2012 SHANGHAI
Summit Meeting on Chemical Regulations
in China, Korea and Japan

Workshop on Safety Assessment of Personal Care Products & New Ingredients in China

October 26th, Shanghai

Introduction to validated alternative methods for safety assessment of personal care products & ingredients and recent updates

The 2nd Shanghai Chemical Summit – Optional Workshop 24-26 Oct. 2012,
WYNDHAM Hotel, 2288 Pudong Avenue, Shanghai, China

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Outline

- Non-animal methods now commonly used
  - OECD Test Guidelines
  - Ranking irritation potential
  - Product efficacy
- Examples of possible testing approaches
  - Eye irritation
  - Skin irritation
  - Oral irritation
  - Phototoxicity
- Standard methods for *in vitro* testing
  - Clear protocols
  - Well-trained staff
  - Appropriate control conditions
  - Good Laboratory Practices

Institute for In Vitro Sciences (IIVS)

Founded as a non-profit laboratory in 1997 to use and promote non-animal methods for toxicology

- Non-profit means there are no owners or shareholders
- Any extra money made must be reinvested into programs at the end of the year
- We are supported by contributions and testing services

This allows IIVS to be a “neutral” party.

We represent many companies and laboratories, not just ourselves.

Institute for In Vitro Sciences
Experience

- We do *in vitro* testing in our laboratories

  We've supplied testing to hundreds of companies for thousands of products and ingredients.

- We teach the methods

  We hold workshops, hands-on training, and lecture courses for companies and organizations internationally

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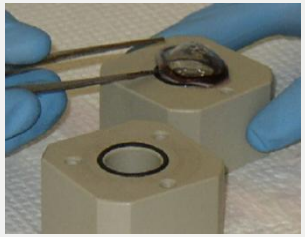
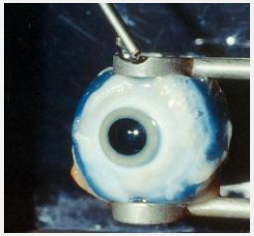
How Companies Use *In Vitro* Methods

For specific regulatory purposes:

- OECD Test Guidelines for severe eye irritation; TG 437 uses the cow cornea and TG 438 uses the chicken eye





- OECD Test Guidelines for skin corrosion; TG 430 uses rat skin, TG 431 uses 3-D reconstructed human tissue, and TG 435 uses an artificial, non-viable barrier

- OECD Test Guideline 432 for phototoxicity uses mouse cells

- OECD Guideline 439 for skin irritation uses 3-D reconstructed human tissue

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How Companies Use *In Vitro* Methods

For ranking irritation potential:

- Companies want to know which of several ingredients, for example, surfactants might be milder, not just whether it is a severe eye irritant or not.
- Companies might want to test prototype products to rank formulations and select the formula with the least chance of being irritant.
- This ultimately can move formulations in the marketplace to be milder and safer to the consumer

For this type of testing the OECD guideline method would likely not be used, but instead a modification of the regulatory procedure. The same cells or tissues might be used, but they would be used in a different fashion.

Companies have a great amount of experience using such *in vitro* methods – Confidence through experience

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How Companies Use *In Vitro* Methods

For investigating efficacy:

- Companies may want to know how a product affects the appearance of the skin

Again, many of the same cells and tissues that they have experience with – for example those that are used in regulatory guidelines – are used to determine endpoints like collagen synthesis.

The cells and tissues are the same, but the questions asked of them are different. All this information helps build the knowledge base of *in vitro* testing, and subsequently the trust in it.

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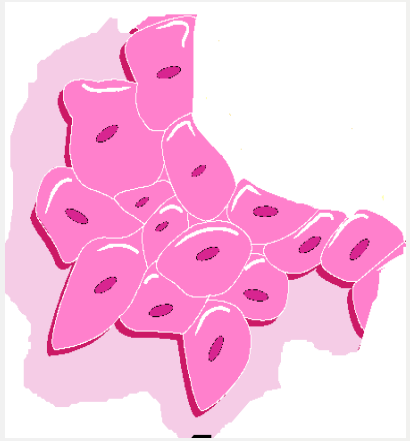
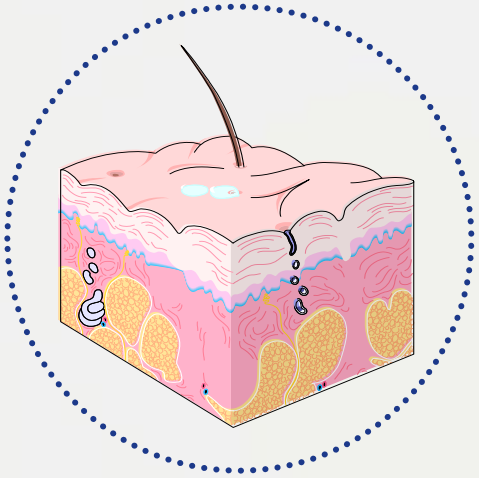
Increasing Sophistication Increases Trust

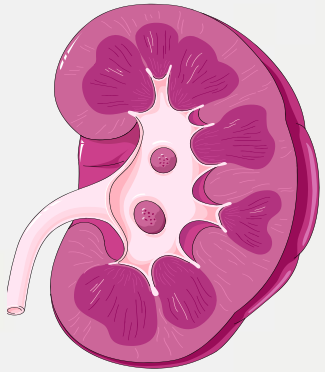
Increasing predictive power



Cells



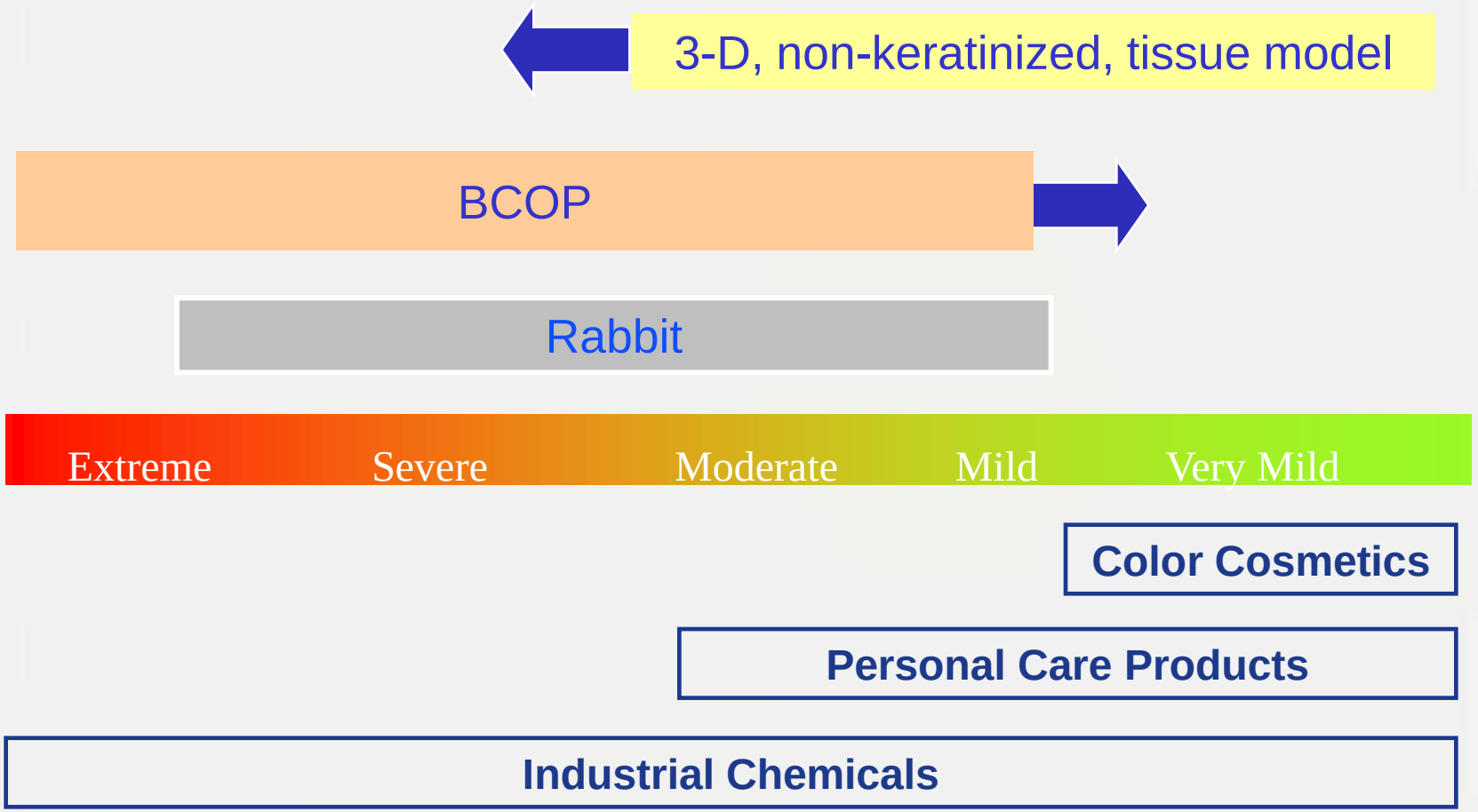
Simple Tissues



Complex Organ Models

Validation - Less evidence of predictivity is needed as in vitro model complexity increases

A Continuum of Sensitivity for Eye Irritation



Example Of BCOP Uses

- The OECD Test Guideline only addresses the most severe irritation, but companies often want to know more.
- Some may test “benchmarks” – products with known history of use in humans – with each BCOP experiment to establish where a new material lies with respect to the known material.
- Histopathology can aid BCOP analysis by providing a “picture” of the results.
- Depth of injury seen in histopathology may give information on reversibility of injury.

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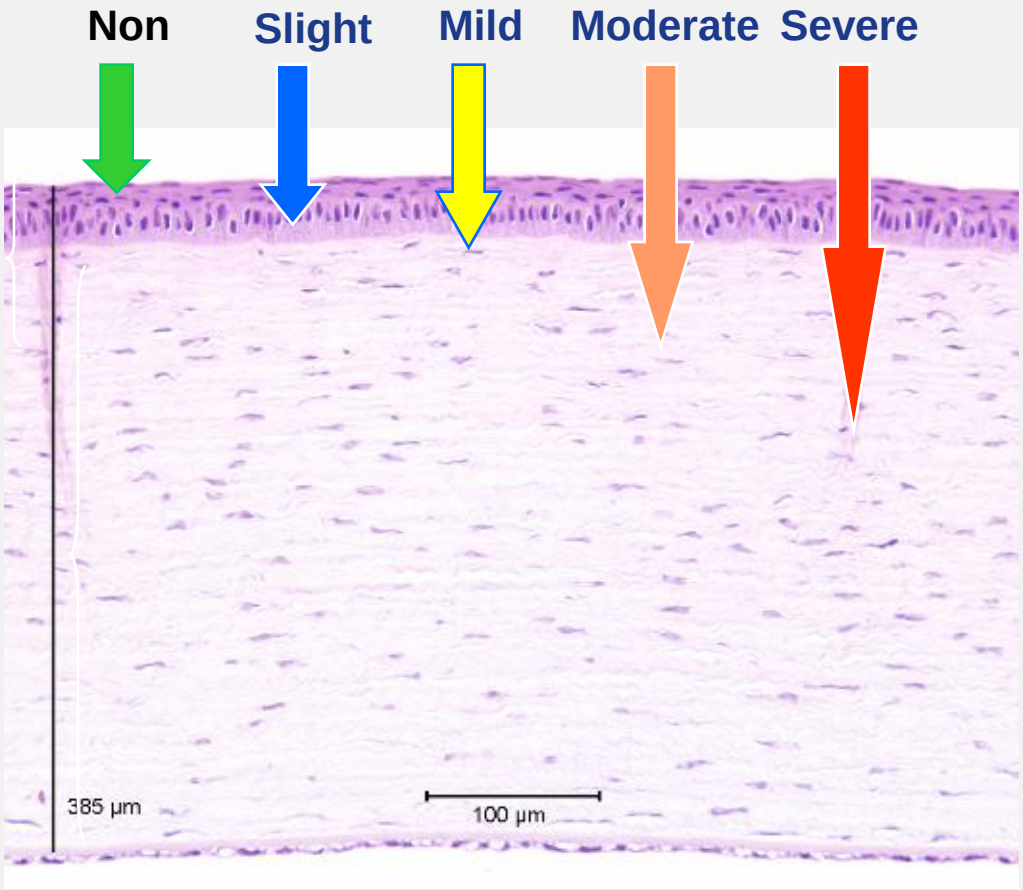
Depth of Injury Model

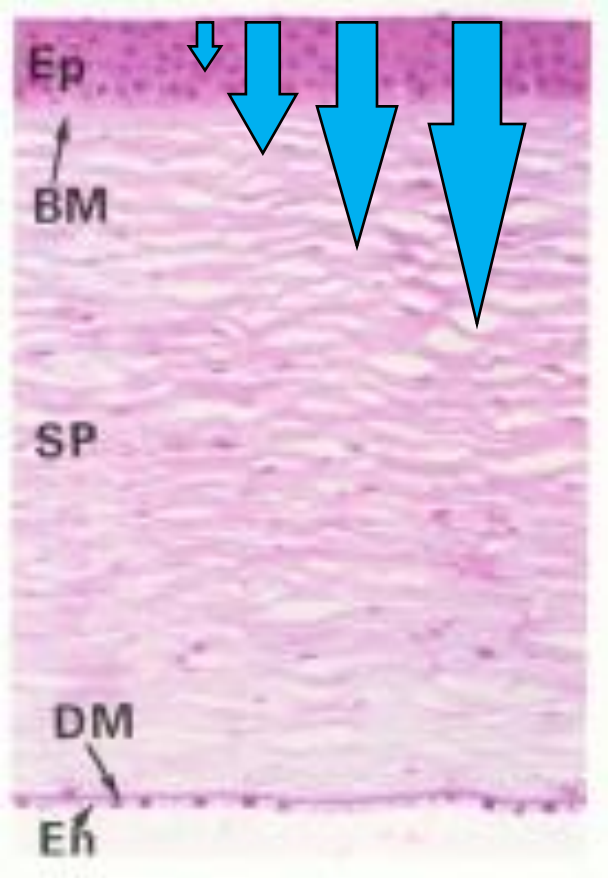
Depth of injury is predictive of the degree and duration of injury



"regardless of the process leading to tissue damage, extent of initial injury is the principal, mechanistic factor determining the outcome of the ocular irritation" - Maurer *et al*., 2002

Based on the work of J. Maurer and J. Jester

BCOP Assay – Direct Evidence of Corneal Damage



- Topical application
- Direct measures of opacity and epithelial integrity
- In Vitro Score = Opacity + 15 x Permeability
- Histopathology allows visualization of corneal damage

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Other BCOP Uses

- For certain cleaning products, the U.S. EPA now accepts the BCOP for other than severe irritation.
- BCOP is part of a testing strategy (“Top-Down/Bottom-Up”) where it can be used to identify “moderate” and “mild” injury as well as severe.
- The EPA requires histopathology to be conducted if the BCOP score is less than severe.
- Others have proposed that the BCOP could also be used to identify non-irritants.

