RISK PROFILE

Glucosamine (GlcN)

CAS No.67-71-0

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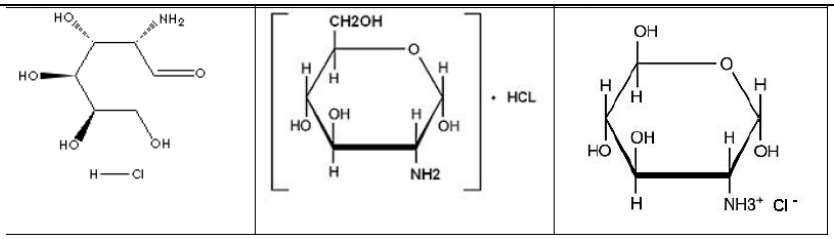
Content of document

1. Identification of substance

Chemical name (IUPAC):	Glucosamine (*) Glucosamine hydrochloride D-Glucosamine sulphate N-acetyl-.alpha.-D-glucosamine (Acetyl glucosamine)
INCI	Glucosamine (*) Glucosamine HCl Glucosamine sulfate Acetyl glucosamine
Synonyms	2-Amino-2-deoxy-D-glucose (*)
CAS No.	3416-24-8 (Glucosamine) 66-84-2 (Glucosamine HCl) 29031-19-4 (Glucosamine sulfate) 10036-64-3 (Acetyl glucosamine)
EINECS No.	222-311-2 (Glucosamine) 200-638-1 (Glucosamine HCl) 249-379-6 (Glucosamine sulfate) 233-115-1 (Acetyl glucosamine)
Molecular formula	$C_6H_{13}NO_5$ (Glucosamine) $C_6H_{13}NO_5$•HCl (Glucosamine HCl) $C_6H_{13}NO_5xH_2SO_4$ (Glucosamine sulfate) $C_8H_{15}NO_6$ (Acetyl Glucosamine)
Chemical structure	Glucosamine (*) and Glucosamine HCl: The structural formula can be represented using different styles of molecular presentation:

	 See Annex I for other glucosamine variants (NTP [online]; Miller & Clegg, 2011).
Molecular weight	179.17 (Glucosamine) 215.63 (Glucosamine HCl) 277.24 (Glucosamine sulfate) 221.21 (Acetyl glucosamine)
Contents (if relevant))	
Physiochemical properties	Glucosamine: Crystals, colorless needles from methanol Melting point: 88 ºC Solubility: Soluble in water and boiling methanol Storage: below 30^{o}C. Glucosamine sulfate is hygroscopic; keep bottle tightly closed to protect from moisture.

2. Uses and Origin

Uses	➢ **Cosmetic products:** Four types of glucosamine amino sugars are most frequently used in cosmetic products: GlcN, GlcN.HCl, GlcN.sulfate, and N-acetyl-GlcN. *Functions according to* • CosIng database: - skin conditioning (N-Ac-GlcN, GlcN.sulfate) - antistatic (GlcN, GlcN.HCl) - hair conditioning (GlcN, GlcN.HCl) • Other: - Relief of discomfort (GlcN) due to overdone sporting exercise (NTP [online]). - Anti-aging ingredient (N-acetyl-GlcN) with anti-oxidant properties (Rivers, 2008). *Concentrations of GlcN being applied* The standard *oral* dose of GlcN.sulfate is 1500 mg/day (Aghazadeh-Habashi & Jamali, 2011). It should be noted that *under-dosing* and *variable chemical potency* of GlcN crystals may explain some of the GlcN controversy in clinical trials (UpToDate [online]; Aghazadeh-Habashi & Jamali, 2011). Creams containing high concentrations (8%, 10%) of GlcN salts (GlcN.HCl and GlcN.sulfate) are available on the market (Annex 2). Development of proprietary transdermal delivery systems is claimed to be key to the functional properties of these high concentrations of

	GlcN compounds. Marketers of these products claim that GlcN creams with less than 7% GlcN may not have pharmaceutical benefits. (Gupta, 2004). *Frequency of use* The EWG Skin Deep cosmetic database (EWG's Skin Deep [online]) lists: 43 products that contain **GlcN** (CAS no 3416-24-8) – anti-aging (20 products) – facial moisturizer/ treatment (19 products) – moisturizer (6 products) – facial cleanser (4 products) – toners/ astringents (3 products) 60 products that contain **GlcN.HCl** (CAS no66-84-2) – anti-aging (29 products) – facial moisturizer/ treatment (25 products) – around-eye cream (9 products) – moisturizer (5 products) – body firming lotion (5 products) 6 products that contain **GlcN.sulfate** (CAS no 29031-19-4) – pain relief (6 products) (medicinal products) – muscle/ joint soreness (3 products) (medicinal products) – anti-aging (1 products) – facial moisturizer/ treatment (1 products) 75 products that contain **N-Acetyl-GlcN** (CAS no 7512-17-6) – anti-aging (13 products) – facial moisturizer/ treatment (12 products) – lipstick (12 products) – antiperspirant/ deodorant (11 products) – foundation (10 products) The German Codecheck.info [online] database lists: – 289 products for GlcN – 64 products for GlcN.HCl – 45 products for GlcN.sulfate – 87 products for N-Acetyl-GlcN ➢ **Food** Most GlcN supplements contain GlcN hydrochloride or GlcN.sulfate although some contain N-Acetyl-GlcN (Integrative Medicine, 2001; The Natural Pharmacist, 2001; cited in NTP [online]). It is typically offered as capsules for oral supplement – 1500 mg GlcN.sulfate (equivalent to 1190 mg glutamine base). (Hathcock & Shao, 2007). ➢ **Medicinal products** GlcN can be taken in pill form or liquid administered though intramuscular injections. In Norway, 6 different pharmaceutical medicinal products containing glucosamines are registered (Felleskatalogen [online]): – Donacom «Rottapharm» powder for mixtures.

