化妆品原料风险评估及功效原料的法规要求
Cosmetic ingredient risk assessment and efficacy requirement
非测试方法在化妆品风险评估中的实际应用
A practice of in *Silico* methods in cosmetic risk assessment

李钟瑞

Intertek 天祥集团

个人介绍

Intertek
Valued Quality. Delivered.

李钟瑞 (Ray.Li)

中国毒理学家

毒理学硕士（英国伯明翰大学）

风险评估师，中国和英国毒理学会成员, 英国皇家生物学会会员

中国日用化学工业信息中心期刊编委

负责化学品的毒理评估、报告审核、卷宗制作和注册等。

目前负责化妆品(口腔产品)和玩具的安全评估和法规咨询

Ray.li@intertek.com

手机：18033132883

QQ: 864002611

Valued Quality. Delivered.

Intertek
Valued Quality. Delivered.

Intertek是全球领先的质量和安全服务公司，可以为众多行业和产品提供相关服务

我们的服务涉及几乎所有行业，包括纺织、玩具、电子、建筑、加热设备、医药、石油、食品和货物扫描等，可以为产品、货物和体系提供包括测试、检验、认证在内的一系列服务。

Intertek实验室和办事处网络遍布全球100多个国家，员工人数超过35,000人。

天祥集团成员，英国富时100强的公司

广东省“国产非特化妆品”备案检验机构 (深圳和广州实验室)

我们的传承

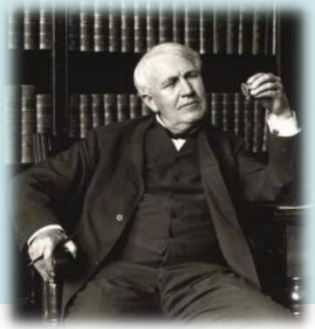
Intertek
Valued Quality. Delivered.

1885

Caleb Brett 创立海事鉴定业务

1896

托马斯·爱迪生(Thomas Edison)成立电灯测试局，后更名为电器测试实验室(ETL)



1911

Virginius Daniel Moody成立Moody Engineering，从事建筑和电力工程项目

2011

Intertek和Moody International联合，服务能力进一步延伸

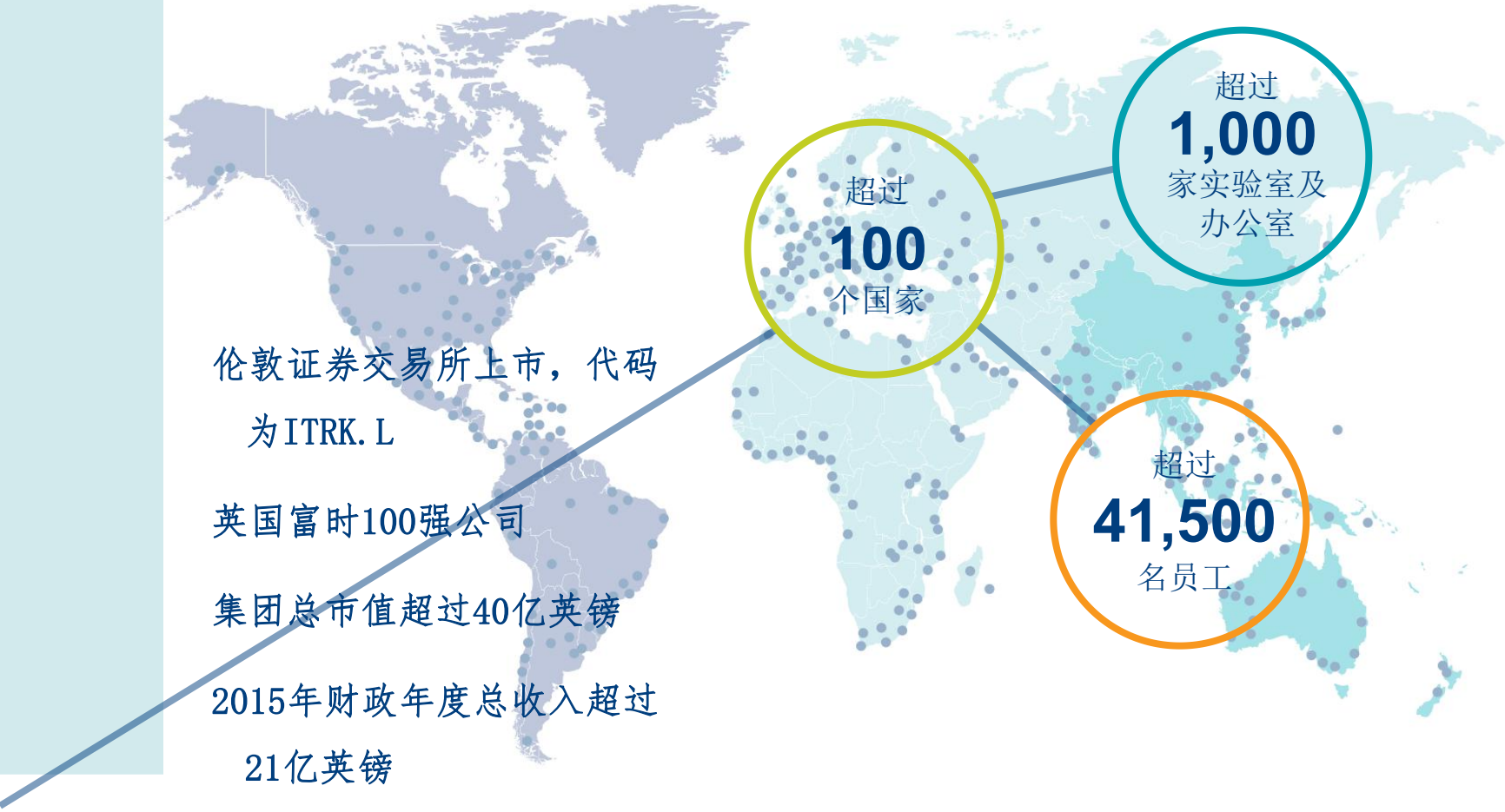
今天

今天的Intertek以**Valued Quality. Delivered.**为企业核心价值

Intertek
Valued Quality. Delivered.

Intertek全球网络

Intertek
Valued Quality. Delivered.



伦敦证券交易所上市，代码为ITRK.L

英国富时100强公司

集团总市值超过40亿英镑

2015年财政年度总收入超过21亿英镑

Intertek 中国区

Intertek
Valued Quality. Delivered.

- 第一家进入中国的外资第三方检测认证机构
- 行业的领导者，以客户为中心
- 全球所有业务线在中国皆有运营
- 在中国得到政府的认可和全力支持
- 为中国企业进入全球市场提供帮助
- 为国外公司进入中国市场提供帮助

化妆品原料风险评估及功效原料的法规要求
Cosmetic ingredient risk assessment and efficacy requirement

李钟瑞

Intertek 天祥集团

1. 什么是“毒”？

2. 什么是 “化妆品风险”？

3. 什么是 “化妆品安全”？

风险评估应该包括的内容

Intertek
Valued Quality. Delivered.

1. 成分（原料）评估 （化妆品卫生规范，已使用化妆品原料名称目录）
2. 杂质的风险评估（安全性风险物质，参考339号文要求）
3. 产品的风险评估（毒理学测试和评估）

成分（原料）评估

成分（原料）评估

1. 化妆品中使用的原料须是已列入到《已使用化妆品原料名称目录》中的成分。

2. 如果产品中所使用原料还未列入《已使用化妆品原料名称目录》需进行化妆品新原料申报和审评，须取得食品药品监督管理总局的审批后方可使用。

3. 原料需满足《化妆品卫生规范》（2007年版）禁止使用和限制使用成分的要求，包括使用范围、最大允许使用浓度、其它限制和要求。

《已使用化妆品原料名称目录》编制说明

（二）《目录》的使用。食品药品监管总局未组织对《目录》所列原料的安全性进行评价，化妆品生产企业在选用《目录》所列原料时，应当符合相关法规、标准的要求，并对原料进行安全风险评估，承担产品质量安全责任。

已使用化妆品原料不等同于可使用化妆品原料！

目录里面很多原料已经被欧盟禁用或者限用。第二次修订删除

成分（原料）评估-建议项目-参考欧美

Intertek
Valued Quality. Delivered.

1. 化妆品中香精需符合国标GB/T 22731-2008《日用香精》中附录A和附录B中规定的十一类加香产品的日用香精及限用香料的最高浓度；国际香精香料协会（IFRA）的香精安全性标准中化妆品的香精使用量不超过IFRA证书规定的最高浓度。

2. 禁止使用被国际癌症研究机构（IARC）纳入的致癌物；禁止使用被欧盟CLP法规（EC No 1272/2008）附录六收录为致癌（Carcinogenic）、致突变（Mutagenic）、或致生殖毒性（Toxic to Reproduction）的物质。

成分（原料）评估-建议项目-参考欧美

Intertek
Valued Quality. Delivered.

