CORSO TEORICO – PRATICO DI VALUTAZIONE DELLA SICUREZZA DEI COSMETICI
15-19 aprile 2013

Caratterizzazione del rischio di

GLYCERIN

CITRIC ACID

CATHECOL

Gruppo 6
Povino M.R. - Samuele A. - Tritella T. - Varana F. - Zacchi E.

GLYCERIN

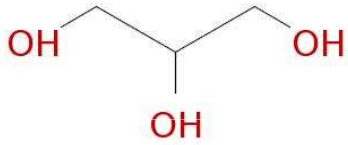
Chemical name: Glycerol, propane-1,2,3,-triol

INCI name: Glycerin

CAS number : 56-81-5

EC number : 200-289-5

Molecular weight: 92.0938



Physical state : liquid

Partition coefficient (water/ 1-octanol): log Pow = -1.75

Purity min required Eur. Ph.: 99,5% (vegetal)

Low volatility

http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d855cc7-316c-2a21-e044-00144f67d249/AGGR-b12f8f16-6ddf-4da9-a959-a179143f5827_DISS-9d855cc7-316c-2a21-e044-00144f67d249.html#section_1.1

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GLYCERIN

Use and mode of action

Ubiquitous use (industrial, professional and consumer products). Glycerol is used **as a constituent** in numerous products and **as an intermediate** in industrial applications for the manufacture of products such as soaps/detergents and glycerol esters.
It is found in consumer products such as pharmaceuticals, cosmetics, tobacco, food and drinks and is present in numerous other products such as paints, resins and paper. For example, it is used as a down hole lubricant in oil and gas fields and **as a wetting agent** in pesticide formulations.
http://www.inchem.org/documents/sids/sids/56815.pdf

The Food and Drug Administration (FDA) includes Glycerin on its list of direct **food additives considered Generally Recognized As Safe** (GRAS), and on its list of approved indirect food additives. Glycerin is also an FDA approved active ingredient in Over-the-Counter (OTC) skin protectant drug products, ear drying products and it an approved demulcent for the eyes.
http://www.cosmeticsinfo.org/ingredient_details.php?ingredient_id=48

The Joint FAO/WHO Expert Committee on Food Additives has not specified an acceptable daily intake for Glycerin
http://www.inchem.org/documents/jecfa/jecmono/v10je06.htm

Glycerin derived from natural sources is listed as exempt from REACH in Annex V(9). In addition to being a critical excipient in the formulation of cosmetics and OTC drugs, glycerin may also be employed as an active ingredient in anorectal, laxative, oral health, ophthalmic and skin protectant drug products when used according to the FDA's US OTC monographs for these categories.
http://www.cosmeticsandtoiletries.com/formulating/function/moisturizer/126530988.html

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GLYCERIN

ADME: Absorption, Distribution, Metabolism and Escretion

Data from studies in humans and animals indicate glycerol is **rapidly absorbed in the intestine and the stomach**, distributed over the **extracellular space** (Lin 1977, Tourtelotte 1970) and **excreted**.
Glycerol is phosphorylated to alpha-glycerophosphate by glycerol kinase predominantly in the liver (80-90%) and kidneys (10-20%) and **incorporated in the standard metabolic pathways to form glucose and glycogen** (Tao 1983, Lin 1977).
Glycerol kinase is also found in intestinal mucosa, brown adipose tissue, lymphatic tissue, lung and pancreas.
Glycerol may also be combined with free fatty acids in the liver to form triglycerides (lipogenesis) which are distributed to the adipose tissues.
The turnover rate is directly proportional to plasma glycerol levels (Bortz 1972).

http://www.inchem.org/documents/sids/sids/56815.pdf

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GLYCERIN

Acute Toxicity

Inhalation

No data available

Dermal

No deaths were observed in a group of 6 rabbits after occlusive dermal application for 8 hours of synthetic or natural glycerol at 18,700 mg/kg bw. (Hine 1953).

For **acute dermal toxicity** a single **LD50 of >18,700 mg/kg** for rabbits is available. No information is available on the acute toxicity of inhaled glycerol.

