RISK PROFILE

Sucralfate

CAS No. 54182-58-0

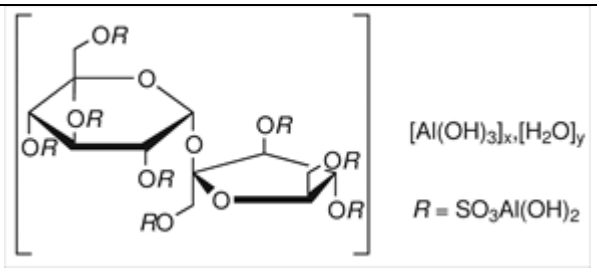
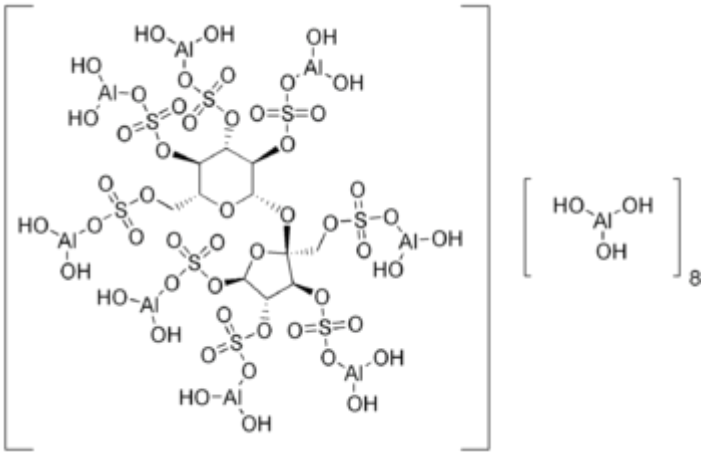
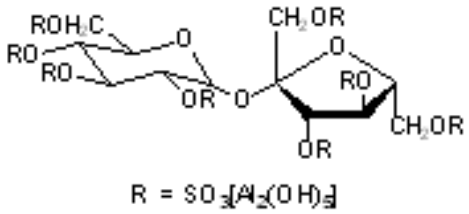
Date of reporting 03.06.2013

Content of document

1. Identification of substance

Chemical name (IUPAC):	Hexadeca-μ-hydroxytetracosahydroxy[μ8-[1,3,4,6-tetra-*O*-sulfo-β-D-fructofuranosyl-α-D-glucopyranoside tetrakis(hydrogen sulfato)(8-)]]hexadecaaluminum
INCI	Aluminum sucrose octasulfate[1]
Synonyms	The INN name, that is used medicinally, is Sucralfate
CAS No.	54182-58-0
EINECS No.	259-018-4
Molecular formula	$C_{12}H_{30}Al_8O_{51}S_8 \cdot 8(H_3AlO_3)$ [2] (footnote 2) , $C_{12}H_{54}Al_{16}O_{75}S_8$
Chemical structure	

[1] Confusingly, the branch of cosmetic industry has for some obscure reason come to write aluminum for the element that scientifically is called aluminium. We hereafter used the scientific term.
[2] http://www.chemblink.com/products/54182-58-0.htm

	 (x= 8 to 10 and y= 22 to 31)  (Source: wikipedia)  Sucralfate is a sucrose aluminium sulphate complex: a-D-glucopyranoside, β-D-fructofuranosyl-, octakis-(hydrogen sulfate)
Molecular weight	2086.74
Contents (if relevant)	1 g tablet of sucralfate contains 207 mg of Al.
Physiochemical properties	White amorphous powder; soluble in dilute hydrochloric acid & sodium hydroxide solution; practically insoluble in water, ethanol, chloroform. Al absorption is greater from water than Al hydroxide or sucralfate and from sucralfate suspension than tablet (Krewski et al., 2007;

	Annex 4). In an acidic environment, sucralfate forms a sticky viscose-gel that adheres to proteinacious exudates within an ulcer crater.

2. Uses and origin

Uses	➢ **Cosmetic products:** *Functions according to* • CosIng database: - Skin conditioning - Maintains the skin in good condition. • Other: - Care of cracked, chapped and peeling lips - Care of irritated, chapped or cracked hands - Diaper sourness *Concentrations of Sucralfate being applied* Lip pomade /lip balm: 2% sucralfate[3] Hand cream: 1% sucralfate *Frequency of use* The EWG Skin Deep [online] database lists 5 cosmetic products containing sucralfate: - hand cream (2 products) - lip balm (2 products) The German Codecheck.info [online] database lists 17 products containing Aluminum sucrose octasulfate/Sucralfate, including after shave and balsam. ➢ **Food** No data available. ➢ **Medicinal products** Sucralfate (tradename: “Antepsin” or “Carafate”) is an oral “anti-ulcer” and gastrointestinal drug. It is used to treat or prevent the recurrence of ulcers by protecting stomach or duodenal lining from the effects of various irritants (e.g. alcohol, acetylsalicylic acid, hydrochloric acid, sodium hydroxide or sodium taurocholate (Toxnet [online]) or stress ulcus (Legemiddelverket[online]). Sucralfate has also been considered as first-line drug therapy in the management of heartburn in pregnancy (Richter, 2005). Sucralfate is used as a topical drug for the healing of several types of epithelial wounds such as ulcers, inflammatory dermatitis, mucositis and burn wounds (Banati et al., 2001). [4]

[3] Application from industry to “Statens Legemiddelverk” in December 3, 2002, for use as an ingredient in skin care products. Claims referring to healing of eczema or contact dermatitis are not allowed.