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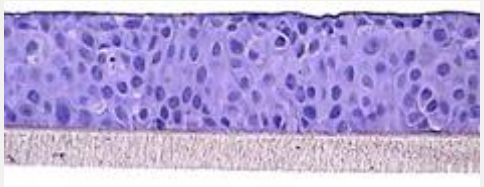
Human Tissue Constructs

Because they are a more sensitive tissue, human tissue constructs, for example EpiOcular™. EpiOral™ (MatTek) or HCE (SkinEthic), are used by some companies to identify very mild or completely non-irritating products or ingredients.

EpiOcular

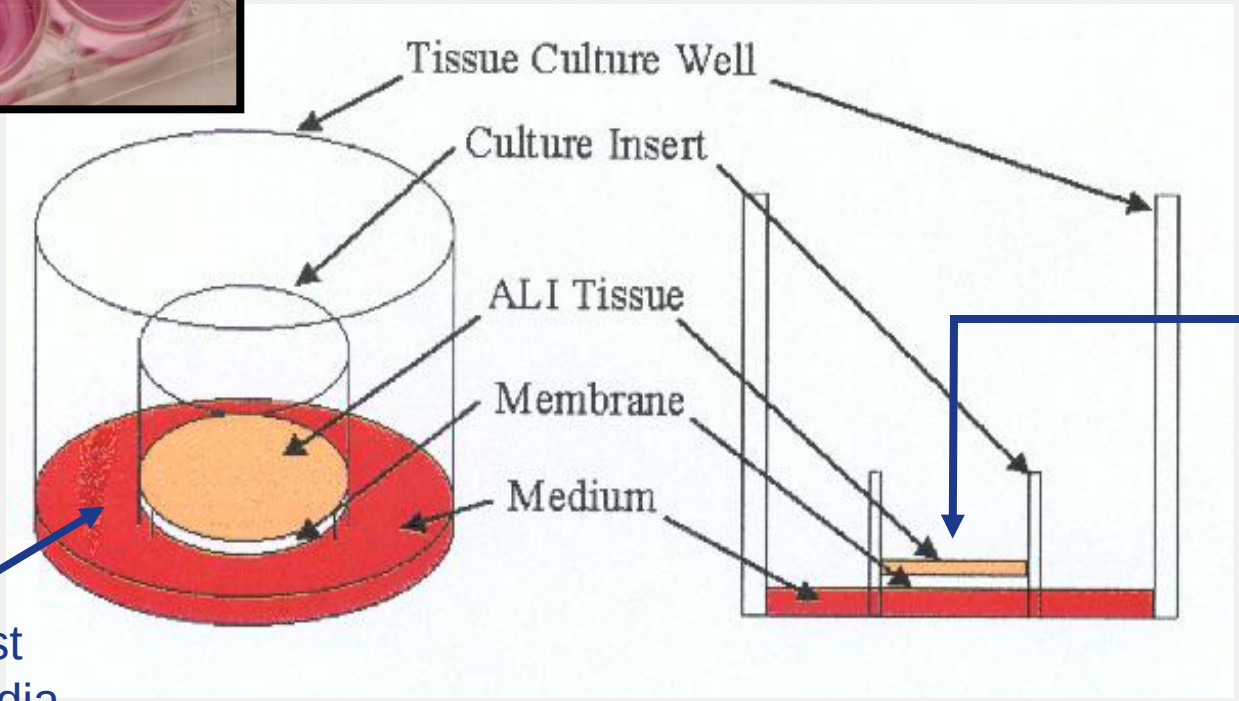
EpiOral



HCE

human tissue type constructs will be used more and more often.

Typical Reconstructed Tissue Treatment

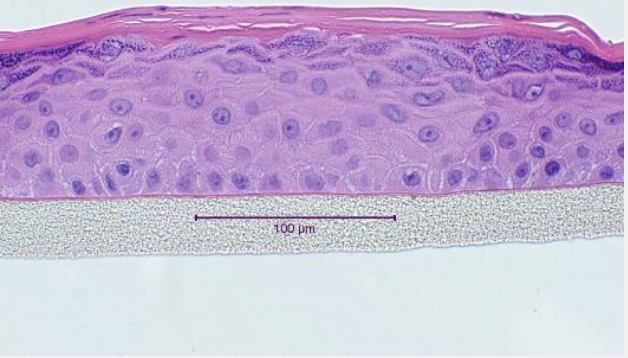


Exposure topically

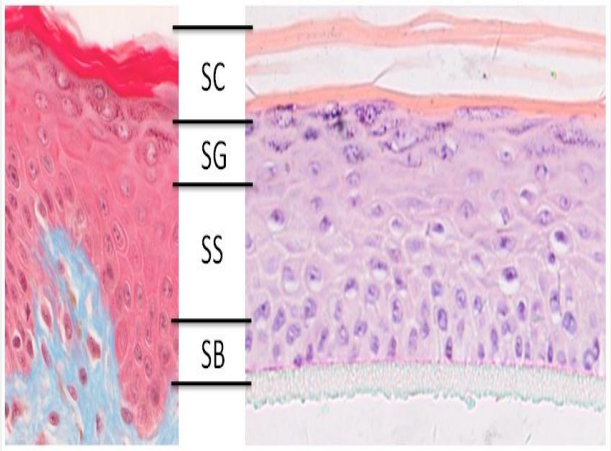
Exposure to test chemical in media

Comparison of Skin Constructs
US, EU and China

EpiDerm

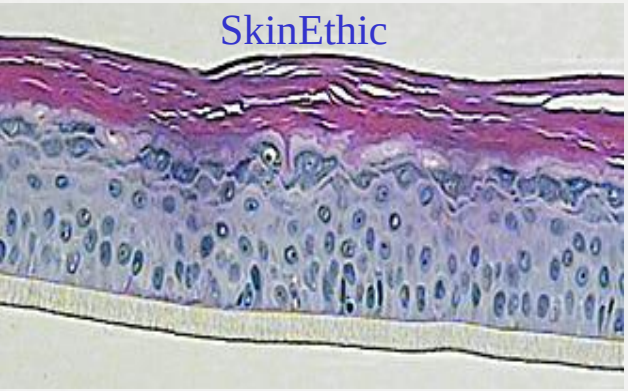


TecSkin Xi'an

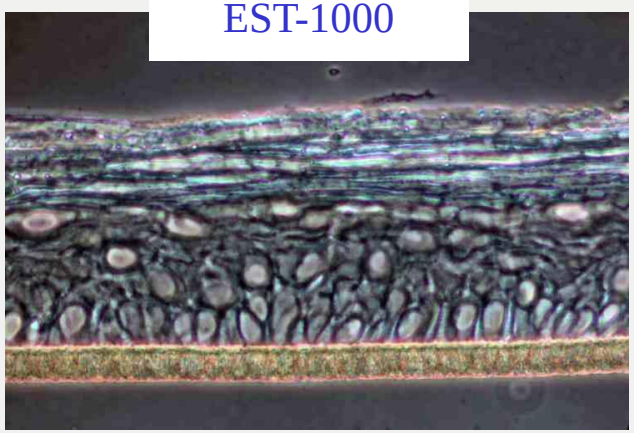


EpiSkin

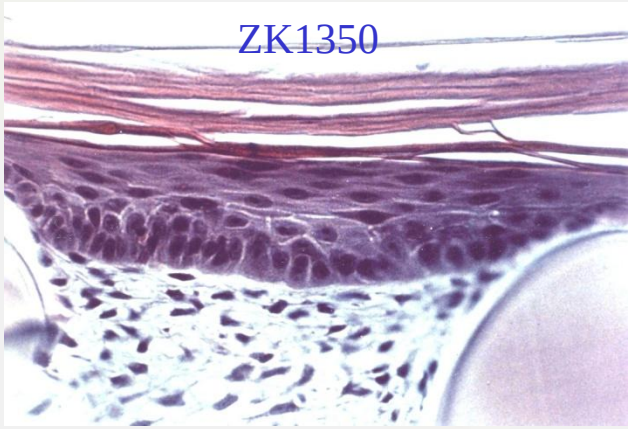
SkinEthic



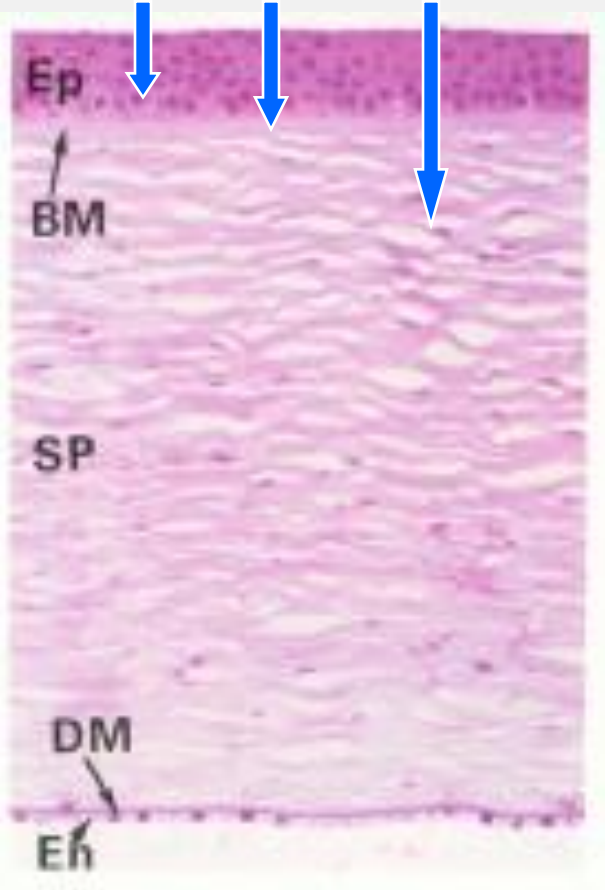
EST-1000



ZK1350



Human Epithelial Constructs



Epithelial human tissue constructs

Topical application

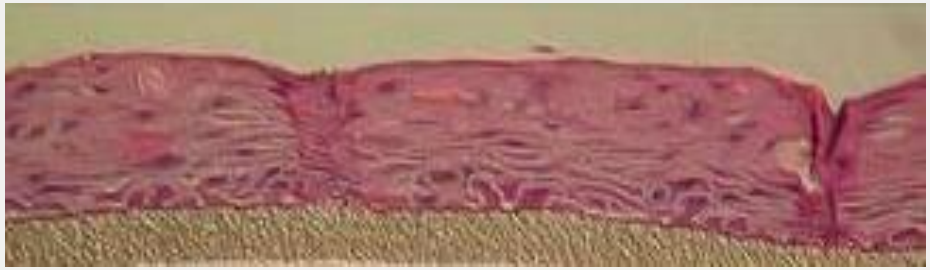
Endpoint is the exposure time required to reach a 50% reduction in viability (ET50, dependent on cytotoxic potential and rate of penetration)