3. 对于未列入《化妆品卫生规范》（2007年版）表2至表7里的成分，可参考其它国家和地区的要求：

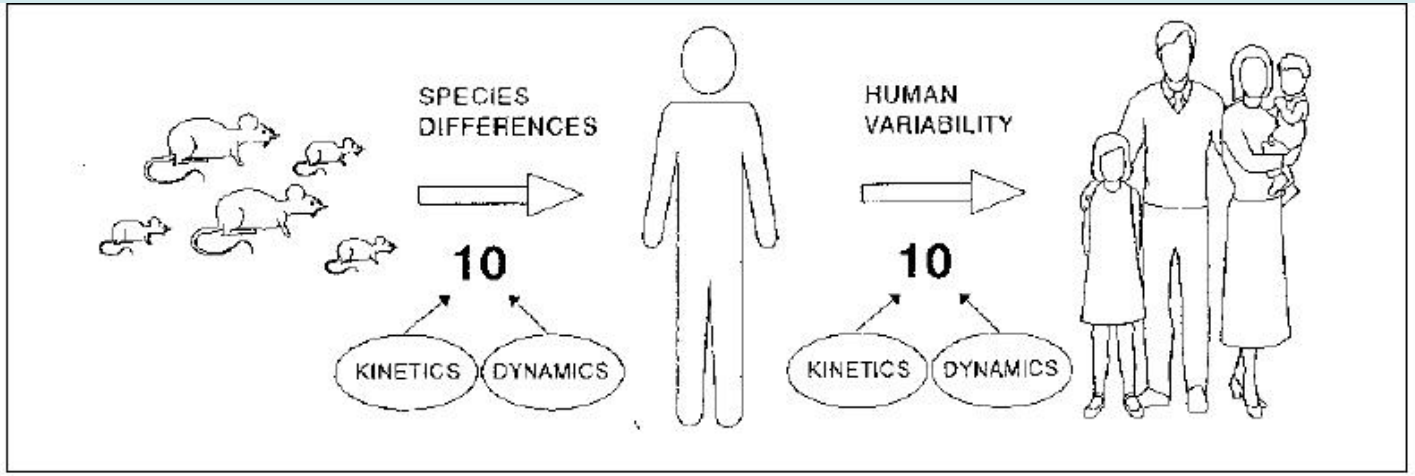
欧盟化妆品法规1223/2009中禁止使用和限制使用成分的规定，以及欧盟消费者安全科学委员会（Scientific Committee on Consumer Safety，SCCS）化妆品成分的使用意见。

美国21CFR及FDA关于化妆品成分使用范围及限制要求，以及美国化妆品成分审查委员会（Cosmetic Ingredient Review, CIR）对化妆品成分的安全评价。

成分（原料）评估-建议项目

4. 长期毒性：对有阈值的原料，确定“未观察到有害作用的剂量水平（NOAEL）”或“观察到有害作用的最低剂量水平（LOAEL）”并结合产品暴露信息计算安全边际（MOS）。通常情况下确保安全边际（MOS）值大于100。（无阈值的化学物质基本都是已经被禁止使用致癌物质，已经禁止做为化妆品原料使用，因此不需要考虑。）

$$\text{安全边际系数 (MoS)} = \frac{\text{未观察到有害作用的剂量水平 (NOAEL)}}{\text{系统暴露量 (SED)}}$$



Margin of Safe 方法

Intertek
Valued Quality. Delivered.

Ingredient 1 with NOAEL available		
Minimum MOS Acceptable	100.000	NOAEL/NOEL
NOAEL (mg/kg bw/d)	100	
Active conc (%)	100.00	
Dermal Absorption %	100.00	

Type of Exposure	Product	Theoretical Maximum Concentration allowed in final cosmetic product	Maximum Concentration allowed in final cosmetic product
Bathing, Showering	Shower gel	35.84%	35.84%
	Hand wash soap	30.03%	30.03%
Hair Care	Shampoo	66.23%	66.23%
	Hair conditionner	166.67%	100.00%
	Hair Styling Products	17.42%	17.42%
Leave on skin &Hair Care Products	Body Lotion	0.81%	0.81%
	Face cream	4.14%	4.14%
	Hand cream	3.06%	3.06%
Make up Products	Liquid foundation	12.66%	12.66%
	Make up remover	12.00%	12.00%
	Eye shadow	303.03%	100.00%
	Mascara	238.10%	100.00%
	Eyeliner	1250.00%	100.00%
	Lipstik / Lip salve	111.11%	100.00%
Deodorant	Deo non spray	4.53%	4.53%
	Deo aerosol spray	4.85%	4.85%
	Deo spray (non ethanol)	10.00%	10.00%
Oral Hygiene	Toothpaste	46.30%	46.30%
	Mouthwash	3.07%	3.07%

原料毒理学端点和数据-建议项目

Intertek
Valued Quality. Delivered.

- Acute toxicity via relevant routes of exposure （急性毒性）
- Eye Irritation and corrosivity: （眼睛刺激性）
- Skin irritation and skin corrosivity （皮肤刺激性）
- Skin sensitisation （皮肤致敏性）
- Dermal/percutaneous absorption （经皮吸收率）
- Repeated dose toxicity (normally 28- or 90-day studies) （长期动物实验数据）
- Mutagenicity/genotoxicity （基因毒性）
- Carcinogenicity （致癌性）
- Reproduction toxicity （生殖毒性）
- Toxicokinetics (ADME studies) （毒代动力学）
- Photo-induced toxicity （光毒性）

单个原料的毒理文档-建议学习

Intertek
Valued Quality. Delivered.

完成毒理文档包括材料：

产品中所使用原料的Certificate of Analysis (COA)、 Technical Data Sheet (TDS)、安全技术说明书（MSDS/SDS）。如果产品使用了香料或香精则要提供国际香精协会证书（IFRA Certificate）和26个致敏源声明。另外，如果产品中使用的动植物提取物，则要原材供应商提供农药残留和所使用防腐剂的信息。

毒理学数据

选取合适的无明显损害作用水平（NOAEL）用于安全阈值计算（Margin of Safe）

MoS 方法不适用于无阈值的致癌物质

$$MoS = \frac{NO(A)EL}{SED}$$

功效原料的法规要求

Intertek
Valued Quality. Delivered.

中国：

1. 化妆品监督管理条例（征求意见稿）

2. 《化妆品标签管理办法》（征求意见稿）

《妆品监督管理条例草案》的第四十三条和《标签管理办法》的第十九条。其中对行业影响最大的是“未经评价验证的，应当在描述声称的功效作用内容结尾标注“上述功效未经评价验证”等字样，字体应与不小于功效声称作用内容的标识字体”。

行业内相对成熟的测试有：保湿、SPF、控油、清洁力测试、抗衰老测试、美白、祛痘、瘦身、除臭、敏感肌肤耐用测试、发用品测试。

但是只有《QB/T 4256-2011 化妆品保湿功效评价指南》和防晒化妆品防晒指数（SPF值）测定方法属于现行有效的标准和方法，还缺乏一个统一的指南和具体方法的细则要求。

《功效实验室评价指南》？？

欧盟 EU

Vertical EU regulation specific to Cosmetic :

- Cosmetic Products Regulation 1223/2009/EC: Articles 20 and 11(2)(d)
- Commission Regulation on the Common Criteria for the justification of claims used in relation to cosmetic products Regulation 655/2013 / EC

In addition :

- European Commission Recommendation on the labelling and efficacy of sunscreen products
- European Commission Recommendation on claims related to the absence of animal tests (claim for non-animal testing??)

Horizontal legislation, e.g.:

- Directive 2005/29/EC on unfair commercial practices (UCP)
- Directive 2006/114/EC on misleading and comparative advertising (MCA)

The List and scope of Common Criteria Defined in EU 655/2013

Intertek
Valued Quality. Delivered.

Legal compliance 合规性

Truthfulness 真实性 **e.g. give you wings**

Evidential support 证据支持

Claims cannot be extrapolated from ingredient properties to the finished product without adequate and verifiable evidence

Honesty 诚实 Eg If the action is linked to specific conditions, such as use in association with other products, this shall be stated

Fairness 公平

'Low in allergens because formulated without preservatives'

Informed decision-making 知情决策

Which claims cannot be applied?

Intertek
Valued Quality. Delivered.