Oral

A number of acute oral toxicity LD50 values for the rat (range from >5000 to 58400 mg/kg) and the mouse (4,250 to 38,000 mg/kg) are reported in the scientific literature, although where values are very similar, it is not always clear whether or not these are from independent studies. Original reports for several secondary reported LD50 values were not available. The LD50 values reported are consistent with the range of values found in the available literature except in one case, where an oral LD50 value of 4250 mg/kg was reported for the mouse (Anon. 1977).

Glycerol is of **very low acute toxicity to mammals**. The range of **acute oral LD50 values** derived from studies in experimental animals is between >4,000 and < 38,000 mg/kg, with the majority of values being between 23,000 and 38,000 mg/kg.

Glycerol is more toxic when administered intravenously, intraperitoneally or subcutaneously.

http://www.inchem.org/documents/sids/sids/56815.pdf

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GLYCERIN

Acute Toxicity

Skin Irritation

No OECD guideline studies are available, however, the data available indicate that **glycerol is not irritating when in contact with the skin.**

Eye Irritation

In an OECD guideline study reported in a secondary source, **slight to moderate corneal irritation** was observed in all rabbits **after 1h, however the effects were found to regress after 24h** and were fully reversed by 48h (Janssen and de Rooy).
The data available indicate that glycerol is **not irritating to the eyes**.

Sensitization

Based on the available information, there is no human or animal data that indicates glycerol to be a skin sensitiser.

Critical effects

Considering the extensive, widespread **dermal exposure** to glycerol in preparations repeatedly applied to the skin, the absence of case reports of humans showing skin reactions is consistent with glycerol having a **very low skin sensitisation potential**.

http://www.inchem.org/documents/sids/sids/56815.pdf

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GLYCERIN

Repeated Dose Toxicity

A considerable number of studies have been performed. However, many of these studies are considered to be of indeterminable reliability due to deficiencies in reporting or methodology, primarily because they were performed before internationalized guidelines were available.

Based on the studies of better quality, it can be concluded that **repeated oral exposure by gavage to glycerol does not induce adverse effects other than local irritation** of the gastro-intestinal tract.

The **2-year study** of Hine (1953) was chosen to establish the overall NOAEL after prolonged treatment of rats with glycerol. It was concluded that the **NOEL is 10,000 mg/kg bw (20% in diet),** which is in agreement with most of the findings. **At this dose level no systemic or local effects were observed** in the parameters investigated. However, it is noted that gavage dosing with bolus administration of glycerol may enhance the local toxicity to the gastrointestinal tract compared with continuous administration via the diet, however, toxic effects are still only seen at relatively high dose levels and do not raise concern.

For **inhalation exposure**, irritant effects were observed at **662 mg/m3**. No other target organ involvement was identified.

The **NOAEL for local effects on the respiratory tract** following exposure by inhalation **is 165 mg/m3**.

Mutagenicity, Genotoxicity, Carcinogenicity

There are **no structural alerts** (expert judgement) which raise concern for the **inherent mutagenic genotoxic and carcinogenic potential of glycerol.**

The weight of evidence indicates that glycerol is of low toxicity when ingested, inhaled or in contact with the skin. http://www.inchem.org/documents/sids/sids/56815.pdf

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GLYCERIN

Exposure scenario

Category of exposure	Type of exposure	Type of products
Consumer exposure	**Dermal**	Cosmetics and pharmaceuticals
		Paints, printing inks, resins
		Paper and plastics
	Oral	Pharmaceuticals
		Cosmetics
		Cellulose films (meat casing, sausage skin)
		Food and drinks
	Inalation	Smoking
Worker exposure	**Inalation**	Production/Processing
	Dermal	Paints, printing inks, resins

http://www.inchem.org/documents/sids/sids/56815.pdf

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GLYCERIN

Case study: Safety Evaluation

Total amount of cosmetics used (A): 32.70 mg/kg bw/d

Concentration of ingredients under study (C): 100% glycerol (Hand cream)

Dermal Absorption expressed as a percentage (DAp): 100%

Default human body weight: 60 kg

Route: dermal

Hand cream: 860 cm^2 area hands.