	– Glucosamine Orifarm «Orifarm Generic» tabl. * – Glucosamin Pharma Nord «Pharma Nord» capsules – Glukosamin «Ferrosan» tabl. * – Perigona «MIP Pharma» tabl. * – Samin «Weifa» tabl. DONA, a GlcN.sulfate formula, is a top selling prescription drug[1] for ostearthritis and joint pain in Europe[2]. Other indications: sports injury; formation and repair of cartilage (Hotfrog [online]). *Classification*: GlcN belongs to the "pharmaco-therapeutic group" of non-steroid anti-inflammatory drugs (NSAID) and is used for low-grade to moderate forms of knee arthritis. GlcN is not used for treatment of acute, painful symptoms, as pain relief appears to be noticeable, at least in some patients, only after a period of 4-5 weeks or more. *Dosages*: one dose packages contain 1178 mg of the active ingredient GlcN (i.e. 1884 mg GlcN.sulfate /sodium chloride corresponding to 1500 mg GlcN.sulfate). (Hathcock & Shao, 2007). *GlcN in combination with methylsulphonyl-methane (MSM) and chondroitin*: A combination of GlcN, chondroitin and MSM are of marketing interest in the management of osteoarthritis (i.e. muscle, joint and arthritis pain relief), but formulation of stable products are challenging (Gupta, 2004). MSM (see separate risk profile) is promoted as having anti-inflammatory and analgesic effects, often in combination with GlcN and/or chondroitin, but its ability to decrease degenerative processes in joints (e.g. osteoarthritis) is as yet unproven (Gregory et al., 2008). *Glucosamine to be re-assessed by Danish Medicines Agency* The Danish Medicines Agency is to re-assess reimbursement to patients who buy GlcN (M01AX05) from pharmacies after clinical studies questioned its efficacy for the alleviation of painful osteoarthritis (Nutraingredients [online]). In this regard, a key factor was a Norwegian study published in the *Journal of the American Medical Association* (JAMA) which questioned the efficacy of glucosamine for patients with chronic low back pain and lumbar arthritis (Wilkens et al., 2010). ➢ **Other products**
Origin (natural/synthesis)	GlcN is an endogenous substance, and a normal constituent of the polysaccharide chains of cartilage matrix and synovial fluid glucosaminoglycans. The three forms of GlcN are commonly available for nutritional supplements and cosmetic products (GlcN.HCl, GlcN.sulfate, and N-

[1] Because DONA is sold as a prescription drug in Europe, it is backed by clinical studies that the other glucosamine supplements sold in the U.S. do not have.
http://weeklyhealthbuzz.com/european-prescription-glucosamine-drug-available-otc-in-the-u-s-for-joint-pain/

[2] available over the counter (OTC) in the U.S. for joint pain

	N-Acetyl-GlcN) are generally derived from chitin, a biopolymer present in the exoskeleton of marine invertebrate animals (Anderson et al., 2005). GlcN has recently become available also from vegetarian sources, circumventing potential problems related to shell fish allergy. Because GlcN is a weak organic base, it must be stabilized as a salt (e.g. GlcN.HCl or co-crystals of GlcN.sulfate with potassium or sodium chloride) (Miller & Clegg, 2011). Animal data have indicate that exogeneous GlcN supplementation has a role in cartilage maintenance and repair, whereas recent clinical trials and a meta-analysis have questioned the efficacy of exogenous GlcN in humans (Anderson et al., 2005, and references therein; Norsk Legemiddelhåndbok [online]); Wilkens et al., 2010; Wandel et al., 2010; Aghazadeh-Habashi & Jamali, 2011). Thus, the Danish Medicines Agency is to re-assess reimbursement policy for patients who buy GlcN (M01AX05) from pharmacies (Nutraingredients [online]). However, there are still unresolved issues regarding the clinical efficacy of glucosamine, one of which is related to methodological weaknesses (Block et al., 2010; Aghazadeh-Habashi & Jamali, 2011).

3. Regulations

Norway	No regulation[3]
EU	No regulation
Rest of the world	No regulation[4]

4. Relevant toxicity studies

Absorption Skin	Sparse information is available regarding skin absorption and transdermal transport of GlcN and its salt forms. GlcN (and chondroitin) salts are charged, highly polar, aqueous soluble, and apparently poor candidates for transdermal absorption (Garner et al., 2007). However, the skin permeation rate was determined to be 13.27 µg/cm^2/h (at 5% concentration), suggesting the possibility of developing a transdermal delivery system (Kanwischer et al., 2005). Israel et al. (2012) reported flux values for the permeation of novel N-N-Acetyl-GlcN mutual pro-drugs through shed snakeskin in

[3] In Norway the mpa has approved 13 different glucosamin preparations (Legemiddelverket [online]). Up till 2008 the Norwegian Medicinal products Agency could upon application not derogate from classification regulation and so allow glucosamine be allowed in other products that medicinal products. This regime has been abandoned since 2008.

[4] U.S.: Glucosamine and its metabolites are not classified as drugs but as nutraceutical/dietary supplements under FDA's Dietary Supplement Health and Education Act of 1994 (DSHEA).

	phosphate buffer (PBS) and PBS-10% ethanol. The results showed fluxes in the range of 5.6 – 85.1 µg/cm^2/h, with acetyl-GlcN-ketoprofen being the most likely candidate for transdermal delivery. Negligible permeability was observed from neat saturated solutions of N-Acetyl-GlcN in known membrane permeation enhancers (ethanol, oleic acid, isopropyl myristate and isopropyl palmitate), using shed snakeskin as a model membrane to human skin. Similar poor results were observed from saturated solutions of N-Acetyl-GlcN in water and phosphate buffer (Garner et al., 2007). However, excellent permeation was demonstrated from saturated solutions of N-Acetyl-GlcN in DMSO and phosphate buffer solutions containing 5 - 25% ethanol as delivery vehicle enhancer. Hence, Garner et al.(2007) concluded that ethanol seems so far to be the best choice as a carrier/enhancer for topical applications of GlcN in humans; i.e. DMSO is not approved for human use in topical or transdermal pharmaceutical products (by FDA). *This demonstrates the proof of principle for the possibility of developing glucosamine salts into a transdermal delivery system.*
GI tractus	*Bioavailability of oral glucosamine:* GlcN is usually taken orally, and although it is effectively absorbed in humans (90%), only 26% bioavailability (orally *vs*. intravenously administered GlcN) indicates that a significant fraction undergoes first-pass metabolism in the liver (review in Anderson et al., 2005; GlcN.HCl Dossier 2006 [online]). Other human and animal studies have reported bioavailability of *oral* GlcN in the range of 19 - 44% (Kanwischer et al., 2005; Miller & Clegg, 2011; Ibrahim et al, 2012; Anderson et al., 2005). *Oral* administration of GlcN, its salts, and N-Acetyl-GlcN are affected by the liver's first-pass metabolism (Setnikar et al, 1986, cited in Garner et al., 2007). It has been reported that these substances are metabolized largely in the gut rather than in the liver (Aghazadeh-Habashi et al 2002, cited in Garner et al. 2007; Aghazadeh-Habashi et al 2006; Simon et al., 2011). A recent study reported that the low glutamine bioavailability in rat was caused, at least partly, by the intestinal micro flora that is efficient in clearing GlcN; antibiotic treatment eradicating the flora abolished the clearing effect (Ibrahim et al., 2012). Thus, the limited oral bioavailability of GlcN over a large dose range (1000–7540 mg) is due to its exclusion by the gut and indicates that the liver is not exposed to high concentrations of GlcN in portal venous blood even when consumed at several times the typical amount (Simon et al., 2011).
Distribution **Metabolism** **Excretion**	The metabolism of GlcN is described in (GlcN.HCl Dossier 2006 [online]). GlcN and its orally delivered salt forms are metabolized to N-Acetyl-GlcN via the hexamine pathway. GlcN or galactosamine plus uronic acid are components of glycosaminoglycans (GAG), which are highly negatively charged molecules linked to proteins to form proteoglycans – basic components of skin, tissue and cartilage (Garner et al., 2007). *Pharmacokinetics*:

	Most *in vitro* studies of GlcN activity on joint tissue have been performed in the 50 – 5000 µM range, although a few have been done at as low as 1 µM (Block et al., 2010). However, pharmacokinetic studies in humans have shown that the *Cmax*[5] *(between 1 and 4 h) after ingestion of recommended GlcN dosing (1500 mg) is remarkably consistent, at approximately 10 µM*. E.g. a single oral dose of GlcN.sulfate given to normal volunteers at 20 mg/kg, which equals a single 1500 mg dose in a 75 kg individual, resulted in very similar Cmax values (mostly determined by mass spectroscopy) at 12, 9, 10 and 11 µM in 4 independent studies (Block et al., 2010). Thus, the high concentrations of GlcN that appears to be active *in vitro* and in animal experiments markedly exceed those used in humans[6], are *not necessarily clinically relevant* to the action of the drug in the post-hepatic metabolism *in vivo* (Block et al., 2010). Very few pharmacokinetic studies exist on the disposition of these agents in articular cartilage. It is estimated that whereas 87% of the original oral dose of *GlcN* is absorbed and excreted, less than 13% is widely distributed in the body. Although GlcN is easily incorporated by chondrocytes into the extracellular matrix – during a period of at least four hours after oral ingestion – it has been estimated that much less than 1% reaches osteoarthritic joints (Garner et al., 2007). GlcN.sulfate is first converted into D-Glucosamine and sulfate ion. More than 50% of D-Glucosamine is non-ionized at the pH in the small intestine, thus glucosamine absorption becomes very fast; about 90% is absorbed from the intestine, and the plasma half-life is 2- 3 hrs. Importantly, once ingested, either GlcN salt form (HCl or sulfate) dissociates and is absorbed as GlcN. Thus, in pharmacokinetic studies, only the GlcN is measured in the serum. Cellular uptake of GlcN is influenced by glucose (Block et al., 2010).
Local toxic effects Irritation Sensitivity	No particular skin and subcutaneous tissue disorders related to the use GlcN have been reported. Rash, itching and flushing is uncommon; ≥ 1/1000 and < 1/100 (Lekemedelsverket [online]) .
Systemic toxic effects	The toxicology of GlcN and its safety in humans has been reviewed by Anderson et al. (2005), Hathcock & Shao (2007), GlcN.HCl Dossier 2006 [online], and Clegg et al. (2006). *None of the clinical trials found adverse effects related to GlcN administration, and therefore, no basis for identifying a LOAEL (or NOAEL).* An alternative method, the "observed safe level (OSL) procedure", was used to identified 2000 mg GlcN (hydrochloride or sulfate salt forms) as the safe upper level (ULS) for supplements (Hathcock & Shao, 2007).

[5] The maximum concentration (Cmax) in human plasma occurs at the time Tmax.

[6] Some of the reported in vitro effects are with extracellular concentrations in the millimolar (mM) range, which are 100 – 1000 fold higher than extracellular concentrations achieved in vivo in joint fluid and tissues (Block et al., 2010).

Acute	GlcN has low acute toxicity. *Oral* administration of GlcN at very large doses (5000 – 15000 mg/kg bw) is well tolerated and is without documented toxicity (Anderson et al., 2005). The acute oral LD50 of GlcN.HCl is greater than 5000 mg/kg.
Repeated dose	Dietary studies in which rats ingested GlcN.sulfate at 2700 mg/kg bw for 52 weeks and dogs ingested 2149 mg/kg bw for 26 weeks, showed no treatment-related adverse effects in either species. Hence, the no adverse effects levels (NOAEL) is 2700 mg/kg bw in rats and 2149 mg/kg bw in dogs (Setnikar et al. 1991, cited in Anderson et al., 2005). A single dose of GlcN.HCl (5000 mg/kg bw) was administered orally to 5 male and 5 female rats over a period of 14 days without any signs of toxic effects. Hence, the NOEL value is 5000 mg/kg bw for GlcN.HCl in rats (Glaza et al. 2002, cited in the GlcN.HCl Dossier 2006 [online]). A number of other studies in various species (rats, dogs, rabbits, and horses) have been conducted to determine the potential adverse effects of repeated oral administration of GlcN over extended time (reviewed in Anderson et al., 2005). E.g. Echard et al. (2001) compared the effects of oral GlcN.HCl administration in relation to the consumption of a baseline diet in 8 male spontaneously hypertensitive rats (SHR) and 8 Sprague-Dawley rats over a period of 9 weeks (cited in Anderson et al., 2005; GlcN.HCl Dossier 2006). Rats were fed 0.5% w/w GlcN.HCl in the diet, which equates to ca. 300 mg/kg bw (estimated to be 10 – 20 times the usual human dose). The authors reported no consistent effects on blood chemical parameters and organ histology, and concluded that oral GlcN appears to be well tolerated and non-toxic under the given study conditions. *Cf. Table 1 in Anderson et al. (2005) and Table XIII.2.2.2-1 in GlcN.HCl Dossier 2006 [online] for more detail and a summary of subchronic / chronic and acute toxicity studies.*
Mutagenicity / genotoxicity	There are no indications that GlcN is mutagenic or genotoxic, based on both *in vitro* and *in vivo* tests (GlcN.HCl Dossier 2006 [online]).
Carcinogenicity	
Reprotoxicity / teratogenicity	
Other effects	Allergic warnings required only for products including GlcN of shell fish origin (Hathcock & Shao, 2012). It is strongly advised that GlcN is not taken together with coumarin anti-coagulants (see adverse effects, section 6).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	None of the clinical trials found adverse effects related to oral glucosamine administration. Hence, there is, by definition, no basis for identifying a LOAEL (or NOAEL) (Hathcock & Shao, 2007). The safety as well as the metabolism and metabolic effects of GlcN