- **Examples of claims related to treating or preventing diseases**
  - Anti-inflammatory 抗炎
  - Enhances the immune system 增强免疫系统
  - Treatment of skin problems such as dermatitis, eczema… 皮炎和湿疹
  - Calming of red and irritated skin 舒缓皮肤发红和刺激
  - Diminishes scars 减少疤痕
  - Repairs damaged skin 修复破损皮肤
  - Stimulating blood circulation
  - Healing sores on lips 治愈嘴唇溃疡
  - Calms pains of oversensitive teeth 镇静牙齿敏感带来的疼痛
  - Reduces gum-bleeding 减少牙龈出血
  - Antiseptic, disinfecting 抗菌 消毒
  - Treatment of diaper rash 治疗尿布疹
  - Against stiff and cold muscles 抗 肌肉僵直和寒冷
  - Solves baldness 解决脱发

Future

By 11 July 2016, the Commission shall submit to the European Parliament and the Council a report regarding the use of claims on the basis of the common criteria (…).

Specific Claims under discussion*:

Free from*

Hypoallergenic 低过敏性

Natural, organic, bio

Environmental claims

Certain claims should be allowed for an informed choice of consumers who want to avoid certain ingredients based on lifestyle or religious reasons

alcohol-free; no animal derived ; fragrance free

非测试方法在化妆品风险评估中的实际应用
A practice of *in Silico* methods in cosmetic risk assessment

李钟瑞

Intertek 天祥集团

Content

Intertek
Valued Quality. Delivered.

1.QSAR定量构效关系

2. TTC 毒理关注阈值

3. Read-Across 交叉参考

4. Mixture Toxicity Estimation 混合物毒性预估

QSAR

Intertek

Valued Quality. Delivered.

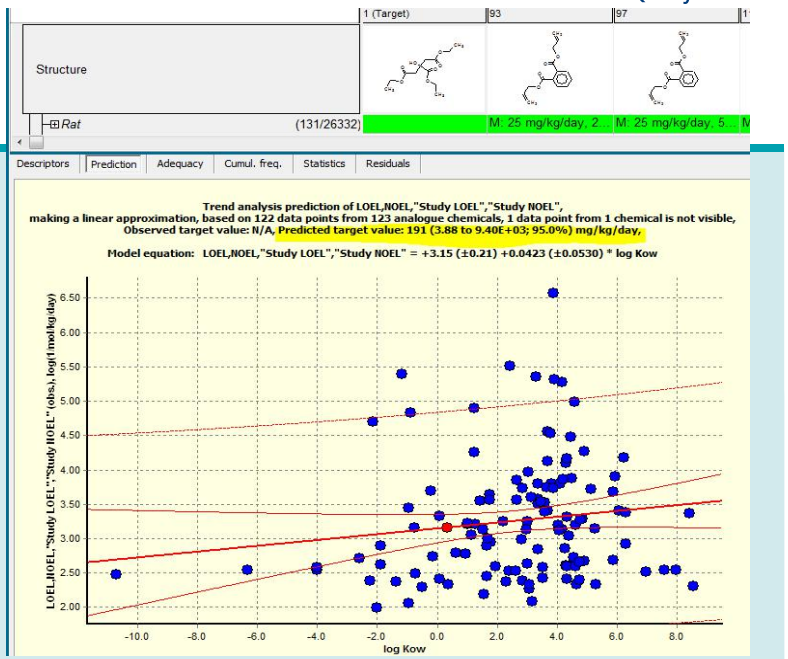
定量构效关系(Quantitative structure-activity relationship)

A QSAR is a mathematical model (often a statistical correlation) relating one or more quantitative parameters derived from chemical structure to a quantitative measure of a property or activity (e.g. a (eco)toxicological endpoint.)

由化学结构式或生物特性的定量参数得出的数学模型。

QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals. 化学结构式和生物活性数据库

Second, QSAR models predict the activities of new chemicals. 预测新的化学物



An example of a QSAR is the prediction of acute toxicity to an invertebrate species (Tetrahymena pyriformis) by means of a regression equation with the partitioning behaviour (log Kow value) of the chemical as a descriptor (Schultz et al, 2002).

QSAR Tools

Intertek
Valued Quality. Delivered.

In Silico tools including **OECD Toolbox, Toxtree, CAESAR, ToxPredict and ConsExpo** are commonly used to generate prediction results to fulfill the data gaps for different kinds of endpoints and exposure via Weight of Evidence approach in the risk assessment.

Currently these tools **can not fully replay** the animal testing due to limitations of accuracy and sensitivity, however those results could be used as supportive evidences to waive unnecessary animal tests and combining with other evidences to indentify hazardous.

(e.g. An irritation study report without details, result is consistent with QSAR)

The SCCS is not accepted the QSAR results for any endpoint, ECHA may **accept the prediction of skin sensitization within other supportive evidence**; FDA may accept the results of Log Kow and BCF; FDA, EFSA and JECFA prefer to use the “Cramer classes” for TTC.

How to use QSAR tools?

Intertek
Valued Quality. Delivered.

Generally, there are three key steps are included to run a prediction in those tools and summarized below:

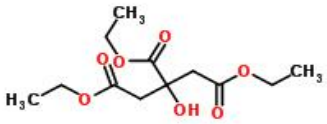
1. Indentify the substance

Chemical structure such as **SMILS** is used often in these tools and such data can be obtained in multiple websites. Chemspider is recommended here because of the accuracy is good. The SMILS in the ChemIDplus is not working well in these tools. Fulfilling the CAS number in the search field and click the button of “search” and SMILS will be displayed in the webpage and then it could copy and paste into the QSAR tools.

OECD Toolbox and ToxPredict are accepted CAS number for starting point, so SMILS is not necessary for both of them. The QSAR tools are also accepted structure data by drawing in the input window.

ChemSpider
The free chemical database

About | More Searches | Web APIs | Help



2D 3D Save Zoom

Triethyl citrate

ChemSpider ID: **13850879**

Molecular Formula: $C_{12}H_{20}O_7$

Monoisotopic mass: 276.120911 Da

▼ Systematic name

Triethyl 2-hydroxy-1,2,3-propanetricarboxylate

▼ SMILES and InChIs

SMILES:
O=C(CC(O)(CC(=O)OCC)C(=O)OCC)OCC Copy

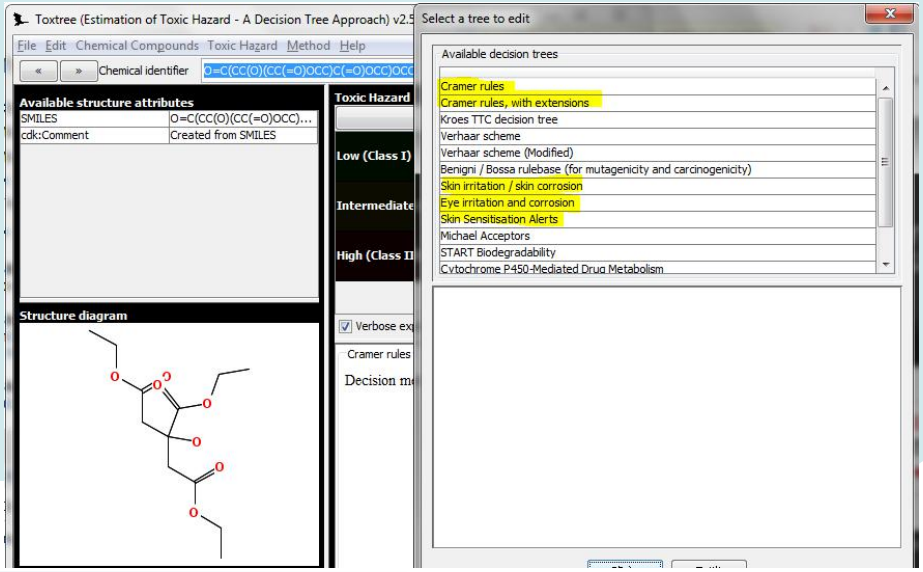
Std. InChI:
InChI=1S/C12H20O7/c1-4-17-9(13)7-12(16,11(15)19-6-3)8-10(14)18-5-2/h16H,4-8H2,1-3H3 Copy