Frequency: 2/day

RF: 1.0

No Observed Adverse Effect Level (NOAEL): 10000 mg/kg bw

Systemic exposure Dosage (SED) = **A** (mg/kg bw/day) x **C** (%)/100 x **DAp**/100= 32,70 mg/kg bw/d

MARGIN of SAFETY = NOAEL / SED = 10000/ 32,70= 305,81

http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf

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http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf

CATECHOL

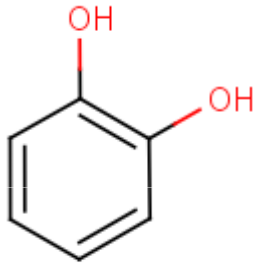
Chemical name: pyrocatechol - 1,2 Benzendiol

INCI name: No INCI name

CAS number : 120-80-9

EC number : 204-427-5

Molecular weight: 110,11 g/mol



Physical state: crystallin solid, faintly musty phenolic, easy sublimation

Vapor density: 3,79

Log Pow: 1,03

Water solubility: 451 g/l

Cosmetic Directive 92/86/EEC Other Directives/Regulations

Annex/Part,Ref : II/408 Functions HAIR DYEING Delisted 01/07/1994

Classificazione CE: Xi,Xn,R21/22,R36/38

http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d855cc7-316c-2a21-e044-00144f67d249/AGGR-b12f8f16-6ddf-4da9-a959-a179143f5827_DISS-9d855cc7-316c-2a21-e044-00144f67d249.html#section_1.1

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CATECHOL

Use and mode of action

Catechol is used as a topical antiseptic, reagent, antifungal preservative on seed potato pieces, photographic developer, and developer in fur dyes.

Catechol is used as **an antioxidant** in many industries including rubber, chemical, dye, photographic, pharmaceutical, fat, cosmetics, and oil.

http://www.osha.gov/dts/sltc/methods/partial/pv2014/2014.html

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CATECHOL

ADME: Absorption, Distribution, Metabolism and Escretion

Catechol, applied as an aqueous solution to human skin membranes, **penetrated very moderately** with a penetration rate of 1.425 µg/cm²/h after a lag time of 6 hours. The permeability constant Kp was calculated to be 1.430 x 10E-3 cm/h

Catechol is **rapidly eliminated** via urine after inhalation exposure (half-life 3 -7h) and seemed to **not potentially bio-accumulate**.

http://apps.echa.europa.eu/registered/data/dossiers/DISS-98776be4-cc47-5274-e044-00144f67d031/AGGR-49b184e8-2058-483a-b6b4-cea352b7da6e_DISS-98776be4-cc47-5274-e044-00144f67d031.html#AGGR-49b184e8-2058-483a-b6b4-cea352b7da6e

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CATECHOL

Toxic Effects

The lethal human dose of catechol is 50 to 500 grams/kilogram, or 1 teaspoon to 1 ounce for a 70 kilogram (150 pound) person, with death resulting from pulmonary failure. **Catechol is a skin, eye, mucous membrane, and pulmonary irritant**. It is **readily absorbed** from the gastrointestinal tract, and **through the skin.**
Catechol can cause elevated blood pressure through vasoconstriction, degeneration of the renal tubes in the kidneys, and diminished liver function.

http://www.osha.gov/dts/sltc/methods/partial/pv2014/2014.html

Acute Toxicity

Inhalation

No data available

Dermal

For **acute dermal toxicity** : DNEL of 1 mg/kgbw/d

Oral

For **oral acute toxcity :** DNEL of 16 mg/kgbw/d

Sistemic Toxicity

Oral

For **oral long term:** DNEL of 0.1 mg/kgbw/d

http://apps.echa.europa.eu/registered/data/dossiers/DISS-98776be4-cc47-5274-e044-00144f67d031/AGGR-145b47d3-84e9-460b-b8f0-7b17a97526e1_DISS-98776be4-cc47-5274-e044-00144f67d031.html#POP_DERMAL_HD

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CATECHOL

Characterization of Risk to Human Health

Based on the weight of evidence assessment by IARC, **a critical effect for characterization of risk to human health is carcinogenicity,** for which a mode of induction involving direct interaction with genetic material cannot be precluded.

