

RISK PROFILE

Aloe vera

CAS No. 85507-69-3¹

Date of reporting 13.05.2013

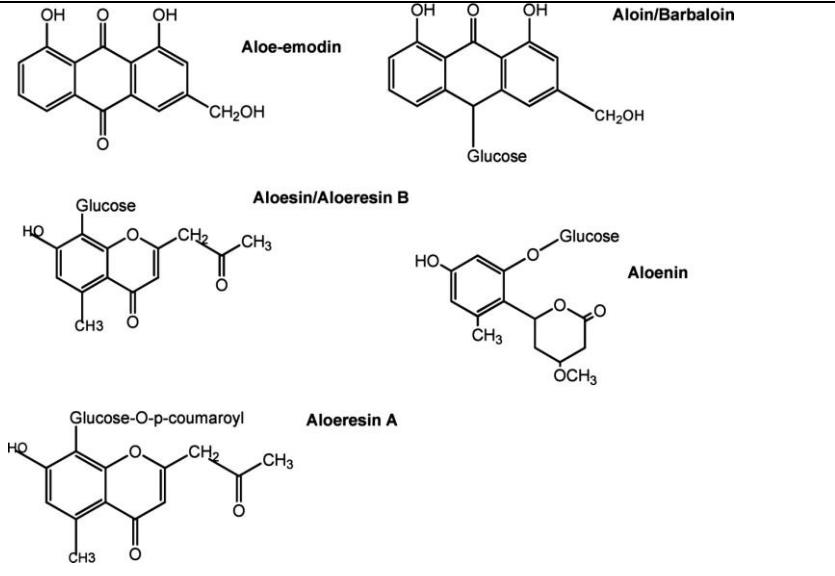
Content of document

1. Identification of substance	p. 1
2. Uses and origin	p. 2
3. Regulation	p. 7
4. Relevant toxicity studies	p. 7
5. Exposure estimates and critical NOAEL/NOEL	p. 13
6. Other sources of exposure than cosmetic products	p. 14
7. Assessment	p. 17
8. Conclusion	p. 19
9. References	p. 20
10. Annexes	p. 23

1. Identification of substance

Chemical name (IUPAC):	Aloe vera extracts contain a wide variety of anthraquinone substances, including aloin A: (10S)-10-Glucopyranosyl-1,8-dihydroxy-3-(hydroxymethyl)-9(10H)-anthracenone (quantitatively most important)
INCI	<i>Aloe barbadensis</i> (Miller) extract
Synonyms	The proper scientific name is <i>Aloe vera</i> (L.) Burm. f. The synonym <i>Aloe barbadensis</i> or <i>Aloe barbadensis</i> (Mill.) or (Miller) is commonly used to refer to aloe vera and can also be seen on many product labels.
CAS No.	85507-69-3 / 94349-62-9 (see Annex 2)
EINECS No.	287-390-8 / 305-181-2 (various Aloe vera substances)
Molecular formula	aloin/barbaloin (C ₂₁ H ₂₂ O ₉ ; Mw 418.4), aloe-emodin (C ₁₅ H ₁₀ O ₅)

¹ Cf. Aloe vera monograph (Council of Europe, 2008), based on an original SNT monograph of Aloe extracts with anthraquinones (RD8/2 -27).

Chemical structure	 <p>Fig.1: Structures of the main Aloe vera latex derived anthraquinones, chromones and antrones (Suga and Hirata 1983; van Wyk et al. 1995, reviewed in (CIR, 2007; Boudreau & Beland, 2006).</p>
Molecular weight	418.4 (aloin/barbaloin), 270.24 (aloe-emodin)
Contents (if relevant)	<p>Anthraquinones: e.g. aloin, aloe-emodin, emodin (see Annex 1). The International Aloe Scientific Council (IASC) standard states that only products containing acemannan, or the beta 1-4 acetylated glucomannans, can be accurately labeled as aloe vera. Acemannan is a naturally occurring polysaccharide that is present in aloe vera and is used as an identifier of the botanical by analytical means. Products that do not contain acemannan are not considered to be true aloe vera based on this standard (IASC [online]).</p>
Physiochemical properties	

2. Uses and origin

Uses	<p>➤ Cosmetic products:</p> <p><i>Functions according to</i></p> <ul style="list-style-type: none"> • CosIng database: (Annex 2) <ul style="list-style-type: none"> – Skin conditioning - Maintains the skin in good condition – Masking - Reduces or inhibits the basic odour or taste of the product – Emollient - Softens and smooth the skin – Humectant - Holds and retains moisture – Oral care - Provides cosmetic effects to the oral cavity, e.g. cleansing, deodorising, protecting • Other: <ul style="list-style-type: none"> – Moisturizing emollient effects²: Aloe vera (<i>Aloe barbadensis</i>) is utilized as an ingredient in a wide range of health and cosmetic products, principally due to its valuable softening
-------------	--

² <http://www.nhs.uk/Conditions/Emollients/Pages/Introduction.aspx>

effects on skin, e.g. face cleansers, hand creams, lotions, shampoos, skin moisturizers and makeup:

- relieves itching caused by mosquito bites (Giftinformasjonens nyhetsbrev, 2008).
- Aloe is used topically for osteoarthritis, burns, sunburns, and psoriasis (mostly unproven effects – and claims that place the product automatically within the scope of the medicinal legislation).
- UV filters (“sun-blocking”): Some of the yellow sap constituents (i.e. anthraquinones) show an inherent ability to absorb UV radiation (CIR, 2007) – i.e. effectively sun blocking agents. In these instances the extract is not termed an UV filter but something else, e.g. a soothing agent. This is because Aloe is not listed as an approved UV filter (for safety reasons) in any industrialized country.

Concentrations of Aloe extracts being applied

Aloe vera is a cactus-like plant that has been used for traditional medical purposes at least two thousand years. *Aloe vera* leaves can be separated in two basic products (see illustration, section “Origin”, below):

- the latex: bitter yellow liquid (‘yellow sap’) from pericycle cell layer beneath the epidermis of the leaf
- the gel: colorless, tasteless substances; inner part of the leaf

For cosmetic products, three distinct preparations of the plant are used: *Aloe vera latex*, *Aloe vera gel*, and *Aloe vera whole leaf extract* (purified ‘decolorized’ or unpurified ‘non- decolorized’ for yellow sap constituents).

Anthraquinone content in different cosmetic products

The anthraquinone content in *Aloe vera* products range from 1400 ppm in products containing the yellow sap ingredient, to less than 20 ppm (trace amounts) in purified whole leaf products or *Aloe vera gel*.

Aloe Vera preparation	Product type	Anthraquinones
(i) Cosmetics containing the <i>Aloe vera yellow sap</i> ingredient	Skin care and special sun protection products (Council of Europe 1989).	Up to 1400 ppm
(ii) Cosmetics containing the <i>Aloe vera whole leaf</i> ingredient, <u>not purified</u> for yellow sap constituents	Sunscreen product	< 180 ppm
(iii) Cosmetics containing the <i>whole leaf</i> ingredient, <u>purified</u> for yellow sap constituents	after-sun product	1 ppm or less in purified <i>Aloe vera</i> products. (e.g. a product with 3% of a 40X concentrate would contain no more