Std. InChIKey:
DOOTYTYQINUNNV-UHFFFAOYSA-N Copy

http://www.chemspider.com/

2. Selecting target endpoints in the QSAR tool

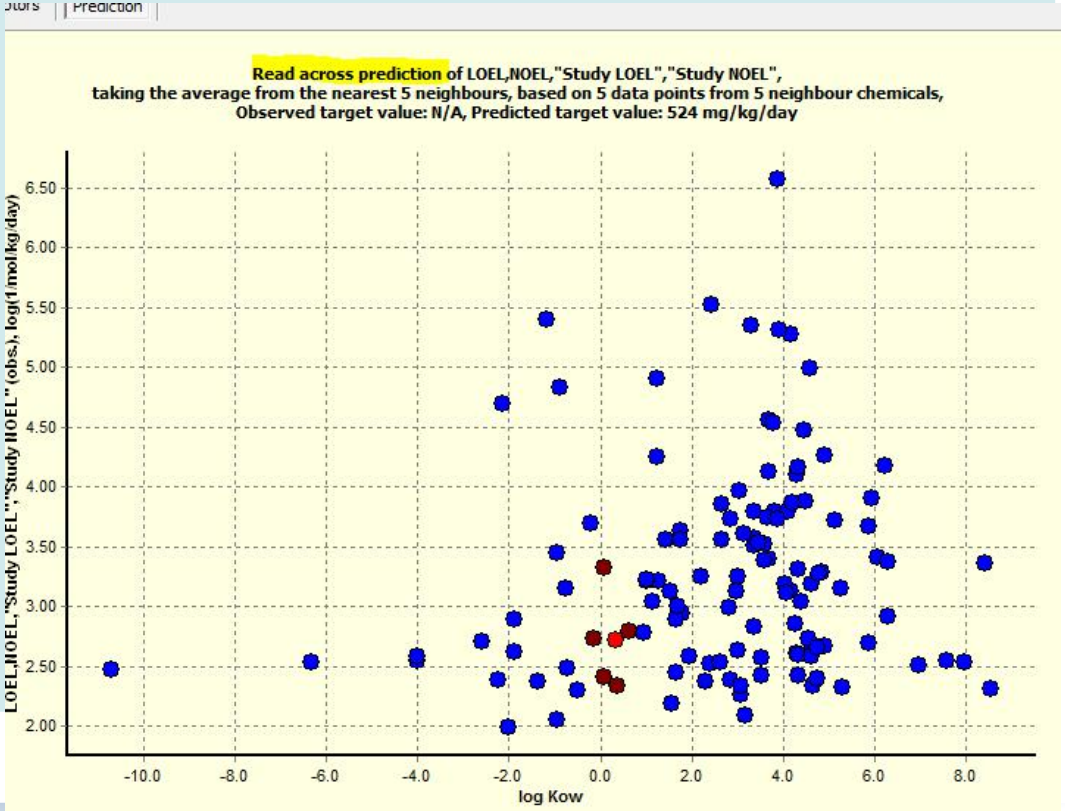
The tools are including multiple endpoints inside and appropriate interesting model(s) shall be chosen. These models are based on scientific theories of model of action or toxic similarity of functional/active groups. Parameters may be required in some specific models to assist prediction such Boiling Point is required to calculate skin and eye irritation in the **Toxtree**, otherwise absent such parameters may cause the model is out of domain and lead false results.



3. Calculation and generating report

Unless OECD Toolbox, QSAR tools are producing qualitative analysis results such as Positive or Negative for sensitizing, CMR properties, the validation of results or out of domain will also be given also for justification.

Currently the result for repeated toxicity is still invalid but it could be used as a supportive evidence for reference.
The confidential and commercial data are involved in the OECD Toolbox, so it is not permit to generate a report in this software sometime.



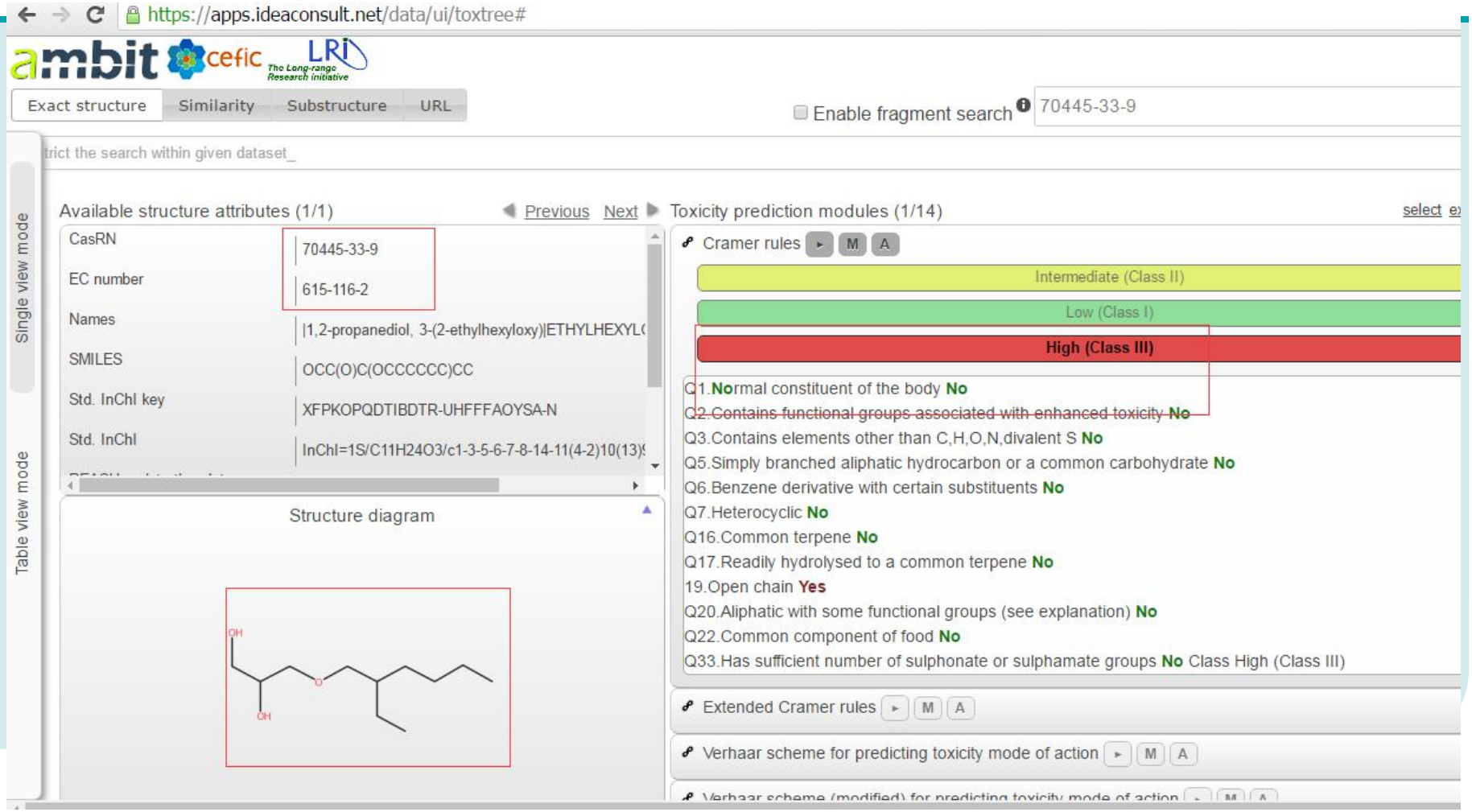
Summary of QSAR

QSAR Tool	Brief Summary	Applied Endpoints	Comments
CAESAR http://www.caesar-project.eu/software/	CAESAR was an EC funded project, which was specifically dedicated to develop QSAR models for the REACH legislation.	bioconcentration factor skin sensitization carcinogenicity mutagenicity developmental toxicity	A web based tool, can generate analysis report
Toxtree http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree	JRC funded project is designed for TTC and certain endpoints.	TTC Skin irritation Eye irritation Skin sensitization Mutagenicity carcinogenicity	A standalone PC Tool can be used to gain the categories based on TTC for the low concentration ingredients or impurities.
EPI Suit http://www.epa.gov/opptintr/exposure/pubs/episuite.htm	Developed by US EPA to gain the prediction of physical/chemical property and environmental fate estimation	Melting point Boiling point Vapor pressure Water solubility Hydrolysis log KOW BCF	A standalone PC Tool, can be used to gain the physical/chemical data.
ToxPredict http://apps.ideaconsult.net:8080/ToxPredict	Company owned tool to predict a toxicity endpoint, free to use.	TTC log KOW Ecotoxicity Multiple endpoints	A web based tool, also including the prediction results from Toxtree. The most advantage is that all the results can be displayed in one slide.
ConsExpo 4.1 http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp	Developed by RIVM to calculate the accurate exposure data for consumer products.	Dermal absorption	The prediction is based on the molecular weight and KOW, only applying to aqueous solutions and not considering the solubility.
OECD ToolBox http://www.oecd.org/document/54/0,3343,en_2649_34379_42923638_1_1_1_1,00.html	Developed by OECD to fulfill the data gaps for (eco)toxicity	Almost all the endpoints	A standalone PC Tool, one of the most powerful QSAR tool including all the databases of OECD members. Can be used to predict different endpoints even NOAELs. But it is time consuming to run the database.

Example of TOXTREE

Intertek
Valued Quality. Delivered.