With respect to **noncancer effects**, the lowest dietary LOEL in the database is 33 mg/kg-bw/day based on effects in the stomach (the apparent target organ) of rats.

http://www.ec.gc.ca/ese-ees/04FDC10E-0C72-41B2-8040-91B7BB43AE38/batch1_120-80-9_en.pdf
Screening Assessment for 1,2-Benzenediol (120-80-9) July, 2008 (Health Canada)

Pyrocatechol is able to act by a stochastic genotoxic mechanism. In view of the mechanism the Committee expects that **pyrocatechol can contribute significantly to the DNA-damage**, and thus to cancer risk, **only above a certain exposure level.**

However, on the basis of the available data no exposure level can be determined at which the contribution becomes noticeable..

http://www.gezondheidsraad.nl/sites/default/files/201105OSH.pdf

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CATECHOL

Exposure scenario

Exposure to catechol can occur through inhalation, ingestion, eye or skin contact, and percutaneous absorption.
http://www.cdc.gov/niosh/docs/81-123/pdfs/0109.pdf (US Dep Health and Hum. Serv. 1995)

The Cosmetic Ingredient Review Expert Panel found insufficient data to conclude that **catechol could be used safely in permanent hair dye products**.
Information was lacking on the extent of oxidation and skin absorption of remaining catechol..
In vitro percutaneous absorption studies were conducted in human and rat skin using a consumer permanent hair dye spiked with 0.6% catechol. **A 30-min application demonstrated 0.4% of the applied dose was absorbed through human skin and 0.2% through rat skin**.
The minimal absorption observed was due to the short exposure time and to partial oxidation of catechol by the dye developer.
The fate of catechol remaining in rat skin after exposure in vitro and in vivo was investigated with additional absorption studies using catechol in ethanol. At 72 h, 24-h application of 4% catechol resulted in **skin absorption of 81% of the applied dose in vitro and 53% in vivo.** Skin levels measured at 24 h remained unchanged after 72 h. **Therefore the skin reservoir did not contribute to the estimated systemic absorption.** A deconvolution technique employed to predict skin absorption using plasma levels from intravenous and dermal administration overestimated in vivo skin absorption due to volatility of catechol in an ethanolic vehicle.

http://www.ncbi.nlm.nih.gov/pubmed/12738194

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CATECHOL

Safety evaluation

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK ASSESSMENT CONCERN

Not belonging to cohort of concern

The International Agency for Research on Cancer (IARC) has classified catechol as a Group 2B, possible human carcinogen.

EPA has not classified catechol with respect to potential carcinogenicity.

http://www.epa.gov/ttnatw01/hlthef/pyrocate.html

Catechol is possibly carcinogenic to humans (Group 2B).

http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-18.pdf

May be present as impurity or trace in raw materials for cosmetic products

Cancerogenic substance with **suspect structural genotoxic alert**

TTC= 0,15 µg/day

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CITRIC ACID

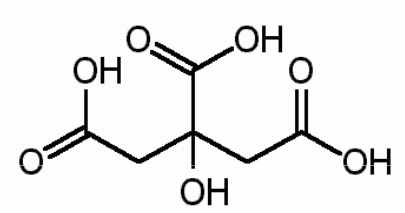
Chemical name: citric acid, hydroxypropane-1,2,3-tricarboxylic acid

INCI name: Citric acid

CAS number : 77-92-9

EC number : #

Molecular weight: 192,124 g/mol



Physical state : solid

Partition coefficient (water/ 1-octanol): log Pow = -1.61 to -1.80

Water solubility: > 10000 mg/L

http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d9b878d-05c8-56aa-e044-00144f67d249/AGGR-9139dd2f-032b-4b52-a8e2-dca35e6bc1f4_DISS-9d9b878d-05c8-56aa-e044-00144f67d249.html#AGGR-9139dd2f-032b-4b52-a8e2-dca35e6bc1f4

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CITRIC ACID

Use and mode of action

Occurrence

Citric Acid is one of the most widely distributed plant acids and occurs in high concentration in lemon juice (5-7%). It is found in a variety of plants and fruits (especially citrus fruits and berries), leaves, roots etc. Citric acid has a vital function in human and animal metabolism. It appears as an intermediate in the basic physiological citric acid or Krebs cycle in every eukaryote cell, one of the most important metabolic pathways.

