RISK PROFILE

Apricot kernel oil (AKO)

CAS No. 72869-69-3

Date of reporting 31.05.2013

Content of document

1. Identification of substance

Chemical name (IUPAC):	Apricot kernel oil
INCI	PRUNUS ARMENIACA KERNEL OIL
Synonyms	Apricot oil
CAS No.	72869-69-3
EINECS No.	272-046-1 / -
Molecular formula	
Chemical structure	
Molecular weight	
Contents (if relevant)	AKO is the fixed oil expressed from the kernels of the Apricot, Prunus armeniaca L., Rosaceae AKO meant for cosmetic purposes is usually produced by cold pressing of the kernel (seed) of wild (bitter) apricots (Asma BM *et al* 2007, Dwivedi DH *et al* 2008). A typical composition of such a seed is as follows (Azou Z *et al* 2009): (w/w)

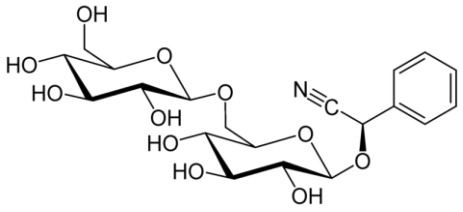
- Fat (triglycerides): 50.3 %
- Protein 27.8 %
- Sugar 11.3 %
- Fiber 3.1 %
- Moisture 5.5 %
- Ash 2.2 %

Annex 1 shows a more detailed chemical composition of the seed according to the Phytochemical database of the American Department of Agriculture[1].

A combination of cold pressing and solvent extraction (petroleum ether, hexane, chloroform-methanol or methanol) yield an AKO that consists of the lipids 92 – 98 %. Besides, that oil consists of smaller amounts of phytosterols like beta-sitosterol. Further, it contains beta-carotene and tocopherols to some extent[2]. The triglyceride acids are mostly oleic acid (51.0 – 83.3 %), linoleic acid (9.6 – 45.9 %) and palmitic acid (3.2 – 10.7 %) (Femenia A *et al* 1995).

A typical extracted oil fraction makes out around 45 % of the weight of the seed. The rest is in the form of a so-called press cake consisting mainly of protein and sugars (Gupta A *et al* 2012).

Like many of the other species of the Rosaceae (Rose) family also the apricot contains considerable amounts in the seed of the cyanogenic glycoside amygdalin. The amygdalin molecule contains a cyanide-substituent (R-CN) that may be liberated as the exceedingly toxic HCN molecule upon contact with water and beta-glycoside and so constitute a plant defense system. As concerns the apricot seed amygdalin concentrations in the range 3 – 12 % have been measured. (Al-Bakri SA *et al* 2010, Yildrum FA *et al* 2010, WHO 2007, Lv W-F, et al, 2005 Femenia A *et al* 1995, List PH *et al*). As is the case with plant secondary metabolites in general also the content of amygdalin in the seed depends upon many factors like soil conditions, harvesting time, climate etc.. An average value might, though, be 5.6 % (Yildrum).



Amygdalin

UIPAC name: [(6-*O*-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy](phenyl)acetonitrile

CAS no. 29883-15-6, Chemical formula is $C_{20}H_{27}NO_{11,}$ MW=

[1] http://www.ars-grin.gov/duke/

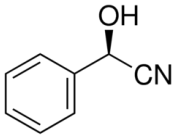
[2] According to Gupta A *et al* 2012 the concentration of tocopherol is in the range 269 – 436 ppm, which makes the seed/oil a valuable source of vitamin E.

457.43 g/ mol

This endogenic substance also is still confusingly named vitamin B17 by some even though it has been cleared up a long time ago it is not a vitamin.

Recent high-resolution Raman imaging have revealed that throughout the seed there are local amygdalin “concentration-spots” (Kraft C *et al* 2012).

Trace amounts in the range 0.5 – 5.0 ppm of the amygdalin aglycon mandelonitrile are also present in the seed. It is located to the seed water fraction. (Miyachi S *et al* 1987)



Mandelonitrile (CAS No 532-28-5)

Mandelonitrile is an unstable molecule that may spontaneously decompose into HCN and benzaldehyde.

Further, the seed contains certain amounts of the enzyme emulsin (β-glucosidase) that in contact with water and upon rupture of the seed may decompose the contained amygdalin into HCN, benzaldehyde and glucose[3]. The seed of (bitter) apricot invariably, contain small amounts of HCN[4]. Newall CA *et al* (1996) determined a HCN level in the seed in the range 0.0020 -0.2000 %. According to another author as much as 0.293 % has been measured (reference in the monograph on apricot in the Herbal Medicines 3rd Edition 2007) EFSA (2004) conveys that up till 0.4 % has been found. HCN may be determined by using Alkaline-titration method (AOAC, 1995; cited in Gupta & Sharma, 2009)[5].

According to the more recent articles by Gupta & Sharma (2009) and Gupta A *et al* (2012), the HCN content in the seed range 0.148 – 0.173 %. They found that extraction of oil caused HCN concentration levels of 0.090 % in the press cake and 0.042 % in the AKO. So according to the finds of these researchers about 25 % of the HCN of the seed ends up in AKO obtained by combined cold pressing and solvent extraction. This partitioning could be explained by the fact that HCN is predominately hydrophilic having a partition coefficient (Log Kow) of -0.7. [6].

Probably, in the seed the HCN goes with the amygdalin so that the mentioned local “concentration-spots” throughout the seed contain both molecules.

[3] Emulsin is localised in particular cells of the seed and, therefore, unable to act upon the amygdalin until the seeds are crushed and water added.

[4] Also sweet apricot seeds contains some amygdalin (and HCN); ca. 0.9 % according to Yildrum.

[5] Official methods of analysis. Association of Official Analytical Chemists, Horwitz, W. (Ed.), 16th ed. Washington, D.C USA.

[6] http://www.atsdr.cdc.gov/toxprofiles/tp8-c6.pdf

	Apparently, the AKO resulting from cold pressing and subsequent solvent extraction does not contain any amygdalin.[7] This tally with it being hydrophilic having a partition coefficients (Log Kow) amounting to -4.34 (estimated)[8]. So, probably, all of it ends up in the press cake. Therefore, producing amygdalin *per se* (for medicinal purposes mostly), the press cake must serve as the raw material source. Amygdalin is extracted from the press cake using boiling 95 % ethanol. Subsequent distillation yield pure amygdalin in the form of an *essential* oil (*Amygdae Essent. Pers*)[9]. We would believe that *virgin* AKO produced *solely* by use of cold pressing – i.e. not also subsequently being refined by use of solvent extraction of the lipids – contains not only some amounts of HCN but also some amounts of amygdalin. This because both molecules are more or less evenly distributed throughout the seed. There is an analogy with, for example, virgin olive oil that contains also some additional amounts of different non-lipid fruit substances. We presume amygdalin blends in well with lipids of the fixed oil since it takes the form of an essential oil when in the pure state. This is in analogy with aromatherapy procedure where small amounts (1/2 – 4 %) of essential oils are mixed with fatty vegetable fixed oils. Seemingly, the literature data on the composition of the AKO have been generated entirely by parties occupied with the nutritional value of the seed (due to the seed's high content of **essential** fatty acids). Therefore, all the data concerning the composition are for AKO, are produced applying solvent extraction refinement. So we observe a void in the literature as to the composition of **virgin** AKO and to which extent this quality contains amygdalin and HCN. We presume, though, it is much more polluted with these toxicants than is the refined quality. We observe that numerous different *unrefined* cold pressed AKO products are offered for sale on the web. These would be 100 % AKO products. For one of them the following announcement is made[10]. "Apricot seed oil is a non-refined product cold pressed from the seeds of apricot. It has mainly moistening properties and is rich in vitamin A and E. The oil is recommended for different types of skin, especially dry, mature and sensitive. A perfect choice for massage. It contains vitamin B17 – so called amygdalin or laetrile." Many other AKO products announced on the web are said to contain B17 (amygdalin) and /or are said to be unrefined (virgin) oils – see Appendix 2 on that. In order to get rid of also the minute remains of HCN in the refined quality as mentioned, Gupta & Sharma developed 4 different modified extraction procedures by which the HCN content in the kernel and the