		than 0.01 ppm anthraquinones)
(iv) Cosmetics containing the Aloe vera <i>gel</i> ingredient	Whole range of cosmetics, including after-sun products	20 ppm (trace concentrations) - up to even 500 ppm occasionally (inter alia). (e.g. a product with 2.5% of a 40X concentrate would usually contain at most 0.2 ppm anthraquinones)
(v) Cosmetics containing a <i>mixture</i> of the <i>gel</i> and the <i>yellow sap</i> ingredient		Test of commercially available products in the US during the 80s showed small amount of Aloe vera, and variable amounts of yellow sap (Danhof et McAnally 1983). It has not been possible to get any information as to the levels of yellow sap constituents measured at that time.
<p><u>Comments:</u> Latex anthraquinones, some of which are carcinogenic, have been removed in decolorized whole leaf extract of Aloe vera during raw material processing.</p> <p><i>Industry standard:</i> For products for <u>topical</u> usage, the Cosmetic Ingredient Review established a limit of 50ppm of aloin, which is the accepted industry standard (CIR, 2007).</p> <p>For <u>oral</u> consumption, the IASC standard for aloin in products is less than 10ppm.</p> <p>NTP study (TR577): aloin: A content of test material approx. 6500 ppm, a figure that almost doubles when the content of aloin B is considered. The NTP test material represents a total aloin content of <i>more than 1000 times greater</i> than the industry standard. Thus, a <i>non-decolorized</i> test material is not representative of the marketplace standard, and it is important to distinguish between the two types of test materials.</p> <p>The use of Aloe vera in cosmetics is not new. A survey of cosmetic formulas published in the branch magazine "The Cosmetics & Toiletries Magazine" demonstrates levels of Aloe vera in concentrations varying from 1% to 98% in leave-on skin products (Henry R, 1979; Council of Europe, 2008).</p> <p>Aloe vera extracts (up to 100%) are frequently used in 'after sun products', which appears to have soothing or cooling effect on sun burns. A minimum concentration of 5 –10% is necessary to get a healing response against skin irritation, and even more for effects against other ailments. Aloe vera gel is applied up to 30% for</p>		

cosmetic purposes only (Nørager, 1995; Council of Europe, 1989, cited in Council of Europe 2008).

Frequency of use

The EWG Skin Deep cosmetic database (EWG's Skin Deep [online]) lists 6105 products containing Aloe vera, distributed among different product categories (Annex 3). Aloe vera leaf extract is found in 1543 products, whereas 2156 products contain Aloe vera gel (both identified by CAS no. 85507-69-3 (cf. Section 1 + Annex 2).

The German Codecheck.info [online] database lists 4779 products containing Aloe Vera, among which 992 products contain Aloe vera gel (April 2013).

An extensive list of product formulation data for aloe-derived ingredients reported to the FDA in 2001 is found in the Cosmetic Ingredient Review report on safety assessment of various Aloe preparations (CIR, 2007; Table 8).

We have not investigated whether the marketplace today contains topical Aloe vera products containing *both* the gel and the yellow sap ingredient.

➤ **Food**

Aloe vera has been widely used as an ingredient in diverse health products; drinks, foods, and supplements. The Aloe vera gel (from the leaves; see Fig. 2, below) is sometimes used as an ingredient in commercial jellies (Facciola, 1990). Aloe vera is used as an alternative solution to conventional synthetic preservatives (Christaki & Florou-Paneri, 2010).

Aloe-derived products are sold as a dietary supplement in the United States. Unlike companies that produce drugs (which must be tested before being sold), the companies that make supplements are *not required to prove* to the Food and Drug Administration (FDA) *that their supplements are safe or effective, as long as they don't claim the supplements can prevent, treat, or cure any specific disease.*

Levels of aloin, the predominant anthraquinone substance in Aloe vera, are less than 1 parts per million (ppm) in most liquid consumer products; however, levels in solid or semi-solid products may be 10-100 times higher (NTP[online] – Aloe vera).

➤ **Medicinal products**

In contrast to the Aloe vera preparations used in cosmetics, beverages and supplements, a dried extracted latex (yellow sap) is defined in the U.S. Pharmacopeia (USP) as a drug - *Aloe Rx* - with strong cathartic effects.

Aloe vera has been used in folk medicine for over 2000 years. Traditionally, aloe was used topically to heal wounds and for various skin conditions (skin wounds, burns, frostbite injuries and skin disorders like acne, dermatitis, psoriasis, eczema), and orally as a laxative. Today, in addition to traditional uses, people take aloe orally to treat a variety of conditions, including diabetes, asthma, epilepsy, and osteoarthritis. However, there is little evidence in the scientific

	<p>literature to substantiate claims of usefulness for systemic conditions other than as a laxative (Boudreau & Beland, 2006; Nørager, 1995, cited in Council of Europe, 2008). According to the industry, concerns about the safety of Aloe vera are related to its association with Aloe Rx.</p> <p>NB! Aloe Rx was <u>removed</u> from the generally recognized as safe (GRAS) list by FDA. In 2002, the FDA required that all over-the-counter (OTC) aloe laxative products be removed from the U.S. market or reformulated because the companies that manufactured them did not provide the necessary safety data. (FDA ruling 2002; cited in NTP, 2011).</p> <p>For more details, see Aloe vera monograph (Council of Europe, 2008).</p> <p>➤ Other products</p>
<p>Origin Natural (exo /endo) Synthetic</p>	<p>➤ <u>General</u></p> <p>Aloe is a large group of different succulent plants consisting of more than 400 different species of Aloe. The leaves of the species Aloe barbadensis Miller (commonly known as Aloe vera) are most often used for production of Aloe ingredients in cosmetic products, in addition to dietary supplements and herbal medicines.</p> <div data-bbox="571 992 1348 1370" data-label="Image"> <p>The diagram illustrates the cross-section of an Aloe vera leaf. It shows a central inner leaf that stores the Aloe vera gel, surrounded by a green rind or cuticle. The outer pulp contains latex and anthraquinones. A small inset shows the whole Aloe vera plant.</p> </div> <p><i>Fig. 2 Aloe vera leaf structure</i></p> <p>Aloe leaves contain a clear <u>gel</u> that is often used as a <i>topical ointment</i>. The gel is the water reservoir of the plant, consisting of approx. 99.5% water and only 0.5% of non-water substances like polysaccharides, phytosterols etc. (e.g. Danhof 1999 + Annex 1).</p> <p>The <i>green part of the leaf that surrounds the gel</i> is used to produce a juice or a dried substance (called <u>latex</u>), taken by mouth.</p> <p><u>Anthraquinones and chromones</u> The latex (or yellow sap) contains anthraquinones, among which the most abundant form is <i>aloin</i> (aloin A) - recognized by FDA as a laxative (removed from OTC laxatives in 2002, see above). Other anthraquinone forms in the yellow sap are <i>Aloe-emodin</i> and <i>emodin</i>.</p> <p><i>Chromones</i> -substances chemically related to anthraquinones (also in pericycle cells), with separate pharmacological properties.</p> <p><i>Other constituents:</i> Mono- and polysaccharides, tannins, sterols,</p>

	<p>organic acids, enzymes, saponins, vitamins, minerals, glucomannan, acemannan, lipids: cholesterol, gamolenic acid (Annex 1).</p> <p>The levels of anthraquinones and chromones are generally reduced by charcoal treatment and filtering before use in consumer products (IASC,1998). Typically, this process lowers the content of e.g. aloin to less than 1ppm before removal of water (IASC 1998, Danhof 1999).</p> <p>For more details, including processing techniques to minimize the content of anthraquinones, see Aloe vera monograph (Council of Europe monograph, 2008) and IASC [online].</p>
--	--

3. Regulation

Norway	Aloe vera gel allowed in all kind of cosmetics, but must not contain anthraquinone glycosides (e.g. aloin, emodin and aloe-emodin). Regulation to be lifted 11. July 2013.
EU	No regulation ³
Rest of the world	No regulation ⁴

4. Relevant toxicity studies⁵

Absorption Skin GI tractus	No data on the dermal absorption/skin penetration of Aloe-derived ingredients were available.
Distribution	<p>Ishii et al., 1987, administered barbaloin (see Figure 1), dissolved in distilled water at 20 mg/ml, orally to male Wistar Rats at a dose of 100 mg/kg. At specific time points after administration, blood was withdrawn from the rats to measure the serum levels of barbaloin. Barbaloin was first seen in the serum 30 minutes (0.092 µg/ml) after administration with maximum concentration (0.337 µg/ml) occurring at 90 minutes. After the 90 minute time point, concentrations of barbaloin decreased smoothly with detection still possible at six hours after administration. Barbaloin (31.1 mg /5ml/kg in 5% gum arabic solution) administered by cecal intubation to male Wistar rats (150-200 g), produced Aloe-emodin-9-anthrone one hour after administration. Aloe-emodin-9-anthrone, a decomposition product of barbaloin, was measured by thin layer chromatography. Aloe-emodin-9-anthrone peaked after four hours of barbaloin administration and was found in cecum at levels of 508 µg/rat, and in the colon at 83 µg/rat (Ishii et al., 1994).</p> <p>Lang (1993) administered Aloe-emodin (see Fig.1) to SPF Brown-Norway rats (numbers not given) orally in a tragacanth (0.3%) suspension at a dose of 4.5 mg/kg. The Aloe-emodin had been previously labeled with 14C. Blood, feces, urine and 24 organs were collected at specific time points to elucidate the distribution of Aloe-emodin. Maximum blood concentrations were reached 1.5-3 hours post</p>

³ EU foodstuffs regulations: a maximum of 0.1 ppm aloin/barbaloin as a flavouring agent is allowed in food and drinks; Regulation (EC) No 1334/2008. Aloe vera can be used by the feed industry according to Annex I of Regulation No 1831/2003.