Production and Use

Citric acid has been produced for many years in high volumes and added to processed food and beverages as flavour or stabilizer. It has been used in pharmaceutical preparations, in household cleaners as well as in many special technical applications.

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CITRIC ACID

ADME: Absorption, Distribution, Metabolism and Escretion

A large body of physico-chemical, toxicological and environmentally relevant data exists for citric acid, many of which are relatively old and some located only in standard reference works and reviews. While the quality of a single result often may be hard or even impossible to assess, the sheer volume and high congruence of the data result in a uniform picture all the same.
http://www.heraproject.com/files/37-F-05-HERA_citricacid_version1_April05.pdf

Citric acid is a metabolic intermediate vital to the TCA respiration pathway found in all animal and plant cells. There is little evidence that citric acid and the citrate salts have deleterious effects, even in large doses. Indeed there is some support for the fact that citric acid in the human diet is favourable by inhibiting the formation of calcium oxalate kidney and bladder stones. This statement is applicable to the citrate salts since once absorbed citrate salts will dissociate into citric acid and their counter-ion

Excretion

Citric acid was found to be excreted by humans through urine at a rate of 3-17 mg/kg body weight/day and through sweat at 0.2 mg/100 ml(1).
[(1) Verschueren K; Handbook of Environmental Data on Organic Chemicals, Vol 1-2, 4th ed. John Wiley and Sons; New York, NY (2001)]

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CITRIC ACID

Human health

Citric Acid has wide dispersive use, it is naturally present in common fruit and vegetables and is added to processed food and beverages. Potential consumer exposure to citric acid as a consequence of its presence in household laundry & cleaning products is expected to be several orders of magnitude below the rats` NOAEL and of little significance when compared with the normal dietary intake. The available information is judged to be adequate for concluding that the use of citric acid in household laundry and cleaning products raises no safety concerns for consumers.

http://www.heraproject.com/files/37-F-05-HERA_citricacid_version1_April05.pdf

Acute Toxicity

Inhalation

No data available

Dermal

LD50 value of 5.4 g/kg bw for male and female mice.

Oral

No data available

http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d9b878d-05c8-56aa-e044-00144f67d249/AGGR-0be42d5c-45cf-42a1-8268-8691623bf9c4_DISS-9d9b878d-05c8-56aa-e044-00144f67d249.html#section_1.1

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CITRIC ACID

Acute Toxicity

Skin Irritation

Reliable study conducted largely in accordance with **OECD 404** and in compliance with **GLP**, found the citric acid to be mildly irritating to the skin of rabbits. Current EC criteria would find the material to be non-irritant.

Eye Irritation

A 0.5 and 2% solution was found irritating to the eye of rabbit when applied repetitively over 7 days as demonstrated by the presence of sporadic nonpersisting areas of necrosis.

Repeated Dose Toxicity

The available data confirm the low acute and (sub)chronic toxicity profile of Citric Acid.
The **NOAEL for repeated dose toxicity (for rats) is 1200mg/kg/d**.
It is not suspected of being a carcinogen nor a reprotoxic or teratogenic agent.
Citric Acid is not mutagenic in vitro and in vivo, and its sensitising potential is seen as low.

(NOAEL = 250 mg/kg (bw) via the intraperitoneal route for both the rat and mice)

Dermal

no signs of systemic toxicity.

http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d9b878d-05c8-56aa-e044-00144f67d249/AGGR-0be42d5c-45cf-42a1-8268-8691623bf9c4_DISS-9d9b878d-05c8-56aa-e044-00144f67d249.html#section_1.1

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CITRIC ACID

Exposure scenario

General Exposure

Monitoring data indicate that **the general population may be exposed to citric acid via ingestion** of food **and dermal contact** with this compound and other products containing citric acid(SRC).