Focuses on damage to the epithelium and upper stroma

Human Tissue Constructs for Oral Care

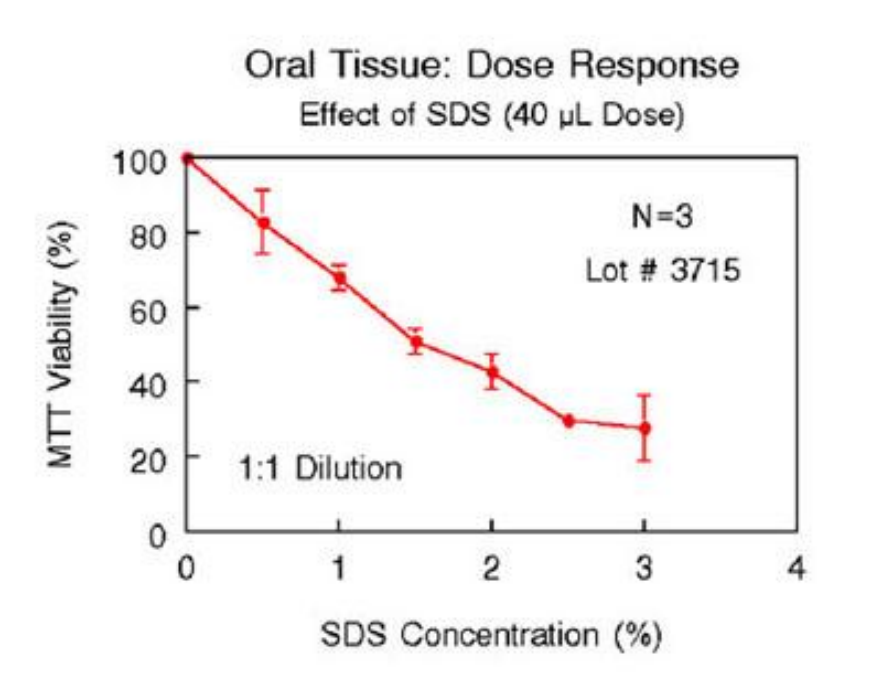
- Three-dimensional tissue construct made from gingival cells
- 8-12 cell layers thick with a squamous appearance on the apical side of the tissue, resembling the inner cheek of the mouth

EpiOral™ Tissue, courtesy MatTek Corp., Ashland, MA, USA



- Provides a more sensitive tissue model than EpiDerm (less sensitive than EpiOcular) and can distinguish potential for irritation differences based on an MTT ET_{50} endpoint
- Can be used for " ingredient and formula screening" of toothpaste, mouthwash formulations for evaluation of irritation potential

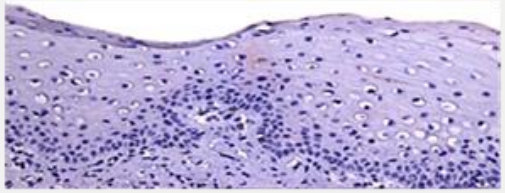
Evaluation of Oral care



Effect of SDS solutions (40 µL) on EpiOral (ORL-200) tissue viability following exposure for 1 hour. SDS concentrations were chosen to be in the range normally present in toothpastes (0.0 – 3.0%). Ref: MatTek Corporation

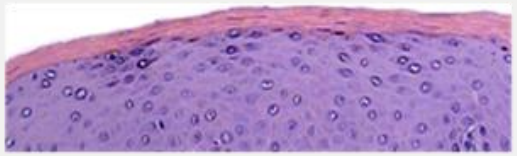
Use of Buccal & Gingival Models

Tissue, courtesy SkinEthic Laboratories, Nice, France

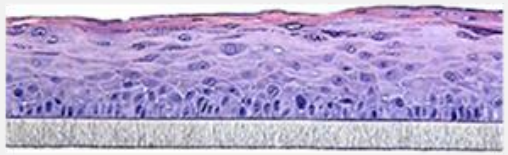


Oral mucosa epithelium *in-vivo*

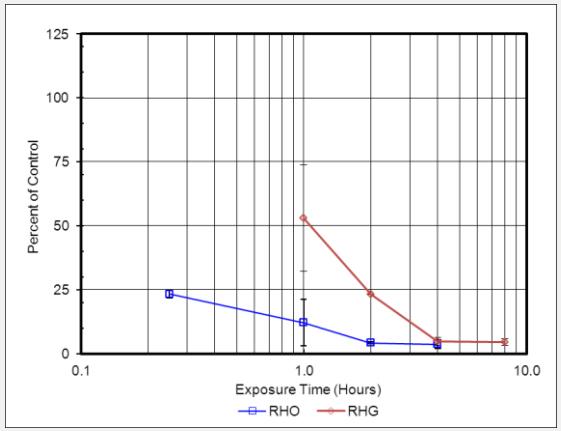
Reconstructed Oral mucosa epithelium *in-vitro*



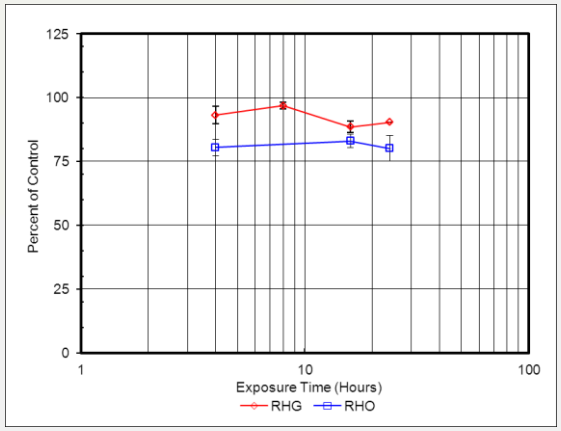
Human gingival epithelium *in-vivo*



Reconstructed gingival epithelium *in-vitro*



Formula "A" – 2% H_2O_2



Formula "B" – 2% Sodium Bicarbonate

Comparison of the toxicity of 2 formulations applied to the different tissue models for increasing time. Wurzburger, *et al.* SOT Poster 2011.

United States Acceptance of Alternatives

- The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was created to evaluate alternative methods for the many different governmental agencies within the US.

- Currently, ICCVAM has only validated alternative methods to show positive results (corrosive, irritant) but not for negative (non-) outcomes

- Certain US governmental agencies, such as Department of Transportation, US Food and Drug Administration, and Environmental Protection Agency, have accepted alternative, non-animal models for certain endpoints.

- FDA has accepted 3T3 phototoxicity, Limulous Amoebocyte Lysate (LAL) assay for pyrogens, cell-based potency assay (CBPA) for Botox^{tm} in lieu of LD_{50}, and cytotoxicity for medical devices.

- The US Environmental Protection Agency has accepted alternatives for insect repellants (BCOP) and for anti-microbial cleaning products (BCOP, EpiOcular, Cytosensor) for ocular endpoints.

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In Vitro Testing Strategy for Ocular Irritation (for EPA anti-microbial cleaning products only)

- Currently, one *in vitro* assay is not sufficient for all eye irritation categories – therefore a bottom-up/top-down strategy was proposed to the EPA

- BCOP will be used to identify Categories I & II (Severe & Moderate)

- EpiOcular will be used to identify and separate III's (Mild) from IV's.(Non-irritating)

- Strategy incorporates conclusions of ECVAM/ICCVAM eye irritation group meeting, working from both ends of toxicity scale.

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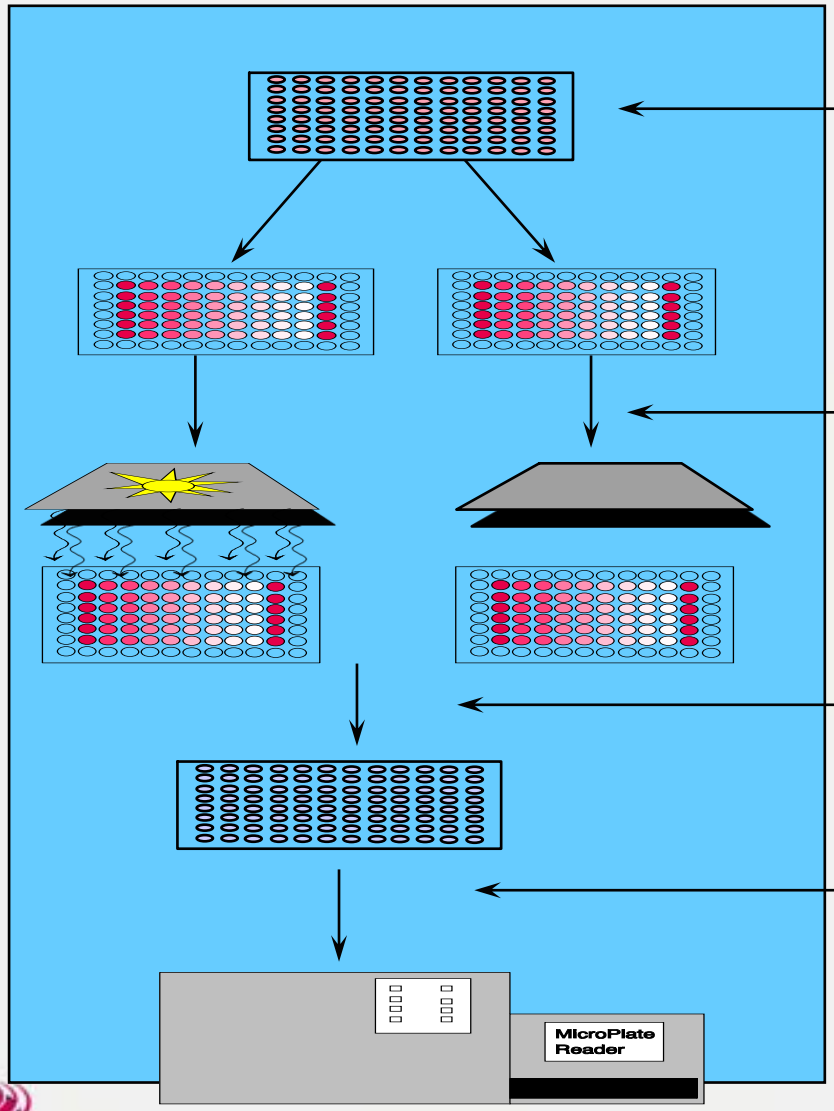
Different Models (Or Uses) May Need Different Protocols

- No two models have exactly the same structure.
  - Different stratum corneum will result in a different exposure
  - Different cell types may have different sensitivities
- Regulatory protocols (skin irritant- yes/no) may use only a single time point
- Product development may need a time course study for resolution

3T3 Neutral Red Uptake Phototoxicity Assay



Seed two 96 well plates with
1×10^4 cells/well

Treat plates with 8 concentrations

Incubate 1 hr

Expose to either UVA (320 - 400 nm)
5 J/cm^2 or darkness for 50 min.

Rinse & add medium
Incubate 24 hrs

Add Neutral Red Medium
Incubate 3 hrs

Rinse & Fix

Read at 550 nm

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Phototoxicity in Engineered Skin for Formulations and Hydrophobic Materials

- Reconstructed human skin could be used in the phototoxicity assay to determine the phototoxic potential of formulations, sunscreens, and cosmetics in a topical-application skin model.
  - 3T3 monolayer phototoxicity assay can not evaluate phototoxicity of formulations or materials insoluble in medium
  - 3T3 system does not address skin barrier functions
- Reconstructed human skin models could address photofilter and photoprotective action of sunscreens

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IIVS- Chinese Efforts

- Enthusiasm on all sides
- Books on alternatives have been and (more being) written and “western” books translated into Chinese
- Development of three (3) in vitro laboratories in China (Beijing, Xi’an, and Guangzhou),to provide in-depth technical training
- At least three workshops in China are being planned in Xi’an TEC (October 2012), BTBU (October 2012) and Sun Yat Sen University (December 2012)
- Requests for IIVS to help with future technical workshops in China and lecture series in safety and non-animal methods

IIVS- Chinese Efforts

- **Development of three in vitro training labs in China**

- **Sun Yat Sen University**

Xi'an Tissue Engineering Center

BTBU

Conclusions

1. OECD *in vitro* Test Guidelines exist for some endpoints; these should be considered for regulatory adoption
2. Existing OECD TG do not solve all toxicology questions. Most companies use more informative modifications of these methods
3. Three dimensional human tissue models have value for the personal care industry and are available internationally
4. High standards should be required of *in vitro* testing laboratories.
5. IIVS is working with several laboratories to develop non-animal testing expertise in China.
6. Proper training is the key for Regulatory acceptance and public safety
7. Globally, additional endpoints will continue to be developed with refinement of existing methods

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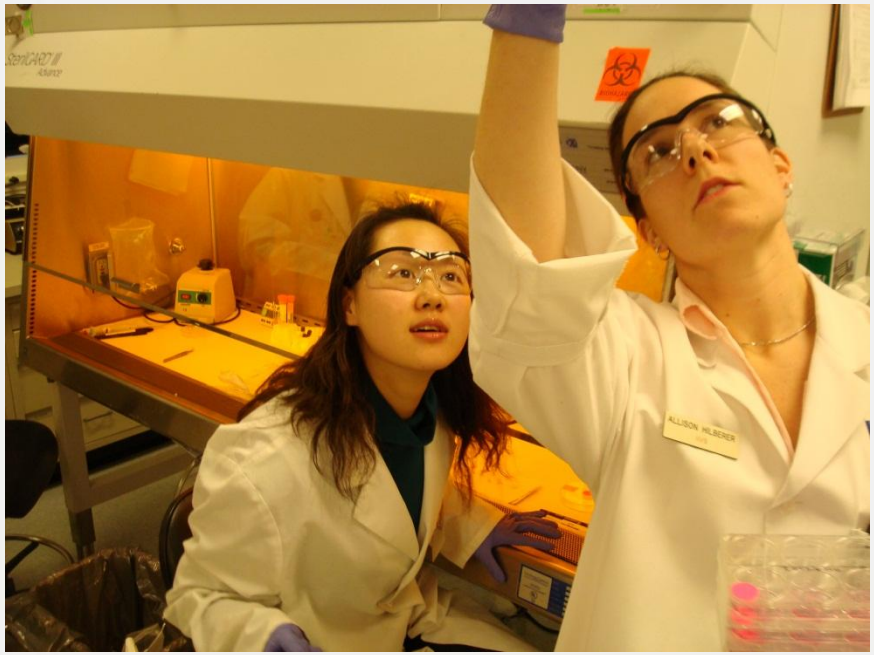
Thank You