	have been reviewed in detail (Anderson et al., 2005; Hathcock & Shao, 2007; Block et al., 2010; see also section 4, above). Based on animal experiments, the no-adverse effect levels (NOAEL) of GlcN.sulfate is 2700 mg/kg bw in rats and 2149 mg/kg bw in dogs. Assuming a 60 kg adult body weight, the 1500 mg daily dose in humans amounts to 25 mg/kg, and the 2000 mg dose equals 33 mg/kg. Extrapolating toxicological animal data suggest that adverse effects of GlcN are unlikely in humans. For the purpose of estimating safety margins for GlcN in cosmetic products: using the lowest NOAEL value (2149 mg/kg), with a bioavailability of 20%, the operational NOAEL value[7] is set at 2149 x 0.20 = **430 mg/kg bw**.
Exposure cosmetic products	The exposure calculations[8] below are based on default values according to Colipa (SCCS [online]). A concentration of 10% GlcN.sulfate is claimed (by the marketer) to be higher than any other topical GlcN.sulfate product available in the market (Annex 2). This is largely confirmed by our internet survey and searches in cosmetic product databases (EWG Skin Deep [online]; codecheck.info [online]). Thus, systemic exposure dose (SED) was estimated for the most relevant cosmetic product types according to Colipa data (SCCS [online]), using 10% GlcN as an illustrative example: • **Body lotion** *according to Colipa data (SCCS [online])*: 10% GlcN.sulfate (cream, body lotion) Calculated relative daily exposure of product: 123.20 mg/kg bw/day Concentration of ingredient in the product: 10% = 0.1 Dermal absorption (SCCS default value): 100% = 1.0 SED = A (mg/kg bw/day) x C(%)/100 x DAp (%)/100 = 123.20 mg/kg bw/day x 0.1 x 1.0 = **12.32 mg/kg bw/day** • **Legs** *according to Colipa data (SCCS [online]):* 10% GlcN.sulfate (cream, both legs) Calculated relative daily exposure of product: 123.20 mg/kg bw/day * 5530 cm^2/15670 cm^2 = 43.5 mg/kg bw/day Concentration of ingredient in the product: 10% = 0.1 Dermal absorption (SCCS default value): 100% = 1.0 SED = A (mg/kg bw/day) x C(%)/100 x DAp (%)/100 = 43.5 mg/kg bw/day x 0.1 x 1.0 = **4.35 mg/kg bw/day** • **Face** *according to Colipa data (SCCS [online]):*

[7] For a 60 kg person, this equals 430 * 60 = 25800 mg /day - approx. 17 times the usual daily human dose; i.e. 1500 mg /day.

[8] A worst case scenario has been estimated using a dermal absorption rate of 13.27 µg/cm^2/h of GlcN.sulfate (5%) in aqueous solution, based on a rat skin permeation study (Kanwischer et al, 2005) (See Annex 3). The assumptions are made that the rat skin permeation rate is the same for glucosamine sulfate at 5% and 10 % concentrations, and that absorption of glucosamine and its salt forms (e.g. sulfate) is equivalent. It was noted that this calculation is most likely an overestimation, but has to be considered?

	10% GlcN.sulfate (cream, face) Calculated relative daily exposure of product: 24.14 mg/kg bw/day Concentration of ingredient in the product: 10% = 0.1 Dermal absorption (SCCS default value): 100% = 1.0 SED = A (mg/kg bw/day) x C(%)/100 x DAp (%)/100 = 24.14 mg/kg bw/day x 0.1 x 1.0 = **2.41 mg/kg bw/day** *Overall SED* (=body lotion + face cream): 12.32 + 2.41 = 14.73 mg/kg bw/day
Margin of Safety (MoS)	MoS (NOAEL/SED): **MoS for body lotion**: SED = 12.32 mg/kg bw/day MoS = 430 /12.32 = **35.0** **MoS for leg cream**: SED = 4.35 mg/kg bw/day MoS = 430 /4.35 = **99.0** **MoS for face cream**: SED = 2.41 mg/kg bw/day MoS = 430 /2.41 = **178.0** MoS (overall exposure from cosmetics): SED = 14.73 mg/kg bw/day MoS = 430 /14.7 = **29.2**

6. Other sources of exposure than cosmetic products

Food and supplements	GlcN.sulfate is the oral form of GlcN most tested and used as oral supplement – capsules containing 1500 mg GlcN.sulfate (equivalent to 1190 mg glutamine base). See also Regenasure Glucosamine functional beverages[9].
Pharmaceuticals	One dose packages contain 1178 mg of the active ingredient GlcN (i.e. 1884 mg GlcN.sulfate /sodium chloride corresponding to 1500 mg GlcN.sulfate).
Other sources	
Adverse side effects – from uses other than cosmetics	None of the clinical trials or systematic reviews have found significant adverse effects related to recommended doses of oral GlcN administration (Miller & Clegg, 2011; Hathcock & Shao, 2007; Wandel et al., 2010). However, EFSA recently confirmed previous BfR risk assessments from 2007 and 2010 that glucosamine may represent a health risk for patients taking coumarin anticoagulants (BfR 2012 [online]). For more details, see below. • ***Anti-coagulants*** A case report published in 2008 reported a potential GlcN – chondroitin sulfate and warfarin interaction in a patient, resulting in an increased international normalized ratio (INR) (Knudsen & Sokol,

[9] http://www.cargill.com/food/wcm/groups/public/@cseg/@food/@all/documents/document/na3056453.pdf