	In Norway, sucralfate is marketed as “Antepsin”, with the following indications (in Norwegian: "Ulcus duodeni. Ulcus ventriculi. Profylaktisk behandling ved stadig residiverende, eller kroniske duodenalsår. Profylakse mot blødninger pga. stressulcus hos kritisk syke pasienter»). Sucralfate has also been shown to have antibacterial activity (in relation to healing of e.g. ulcers). See also: http://en.wikipedia.org/wiki/Sucralfate ➢ **Other products**
Origin Natural (exo /endo) Synthetic	Sucralfate is an Al salt of a sulfated disaccharide (for molecular structure, see section 1). 1g of sucralfate contains 207 mg of Al. *Mechanism of Action*: The protectant and healing effects of sucralfate are exerted through local, rather than systemic, action (see section 4 for toxicity). *Band-aid*: Sucralfate mainly serves as a “Band-aid®”, by forming an adherent coating at low pH. At higher pH sucralfate may remain in suspension and improve the gastric environment by adsorbing pepsin, buffering hydrogen ions, increasing bicarbonate secretion etc. Al is poorly absorbed from the intact gastrointestinal tract. Sucralfate does not affect gastric acid output or enzyme trypsin or pancreatic amylase activity (i.e. is not an antacid). Sucralfate forms a large complex with proteins (primarily albumin and fibrinogen) that adheres to the ulcer to form a relatively persistent barrier against acid, pepsin, and bile acid penetration, permitting healing to occur (Toxnet[online]). Sucralfate may decrease the rate of gastric emptying. Sucralfate may have some cytoprotective effects, possibly by stimulation of prostaglandin E2 and I2.

3. Regulation

Norway	Maximum allowed concentration: 2% (skin care products only)[5].
EU	No regulation
Rest of the world	No regulation

[4] An ulcer is a sore on the skin or a mucous membrane, accompanied by the disintegration of tissue. Ulcers can result in complete loss of the epidermis and often portions of the dermis and even subcutaneous fat. Ulcers are

[5] Cf. National Norwegian cosmetics regulation to be lifted 11 July 2013

4. Relevant toxicity studies

Absorption Skin	Studies on dermal absorption of sucralfate are missing. It has been reported that significantly burned patients using a 7% sucralfate cream to their skin twice daily did not show detectable serum Al levels in their blood samples (Banati et al. 2001; Burkhart et al., 2009).
GI tractus	Sucralfate is only minimally absorbed from the gastrointestinal tract upon oral intake. Most of the small amounts absorbed - up to 2.2% of a dose in one study using healthy males - are excreted primarily in the urine as intact sulphated disaccharide ((Giesing et al., 1982;Banati et al., 2001; Allain et al., 1990;DrugSafety.com [online]). In rats only 3-5% of an oral dose of ^{14}C-labelled sucralfate was absorbed during a period of 96 hours (Toxnet [online]; Legemiddelverket[online]). In six volunteer persons, the excretion of labelled sucralfate into urine was 0.5 - 2.2% over a period of four days (Legemiddelverket[online]). Allain et al. (1990) measured the plasma and urine Al concentrations in healthy subjects after oral administration of sucralfate (a total dose of 4 g/day for 21 days). A small but significant increase in plasma Al concentration and a somewhat greater increase in urinary Al excretion were found. On average, plasma Al increased from about 2 µg/l to more than 5 µg/l, and 24h urine Al increased from less than 5 µg to more than 30 µg. The urinary Al remained higher than normal 5 and 10 days after terminating sucralfate administration. The increases were presumed to reflect gastrointestinal absorption of Al. The results with sucralfate were similar to Al phosphate, another salt that is poorly absorbed from the gastrointestinal tract. Although studies in normal subjects showed no increases in plasma Al during ingestion of sucralfate (Kinoshita et al., 1982), it has been argued that plasma Al levels are poor indices of Al absorption in normal subjects; i.e. analysis of the levels of aluminum in the urine is much more sensitive than in the blood to determine how much aluminum has been absorbed (Milliner et al., 1984, cited in Robertson et al., 1989). A case report and study data indicate that sucralfate is a source for Al absorption and can cause Al toxicity in a patient with end-stage renal failure, who was given sucralfate to treat gastritis (Robertson et al., 1989). Recurrent seizures and bone pain developed and the individual was diagnosed as having aluminum-related osteomalacia (softening of the bone with symptoms of weakness, pain, weight loss and bone fracture). A study revealed that the absorption of Al increases during treatment with sucralfate, as seen by an increase in Al in the urine but not in the blood. Also normal volunteers showed similar absorption of Al during ingestion of both sucralfate and Al hydroxide. Thus, caution should be taken when patients with renal disease are treated with the non-antacid drug sucralfate for ulcers or gastritis; such treatment should be for only short periods of time. See also: Sucralfate – solubility and absorption (Annex 4).
Distribution	Distribution of sucralfate into human body tissues and fluids after systemic absorption has not been determined (Legemiddelverket[online]).

	In Europe, the total body burden of Al in healthy human subjects has been reported to be approximately 30–50 mg/kg bw. Following oral administration of sucralfate in animals, the drug is only minimally distributed into tissues. Approx. 95% of the dose remains in the GI tract, with only small amounts being distributed into liver, kidneys, skeletal muscle, adipose tissue, and skin. It is not known if sucralfate crosses the placenta or is distributed into milk. (Toxnet[online]). Rat bone, but not brain, contained significantly increased levels of Al after feeding laboratory animals a diet containing 570 mg sucralfate/kg for 8 weeks. The consumption of Al was approximately 4 mg/kg/day (Burnatowska-Hledin & Mayor,1984; cited in Krewski et al., 2007).
Metabolism	The sucrose sulfate part of sucralfate is not metabolized. The half-life, distribution volume, protein binding and tissue distribution of sucralfate in humans is unknown (Legemiddelverket[online]).
Excretion	In animals, more than 90% of an orally administered dose of sucrose sulfate is excreted unchanged in feces within 48 hours. The small amount (3-5%) of sucralfate that is absorbed as sucrose sulfate is excreted unchanged in urine within 48 hours. In animals, the elimination half-life of sucrose sulfate ranges from 6-20 hours (Toxnet[online]). Absorbed Al is eliminated primarily by the kidneys, presumably as Al-citrate, and excreted in the urine. Unabsorbed Al is excreted in the faeces.
Local toxic effects Irritation Sensitivity	Topical application of a 7% sucralfate cream to affected skin regions was well tolerated and did not cause skin irritation in patients with intertrigo[6] (Burkart et al., 2009). Likewise, sucralfate cream is promoted as an effective topical agent in the treatment of both second and third degree burns. It does not appear to have any toxic allergic or systemic effects even after chronic use (Banati et al., 2001). More than 4000 people have reported side effects when taking oral sucralfate over a period of almost 15 years, among them 164 (3.8%) with skin rashes (Annex 3). There have been reports of hypersensitivity reactions to oral sucralfate. These include urticaria (hives), angioedema, respiratory difficulty and rhinitis. Topically applied sucralfate appears not to be of safety concerns.
Systemic toxic effects Acute	In open-label trials with sucralfate conducted in Japan, France, and Latin America involving 1,600 subjects, side effects were reported in only 44 subjects, with the most common complaint being constipation (in 23 subjects) (Fisher, 1981). In the United States, safety evaluations of sucralfate were similar to those obtained in other countries, with only 12.9% of subjects treated with sucralfate (232) reporting side effects. The incidence of side effects in the placebo-treated group was about 12.1%. Acute oral toxicity studies in animals could not demonstrate a lethal dose, using doses up to 12 g/kg body weight, (Sucralfate monograph, AptalisPharma[online]).