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化妆品与健康

—— 上海市疾病预防控制中心的实践与经验

发言人: 李 竹

2012.10.26

SCDC
上海市疾病预防控制中心
SHANGHAI MUNICIPAL CENTER
FOR DISEASE CONTROL & PREVENTION

化妆品与健康

我们的实践与经验

展　望

化妆品在中国

从公元前一千多年的商朝末期的“燕支”到民族化妆品的骄傲

化妆品在中国的历史源远流长

改革开放后，化妆品市场蓬勃发展。2011年中国化妆品(护肤品) 销售额已经突破2000亿元，市场规模继续保持全球第三。

化妆品对健康的影响

心理
正面影响

生理
正面影响

心理
负面影响

生理
负面影响

化妆品皮肤不良反应等

化妆品对健康的负面生理影响

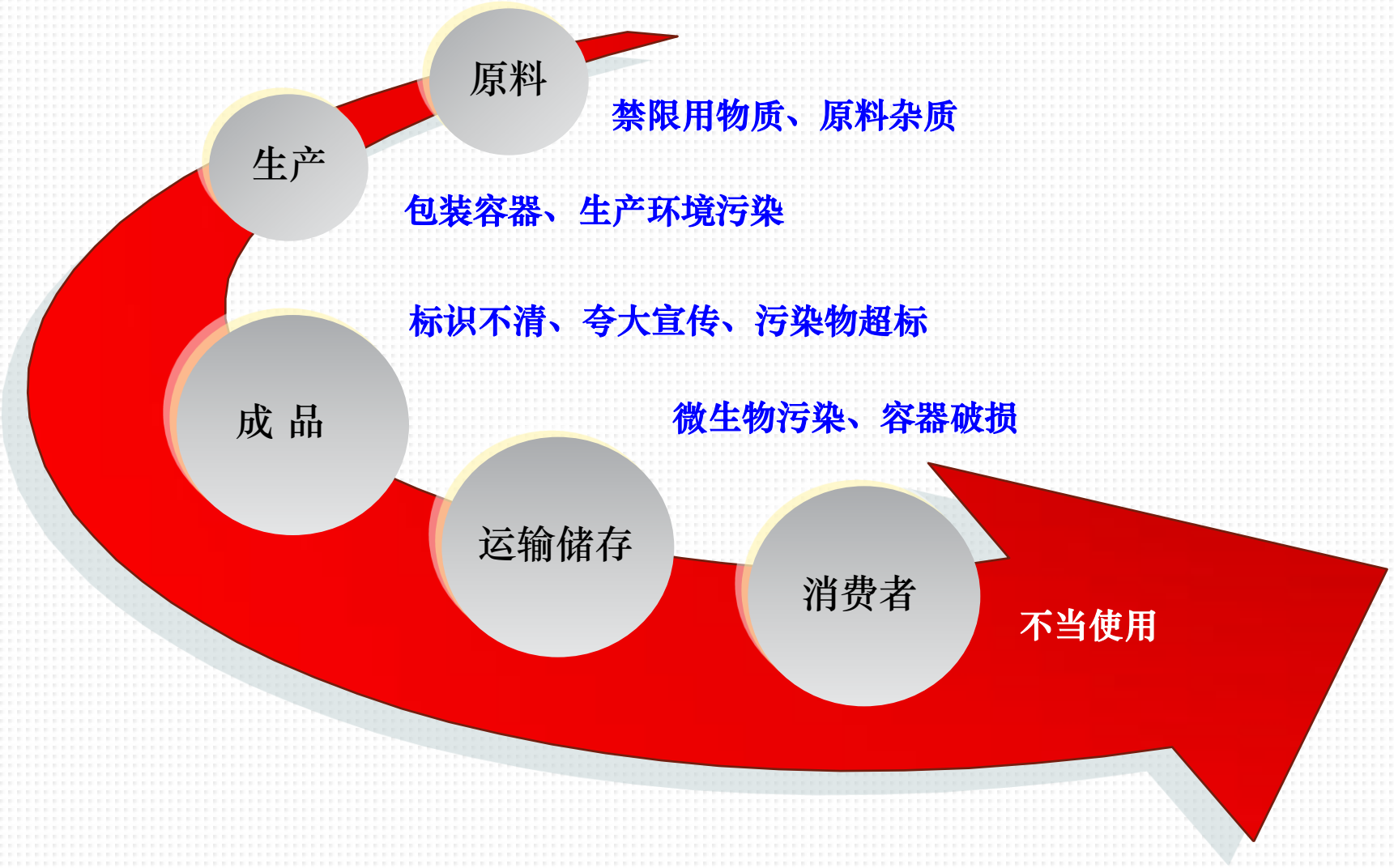
潜在的风险

- 致病微生物
- 重金属（铅、砷、汞等）
- 可能存在的“三致”物质（致畸、致癌、致突变）
- 过敏性物质

超过安全限值

皮肤、其他脏器或系统性不良损害

化妆品可能对健康造成影响的环节



化妆品行政许可检验

- 终产品

——“特殊用途”：育发、染发、烫发、脱毛、美乳、健美、除臭、祛斑、防晒

——“非特殊用途”

具体检测项目根据产品类别、宣称、配方来确定

《化妆品行政许可检验管理办法》（国食药监许[2010]82号）

- 化妆品新原料

具体要求见《化妆品新原料申报与审评指南》（国食药监许[2011]207号）

化妆品行政许可检验 —— 举例

某防晒化妆品

		检测项目
类别	防晒	菌落总数、粪大肠菌群、金黄色葡萄球菌、铜绿假单胞菌、霉菌和酵母菌 汞、铅、砷、防晒剂 多次皮肤刺激性试验、皮肤变态反应试验、 皮肤光毒性试验 人体皮肤斑贴试验、防晒指数（SPF值）测定
类别	祛斑	氢醌、苯酚、pH值
配方	乙醇11%（≥ 10%）	甲醇
用途	可用于眼周	急性眼刺激性试验
宣称	不易引起粉刺	抗生素、甲硝唑
宣称	PA++	长波紫外线防护指数（PFA值）测定
宣称	适合游泳等户外活动	防水性能测定

化妆品与健康

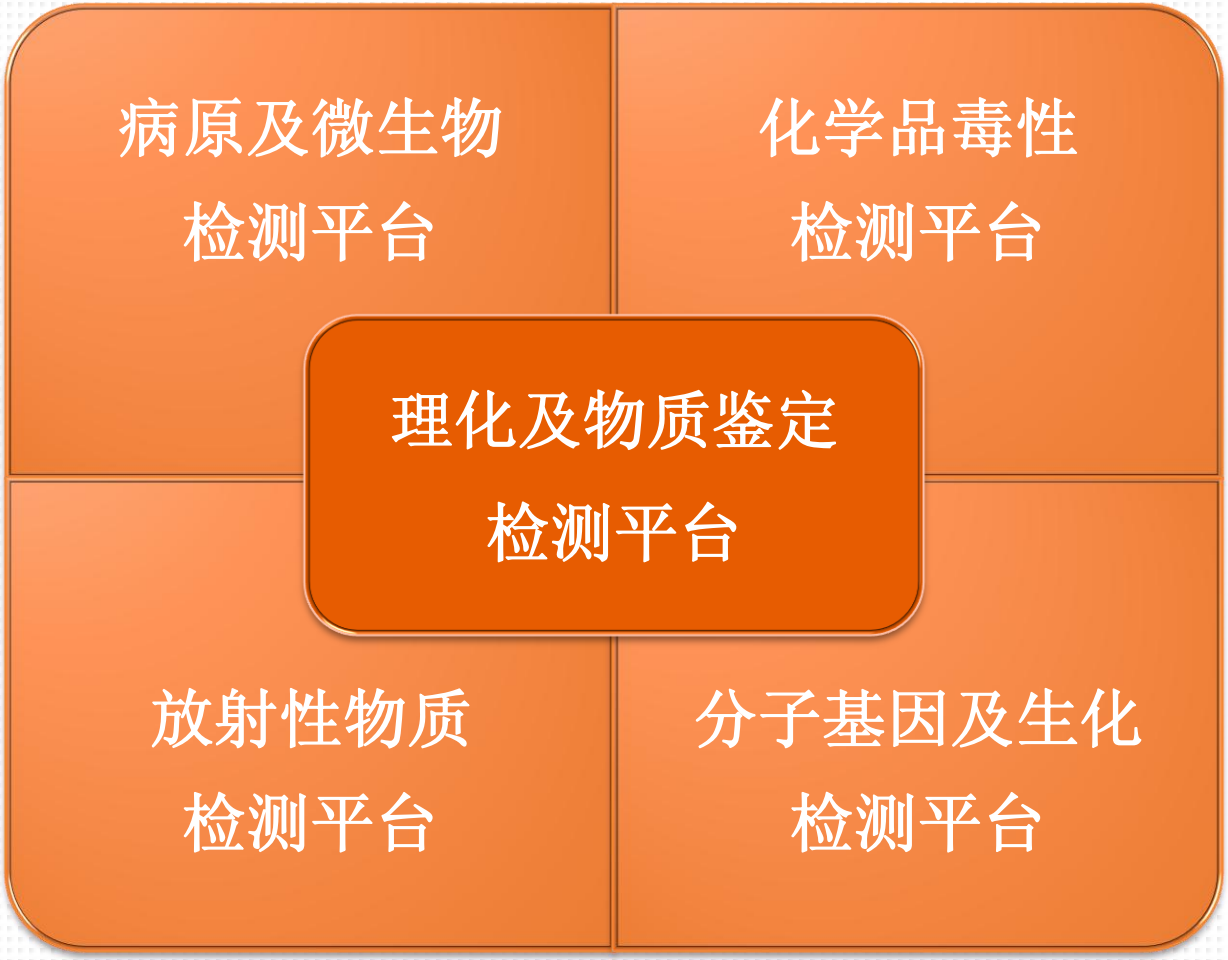
我们的实践与经验

展　望

中心的职责与定位

1. 实施政府卫生防病职能的专业机构
2. 在市政府卫生行政部门领导下，组织实施全市卫生防病工作的技术保障部门
3. 承担对区县防治机构的业务指导、考核和技术示范职能

强大的检测评价能力


病原及微生物
检测平台
化学品毒性
检测平台
理化及物质鉴定
检测平台
放射性物质
检测平台
分子基因及生化
检测平台

单位所获资质（1）

- 卫生部化学品毒性检测鉴定机构（甲级）
- 卫生部涉水产品检验机构
- 卫生部建设项目职业病危害评价机构（职业卫生，甲级）资质
- 卫生部建设项目职业病危害评价机构（放射防护，甲级）资质
- 国家食品药品监督管理局保健食品功能学检验机构
- 农业部农药登记试验单位（卫生杀虫剂）资质
- 农业部农药登记毒理学试验单位资质
- 农业部新化学物质测试机构
- 公共场所集中空调通风系统卫生学评价机构（甲级）
- 上海市消毒产品检验机构
- 进口卫生用品和一次性使用医疗用品检验机构

单位所获资质（2）

- 卫生部认定的消毒产品新增脊椎灰质炎疫苗病毒灭活和黑曲霉菌杀灭效果检验
- 卫生部认定的省级脊髓灰质炎检测合格实验室
- 卫生部认定的艾滋病抗体确认实验室
- 卫生部结核病（上海）参比实验室
- 卫生部碘缺乏病合格实验室
- PulseNet网络实验室（上海区域中心实验室）
- 上海市产品毒性质量监督检验站
- 上海市艾滋病检测中心
- 上海市中毒控制中心办公常设机构
- 上海市卫生局指定医疗事故争议中现场实物检验机构
- 科技事业单位国家一级档案

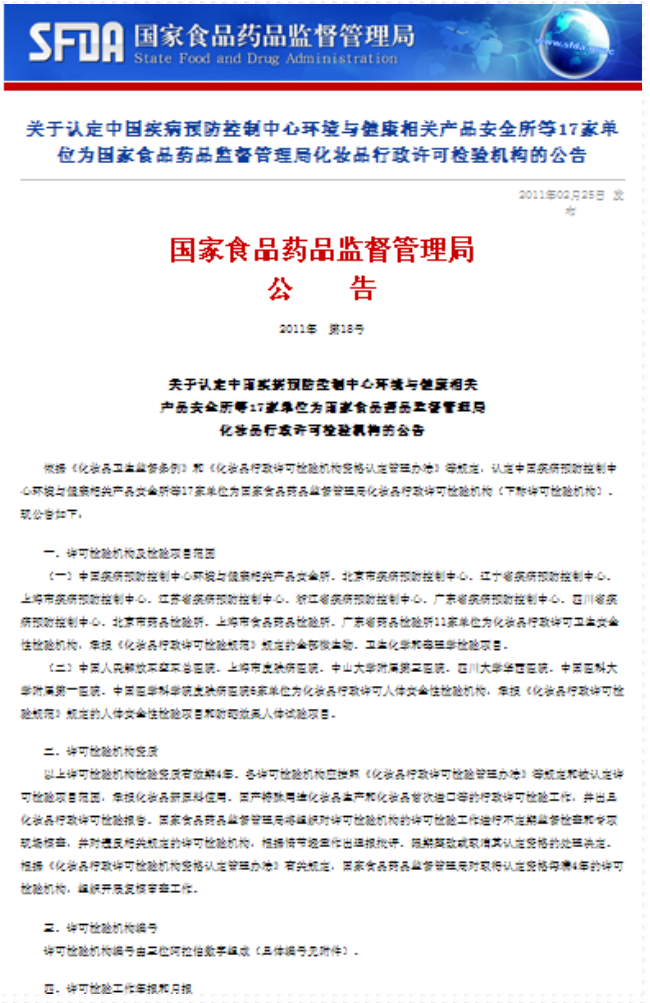
单位所获资质（3）

上海市疾控中心

1999年卫生部认定的三家部级检验机构之一

2011年SFDA首批认定的行政许可检验机构

2011年SFDA首批认定的备案检验机构



SFDA 国家食品药品监督管理局 State Food and Drug Administration

关于认定中国疾病预防控制中心环境与健康相关产品安全所等17家单位为国家食品药品监督管理局化妆品行政许可检验机构的公告

2011年02月25日 发布

国家食品药品监督管理局

公　　告

2011年　第18号

关于认定中国疾病预防控制中心环境与健康相关产品安全所等17家单位为国家食品药品监督管理局化妆品行政许可检验机构的公告

根据《化妆品卫生监督条例》和《化妆品行政许可检验机构资格认定管理办法》等规定，认定中国疾病预防控制中心环境与健康相关产品安全所等17家单位为国家食品药品监督管理局化妆品行政许可检验机构（下称许可检验机构），现公告如下。