	2008). This prompted further searches for increased INR in patients taking GlcN supplements, identifying altogether 43 cases. In the majority of cases the increases were symptomless changes in lab values, in some cases with hemorrhages in various organs, and in one case with the consequence of a severe cerebral haemorrhage (REF). GlcN is contraindicated in individuals with active bleeding (e.g, peptic ulcer, intracranial bleeding). It should be used with caution in individuals taking anticoagulant medications, including warfarin, aspirin, aspirin-containing products, and NSAIDs (UpToDate [online]). See also Annex 4. Norwegian Medicines Handbook states that GlcN in combination with warfarin results in increased INR and increased risk for bleeding, often with INR increases in the range of 4–12 (Norsk legemiddelhåndbok [online]). In light of the potential risk of bleeding associated with increased INR, *several authorities urge patients not to take GlcN if they are taking warfarin (Coumadin).* • ***Antibiotics*** GlcN can affect the effectiveness of some antibiotics; it can strengthen the effect of tetracycline and lessen the effect of penicillin and chloramphenicol. (GlcN.com [online]). • ***Others*** *GlcN and insulin resistance*: Whereas an association between increased intracellular GlcN levels and insulin resistance has been observed in animal studies, no significant differences have been found in humans (reviewed in Miller & Clegg, 2011; Block et al., 2010; Legemiddelverket [online]; Annex 4). *GlcN and chemotherapy:* Moderate to minor interaction of GlcN in combination with antimitotic chemotherapy drugs have been reported, but the clinical relevance has not been established (Annex 4).

7. Assessment

GlcN is widely used both in Europe and the US to ease pain and disability of knee osteoarthritis (without curing the underlying disease), perhaps by working as a NSAID. It has also gained interest in fitness and athletics communities because of (unproven) claims that it has cartilage building and lubricant properties for joints. Although there is controversy regarding its clinical efficacy, *none of the clinical trials have found adverse effects related to GlcN administration, and therefore, there is no basis for identifying a LOAEL (or NOAEL).*

General toxicity
Studies examining the potential toxicity of GlcN in various animal species (e.g. rats, dogs, mice rabbits, and horses), as well as clinical trials and systematic reviews, have indicated that GlcN is safe at recommended use levels and conditions (Anderson et al., 2005; GlcN.HCl dossier 2006 [online];Miller & Clegg, 2011).

Most animal and in vitro studies have used supra-physiological concentrations of GlcN (50 – 500 µM), which greatly exceeds the observed peak plasma concentration (Cmax) of 10 µM (range 2.7 – 17.4 µM) after clinically relevant GlcN doses of 1500 mg/day in human studies (Miller & Clegg, 2011; Ibrahim et al., 2012). Thus, the many observations obtained from animals infused with GlcN, and following the exposure of cells to high concentrations (µM rather than mM range) of GlcN in culture, must be interpreted with caution (Simon et al., 2011). Further studies should focus on investigating effects in experimental systems at clinically relevant doses of GlcN (Block et al., 2010).

Based on sub-chronic and chronic animal studies, the no-adverse effect levels (NOAEL)[10] of GlcN.sulfate is 2700 mg/kg bw in rats and 2149 mg/kg bw in dogs (Anderson et al., 2005; GlcN.HCl dossier 2006 [online]; Lekemedelsverket [online]). Assuming a 60 kg body weight of an adult person, the recommended 1500 mg daily dose of GlcN amounts to 25 mg/kg, whereas the 2000 mg dose equals 33 mg/kg. Hence, extrapolating toxicological animal data suggest that adverse effects of GlcN are unlikely in humans.

Cosmetics
Systemic exposure dose (SED) was calculated for various cosmetic product categories, using 10% GlcN.sulfate as an illustrative example. A wide range of exposure levels were taken into consideration, e.g. body lotion (large body surface, 15670 cm^2), sports cream (e.g. legs - medium body surface, 5530 cm^2), and face cream (small body surface, 565 cm^2).

In the margin of safety calculations we used a NOAEL value of 430 mg/kg/day (no observed adverse effect at the highest level of GlcN examined), resulting in MoS values of:

MoS (body cream): 430 /12.32 = 35.0
MoS (leg cream): 430 /4.35 = 99.0
MoS (face cream): 430 /2.41 = 178.0

MoS (overall exposure from cosmetics): 430 /14.73 = 29.2

Because the NOAEL is based on animal data, a MoS of 100 (or more) represents a sufficient safety margin. Thus, use levels up to 10% would be acceptable for cosmetic products covering small to medium body surface areas (e.g. legs, knees and elbows), whereas products aimed at the total body would exceed the safety margin.

Food supplements
Legally, food supplements are defined as food. The principal sources of human exposure to GlcN products occur from the ingestion of dietary supplements and sports beverages (NTP [online]), with typical use levels of 1275 mg/person /day. This equals a SED of approx. 20 mg/kg bw/day, which is higher than exposure from 10% GlcN cream covering the whole body (SED = 12.4 mg/kg bw/day).

[10] No adverse observed effect at even the highest concentration

GlcN in food supplements is present in quantities that are probably too low to have similar pharmacological effects as those reported in animal and in vitro systems (Block et al., 2010; Simon et al., 2011). There is no evidence for negative long-term health effects of GlcN ingested as dietary supplement; cf. GRAS (Generally Regarded As Safe) status for Cargill's Regenasure (Regenasure GlcN [online]).

Medicinal products
One dose packages contain 1178 mg of the active ingredient GlcN; i.e. 1884 mg GlcN.sulfate /sodium chloride corresponding to 1500 mg GlcN.sulfate (Legemiddelverket [online]).

Total exposure
Regulations and labeling of GlcN vary from country to country. Regardless of whether GlcN is marketed for use in dietary supplements, cosmetic products, or a OTC drug, the substance in most cases is used for the same purpose (e.g. relief of arthritic complaints). Thus, it can be questioned whether cumulative exposure levels from all sources (supplements, cosmetic products, and OTC drugs) would represent a realistic scenario in the risk assessment of GlcN.

Risk groups[11]:
BfR has already assessed the health risks associated with GlcN in food supplements in an opinion (BfR, 2007) and identified three risk groups in a BfR opinion from 2010:

(i) Diabetics and/or individuals. Current evidence from clinical studies suggests that oral glucosamine has no adverse effects on glucose metabolism in normal and diabetic individuals (Simon et al., 2011; Anderson et al., 2005). The issue was raised years ago as animal studies have shown an association between increased intracellular GlcN and insulin resistance (cited in Miller and Clegg, 2011). This may be related to supra-physiological doses used in animal and in vitro experiments.

