

RISK PROFILE

Ibuprofen

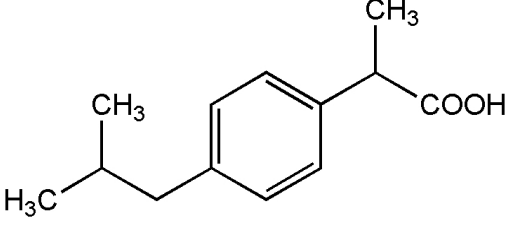
CAS No. 15687-27-1

Date of reporting 14.02.2012

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1. Identification of substance

Chemical name (IUPAC):	2-[4-(2-methylpropyl)phenyl]propanoic acid
INCI	Ibuprofen
Synonyms	
CAS No.	15687-27-1
EINECS No.	239-784-6
Molecular formula	C ₁₃ H ₁₈ O ₂
Chemical structure	
Molecular weight	206.3
Contents (if relevant)	
Physiochemical properties	Appearance: Colourless, solid crystalline substance Boiling point: 212-251°C Melting point: 75-77°C Log P _{ow} : 3.97

	<p>Vapor pressure: 4.74E-05 mmHg at 25°C Solubility (water): 21 mg/L at 25 °C</p> <p>References: (Council of Europe, 2008; PubChem Compound [online]; Lerdkanchanapom et al., 1997).</p>
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2. Uses and origin

Uses	<p>➤ Cosmetic products: Ibuprofen is used in sport massage products in some countries.</p> <p>Functions according to</p> <ul style="list-style-type: none"> ○ <i>CosIng database</i> "Skin conditioner" - Maintains the skin in good condition (CosIng [online]). <p><i>Frequency of use</i> No cosmetic products found at EWG's Skin, an online database provided by the Environmental Working Group, or at Codecheck.info, a German online cosmetic product database (Codecheck [online]; EWG's Skin Deep [online]).</p> <p>In some countries, ibuprofen is used in products for sport massage (Council of Europe, 2008). Provided the claims made concerns only effect on/in skin and there is no mention of any anaesthetic (pain removing) effect or effect on tissue beneath the skin. The sport massage products are considered cosmetic products in Norway.</p> <p><i>Concentrations being applied</i> The concentration of 5 % ibuprofen is commonly used in sport massage balms (Council of Europe, 2008).</p> <p>➤ Medicinal products/applications Ibuprofen is a common nonsteroidal anti-inflammatory drug (NSAIDs) used in the treatment of pain and inflammation available in various dosage forms. For topical treatment it is available as 5 % cream, gel or spray solution for the treatment of local muscle inflammation and pain.</p> <p>➤ Food and drinking water Data not retrieved.</p>
Origin Natural (exo /endo) Synthetic	Synthetic

3. Regulation

Norway	No regulation.
EU	No regulation.
Rest of the world	No regulation.

4. Relevant toxicity studies

Absorption Skin GI tractus	Ibuprofen is absorbed from the gastrointestinal tract, and peak plasma concentrations occur about one to two hours after intake. One study showed that the absorption after topical application is about 5 % of that obtained after orally administration (Council of Europe, 2008). This was confirmed by another study, where there was a 4 % skin penetration after topical application of a 5 % gel formulation. The same study also showed that skin penetration of ibuprofen might be higher, up to 25 % when applied as a spray solution (Hadgraft et al., 2003).
Distribution	Ibuprofen is 90-99% bound to plasma proteins (Council of Europe, 2008).
Metabolism	Ibuprofen is extensively metabolized in the liver, and only 1 % is excreted as the parent compound. Ibuprofen has a half-life of about two hours (Council of Europe, 2008).
Excretion	Ibuprofen is rapidly excreted in the urine (Council of Europe, 2008).
Local toxic effects Irritation Sensitivity	Ibuprofen has been known to cause allergic dermatitis. Local irritation has been reported after topical application of gels and creams. There is no evidence that topical application of ibuprofen can cause phototoxicity or photosensitisation. There is no available data for eye irritation (Council of Europe, 2008).
Systemic toxic effects Acute Repeated dose Mutagenicity /genotoxicity Carcinogenicity Reproductive toxicity / teratogenicity	<p>Toxic doses cause central nervous system depression. Death resulted from perforation of the lower intestine. LD₅₀ mice (oral): 1300 mg/kg bw LD₅₀ mice (intraperitoneally): 600 mg/kg bw LD₅₀ rats (oral): >1200 mg/kg bw (Council of Europe, 2008).</p> <p>Toxic dose for ibuprofen varies. However, there are some indications for the doses that are toxic. 300-400 mg/kg for children has been shown to give moderate to severe poisoning). In adults, 20-30 g has caused severe poisoning, 9 g have caused moderate poisoning, and 6 g have affected the kidneys in patients with risk factors (kidney- and heart-disease, use of ACE-inhibitors or diuretics, and hypotension) (Norwegian Medicines Agency [online]).</p> <p>The NOAEL was observed to be 16 mg/kg bw/day in a 52-week study in primates where ibuprofen was administered orally at 16, 40 and 100 mg/kg bw/day (Council of Europe, 2008).</p> <p>No evidence for mutagenicity/genotoxicity (Council of Europe, 2008).</p> <p>The majority of studies show no carcinogenic activity of ibuprofen (Adams et al., 1969; Adams et al., 1970; Lessel et al., 1976; Lessel et al., 1971). One study showed that feeding of rats with 0, 20, 40, 60 or 120 mg ibuprofen/kg/day in food for two years gave a dose-dependent increase in the induction of gastric lesions and an increase in the number of kidney papillomas at the two highest doses (Lessel, 1975).</p> <p>Ibuprofen is present in low levels (1 % of the concentrations in blood plasma) of breast milk. However, it is known that NSAIDs has a role in the premature closure of fetal ductus arteriosus in utero (Council of Europe, 2008).</p>

