

RISK PROFILE

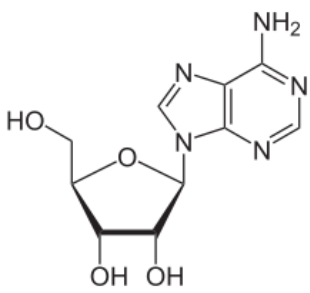
Adenosine CAS No. 58-61-7

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1. Identification of substance

Chemical name (IUPAC):	6-Amino-9-beta-D-ribofuranosyl-9H-purine
INCI	Adenosine
Synonyms	9-b-d-ribofuranosyl-9H-purin-6-amine, adenine riboside
CAS No.	58-61-7
EINECS No.	200-389-9
Molecular formula	C ₁₀ H ₁₃ N ₅ O ₄
Chemical structure	
Molecular weight	267.2 g/mol

Contents (if relevant)	
Physiochemical properties	<p>Appearance: White solid crystalline substance Melting point: 187-190 °C (Decomposes) log K_{ow} = -1.05 Vapor pressure: 6 x10⁻¹⁵ mm Hg at 25 °C Solubility (water): 5.1 g/L at 25 °C</p> <p>References: (CosIng [online]; PubChem Compound [online]; Medsafe [online]).</p>

2. Uses and origin

Uses	<p>➤ Cosmetic products:</p> <p><i>Function according to:</i></p> <ul style="list-style-type: none"> ○ CosIng database <p>”Skin conditioning” - Maintains the skin in good condition (CosIng [online]).</p> ○ Other <p>Adenosine enhances skin condition by increasing cell size of human skin fibroblasts, a cell type in the dermis (Patents.com [online]).</p> <p><i>Frequency of use</i></p> <p>At Codecheck.info, a German online database 213 products that contain adenosine were listed.</p> <p>At EWG's Skin, a total of 17 products were identified.</p> <p>For both databases, the vast majority of the products containing adenosine were anti-aging products for face or eyes. But other product categories were also identified, such as hand cream, body lotion, tanning oil/cream and anti-hair loss treatment.</p> <p>(Codecheck [online]; EWG's Skin Deep [online]).</p> <p><i>Concentrations being applied</i></p> <ul style="list-style-type: none"> • Anti-aging creams: 0.01-0.1 % (information obtained from industry) • Anti-hair loss products: 0.75 % (Oura et al., 2008) • Tanning oil: unknown • Body lotion: unknown <p>➤ Medicinal products/applications</p> <p>Adenosine is a cardiac depressant and vasodilator used as an antiarrhythmic and as an adjunct in myocardial perfusion imaging.</p>
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	<p>Indications (drugbank):</p> <ul style="list-style-type: none"> • Analgesics • Vasodilator Agents • Antiarrhythmic Agents • Anti-Arrhythmia Agents • Cardiac drugs <p>Used as an initial treatment for the termination of paroxysmal supraventricular tachycardia (PVST), including that associated with accessory bypass tracts, and is a drug of choice for terminating stable, narrow-complex supraventricular tachycardias (SVT).</p> <p>➤ Food</p> <p>Data not retrieved.</p>
<p>Origin Natural (exo /endo) Synthetic</p>	<p>Adenosine is a purine nucleoside consisting of adenine and ribose; a component of RNA that occurs in all cells of the body.</p>

3. Regulation

<p>Norway</p>	<p>According to the current Norwegian Cosmetic Products Regulation Adenosine is allowed in cosmetic products at concentrations up to 0.1 % in anti-aging products only. Adenosine is prohibited in all other cosmetic products. This regulation will be removed on 11 July 2013</p>
<p>EU</p>	<p>No regulation.</p>
<p>Rest of the world</p>	<p>No regulation.</p>

4. Relevant toxicity studies

<p>Absorption Skin GI tractus</p>	<p>Consulting with industry we have reason to believe that when in a cream at a low concentration and applied on skin with a thickness 2mg/cm², skin absorption range up till about 2 %.</p> <p>GI tractus: not applicable</p>
<p>Distribution, metabolism and excretion</p>	<p>Intravenously administered adenosine is removed from the circulation very rapidly. Following an intravenous bolus, adenosine is taken up by erythrocytes and vascular endothelial cells. The half-life of intravenous adenosine is estimated to be less than 10 seconds. Adenosine enters the body pool and is primarily metabolized to inosine and adenosine monophosphate (AMP). Excess adenosine is excreted in urine (Medsafe [online]).</p>
<p>Local toxic effects Irritation Sensitivity</p>	<p>Adenosine showed no skin or eye irritation potential in a battery of the conventional tests for these toxicity end points – except that It turned out to be slightly irritant to eyes in a particular <i>in vitro</i> test (HET-CAM assay). Neither did it show a sensitisation potential in the Magnusson and Kligman maximization method (industry data)</p> <p>Adenosine does not absorb in the ultraviolet light spectrum, and is therefore not likely to have phototoxic potential</p>