(ii) Patients with a known risk for cardiovascular disease (BfR, 2010): Monitoring of blood lipid levels has previously been recommended, since hypercholersterolemia has been noticed in a few cases in patients treated with GlcN. However, there are no health concerns that require any notice on the health risk for this consumer group in light of new knowledge (See also Legemiddelverket [online][12]).

(iii) Persons taking blood coagulation inhibitors (i.e. Coumarin anticoagulants (BfR, 2012):
The European Food Safety Authority (EFSA) has recently (November 25, 2011) confirmed that GlcN can pose health risks to those taking anti-blood clotting drugs, after the issue was raised some years ago by German authorities (EFSA [online], BfR, 2012; Nutraingredients [online]). EFSA's NDA panel concluded there was risk albeit inconclusive, stating:

> *However, data are lacking to establish a dose-response relationship and there is insufficient information to conclude on a mechanism for an interaction between glucosamine and warfarin.*
> *Main conclusions: Although the level of risk cannot be ascertained due to insufficient data, the EFSA concludes there is a risk of interaction between glucosamine and coumarin anticoagulants in some individuals which can lead to further haemorrhage.*

Interaction with antibiotics:
GlcN can affect the effectiveness of some antibiotics; it can strengthen the effect of tetracycline and lessen the effect of penicillin and chloramphenicol, but the clinical relevance of this interaction is thought to be limited (Glucosamine.com [online]; Lekemedelsverket [online]).

[11] GlcN products are not associated with adverse effects, even after long term use. Previous reports that cholesterol is increased in response to GlcN are not confirmed in later studies. A Cochrane review concludes that the safety of GlcN is similar to placebo (Towheed TE et al. (2007) Glucosamine therapy for treating osteoarthritis. Cochrane Libarary 2007; 1. http://www.legemiddelverket.no/templates/InterPage____53492.aspx
[12] http://www.legemiddelverket.no/templates/InterPage____28563.aspx

8. Conclusion

When only cosmetic products are considered, no adverse effects of GlcN such as skin allergy or irritations have been reported. Furthermore, n*one of the clinical trials found adverse effects related to GlcN administration, and therefore, no basis for identifying a LOAEL (or NOAEL).*

GlcN is safe in cosmetic products at the usage levels and conditions specified below, in compliance with the requirement that MoS must be greater than 100 (some data based on animal studies). Furthermore, the derived NOAEL takes into account an assumed oral bioavailability[13] of 20% and a default value of 100% dermal absorption (cf. SCCS guidelines).

Maximum use levels:
Face cream: (10 x 178) /100 =18%
Leg cream: (10 x 99) /100 = 10%
Body lotion: (10 x 35) /100 = 3.5%

The total use level of GlcN in cosmetic products should not exceed: (10 x 29.2) / 100 = 3 %

Remarks:
Additional safety measure in the form of a warning in the label seem necessary

- Must not be used by person allergic to shellfish

[13] For discussion of oral bioavailability, see Simon et al., 2011.

9. References

Aghazadeh-Habashi A, Jamali F. The glucosamine controversy; a pharmacokinetic issue. J Pharm Pharm Sci. 2011;14(2):264-73. Review. PubMed PMID: 21733414.

Aghazadeh-Habashi A, Ibrahim A, Carran J, Anastassiades T, Jamali F. Single dose pharmacokinetics and bioavailability of butyryl glucosamine in the rat. J Pharm Pharm Sci. 2006;9(3):359-64. PubMed PMID: 17207418.

Black C, Clar C, Henderson R, MacEachern C, McNamee P, Quayyum Z, Royle P, Thomas S. The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation. Health Technol Assess. 2009 Nov;13(52):1-148. Review. PubMed PMID: 19903416.

Block JA, Oegema TR, Sandy JD, Plaas A. The effects of oral glucosamine on joint health: is a change in research approach needed? Osteoarthritis Cartilage. 2010 Jan;18(1):5-11. Epub 2009 Sep 1. Review. PubMed PMID: 19733270

Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, Bradley JD, Bingham CO 3rd, Weisman MH, Jackson CG, Lane NE, Cush JJ, Moreland LW, Schumacher HR Jr, Oddis CV, Wolfe F, Molitor JA, Yocum DE, Schnitzer TJ, Furst DE, Sawitzke AD, Shi H, Brandt KD, Moskowitz RW, Williams HJ. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808. PubMed PMID: 16495392.

EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal **2012**;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665. Available at: www.efsa.europa.eu/efsajournal.htm

Garner ST Jr, Israel BJ, Achmed H, Capomacchia AC, Abney T, Azadi P. Transdermal permeability of N-acetyl-D-glucosamine. Pharm Dev Technol. 2007;12(2):169-74. PubMed PMID: 17510888.

Gregory PJ, Sperry M, Wilson AF (2008) Dietary Supplements for Osteoarthritis. Am Fam Physician 77:177-184.

Hathcock JN, Shao A. Risk assessment for glucosamine and chondroitin sulfate. Regul Toxicol Pharmacol. 2007 Feb;47(1):78-83. Epub 2006 Aug 30. Review. PubMed PMID: 16942821.

Ibrahim A, Gilzad-Kohan MH, Aghazadeh-Habashi A, Jamali F. Absorption and bioavailability of glucosamine in the rat. J Pharm Sci. 2012 Apr 4. doi:10.1002/jps.23145. [Epub ahead of print] PubMed PMID: 22488120.

Israel B, Garner ST, Thakare M, Elder D, Abney T, Azadi P, Beach JW, Price JC, Ahmed H, Capomacchia AC. Transdermal permeation of novel n-acetyl-glucosamine/NSAIDs mutual prodrugs. Pharm Dev Technol. 2012 Jan-Feb;17(1):48-54. Epub 2010 Sep 21. PubMed PMID: 20858066.

Kanwischer M, Kim SY, Kim JS, Bian S, Kwon KA, Kim DD. Evaluation of the physicochemical stability and skin permeation of glucosamine sulfate. Drug Dev Ind Pharm. 2005 Jan;31(1):91-7. PubMed PMID: 15704860.

Knudsen JF, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: case report and review of the literature and MedWatch database. Pharmacotherapy. 2008 Apr;28(4):540-8. Review. PubMed PMID: 18363538.