⁴ US FDA has approved the internal use of gel as a dietary supplement. FDA has banned the use of cathartic anthraquinone-containing over-the counter drugs (US FDA, 1999).

⁵ Blue text is taken from the Aloe vera monograph (Council of Europe, 2008).

	<p>administration and were 248 ng (males) and 441 ng (females) equivalents of Aloe-emodin/ml. During the first six hours post administration there were no differences in organ concentrations between the males and females; however, in later samples females had higher concentrations than the males. The liver and kidney were the only organs that had higher concentrations of Aloe-emodin than plasma. Plasma protein binding of Aloe-emodin was determined in vitro and ex vivo. The results were an in vitro binding of 98-99% and an ex vivo binding of 86-96%. No sex differences were found (CIR, 2007).</p>
Metabolism	<p>In the plant the anthraquinone mixture mainly consists of Aloin – normally around 20% (Groom et Reynolds, 1987). When metabolised it can be transformed into aloe-emodin.</p> <p>The hepatic microsomes derived from various animal species transformed emodin (1,3,8-trihydroxy-6-methylanthraquinone), into an unidentified anthraquinone, along with 2-hydroxy-, 4-hydroxy- and 7-hydroxyemodins. This major metabolite was identified as omega-hydroxy-emodin (1,3,8-trihydroxy-6-hydroxymethylanthraquinone). Among 7 animal species, the highest activity to produce this omega-hydroxy-emodin was observed in the hepatic microsomes of guinea pig and rat, followed by mouse and rabbit. The microsomal activity to convert emodin into omega-hydroxyemodin was accelerated by the pretreatment of animals with phenobarbital, and inhibited by SKF 525A. The microsomal hydroxylation reactions of the methyl residue and the anthraquinoid nucleus of emodin were presumed to be catalyzed regionspecifically by multiple forms of cytochrome P-450 (Murakami et al., 1987).</p> <p>The metabolism of emodin (1,3,8-trihydroxy-6-methylanthraquinone) was studied. With rat liver microsomes, the formation of two emodin metabolites, omega-hydroxyemodin and 2-hydroxyemodin, was observed. The formation of omega-hydroxyemodin seems to be catalyzed by several cytochrome P450 enzymes at low rates. Data from this study suggest the involvement of cytochrome P450 1A2 in the formation of this metabolite. However, other cytochrome P450 enzymes also seem to catalyze this reaction. The anthraquinone chrysophanol (1,8-dihydroxy-3-methylanthraquinone) is transformed in a cytochrome P450-dependent oxidation to aloe-emodin (1, 8-dihydroxy-3-hydroxymethylanthraquinone) as the major product formed (Mueller et al., 1998).</p>
Excretion	<p>75% of a dose given to SPF Brown-Norway rats was excreted in the feces within the first two days (CIR, 2007).</p>
Local toxic effects Irritation Sensitivity	<p><u>Skin irritation:</u> There have been reports of burning sensation after topical application, allergic contact dermatitis and mild itching (Fulton, 1990; Schmidt et Greenspoon, 1991; Syed et al., 1996; Williams et al., 1996). All of these adverse effects are relatively mild and reversible upon cessation of application. In an US Patent, McAnally (April 5 1988), expressed this view: "More recent studies indicates that the <i>yellow sap</i> is toxic to human skin cells (Danhof, 1999) and should be minimised in topical products where it comes in contact with broken or damaged skin. Idiosyncratic hypersensitivity has been demonstrated in processed Aloe vera gel that consists of a variable mixture of yellow sap".</p> <p><u>Skin sensitivity:</u> Aloin must be regarded as a potential sensitizer (Cronin, 1968). In a case of allergic dermatitis caused by Aloes, the sensitising agent was found to</p>

	<p>be emodin (Jadassohn, 1926). A 47-year-old man exhibited hypersensitivity after 4 years of oral and topical Aloe. He presented with a pruritic eczematous eruption (Morrow et al., 1980). Another patient, who applied a gel topically, developed a widespread, erythematous, scaly, palpular eruption (Hogan, 1988). The latter author mentioned four similar reports of contact dermatitis in the literature.</p> <p>Hunter DH et Frumkin (1991) reported that: “Three women and one man aged forty-one to sixty-five years experienced a severe burning sensation following the application of Aloe Vera or vitamin E preparations to a skin area that had been subjected to a chemical peel or dermabration. Subsequently, a severe dermatitis occurred that required hospitalisation of one patient and intravenous administration of steroids....Patients undergoing dermabration or chemical peel procedures should be cautioned specifically against the use of Aloe vera or vitamin E topically in the first weeks after surgery”.</p>
<p>Systemic toxic effects Acute</p> <p>Repeated dose Mutagenicity /genotoxicity</p>	<p><i>Aloe barbadensis</i>-derived ingredients (aka Aloe vera) were not toxic in acute oral studies using mice (at doses up to 3 g/kg) and rats (dose not given). In parenteral studies, the LD₅₀ was >200 mg/kg bw (mice), >50 mg/kg bw (rats), and >50 mg/kg bw (dogs). For intravenous administration, LD₅₀ values were >80 mg/kg bw (mice), >15 mg/kg bw (rats), and >10 mg/kg bw (dogs) (CIR, 2007).</p> <p>For intraperitoneal (i.p) injection of emodin, LD₅₀ (mice) was 35 mg/kg bw (Lewis, 1996).</p> <p>Avila et al. (1997) refer to the work of other researches as regards to genotoxic properties: “...and to be mutagenic to a Salmonella strain sensitivity to a wide variety of oxidative mutagens. Quinones can induce such an effect, possibly reacting with protein thiol groups or by production of activated oxygen species (Chapman, 1995; O’Brien 1991)...Indeed, aloin was transformed, when administered orally to rats, to aloe-emodin in the large intestine (Ishii et al., 1990) and this quinone may be regarded as complete carcinogen by its structural characteristics (Wölfle et al., 1990).”</p> <p>Mueller & Kasper (1995) reported in a literature review genotoxicity data on a series of anthraquinones present in laxatives. Lucidin, danthron and emodin, which are present in Aloe to some extent, have a genotoxic and carcinogenic potential.</p> <p>Mueller et al. reported in 1996 that emodin, danthron and aloe-emodin were tested in a number of in vitro assay systems (mutation). For example all three induced tk-mutations in mouse lymphoma L5178Y cells. Induction of micronuclei also occurred in the same line, and was dose-dependent with the potency ranking being danthron>aloe-emodin>emodin. Furthermore, they found that emodin and danthron bound non-covalently to DNA and inhibited topoisomerase II activity. Interestingly, they say, in these latter systems emodin was more potent than danthron. The authors were of the opinion that given clear-cut evidence of genotoxic activity for all three, further research on the human cancer risk of these compounds may be warranted.</p> <p>In a follow-up study, Mueller SO et al. (1998) reported that the genotoxic effect of anthraquinones is, at least in part, mediated by non-covalent DNA-binding.</p> <p>As regards aloe-emodin - which differs from emodin by having a hydroxymethyl group instead of a methyl group in the 3-position –</p>