Systemic toxic effects	
Acute and repeated doses	<p>LD₅₀ mice (oral): >20 g/kg LD₅₀ mice (intraperitoneal): >500 mg/kg</p> <p>Mild side effects such as facial flushing, shortness of breath, a feeling of tightness across the chest, nausea, headache, dizziness, discomfort in the throat, neck or jaw, are common after treatment with adenosine (1-10 %). Serious side effects can occur, but are rare; irregular or slow heartbeat, breathing problems and severe allergic reaction (Medsafe [online]).</p>
Mutagenicity /genotoxicity	Adenosine tested negative for mutation in the Salmonella/Mammalian Microsome Assay. Adenosine, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations.
Carcinogenicity	No available data.
Reproductive toxicity / teratogenicity	<p>In rats and mice, adenosine administered intraperitoneally once a day for 5 days at 50, 100 and 150 mg/kg caused decreased spermatogenesis and increased numbers of abnormal sperm.</p> <p>It is not known whether adenosine passes into breast milk. Adenosine as pharmaceutical is not recommended to be used during pregnancy.</p>
Other effects	Bronchospasm in patients with asthma after intravenous administration of adenosine have been reported (DeGroff et al., 1994; Drake et al., 1994; Bennet-Guerrero et al., 1994).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	<p>The lowest effective dose required for tachycardia termination is 42-150 µg/kg bw (Chang et al., 2002) -- LOEL: 42 µg/kg bw = 0.042 mg/kg bw</p> <p>NOEL can be obtained conventionally by dividing LOEL by 3: NOEL: 0.042 mg/kg bw / 3 = 0.014 mg/kg bw</p>
Exposure cosmetic products	<ul style="list-style-type: none"> • Anti-aging face cream Calculated relative daily exposure (mg/kg bw/day) : 24.14 Dermal absorption, default value, SCCS: 2% = 0.02 Assumed concentration in product: 0.1 % = 0.001 Calculation of SED: 24.14 mg/kg bw/day x 0.02 x 0.001 = 0.00048 mg/kg bw/day • Anti-aging eye cream Daily exposure (mg/kg bw/day) : 2¹ Dermal absorption, default value, SCCS: 2% = 0.02 Assumed concentration in product: 0.1 % = 0.001 Calculation of SED: 2 mg/kg bw/day x 0.02 x 0.001 = 0.00004 mg/kg bw/day

¹ See annex for calculation.

	<ul style="list-style-type: none"> • Anti-hair loss products Daily exposure (mg/kg bw/day) : 14¹ Dermal absorption, default value, SCCS: 2% = 0.02 Assumed concentration in product: 0.1 % = 0.001 Calculation of SED: 14 mg/kg bw/day x 0.02 x 0.001 = 0.0003 mg/kg bw/day • Body lotion Calculated relative daily exposure (mg/kg bw/day) : 123.20 Dermal absorption, default value, SCCS: 2% = 0.02 Assumed concentration in product: 0.1 % = 0.001 Calculation of SED: 123.20 mg/kg bw/day x 0.02 x 0.001 = 0.0025 mg/kg bw/day • Hand cream Calculated relative daily exposure (mg/kg bw/day) : 32.70 Dermal absorption, default value, SCCS: 2% = 0.02 Assumed concentration in product: 0.1 % = 0.001 Calculation of SED: 32.70 mg/kg bw/day x 0.02 x 0.001 = 0.00065 mg/kg bw/day • Tanning oil Calculated relative daily exposure (mg/kg bw/day) : 123.20² Dermal absorption, default value, SCCS: 2% = 0.02 Assumed concentration in product: 0.1 % = 0.001 Calculation of SED: 123.20 mg/kg bw/day x 0.02 x 0.001 = 0.0025 mg/kg bw/day
Margin of Safety (MoS)	<p>MoS for adenosine in anti-aging face cream: SED: 0.00048 mg/kg bw/day MoS: 0.014/ 0.00048 = 29</p> <p>MoS for adenosine in anti-aging eye cream: SED: 0.00004 mg/kg bw/day MoS: 0.014/ 0.00004 = 350</p> <p>MoS for adenosine in anti-hair loss products: SED: 0.0003 mg/kg bw/day MoS: 0.014/ 0.0003 = 51</p> <p>MoS for adenosine in body lotion: SED: 0.0025 mg/kg bw/day MoS: 0.014/ 0.0025 = 6</p> <p>MoS for adenosine in hand cream: SED: 0.00065 mg/kg bw/day MoS: 0.014/ 0.00065 = 21</p> <p>MoS for adenosine in tanning oil: SED: 0.0025 mg/kg bw/day MoS: 0.014/ 0.0025 = 6</p>

² The relative daily exposure value for body lotion have been used.