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5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	<p>The therapeutic range is 10-40 µg/ml (serum concentration) (Norwegian Medicines Agency [online]). Volume of distribution for ibuprofen is 0.1 L/kg (Wood et al., 2006). This means that with a serum concentration of 10 µg/ml, the total amount of Ibuprofen in the body is 1 mg/kg (see annex for calculation).</p> <p>As pharmaceuticals used in cosmetic products should not exert an anaesthetic effect, it is appropriate to use the lowest effective dose level as LOEL in risk assessment of these bioactive compounds.</p> <p>LOEL: 1 mg/kg bw/day NOEL = LOEL/ 3¹ = 1 mg/kg bw/day / 3 = 0.33 mg/kg bw/day</p>
Exposure cosmetic products	<p>Systemic exposure dose (SED) for ibuprofen in humans:</p> <ul style="list-style-type: none"> • Sport massage balm Frequency of application: 1/day Concentration in product: 5 % = 0.05 Dermal absorption: 5 % = 0.05 Typical body weight of human: 60 kg Skin surface area²: 1611 cm² (see annex for calculation) <p>Amount of product applied: 1mg/cm² (default value, SCCS) x 1611 cm² x 1/day: 1611 mg/day Amount of ingredient: 1611 mg x 0.05 (dermal absorption) x 0.05 (concentration in product) x 1/day = 4 mg</p> <p>Calculation of SED: 4 mg / 60 kg = 0.07 mg/kg bw/day</p>
Margin of Safety (MoS)	<p>NOEL: 0.33 mg/kg bw</p> <p>MoS for ibuprofen in sport massage balm: SED: 0.07 mg/kg bw/day MoS: 0.33/ 0.07 = 5</p>

6. Other sources of exposure than cosmetic products

Food stuffs	Not reported.
Pharmaceuticals	<p>Tablet and mixture preparations of ibuprofen: recommended maximum dose for adults and children over 40 kg depends on the treatment cause; for analgesic effect: 800-1200 mg/day divided on 3-4 doses, anti-inflammatory effect: 2400 mg or more per day. Recommended doses for children less than 40 kg range from 100-200 mg 4 times a day, depending on body weight. Gel-preparations of ibuprofen: recommended maximum dose for adults and children >12 years is 15 g/day (Norsk Legemiddelhåndbok [online]).</p>

¹ When making use of the Lowest Observed (Adverse) Effect Level (LO(A)EL) instead of the NO(A)EL, the SCCS usually takes into consideration an additional factor of 3 in the calculation of the MoS. Scientific Committee on Consumer Safety, The SCCS'S notes of guidance for the testing of cosmetic ingredients and their safety evaluation, the 7th revision, p 54.

² "The rule of nine", often used to calculate burn percentage in adults, have been used to estimate the exposed skin surface area.

Other sources	Data not retrieved.
Adverse side effects - from uses other than cosmetics	<p>Tablets and gel of ibuprofen: there are indications that high daily doses for a prolonged time (e.g. 2400 mg/day), are associated with small increase in risk for arterial thrombosis (such as heart attack or stroke). Longtime-use can also lead to the development of headaches. Gastrointestinal damage is a severe side-effect of ibuprofen-use, which can be fatal. Hypersensitivity has also been observed, and even though it is rare after intake of ibuprofen, it is a possible fatal complication. The use of ibuprofen for persons with reduced kidney function and asthma should be minimized. Ibuprofen is not recommended for women trying to get pregnant, as it can reduce fertility. Also, it should not be used during pregnancy. Breast milk contains only 1 % of the levels present in blood plasma. Thus, breastfeeding while using ibuprofen-preparations is considered to be safe (Norsk Legemiddelhåndbok [online]).</p> <p>Only gel-preparations of ibuprofen: A common side effect (>1/100) of topical application of gel containing ibuprofen are itching and erythema of the skin, a more rare side-effect (<1/1000) is gastrointestinal discomfort as abdominal pain. Ibuprofen exerts several interactions with other drugs and with ethanol (Norsk Legemiddelhåndbok [online]).</p> <p>Ibuprofen may provoke asthma attacks in persons allergic to salicylates and other NSAIDs. Persons who have been sensitized will have increased risk for intense itching and blisters when using cream with ibuprofen (Council of Europe, 2008). Cases of erythema multiforme bullosum and epidermal necrolysis have been reported after intake of ibuprofen (Sternlieb et al., 1980).</p>

7. Assessment

The safety for the use of ibuprofen in cosmetic products has been examined by the Council of Europe (Council of Europe, 2008). It was concluded that there are not sufficient data to warrant any conclusion regarding exposure to ibuprofen from the use of cosmetic products.

