMVA+BCOP

• Skin Irritation: Monolayer cell +3D Skin Model

• oral mucous membrane irritation

• Establishing an in vitro screening test for developmental neurotoxicity

• Personal care products in vitro test based

•TRP channels family at infant skin development and mechanism of mediated skin sensitization

•Anti-irritation study by 3D skin model

In Vitro Skin irritation/anti-irritation

In Vitro Skin Corrosion-MTT (Episkin-C)

In Vitro Skin Irritation-MTT (Episkin-M)

In Vitro Skin Irritation -MTT+ILa (Episkin-I)

Keratinocyte testing for skin irritation for ingredients – cytokines

In Vitro Skin Irritation Inhibition Assay by skin model-MTT+ILa (SDS)

In Vitro Skin Irritation Inhibition Assay by skin model-MTT+ IL-8+PGE2 (PMA)

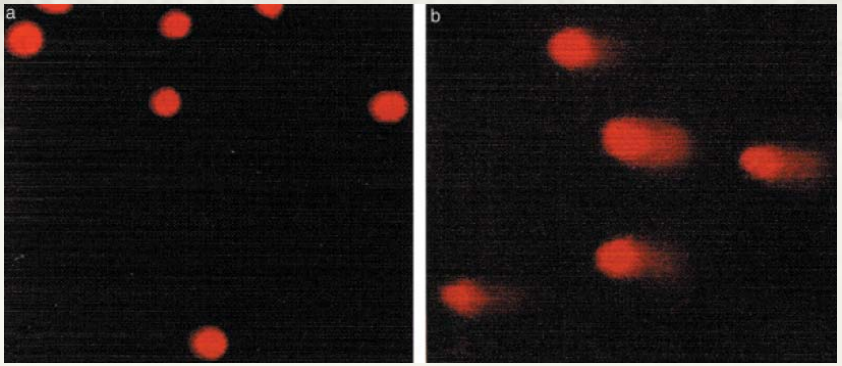
Keratinocyte anti chemoline/ cytokine assay(IL-8\CXCL-1\PGE2)

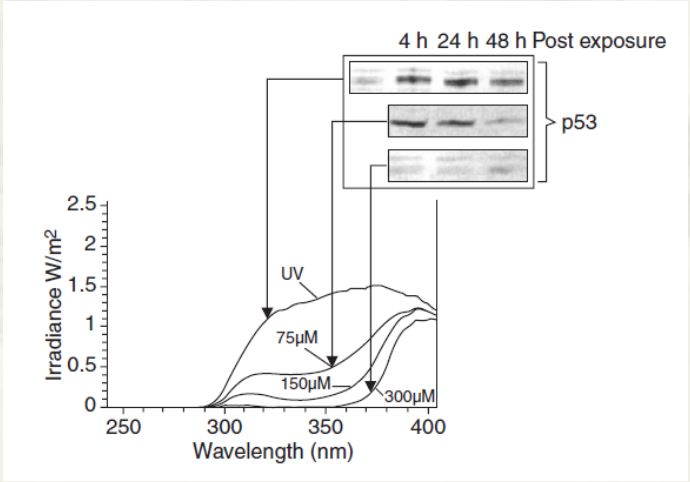
Antimicrobial peptide assay β-defensin release

In Vitro Efficacy Testing

Epidermal Protection Against UV and free radical

NHK anti-oxidant assay induced by UVB--MTT, lipid peroxide (C11-Fluor probe)
NHK anti-oxidant assay induced by UVB or chemical ---JNK1/2 phosphorylation
Skin model(Episkin) sunburn cell assay-histology
3D Human skin model anti-oxidant assay induced by UVB or H_2O_2 -- MTT,MDA





In Vitro Efficacy Testing

Keratinocytes, structure and function of epidermal barrier

NHK migration or proliferation -imaging and /or maker expression
Epidermis to dermis migration-imaging
NHK differentiation-- marker expression and ECIS
Skin model(Episkin) differentiation--marker expression
NHK or Skin model/ Episkin Hyaluronic acid synthesis or hyaluronidase inhibition
Proteoglycan of ECM by NHK or Skin model/ Episkin by fluorescence
Cell adhesion and cell junction by NHK or Skin model/Episkin--fluorescence