[6] Intertrigo is irritant dermatitis, usually found in skin folds, that is caused by rubbing, increased temperature, and moisture.

Repeated dose Mutagenicity /genotoxicity	Mutagenicity studies have not been conducted with sucralfate to date (Toxnet [online]).
Carcinogenicity	Sucralfate has no known carcinogenic risks, as reported in a survey reviewing carcinogenicity in animals and humans of 535 marketed pharmaceuticals. For long-term carcinogenesis assay in mice, results were negative at a dose of 1g/kg/day. (x0.7, in the table of the original publication, denotes the ratio [high animal dose (mg/m^2)/maximum recommended human dose (mg/m^2)].) (Brambilla et al., 2012). Chronic toxicity studies in mice and rats at (oral) doses up to 1 g/kg (12 times the usual human dose[7]) over 24 months showed no evidence of drug-related tumorigenicity.
Reprotoxicity / teratogenicy	There is no evidence that sucralfate represents a risk to the fetuses of pregnant women with normal renal function at recommended use levels; i.e. developmental and/or reproductive toxicity, or neurotoxicity; cf. "Sucralfate in Pregnancy and Breastfeeding" (Drugsafety.com[online]). Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times (50 * 83 mg = 4150 mg?) the human dose and have revealed no evidence of harm to the fetus due to sucralfate (Toxnet [online]). In rats, dosages up to 38 times those used in humans caused no impaired fertility Drugsafety.com[online].
Other effects	<u>*Adverse effects related to the Al content of sucralfate*</u> The *potential foetal toxicity of sucralfate relates to its Al content* (AFSSAPS, 2011; JECFA, 2012; VKM, 2013). Sucralfate is a source of bioavailable Al - each 1 g (tablet) of sucralfate contains 207 mg of Al. JECFA found one study of rats exposed to Al-citrate (one of the more soluble Al compounds) in the drinking water, with reported adverse effects on development and neurotoxicity (JECFA, 2012). Based on the NOAEL of 30 mg/kg bw/day, and applying an uncertainty factor of 100 for inter- and intraspecies variation, a new PTWI of 2 mg/kg bw/week was established, with relevance to all Al compounds in food, including additives (VKM, 2013). For conversion into systemic dose, cf. section 6. *Osteomalacia and encephalopathy*: Dialysis patients - impaired renal function: Aluminium is retained by individuals with impaired kidney function, which can lead to osteomalacia (softening of the bone with symptoms of weakness, pain, weight loss and bone fracture) and encephalopathy (an abnormal condition of the structure or function of the tissues of the brain). Other groups with reduced renal function: Kidney function declines with age. Therefore, <u>elderly people</u> may be at greater risk for developing high Al levels while using sucralfate with other products that contain Al (e.g., antacids). <u>Premature infants</u> fed by parenteral route may experience increased susceptibility to adverse effects related to chronic high exposure of Al. Commercially available fluids for parenteral nutrition (intravenous

[7] Human dose: 1/12 of 1000 mg = 83 mg/kg; for a 60 kg person: 83 mg/kg * 60 kg = 5000 mg.

	feeding) used to contain high levels of Al, and should be regulated (AFSSAPS [online]).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	A NOAEL value for sucralfate in humans has not been established.
Exposure cosmetic products	
Margin of Safety (MoS)	Not estimated for sucralfate - because NOAEL is not available

6. Other sources of exposure than cosmetic products

Food stuffs	The EFSA Panel established a Tolerable Weekly Intake (TWI) of 1 mg Al/kg body weight/week, the same as the levels set by the Joint FAO / WHO (JECFA) expert committee in 2006. The TWI value takes into account a safety factor of 100 and an uncertainty factor of 3 (for the potential for bioaccumulation), and applies to all Al compounds present in food, including food additives. References: EFSA (2008), EFSA (2011). In 2012, JECFA established a new provisional tolerable weekly intake (PTWI) of 2 mg Al/kg bw/week based on new animal studies, and withdrew the PTWI of 1 mg/kg bw/week (JECFA, 2012). VKM estimated the total exposure to Al from food as a systemic exposure (VKM, 2013). Taking into account low oral bioavailability (0.1%) and assuming similar toxicity following oral and dermal exposure to Al, converted values of 1 µg Al/kg bw/week (TWI) and 2 µg Al/kg bw/week (PTWI) were used for systemic exposure. The estimated mean dietary exposure for Norwegian adults is 0.29 mg Al/kg bw/week, comparable to other European countries (EFSA, 2008), while the 95-percentile exposure was 0.67 mg/kg bw/week (VKM, 2013). VKM found similar values for other age groups that may have additional exposure to Al through the use of cosmetic products In addition to the diet (9-year-old children and 13-year-old adolescents. The French food safety agency found that the potential risk of overexposure from food is low, and that estimated total intake of all food categories combined remains below the TWI of 1 mg/kg bw/week, including infants (AFSSAPS, 2011).
Pharmaceuticals	1 g tablet of sucralfate contains 207 mg Al. Recommended daily dosage 1 g x 2 = 2 g (prophylactic use) (Legemiddelsiden[online]). Following administration of 1 g of sucralfate (tablets or suspension) four times a day to individuals with normal renal function, approximately 0.001% to 0.017% of the Al content of sucralfate is absorbed and excreted in the urine – with an estimated Al load of between 8 µg and 136 µg following a 4 g daily dose. These values were determined in individuals with intact gastrointestinal mucosa, but are likely similar in individuals with ulcerated gastrointestinal mucosa. (Aptalispharma.com[online]) Individuals with normal renal function excrete absorbed Al and can respond to an increased Al load by increasing urinary excretion. Overdose: Al toxicity due to a one-time overdose would not be expected, especially in an individual with normal kidney function. Very high doses (50X) have been administered to laboratory animals without mortality. However, Al toxicity in dialysis patients and other susceptible people (elderly; premature children) is of serious concern. Reduced ability to