6. Other sources of exposure than cosmetic products

Food stuffs	Data not retrieved.
Pharmaceuticals	<p>Adenocor is only given in hospitals, commonly as a 0.3 % intravenous infusion. The effect of adenosine only lasts for a couple of minutes. The Maximum Recommended Therapeutic Dose for adenosine is 2 mg/kg bw/day (FDA U.S. [online]).</p> <p>Adenosine should not be used in the case of:</p> <ul style="list-style-type: none"> • asthma or other lung disease • recent heart transplantation • other problems with your heart or heart rhythm • severe low blood pressure <p>Interactions: The effects of adenosine are antagonized by methylxanthines such as caffeine and theophylline. In the presence of these xanthines, larger doses of adenosine may be required. Adenosine effects are potentiated by dipyridamole, a drug that inhibits thrombus formation. Carbamazepine, an anticonvulsant and mood-stabilizing drug, has been reported to increase the degree of heart block produced by other agents. As the primary effect of adenosine is to decrease conduction through the A-V node, higher degrees of heart block may be produced in the presence of carbamazepine (PubChem Compound [online]).</p>
Other sources	
Adverse side effects - from uses other than cosmetics	The drug has negative chronotropic, dromotropic, and inotropic effects on the heart by slowing conduction time through the AV node and interrupting AV nodal reentry pathways. (Drugbank)

7. Assessment

Adenosine is endogenously present in all cells of the body. As a drug, it is only given in a hospital setting. The use of adenosine in cosmetic products has expanded the last ten years due to the discovery of the anti-wrinkle/anti-aging properties of adenosine.

As we are of the opinion that bioactive compounds used in cosmetic products should not cause adverse effects nor exert a prominent biological effect like influencing with the functioning of the heart. Therefore, 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 six different cosmetic product categories that contain adenosine; anti-aging face cream, anti-aging eye cream, anti-hair loss product, body lotion, hand cream and tanning oil. Since the NOEL is based on human data, a MoS of 10 is sufficient as a safety margin.

MoS for adenosine in anti-aging face cream =	29 (when usage limit is 0.1 %)
MoS for adenosine in anti-aging eye cream =	350 (when usage limit is 0.1 %)
MoS for adenosine in anti-hair loss product =	51 (when usage limit is 0.75 %)
MoS for adenosine in body lotion =	6 (when usage limit is 0.1 %)
MoS for adenosine in hand cream =	21 (when usage limit is 0.1 %)
MoS for adenosine in tanning oil =	6 (when usage limit is 0.1 %)

SED for the anti-aging creams for face and eye and the anti-hair loss product yields a MoS greater than the desired MoS of 10, whereas this is not the case for the body lotion and tanning oil

A MoS of 10 for cosmetics containing adenosine will give this usage limit:

Anti-aging face cream:	0.29 % (Calculation: $29 \times (0.1/10) = 0.29$)
Anti-aging eye cream:	3.5 % (Calculation: $350 \times (0.1/10) = 3.5$)
Anti-hair loss product:	0.51 % (Calculation: $51 \times (0.1/10) = 0.51$)
Body lotion:	0.06 % (Calculation: $6 \times (0.1/10) = 0.06$)
Hand cream:	0.21 % (Calculation: $21 \times (0.1/10) = 0.21$)
Tanning oil:	0.06 % (Calculation: $6 \times (0.1/10) = 0.06$)

The skin penetration value obtained from industry might not be accurate with the use of a vehicle that enhances the uptake of adenosine (Kadir et al., 1988). It is well known that especially as concerns anti-wrinkling and other anti-age cosmetics products potent vehicles are used that enhance the flux through skin many times. Therefore, as a precautionary, the adenosine should only be used for anti-aging creams for face and eyes at concentrations up to 0.1 % - and not in any other cosmetic products.

8. Conclusion

Adenosine should only be used for anti-aging creams for face and eyes at concentrations up to 0.1 % - and not in any other cosmetic products.

The products should carry the following warning texts

- Not to be used in connection with adenosine medical treatment

9. References

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10. Annexes

Calculated relative daily exposure (mg/kg bw/day) for eye cream

There are currently no existing daily exposure value or estimated surface area for eye cream. Therefore, we have used the surface area for eye shadow x 5 as an estimate of the applied surface area for eye cream.

Calculation:

Surface area – eye shadow: 24 cm²

Surface area – eye cream: 24 cm² x 5 = 120 cm²

Amount applied (default value): 1 mg/cm²

Body weight (default value): 60 kg

Daily exposure: 120 cm² x 1mg/cm² / 60 kg = **2 mg/kg**

Calculated relative daily exposure (mg/kg bw/day) for anti-hair loss products

There are currently no existing daily exposure value or estimated surface area for eye cream. Therefore, we have used the ½ of the area of hands and 1/3 of the area of head.

Calculation:

Surface area – ½ area hand: 860 cm² / 2 = 430 cm²

Surface area – 1/3 area head: 1160 cm² / 3 = 387 cm²

Surface area – anti-hair loss product: 430 cm² + 387 cm² = 817 cm²

Amount applied (default value): 1 mg/cm²

Body weight (default value): 60 kg

Daily exposure: 817 cm² x 1mg/cm² / 60 kg = **14 mg/kg**