McAlindon T. Why are clinical trials of glucosamine no longer uniformly positive? Rheum Dis Clin North Am. 2003 Nov;29(4):789-801. Review. PubMed PMID:14603583.

Miller KL, Clegg DO. Glucosamine and chondroitin sulfate. Rheum Dis Clin North Am. 2011 Feb;37(1):103-18. Epub 2010 Dec 4. Review. PubMed PMID: 21220090.

Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ. 2010 Sep 16;341:c4675. doi: 10.1136/bmj.c4675. Review. PubMed PMID: 20847017; PubMed Central PMCID: PMC2941572.

Usha PR and Naidu MU, "Randomised, Double-Blind, Parallel, Placebo-Controlled Study of Oral Glucosamine, Methylsulfonylmethane and Their Combination in Osteoarthritis," Clin Drug Investig, 2004, 24(6):353-63. [PubMed 17516722]

Sawitzke AD, Shi H, Finco MF, Dunlop DD, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE, Bingham CO, Reda DJ, Moskowitz RW, Williams HJ, Clegg DO. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. Ann Rheum Dis. 2010 Aug;69(8):1459-64. Epub 2010 Jun 4. PubMed PMID: 20525840; PubMed Central PMCID: PMC3086604.

Simon, R. R., Marks, V., Leeds, A. R. and Anderson, J. W. (2011), A comprehensive review of oral glucosamine use and effects on glucose metabolism in normal and diabetic individuals. Diabetes Metab. Res. Rev., 27: 14–27. doi: 10.1002/dmrr.1150. *Simon is an employee of Cantox Health Sciences International, and financial support from Cargill for consulting services has been obtained*

Wilkens P, Scheel IB, Grundnes O, Hellum C, Storheim K. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: a randomized controlled trial. JAMA. 2010 Jul 7;304(1):45-52. PubMed PMID: 20606148.

Online:

BfR 2012. Available at: http://www.bfr.bund.de/en/press_information/2012/07/glucosamine_in_food_supplements__risky_also_for_patients_taking_coumarin_anticoagulants-128855.html (accessed May 16, 2012).

Codecheck.info [online]. Available at: http://www.codecheck.info/product.search?q=glucosamine&OK=Suchen (accessed April 29, 2012).

CosIng, European Commission, Health and Consumers, Cosmetics. Available at: http://ec.europa.eu/consumers/cosmetics/cosing/ (accessed April 29, 2012)

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Statement on the safety of glucosamine for patients receiving coumarin anticoagulants. EFSA Journal 2011;9(12):2473. Available at:

EWG's Skin Deep © Cosmetic Safety Database. Environmental Working Group. Available at: http://www.ewg.org/skindeep/search.php?query=glucosamine (accessed April 29, 2012).

FDA. Available at: http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/GeneralUseofMedicine/UCM229033.pdf (accessed May 4, 2012).

Felleskatalogen. Available at: http://www.felleskatalogen.no/medisin/pasient/pil-donacom-rottapharm-548102 (accessed May 3, 2012).

Glucosamine.com. Available at: http://www.glucosamine.com/eu/glucosamine-7 (accessed May 4, 2012).

GlcN.HCl dossier 2006. Cargill. Available at: http://www.food.gov.uk/multimedia/pdfs/glucosamineappdossier.pdf (accessed May 8, 2012).

Hotfrog. Available at: http://www.hotfrog.in/Companies/Green-Plus-Healthcare/Antibacterial-Antibiotics-Anti-inflammatory-and-analgesic-Anti-histaminic-Antimalerial-Generic-formulations-Pharmaceuticals-295471 (accessed May 8, 2012).

Legemiddelhåndboka. Available at: http://legemiddelhandboka.no/Generelle/s%C3%B8ker/glukosamin/111423#i112038 (accessed May 3, 2012).

Legemiddelverket. Available at: http://www.legemiddelverket.no/templates/InterPage____53492.aspx (accessed May 18, 2012).

Lekemedelsverket. Glucosamine Navamedic tablet ENG. Available at: http://www.lakemedelsverket.se/SPC_PIL/Pdf/enhumspc/Glucosamine%20Navamedic%20tablet%20ENG.pdf

Mayoclinic. Available at: http://www.mayoclinic.com/health/glucosamine/NS_patient-glucosamine/DSECTION=evidence (accessed April 27, 2012)

NTP (2002). NIEHS, NIH gov. Prepared for NCI by Technical Resources International, Inc. to support nomination under contract no. N02-CB-07007 (CSWG:05/02; NTP: 9/02. Available at: http://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/glucosamine.pdf (accessed May 2, 2012).

Nutraingredients. Glucosamine to be re-assessed by Danish Medicines Agency. Available at: http://www.nutraingredients.com/Industry/Glucosamine-to-be-re-assessed-by-Danish-Medicines-Agency (accessed May 14, 2012).

Regenasure glucosamine. Available at: http://www.cargill.com/food/na/en/products/health-promoting-ingredients/regenasure-glucosamine/about-regenasure-glucosamine/GRAS/index.jsp (accessed May 15, 2012).

SCCS. The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation. 7th revision. Available at: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_004.pdf (accessed May 15, 2012).

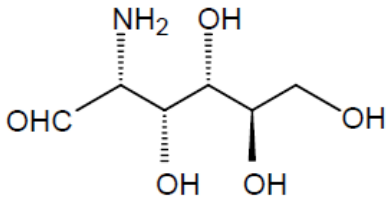
UpToDate. Available at: http://www.uptodate.com/contents/glucosamine-sulfate-natural-drug-information (accessed May 3, 2012)

Webmd. Available at: http://www.webmd.com/vitamins-supplements/ingredientmono-807-GLUCOSAMINE%20SULFATE.aspx?activeIngredientId=807&activeIngredientName=GLUCOSAMINE%20SULFATE (accessed April 27, 2012)

10. Annexes

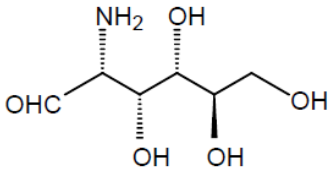
Annex I: Glucosamine and variants

- **Glucosamine:**



$C_6H_{13}NO_5$ Mol. wt.: 179.17

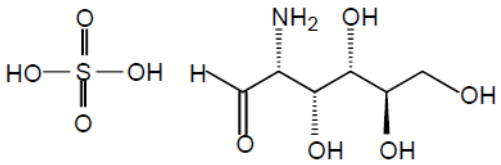
- **Glucosamine • HCl**:



• HCl

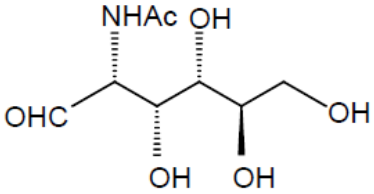
$C_6H_{13}NO_5 \cong HCl$ Mol. wt: 215.63

- **GlcN.sulfate:**



$C_6H_{13}NO_5xH_2SO_4$ Mol. wt.: 277.24

- **N-Acetyl-glucosamine**:



$C_8H_{15}NO_6$ Mol. Wt.: 221.21

Annex 3: Exposure assessment

The exposure calculations below are based on (a) default values according to Colipa and (b) a dermal absorption rate of 13.27 µg/cm^2/h of GlcN.sulfate (5%) in aqueous solution, based on a rat skin permeation study (Kanwischer et al, 2005)[14].

A concentration of 10% GlcN.sulfate is claimed (by the marketer) to be higher than any other topical GlcN.sulfate product available in the market.

The systemic exposure dose (SED) according to Colipa data (SCCS [online]), using 10% GlcN as an illustrative example, is presented in section 4 above and included here as a point of reference.

Body lotion
(a) according to Colipa data (SCCS [online]):
10% GlcN.sulfate (cream, body lotion)
Calculated relative daily exposure of product: 123.20 mg/kg bw/day
Concentration of ingredient in the product: 10% = 0.1
Dermal absorption (SCCS default value): 100% = 1

SED = A (mg/kg bw/day) x C(%)/100 x DAp (%)/100
= 123.20 mg/kg bw/day x 0.1 x 1 = **12.32 mg/kg bw/day**

This results in a systemic availability of:
740 mg/day (women, 60 kg) and
912 mg/day (men, 74 kg).

(b) using actual dermal absorption rate (from animal studies):
- Dermal absorption rate:13.27 µg/cm^2/h
- Area of body (- area head): 15670 cm^2
- Frequency of application: 2.28
- Dermal absorption corresponding to area of body (- area head) during a period of 24h[15]:
13.27 µg/cm^2/h * 15670 cm^2 * 24h * 2.28 = 11377 mg/day.

SED (body, women): 4990/60 = **189.6 mg/kg bw/day**
SED (body, men): 4990/74 = **153.7 mg/kg bw/day**

- **Legs**

(a) according to Colipa data (SCCS [online]):
10% GlcN.sulfate (cream, both legs)
Calculated relative daily exposure of product:
123.20 mg/kg bw/day * 5530 cm^2/15670 cm^2 = 43.5 mg/kg bw/day
Concentration of ingredient in the product: 10% = 0.1
Dermal absorption (SCCS default value): 100% = 1

SED = A (mg/kg bw/day) x C(%)/100 x DAp (%)/100
= 43.5 mg/kg bw/day x 0.1 x 1 = **4.35 mg/kg bw/day**

I.e. systemic availability of:
260 mg/day (women, 60 kg) and
322 mg/day (men, 74 kg).

[14] For the assessment we are making the assumption that the rat skin permeation profile of glucosamine sulfate (5%) in aqueous solution is the same for 10% glucosamine sulfate. Furthermore, absorption of glucosamine sulfate and glucosamine is considered to be equivalent.
[15] The presumption that glucosamine is absorbed to the same extent when applied once over a period of 24h is most likely very conservative.

(b) using actual dermal absorption rate (from animal studies):
Dermal absorption rate: 13.27 µg/cm^2/h
Area of legs (5530 cm^2):
Frequency of application: 2
Dermal absorption corresponding to area of legs during a period of 24h:
13.27 µg/cm^2/h * 5530 cm^2 *24h * 2 = 3522 mg/day.

SED (legs, women): 3522/60 = **58.7 mg/kg bw/day**
SED (legs, men): 3522/74 = **47.6 mg/kg bw/day**

- **Face**

(a) according to Colipa data (SCCS [online]):

10% GlcN.sulfate (cream, face)
Calculated relative daily exposure of product: 24.14 mg/kg bw/day
Concentration of ingredient in the product: 10% = 0.1
Dermal absorption (SCCS default value): 100% = 1

SED = A (mg/kg bw/day) x C(%)/100 x DAp (%)/100
= 24.14 mg/kg bw/day x 0.1 x 1 = **2.41 mg/kg bw/day**

The resuls in a systemic availability of:
145 mg/day (women, 60 kg) and
178 mg/day (men, 74 kg).

(b) using actual dermal absorption rate (from animal studies):
Dermal absorption rate: 13.27 µg/cm^2/h
Area of face (565 cm^2):
Frequency of application: 2.14
Dermal absorption corresponding to area of face during a period of 24h:
13.27 µg/cm^2/h * 565 cm^2 * 24 * 2.14= 385.1 mg/day.

SED (face, women): 385/60 = **6.4 mg/kg bw/day**
SED (face, men): 385/74 = **5.2 mg/kg bw/day**

(a) Overall SED (=body lotion + face cream): 12.32 + 2.41 = 14.73 mg/kg bw/day
(b) Overall SED (= body lotion + face cream): 189.6 + 6.4 = 196 mg/kg bw/day

Annex 4:

Warnings and Interactions

Toxicity:
No known toxicity or serious side effects reported

Contraindications:
Contraindicated in individuals with active bleeding (eg, peptic ulcer, intracranial bleeding).
Use with caution in individuals with a history of bleeding, hemostatic disorders, or drug-related hemostatic problems. Use with caution in individuals taking anticoagulant medications, including warfarin, aspirin, aspirin-containing products, NSAIDs, or antiplatelet agents (eg, ticlopidine, clopidogrel, dipyridamole). Discontinue use prior to dental or surgical procedures (generally at least 14 days before).

Allergies:
Use with caution in individuals with allergy to shellfish.

Others:
Occasional reports of mild gastrointestinal discomfort or stomach upset. Based on animal studies, may alter glucose regulation/insulin sensitivity; use with caution in individuals with diabetes.

May cause drowsiness, somnolence, or insomnia. Use with caution when driving or operating heavy machinery.

Use with caution in individuals with renal impairment

UpToDate [online]; Helsebiblioteket [online]