[(1) NIOSH; International Safety Cards. Citric Acid. 77-92-9. Available at http//www.cdc.gov/niosh/ipcs/nicstart.html as of April 26, 2006.]

The citrate ingredients most commonly used in cosmetics are Citric Acid, Sodium Citrate, Tributyl Citrate and Triethyl Citrate. Citric Acid and Sodium Citrate may be **used in all types of cosmetic products** including, baby products, make-up, lipstick, bath products, soaps and detergents, hair dyes and colors, and hair and skin care products. Tributyl Citrate and Triethyl Citrate may be used in bath products, other cleansing products, and creams and lotions.

CIR Safety Review: Citric Acid, Calcium Citrate, Potassium Citrate, Sodium Citrate and Triethyl Citrate are GRAS **for use in food**. In addition, Citric Acid is a normal component of the body. Therefore, the CIR Expert Panel focused on the potential for Citric Acid and its salts and esters to cause adverse effects when placed on the skin. At concentrations used in cosmetics and personal care products, Citric Acid and its salts and esters were not eye irritants, nor did they result in skin irritation or sensitization. The CIR Expert Panel noted that **although Citric Acid could be considered an alpha-hydroxy acid**, it is also a beta-hydroxy acid. Structurally, Citric Acid is a tricarboxylic acid. This makes it **distinct** from the alpha-hydroxy acids previously reviewed by the CIR Expert Panel (for example lactic acid and glycolic acid). The CIR Expert Panel concluded that the concern about increased sun sensitivity resulting from the use of alpha-hydroxy acid containing products was not relevant to products containing Citric Acid and its salts and esters. Based on the available data, the CIR Expert Panel concluded that **Citric Acid and its salts and esters were safe for use in cosmetics.** http://www.cosmeticsinfo.org/ingredient_details.php?ingredient_id=372

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CITRIC ACID

Exposure scenario

The Joint FAO/WHO Expert Committee on Food Additives has not specified an Acceptable Daily Intake for Citric Acid or its Calcium, Potassium or Sodium salts.
http://www.inchem.org/documents/jecfa/jecmono/v05je24.htm
AHAs are safe in cosmetics if:

- AHA concentration < 10%
- pH of formula not < 3.5

Potential impairment of the skin barrier function after topical application of AHA

Whilst the SCCNFP agreed previously that available data showed no increase in TEWL or dermal penetration of reference compounds after long-term use of AHA (up to 10 % at pH 3.5), concerns were raised over effects potentially occurring after short-term uses prior to adaptive changes of the skin. Considering skin renewal rate, a maximum effect (if any) on skin barrier function should be visible between 8-14 days. In Submission IV presented by the Cosmetic Industry, several studies are included evaluating the skin barrier function by TEWL as well as the influence of AHA in the potential increase of skin penetration of several model compounds.
The experimental data presented on the skin penetration study are inadequate for proper evaluation.

AHA and UV sensitivity

In a previous evaluation, it was established that high concentrations of AHA (10 % at a low pH) could increase the skin's sensitivity to the sun. The SCCNFP proposed that a NOAEL for MED or SBCs production should be identified and serve as the decisive concentration for consumer information (e.g., potential sun alert statement).
http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out284_en.pdf

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CITRIC ACID

Case study: Safety Evaluation

Total amount of cosmetics used (A): 2,79 mg/kg bw/d

Concentration of ingredients under study (C): 10% citric acid (shower gel)

Dermal Absorption expressed as a percentage (DAp): 100%

Default human body weight: 60 kg

Route: dermal

Total Body area: 17500 cm^2

Frequency: 1,43/day

RF: 1.0

No Observed Adverse Effect Level (NOAEL): 1200 mg/kg bw

Systemic exposure Dosage (SED) = **A** (mg/kg bw/day) x **C** (%)/100 x **DAp**/100= 32,70 mg/kg bw/d

MARGIN of SAFETY = NOAEL /SED = 1200/ 0,279= 4301

http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf

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http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf