RISK PROFILE

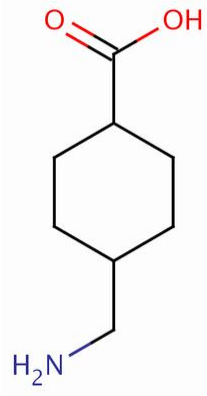
Tranexamic acid

CAS No.1197-18-8

Date of reporting 14.02.2012

Content of document

1. Identification of substance

Chemical name (IUPAC):	4-(aminomethyl)cyclohexane-1-carboxylic acid
INCI	Tranexamic acid
Synonyms	m-tranexamic acid
CAS No.	1197-18-8
EINECS No.	214-818-2
Molecular formula	$C_8H_{15}NO_2$
Chemical structure	
Molecular weight	157.2
Contents (if relevant)	
Physiochemical properties	Appearance: White, solid crystalline substance Boiling point: 300.201 °C at 760 mmHg Melting point: >300°C

	Log $P_{ow:}$ 1.027 Vapor pressure: 0 mmHg at 25°C Solubility (water): soluble in water Density: 1.096 g/cm^3 References: (Council of Europe, 2008; ChemSpider [online]; M.C. Biotec [online]).

2. Uses and origin

Uses	➢ **Cosmetic products:** *Functions according to:* o CosIng database "Astringent" - Contracts the skin "Skin conditioning" - Maintains the skin in good condition (CosIng [online]). o Other Tranexamic acid is used as a skin whitening agent in leave-on skin products (Maeda et al., 1998). *Frequency of use* In a search at Codecheck.info, tranexamic acid showed up as an ingredient in one cosmetic product, whereas none was found at EWG's Skin Deep (Codecheck [online]; EWG's Skin Deep [online]). In 2002, a large cosmetics company discovered the whitening capability of tranexamic acid and since then the use of this compound in cosmetics has expanded. In an online search we identified several products containing tranexamic acid. Information can be provided if desired. *Concentrations being applied* Tranexamic acid is used in cosmetics in concentrations up to 3 % (obtained from an online search – information can be provided if desired). ➢ **Medicinal products/applications** Tranexamic acid, is a synthetic lysine analogue, which is used as an antifibronlytic drug that inhibits the activation of plasminogen to plasmin (Astedt, 1987), and is widely used for the prevention and management of oral cavity bleeding, nosebleed, gastrointestinal bleeding, and menorrhagia. The drug is used to prevent excess bleeding in cardiac surgery. Tranexamic acid is also used as an oral medicine and as intradermal injections for treating melasma (Sehgal et al., 2011), a tan or dark skin discoloration. ➢ **Food and drinking water** Data not retrieved.
Origin Natural (exo /endo) Synthetic	Synthetic

3. Regulation

Norway	No regulation[1].
EU	No regulation.
Rest of the world	Tranexamic acid is approved as a whitening agent at 2-3 % concentration in Taiwan and 1.5-2% in Japan. Malaysia classifies the ingredient as a poison. Thailand has products in the market containing up to 7 % tranexamic acid (Asean Cosmetic Association [online]).

4.

5. Relevant toxicity studies

Absorption Skin GI tractus	About 30 to 50 % of an oral dose is absorbed in humans. No data exists for skin absorption or penetration (Council of Europe, 2008).
Distribution	A dose of 1 gram (adult and normal body weight) results in a plasma concentration of 8-10 mg/L. Tranexamic acid does not bind to serum albumin (Council of Europe, 2008).
Metabolism	Possible routes of biotransformation are acetylation or deamination followed by oxidation or reduction. After oral administration approximately 50% of the parent compound, 2% of the deaminated dicarboxylic acid, and 0.5% of the acetylated product are excreted. The biological half-life is 2-3 hours (Council of Europe, 2008).
Excretion	Urinary excretion is the main route of elimination (Council of Europe, 2008).
Local toxic effects Irritation Sensitivity	Tranexamic acid is non-irritant in the cutaneous irritation test in the rabbit and slightly irritant in the ocular irritation test in rabbits (Council of Europe, 2008). In one study, it was shown that tranexamic acid may cause irritation and allergy (Council of Europe, 2008).
Systemic toxic effects Acute Repeated dose	In mice and rats, the lethal oral doses exceed 5-10 g/kg body weight and the intravenous injection LD_{50} values are in the range of 1-1.5 g/kg body weight (Pfizer Canada Inc, 2010). Several subacute and chronic toxicity studies with repeated oral (rats: 1-5 g/kg for 10 weeks, dogs: 100-500 mg/kg for 4 months), intraperitoneal (rats: 0-1000 mg/kg for 2 weeks) and intravenous (dogs: 20-500 mg/kg for 1 month and 1 g/kg for 3 days, rabbits: 60-180 mg/kg for 13 days) dosing of tranexamic acid have been performed in experimental animals. For the highest doses in the subacute studies in rats, mice and rabbits, only mild symptoms were observed, such as vomiting, diarrhea/loose stools, decreased body weight gain, and tachypnea (only with intraperitoneal administration) (Pfizer Canada Inc, 2010). In one oral chronic toxicity study where dogs received 200-1600 mg/kg/day for one year, eye damage was observed. This finding was not observed in a life-long feeding study performed in rats (Pfizer Canada Inc, 2010).

[1] The Norwegian medicinal products agency considered tranexamic acid a medicinal remedy. Because of that up till 2008 topical products containing this substance waas considered medicine – meaning a topical product containing it as automatically classified a medicine. Applications for allowance to use the substance for other purposes (cosmetics) were rejected. This regime has since been lifted.

Mutagenicity /genotoxicity/ carcinogenicity	No mutagenic activity was seen for tranexamic acid in several in vitro and in vivo test systems (Council of Europe, 2008). In one carcinogenicity study where rats were given tranexamic acid in high doses, biliary hyperplasia, cholangioma and adenocarcinoma of the liver were found. These findings have not been observed in several other carcinogenicity studies with tranexamic acid (Pfizer Canada Inc, 2010).
Reproductive toxicity / teratogenicity	Tranexamic acid crosses the placenta. After an intravenous injection of 10 mg/kg, the concentration can rise to about 30 µg/ml of fetal serum. Tranexamic acid also passes over into breast milk during lactation in concentrations 1/100 of the corresponding serum levels. However, no harmful effects have been reported (Pfizer Canada Inc, 2010).

6. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	LOAEL (oral, dogs, eye damage): 200 mg/kg bw NOAEL = LOAEL/ 3 [2] = 200 mg/kg bw/day / 3 = 67 mg/kg bw/day
Exposure cosmetic products	**Systemic exposure dose (SED) for tranexamic acid in humans:** • ***Whitening lotion/cream/gel*** Skin surface area: 15,670 cm^2 Frequency of application (product description): 1/day Body weight: 60 kg (SCCS, default value) Amount applied of product: 15,670 cm^2 x 1 mg/cm^2 (SCCS, default value) = 15,670 mg Amount applied of product/ body weight: 15,670 mg / 60 kg = 261 mg/kg bw/day Concentration in product: 3 % = 0.03 Dermal absorption: 100 % = 1 Amount of ingredient: Calculation of SED: 261 mg/kg bw/day x 0.03 x 1 = **7.8 mg/kg bw/day** • ***Facial mask and face cream (used values for face cream)*** Skin surface area: 565 cm^2 Frequency of application (product description): 1/day Body weight: 60 kg (SCCS, default value) Amount applied of product: 565 cm^2 x 1 mg/cm^2 (SCCS, default value) = 565 mg Amount applied of product/ body weight: 565 mg / 60 kg = 9.4 mg/kg bw/day Concentration in product: 3 % = 0.03 Dermal absorption: 100 % = 1

[2] When making use of the Lowest Observed (Adverse) Effect Level (LO(A)EL) instead of the NO(A)EL, the SCCS usually takes into consideration an additional factor of 3 in the calculation of the MoS. Scientific Committee on Consumer Safety, The SCCS'S notes of guidance for the testing of cosmetic ingredients and their safety evaluation, the 7th revision, p 54.

	Amount of ingredient: Calculation of SED: 9.4 mg/kg bw/day x 0.03 x 1 = **0.28 mg/kg bw/day**
Margin of Safety (MoS)	NOEL: 67 mg/kg bw ***MoS for tranexamic acid in whitening lotion/cream/gel:*** SED: 7.8 mg/kg bw/day MoS: 67/ 7.8 = 9 ***MoS for face cream and facial mask:*** SED: 0.028 mg/kg bw/day MoS: 67/ 0.28 = 239

7. Other sources of exposure than cosmetic products

Food stuffs	Data not retrieved.
Pharmaceuticals	Recommended daily dosage is 2-3 tablets (500 mg) 2-3 times a day, although this varies with the cause of treatment. In case of reduced kidney function, there is a lower dosage recommendation (5-30 mg/kg bw/day depending on the serum creatinine concentration) because of the risk of accumulation of the drug. For intravenous administration the recommended doses are 5-10 ml (100 mg) 2-3 times a day, and for reduced kidney function the recommendation is 5-20 mg/kg bw/day depending on the serum creatinine concentration (Norwegian Medicines Agency [online]). The drug should not be used in the case of an active thromboembolic disease, subarachnoid haemorrhage, and hypersensitivity to tranexamic acid.
Other sources	Data not retrieved.
Adverse side effects - from uses other than cosmetics	In humans, ingestion of 37 gram of tranexamic acid caused mild intoxication symptoms after gastric lavage. Symptoms of intoxication may be nausea, diarrhoea, dizziness, headache, vomiting orthostatic symptoms and hypotension (Pfizer Canada Inc, 2010). Three reports of visual disturbance or eye pain have been reported in patients with intravenous administration of tranexamic acid (Australian Government, 2010).

8. Assessment

The safety for the use of tranexamic acid in cosmetic products has been examined by the Council of Europe (Council of Europe, 2008). It was concluded that due to lack of data it was not possible to reach a conclusion on the use of tranexamic acid in cosmetic products.

Tranexamic acid is used as an antifribronlytic drug and to treat melasma. Since 2002, the tranexamic acid have been used as a skin whitening agent in various leave-on products, although to which extent is currently not known. Tranexamic acid show low acute and repeated dose toxicity, and there are no known cases of overdose with tranexamic acid in humans. There are three concerns:
i) repeated use of tranexamic acid (oral and intravenous) has been reported to cause eye damage and visual disturbance, and ii) tranexamic acid crosses the placenta, iii) tranexamic acid can accumulate in persons with reduced kidney function.

The LOAEL value was obtained by using the lowest concentration which caused eye damage in dogs exposed orally to tranexamic acid for one year. The LOAEL value was divided by three to obtain a NOAEL value. We have estimated the margin of safety (MoS) for two different cosmetic product categories that may contain tranexamic acid: i) whitening lotion/cream/gel for the whole body, and ii) facial mask/face cream. The NOAEL value is based on a chronic oral animal toxicity study. Since data for dermal absorption is currently not available, we used a default value of 100%. However, the bioavailability of oral tranexamic acid is in the range of 30 – 50 %. Since the NOAEL is based on an oral animal study, a MoS of 200 is believed to be sufficient as a safety margin.

MoS for whitening lotion/cream/gel = 9 (when usage limit is 3 %).
MoS for face cream and facial mask = 239 (when usage limit is 3 %).

The systemic exposure dose calculated for whitening lotion/cream/gel meant for use on the whole body yields a MoS below the minimum requirement of 200, whereas the MoS for face cream/facial mask is at an acceptable level. Although tranexamic acid is not widely used, it is still used to treat certain condition. Doses over 4000 mg/day (67 mg/kg bw) are sometimes used, however, for persons with a reduced kidney function, the recommended doses are 5-30 mg/kg bw. The systemic exposure dose for whitening lotion/cream/gel and for face cream/facial mask were 7.8 mg/kg bw and 0.28 mg/kg bw, respectively. It is clearly that the use of 3 % tranexamic acid in lotion meant for the whole body not be considered safe. However, the contribution from face cream/facial mask of 0.28 mg/kg is much smaller, and should therefore not present any hazard when taken simultaneously as a drug, even in persons with reduced kidney function.

9. Conclusion

In conclusion, we consider tranexamic acid is safe for use in face cream and facial mask at a concentration of 3 %, but should be prohibited in all other cosmetic products. In addition, the products containing tranexamic acid should be labeled with *“not recommended for use by pregnant women*”.

We propose the following usage limits for tranexamic acid:

Facial mask/face cream: 3 %

10. References

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