Anti-aging assay

Aged fibroblast prevention by inhibition β-galactosidase
Aged fibroblast tropoelastin synthesis
Aged fibroblast ECM assay or procollagen synthesis by staining
MMPS release assay by chemicals stimulation

紫外线光损伤的生物学
----美白剂筛查的整合测试

促进角质剥离
表皮周转/**黑色素排出**

枣 果

Promotion of skin turnover

阻止紫外线

1

Chamomilla ET,
氨甲环酸

阻止炎症因子 产生
抑制黑色素细胞活化

黄芩根

Inhibition of ET-1 production

2

Melanocyte

茵陈蒿花

Inhibition of melanin uptake

5

CHANEL PRECISION
Blanc Essential series

甘草类黄酮

3

Anti-tyrosinase activity

4 白皮

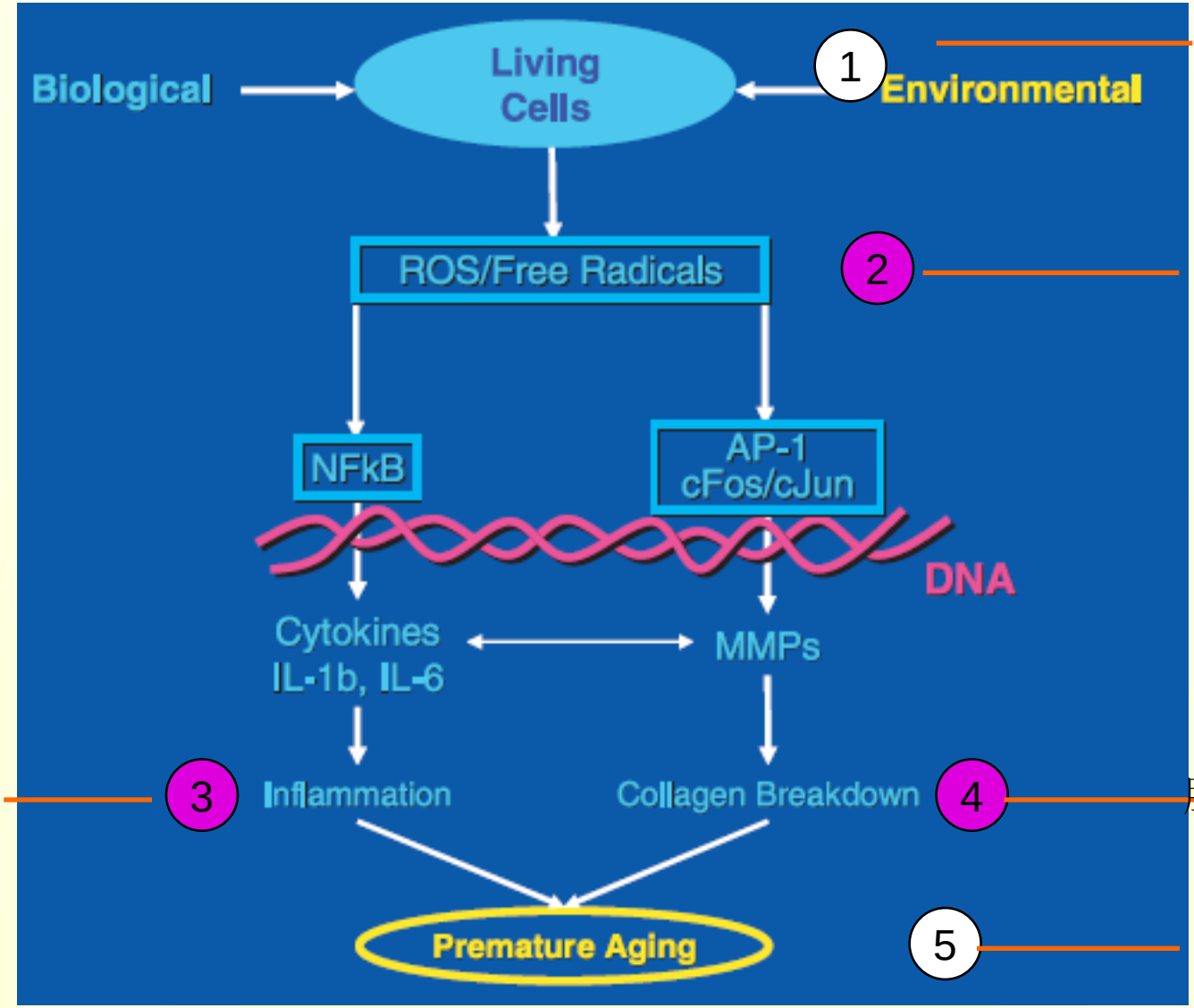
抑制黑色素小体
抑制黑色素小体成熟-转运-传递

Inhibition of melanin production

OLAY (P&G)
Natural White Healthy Fairness

抑制黑色素合成
抑制Tyrosinase,Tyrp1,促进分解
熊果苷、曲酸、鞣花酸、亚油酸，Magnolignan，甲氧基水杨酸钾

皮肤细胞老化过程及整合测试



1 防晒/抗紫外线

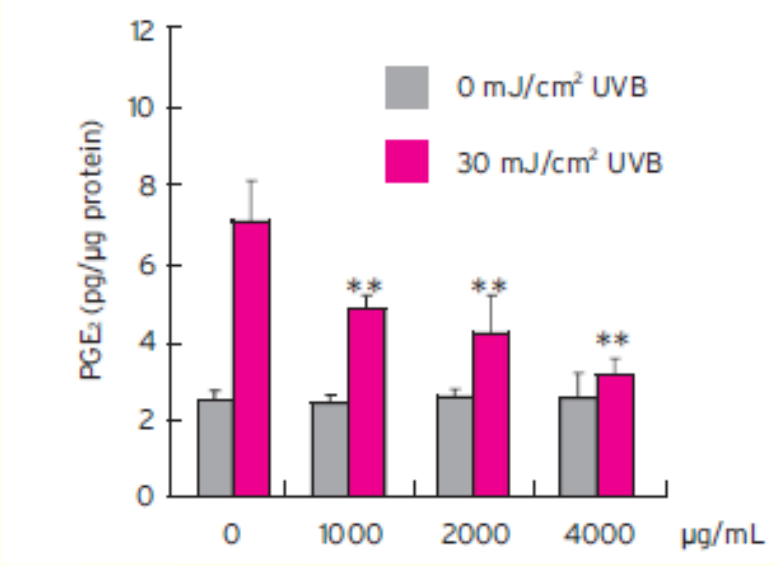
2 抗氧化/自由基

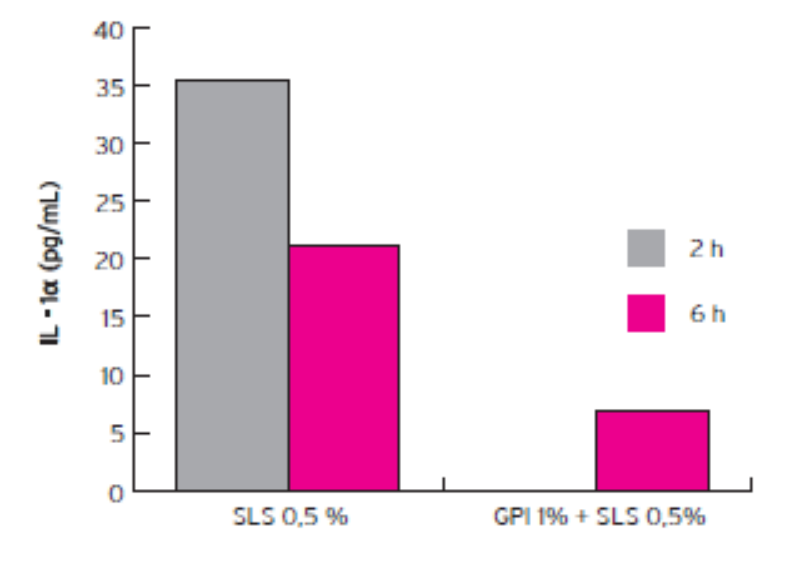
抗炎 3

4 胶原和弹性蛋白

5 清除老化产物

抗炎症试验*Anti inflammation assay*





Keratinocytes were pretreated with different concentrations of test substance for 24h, then exposed to UVB, PGE2 secreted were quantified by ELISA.

Test substance with or without SLS is applied for 24h on Episkin. After exposure, collected medium and assay the IL-1α by ELISA.

要创新不要炒作

上海某高校2009年硕士论文：“**化妆品安全性评价中皮肤毒性若干替代实验方法的研究**”

-----***通过构建重组人EpiDerm****皮肤模型，建立检测化妆品的皮肤腐蚀性/刺激性的替代实验方法*

河北某高校2011年硕士论文“**利用体外构建的组织工程皮肤模型进行皮肤刺激性检测的相关研究**”

----*根据欧洲替代实验确认中心20种物质的检测结果显示两种模型都适用于进行皮肤刺激性检测，而****利用永生化细胞构建的皮肤模型****的敏感性和特异性均高于利用原代培养细胞构建的皮肤模型。*

2013年河北某高校硕士论文“皮肤模型的构建及在检测药物化妆品中的应用”

----*本研究获得主要结果包括构建了皮肤表皮模型；****模型验证过程中，与动物试验进行对比****，准确率达70%。*

2015年某作者文章(审稿)：“SkinEthicTM重组皮肤模型对无水乳液的刺激性评估”

---- ***SkinEthicTM购于美国MatTek公司****。*

……

支持国内企业使用替代方法

目前化妆品动物实验存在的问题：

1. 动物实验质量：行政许可？CNAS认可？AAALAC认证？
2. 非特备案检测机构恶性竞争?
3. 动物实验结果的使用

-----目的：合格？不合格？

-----作用：保证产品安全？提升产品质量？

-----报告内容：过于简单，过程不透明，GLP规范？

4.安全性测试的看法

----越便宜越好？

----只是为了报批或报告？

----了解产品的安全性？为了质量持续改进？

接受和应用替代方法，你准备好了吗？

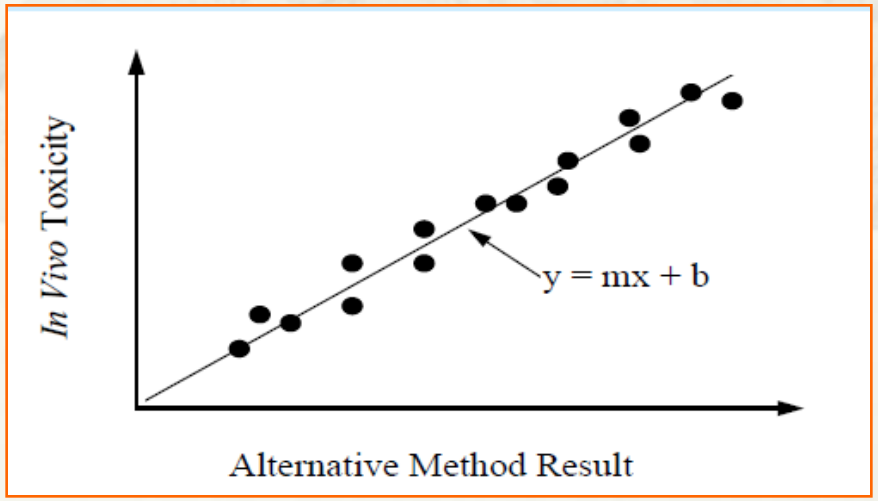
附、替代方法的标准化与验证

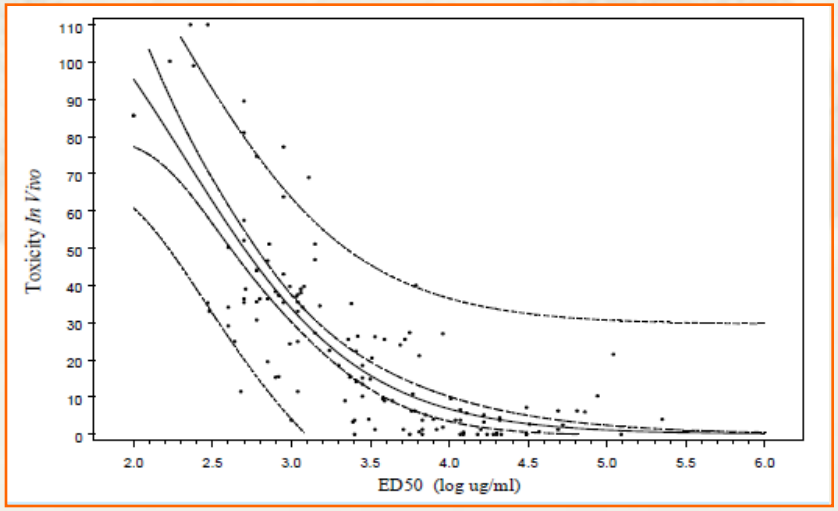
体外实验≠替代方法

替代方法=体外实验+预测模型

预测模型

体内与体外的相关性：可能很简单，可能很复杂





替代方法的标准化与验证

什么是验证Validation?

为了明确的目的，对特定试验、方法、程序或评价的相关性和可靠性建立程序的过程。

为什么要验证？

---与体内试验不同的系统的评价模型

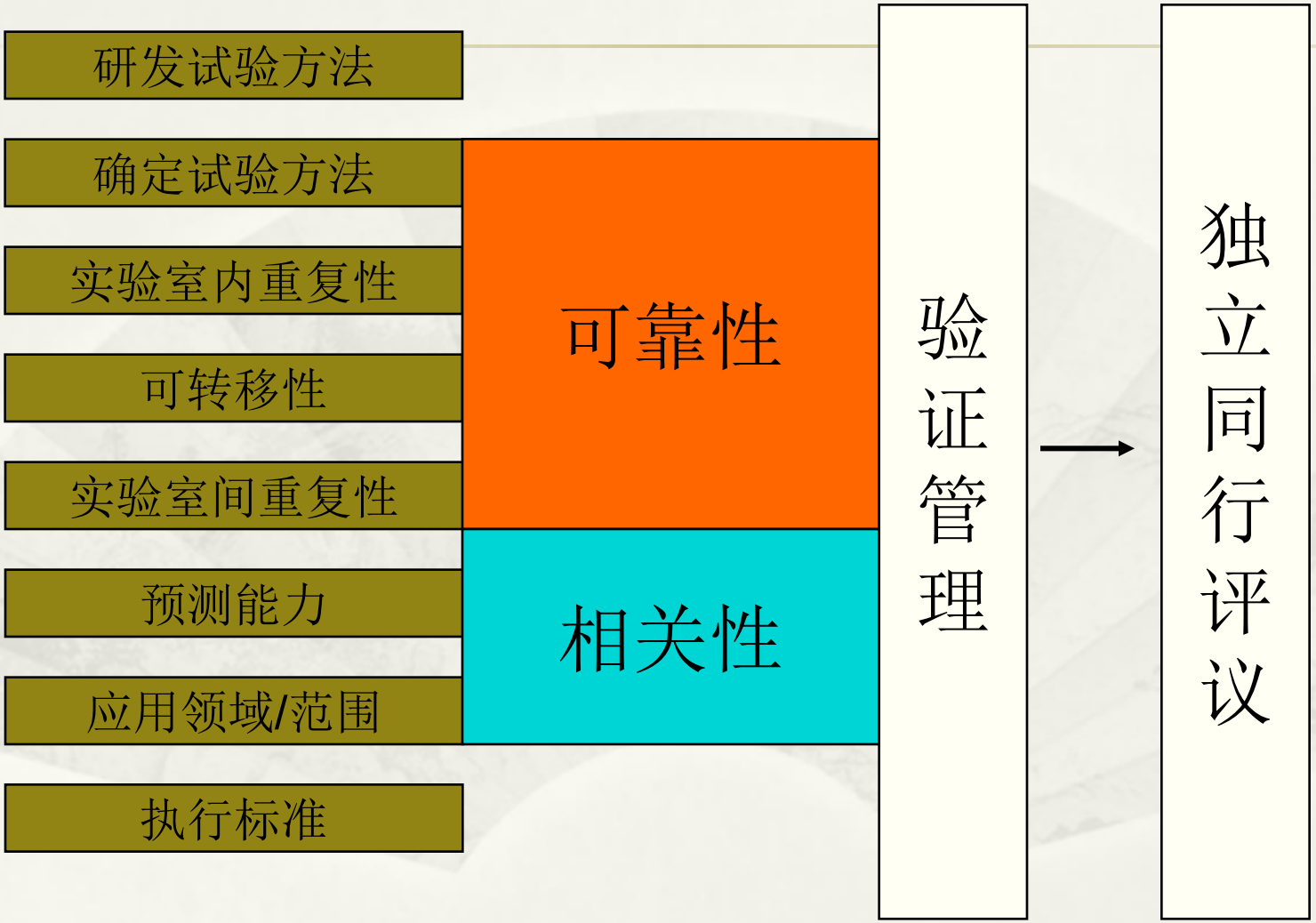
---替代技术成为趋势

---技术革新和毒理学现代需要

---与动物试验比较

---说明与人体健康的相关性

验证的目的



×为了替代而替代，无健康或环境相关性

验证的评价指标

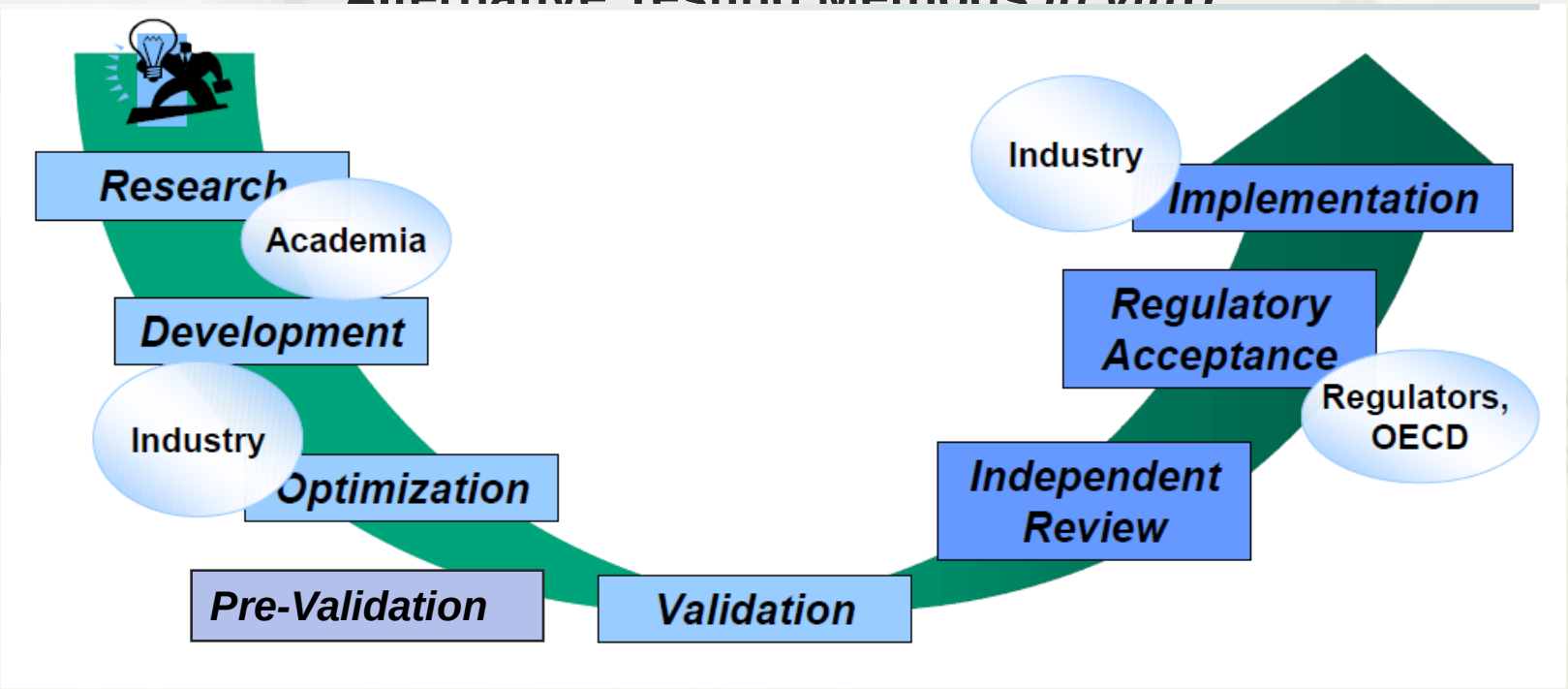
试验结果	参考受试物质		总计
	阳性	阴性	
阳性	a	b	a+b
阴性	c	d	c+d
总计	a+c	b+d	a+b+c+d

再现性Reproducibility，准确性Accuracy，假阳性False positive
假阳性率False positive rate，假阴性False negative，
假阴性率False negative rate，重复性 Repeatability，
预测性Predictivity，可靠性Reliability，敏感性Sensitivity
特异性Specificity，混合率 Prevalence，预测模型Prediction models
普适性或可转移性Transferability

Procedure of Validation

验证的标准：化妆品体外替代试验方法验证和认可规程（SN/T 3898)

Guideline for the Validation and Acceptance of Cosmetics Alternative Testing Methods *in vitro*



学术探索与创新

1 替代方法共识平台

Chinese Center for Alternatives Research & Evaluation (CCARE)

http://www.vitrotox.com

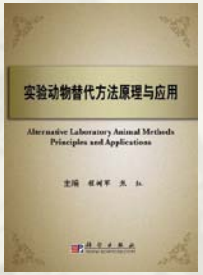
2.学术专著

《实验动物替代方法原理与应用》科学出版社,2006-2010

《3R和仁慈准则》2014

《化妆品科学与评估》6卷本，2014—2016

《预测毒理学与替代技术指南》, 2010-2015



体外实验方法的实操培训

2010～2014

"This is ridiculous. We can't test the products on animals, but should we test them on human beings instead?"

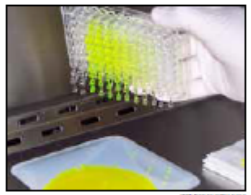
XENOPOLITES,A

"Animals are animals and human beings are human beings. The results of tests conducted on animals do not necessarily reflect the effects ... on human beings."

ZHANG QUANSHUN,

Testing: A humane move, or a cosmetic change?

Researchers at a training session into alternative procedures for eye irritation tests that do not require the use of live animals.



Researchers at the Institute for In Vitro Sciences in the United States conduct a photoirritancy test on cosmetic products using the in vitro methods.

> There will be some initial set-up costs for Chinese cosmetic companies while they retrain their staff to conduct in vitro tests. However the use of validated alternative tests will be both cheaper and faster than using animals, so the companies will benefit greatly from this saving in due course."
>
> JUDY MACARTHUR CLARK,

> There is a need for a national coordination mechanism to popularize alternative testing methods"
>
> CHENG SHILUN,

A late start

An inevitable shift

Popularization

验证活动举例

3T3 中性红摄 取光毒性验证

EU → In the year 2000 for the first time in vitro toxicity test accepted by the EU into Annex V of Directive 67/548/EEC on the Classification, Packaging and Labelling of Dangerous Substances.

OECD → 2004 worldwide acceptance of the 3T3NRU PT test

多中心皮肤刺激性测试验证项目

----EpiSkin重建表皮模型的应用

Multi-Center Study of an *in vitro* Alternative Method

--Validation of *in vitro* Skin Irritation Testing Method Using EpiSkin Model

谢谢！

程树军 博士 研究员

广东出入境检验检疫局技术中心

网站：http://www.vitrotox.com

替代方法研究评价中心

Email：chengsj@126.com；

电话：020-38290670；13602811627

地址：广州市珠江新城花城大道66号检验检疫大厦B1212