Carcinogenicity	<p>Westendorf et al.,1990, reported on the genotoxicity in a broad spectrum of in vitro assays. Positive results were obtained in the Ames test with strains TA 1537, TA1538, TA98 and TA1978. In the HPRT test (assay in V79 cells) no reproducible induction was obtained, while UDS and cell transformation was induced.</p> <p>Also Heidemann et al. (1996) found that aloe-emodin has genotoxic properties in vitro. Positive results were obtained in the chromosomal aberration assay with CHO cells, as well as in the Ames test (frame shift mutations in strains TA 1537, TA1538 and TA989). Further information about a possible reaction with DNA was derived from an in vivo USD assay (In vivo /in vitro unscheduled DNA).</p> <p>Heidemann et al. (1996), performed also gene mutation assay with mammalian cells in vitro (HPRT assay in V79 cells) - undertaking in addition in vivo micronucleus assay in bone marrow cells of NMR1 mice and a chromosome aberration assay in bone marrow cells of Wistar rats. Neither of these tests was positive. Also hepatocytes of male Wistar rats that were treated showed DNA damage via repair synthesis. The authors came to conclude that a genotoxic risk for man is unlikely.</p> <p>In the Micronucleus test the single oral dose applied was 1 500 mg/kg bw. The authors did not report about toxic effects of any kind in the animal. Possibly the dose was too low for the aloe-emodin molecule to reach the bone marrow so as to cause a mutation effect. It cannot be completely ruled out; therefore, that aloe-emodin is genotoxic to man after all.</p> <p>Since anthraquinones like emodin and aloe-emodin can display a genotoxic action, viz. reacting with the DNA molecule, they may possibly also be carcinogens like benzopyrene. This viewpoint is shared by Siegers et al. (1993), who has suggested that long and uncontrolled use of Aloes as a cathartic remedy might cause rectum cancer.</p> <p>On the basis of retrospective and prospective studies concerning occurrence of colorectal adenocarcinomas and carcinomas Siegers et al. (1993) came to conclude that with chronic over-use and abuse of anthranoid laxatives there appears to be an increased risk (3.04) for tumorigenesis.</p> <p>Update: Aloe and cancer</p> <p>A two-year National Toxicology Program (NTP) study on oral consumption of non-decolorized whole leaf extract of Aloe vera (2011) <i>found clear evidence of carcinogenic activity in male and female rats, based on tumors of the large intestine</i> ^{6,7}. According to NTP “<i>there was no evidence of carcinogenic activity in mice. From what we know right now, there is nothing that would lead us to believe that these findings are not relevant to humans. However, more information, including how individuals use different types of Aloe vera products, is needed to determine the potential risks to humans</i>”.</p> <p>Aloe <i>reduced</i> cancer-cell growth when tested on rats with liver cancer, but stimulated cancer-cell development when the same test was done on cultured human liver-cancer cells (Ref: American Cancer Society). Aloe</p>
-----------------	--

⁶ Read more: <http://www.livestrong.com/article/486310-is-aloee-juice-harmful/#ixzz26FU9fq9s>

⁷ http://www.niehs.nih.gov/health/materials/aloee_vera_508.pdf

<p>Reprotoxicity / teratogenicity</p>	<p>appears to promote blood vessels development necessary for cancer cell growth, Another recent laboratory study reported that aloe promotes the growth of endothelial (blood vessel) cells, raising the concern that it might promote angiogenesis (growth of blood vessels that help "feed" a cancer). Thus, the effects of Aloe on cell growth and cancer appear to be complex, and at least partly dependent on the study system.</p> <p>Note that there are dramatic differences in anthraquinone levels in different Aloe vera plant preparations:</p> <ul style="list-style-type: none"> - the NTP study used a <u>non-decolorized</u> Aloe vera <u>whole leaf extract</u> (unpurified, <i>high</i> anthraquinones) - concentration of aloin was approximately 12900 ppm in the 90-day study and 6300 ppm in the 2-year study (Boudreau et al., 2012). - In contrast, Aloe vera preparations in the marketplace contain Aloe vera gel or <i>decolorized</i> whole leaf extract as ingredients, removing anthraquinones and some of the components which are linked to carcinogenic activity - total aloin was present at <0.1 ppm in the purified <u>decolorized whole leaf juice</u> reported by Shao et al. (2013), see below. <p>Shao et al (2013) support the notion that the high levels of anthraquinone present in orally administered, non-purified whole leaf Aloe vera extract may be responsible for the adverse effects observed on the colon. These authors reported a complete absence of any adverse effects of decolorized (low anthraquinone) whole leaf Aloe vera extract on the gastrointestinal tract (based on histological alterations) in F344 rats, under conditions closely matching the design of the 2-year NTP study in F344 rats.</p> <p>In line with this, no genotoxic effects have been observed following oral administration of Qmatrix (which is a standardized Aloe vera inner leaf gel extract that has not been heated after extraction from the leaf) to rats after 90 days (Williams et al., 2010).</p> <p><i>Aloesin</i>, an aromatic chromone chemically related to anthraquinone and also present in Aloe vera, did not cause adverse effects in Sprague-Dawley rats - up to a maximum dose of 1000 mg/kg bw/day (NOAEL) over 90 days (Lynch et al., 2011). Thus, aleosin has a toxicity profile different from Aloe-derived anthraquinones, consistent with its presumed safe use in cosmetics (CIR, 2007), and supporting its potential use as a functional food ingredient (Lynch et al., 2011).</p> <p>In summary, Aloe-emodin is mutagenic in almost all <i>in vitro</i> tests. <i>In vivo</i>, the NTP rat study gives reason for serious concern, providing support for the idea that high levels of anthraquinones are responsible for the adverse effects observed on the colon. How these findings translate to human risk requires more information: in particular, what are the constituents, their levels in human products, and the patterns of human exposure (NTP, 2011).</p> <p>Developmental and reproductive toxicity: In one study, emodin was administered in feed to timed-mated Sprague-Dawley (CD) rats. The rat maternal LOAEL was 1 700 ppm based on maternal body weight and weight gain; the NOAEL was 850 ppm. The rat developmental toxicity NOAEL was greater than 1 700 ppm; a LOAEL for rat developmental toxicity was not established. In mice, the maternal toxicity LOAEL was 6 000 ppm based on reduction of maternal body weight and weight gain; the NOAEL was 2 500 ppm. The developmental toxicity LOAEL was 6 000 ppm, based on reduction of fetal body weight; the NOAEL was 2 500 ppm (Jahnke et al., 2004).</p>
---	---

Other effects

Phototoxicity:

CIR (2007) refers to clinical assessment of phototoxicity in response to Aloe vera gel (65%), Aloe concentrate (0.75%) or Aloe leaf extracts with aloin/anthraquinone levels up to 5 ppm. No dermal phototoxicity was observed.

Update:

Two studies published in 2010 reported opposite effects regarding skin cancer in mice. In one study of mice treated with chemicals that cause skin cancer, aloe products (applied to the skin and taken by mouth) *reduced* the number of skin cancers.

However, in the other study, certain aloe products *increased* the number of skin cancers (especially in female mice) caused by ultraviolet light (NTP Technical Report 553, 2010). Both aloe *whole leaf extract* and *decolorized leaf extract* had a weak enhancing effect on the photocarcinogenic activity of simulated solar light in both male and female hairless mice. The effects were related to histopathological changes, whereas no visible changes in the skin were observed. The identity of the substance(s) responsible for the effect(s) is not known.

Cytotoxicity:

In a high enough concentration the anthraquinones can be toxic.

Human:

Danhof and McAnally conducted in 1983 an in vitro study where they treated cultured human skin cells (fibroblasts) with varying concentrations of fresh yellow sap, fresh-from-the leaf-gel and four commercial Aloe products collected from the marketplace. The yellow sap proved to be cytotoxic at all dose levels, whereas fresh gel wasn't:

Material tested	Percent of yellow sap or Fresh gel			
	1	10	15	30
Yellow Sap	Total Kill	Total Kill	Total Kill	Total Kill
Total				
Fresh gel	233	650	795	882

Two of the collected Aloe products tested positive confirming an earlier study that showed that commercially prepared Aloe purchased at the health food store was cytotoxic. It was concluded that the reason why these products showed cytotoxic properties in vitro, was that they not only contained the gel but also yellow sap in comparatively high levels (Danhof et McAnally, 1983).