一、许可检验机构及检验项目范围

（一）中国疾病预防控制中心环境与健康相关产品安全所、北京市疾病预防控制中心、辽宁省疾病预防控制中心、上海市疾病预防控制中心、江苏省疾病预防控制中心、浙江省疾病预防控制中心、广东省疾病预防控制中心、四川省疾病预防控制中心、北京市药品检验所、上海市食品药品检验所、广东省药品检验所11家单位为化妆品行政许可卫生安全性检验机构，承担《化妆品行政许可检验机构》规定的全部微生物、卫生化学和毒理学检验项目。

（二）中国人民解放军第三军医大学、上海市皮肤病医院、中山大学附属第三医院、四川大学华西医院、中国医科大学附属第一医院、中国医学科学院皮肤病医院6家单位为化妆品行政许可人体安全性检验机构，承担《化妆品行政许可检验机构》规定的人体安全性检验项目和耐刺激类人体试验项目。

二、许可检验机构资质

以上许可检验机构检验资质有效期4年，各许可检验机构应按照《化妆品行政许可检验管理办法》等规定和被认定许可检验项目范围，承担化妆品新原料申报、国产特殊用途化妆品生产和化妆品首次进口等的行政许可检验工作，并出具化妆品行政许可检验报告。国家食品药品监督管理局将组织对许可检验机构的许可检验工作进行不定期监督检查和专项现场核查，并对遇及相关规定的许可检验机构，根据情节轻重作出通报批评、限期整改或取消其认定资格的处理决定。根据《化妆品行政许可检验机构资格认定管理办法》有关规定，国家食品药品监督管理局对取得认定资格每满4年的许可检验机构，组织开展反复核查工作。

三、许可检验机构编号

许可检验机构编号由英文阿拉伯数字组成（具体编号见附件）。

四、许可检验工作年报和月报

化妆品领域开展的相关工作

- 参与法规标准的制订

  《卫生规范》、《禁限用物质名单》、《检验规范》、《检验机构管理办法》…

  目前中心共有 5 名SFDA化妆品审评专家

- 科研

  防晒化妆品功能仪器评价方法、化妆品皮肤不良反应流行病学调查…

化妆品领域开展的相关工作

- 检验方法的建立

动物替代实验 体外光毒（3T3中性红摄取）、
体外微核（CHL细胞）、
体外眼刺（牛眼、鸡胚）、
体外致敏（局部淋巴结）、
体外皮刺（皮肤模型）….

风险物质及理化项目检测（二恶烷、稀土元素、邻苯二甲酸酯类、
糖皮质激素、磺胺类、三氯卡班、
苯氧异丙醇、奎宁、香豆素….）

“化妆品促进健康生活”理念的推广

第一届国际化妆品与健康论坛，2011 上海

我们的服务

合作研究

信息公开

邮寄报告

企业座谈

化妆品与健康

我们的实践与经验

展　望

未来发展的展望

1. 提高检测能力，满足禁限用物质及风险物质检测需求
2. 充分利用化学品毒性检测平台，服务于化妆品风险评估
3. 逐步建立动物替代试验体系
4. 健全化妆品功效评价体系
5. 加强化妆品不良反应监测
6. 尝试开展化妆品与人体健康效应的流行病学研究

如何联系我们

上海市疾病预防控制中心

(Shanghai Municipal for Diseases Control & Prevetion, SCDC)

电话：86-21-62758710 ext. 1802 or 1803

传真：86-21-62192754

E-mail: huanwei3@scdc.sh.cn

website：www.scdc.sh.cn （社会服务/卫生评价及检测）

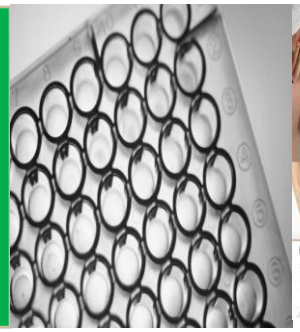
提供详细资料下载

谢　谢

Thank you

SCDC
上海市疾病预防控制中心
SHANGHAI MUNICIPAL CENTER
FOR DISEASE CONTROL & PREVENTION

Requirements on Specifications of Cosmetic Ingredients



Enabling Chemical Compliance for A Safer World

26 Oct 2012, April Guo, Regulatory Affairs Specialist
Email: april.guo@cirs-reach.com

CHEMICAL INSPECTION & REGULATION SERVICE

Contents

- Common Safety Issues of Cosmetics

- Risk Assessment of Cosmetics in China

- Requirement on Specification of Cosmetic Raw Material

CHEMICAL INSPECTION & REGULATION SERVICE

Part I

Common Safety Issues of Cosmetics

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Safety Issues of Cosmetics

- On a daily basis, people use an average of **10 to 15** personal care products.
- Based on the EWG recent statistics, people apply an average of **126 to 178** different ingredients to their skin daily.

- ✓ Eye irritations;
- ✓ Bacteria contamination;
- ✓ Irritation and scratches on the eye;
- ✓ Fire hazards, in the case of aerosol products such as hairspray;
- ✓ Allergic reactions or sensitivity to ingredients.

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What are the safety risk substances?

Safety Risk Substances are the components (impurities or additives) that may cause potential harm to human health resulted from raw materials or brought in during the production process.

- **CMR substances**
- **Residual monomers**
- **Solvent**
- **Other impurities**

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Common safety risk substances in cosmetics

Type of cosmetic products	Safety risk substances
Anti-aging creams	lactic, glycolic, AHA and BHA acids
Hair dyes, especially dark permanent dyes	arylamines
Liquid hand soaps	triclosan/triclocarban
Nail polish and removers	formaldehyde, DBP or toluene (which can be contaminated with benzene)
Skin lighteners	hydroquinone
Heavily scented products	fragrance
Moisturizers, ointments and skin creams	petrolatum (which can be contaminated with PAHs)
Fungicides, shaving creams, hair gels and hair coloring	nonylphenol
Hair spray, gel, mousse or shaving cream	isobutane, a propellant that can be contaminated with 1,3-butadiene
Sunscreens with UV filters	mimic estrogen

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Part II

Risk Assessment of Cosmetics in China

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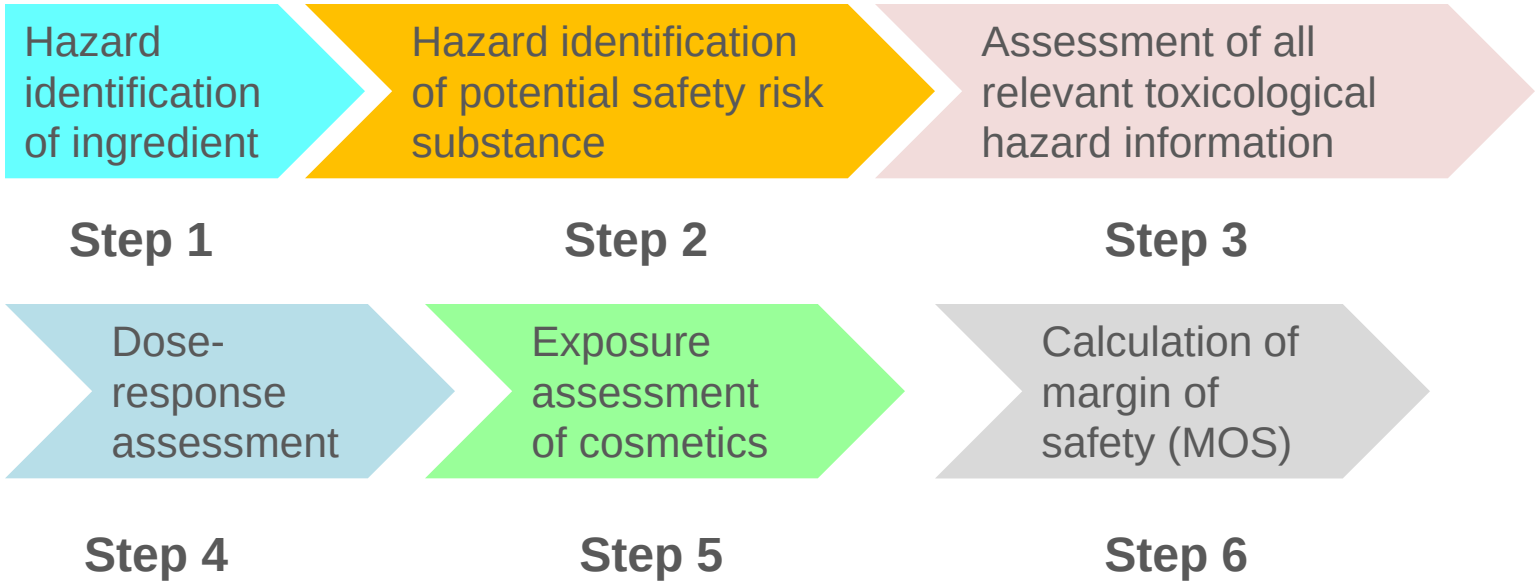
How to assess the safety of cosmetics?

Risk assessment is a process to identify potential hazards and analyze what could happen if a hazard occurs.

Follow the sixth steps as below:



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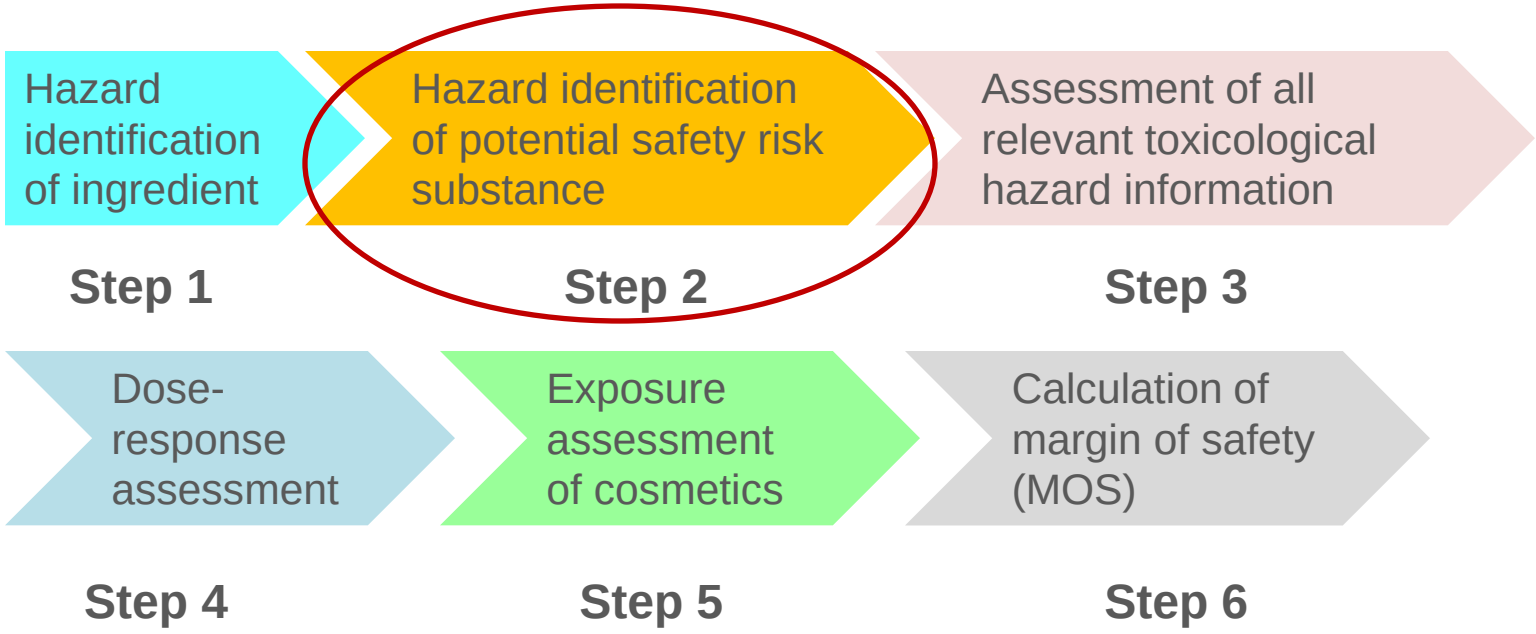
Safety Assessment of Cosmetics in China

In China, safety assessment is only required for potential safety risk substances in cosmetics rather than ingredient itself.

Follow the sixth steps as below:



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Safety risk substances exempt from quantitative risk assessment

➢ **Guidelines on the Risk Assessment of Potential Safety Risk Substances in Cosmetics (Notice, no 339)—23rd Aug 2010**

关于印发化妆品中可能存在的安全性风险物质风险评估指南的通知
国食药监许[2010]339号

✓Listed in Hygienic Standard for Cosmetics (2007) complying with the corresponding requirements

✓Restricted in other countries and below the concentration limit (evidence required)

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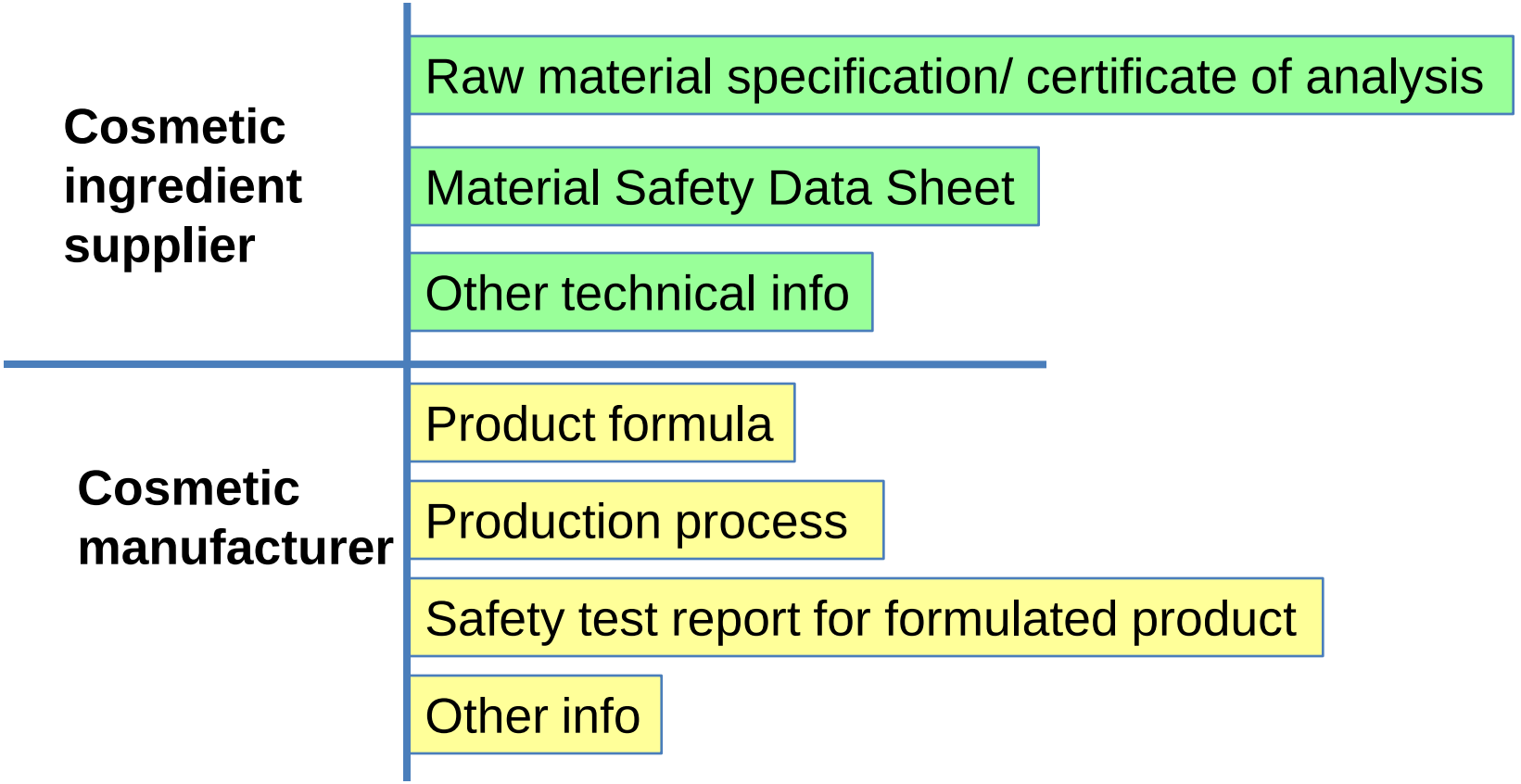
Basic Information for safety assessment



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Identification of Safety Risk Substances

- Origin of ingredients (synthetic, plant-derived, animal-derived)
- Extraction method and part of plant for plant ingredient
- Additives (preservative, colorant)
- By-products (depending on the production process)
- Impurities (CMR, solvent, residual monomers)

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Part III

Requirement on Specification of Cosmetic Raw Material

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SFDA Registration of Cosmetics in China

Testing

Gathering documents from cosmetic manufacturer

Gathering documents from ingredient supplier

Preparing & submitting dossier

SFDA review

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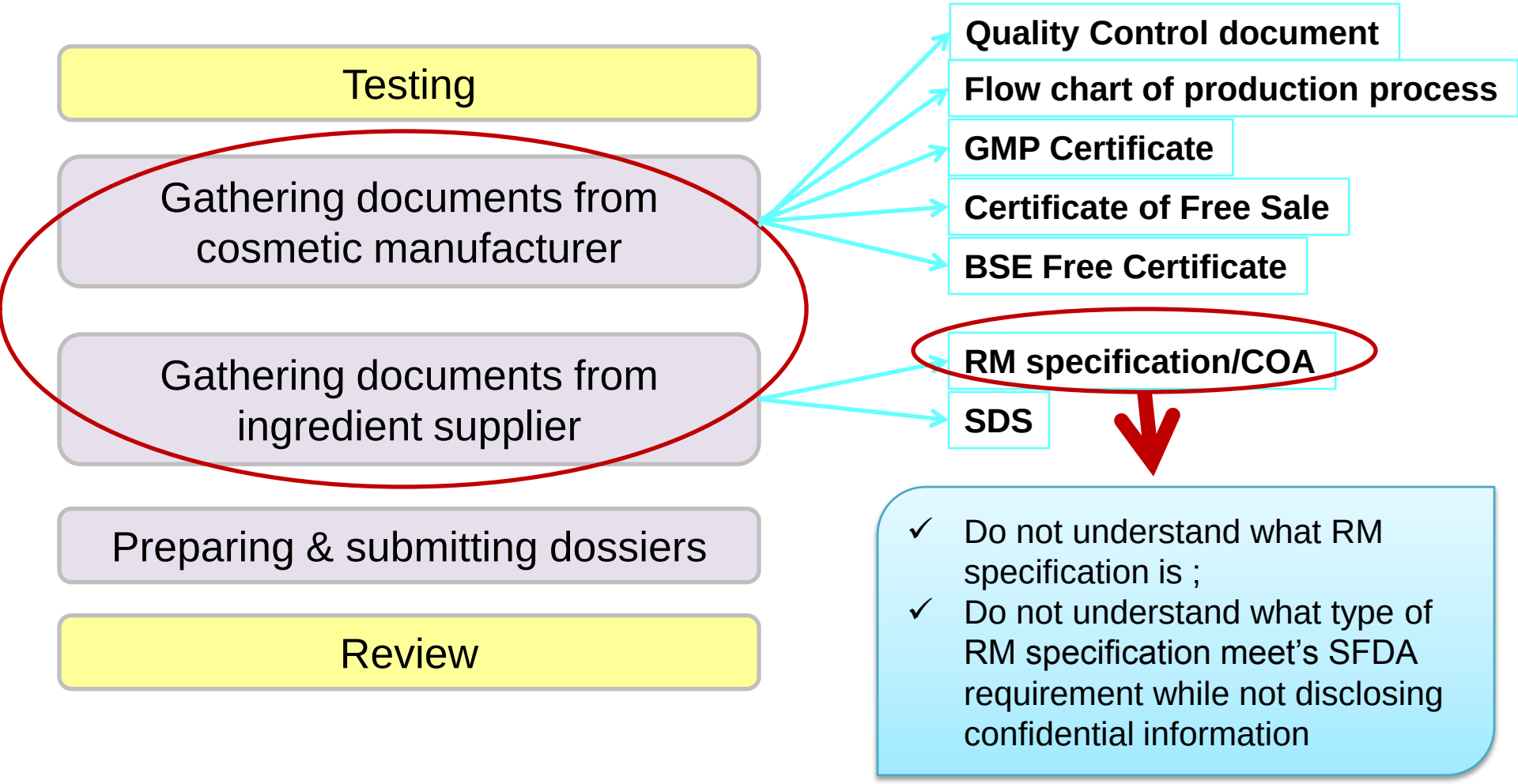
SFDA Registration of Cosmetics in China



Example of a good RM specification

	Spec. Values		Method
Assay			
mica	55.0 - 64.0	%	MERCK
TiO2	36.0 - 45.0	%	MERCK
Particle size (80% within the range 5.0-25.0 µm)	conforms		laser diffraction
Particle size (d50)	7.0 - 14.0	µm	laser diffraction
screening test (< 0.150 mm)	conforms		MERCK
pH-value (10 % aqueous slurry)	8.0 - 11.0		ISO 787-9
Loss on drying (105 °C)	= 0.5	%	ISO 787-2
Heavy metals			
As	= 0.0002	%	MERCK
Ba	= 0.0050	%	MERCK
Cd	= 0.0003	%	MERCK
Cr	= 0.0100	%	MERCK
Cu	= 0.0050	%	MERCK
Hg	= 0.0001	%	MERCK
Ni	= 0.0010	%	MERCK
Pb	= 0.0010	%	MERCK
Sb	= 0.0001	%	MERCK
Zn	= 0.0050	%	MERCK
Visual and colorimetric evaluation	conforms		MERCK
Microbiological purity			
aerobic bacteria	= 100	CFU/g	MERCK
Yeasts and moulds	= 100	CFU/g	MERCK
Gram negative bacteria	absent in 1 g		MERCK
E.coli	absent in 1 g		MERCK
Pseudomonas aeruginosa	absent in 1 g		MERCK
Staphylococcus aureus	absent in 1 g		MERCK
Salmonella species	absent in 1 g		MERCK
Candida albicans	absent in 0.5 g		MERCK

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Example of a good RM specification

	Spec. Values		Method
Assay			
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Staphylococcus aureus	absent in 1 g		MERCK
Salmonella species	absent in 1 g		MERCK
Candida albicans	absent in 0.5 g		MERCK

Physical-chemical property such as purity, pH value, visual evaluation.

Composition data & quality control target of hazardous impurities

Microbiological characteristics

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How to prepare a compliant RM specification?

A+B → D

D	≧90%
A	≦1%
B	≦1%
Visual evaluation	Conforms
pH-value	8.0-10.0
Heavy methals	
1) Pb	≦10ppm
2) As	≦2ppm
3) Hg	≦1ppm
Microbiological purity	
1) Colony Count	<10 CFU/g
2) Total Molds and Yeast Count	<10 CFU/g
3) Pseudomonas aeruginosa	Not Detected
4) Staphylococcus aureus	Not Detected
5) Fecal coliform	Not Detected
Additional data	Please refer to the following data

By-products depending on the production process	None
Impurities	
1) Heavy methals	
2) Ethylene oxide	
3) 1,4-Dioxan	
4) Nitrosamines	
5) Dioxine	
6) Benzol	
7) Phenol	
8) Polycyclic aromatic hydrocarbons (PCB, PCP)	
9) Monomer	
10) Pesticides	
……	

General information

Other info depending on production process

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How to prepare a compliant RM specification?

A+B → D

D	≥90%
A	≤1%
B	≤1%
Visual evaluation	Conforms
pH-value	8.0-10.0
Heavy methals	
1) Pb	≤10ppm
2) As	≤2ppm
3) Hg	≤1ppm
Microbiological purity	
1) Colony Count	<10 CFU/g
2) Total Molds and Yeast Count	<10 CFU/g
3) Pseudomonas aeruginosa	Not Detected
4) Staphylococcus aureus	Not Detected
5) Fecal coliform	Not Detected
Additional data	Please refer to the following data

1) To meet the requirements of formulation; or
2) To ensure MoS ≥100

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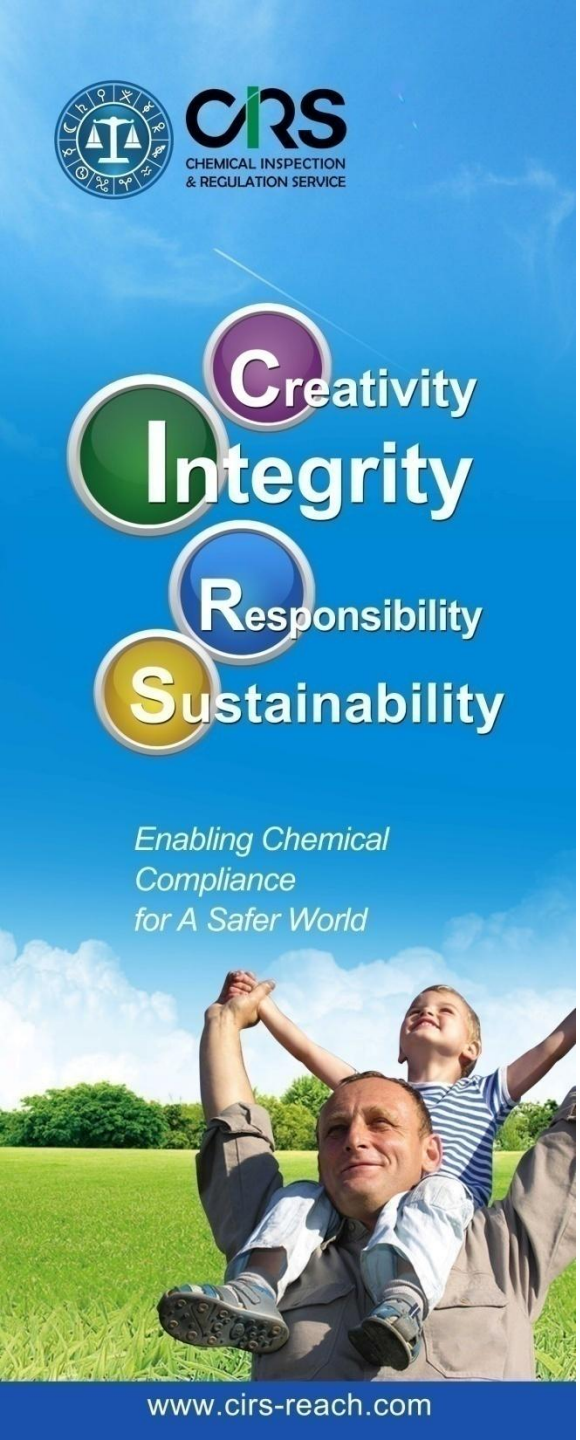

Thank You!

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Shanghai•24-25 Oct 2012
Summit Meeting on Chemical Regulations
in China, Korea and Japan

CHEMICAL INSPECTION & REGULATION SERVICE

Risk Assessment: China New Substance Notification vs New Cosmetic Ingredient Approval

Enabling Chemical Compliance for A Safer World

Yunbo Shi, CIRS, 26th Oct 2012
Workshop on Safety Assessment of Personal Care Products & New Ingredients in China

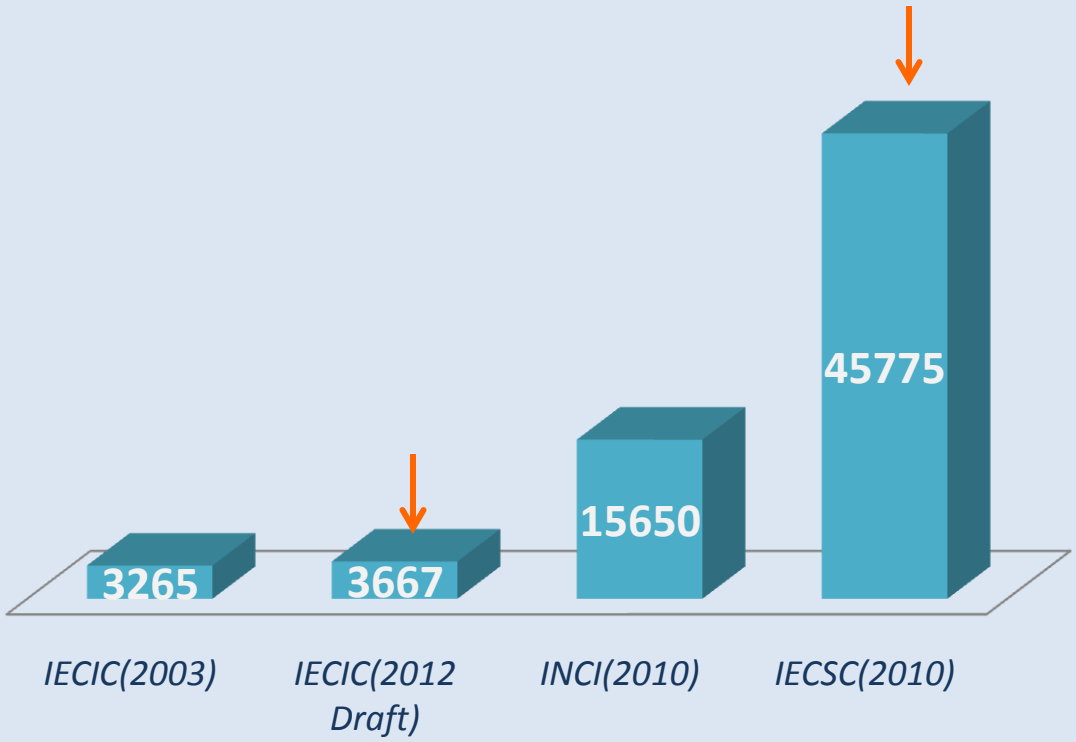
Email: yunbo.shi@cirs-reach.com

Table of Contents

Chapter I:

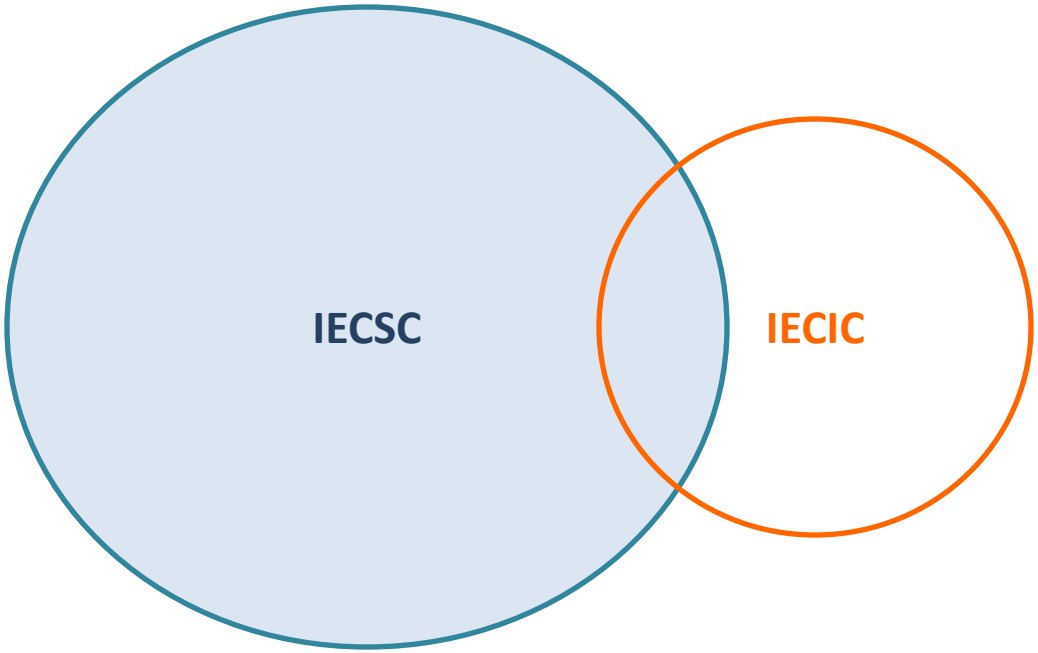
Background Introduction

IECSC(2010) vs IECIC vs INCI (2010)



IECIC: Inventory of Existing Cosmetic Ingredients in China
INCI: International Nomenclature of Cosmetic Ingredients
IECSC:Inventory of Existing Chemical Substances Produced or Imported in China

The Relationship Between IECSC and IECIC



Examples:

1. TRISODIUM ETHYLENEDIAMINE DISUCCINATE: IECIC(**Y**), IECSC(N)
2. Many water-based plan extracts: IECIC(**Y**), IECSC(N).
3. Existing chemical substance(non cosmetic use): IECIC(N), IECSC(**Y**).

Requirements for New Cosmetic Ingredient(NCI)

Country	Requirements
China	■ *Requiring SFDA's approval for all new cosmetic ingredients;* ■ *Notification to MEP if a new ingredient belongs to a new substance(not listed on IECSC);*
Australia	■ *Requiring National Industrial Chemicals Notification and Assessment Scheme* (NICNAS)'s approval for all new cosmetic ingredients;
EU	■ *Approval required for new cosmetic ingredients used as UV filters, preservatives, colorants and hair dyes.*
US	■*FDA's approval required for new cosmetic colorants;*

New Substance Notification(NSN) vs NCI Approval

Required Information	NSN(>1t/y)	NCI
Substance identification(including analytical data)	*Y*	*Y*
Tonnage information	*Y*	*N*
Description of manufacturing process	*Y(if produced in China)*	*Y*
Exposure information(use,etc)	*Y*	*Y*
Physio-chemical data	*Y*	*Y*
Toxicology data	Y	Y
Eco-toxicology data	*Y*	*N*
GHS classification & labelling	*Y*	*N*
SDS	*Y*	*N*
Risk assessment report	*Y*	*Y(**different**)*
Guidance available for data waiver?	*Y*	*Y*
R&D report, quality & safety control measures, ingredient specification, assessment of safety risk substances	*N*	*Y*

New Substance Notification(NSN) vs NCI Approval

Other Items	NSN(>1t/y)	NCI
Communication with Authorities	*Easy(CRC)*	*Difficult(SFDA)*
Review & Approval Process	*Long*	*Long*
Uncertainty	*Relatively Small*	*Big*
Alternative to Animal Test	*More Open*	*Hard to Accept*

Risk Assessment: NSN vs NCI

	NSN	*NCI*
Human Health	❑ *Qualitative* ❑ *Calculation of RC$_{health.}$*	❑ *Quantitative* ❑ *Calculation of MOS/MOE*
Environment	❑ *1-10t/y, Qualitative* ❑*>10t/y, Quantitative* ❑*PNEC/PEC?*	❑ *Not required*

Chapter II:

Risk Assessment for NSN & Case Study

Human Health Assessment: NSN

- **To determine risk level by calculating RC_{health}**

Risk Level	RC_{health}
Extremely High Risk	16-12
High Risk	11-8
Medium Risk	7-4
Low Risk	3-1

$$RC_{health} = HAZARD_{health} \times EXPOSURE_{health}$$

If risk level is high, implement risk management measures to reduce exposure!

Human Health Assessment: NSN

$$Rc_{health} = HAZARD_{health} \times EXPOSURE_{health}$$

Hazard Class	$HAZARD_{health}$
Acute Toxicity	❑ *Category 1-> (4)* ❑ *Category 2-> (3)* ❑ *Category 3-> (2)* ❑ *Category 4&5-> (1)*
Eye Irritation	❑ *Category 1-> (3)* ❑ *Category 2A-> (2)* ❑ *Category 2B-> (1)*

In case of multiple GHS Classifications, choose the highest score (do not add).

Tonnage Factors (Q)	Exposure Factors（R_E）		
	High	Medium	Low
Large	Extremely high exposure(4)	High Exposure (3)	Medium Exposure (2)
Medium	High Exposure (3)	Medium Exposure (2)	Low Exposure (1)
Small	Medium Exposure (2)	Low Exposure (1)	Low Exposure (1)

Human Health Assessment: NSN

❑ Tonnage Factors(Q)

1000+t/y	10-1000t/y	1-10t/y
Large	Medium	Small

❑ Exposure Factors(R_E)

$R_E=S_{HE}/S_{HEmax,}$ (See next slide)

High	Medium	Low
$R_E \geq 0.7$	**$0.4 \leq R_E < 0.7$**	**$R_E < 0.4$**

S_{HE}: Integration of exposure factors

Human Health Assessment: NSN

❑ S_{HE}: Integration of exposure factors

$$S_{HE}=A+B+C=\Sigma A_i \cdot p_i \cdot + \Sigma B_j \cdot p_j + \Sigma C_k \cdot p_k$$

$$S_{HEmax}=\Sigma A_{imax} \cdot p_i \cdot + \Sigma B_{jmax} \cdot p_j + \Sigma C_{kmax} \cdot p_k$$

Effect factors(Part of Table A)	Potential exposure contribution(A_i)				Weight (p_i)
A2 Liquid(BP, Vapor pressure)	3	2	1	0	3
A7 Eye Irritation	3	2	1		2
A8 Efficiency of Detection Method		2	1	0	1

Three tables in guidelines.

A: Phys-chemical properties, skin/eye irritation classification etc

B: Exposure and waste information during production.

C: Storage/transportation/treatment of waste etc

Human Health Assessment: NSN

Case Study: Substance A,100-1000t/y, acute toxicity category 2, eye irritation category 2B, solid, intermediate in a closed system.

- $HAZARD_{health}$ =3;
- Tonnage Factors(Q)= Medium;
- R_E＜0.4;
- $EXPOSURE_{health}$ =1;
- $RC_{health}=HAZARD_{health}\times EXPOSURE_{health}$ = 3;
- Low Risk.

Chapter III:

Risk Assessment for NCI & Case Study

Human Health Assessment for NCI: A Few Concepts

❑ Local Toxicity

- ➢ Skin/eye Irritation, skin sensitization and photo-toxicity

❑ Systematic Toxicity

- ➢ Acute/chronic toxicity, carcinogenic, mutagenic and reproductive toxicity

❑ No-Observable-Adverse-Effect-Level(NOAEL)

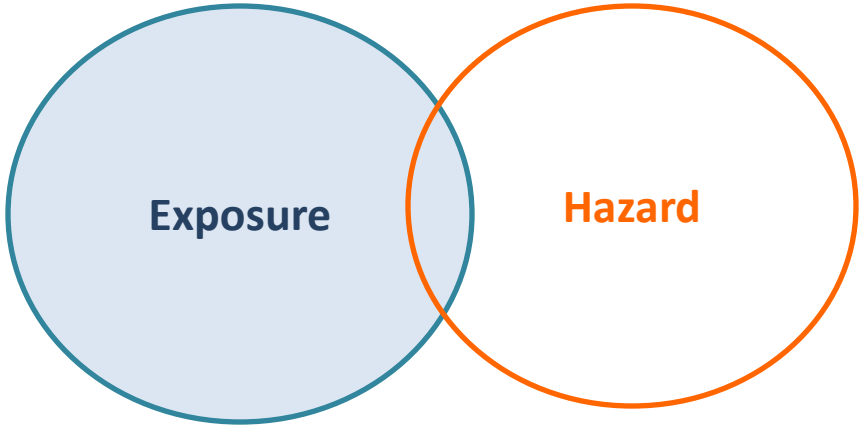
- ➢Intrinsic hazard property of a substance
- ➢Usually obtained from animal test (sub-chronic or chronic)

❑ Systematic Exposure Dosage(SED)

- ➢ The amount of chemical entering human blood and reaching organ;
- ➢ Obtained by modeling & calculations;

Human Health Assessment: NCI

❑ To Calculate Margin of Safety(MOS)*



Hazard Assessment — Step 1

Dose-response assessment(NOAEL) — Step 2

Exposure Assessment(SED) — Step 3

Risk Characterization — Step 4

Risk

$$MOS = \frac{NOAEL}{SED} > 100, Safe!$$

**MOE for non-threshold compounds*

Human Health Assessment: NCI

❑ Calculation of SED by Use Area

$$SED = \frac{DA_a\left(\mu g/cm^2\right)\times 10^{-3}\, mg/\mu g \times SSA\left(cm^2\right)\times F\left(day^{-1}\right)\times R}{60kg}$$

——SED：Systematic exposure dosage，Unit: mg/kg·d bw;

——**DA_a：Dermal absorption by area, Unit: μg/cm^2;**

——SSA：Exposed skin area，Unit : cm^2;

—— F：Frequency of use，Unit: day^{-1};

—— R：Retention factor;

—— 60kg：Default human body weight.

Human Health Assessment: NCI

❑ Calculation of SED by Use Amount

$$SED = \frac{A(g/day) \times 1000mg/g \times C(\%)/100 \times DA_P(\%)/100}{60kg}$$

——SED：Systematic exposure dosage，Unit: mg/kg·d bw;
——A：Amount of product applied per day, Unit: g/d ;
—— C：Concentration of ingredient in product;
—— DA_P：Dermal absorption by penetration; default value is 100%;
—— 60kg：Default human body weight - adult.

Human Health Assessment: NCI

❑ Some Reference Values for Calculation of SED

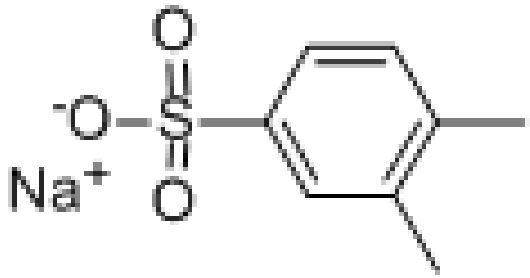
Cosmetics Type	RIFM Data		EPA Data	Use Parameters Suggested in Guidelines			
	Use Area(cm2)	Reference Part	Use Area(cm2)	Amout per use(g)	Frequency of Use	Retention Factor	Use per day(g)
Shampoo	1440	1/2 Head Area+ Both Hands	1430	**8**	**1 per day**	**0.01**	**0.08**
Facial Cream	565	1/2 Head Area(Female)	555	0.8	2 per day	1	1.6

- From Guidelines for Risk Assessment of Cosmetic Raw Materials(2011 draft edition) – MoH
- Different models available such as ECETRA's exposure scenarios for personal care products.

❑ Dermal absorption data is usually obtained by test;

Human Health Assessment: NCI

❑ Case Study

Substance Name	xylenesulfonic acid, sodium salt
CAS Number	1300-72-7
Molecular Structure	
Use	**1-5**% in Shampoo as coupling agent

Human Health Assessment: NCI

❑ Hazard Assessment

Data Endpoints	Toxicology Data
Acute Toxicity	Oral rat LD50 >5000 mg/kg Oral rat LD50 7200 mg/kg Oral rat LD50 16,200 mg/kg
Skin/Eye Irritation	**Eye Irrit. 2 H319: Causes serious eye irritation.**
Sensitization	Not a sensitizer
Photo-toxicity	Not available/required
Repeated Dose Toxicity	NOAEL(Rat, Dermal, 90d):800/mg/kg bw
	NOAEL(Male Mouse, Dermal, 90d): 540/mg/kg bw
	NOAEL(Female Mouse, Dermal, 90d):440/mg/kg bw
Mutagenicity	Not positive in-vivo or invitro.
Carcinogenicty	Not positive
Toxicity for Reproduction	Not available(90d does not show toxicity)

Data source:
ECHA Website

Human Health Assessment: NCI

❑ Hazard assessment- Local Effects

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye Effects Category 1 or Skin Corrosive Category 1A, 1B, 1C	≥ 3 %	≥ 1 % but < 3 %
Eye Effects Category 2		≥ 10 %
(10 × Eye Effects Category 1) + Eye effects Category 2		≥ 10 %

- Below concentration limit 10%;
- Mixture will not be classifies as eye irritation Category 2;
- Dilution with water;

Human Health Assessment: NCI

❑ Dose-response assessment – Systematic

Data Endpoints	Toxicology Data
Acute Toxicity	Oral rat LD50 >5000 mg/kg Oral rat LD50 7200 mg/kg Oral rat LD50 16,200 mg/kg
Skin/Eye Irritation	Eye Irrit. 2 H319: Causes serious eye irritation.
Sensitization	Not a sensitizer
Photo-toxicity	Not available/required
Repeated Dose Toxicity	NOAEL(Rat, Dermal, 90d):800/mg/kg bw
	NOAEL(Male Mouse, Dermal, 90d): 540/mg/kg bw
	NOAEL(Female Mouse, Dermal, 90d):440/mg/kg bw
Mutagenicity	Not positive in-vivo or invitro.
Carcinogenicty	Not positive
Toxicity for Reproduction	Not available(90d does not show toxicity)

NOAEL(Dermal): 440mg/kg bw

Data source:
ECHA Website

Human Health Assessment: NCI

❑ Exposure assessment (SED) – by use amount

$$SED = \frac{A(g/day) \times 1000mg/g \times C(\%)/100 \times DA_P(\%)/100}{60kg}$$

$$= \frac{0.08(g/day) \times 1000mg/g \times 5(\%)/100 \times 100(\%)/100}{60kg}$$

$$= 0.067mg/d/kgbw$$

——A：Amount of product applied per day, **0.08g/d (Shampoo)** ;
—— C：Concentration of ingredient in product : **max. 5%**;
—— DA_P：Default value is 100%(Conservative);
—— 60kg：Default human body weight - adult.

Human Health Assessment: NCI

- **Risk characterization (Calculation of MOS)**

$$MOS = \frac{NOAEL}{SED} = \frac{440}{0.067} =>> 100, Safe!$$

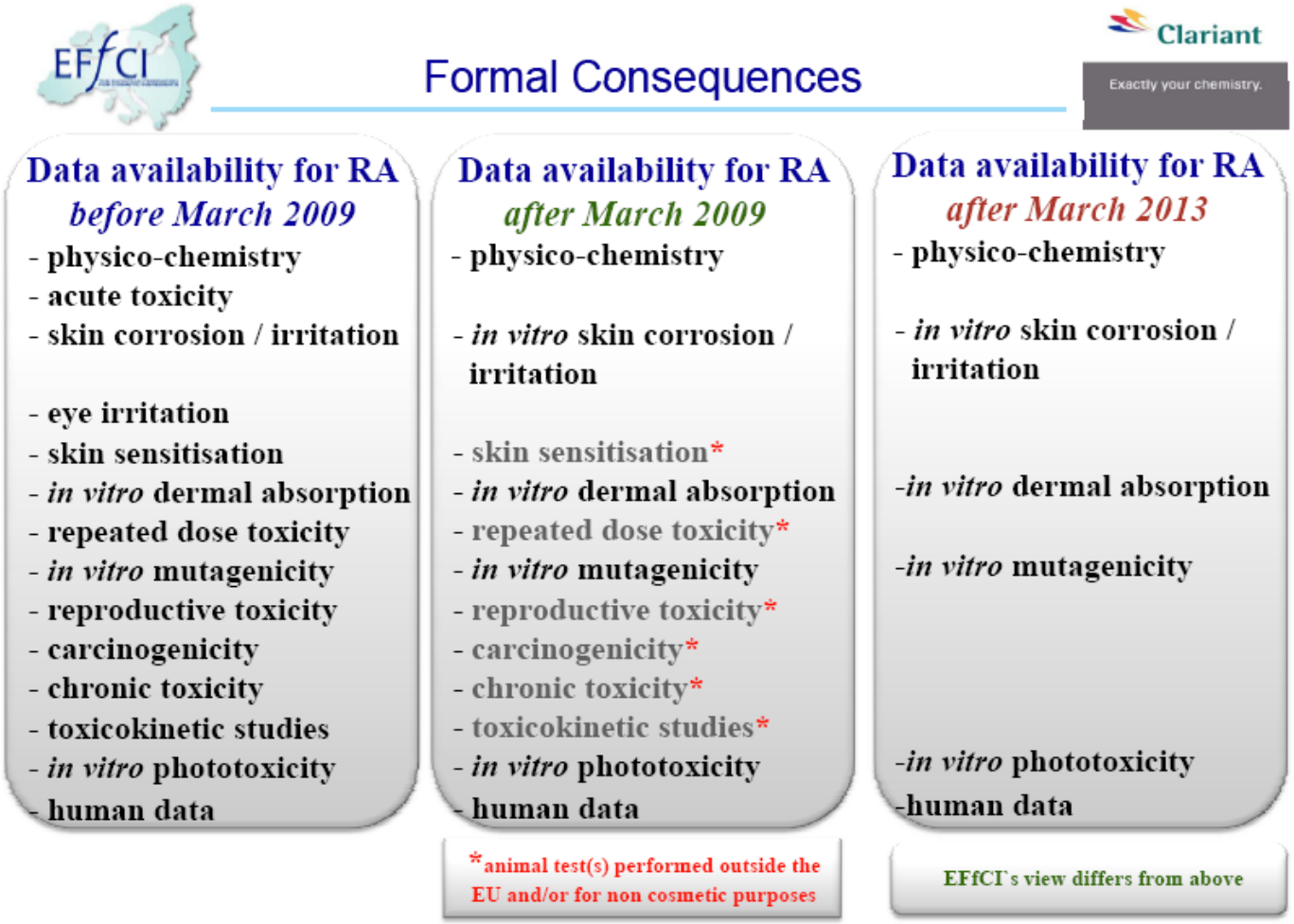
Human Health Assessment: NCI

- **Make it challenging**

  - **Safety assessment of impurities & additives;**
  - **Safety assessment of CMR substances;**
  - **Data evaluation & NOAEL derivation;**
  - **Analytical methods for ingredient & impurities**

Human Health Assessment: NCI

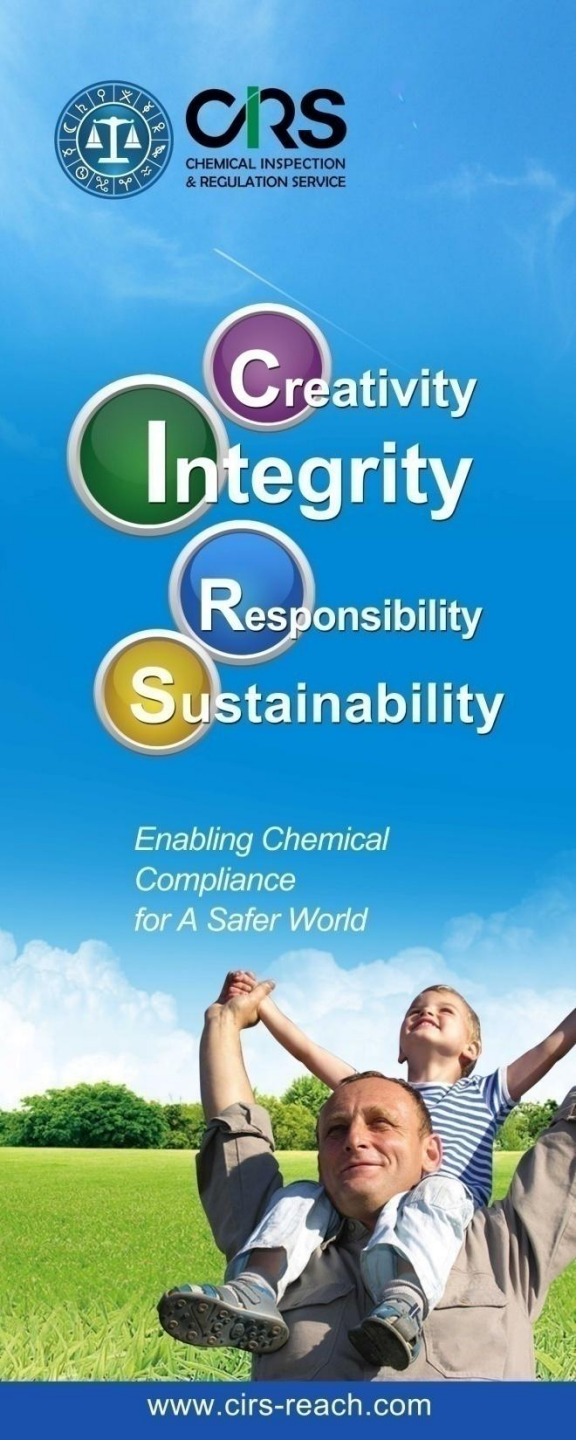
❑ Make it more challenging: No Animal Data



From Dr Reinhard Kreiling - Clariant

Summary

- ❑ Data required for NSN & NCI compared
- ❑ Human Health Assessment for NSN & Case Study
- ❑ Human Health Assessment for NCI & Case Study
- ❑ Challenges with NCI registration



Thank You!

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