乙基己基甘油



Verhaar scheme for predicting toxicity mode of action	Verhaar scheme (modified) for predicting toxicity mode of action	Eye irritation	Skin irritation
Class 1 (narcosis or baseline toxicity)	Class 1 (narcosis or baseline toxicity)	Serious lesions to the eye	Irritating to skin

Aqua toxin alert

Eye irritation alert

Skin irritation alert

Skin sensitisation alerts (M. Cronin)	DNA binding	Protein binding
Alert for SNAr identified.: NO	Alert for SN1 identified.: NO	Alert for SNAr identified.: NO
Alert for Schiff base formation identified.: NO	Alert for Schiff base formation identified.: ...	Alert for Schiff base formation identified.: ...
Alert for Michael Acceptor identified.: NO	Alert for Michael Acceptor identified.: NO	Alert for Michael Acceptor identified.: NO
Alert for Acyl Transfer agent identified.: NO	Alert for Acyl Transfer agent identified.: NO	Alert for Acyl Transfer agent identified.: NO
Alert for SN2 identified.: NO	Alert for SN2 identified.: NO	Alert for SN2 identified.: NO
No skin sensitisation reactivity domains alerts identified.: ...	No protein binding alerts identified.: YES	No protein binding alerts identified.: YES

Michael acceptors	Benigni/Bossa rules for carcinogenicity and mutagenicity	In vitro mutagenicity (Ames test) alerts by ISS
Not reactive via Michael addition	Structural Alert for genotoxic carcinogenicity: NO	Structural Alert for S. typhimurium mutagenicity: NO
	Structural Alert for nongenotoxic carcinogenicity: YES	No alerts for S. typhimurium mutagenicity: YES
	Potential S. typhimurium TA100 mutagen based on QSAR: NO	Potential S. typhimurium TA100 mutagen based on QSAR: NO
	Unlikely to be a S. typhimurium TA100 mutagen based on QSAR:...	Unlikely to be a S. typhimurium TA100 mutagen based on QSAR
	Potential carcinogen based on QSAR: NO	For a better assessment a QSAR calculation could be applied.: I
	Unlikely to be a carcinogen based on QSAR: NO	Error when applying the decision tree: NO
	For a better assessment a QSAR calculation could be applied.: NO	
	Negative for genotoxic carcinogenicity: YES	
	Negative for nongenotoxic carcinogenicity: NO	
	Error when applying the decision tree: NO	

No alert for skin sensitization; No DNA binding; No protein binding

No potential for Carcinogenicity and mutagenicity; No alert for Ames test

Classification in EU C&L Inventory

Intertek
Valued Quality. Delivered.

408-080-2		70445-33-9

Notified classification and labelling according to CLP criteria

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Classification affected by Impurities / Additives	Additional Notified Information	Number of Notifiers	Joint Entries	
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)							
Eye Dam. 1	H318	H318		GHS05 Dgr				State/Form IUPAC Names	844	✔	
Aquatic Chronic 3	H412	H412									
Eye Dam. 1	H318	H318		GHS07 GHS05 Dgr				State/Form IUPAC Names	37	✔	
Acute Tox. 4	H332	H332									
Aquatic Chronic 3	H412	H412									
Eye Dam. 1	H318	H318		GHS07 GHS05 Dgr				State/Form IUPAC Names	2	✔	
Acute Tox. 4	H332	H332									

Incorrect prediction: Skin irritation and Acute toxicity?

http://echa.europa.eu/ja/registration-dossier/-/registered-dossier/16725/7/4/2/?documentUUID=56f54b02-377d-407a-8cc0-89450cabebce

http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/122840

Conclusion for QSAR

Intertek
Valued Quality. Delivered.

EPI Suit is recommended to predict physical/chemical properties. e.g. Log Kow.

ToxPredict/Toxtree is recommended here to predict toxicity due to its convenience and easy to use.

ConsExpo 4.1 is suggested for exposure assessment (inhalation).

Although OECD toolbox is very powerful, but it will cost from 30 minutes to few hours to get the results due to calculating thousands of chemicals and multiple QSAR models are included.

Toxtree, ToxPredict and OECD Toolbox can identify the category of Cramer rules for substance and hence associating with exposure dose for TTC assessment.

Low concentration ingredient 风险评估

Intertek
Valued Quality. Delivered.

杂质和低浓度原料的造成急性毒性和刺激性 的风险非常低，通常情况下不考虑。

杂质和低浓度原料的长期毒性，生殖毒性，致突变性和致癌性需要重点关注。

有阈值和无阈值两种

长期毒性和生殖毒性有阈值，则计算安全限值（Margin of Safe, MoS）,每日耐受摄入量(tolerable daily intake, TDI)

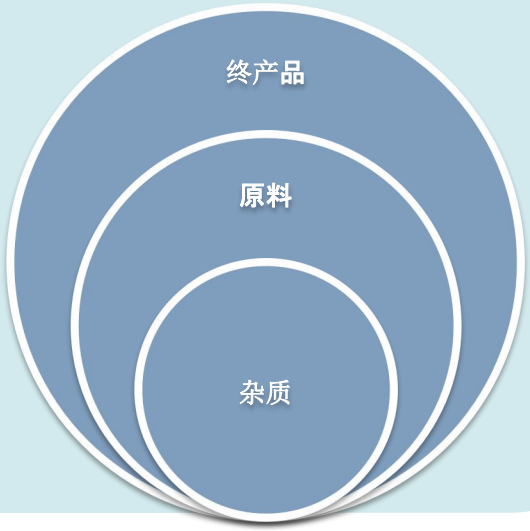
致突变性导致的致癌性通常认为是无阈值。

则通过 暴露限值（Margin of Exposure，MOE),

毒理安全阈值（Threshold of Toxicity Concern，TTC），

允许日暴露量（Permitted daily exposure, PDE），

Expedited No Significant Risk Level ..



毒理关注阈值（TTC）方法

Intertek
Valued Quality. Delivered.

如果化妆品原料或杂质的毒性学信息缺乏，如何评估?

TTC方法目前已被美国食品和药品管理局（FDA）、联合食品添加剂专家委员会（JECFA）、欧洲食品安全局（EFSA），欧洲药品评估局（EMEA）和欧盟消费品科学委员会（SCCS）接受并用于食品包装和接触材料、食品添加剂、药物中基因毒性杂质和化妆品原料和杂质的风险评估。

COMMISSION IMPLEMENTING DECISION Guidelines on Annex I to Regulation (EC) No 1223/2009

An example where this could apply would be the presence of a substance in the cosmetic product at a low level, with the expected (worst case) exposure levels being below the appropriate **threshold of toxicological concern (TTC) values.**

该方法适用于化妆品原料和杂质评估

毒理学关注阈值

Threshold of Toxicological Concern

Background

TTC的概念源于20世纪90年代Munro提出的法规关注阈值（Threshold of Regulation, TOR），TOR是被US FDA用于监管低暴露水平的食品接触材料，并建立了1.5μg/person/day (0.025 μg/kg bw/day)的安全摄入浓度。

TOR源于在致癌风险为百万分之一的致癌风险时的水平暴露的上限估算值（动物到人外推），1.5μg/person/day被认为是对在结构上无遗传毒性或不和DNA反应的化学物的安全边界值。这种方法促使TTC值在非致癌效应化学物上的开发。

TTC是一个风险评估工具，在低于该暴露水平时，毒性效应不会发生。该值是从已知的数据库中的化学物质（该类化学物质的结构已知但是毒理学数据较少甚至没有）外推得出。

1996年Munro等人提出3 种Cramer 结构类别的NOAEL值的各自分布（用613种化学物的2941个 NOAEL值，包括工业化学物，药物，食物化学物，环境化学物，农业和消费者化学物， 其中Cramer class I （137种），II（28种）和III （448种））。

依据最敏感的物种，性别和毒理学终点，选取最为保守的NOAEL值。每一类的物质的第五百分位值的NOAEL值被计算并转化成60 kg人体的摄入水平。在第五百分位值的NOAEL值转换成TTC时， 100×安全系数（动物的毒理学数据进行健康指导值的默认的安全因子）被用。

最终得出三类结构的TTC值分别为**1800，540，90 μg/person/day**。首次建立了以结构类为基础的多层次的TTC方法。

表 1 Cramer 结构类别的具体分类

结构类别	定义
I 类	指具有简单的化学结构，有效的代谢模型暗示经口毒性低（如：L-甘氨酸，甘露醇和丙二醇）
II 类	关于该物质的代谢，药理和毒理学信息知之较少，但是没有较明确的毒性，通常分为 2 类：1 类为带有功能集团或者是类似的，但是对 I 类的功能基团（烯丙基和炔烃）较活跃。另一种为结构较 1 类复杂的，但是多数是食品复合物。
III 类	无有力的证据保证其安全性或者暗示有明显的毒性