Animals:

Avila et al., 1997 reported as follows:

"...on certain tests which show that the toxic activity of a low molecular weight fraction (LMWF) of a Aloe vera gel can be compared to that of the well-known toxic substances aloe-emodin and aloin. When exposed to monolayers of chicken fibroblasts the LMWF induced disruption of intercellular junctions and detachment of individual cells from the bottom of the flask, with formation of cell-free gaps in the monolayer. The author's advice that every effort must be made to limit the amounts of these toxins in the commercially prepared gel products."

Immunomodulatory properties: (topical Aloe gel) – may improve wound healing and skin inflammation. Huang et al. (1992) described some

	immunosuppressive properties pertaining to emodin – which they also considered to be a free radical generator.
--	--

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	Not sufficient data to set a threshold level for toxicological critical effect of Aloe vera extracts.
Exposure cosmetic products	Not sufficient data
Margin of Safety (MoS)	

6. Other sources of exposure than cosmetic products

<p>Food stuffs</p>	<p>The industry standard upper limit of aloin is <u>10 ppm</u> in <i>orally</i> ingested products. No labeling requirements for aloin content (industry usually processes the Aloe vera leaf to make a <i>decolorized</i> whole leaf extract to remove aloin⁸).</p> <p>Aloe as flavouring preparation in food and drinks must not contain more than 0.1 ppm aloin (Regulation (EC) 1334/2008).</p> <p>Usual consumption as traditional foodstuff in a normal diet. [Aloe <i>barbadensis</i>, aloin =0.1mg/kg].⁹</p>
<p>Pharmaceuticals</p>	<p>Aloe vera is not a regulated drug; i.e. variable strength, purity, or safety of these products.</p> <p>Despite its widespread popularity scientific evidence on the Aloe vera gel remains sparse. This may partly be due to the many possible indications for Aloe vera (gel or leaf extract). Because information on the precise chemical composition of the Aloe vera preparations is lacking, results from various studies should be interpreted with caution with regard to reproducibility of stated effects.</p> <p>The FDA has ruled that Aloe is not safe as a stimulant laxative (FDA, 2002); MSKCC[online]).</p>
<p>Other sources</p>	
<p>Adverse side effects - from uses other than cosmetics</p>	<p>Aloe vera juice Antidiabetic medication (glitazones, sulphonyl urea derivatives, others) and insulin: increased hypoglycemic effects (Legemiddelhåndboka [online]).</p> <p>Possibly or likely safety concerns (MedlinePlus[online]; UpToDate[online]).</p> <p>Aloe <i>gel</i> is <i>likely safe</i> when applied to the <i>skin</i> and <i>possibly safe</i> when taken by <i>mouth</i> in adults. Occasionally, aloe gel might cause burning and itching of the skin.</p> <p>Aloe <i>latex</i> is <i>possibly unsafe</i> at any dose, but <i>likely unsafe</i> when taken in high doses. Aloe latex can cause some side effects such as stomach pain and cramps. Long-term use of large amounts of aloe latex might cause diarrhea, kidney problems, blood in the urine, low potassium, muscle weakness, weight loss, and heart disturbances. <i>Taking aloe latex 1 gram per day for several days can be fatal.</i></p> <p>There have been a few reports of liver problems in some people who have taken an <i>aloe leaf extract</i>; however, this is uncommon. It is thought to only occur in people who are extra sensitive (hypersensitive) to aloe.</p> <p>Special precautions & warnings: <i>Pregnancy or breast-feeding: Aloe - either gel or latex - is possibly</i></p>

⁸ In many cases, manufacturers of oral products containing Aloe vera use a charcoal filtration process to decolorize and remove some of the components from the leaf, including anthraquinones. Anthraquinones act like laxatives. Some anthraquinones have previously been shown to be carcinogenic.

⁹ <http://www.efsa.europa.eu/en/scdocs/doc/1489.pdf>

unsafe when taken by mouth. There is a report that aloe was associated with miscarriage. It could also be a risk for birth defects. Do not take aloe by mouth if you are pregnant or breast-feeding.

Children: Aloe is *possibly unsafe* for children when taken by mouth. Children younger than 12 years old may experience abdominal pain, cramps, and diarrhea.

Diabetes: Some research suggests aloe might lower blood sugar. If you take aloe by mouth and you have diabetes, monitor your blood sugar levels closely.

Intestinal conditions such as Crohn's disease, ulcerative colitis, or obstruction: Do not take aloe latex if you have any of these conditions. Aloe latex is a bowel irritant. Remember, products made from whole aloe leaves will contain some aloe latex.

Hemorrhoids: Do not take aloe latex if you have hemorrhoids. It could make the condition worse. Remember, products made from whole aloe leaves will contain some aloe latex.

Kidney problems: High doses of aloe latex have been linked to kidney failure and other serious conditions.

Surgery: Aloe might affect blood sugar levels and could interfere with blood sugar control during and after surgery. Stop taking aloe at least 2 weeks before a scheduled surgery.

Self-treatment may cause serious harm

The following has been collected from the «Martindale the Extra Pharmacopoeia»:

Although Aloe vera has for many years been used as an ingredient in cosmetics such as face and hand creams, lotions, and skin moisturisers the FDA has recently become concerned about the widespread distribution of Aloe Vera products promoted for self-treatment of human complaints. Exaggerated and unsubstantiated claims are being made that these products can cure or alleviate a variety of unrelated conditions including colitis, asthma, glaucoma, haemorrhoids, arthritis, acne, anaemia, tuberculosis, cancer, diabetes, depressions multiple sclerosis and even blindness. Such products are often sold as food supplements and cosmetics in health stores but the manufacturer are careful to make no health claims on the product labels and in order to remove them from the market FDA would have to prove them to be adulterated or misbranded. Serious harm may follow when proper medicinal treatment of serious illness is neglected or abandoned in favour of such products with no proven value.

Warnings:

Aloe vera gel should not be confused with aloe juice or aloe latex, both of which contain anthraquinone, a cathartic laxative. Aloe vera taken for internal use should be discouraged due to possible adverse effects and inconclusive clinical data. Aloe vera injections for cancer patients have resulted in several deaths.

The FDA published a requirement that non-pasteurized aloe be labeled with a warning sticker (FDA, 2000).

Interactions:

Major -Do not take aloe in combination with Digoxin (Lanoxin). When taken by mouth, aloe latex is a type of laxative called a stimulant laxative. Stimulant laxatives can decrease potassium levels in the body. Low potassium levels can increase the risk of side effects of digoxin (Lanoxin). (UpToDate [online]).

Moderate – see MedlinePlus[online]

Herb-Drug Interactions

- **Cytochrome P450 substrates:** In vitro, aloe vera juice was found to inhibit CYP3A4 and CYP2D6 and can affect the intracellular concentration of drugs metabolized by these enzymes (MSKCC [online], reference 24).

Oral

- **Glyburide:** Aloe may increase hypoglycemic effects.
- **Diuretics:** Aloe may have additive hypokalemic effect due to diarrhea if used for a prolonged period.
- **Digoxin:** Aloe may have additive hypokalemic effect due to diarrhea if used for a prolonged period.

Topical

- **Hydrocortisone:** Aloe may increase anti-inflammatory effects (MSKCC [online], reference 15).
- **Sevoflurane:** Aloe may have additive antiplatelet effect causing excessive bleeding during surgery (MSKCC [online], reference 12).

Potential interactions between Aloe vera and warfarin (or other anti-coagulants) have not been observed in Norway (RELIS [online]), but *RELIS recommends that herbal supplements containing Aloe are not taken in combination with warfarin.*

7. Assessment

Aloe vera is widely used in a variety of cosmetics including creams and toiletries, but is also sold in the beverage and dietary supplement industries. Aloe vera makes up 99% of the aloe market.

Aloe vera is processed by using the entire leaf and removing the hydroxy-antraquinones while retaining many of the components found in the fresh leaf. Aloe vera (purified extract or gel) is almost free of the hydroxy-antraquinones with contaminant levels (usually) ranging from 50 ppm to less than 1 ppm.

General toxicity:

Many of the adverse effects of Aloe vera preparations are believed to be related to the anthraquinone content. Approx. 80 phenolic anthraquinones (including aloin and aloe-emodin) are produced by the pericyclic cells just below the epidermis, and is found in Aloe preparations as bitter yellow latex (juice), also known as yellow sap.

Some of the anthraquinones have been shown to be gastrointestinal irritants with cathartic properties (CIR, 2007).

A recent NTP study demonstrated increased incidence of tumors in animals that drank water containing 60 ppm of aloin daily for nearly their entire lifetime. This should be compared to the industry standard, which states levels of aloin < 10 ppm (oral ingestion) and <50 ppm (topical usage).

The increased incidence of colon adenomas and carcinomas in the NTP study was related to intake of *non-decolorized* (unpurified, high anthraquinone) Aloe vera leaf extracts, supporting the notion that anthraquinones are responsible mediators of the adverse effects on the colon (NTP study, Boudreau et al., 2012). These findings are of possible relevance also to humans.

In contrast, similar concentrations of purified *decolorized* (low anthraquinone; <0.1 ppm aloin) whole leaf Aloe vera juice did not give rise to findings of any toxicological significance during a 13 week oral feeding experiment in rats (Shao et al., 2013).

There are concerns for various adverse side effects - from uses other than cosmetics – usually related to oral intake of Aloe *latex* rather than *Aloe gel*.

Cosmetic products

Almost 10% of all cosmetic products on the market contain Aloe Vera gel, and in some product categories almost 90%. The Aloe vera gel is generally believed to be safe, as the gel usually contains only trace amounts of anthraquinones (as contaminants).

Systemic effects:

There is a lack of data as concerns the ability of various anthraquinones to permeate the skin barrier, and the safety of topical Aloe vera ingredients related to systemic toxicity has not been assessed.

Local (topical) effects:

Topical application of Aloe vera gel is regarded as safe as assessed by the Cosmetic Ingredient Review (CIR) Expert Panel (CIR, 2007). Aloe *purified whole leaf extract* (low anthraquinone) is also considered to be safe for topical use.

However, case reports of contact dermatitis, erythema, and skin hypersensitivity in response to topically applied Aloe gel preparations have been reported. Allergic reactions in gels have been attributed in most cases to anthraquinone content, which is considered an impurity from the leaf extract of Aloe vera (reviewed in Grundmann, 2012; (Williams et al., 2010).

Whereas there is weak evidence for photo toxicity (see NTP report, 2010), levels of anthraquinones less than 50 ppm appear to be too low to induce photo toxicity (Shao et al., 2013).

Industry-established safe levels (CIR, 2007):

Anthraquinones (e.g. aloin/barbaloin and emodin) are undesirable contaminants of Aloe vera extracts, and yellow sap ingredients should be kept at a minimum in topical products where it can come in contact with broken or damaged skin (The US Patent referred to in McAnally, 1988). Aloe vera *latex* (high anthraquinone) is associated with adverse effects and interactions with medicinal agents.

The voluntary industry maximum (FDA, 2000) specifies that *anthraquinone levels* should be kept below 50 ppm, regardless of Aloe species. CIR concluded that a concentration of anthraquinones below 50 ppm in a product is adequately safe, after considering the data on several Aloe vera extracts (CIR, 2007). This is also supported by data from animal experiments (Shao et al., 2013).

Food supplements and herbal products

Aloe vera is frequently used in dietary supplements.

In 0.5% aloe vera solution for oral consumption, aloin should not exceed 10 ppm (Grundmann, 2012).

EU foodstuff regulation allows a maximum of 0.1 ppm aloin/barbaloin to be used for flavouring purposes in food and drinks; cf. Regulation (EC) No 1334/2008. H

Aloe gel has also been approved by the FDA as a natural flavoring, so small quantities may be used in foods.

Most supplements have not been tested to find out if they interact with medicines, foods, or other herbs and supplements. Even though some reports of interactions and harmful effects may be published, full studies of interactions and effects are not often available. Because of these limitations, any information on ill effects and interactions below should be considered incomplete (American Cancer society [online]).

It is recommended that pregnant and breastfeeding women, as well as young children, do not ingest Aloe gel.

Aloesin, an aromatic chromone present in various Aloe species has been promoted as a potential functional food ingredient. Chromones are substances chemically related to anthraquinones, but do not share the toxicity profile associated with the anthraquinones or with Aloe vera extracts known to contain anthraquinones (Lynch et al., 2011).

Medicinal products

Although Aloe Vera has for many years been used as an ingredient in cosmetics, further evidence is needed to support claims as to the effectiveness of Aloe vera products against a variety of other conditions¹⁰. Such products are often sold as food supplements and cosmetics in health stores, and self-treatment may cause serious harm.

¹⁰ The FDA has recently become concerned about the widespread distribution of Aloe Vera products promoted for self-treatment of human complaints. Exaggerated and unsubstantiated claims are being made that these products can cure or alleviate a variety of unrelated conditions including colitis, asthma, glaucoma, haemorrhoids, arthritis, acne, anemia, tuberculosis, cancer, diabetes, depressions multiple sclerosis and even blindness.

8. Conclusion

We propose that Aloe vera ingredients are allowed in all kinds of cosmetics, but *anthraquinone* levels must not exceed **1 ppm**¹¹.

• References

- Avila H, Rivero J, Herrera F, Fraile G (1997): Cytotoxicity of a low molecular weight fraction from Aloe vera (Aloe barbadensis Miller) gel. *Toxicol*, 35 (9):1423-30
- Christaki EV & Florou-Paneri PC (2010). Aloe vera: A plant for many uses. *J. Food Agriculture & Environment* 8(2): 245-49.
- Cosmetic Ingredient Review Expert Panel (2007). Final report on the safety assessment of AloeAndongensis Extract, Aloe Andongensis Leaf Juice, Aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadensis Flower Extract, Aloe Barbadensis Leaf, Aloe Barbadensis Leaf Extract, Aloe Barbadensis Leaf Juice, Aloe Barbadensis Leaf Polysaccharides, Aloe Barbadensis Leaf Water, Aloe Ferox Leaf Extract, Aloe Ferox Leaf Juice, and Aloe Ferox Leaf Juice Extract. *Int J Toxicol*. 26 (Suppl 2):1-50. Review. PubMed PMID: 17613130.
- Council of Europe (1989). Monograph on Aloe barbadensis within the Council of Europe «Plant preparations used as ingredients of cosmetic products», 1st edition /Strasbourg 1989.
- Council of Europe (2008). Aloe vera. Active ingredients used in cosmetics: safety survey (2008). ISBN 978-92-871-6298-4
- Cronin E (1968). Studies in contact dermatitis. XVIII. Dyes in clothing. *Trans. Rep. St John's Hosp. Derm. Soc. Lond.*: 54: 156.
- Danhof IE (1999). This refers to an article called «The whole leaf advantage» by the North Texas Research Laboratory researcher Ivan E Danhof – an excerpt of which can be found at the internet address: http://www.simplynaturalproducts.com/library/Aloe_Vera/danhof3.html. Dr. Ivan Danhof, is an American physician who has worked with topical Aloe products in the cosmetic industry for 30 years
- Danhof IE (May 1999). Personal communication by fax with the Norwegian delegation to the Council of Europe 3rd and 4th May 1999
- Danhof IE and McAnally BE (1983). Stabilised Aloe Vera: Effect on Human Skin Cells. *Drug and cosmetic ind.*: 52-54, p. 105 - 106
- Facciola S. (1990). *Cornucopia - A Source Book of Edible Plants*. Kampong Publications; ISBN 0-9628087-0-9
- Foster M, Hunter D, Samman S (2011). Evaluation of the Nutritional and Metabolic Effects of Aloe vera. In: Benzie IFF, Wachtel-Galor S, editors. *Herbal Medicine: Biomolecular and Clinical Aspects*. 2nd edition. Boca Raton (FL): CRC Press. Chapter 3. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK92765/>
- Fulton JE (1990). The stimulation of postdermabrasion wound healing with stabilized Aloe vera gel-polyethylene oxide dressing. *J Dermatol Surg Oncol*: 16: p. 460-7
- Jahnke GD, Price CJ, Marr MC, Myers CB, George JD (2004). Developmental toxicity evaluation of emodin in rats and mice. *Birth Defects Res B Dev Reprod Toxicol.*;71(2):89-101

¹¹ The current Norwegian cosmetic products regulation to be removed 11 July 2013 sets forth that Aloe vera gel to be used in cosmetic products must not contain anthraquinones. Administrating this law over the years the Norwegian Food Safety Authority have held that in practice the expression “*must not contain*” means not more than 1 ppm. This rule has been based on safety assessments contained in a non-published monograph on Aloe extracts by the former Norwegian agency the “Statens næringsmiddeltilsyn” (SNT). The latter paper was distributed the Council of Europe expert committee on cosmetic products assessed the safety of use of aloe vera ingredients – a work that resulted in the Aloe vera monograph of the Council of Europe, 2008.