	remove Al from the body increases the risk of Al toxicity, with more or less subtle signs and symptoms (e.g. weak bones, muscle and bone pain, confusion or other mental changes) that develop over a long period of time.
Other sources	
Adverse side effects - from uses other than cosmetics	Although Al is implicated in the etiology of Alzheimer and other neuro-degenerative diseases, it has not been established that Al is the cause of dementia. EFSA does not consider exposure to Al via food to constitute a risk for developing Alzheimer's disease (EFSA, 2011). EFSA also finds no evidence that Al is a human carcinogen at dietary relevant doses. Sucralfate is well tolerated, with few adverse effects reported. Constipation is the most frequent adverse effect, occurring in approximately 2% of patients (Toxnet [online]; Rx list[online]). In rare reports describing sucralfate overdose, most patients remained asymptomatic. Adverse effects reported in less than 0.5% of patients include diarrhea, nausea/vomiting, gastric discomfort, indigestion, flatulence, dry mouth, rash, pruritus, headache, dizziness, back pain, drowsiness, and vertigo, which rarely require discontinuation of sucralfate. (Drugs.com [online]; Rx list [online]). There have been reports of hypersensitivity reactions to sucralfate. These include urticaria (hives), angioedema, respiratory difficulty and rhinitis. A causal relationship has not yet been established (Parkinson[online]). Sucralfate is used in the management of peptic ulcer. At pH < 4, extensive polymerization occurs and a sticky viscid gel is formed. The French System of Pharmacovigilance has issued advise that caution for adults in intensive care unit being fed by nasogastric tube; sucralfate is contraindicated in premature babies and dysmature newborn babies receiving sucralfate (Guy & Ollagnier, 1999). Bezoars[8] have been reported in patients treated with sucralfate (Rx list[online]). The majority of patients had underlying medical conditions that may predispose to bezoar formation (such as delayed gastric emptying) or were receiving concomitant enteral tube feedings. *Interactions*: Effects on GI absorption of drugs Sucralfate may bind to a number of drugs in the GI tract, e.g. warfarin and possibly other oral anticoagulants, thereby reducing the extent of absorption (Drugs.com[online]; Legemiddelsiden.no[online]). Sucralfate is known to reduce absorption of tetracycline and phenytoin. Because of the potential of sucralfate to alter the absorption of some drugs, sucralfate should be administered separately from other drugs. Instruct patients to administer other drugs at least 2 hours before sucralfate and monitor patients appropriately if alteration in bioavailability of the other drug(s) is critical.

[8] http://www.rxlist.com/script/main/art.asp?articlekey=8898

7. Assessment

General toxicity:

Sucralfate is a non-antacid that is commonly used to treat peptic ulcers and gastritis, but has recently been used as a topical drug for the healing of several types of epithelial wounds such as ulcers, inflammatory dermatitis, mucositis and burn wounds (Masuelli et al., 2010). In cosmetics, sucralfate is used as a skin conditioning agent.

Sucralfate mainly serves as a "Band-aid®", by forming an adherent coating at low pH. Thus, the action of sucralfate is local rather than systemic as the drug is only minimally absorbed from the gastrointestinal tract. The minute amounts absorbed are primarily excreted in the urine. At higher pH sucralfate may remain in suspension and improve the gastric environment by adsorbing pepsin, buffering hydrogen ions, increasing bicarbonate secretion etc. However, sucralfate does not affect gastric acid output or enzyme activity (i.e. is not an antacid).

Oral ingestion of sucralfate is well tolerated, with few adverse effects reported. Constipation is the most frequent adverse effect, occurring in approx. 2% of patients. There have been (case) reports of hypersensitivity reactions to oral sucralfate, which include *urticaria* (hives), angioedema, respiratory difficulty and rhinitis. A causal relationship has not yet been established.

There is no evidence that recommended use levels of sucralfate represent a risk to healthy people. However, sucralfate should be avoided in patients with chronic renal failure, because of increased risk of Al toxicity, including osteomalacia and encephalopathy. Sucralfate is not for use in children and its safety for nursing mothers is uncertain due to lack of safety data.

Chemically, sucralfate is a sucrose sulfate complex containing 21% of Al, and potential adverse effects are most likely related to its Al content.

Cosmetics:
In cosmetics, sucralfate is used as a skin conditioning agent, especially to help the care of cracked, chapped and peeling lips as well as chapped or cracked hands.

Topically applied sucralfate appears not to be of systemic safety concerns. There have been reports of hypersensitivity reactions to oral sucralfate. These include urticaria (hives), angioedema, respiratory difficulty and rhinitis.

However, potential adverse effects of sucralfate are most likely related to its Al content (21% of Al); i.e. a 2% sucralfate cream (the maximum level according to the current Norwegian regulation) contains 0.42% (2 x 0.21) Al. The risk assessment is based on Al derived from sucralfate takes into account both low and high exposure scenarios in people with normal intact skin and damaged (cracked) skin, respectively. The calculations are shortly outlined and summarized in the table below. For detailed calculations – see Annex 6.

Estimation of systemic aluminium exposure (based on 2% sucralfate cream, containing 21% Al)

Systemic exposure dose (SED) of Al (derived from sucralfate) was calculated according to SCCS's guidelines (SCCS[online], SCCS/1358/10).

Equation: SED = A(mg/kg bw/day) x C(%) x DAp(%),
where A = estimated daily exposure; C = concentration of substance, and DAp = dermal absorption.

Two scenarios: low exposure (A), high exposure (B)

A. Low exposure (intact skin):
SED, hands (low): 32.70 x (0.02 x 0.21) x 0.00005 = 0.000006867 mg/kg bw/day
-> Total weekly intake = 0.000007812 mg/kg bw/day x 7 = **0.000055 mg/kg bw/week of Al**
-> 0.05 µg/kg bw/week (Dap_1)

-> 0.81 µg/kg bw/week (Dap_2)

B. High exposure (damaged skin):
SED, hands (high): 32.70 x (0.02 x 0.21) x 0.001 = 0.000137 mg/kg bw/day
-> Total weekly intake = 0.00138 mg/kg bw/day x 7 = 0.0**0096 mg/kg bw/week of Al**
-> 0.96 µg/kg bw/week (Dap_1')
-> 16.3 µg/kg bw/week (Dap_2')

C. Low exposure (intact normal lips)
SED, lips (high): 0.90 x (0.02 x 0.21) x 0.00005 = 0.00000019 mg/kg bw/day
-> Total weekly intake = 0.00000378 mg/kg bw/day x 7 = 0.0**0000132 mg/kg bw/week of Al**
->0.001 µg/kg bw/week (DAp_1)
->0.022 µg/kg bw/week (DAp_2)

D. High exposure (cracked lips)
SED, lips (high): 0.90 x (0.02 x 0.21) x 0.001 = 0.00000378 mg/kg bw/day
-> Total weekly intake = 0.00000378 mg/kg bw/day x 7 = 0.0**00265 mg/kg bw/week of Al**
->0.027 µg/kg bw/week (DAp_1')
->0.45 µg/kg bw/week (DAp_2')

Results are summarized in the table below

Summary table – systemic exposure dose of Al (µg/kg bw/week) from sucralfate in cosmetics and food (other cosmetic products containing Al is not taken into account in the table –see comments below)

	Bioavailability (0.001%)	Bioavailability (0.017%)
A. Cosmetics		
Intact skin	0.05	0.81
Damaged skin	0.96	16.3
Intact lips	0.001	0.022
Cracked lips	0.027	0.45
Total (intact normal skin/lips)	0.05	0.83
Total (damaged/cracked skin/lips)	0.99	16.8
B. Food		
Mean exposure*	0.29	0.29
High exposure*	0.67	0.67
C. Cosmetics + Food		
Intact skin/lips	0.34 (= 0.05 + 0.29)	1.50 (= 0.83 + 0.67)
Damaged skin/lips	1.28 (= 0.99 + 0.29)	17.5 (= 16.8 + 0.67)

*) Estimated systemic exposure of Aluminium in food (VKM, 2013)

Foods and supplements
The mean dietary exposures for Norwegian adults are 0.29 and 0.67 mg Al/kg bw/week for mean and high exposures, respectively (VKM, 2013). Similar results were found for other age groups (9-year-old children and 13-year-old adolescents) that may have additional exposure to Al through the use of cosmetic products In addition to the diet.

Based on an oral bioavailability of 0.1% for Al, the systemic exposure from the diet amounts to **0.29 and 0.67 µg Al/kg bw/week** for mean and high exposures, respectively.

Total systemic exposure from cosmetics and food:

Comments:

Normal (intact) skin: *The estimated total systemic exposure (SED) of Al from intake of food and cosmetics (hand cream / lipstick) containing 2% sucralfate is 0.34 – 1.50 µg/kg bw/week (adults).* This is below the PTWI of 2 µg/kg bw/week established by JECFA (2012).

Damaged (cracked) skin:*The estimated total systemic exposure of Al from food and cosmetics containing 2% sucralfate is* 1.28 – 17.5 µg/kg bw/week.

Additional contribution from lipstick / lip gloss containing Al (VKM, 2013):
VKM estimated SED of 0.22 and 4.3 µg Al /kg bw/week for persons using lipstick/lip gloss daily (other sources than sucralfate), referring to two scenarios with intact and damaged skin, respectively (VKM, 2013).

Additional contribution from lipstick / lip gloss + antiperspirants containing Al (VKM, 2013)
When including both the use of lipstick/lip gloss + antiperspirants (for adults), SED values of 31 and 601 µg Al/kg bw/week were estimated for the standard and worst case scenarios, respectively.

Medicinal agents:
Estimated Al load is between 8 (0.13 µg/kg bw/day x7 = 1.04 µg/kg bw/week) and 136 µg (2.27 µg/kg bw/day x7 =15.9 µg/kg bw/week) following a 4 g daily oral dose of sucralfate (Aptalispharma.com[online]). (Recommended daily dosage is 2 g for prophylactic use).

8. Conclusion

Maximum allowed concentration (skin care products only):

- **Lipstick /lip pomade /lip balm: 2% sucralfate**
- **Hand cream: 2% sucralfate (intact skin)**

Remarks/Warnings:

- Not to be used on damaged skin.
- Sucralfate should be avoided in patients with chronic renal failure, because of increased risk of Al toxicity, including osteomalacia and encephalopathy. Sucralfate is not for use in children and its safety for nursing mothers is uncertain due to lack of safety data.

Other comments:
For persons with normal intact skin, the estimated total systemic exposure dose of Al from food and cosmetic products containing 2% sucralfate (i.e. hand cream + lipstick) is in the range of *0.34 to 1.50 µg/kg bw/week*, which is below the PTWI of 2 µg/kg bw/week.

Total SED from food and cosmetics, excluding antiperspirants:
SED values of 0.22 and 4.3 µg Al/kg bw/week have been estimated for lipstick /lip gloss, i.e. scenarios with intact and damaged skin, respectively (VKM, 2013).

Thus, a total SED of 0.56 (0.34 + 0.22) to 1.72 (1.50 + 0.22) µg/kg bw/week was estimated for systemic exposure of Al from food + cosmetics (with 2% sucralfate) + cosmetics (Al from other sources than sucralfate) in persons with intact skin/lips. This range is still below the PTWI of 2 µg/kg bw/week.

Use of lipstick with 2% sucralfate for cracked lips results in SED in the range of 0.027 to 0.45 µg/kg bw/week (see table above, section 7), i.e. total SED for food and cosmetic products (excluding antiperspirants) just below 2 µg/kg bw/week (= PTWI).

SED for antiperspirants:
SED values of 31 and 601 µg Al/kg bw/week from antiperspirants (standard and worst case scenarios, respectively) greatly exceed PTWI (or TWI) alone, without contribution from other sources.

Thus, a recent VKM (2013) risk assessment of Al found that daily use of antiperspirants will substantially reduce the safety margin and may increase the risk of adverse effects, particularly for persons shaving/waxing their armpits often or having impaired skin caused by skin conditions such as eczema. For this scenario the exceedance of TWI/PTWI was 300-940 fold (VKM, 2013).

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10. Annexes

Annex 1: Examples of sucralfate in cosmetic products on the market – retrieved 25.10.2012

Annex 2:

Acute toxicity (Toxnet [online])

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
infant	TDLo	oral	1276mg/kg/3D- (1276mg/kg)	CARDIAC: PULSE RATE	Clinical Pediatrics Vol. 35, Pg. 423, 1996. Link to PubMed
mouse	LD50	intraperitoneal	> 8gm/kg (8000mg/kg)		Drugs in Japan Vol. 6, Pg. 374, 1982.
mouse	LD50	oral	> 8gm/kg (8000mg/kg)		Drugs in Japan Vol. 6, Pg. 374, 1982.
mouse	LD50	subcutaneous	> 8gm/kg (8000mg/kg)		Drugs in Japan Vol. 6, Pg. 374, 1982.
rat	LD50	intraperitoneal	> 4gm/kg (4000mg/kg)		Drugs in Japan Vol. 6, Pg. 374, 1982.
rat	LD50	oral	> 12gm/kg (12000mg/kg)		Drugs in Japan Vol. 6, Pg. 374, 1982.
rat	LD50	subcutaneous	> 4gm/kg (4000mg/kg)		Drugs in Japan Vol. 6, Pg. 374, 1982.

Annex 3: Side effects – oral intake sucralfate

http://www.ehealthme.com/print/ds14421663 (accessed May 13, 2013)

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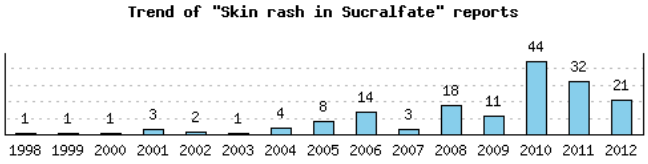
eHealthMe real world study

On Apr, 22, 2013: 4,311 people reported to have side effects when taking Sucralfate. Among them, 164 people (3.80%) have Skin Rash.



Time on Sucralfate when people have Skin rash * :

	< 1 month	1 - 6 months	6 - 12 months	1 - 2 years	2 - 5 years	5 - 10 years	10+ years
Skin rash	94.44%	0.00%	5.56%	0.00%	0.00%	0.00%	0.00%

Gender of people who have Skin rash when taking Sucralfate * :

	Female	Male
Skin rash	51.65%	48.35%

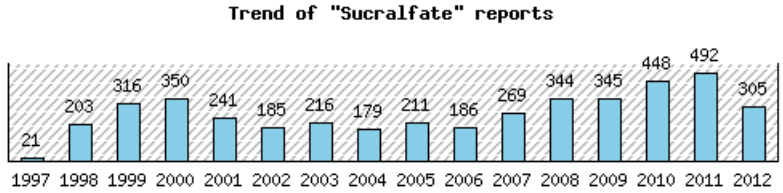
Age of people who have Skin rash when taking Sucralfate * :

	0-1	2-9	10-19	20-29	30-39	40-49	50-59	60+
Skin rash	0.00%	0.73%	0.73%	1.46%	10.95%	11.68%	26.28%	48.18%

Severity of Skin rash when taking Sucralfate ** :

n/a

On May, 11, 2013: **4,311** people who reported to have side effects when taking Sucralfate are studied



Most common Sucralfate side effects*:

If people were to have side effects while taking Sucralfate, what are they:

(1) Pyrexia: 709 reports. It's more common among males aged 60+ years old

(2) Vomiting: 554 reports. It's more common among females aged 60+ years old

(3) Diarrhoea: 551 reports. It's more common among females aged 60+ years old

(4) Dyspnoea: 535 reports. It's more common among females aged 60+ years old

(5) Asthenia: 498 reports. It's more common among females aged 60+ years old

(6) Nausea: 372 reports. It's more common among females aged 60+ years old

(7) Pain: 267 reports. It's more common among females aged 60+ years old

(8) Pneumonia: 240 reports. It's more common among males aged 60+ years old

(9) Fatigue: 227 reports. It's more common among females aged 60+ years old

(10) Constipation: 182 reports. It's more common among females aged 60+ years old

Annex 4: Sucralfate - solubility and absorption

Sucralfate, like Al hydroxide, is insoluble in water but soluble in acid and base. Sucralfate exhibits oral bioavailability comparable to that of Al hydroxide, but lower than that of soluble Al species. Al bioavailability from sucralfate in the rabbit was 0.6%, from Al lactate 0.63%, and 0.57% to 1.16% from Al chloride and nitrate (Yokel & McNamara,1988; cited in Krewski et al., 2007). In the rat, oral Al bioavailability was 0.015% from Al hydroxide and sucralfate, 0.037% from Al lactate and Al chloride, and 1.49% from Al citrate (Froment et al., 1989a; cited in Krewski et al., 2007).

There is evidence of greater Al absorption from more soluble Al species. Al borate, glycinate, hydroxide and sucralfate are much less soluble in water than Al chloride, lactate, nitrate and citrate and were generally less well absorbed (0.27, 0.39, 0.45 and 0.60 vs. 0.57, 0.63, 1.16 and 2.18%, respectively (Yokel & McNamara, 1988; cited in Krewski et al., 2007). Similarly, Al hydroxide and sucralfate are less soluble at pH 3, 6 and 7 than Al lactate and chloride and were also less well absorbed (0.015 vs. 0.037%), based on urinary Al excretion (Froment et al., 1989a; cited in Krewski et al., 2007).

Solubility Oral bioavailability of Al from quite insoluble forms, such as Al hydroxide and sucralfate, was generally reported to be quite low, e.g. ~0.001 to 0.007% (Haram et al., 1987; Weberg & Berstad, 1986), whereas from drinking it water was ~0.22 and 0.35% (Priest et al., 1998; Stauber et al., 1999). Higher plasma levels were observed after oral administration of sucralfate in suspension than in tablet form (Conway et al., 1994). This is not consistent with the notion that bioavailability is independent of the chemical species of the Al (Reiber et al.,1995), a notion which does not appear to be valid.

All citations above from Krewski et al (2007).

Al is poorly absorbed from the intact gastrointestinal tract. Following administration of 1 g of sucralfate (tablets or suspension) four times a day to individuals with normal renal function, approximately 0.001% to 0.017% of sucralfate's Al content is absorbed and excreted in the urine. This results in an Al load of between 0.008 mg and 0.136 mg following a 4 g daily dose. Individuals with normal renal function excrete absorbed Al and can respond to an increased Al load by increasing urinary excretion. (AptalisPharma[online]).

Annex 5

French risk assessment related to the use of Al in cosmetic products –www.afssaps.fr

Conclusion:

The French Food Safety Authority (AFSSAPS) evaluated the exposure and potential health effects related to dermal exposure of Al (AFSSAPS, 2011). This absorption is very poorly understood, due to poor quality of studies, and recent in vitro studies were used to estimate dermal absorption of Al (two scenarios –intact and damaged skin). In conclusion of the risk assessment, AFSSAPS recommends to restrict the concentration of Al in cosmetic products at 0.6% and not to use cosmetics containing Al on damaged skin.

Translation (summary)

Summary

The safety of Al uptake from food-contact articles, medicinal and cosmetic products is frequently questioned. It is particularly incriminated in the development of Alzheimer's disease. In 2003, a common scientific opinion from the French health and safety agencies, entitled "Assessment of health risks related to exposure of the French population to Al" (AFSSAPS/AFSSA/INVS, 2003) was published. This opinion highlighted the lack of relevant data on dermal absorption of cosmetic products containing Al.

In 2004, Darbre et al. (2003) published works indicating a link between the use of underarm cosmetics such as Al-based antiperspirants and breast cancer.

Following a request from the Directorate General for Health, the AFSSAPS was requested to provide a scientific opinion on the safety of Al from cosmetic sources.

The present risk assessment takes into account both the recent dermal absorption study provided by industry and summarized toxicological data, partly based on the recent opinion provided by the European Food Safety Authority (EFSA, 2008b).

More than twenty-five Al compounds can be used in cosmetic products. The Al chlorohydrate is one of the most widely used, especially as anti-transpirant.

The oral bioavailability of the Al ion from drinking water in humans and experimental animals was estimated to be in the range of 0.3%, whereas the bioavailability of Al from food and beverages is generally considered to be lower, about 0.1%. Widely distributed throughout the body, Al can enter the brain and reach the placenta and fetus. Its half-life is very variable according to studies and can reach several years when administered chronically. Its elimination is mainly renal.

The absorption of Al after dermal exposure is very poorly understood. The available studies are of poor quality and are not carried out according to the current requirements. The recent in vitro study on human skin allowed estimating the dermal absorption. In this study, the estimated quantities of Al absorbed via a daily exposure to an antiperspirant containing 20% of Al chlorohydrate (5% Al) were obtained using two scenarios.
The first scenario corresponds to the exposure of intact skin, and leads to a dermal absorption rate of 0.5%; the second scenario corresponds to the exposure of damaged skin, and results in an absorption rate of 18%. Thus it is of 2.1 mg Al/kg bw./d. in the first scenario and 75 mg Al/kg bw./d. in the second scenario.
In conclusion, the margin of safety is 11 in intact skin exposure conditions and less than 1 in the case of damaged skin exposure conditions.

The irritant potential of Al is insufficiently studied in animals. However, cases of skin irritations associated with cosmetic products containing Al chlorinated compounds were reported in humans.

Additional data would be needed to confirm the risk of irritation associated with these products. Cases of sensitization are rare. Repeated dose administration in laboratory animals showed that several Al containing compounds have the potential to produce neurotoxicity (mice, rats) and to affect the male reproductive system (dogs). In addition, after maternal exposure, embryotoxicity (mice) was observed and the developing nervous system in the offspring (mice, rats) (EFSA, 2008) was affected. Contrary to the EFSA assessment, the AFSSAPS retained the NOAEL of 22 mg/kg bw./d., obtained in a study performed in dogs and based on a decreased body weight and histopathological changes of the kidney and liver.
Human effects (neurotoxicity, anemia…) are known in patients undergoing dialysis and thereby chronically exposed parenterally to high concentrations of Al, as well as in premature infants fed by parenteral route. Systemic dose of 5 mg Al/kg bw./d is considered safe by the Food and Drug Administration for the use of parenteral fluids for two populations with reduced kidney function as premature infants and patients with renal impairment.

The EFSA noted that the indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, are unlikely to be of relevance for humans exposed to Al via the diet. In addition, the animal studies did not show any carcinogenic potential. More, epidemiological data do not establish any conclusive link between dermal Al exposure and development of cancer. In conclusion, there are insufficient data to establish a clear relationship between the use of underarm Al-based antiperspirants and breast cancer. This risk assessment shows that exposure to antiperspirant products with concentrations of 20% Al chlorohydrate does not ensure consumer safety under normal conditions of use.

In addition, as the present risk assessment does not take into account the total exposure to various cosmetic products likely to contain Al, these conclusions are subject to change thereafter, based on an assessment taking into account the different product categories and their uses. Specific data to other exposure conditions (quantities, dermal absorption, toxicity) could be provided to refine the risk assessment related to the use of Al in other cosmetic products.

In conclusion of this risk assessment the Afssaps recommends:
• to restrict the concentration of Al in cosmetic products at 0.6%. This value is deliberately expressed in Al, so that it can apply to different used forms in cosmetic products;
• not to use cosmetics containing Al on damaged skin. Indeed, given the high absorption reported in these conditions, it is necessary to inform consumers that antiperspirants or deodorants products containing the Al should not be used after shaving or if the consumer's skin is affected by small cuts. The Afssaps recommends this information to be clearly indicated on the packaging.

Keywords: Al, cancer, risk assessment, antiperspirants, cosmetics, recommendations

Annex 6: Calculations

Calculations of systemic aluminium exposure dose (based on 2% sucralfate cream, containing 21% Al).

Equation: SED = A(mg/kg bw/day) x C(%) x DAp(%); cf. SCCS notes of guidance.

A. Low exposure (intact skin):
SED, hands (low): 32.70 x (0.02 x 0.21) x 0.00005 = 0.000006867 mg/kg bw/day
-> Total weekly intake = 0.000007812 mg/kg bw/day x 7 = **0.000055 mg/kg bw/week of Al**

-> 0.048 µg/kg bw/week (bioavailability: 0.001%, Dap_1)
-> 0.81 µg/kg bw/week (bioavailability: 0.017%, Dap_2)

B. High exposure (damaged skin):
SED, hands (high): 32.70 x (0.02 x 0.21) x 0.001 = 0.000137 mg/kg bw/day
-> Total weekly intake = 0.00138 mg/kg bw/day x 7 = 0.0**0096 mg/kg bw/week of Al**

-> 0.96 µg/kg bw/week (bioavailability: 0.001%, Dap_1)
-> 16.3 µg/kg bw/week (bioavailability: 0.017%, Dap_2)

Systemic exposure dose (SED) of Al (derived from sucralfate) was calculated according to SCCS's guidelines (SCCS[online]).

Equation:
SED = A(mg/kg bw/day) x C(%) x DAp(%), where

A (mg/kg bw/day) = Estimated daily exposure to a cosmetic product per kg body weight, based upon the amount applied and the frequency of application (for calculated relative daily exposure levels for different cosmetic product types, see Table 3, section 4-2).

A (hands) = 32.70 mg/kg bw/day*
A (lips) = 0.90 mg/kg bw/day*

*) SCCS guidelines: Table 3 - Estimated daily exposure levels for different cosmetic product types according to Colipa (Cosmetics Europe) data [SCCNFP/0321/00; Hall et al. 2007, 2011, in SCCS[online].

C(%) = Concentration of the substance under study in the finished cosmetic product on the application site.

Sucralfate, cream: 2% = 0.02
Corresponding amount of Al: 0.02 x 0.21 = 0.0042

DAp(%) = Dermal Absorption expressed as a percentage of the test dose assumed to be applied in reallife conditions. In case the in vitro dermal absorption assay was not performed under in-use conditions, an additional correction factor can be introduced.

DAp (intact skin, low) = 0.5% = 0.005#
DAp (cracked skin, high) = 10% = 0.1#

#) based on bioavailability of Al in antiperspirants (Al chlorohydrate, moderately soluble): 0.1%
Dermal absorption rates of 0.5% and 10% for normal intact skin and damaged/cracked skin, respectively – cf. AFSSAPS (2011), VKM (2013).

"Scaled" dermal absorption of sucralfate (nearly insoluble Al compound) – based on experimental values for Al chlorohydrate in antiperspirants (moderately soluble Al substance)

The bioavailability of Al in antiperspirants (Al chlorohydrate) is estimated to be 0.1% (based on oral intake?).

Bioavailability of Al in sucralfate (insoluble) is reported to be in the range of 0.001% to 0.017% (see Sucralfate product monograph, Aptalispharma.com[online]).

Experimental dermal absorption for Al in antiperspirants (in the form Al chlorohydrate) ranges between approx. 0.5% and 10% for normal and damaged skin, respectively.

Thus, 0.5% dermal absorption of Al in normal skin (experimentally determined for Al in antiperspirant with bioavailability 0.1%), is adjusted with a scaling factor that takes account of differences in bioavailability for Al in antiperspirants (moderately soluble) and sucralfate (nearly insoluble). See first calculation below.

Bioavailability: 0.001%
DAp_1 (intact skin, low) = 0.5% x 0.001 /0.1 =0.005% =0.00005
DAp_1' (cracked skin, high) = 10% x 0.001 /0.1 = 0.1% = 0.001

Bioavailability: 0.017%
DAp_2 (intact skin, low) = 0.5% x 0.017 /0.1 =0.085% =0.00085
DAp_2' (cracked skin, high) = 10% x 0.017 /0.1 = 1.7% = 0.017

Two scenarios: low exposure (A), high exposure (B)

A. Low exposure (intact skin):
SED, hands (low): 32.70 x (0.02 x 0.21) x 0.00005 = 0.000006867 mg/kg bw/day
-> Total weekly intake = 0.000007812 mg/kg bw/day x 7 = **0.000055 mg/kg bw/week of Al**

-> 0.048 µg/kg bw/week (Dap_1)
-> 0.81 µg/kg bw/week (Dap_2)

B. High exposure (damaged skin):
SED, hands (high): 32.70 x (0.02 x 0.21) x 0.001 = 0.000137 mg/kg bw/day
-> Total weekly intake = 0.00138 mg/kg bw/day x 7 = 0.0**0096 mg/kg bw/week of Al**

-> 0.96 µg/kg bw/week (Dap_1')
-> 16.3 µg/kg bw/week (Dap_2')

C. Low exposure (intact normal lips)
SED, lips (high): 0.90 x (0.02 x 0.21) x 0.00005 = 0.00000019 mg/kg bw/day
-> Total weekly intake = 0.00000378 mg/kg bw/day x 7 = 0.0**0000132 mg/kg bw/week of Al**

->0.001 µg/kg bw/week (DAp_1)
->0.022 µg/kg bw/week (DAp_2)

D. High exposure (cracked lips)
SED, lips (high): 0.90 x (0.02 x 0.21) x 0.001 = 0.00000378 mg/kg bw/day
-> Total weekly intake = 0.00000378 mg/kg bw/day x 7 = 0.0**00265 mg/kg bw/week of Al**

->0.027 µg/kg bw/week (DAp_1')
->0.45 µg/kg bw/week (DAp_2')

Summary table – dermal absorption of Al from sucralfate

	Bioavail (0.001%)	Bioavail (0.017%)
A. Cosmetics		
Intact skin	0.05	0.81
Damaged skin	0.96	16.3
Intact lips	0.001	0.022
Cracked lips	0.027	0.45
Total (intact normal skin/lips)	0.05	0.83
Total (damaged/cracked skin/lips)	0.99	16.8
B. Food		
Mean*	0.29	0.29
High*	0.67	0.67
C. Cosmetics + Food		

*) Bioavailability for Al in food: 0.1%

The French Food Safety Authority (AFSSAPS) evaluated the exposure and potential health effects related to dermal exposure of Al (AFSSAPS, 2011). This absorption is very poorly understood, due to poor quality of studies, and recent in vitro studies were used to estimate dermal absorption of Al (two scenarios –intact and damaged skin). In conclusion of the risk assessment, AFSSAPS recommends to restrict the concentration of Al in cosmetic products at 0.6% and not to use cosmetics containing Al on damaged skin.