表 2 Cramer 结构类别的 TTC 值

结构类别	NOAEL（第 5 百分位值）（mg/kg·d）	TTC（μg/person·day）
I 类	3.0	1800
II 类	0.91	540
III 类	0.15	90

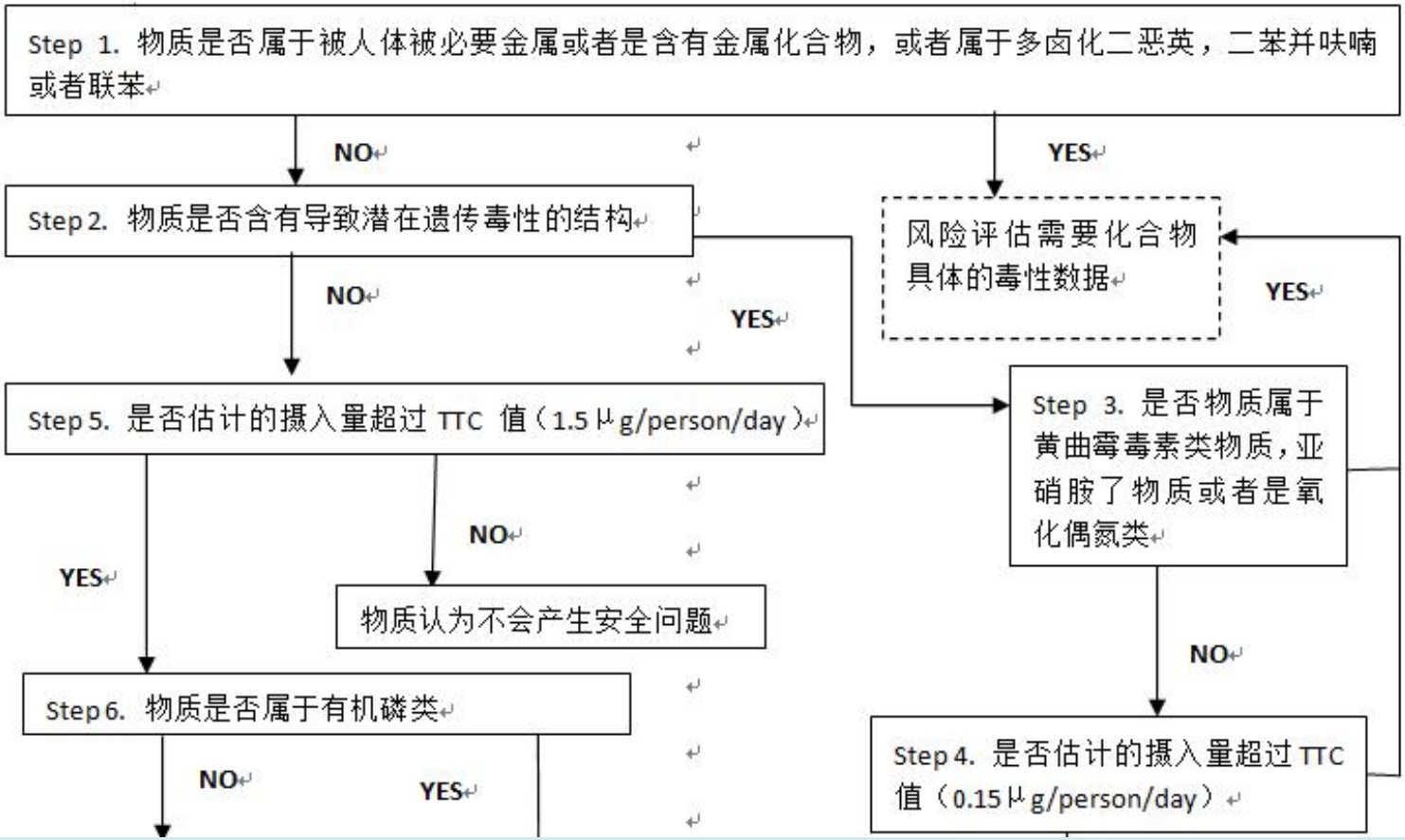
争议和进一步发展

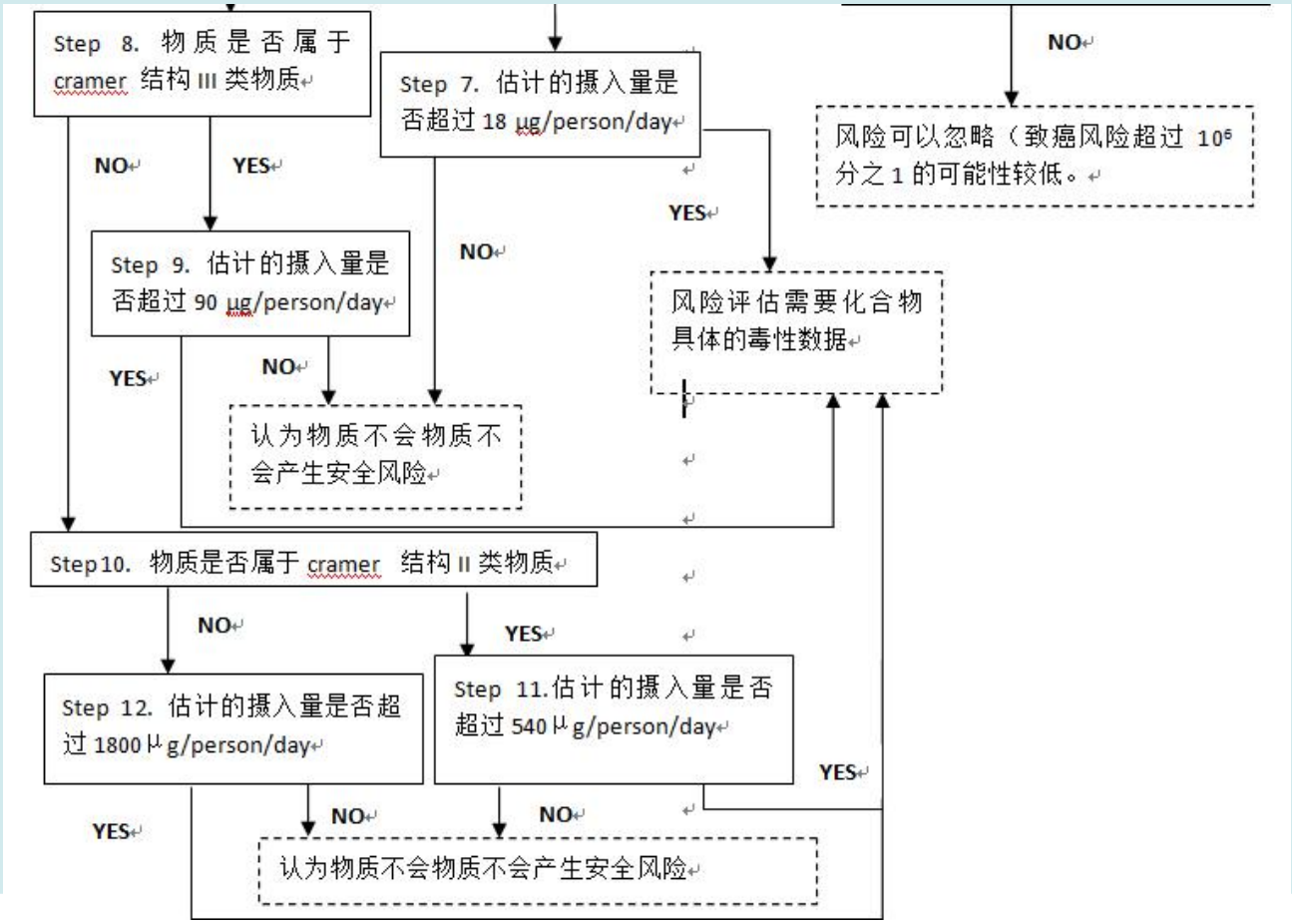
免疫毒性，发育毒性，神经毒性和发育神经毒性及内分泌干扰和过敏性。

（欧盟国际生命科学会ILSI， 1999 ）

Kroes 等人2004发表了**关于针对特定结构的遗传毒性致癌物的TTC值0.15μg/person/day**（由TD_{50}线性外推出来的致癌风险为百万分之一的理论上限值）和有机磷化合物的单独的TTC值18μg/day。

2004 年kroes还开发了逐步决策树（见下图），**该方法排除了不能被TTC方法评估的特定类型的化合物。这样做的原因：**在数据库中没有类似结构的物质；已经建立的已有的风险评估方法（重金属和TCDD类化学物）；它们是强有力的致癌物（黄曲霉毒素，N-亚硝基化合物和氧化偶氮类等所谓的关注群（Cohort of Concern，CoC类物质）。对于CoC类物质单个的TTC值被开发。





TTC为0.15μg/person/day的已更改应用于带有遗传结构警示的致癌物。并考虑对于没有结构警示的致癌物采用**TTC值1.5μg/person/day比较适合。**

2016年WHO和EFSA联合发布了TTC方法综述和新的TTC决策树的开发对上图中的决策树进行了修订，修订内容如下：

将步骤1中物质是否属于被人体被必要金属或者是含有金属化合物，或者属于多卤化二恶英，二苯并呋喃或者联苯更改为物质是否属于被排除的类别。

步骤2中将物质是否含有导致潜在遗传毒性的结构修改为物质是否具有警示结构，物质具体的致基因毒性数据（如Ames 结果显示物质具有DNA致癌潜能）。如果属于该类，直接按照TTC值为0.0025μg/kg /day （体重 60 kg，即0.15μg/person/day）处理，删除步骤3.