- Groom QJ and Reynolds T (1987). Barbaloin in Aloe Species. *Planta Med*: 53: 345 – 348
- Heidemann A; Voelkner W; Mengs U (1996). Genotoxicity of Aloeemodin in vitro and in vivo. *Mutation Research*: 367 (3): 123-33.
- Henry R (1979). An updated review of *Aloe vera*. *Cosmetics and Toiletries* 54:42-50.
- Hogan DJ (1988). Widespread dermatitis after topical treatment of chronic leg ulcers and stasis dermatitis. *Can Med Assoc J*; 138: 336-8.
- Huang HC, Chang JH, Tung SF, Wu RT, Foegh ML, Chu SH (1992). Immunosuppressive effect of emodin, a free radical generator. *European Journal of Pharmacology*: 211(3): 359-64.
- Hunter DH and Frumkin A (1991). Adverse Reactions to Vitamin E and Aloe Vera Preparations After Dermabrasion and Chemical Peel. *Cutis*: 47: 193-196.
- IASC (1998). Fax 10 June 1998 from Gene Hale of the International Aloe Science Council Inc (IASC)/Irving Texas USA to the Norwegian delegation
- Ishii Y, Tanizawa H and Takino Y (1987). Determination of Barbaloin in Rat Serum. *Chem Pharm Bull (Tokyo)*. 35: 4642-4644.
- Ishii Y, Tanizawa H, and Takino Y (1994). Studies of Aloe. V. Mechanism of Cathartic Effect. *Biol Pharm Bull*. 17: 651-653.
- Jadassohn, W. Quoted by Touton, K (1926). in: *Handbuch der Haut und Geschlechtskrankheiten*, Pt. 1. Berlin, Springer.: 4
- Lee CK et al. (1997). prevention of ultraviolet radiation-induced suppression of accessory cell function of Langerhans cells by Aloe vera gel components. *Immunopharmacology* 37: 153-162.
- Leung AY. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics*. Toronto, Ontario: John Wiley & Sons Inc: 24
- Lewis, R.J (1996). *Sax's Dangerous Properties of Industrial Materials*. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold: 2322
- Martindale the extra pharmacopoeia (1995). p. 1075 (dry weight of sap contains 28% anthraquinones calculated as Aloin).
- Morrow DM et al. (1980). Hypersensitivity to Aloe. *Arch Dermatol*: 116: 1064-1065
- Mueller SO, Stopper H, Dekant W (1998). *Drug Metab Dispos*. 26(6): 540-6.
- Mueller L, Kasper P (1995). OTC pharmaceuticals and genotoxicity testing; the paracetamol, anthraquinone, and griseofulvin cases. *Archives of toxicology supplement* 17: 312-25
- Mueller SO, Eckert I, Lutz WK, Stopper H (1996). Genotoxicity of the laxative drug components emodin, Aloe-emodin and danthron in mammalian cells; topoisomerase II mediated? *Mutation Research*: 371(3-4):165-73.
- Mueller SO, Lutz WK, Stopper H (1998). Factors affecting the genotoxic potency ranking of natural anthraquinones in mammalian cell culture systems. *Mutat Res*: 414(1-3): 125-9.
- Murakami H, Kobayashi J, Masuda T, Morooka N, Ueno Y (1987). Omega-Hydroxyemodin, a major hepatic metabolite of emodin in various animals and its mutagenic activity. *Mutat Res* 180 (2): 147-53.
- Nørager DM (1995). Aloe-vidundermiddel eller døgnflue. *FARMACI*: Nr 3-95
- Reuter J, Merfort I, Schempp CM (2010). Botanicals in dermatology: an evidence-based review. *Am J Clin Dermatol*.11(4):247-67. doi: 10.2165/11533220-000000000-00000. Review. PubMed PMID: 20509719.
- Schmidt JM, Greenspoon JS (1991). Aloe vera dermal wound gel is associated with a delay in wound healing. *Obstet Gynaecol* (78) 115-17.

Siegers CP, von Hertzberg-Lottin E, Otte M, Schneider B (1993). Anthranoid laxative abuse — a risk for colorectal cancer? *Gut*: 34(88): 1099-1101.

Steinberg D (1998). Frequency Use of Botanicals. *Cosmetics & Toiletries magazine* 1134: 73-77.

Syed TA, Ahmad SA, Holt AH, Ahmad SH, Afzal M (1996). Management of psoriasis with Aloe vera extract in a hydrophilic cream: a placebo-controlled, double-blind study. *Trop Med Int Health*: 1: 505-9.

Thomas DR, Goode PS, LaMaster K, Tennyson T (1998). Acemannan hydrogel dressing versus saline dressing for pressure ulcers. A randomised, controlled trial. *Adv Wound Care Oct*, 11(6): 273-276

United States Patents (1988). Patent Number 4.735.935; date of patent Apr 5, (1988). Title: Process for preparation of Aloe products produces thereby and compositions thereof. Inventor: Bill H. McAnally.

Vogler BK, Ernst E (1999). Aloe Vera: A systematic review of its clinical effectiveness. *Br J Gen Pract*: 49: 823-8

Visuthikosol V, Chowchuen B, Sukwanarat Y, Sriurairatana S, Boonpucknavig V. (1995). Effect of Aloe vera gel to healing of burn wound: a clinical and histologic study. *J. Med. Assoc of Thailand*; 78 (8): 403-9.

Westendorf J, Marquardt H, Poginsky B, Dominiak M, Schmidt J, Marquardt H (1990). Genotoxicity of naturally occurring hydroxyanthraquinones. *Mutat Res*: 240(1): 1-12.

Williams LD, Burdock GA, Shin E, Kim S, Jo TH, Jones KN, Matulka RA (2010). Safety studies conducted on a proprietary high-purity aloe vera inner leaf fillet preparation, Qmatrix. *Regul Toxicol Pharmacol*. 57(1):90-8. Epub 2010 Jan 22. PubMed PMID: 20096744.

Williams MS, Burk M, Loprinzi CL Hill M, Schomberg PJ, Nearhood K, O'Fallon JR, Laurie JA, Shanahan TG, Moore RL, Urias RE, Kuske RR, Engel RE, Eggleston WD (1996). Phase III double-blind evaluation of an Aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. *Int J Radiat Biol Phys*: 36: 345-9

Online:

American Cancer Society. Aloe. Available at:

<http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/herbsvitaminsandminerals/aloe> (Accessed May 08, 2013).

Codecheck.info. Available at: <http://www.codecheck.info/product.search?q=aloe+vera&OK=Suchen> (accessed Apr 08, 2013).

EMA, European Medicines Agency. Assessment report on Aloe Barbadensis Miller and Aloe (various species, mainly Aloe ferox miller and its hybrids. Available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPA_assessment_report/2009/12/WC500017830.pdf (accessed May 8, 2013).

EWG's Skin Deep © Cosmetic Safety Database. Environmental Working Group. Available at:

http://www.ewg.org/skindeep/ingredient/700269/ALOE_BARBADENSIS_%28ALOE_VERA%29_GEL/ (Accessed Apr 08, 2013).

FDA, 2000: Message on the Internet about HACCP Inspections at Aloe Product Manufacturers

(<http://www.iasc.org/haccp.html>).

FDA, 2002. Status of Certain Additional Over-the-Counter Drug Category II and III Active Ingredients.

<http://www.fda.gov/ohrms/dockets/98fr/050902a.htm>. Accessed June 15, 2012.

Giftinformasjonen, 2008. Myggmidler – behandlingsanbefaling ved forgiftning. Available at:

<http://www.helsebiblioteket.no/Forgiftninger/Alle%2banbefalinger/Myggmidler%2b-%2bbehandlingsanbefaling%2bved%2bforgiftning.9151.cms>

IASC, International Aloe Scientific Council. Available at: <http://www.iasc.org/faq.html> (accessed May 7, 2013).

MedlinePlus. Aloe. The U.S. National Library of Medicine and National Institutes of Health. Available at:

<http://www.nlm.nih.gov/medlineplus/druginfo/natural/607.html> (accessed Sep 13, 2012).

MSKCC, Memorial Sloan-Kettering Cancer Center. Aloe vera. Available at: <http://www.mskcc.org/cancer-care/herb/aloe-vera#references> (accessed May 7, 2013).

NTP Technical Report (TR) 553, 2010. NTP technical report on the photocarcinogenesis study of Aloe vera [CAS NO. 481-72-1 (Aloe-emodin)] in SKH-1 mice (simulated solar light and topical application study). Available at: http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR553.pdf

National toxicology program (NTP). Aloe vera. Available at: http://www.niehs.nih.gov/health/materials/aloe_vera_508.pdf (accessed June 10, 2013)

RELIS. 2005. Interaksjon mellom warfarin og aloe vera? Available at: [http://relis.arnett.no/Utrekning_Ekstern.ASPX?RELIS=2&S=2612&L="](http://relis.arnett.no/Utrekning_Ekstern.ASPX?RELIS=2&S=2612&L=) (accessed Sep 13, 2012).

RELIS. 2007. Multichi Energy og Livex. Available at: http://relis.arnett.no/Utrekning_Ekstern.aspx?Relis=5&S=1452 (accessed Sep 13, 2012).

Legemiddelhandboka. Available at: <http://legemiddelhandboka.no/Generelle/søker/+%2Baloe/94085#i95315>
UpToDate. Topical Aloe. Available at: <http://www.uptodate.com/contents/topical-aloe-natural-drug-information> (accessed Sep 13, 2012).

9. Annexes

Annex 1:

TABLE 3.1 Classes and Selected Examples of Phytochemicals in Aloe vera

Class	Compound
Anthraquinones/anthrones	Aloe-emodin, aloetic-acid, anthranol, aloin A and B (or collectively known as barbaloin), isobarbaloin, emodin, and ester of cinnamic acid
Carbohydrates	Pure mannan, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, pectic substance, xylan, and cellulose
Chromones	8-C-glucosyl-(2'-O-cinnamoyl)-7-O-methylaloediol A, 8-C-glucosyl-(S)-aloesol, 8-C-glucosyl-7-O-methyl-(S)-aloesol, 8-C-glucosyl-7-O-methylaloediol, 8-C-glucosylnoreugenin, isoaloesin D, isorabaichromone, and nealoesin A
Enzymes	Alkaline phosphatase, amylase, carboxypeptidase, catalase, cyclooxygenase, cyclooxygenase, lipase, oxidase, phosphoenolpyruvate carboxylase, and superoxide dismutase
Inorganic minerals	Calcium, chlorine, chromium, copper, iron, magnesium, manganese, potassium, phosphorous, sodium, and zinc
Vitamins	B1, B2, B6, C, E, and folic acid
Miscellaneous, including organic compounds and lipids	Arachidonic acid, γ -linolenic acid, steroids (campesterol, cholesterol, β -sitosterol, triglycerides, triterpenoid, gibberellin, lignins, potassium sorbate, salicylic acid, uric acid, β -carotene, and choline
Amino acids	Alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, and valine
Proteins	Lectins and lectin-like substance
Saccharides	Mannose, glucose, L-rhamnose, and aldopentose

Sources: Vogler, B., and E. Ernst. 1999. *Br J Gen Pract* 49:823–28; Dagne, E., D. Bisrat, A. Viljoen, and B. E. Van Wyk. 2000. *Curr Org Chem* 4:1055–78; Choi, S., and M. H. Chung. 2003. *Semin Integr Med* 1:53–62; International Aloe Science Council. 2004. <http://www.iasc.org/aloemarket.html> (accessed August 18, 2009); Ni, Y., D. Turner, K. M. Yates, and I. Tizard. 2004. *Int Immunopharmacol* 4:1745–55; Hamman, J. H. 2008. *Molecules* 13:1599–616.

From: Chapter 3, Evaluation of the Nutritional and Metabolic Effects of Aloe vera



Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition.
Benzie IFF, Wachtel-Galor S, editors.
Boca Raton (FL): CRC Press; 2011.

Copyright © 2011 by Taylor and Francis Group, LLC.

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Annex 2: CosIng database (Apr 08, 2013)

#	INCI Name/Substance Name	CAS No.	EINECS/ELINCS No.	Restriction/ Annex-Part-Ref #
1.	<u>ALOE BARBADENSIS CALLUS CULTURE EXTRACT</u>	85507-69-3 / 94349-62-9	287-390-8 / 305-181-2	
2.	<u>ALOE BARBADENSIS EXTRACT</u>	85507-69-3 / 94349-62-9	287-390-8 / 305-181-2	
3.	<u>ALOE BARBADENSIS FLOWER EXTRACT</u>	85507-69-3 / 94349-62-9	287-390-8 / 305-181-2	
4.	<u>ALOE BARBADENSIS LEAF</u>	8001-97-6	-	
5.	<u>ALOE BARBADENSIS LEAF EXTRACT</u>	85507-69-3 / 94349-62-9	287-390-8 / 305-181-2	
6.	<u>ALOE BARBADENSIS LEAF JUICE</u>	85507-69-3 / 94349-62-9	287-390-8 / 305-181-2	
7.	<u>ALOE BARBADENSIS LEAF JUICE POWDER</u>	85507-69-3 / 94349-62-9	287-390-8 / 305-181-2	
8.	<u>ALOE BARBADENSIS LEAF POLYSACCHARIDES</u>			
9.	<u>ALOE BARBADENSIS LEAF POWDER</u>	85507-69-3 / 94349-62-9	287-390-8 / 305-181-2	
10.	<u>ALOE BARBADENSIS LEAF WATER</u>	85507-69-3 / 94349-62-9	287-390-8 / 305-181-2	

Annex 3: EWG database (frequency of use)

EWG's Skin Deep © Cosmetic Safety Database. Environmental Working Group. Available at:
<http://www.ewg.org/skindeep/ingredient/700269/ALOE BARBADENSIS %28ALOE VERA%29 GEL/>
(Accessed Apr 08, 2013).

ALOE BARBADENSIS (ALOE VERA) LEAF EXTRACT

CAS 85507-69-3

lipstick (307 products)

moisturizer (173 products)

lip gloss (131 products)

facial moisturizer/ treatment (123 products)

anti-aging (77 products)

Show all 1,543 products that contain ALOE BARBADENSIS (ALOE VERA) LEAF EXTRACT.

ALOE BARBADENSIS (ALOE VERA) GEL

CAS 94349-62-9

moisturizer (426 products)

facial moisturizer/ treatment (324 products)

facial cleanser (221 products)

anti-aging (199 products)

body wash/ cleanser (188 products)

Show all 3,043 products that contain ALOE BARBADENSIS (ALOE VERA) GEL.

ALOE BARBADENSIS (ALOE VERA)

CAS 8001-97-6

moisturizer (209 products)

body wash/ cleanser (161 products)

facial moisturizer/ treatment (108 products)

facial cleanser (88 products)

shampoo (83 products)

Show all 1,290 products that contain ALOE BARBADENSIS (ALOE VERA).