Ibuprofen is a common used non-prescription drug for pain and inflammation and is available as tablets and mixtures (200-600 mg), gel, cream and spray (5 %). Ibuprofen has been used extensively in both oral and topical preparations for years with only few reported severe adverse effects. The use of ibuprofen in cosmetics is limited. However, it is used in some sport massage balms in concentrations up to 5 %. There are some aspects that need to be considered when assessing the safety of acetaminophen in cosmetics:

Adverse renal effects can occur at relatively low doses, especially in patients with risk factors.

- i) The potential for hypersensitivity reactions, such as provocation of asthma attacks and skin irritation should be considered. Although, they will probably present a much lower risk regarding the low exposure doses from cosmetics.
- ii) Gastric mucosal damage can occur with topical application of ibuprofen, although less frequent than if ibuprofen is taken orally.
- iii) Ibuprofen can temporarily reduce fertility in women, and is not recommended for use under pregnancy. Therefore the product packaging should display a warning. Note that breastfeeding while using ibuprofen-preparations is considered to be safe.

Due to the concerns listed above, we chose to use the lowest effective drug dose divided by three as a NOEL value. We have estimated the margin of safety (MoS) for one cosmetic product category that contain ibuprofen; sport massage balm. Since the NOEL is based on human data, a MoS of 10 is sufficient as a safety margin.

MoS for sport massage balm = 5 (when usage limit is 5 %)

A MoS of 10 will give these usage limits:

Sport massage balm: 2.5 % (Calculation: $5 \times (5/10) = 1.7$)

A concentration of 5 % for the sport massage balm yields a lower MoS than acceptable – by reducing the concentration in product down to 2.5 % we achieve the required MoS of 10. At a concentration of 2.5 %, and assuming that the sport massage balm is used on eighth of the legs and arms and half the area of hands, the systemic exposure dose for ibuprofen is 0.035 mg/kg bw/day (2.1 mg/day), which is low in comparison with the doses of ibuprofen used as a pharmaceutical (1200 to more than 2400 mg/day). Since we have only identified the use of ibuprofen in sport massage balms, the total exposure (cosmetics and medicinal products) does not yield a toxic dose. We consider that the exposure of ibuprofen from sport massage balms with a concentration of 2.5 %, do not or only to a minimum increase the risk of unwanted effects.

8. Conclusion

We propose the following usage limits for ibuprofen to be 2.5 % in *sport massage balms*, but *prohibited* in all *other cosmetic products*.

In addition, the sport massage balm products should *display a precaution label* concerning three aspects:

- Not to be used by person hypersensitive towards analgesic nonsteroidal antiinflammatory drug (NSAID).
- Risk of temporary reduced fertility
- Not to be used in last trimester of pregnancy

Remark: If ibuprofen is claimed to relieve pain or discomfort in muscles, it will not be considered a cosmetic product, but rather be classified a medicinal product. A maximum level of 2.5 % will probably not cause any recognizable pain relieving effect.

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9. Annexes

Calculation of skin surface (based on “the rule of nine”):

The rule of nine is a way to calculate the percentage of the body surface that is affected and is often used to calculate the burn percentage.

Each leg constitutes 18% (front = 9%, back = 9%)

Each arm = 9% (front = 4.5%, back = 4.5%)

1/8 area of each leg: $(18+18\%)/8 = 4.5\%$

1/8 area of each arm: $(9+9\%)/8 = 2.25\%$

Skin surface area: $9\% + 4.5\% = 6.75\% = 17,500\text{ cm}^2$ (total body surface) $\times 0.0675 = 1181\text{ cm}^2$

It is necessary to include half the area of the hands, since they will be exposed during application.

½ area hands (SCCS, default value): 430 cm^2

Total skin surface area: $430\text{ cm}^2 + 1181\text{ cm}^2 = 1611\text{ cm}^2$

Calculation of the lowest effective dose:

Lowest drug serum concentration that yield a therapeutic effect: $10\text{ }\mu\text{g/mL} = 10\text{ mg/L}$

Volume of distribution (V_D): 0.1 L/kg

$V_D = \text{Total amount of drug in the body} / \text{Drug blood plasma concentration}$

Total amount of drug in the body = $V_D \times \text{Drug blood plasma concentration}$
= $0.1\text{ L/kg} \times 10\text{ mg/L}$
= **1 mg/kg**