TTC单位由μg/person/day更改为μg/kg /day。

SCCS, SCHER and SCENIHR, Opinion on Use of the Threshold of Toxicological Concern (TTC) Approach for Human Safety Assessment of Chemical Substances with focus on Cosmetics and Consumer Products, SCCP/1171/08.

The SCs accept in principle the division into **Cramer Classes I and III.** When assigning a chemical to the lowest toxicity class (**Class I, 1800 µg/person/d** corresponding to **30 µg/kg bw/d** for substances with no genotoxicity alert)

目前SCCS 只接受Carmer I 和III 类。

Cramer rules	Extended Cramer rules
High (Class III)	High (Class III)

TTC value: 90 ug/ day

Impurity 6 (Chemical name/INCI name) Cramer Class III :			
Type of Exposure	Product	Maximum Concentration allowed in product	
		Thoretical Max Concentration (%)	Max Concentration (%)
Bathing, Showering	Shower gel	0.04737%	0.04737%
	Hand wash soap	0.04500%	0.04500%
Hair Care	Shampoo	0.08182%	0.08182%
	Hair conditionner	0.22500%	0.22500%
	Hair Styling Products	0.02250%	0.02250%
Leave on skin &Hair Care Products	Body Lotion	0.00115%	0.00115%
	Face cream	0.00584%	0.00584%
	Hand cream	0.00417%	0.00417%
Make up Products	Liquid foundation	0.01765%	0.01765%
	Make up remover	0.01800%	0.01800%
	Eye shadow	0.45000%	0.45000%
	Mascara	0.36000%	0.36000%
	Eyeliner	1.80000%	1.80000%
	Lipstik / Lip salve	0.15000%	0.15000%
Deodorant	Deo non spray	0.00600%	0.00600%
	Deo aerosol spray	0.00629%	0.00629%
	Deo spray (non ethanol)	0.01304%	0.01304%
Oral Hygiene	Toothpaste	0.06522%	0.06522%
	Mouthwash	0.00417%	0.00417%

交叉参考

READ-ACROSS

Read-Across

Intertek
Valued Quality. Delivered.

Hypothesis that similar compounds should have similar biological activities.

A **chemical category** is a group of chemicals whose physico-chemical and human health and/or environmental toxicological properties and/or environmental fate are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristic).

mono-, di-, tri-, tetra-, and penta- ethylene glycols; Oxo alcohols C9 to C13 ;

Methanolates category under the OECD HPV programme (http://cs3-hq.oecd.org/scripts/hpv). potassium and sodium methanolate and both react rapidly in water to form the corresponding hydroxide

The term **analogue approach** is used when the grouping is based on a very limited number of chemicals, where trends in properties are not apparent.

isobutanol (CAS No 78-83-1), p-chlorotoluene (CAS No 106-43-4), and methyltriacetoxysilane (CAS No 4253-34-3). These initial assessments are available from UNEP Chemicals (http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html).

Intertek

Valued Quality. Delivered.

Read-across is a technique for data gap filling in which information for one or more source chemicals is used to make a prediction for a target chemical, which is considered to be similar in some way.

OECD Toolbox and ChemIDplus could give some indications for reference chemical or group

US-EPA

http://www.epa.gov/opptintr/newchems/pubs/chemcat.htm

OECD HPV Chemicals Programme

http://cs3-hq.oecd.org/scripts/hpv/

1 Read-Across and Grouping

Intertek
Valued Quality. Delivered.

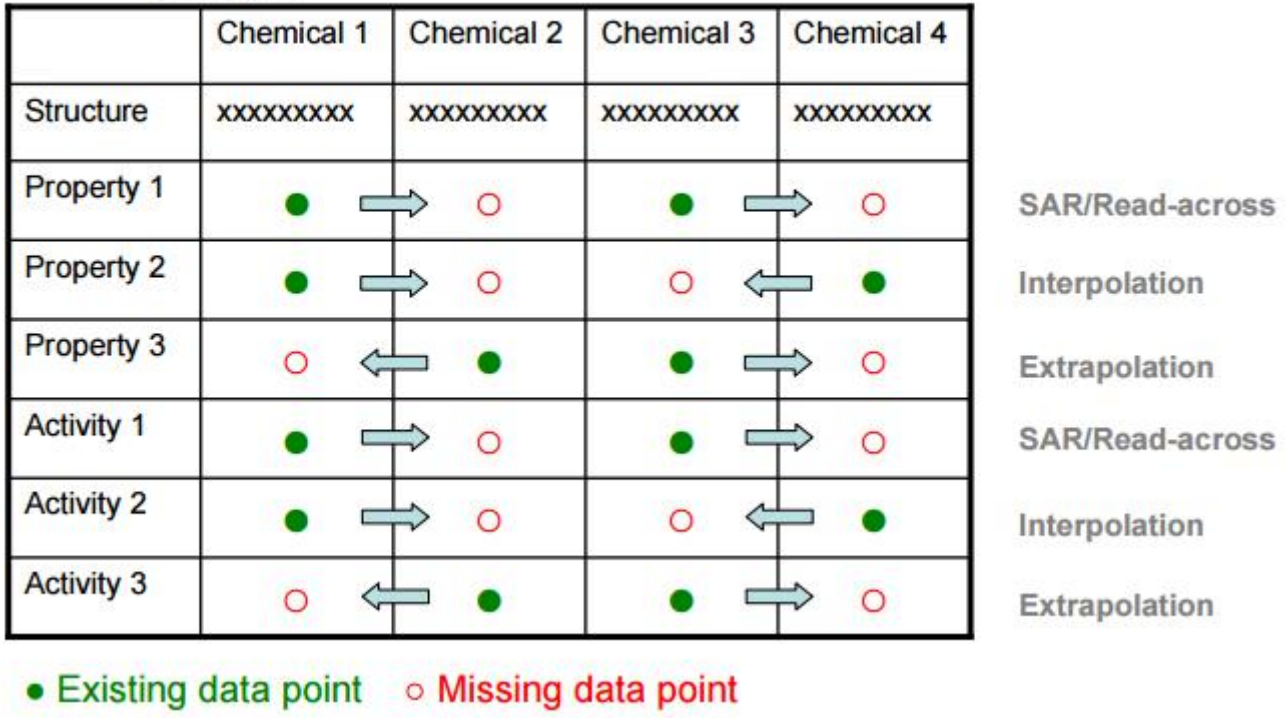
Read-across can be performed in the following ways to fill data gaps:

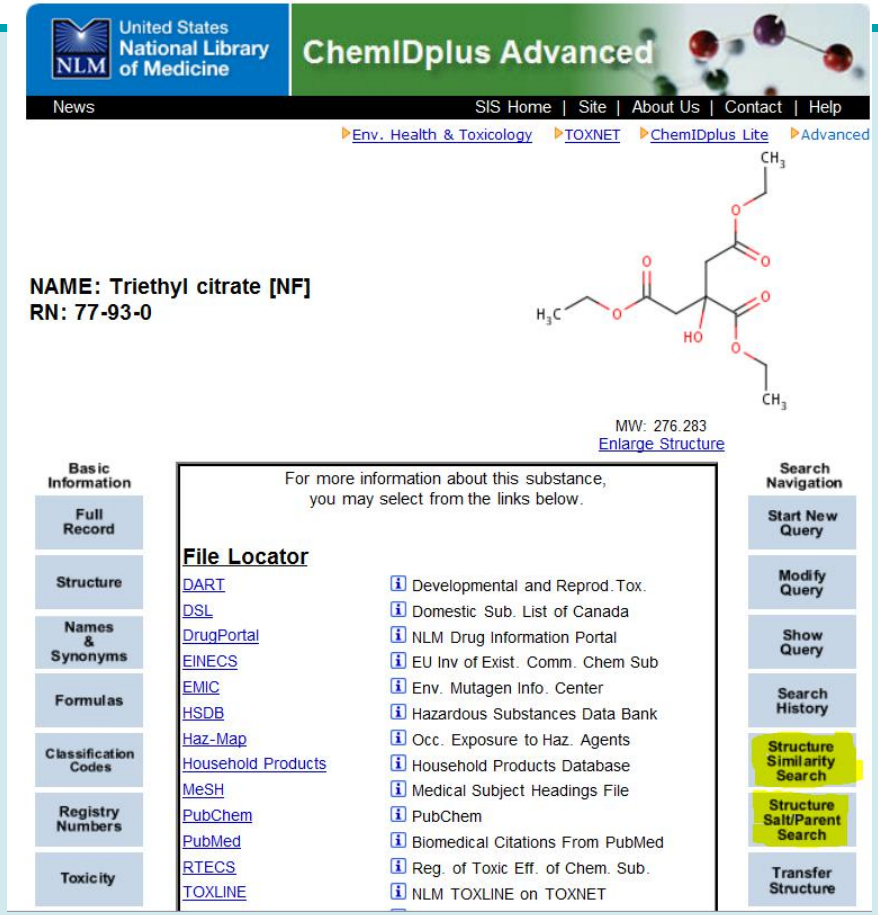
1. One-to-one (one analogue used to make an estimation for a single chemical)
2. One-to-many (one analogue used to make estimations for two or more chemicals)
3. Many-to-one (two or more analogues used to make an estimation for a single chemical)
4. Many-to-many (two or more analogues used to make estimations for two or more chemicals)

The one-to-one is often used due to its less complexity and requirements for the data.

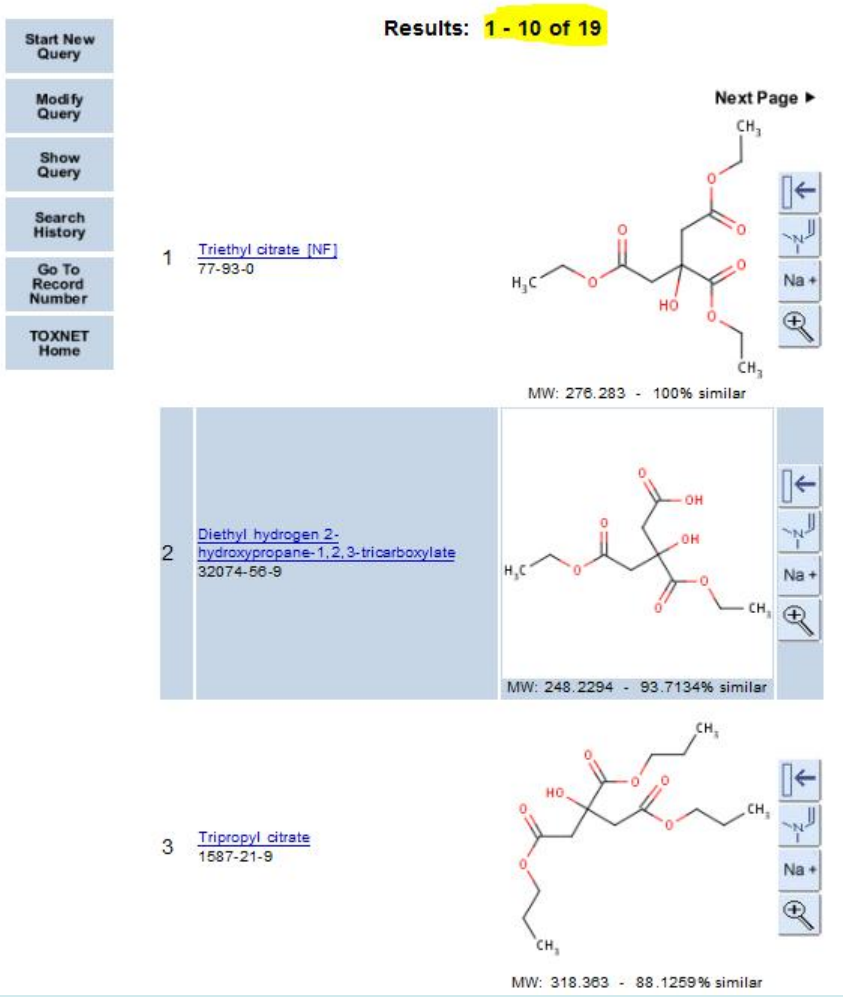
(ECHA Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals is recommended here for further reference. IUCLID 5)

Figure R.6-3: Graphical representation of a chemical category and some approaches for filling data gaps





Click the highlighted of "Structure similarity search" button in the webpage and overall 19 similar substances was indentified and part of results is presented below:



The most similar chemicals within rich data could be used as references.

Structure salt/parent search is not applicable for this case but could also be selected for other substances.

Conclusion:

Intertek
Valued Quality. Delivered.

The EU SCCS and Cosmetic Regulation have accepted Read-across on case-by-case basis and same to CIR. In some way, QSAR could be considered as a kind of Read-Across (Many-to-one) but expert judgment process is contained in the software.

READ-ACROSS 方法CIR 用的很多，SCCS用的很少

Oleths (油醇聚醚)：

Panel concludes that Oleth -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -15, -16, -20, -23 -25, -30, -40, -44, and -50 are safe in the present practices of use.

Read-Across 多见于官方，协会或工作的评估。

混合物毒性判断的经验原则GHS

Intertek
Valued Quality. Delivered.

Acute Toxicity Bridging Principles - Dilution

substance/mixture A (LD_{50} = 50 mg/kg) + substance/mixture B (Classification known) = Mixture C of A+B (Not Tested)

- **If 'B' is water or is *totally non-toxic*, then classification of 'C' can be calculated**
  - LD_{50} of 'A' = 50 mg/kg (Acute Cat. 2) ➔ it is diluted with same amount of water
    ↳ toxicity of 'C' is estimated to be 100 mg/kg (Acute Cat. 3)
- **If 'B' is classified but has a hazard classification lower than the toxic component 'A', then 'C' can be classified as for 'A' (worst case approach).**
  - Classification of 'B' = Acute Cat. 3
    LD_{50} of 'A' = 50 mg/kg (Acute Cat 2) (= most toxic component)
    ↳ 'C' can be classified as Acute Cat. 2

$$\frac{100}{ATEmix} = \sum_{n} \frac{Ci}{ATE_i}$$

这里：

C_i = 成分 i 的浓度

n 个成分，并且 i 从 1 到 n

ATE_i = 成分 i 的急性毒性估计值

产品皮肤刺激性 GHS

Intertek
Valued Quality. Delivered.

表 3.2.3：使混合物划为皮肤危险物(第 1、第 2 或第 3 类)的划为皮肤第 1、第 2 或第 3 类的混合物成分浓度

划为以下类别的成分总和	使混合物划为以下类别的浓度：		
	皮肤腐蚀物	皮肤刺激物	
	第 1 类 (见下面的注)	第 2 类	第 3 类
皮肤第 1 类	≥ 5%	≥ 1% 但 < 5%	
皮肤第 2 类		≥ 10%	≥ 1% 但 < 10%
皮肤第 3 类			≥ 10%
(10 x 皮肤第 1 类) + 皮肤第 2 类		≥ 10%	≥ 1% 但 < 10%
(10 x 皮肤第 1 类) + 皮肤第 2 类 + 皮肤第 3 类			≥ 10%

产品眼睛刺激性GHS

Intertek
Valued Quality. Delivered.

表 3.3.3：使混合物划为眼部危险物(第 1 或第 2 类)的划为皮肤第 1 类和/或眼部第 1 或第 2 类的混合物成分浓度

划为以下类别的成分总和：	使混合物划为以下类别的浓度：	
	不可逆眼部效应	可逆眼部效应
	第 1 类	第 2 类
眼部或皮肤第 1 类	≥ 3%	≥ 1% 但 < 3%
眼部第 2/2A 类		≥ 10%
(10 x 眼部第 1 类) + 眼部第 2/2A 类		≥ 10%
皮肤第 1 类 +眼部第 1 类	≥ 3%	≥ 1% 但 <3%
10 x (皮肤第 1 类 +眼部第 1 类) + 眼部第 2A/2B 类		≥ 10%

Ref

ECHA Chapter R.6: QSARs and grouping of chemicals

http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

OECD ToolBox

http://www.qsartoolbox.org/

ChemSpider

http://www.chemspider.com/

ChemID*plus*

http://chem.sis.nlm.nih.gov/chemidplus/

Toxtree

http://toxtree.sourceforge.net/predict/

ToxPredict

https://apps.ideaconsult.net/ToxPredict

Questions?