[7] http://www.shenet.se/ravaror/aprikosolja.html
[8] http://www.thegoodscentscompany.com/episys/ep1233651.html
[9] http://botanical.com/botanical/mgmh/a/apric050.html
[10] http://www.e-naturalne.pl/en_US/p/Apricot-seed-oil-unrefined-/471

	oil could be brought down from the mentioned levels to nil. (Gupta & Sharma 2009).[11] Finally, according to the Phytochemical database of the American Department of Agriculture the seed contains even some amounts of the hormones alpha-estradiol[12] and estrone (E1) (List PH *et al*). Independent of this database the author Ning DD *et al* (1990) also informs that the seed contains beta-estradiol (E2) and E1. Further, and also independent of the database, a third source informs that the seed contains both free and conjugated estradiol and E1 in a separate oestrogenic fraction that makes out 0.09 % of the seed by weight. (Monograph on apricot in the Herbal Medicines 3rd Edition 2007 wherein it is referred to Awad O 1973). These hormones can also be synthesized in small quantities by other plants [13]. Scanning through the internet we saw only two companies, a Chinese,[14] and a British one, [15] claim the apricot **seed** they market contains estradiol and estrone,[16] Even though marketers for some reason rarely feature this content [17] it probably occur frequently if not regularly. These oestrogens are inherently more potent in their oestrogenic feminising effect than any **typical** phytoestrogen [18] not to speak of some synthetic chemical having attracted much interest in recent years like, for example, some of the parabens and bisphenol A.. E1 and E2 are the two foremost human feminine sex-hormones. In view of their lipophilic character - Log Kow of 3.94 and 3.43 respectively (Ying GG *et al* 2002) – we would expect them to be present even in *refined* AKO.

[11] Immersion in 5 ppm beta glucosidase solution (very expensive), Immersion in 25% salt solution, Blanching, Immersion in 10 % Sodium thiosulphate solution

[12] Competition curves show that 17 alpha-estradiol binds to the cytosol oestrogen receptor with about one third the affinity of 17 beta-estradiol (E2) (Wikipedia).

[13] According to the Phytochemical database of the American Department of Agriculture the plant *phaseolus vulgaris*, i.e. common beans, produce beta-estradiol (E2). Further, according to this source the following plants produce estrone (E1): *punica granatum* which is pomegranate (17 ppm in the seeds), apple (0.1 ppm in the seed), hops (fruit), olive (seed) and date palm (seed). The following two plants also produce estradiol: pomegranate (seed) and hops (fruit). Hops which is one of the ingredients going into brewing of bear is, by the way, known for its ability to make some men develop feminine traits like breasts.

[14] Xi'an Reputation Technology Co.ltd

[15] http://www.chemfaces.com/direct/Prunus-armeniaca-L-20294.html

[16] http://www.china-telecommunications.com/products-search/organic_apricot_seed-pz1d0626e-zdb15b2.html
http://www.china-telecommunications.com/products-search/organic_apricot_seeds-pz21a6bee-zd8ce34.html

[17] The following statement recently put by the Turkish authors Yilmaz T *et al* (2013), they promoting the beneficial nutritional traits of apricot, may explain the resentment against mentioning anything about the content of oestrogens in apricot:

> *Despite the large number of studies conducted, there is still no clear evidence whether phytoestrogen intake has a beneficial or detrimental effect on human health and further research has been recommended by authors (21, 22).*

[18] The molar excess to achieve 50 % inhibition of the 3H-E binding to the oestrogen receptor is (Matsumura A *et al*, 2005):. E2; 1, Coumestrol: 35, 8-Prenylnaringenin: 45 (in Hops), Deoxymiroestrol: 50, Mistrol: 260, Genistein 1000 (in soy), equol: 4000.

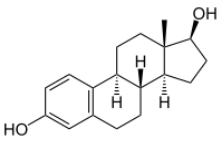
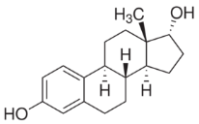
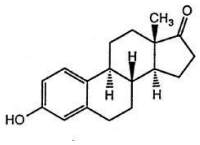
	Estrogens have anti-aging effect on the skin in post-menopausal women (Stenson S *et al* 2007). Topical application of beta-estradiol (E2) at low 0.01% (100 ppm) for two weeks stimulates collagen production in sun-protected skin (Rittié L *et al* 2008). Also several older studies on the anti-aging effect of estradiol in women showed significant effects at 100 ppm (Elsner P and Maibach HI 2000). When in the first half of the 50s the FDA first started to intervene against cosmetic anti-wrinkling hormone products out of safety concerns there where several such products on the market - in Europe also. For information on this, see the historical overview by James Bennet 23rd April 2013[19] .Apparently, the content of estradiol in these products from the past varied from 5 ppm and up till 526 ppm. Allegedly, according to these old records, down to 25 ppm were considered effective concentrations. The FDA took – and still takes - action against products with more than 35 ppm[20]. A company behind a product containing 116 ppm stipulated a recommended daily dosage of 0.03 mg estradiol (James Bennet). That would be a dose applied onto the skin. Assuming a skin penetration rate of 10 % *(inter alia*) and a body weight of 60 Kg that dose on the skin correspond to a systemic dose per day as little as 0.00005 mg/Kg bw. The smallness tally with the observation that hormones execute their different effects in the body at vanishingly small concentrations. A therapeutic dose of **oral** estradiol for hormone-replacement therapy (HRT) in adults is 0.05 mg/d (Li S-T *et al* 2002).[21] HRT also involves **transdermal** doses of estradiol in the range from 0.025 mg/d to 0.1 mg/d (Wikipedia/ British Medical Association, 1997). These dosages also have a proven rejuvenating effect in the skin of postmenstrual women. And they are about of the same minute size as the dosages received by use of the mentioned cosmetic creams. So, only very small dosages of estrogens taken up in the body over the epithelia/skin have significant physiological effects. We, therefore, do not consider it entirely unbelievable that AKO containing only trace amounts of alpha-estradiol, E1 and E2 execute a slight anti-wrinkling effect. Alpha-estradiol, E1 and E2 has since 21 February 1989[22] been prohibited in cosmetic products as ingredients in their own respect. They are now listed in CosIng under the provision II/260 of the EU

[19] Most hormone cosmetic creams produced up until the 1960s that actually contained estrogens – rather than skin extracts, dried glands, placenta or other materials – consisted of estrone, estradiol and estriol, as well as equilin and equilenin if the estrogens were extracted from the urine of pregnant mares. There is definite support for the anti-wrinkling effect produced by the use of hormone cosmetics based on (a) the thickening of the epidermis, (b) plumping of the collagen fibers. Ref: the source James Bennett that edit the internet page "**Cosmetics and skin /** Stories from the history and science of cosmetics, skin care and early Beauty Culture" at http://www.cosmeticsandskin.com/bcb/hormone-creams.php

[20] 10 000 I.U. per ounce. 10 000 i.U. estradiol corresponds to 1 mg (MERCK Index).An American ounce is equal to 28.5 gram.

[21] http://www.goodbyepms.com/shampoo.htm

[22] amending directive 98/174/EEA

	regulation 1223/2009. This provision does not mean, though, that AKO containing these substances is forbidden as ingredients in cosmetics. Irrespective of the trace levels , AKO with all its natural constituents are allowed in cosmetics, provided that it can be used safety. So even though all the mentioned hormone products from the past are currently forbidden AKO can find use as kind of anti-aging hormone product. Provided, of course, that it contain workable amounts of these oestrogens. The information that the seed contains an oestrogen fraction that outdoes as much as 900 ppm of the seed may indicate that AKO actually can function as an anti-wrinkling agent.  Beta estradiol (E2)  Alpha estradiol  Estrone (E1)
Physiochemical properties	Gupta A *et al* (2012) provides some data.. AKO is quite strongly unsaturated and tends, therefore, to go rancid fairly quickly,

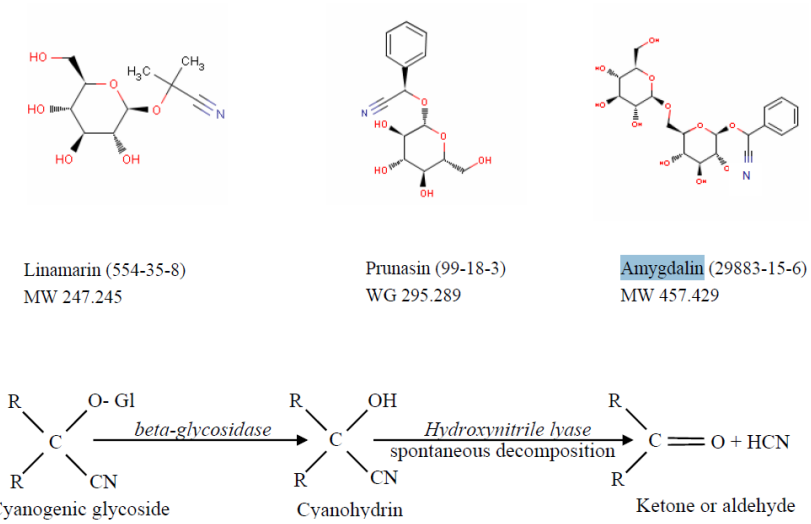
2. Uses and origin

Uses	➢ **Cosmetic products:** *Functions according to* • CosIng database: - Emollient - Softens and smooth the skin - Emulsifying - Promotes the formation of intimate mixtures of non-miscible liquids by altering the interfacial tension - Surfactant - Lowers the surface tension of cosmetics as well as aids the even distribution of the product when used - Skin conditioning - Maintains the skin in good condition • Other: - Skin care products, supposed to be well suited for people with dry skin, e.g. elderly - Carrier oil – e.g. base for aromatherapy mixtures –mixed with other oils to facilitate spreading. It is readily absorbed without leaving a residue behind on the skin surface - AKO is high in vitamins A (beta-carotene) and E. Other functions: sooth irritated skin while also moisturizing; keep the skin smooth and flexible. AKO is used in lotions, creams, balms, and frequently in massage oils, as well as in soaps.

	Being light-textured AKO has softening effect on the skin and is ideal for massage of the delicate skin around the eye and on the throat. It also makes a good base for the treatment of dry, sensitive, chapped and mature skin due to its skin tightening ability and slight astringent quality. *Concentrations of AKO being applied* One suppliers of AKO - and other herbal oils - recommends that producers of ready to use cosmetic products incorporate this much AKO in the products: [23] Lotions and Creams: 2 - 30% Body and Lip Balms: 5 - 50% Bar Soap: 3 - 12.5% Information provided in Annex 3 also indicates that the usage levels are very high. Even numerous 100 % unrefined AKO for cosmetic use are being offered for sale on the web- see Annex 2. *Frequency of use* The EWG Skin Deep [online] database lists 35 concrete cosmetic products containing AKO (Annex 4). The German Codecheck.info [online] database, on the other hand lists as many as 626 products (May 29, 2013) that contain AKO. According to a source AKO is also often being fraudulently added to almond oil.[24] The main utilizer of AKO is the cosmetic industry (Silem A *et al* 2006). ➢ **Food** The fatty acid composition of (refined) AKO is considered suitable for replacement of vegetable oil (e.g. biscuits and cakes). Also it is used for culinary flavoring purpose. A liqueur manufactured in France called Eau de Noyaux is made from apricot seed. AKO has Generally Recognized as Safe (GRAS) status in the United States. ➢ **Medicinal products** AKO is used as a vehicle for pharmaceutical preparations. See further information in part 6 under pharmaceuticals.
Origin Natural (exo /endo)	The apricot (fruit of the *Prunus armeniaca* tree) encloses a hard nut surrounding a droplet shaped reddish-brown seed or pit. At the core of the

[23] Majestic Mountain Sage 2490 South 1350 West Nibley, Utah 84321 / https://www.thesage.com/index.html

[24] http://www.altmd.com/Articles/Apricot-Seed--Encyclopedia-of-Alternative-Medicine

Synthetic	pit is the kernel, which can be pressed to yield AKO which is quite similar to almond and peach oil (Gupta & Sharma, 2009). *Toxicity* The toxicity of apricot kernels is caused by cyanide (HCN) which, as explained above, is released by enzymatic hydrolysis of amygdalin - the predominant cyanogenic glycoside variant in apricot kernels.[25] Cyanogenic glycosides such as amygdalin are considered non-toxic until HCN is released. This usually occurs as a result of enzymatic hydrolysis by β-glucosidases (following grinding of plant tissue) or by the gut micro-flora. It is noteworthy that these enzymes are not found in mammalian cells. As a result, amygdalin is 40 times more toxic by the oral route as compared to intravenous injections (HSDB[online]).  Figure 1. Structures of common plant-derived cyanoglycosides and principle pathway of HCN formation. *Mechanism of action*: Cyanide acts through the inhibition of cytochrome c oxidase in the respiratory electron transport chain of the mitochondria, impairing both oxidative metabolism and the associated process of oxidative phosphorylation. Thereby it causes death through energy deprivation. *Purification of amygdalin* As mentioned, amygdalin can be brought to (almost) complete removal by optimizing the oil extraction technology (Gupta & Sharma, 2009; Beyer & Melton, 1990).

[25] Around 60 cyanogenic variants are known in more than 2000 plant species (EFSA, 2004).

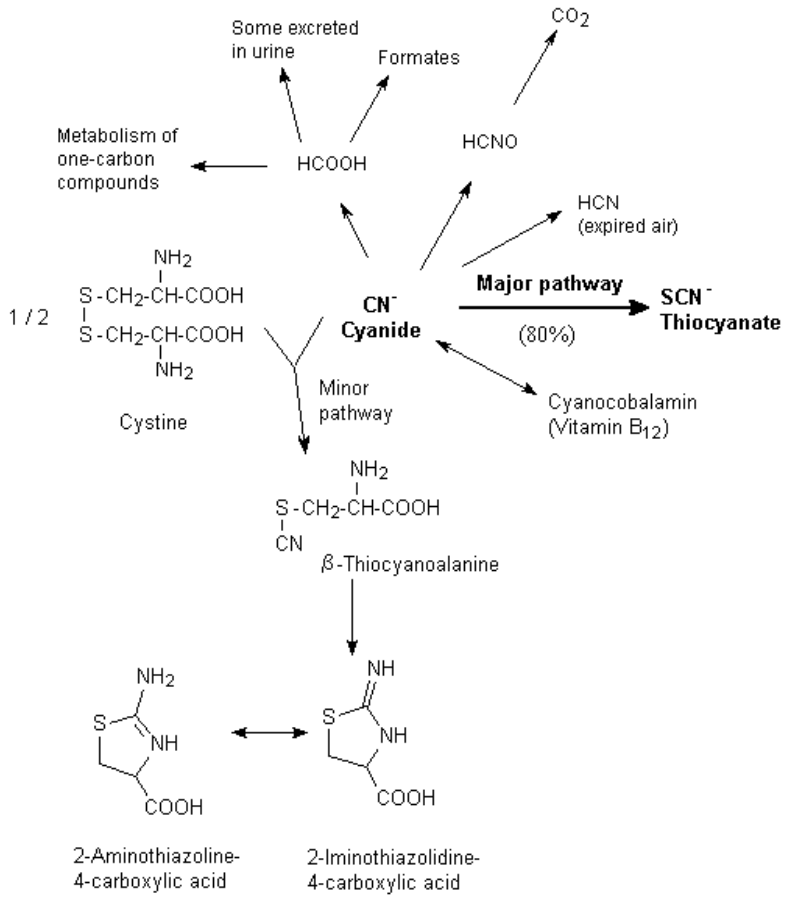
3. Regulation

Norway	Purity requirement: Must not contain cyanides[26]
EU	No regulation
Rest of the world	No regulation

4. Relevant toxicity studies

Absorption Skin / GI tractus	AKO is known to be readily absorbed into the skin, and can also enhance penetration of other components. In a study evaluating vehicle effects on *in vitro* skin permeation of model drugs caffeine and testosterone, PEG-6 esters of AKO facilitated the flux and diffusivity of caffeine across the stratum corneum, when compared to the much used and powerful vehicle propylene glycol (Bonina *et al.,* 1993). AKO is considered to be relatively free from HCN – see above. If subjected to newly developed purification procedure no HCN is contained. Purified solvent extracted AKO also do not contain amygdalin. However, also many unrefined (virgin) AKO products are in use for cosmetic purposes. We would believe this oil to contain up till 0.2 % HCN and additionally on average ca. 5.6 % amygdalin (*inter alia*). Even higher amounts of both HCN (0.4 %) and amygdalin (12 %) have been measured, though. Following oral administration amygdalin are hydrolyzed by β-glucosidases in the gut microflora..The released HCN is readily absorbed and rapidly distributed in the body via the blood (EFSA, 2004; HSDB[online]). To the extent amygdalin is absorbed intact into the body over the gut epithelium - or over the skin – it is normally not bio-transformed to HCN, i.e. it is relatively non-toxic when taken up in the body reaching circulation. See, however below about tests that apparently showed that under certain condition some of the amygdalin taken in orally spit off HCN never the less.. It is noted that not only *gut bacteria* show beta-glycosidase activity. So does also some of the *bacteria of the skin micro-flora*. Among these are the commonly occurring bacteria *Pseudomonas aeruginosa* (Hildebrand DC *et al* 1964), *Staphylococcus aurus* (Al-Bakri SA *et al* 2010, Hildebrand DC *et a*l 1964) and *Propionbacterium acnes* (Sadia A *et al* 2010). We hold it probable, therefore, that **virgin** AKO when applied on to the skin are somewhat enriched in HCN because of the enzymatic action of these bacteria, The formed HCN subsequently is rapidly and fully absorbed into the body. The permeability constant measured for the cyanide ion in aqueous solution was 3.5×10^{-4} cm/h, and that calculated for hydrogen cyanide

[26] Current Norwegian cosmetics regulation- to be lifted 11 July 2013;

	was 1 × 10^{-4} cm/h (Dugard, 1987 in INCEM /WHO monograph on HCN/CN 2004). In lack of concrete data we assume a skin penetration rate of 100 %.
Distribution	
Metabolism	Even AKO produced by use of solvent extraction contain minute amounts of HCN. Virgin AKO conceivably contains some amygdalin additional to HCN. Bacterial micro flora of the gut epithelia or on the skin bio-transform amygdalin into HCH. Following uptake in the body HCN is metabolically converted to the less toxic thiocyanate (HSDB[online]; EFSA, 2004). Acute toxicity occurs when the metabolic detoxification capacity of the body is exceeded. See also INCHEM / WHO 2004 monograph that provides the following overview as to metabolism/ catabolism:  The limiting factor in cyanide metabolism is the low concentration of the sulphur-containing substrates in the body — primarily thiosulfate, but also cystine and cysteine.
Excretion	Rats treated orally with 2 mg cyanide/kg bw excreted 47% of the dose in the urine within 24 h (Farooqui & Ahmed, 1982 in WHO 2004). The half-time for hydrogen cyanide elimination is about 1h. (WHO 2004).

Local toxic effects Irritation Sensitivity	The Danish EPA in a report 2002 based on a literature survey on AKO expressed it had not found any data on allergy, irritation and phototoxixcity (Danish EPA 2002). Administration of sodium cyanide (1.7-5.3 mg/ Kg day) to the inferior conjunctival sac of rabbits resulted in irritation, lacrimation and conjunctival hyperaemia immediately after treatment (UK HPA 2012). Cyanides are considered only weakly irritating to the skin and eye (WHO 2004)
Systemic toxic effects	The systemic effects of an AKO expressed from **mild** seed – which do not contain appreciable amounts of amygdalin - were assessed in a 13-week feeding study in rats. The animals were fed a diet containing 10% such AKO. No toxic effects were observed and no macroscopic or microscopic lesions in any of the organs were found (WHO 2007). There are no other data available on AKO *per se* but on amygdalin and HCN/ cyanide.
Acute	***Amygdalin*** Toxicity following parenteral absorption of amygdalin is low. However, cyanide poisoning has been reported in rats following i.p. administration of laetrile, suggesting another mechanism of hydrolysis than that involving beta-glycosidase had occurred (Herbal medicine 3rd edition 2007). Following i.p. daily administration of 250.0, 500.0 or 750.0 mg/kg bw of amygdalin to rats for 5 days, mortalities were 30.8%, 44.1% and 56.8%, respectively. The mode of death and the elevated serum cyanide levels in the dying animals strongly suggested cyanide poisoning as the cause of death (*WHO 2007)*. So these experiments indicate that although β-glycosidase is not present in mammalian cells, body tissues to some extent are nevertheless somehow capable of splitting off HCN from the amygdalin molecule. The dosages used in the last mentioned experiment were exceptionally large – and can never be attained administrating AKO dermally or orally in real life.
Analgesic effect	Amygdalin show analgesic effect. In the hot plate and acetic acid induced writhing tests in mice, the analgesic median effective doses (ED50) were 457.0 mg/kg bw and 288.0 mg/kg bw, respectively. However, at these doses, amygdalin could not substitute for morphine in morphine-addicted rats in relieving withdrawal syndrome. Effect is not subject to tolerance development (WHO 2004).
Aglycon possess genotoxic properties	Studies have shown that the aglycon mandelonitrile is a mutagenic molecule (Chandler RF *et al* 1984). ***HCN / -CN*** Information related to acute toxic effects of cyanide from e.g.

	consumption of stone fruit kernels has been briefly summarized in Annex 5.
Acute	The lethal **oral** dose in humans is about 0.5 – 3.5 mg HCN /kg bw (EFSA, 2004; BfR, 2007). The lowest reported **oral** lethal dose for humans is 0.54 mg/kg bw, and the average absorbed dose at the time of death has been estimated at 1.4 mg/kg bw (calculated as HCN). (WHO 2004). According to the source UK HPA (2012) referring to WHO 2004 the **dermal** LD_{50} following application of cyanides in aqueous solutions to rabbit **skin**, have been reported in the range of 7-10 mg/ kg bw. Toxicity is markedly greater following application to abraded skin. LD_{50} for hydrogen cyanide in humans have been estimated to 1.1 mg/kg bw for intravenous administration and 100 mg/kg after **skin exposure** (Rieders, 1971 in WHO 2004).
Repeated dose	See below under neurotoxicity/other toxicity where a 13-week repeated-dose toxicity study in rats is mentioned. At 12.5 mg cyanide/kg bw per day, there were slight changes in the male reproductive tract considered possibly significant to humans. The no-observed-adverse-effect level (NOAEL) for these effects was 4.5 mg/kg bw per day. Another 13-week behaviour study in mini-pigs suggested a LOAL of 1.2 mg cyanide/kg bw/day. Forty-six male adult inbred Wistar rats were used in four experimental groups and one control group and treated with 0, 0.12, 0.36, 1.2, and 3.6 mg cyanide/kg bw per day in the drinking-water for 15 days. The high-dose group exhibited a 70% lower body weight gain than the control animals. In qualitative histological analysis, without statistical treatment or morphometric analysis, changes were observed in the kidney, liver, and thyroid. Cytoplasmic vacuolation, considered to reflect hydropic degeneration of proximal tubular epithelial cells, was noted in animals treated at doses of 1.2, and 3.6 mg cyanide/kg bw per day and in hepatocytes of those animals treated at a dose of 3.6 mg cyanide/kg bw per day. A dose-dependent increase in the number of reabsorption vacuoles on follicular colloid in the thyroid gland was noted in all animals of the experimental groups. No changes were observed in serum triiiodothyronine (T_3), thyroxine (T_4), creatinine, or urea levels; a decrease was observed in serum alanine aminotransferase (ALAT) activity at the two lowest exposure levels. Serum aspartate aminotransferase (ASAT) was elevated by 30% at the two lowest dose levels and by 21% at the 1.2 mg cyanide/kg bw per day dose; it was decreased by 29% at the highest dose level (Sousa et al., 2002 in WHO 2004).
Mutagenicity /genotoxicity	There are no studies on which to assess the genotoxicity of hydrogen cyanide per se. However, sodium cyanide, was not mutagenic in Ames tests using S. typhimurium strains TA100, TA1535, TA97, or TA98 with or without exogenous metabolic activation. Similarly, potassium cyanide was negative in Ames tests using S.typhimurium strains TA1535, TA1537, TA1358, TA98 and TA100. It has been stated that the weight of evidence is that cyanide is not genotoxic (UK HPA 2012). Hydrogen cyanide has no structural alerts for DNA reactivity and in view of this and from the battery of Ames tests (all negative) on its simple salts

	it is concluded that cyanide does not have any significant mutagenic properties. (UK HPA 2012).
Carcinogenicity	Very little data are available from long-term toxicity and carcinogenicity studies with cyanogenic glycosides, or with cyanides (EFSA, 2004; HSDB[online]). Only adequate study we saw is an old two-year feeding study in which, rats were provided with food fumigated with hydrogen cyanide, with customised jars used to limit loss through volatilisation. Intakes in treated animals were 4.3 mg/ kg bw day and 10.8 mg/ Kg bw day. No treatment related effects on survival or growth rate, signs of toxicity or haematological or histopathological changes in examined organs was noted and a NOAEL of 10.8 mg /Kg bw day was established [UK HPA 2012 referring to WHO 2004 which refer to Howard JW *et al* 1955]. WHO is of the view that because of the small group size this study is not informative with regard to the possible carcinogenicity of cyanides.
Reprotoxicity / teratogenicy	There are limited data that indicate that continued exposure to high doses of sodium cyanide may be teratogenic in man, however the clinical relevance of this data is unclear; and no syndromes of human malformation after exposure to cyanide compounds have been reported. Cyanide ions can, however, cross the placenta and maternal exposures to high concentrations of cyanide ion may therefore be toxic to the foetus (UK HPA 2012). . In a study using hamsters, sodium cyanide (78.7-80.9 mg /kg bw day) was administered by continuous infusion by mini-pumps on days 6-9 of gestation. A range of developmental abnormalities were reported including neural tube defects, exencephaly, encephalocele and malformations of the heart, limbs or tail [28]. Maternal toxicity was apparent in the majority of dams and included weight loss, dyspnoea, in-coordination and hypothermia. Removal of the pumps resulted in improvement and recovery of findings in the dams. The incidence of both maternal and foetal toxicity was reduced in animals that were co-administered sodium thiosulphate and sodium cyanide, providing support for its use in antidote regimens for cyanide intoxication [28]. Based on limited data, it was concluded that cyanide induces developmental effects only at doses that are overtly toxic to the mothers [1].(UK HPA 2012)
Neurotoxicity and other effects	Due to its high dependency on oxidative metabolism and limited anaerobic capacity, the central nervous system is particularly vulnerable to cyanide intoxication. Consumption of food containing cyanogenic glycosides has been linked to several different diseases affecting mainly the nervous system[27]. Also some animal studies may indicate that long term exposure to low levels of cyanide lead to neurological defect that

[27] WHO (2004) mention the following examples: tropical ataxic neuropathy in Nigeria, spastic paraparesis (called mantakassa in Mozambique and konzo in the Democratic Republic of the Congo) in Cameroon, Central African Republic, Mozambique, Tanzania, and the Democratic Republic of the Congo (formerly Zaire), as well as retrobulbar neuritis and optic atrophy associated with pernicious anaemia

cause behavioral disturbances (UK HPA).

WHO (2004)

- Neurotoxicity / reproduction toxicity

In a 13-week repeated-dose toxicity study in which cyanide was administered in drinking-water, there were no clinical signs associated with central nervous system effects or histopathological effects in the brain or thyroid of rats or mice exposed to doses up to 12.5 mg and 26 mg cyanide/kg body weight per day, respectively. At 12.5 mg cyanide/kg body weight per day, there were slight changes in the reproductive tract in male rats, which, although they apparently would not affect fertility in rats, are possibly significant to humans. The no-observed-adverse-effect level (NOAEL) for these effects was 4.5 mg/kg body weight per day. The examination of neurotoxicity in this study was limited to clinical observation and optical microscopy in autopsy (ATSDR, 1997 in WHO 2004).

A few available studies specifically intended to investigate neurotoxicity, have reported adverse effects at exposure levels of 1.2 mg cyanide/kg bw per day in rats and 0.48 mg cyanide/kg bw per day in goats. WHO expresses that these studies suffer from weaknesses that preclude their quantitative assessment. No quantification or statistical analysis of the findings was presented (goat).

WhO also mention, however, one neurotoxicity/behavioural study in particular. This is the one of Jackson (1988) that involves experimenting with miniature pigs. :

> The effects of cyanide on behaviour were studied in fasted 25-week-old miniature pigs (12 litter mates: 5 females and 7 castrated males) randomized in four groups. The animals were dosed daily for 24 weeks with a single bolus of cyanide as aqueous potassium cyanide just prior to the daily feeding. The doses were 0, 0.4, 0.7, or 1.2 mg cyanide/kg body weight, chosen to be equivalent to those consumed by West Africans in their diet (Jackson et al., 1985). Every 6 weeks, thyroid function (T_3 and T_4) and fasting blood glucose were measured, but not thyroid-stimulating hormone (TSH). Daily observations were made of clinical signs and various behavioural measurements, including social, antagonistic, exploratory, learning, feeding, and excretory behaviour. In all treatment groups, dose-related decreases were evident from week 6 in blood levels of T_3 and T_4, and an increase in fasting blood glucose was noted, particularly in top-dose animals. Statistical analysis was not provided for each dose group versus control, but changes in top-dose animals appeared significant by week 18; by week 24, decreases of 35% for T_3 and 15% for T_4 and an increase of 60% in fasting blood glucose were observed. Behavioural observations revealed a picture of decreased high energy-demanding behaviour, such as exploration and aggression, slower eating, more frequent drinking, and shivering consistent with the decreased thyroid activity. A LOAEL of 1.2 mg/kg body weight per day could be suggested from this study (Jackson, 1988).

The study of Jackson involved a very small number of animals (three

Human data	animals in four groups) and limited statistical analysis. • Goitre The endocrine system is also a potential target for long-term toxicity, as a function of continued exposure to thiocyanate, which prevents the uptake of iodine in the thyroid and acts as a goitrogenic agent. Occupationally workers exposed to HCN have developed goite and concomitantly also signs of neurotoxicity (WHO) WHO is of the view that limited information on exposure and confounding factors precludes the use of studies on people exposed at work in hazard characterization.
Miscellaneous effects caused by surplus **oestrogens**	***Possible health injuries due to presence of estradiol and estrone (E1) in AKO*** The systemic dosages received over skin using hormonal cosmetic products are about of the same magnitude as dosages received in transdermal post-menopausal oestrogen therapy *(inter alia*). Women subjected to such medicinal regime experience occasionally side effects like elevated blood pressure and hypercoagulability (blood clots). Medilexicon [28]. Besides, although being a controversial subject, there are also indications they have a higher risk of breast cancer, heart disease and stroke (textbook). The FDA is of the view that 1 mg oestrogen per ounce (28.5 g) – i.e. 35 ppm - is an acceptable amount for **cosmetic hormone creams**, as long as the amount used are no greater than 2 ounces per month, i.e., a user would have an exposure of ca. 0.07 mg or less of oestrogens per day on skin. See Annex 6.

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	Transdermal hormone-replacement therapy (HRT) involves doses on skin of estradiol in the range from 0.025 mg/d to 0.1. Assuming a skin penetration rate of 10% (literature data in Zatz JL 1993) and a body weight of 60 Kg this means that the transdermal HRT involves a daily systemic dosage of low 0.000042 mg/Kg bw. Such dosages apparently, involve a certain risk for hypertension and blood clothing (*inter alia*). So this dosage, although apparently tolerable in medicinal therapy, cannot be considered safe in the context of cosmetic products. FDA apparently think a systemic exposure amounting to no more than 0.000011 mg/Kg bw is safe. Seemingly, however, this is more of a lowest possible anti-wrinkling effect level than a level below which the exposure is safe.

[28] http://www.medilexicon.com/drugs/estradiol_transdermal_system.php

	A NOAEL for the hypertension and a blood clothing effect seems not to have been determined. Therefor, we will not base our risk assessment on these effects but on the mentioned toxicity effects of the cyanides. The WHO Guidelines for Drinking-water Quality (WHO, 2003) derived a tolerable daily intake of 12 µg HCN /kg body weight by considering 1.2 mg/kg body weight in the Jackson (1988) study as a LOAEL and applying an uncertainty factor of 100. When not able to determine a NOAEL on available toxicity data the scientific committee of the European Commission (SCCS) establish, generally, a NOAEL dividing LOAEL values with a factor of 3. This is customary toxicological practice also. NOAEL = LOAEL/3 = 1.2 / 3 = 0.4 mg HCN /Kg bw day.
Exposure cosmetic products	For illustrative purpose we assume a **virgin** AKO containing 5.6 % amygdalin and 0.2 % HCN be used for the following cosmetic purposes: Body lotion: 25% Massage oil 100 % Face creams: 15% Because the skin bacterial flora notoriously contains beta-glycosidase amygdalin, probably, splits off HCN enzymatically when applied topically. We have no information about how much of the applied amygdalin is decomposed into HCN. In order to get an idea about how much influence the decomposing may have on the exposure and the margin of safety, we in one alternative assume 100 % decomposing and in another no decomposing at all. 5,6 % amygdalin corresponds to 0.33 % HCN. So in the 100% alternative we assume that 0.53 % HCN is available for skin absorption. We recon with a HCN skin penetration rate of 100 % **The alternative with 100 % decomposing of amygdalin** • Body lotion Calculated relative daily exposure of product: 123.20 mg/kg bw/day (SCCS default value) Concentration of HCN in the product 0.53 x 0.25 % = 0.13 % SED = 123.20 x 0.0013 x 1.0 = **0.16 mg /kg bw /day** • Massaging oil

	Premise for amount of oil being applied on to skin for one full body massaging is set to 40 ml corresponding to 40 000 mg (aromatherapy practice) [29]. Body weight premise: 60 Kg (SCCS guide) Concentration of ingredient in the product: 0.53% Frequency; 1 massage treatment per month (assumed) SED = 40 000 x 0.0053 x 1.0 / 60 = 3.5 mg/kg bw / month SED per day: 3.5 / 30 = **0.11 mg /kg bw** • Face cream Calculated relative daily exposure of product: 24.14 mg/kg bw/day (SCCS default value) Concentration of HCN in the product: 0.53 x 0.15 % = 0.08 % Dermal absorption (assumed): 100% = 1.0 SED = 24.14 x 0.0008 x 1.0 = **0,02 mg/ kg bw** **The alternative with no decomposing of amygdalin** • Body lotion Calculated relative daily exposure of product: 123.20 mg/kg bw/day Concentration of HCN in the product 0.20% x 0.25 % = 0.05 % SED = 123.20 x 0.0005 x 1.0 = **0.063 mg /kg bw** • Massaging oil Concentration of HCN in the product: 0.20% SED = 40 000 x 0.002 x 1.0 / 60 = 1.3 mg/kg bw / month SED per day: 1.3 / 30 = **0.043 mg /kg bw** • Face cream Calculated relative daily exposure of product: 24.14 mg/kg bw/day Concentration of HCN in the product: 0.2 x 0.15 % = 0.03 % Dermal absorption (assumed): 100% = 1.0 SED = 24.14 x 0.0003 x 1.0 = **0,007 mg/ kg bw**
Margin of Safety (MoS)	MoS = NOAEL/SED

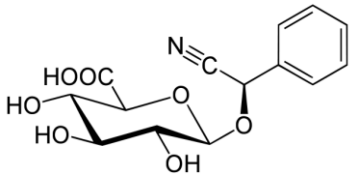
[29] On the background of information about aroma therapy practice as conveyed by the source http://nativessentials.com/shop/en/content/11-how-to-use-plant-oils we apply 40 ml (40 000 mg) as the amount of oil being consumed in a single full body massage treatment:

- **Woman size M/L full body massage** approx. 30/40 ml of carrier oil + 15/18 drops of essential oil.
- **Man size L/XL full body massage** approx. 40/50 ml of carrier oil + 20/25 drops of essential oil
- **Six months old baby full body massage** 10 ml of carrier oil + 0.5 (half) drop of Essential Oil*
- **Adult Foot massage** 10 ml of carrier oil + 5/6 drops of essential oil

	The alternative with 100 % decomposing of amygdalin MoS (Body lotion) = 0.4 /0.16 = 2.5 MoS (Massaging oil) = 0.4 /0.11 = 3.6 Mos (Face cream) = 0.4 /0.02 = 20 **The alternative with no decomposing of amygdalin** MoS (Body lotion) = 0.4 /0.062 = 6.5 MoS (Massaging oil) = 0.4 /0.043 = 9.3 Mos (Face cream) = 0.4 /0.007 = 57 Like WHO and EFSA we assume a MoS acceptable value of at least 100. Hence, regardless of whether amygdalin splits of HCN on skin or not the estimated MoS values are much too low and cannot be accepted.

6. **Other sources of exposure than cosmetic products**

Food stuffs	AKO can potentially be used to replace vegetable oil in biscuits and cakes. However, we have not found data for use levels and frequency in food stuff. As concerns toxicity of HCN released from cyanogenic glycosides, EFSA published an opinion in 2004, in which the sources and potential levels of HCN liberated from cyanogenic glycosides were reported. According to EFSA the normal level in apricot kernels is 120 – 4000 mg HCN /kg food (i.e. 0.012 – 0.4 %). The following observations relating to hydrocyanic acid (HCN) is from the EFSA (2004) opinion: In the UK, the Food Standards Agency (FSA) has been advised that apricot kernels would be considered foods regardless of the cyanide content unless they presented themselves as medicines by claiming to treat, cure, or prevent a medical condition. Limited data from the UK show that the average and high (97.5 percentile) daily intake of HCN from its use in flavors or flavor ingredients were 46 and 214 µg/person, which correspond to approx. 0.8 and 3.6 µg/kg bw/day respectively. Data from a Norwegian dietary survey (NORKOST 1997) show that the average and high (97.5 percentile) daily intake of HCN among consumers is 95 and 372 µg/person and 1.4 and 5.4 µg/kg bw/day. Cassava flour is used mainly outside Europe; a consumption of 200 g/person would result in an estimated intake of 30 µg HCN/kg bw for a 60 kg adult. In accordance with JECFA, such an intake would not be associated with acute toxicity - JECFA evaluated cyanogenic glycosides in 1992 and concluded that *a level up to 10 mg HCN/kg food is not associated with acute toxicity*. The current EU regulatory status – cf. Annex III of Regulation (EC) No

	1334/2008 on flavourings – states that the actual maximum limits for HCN in food and beverages are as follows: (a) 50 mg/kg (50 ppm) in nougat, marzipan or its substitutes or similar products, (b) 35 mg/kg (35 ppm) in alcoholic beverages and (c) 5 mg/kg (5 ppm) in canned stone fruit. HCN may not be added to such food stuff as such. The highest level of HCN found in retail marzipan paste is 20 mg HCN/kg. For a 60 kg person consuming 100 g marzipan with such a level, the intake would be approx. 2 mg HCN or 0.03 mg/kg bw. The EFSA panel concluded that "*the current exposure to cyanide from flavouring ingredients (97.5th percentile) is unlikely to give rise to acute toxicity. For chronic exposure, the overall data were not considered adequate to establish a numerical no-observed adverse effect level (NOAEL) or Tolerable daily intake (TDI) in humans (EFSA, 2004). In view of the lack of data, the Panel supported the application of limits for the presence of HCN in foods and beverages*". In 1993, JECFA reached a similar conclusion.[30]
Pharmaceuticals	The apricot kernel oil can be utilized in different pharmaceutical preparations. WHO 2007: ***Uses described in pharmacopoeias and well established documents*** Internally as a decoction, after processing by dipping in boiling water and stir-frying until yellow (*4*), for symptomatic treatment of asthma, cough with profuse expectoration and fever. The seed oil is used for treatment of constipation (*3, 4*). ***Uses described in traditional medicine*** Treatment of gynaecological disorders, skin hyperpigmentation, headache and rheumatic pain (*8*). The seed oil is used in the form of eardrops for inflammation and tinnitus, and for treatment of skin diseases (*17*).
Other sources	Laetrile, a patented purified, semi-synthetic form of amygdalin is a partly man-made molecule that shares only part of the amygdalin structure:  **Laetrile** (CAS no. 1332-94-1). MW=309.2714 g/mol. Laetrile is also classified as a cyanogenic glycoside. Both Laetrile® and amygdalin have been promoted and sold as "vitamin B-17", although neither compound is a vitamin. Laetrile has

[30] In 1993 JECFA concluded: Because of a lack of quantitative toxicological and epidemiological information, a safe level of intake of cyanogenic glycosides could not be established. EFSA similarly concluded that adequate long-term toxicity studies in animals are not available to derive a NOAEL on which to base a numerical TDI (EFSA, 2004).

	been marketed in Mexico and other countries outside the US as an alternative anti-cancer drug [31],[32]. The popularity of Laetrile peaked in 1978, when reportedly 70000 people had been treated with this agent. There is no scientific evidence for claims that Laetrile/amygdalin is effective against cancer, and major safety concerns were highlighted; i.e. cyanide poisoning (National Cancer Institute [online]; Milazzo et al., 2007, 2011, cited in Cam-cancer.org[online]; NaturalStandard.com[online]). A Norwegian newspaper (VG) article in 2009 cautioned about the alternative anti-cancer treatment 'vitamin B17' – i.e. Laetrile/amygdalin[33], after reports that patients had been hospitalized with cyanide poisoning after taking the substance. Several deaths have been attributed to Laetrile (Braico et al., 1979). There is currently a lack of available scientific evidence to recommend any medicinal dosing for apricot kernel in adults. Apricot kernels (approximately 7-10) taken by mouth may be a lethal dose (Naturalstandard.com[online]).
Adverse side effects - from uses other than cosmetics	As far as we know, there is few, if any, case reports in the medicinal literature about adverse effects related to the use of AKO, either in cosmetics, food stuffs or pharmaceutical products. Below is a short summary of *adverse effects mainly caused by intake of apricot kernels and/or Laetrile,* which both contain amygdalin and may cause cyanide poisoning. The level associated with fatal human poisoning amounts to 2100 – 3120 mg HCN/kg product (0.21 – 0.31 %). The symptoms include: Nausea and vomiting Headache Dizziness Blue color of the skin due to a lack of oxygen in the blood (hypoxia) Liver damage Abnormally low blood pressure Droopy upper eyelid Trouble walking due to damaged nerves Fever Mental confusion Coma Death More severe adverse events (i.e. cyanide poisoning) are seen when Laetrile is administered orally than when it is given by injection, as intestinal bacteria contain enzymes that promote the release of cyanide in the digestive system (Newmark et al., 1981; EFSA, 2004). *Allergy*:

[31] Laetrile® and amygdalin are not approved by the Norwegian Medicines Agency (Legemiddelverket) as a treatment for cancer, and marketing of these substances are not allowed. They are also not allowed marketed as dietary supplements.
[32] Laetrile® and amygdalin are not approved by the U.S. Food and Drug Administration (FDA).
[33] http://www.vg.no/iphone/article.php?artid=564367

	Avoid in individuals with a known allergy or hypersensitivity to Laetrile™, apricot, its constituents or the Rosaceae family. Symptoms of allergy may include urticaria ("hives") or rash *Pregnancy and Breastfeeding* Apricot kernels should be avoided in pregnant and breastfeeding women due to a lack of safety data. *Interactions with Drugs* Apricot kernels may cause decreases in blood pressure, and therefore may interact with blood pressure lowering medications. Use cautiously in patients with abnormal heart rhythms, due to reports of rapid heartbeat with amygdalin use (RELIS[online]). *Interactions with Herbs and Dietary Supplements* Use cautiously in patients taking vitamin C or those consuming foods rich in vitamin C, as vitamin C has been shown to increase conversion of amygdalin to cyanide and to reduce body stores of cysteine, which is used to detoxify cyanide. A report suggests increased risk of cyanide toxicity by co-ingesting amygdalin with a megadose of Vitamin C (4800mg) (Bromley et al., 2005). *Other side effects and warnings* RELIS[online] – Amygdalin.

7. Assessment

The potential toxicity of apricot kernels depends primarily on their capacity to produce cyanide.

AKO is a frequent ingredient in cosmetic products that is used in high concentration – even up till 100%. It can be used freely on the market. Up till 11 June 2013, the Norwegian legislation required cyanide not to be present in AKO.

Apricot kernels normally contain considerable amounts of the constituent amygdalin (3- 12 %). Under certain conditions amygdalin release cyanide which is exceedingly toxic. This release is caused by enzymatic hydrolysis of beta-glycosidase in bacterial micro flora. Also common skin bacteria show beta-glycosidase enzymatic activity.

Cyanide is not present in biologically significant amounts in AKO obtained from the apricot seed/kernels using additional solvent extraction. Virgin AKO obtained solely by cold pressing most probably contains significant amounts of both cyanide and amygdalin as does the kernel (seed).

Enzymatic hydrolysis of amygdalin may liberate even larger amounts of cyanide on epithelia/skin. These amounts are easily absorbed into the body over the skin and may cause, if not death, so neural injuries in the brain, thyroid malfunctioning and changes in the male reproductive tract. On the basis of these toxic effects of cyanide we are of the opinion a no-adverse effect level (NOAEL) of 0.4 Kg bw per day can be established. Margin of safety (MoS) calculation applying this NOAEL in combination with realistic exposure estimates show too low MoS values regardless of whether amygdalin decompose into cyanide on the skin or not. In event decomposing is complete, the margins calculated is in the low range of 3-20. If no decomposing occurs, MoS is in the range 7 – 57. The MoS necessary to prevent health damage in the consumer is at least 100 (WHO and EFSA). So, exposure for non-lethal dosages for a long time using different cosmetics products may be injurious to the body.

Exposure for cyanide *via* cosmetic products comes on top of the exposure for same *via* different foodstuff products. The risk posed by the latter exposure, is controlled by regulations in the foodstuffs legislation. However, measures need to be taken in order to control the additional exposure caused by cosmetic products.

All AKO can be purified so that it contains neither amygdalin nor cyanide. Many AKO's utilized for cosmetic purposes are sufficiently purified. There is no reason why not all AKO going into cosmetic products should be completely free of cyanide.

8. Conclusion

Apricot kernel oil can be used in all cosmetics given that hydrocyanic acid (HCN) is removed.

Purification requirements:
Cyanide analyses must be according to well established and/or standardized methods, at laboratories with systems for quality control of the analyses.

Cyanide toxicity is of potential concerns when it comes to substances derived from apricot kernels. However, AKO generally contains amounts of HCN, which can be brought to almost complete removal by appropriate extraction/purification techniques (see e.g. Gupta & Sharma, 2009 and references therein).

Thus, we consider AKO safe for use in cosmetics when it is free from cyanide (assessed using standardized methods) and formulated to be non-irritating.

Allergies:

AKO should be avoided in individuals with a known allergy or hypersensitivity to Laetrile™, apricot, its constituents or the Rosaceae family. Symptoms of allergy may include urticaria ("hives") or rash.

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10. Annexes

Annex 1 / Seed chemical composition

This following overview as to the chemical composition of the Apricot kernel (seed) is taken from the phytochemical database of the American Department of Agriculture. It can be retrieved on the Internet at the address:
http://www.ars-grin.gov/duke/

Chemical	Part	Lo ppm	Hi ppm	Reference
ALPHA-ESTRADIOL	Seed			HHB
AMYGDALIN	Seed		80000	HHB
ASH	Seed	10000	30000	HHB
BETA-CAROTENE	Seed		0	CRC
BETA-GLUCOSIDASE	Seed			CAN
BETA-SITOSTEROL	Seed			DUKE1992A
CALCIUM	Seed	930	1522	SMO
CAMPESTEROL	Seed			DUKE1992A
CARBOHYDRATES	Seed		140000	DUKE1992A
CHOLESTEROL	Seed			CAN
COPPER	Seed	1	16	SMO USA
CYANIDE	Seed	20	2000	CAN
DELTA-24-CHOLESTEROL	Seed			HHB
DEXTROSE	Seed	81000	116000	DUKE1992A
EO (essential oil)	Seed	8000	16000	DUKE1992A
ESTRONE	Seed			HHB
FAT	Seed	400000	514000	HHB
FIBER	Seed		33000	DUKE1992A
LINOLEIC-ACID	Seed	56000	411200	HHB
MAGNESIUM	Seed		1750	SMO
NEO-CHLOROGENIC-ACID	Seed			CAN
OLEIC-ACID	Seed	248000	411200	HHB JAD
PANGAMIC-ACID	Seed			HHB
PHOSPHORUS	Seed		3000	DUKE1992A
POTASSIUM	Seed	4180	7783	DUKE1992A
PROTEIN	Seed		315000	DUKE1992A

SODIUM	Seed	18	19	SMO
ZINC	Seed	2	38	SMO USA

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CAN: Newall, C. A., Anderson, L. A. and Phillipson, J. D. 1996. Herbal Medicine - A Guide for Health-care Professionals. The Pharmaceutical Press, London. 296pp.

The hebalist Steve Blake mentions the same constituents of the apricot seed in his book MEDICINAL PLANT CONSTITUENTS (2004) – except that he also adds the following ones. The book can be retrieved on the web at
http://www.naturalhealthwizards.com/MedicinalPlantsConstituentSample.pdf

Substance	%
Iron	0.004 – 0.005
Manganese	0.001
Squalene	0.002
Vitamin B2	0.00053

WHO in its monograph on Selected medicinal plants Vol. 3 informs that the kernel contains (WHO 2007):

- not less than 3.0% amygdalin determined by titrimetric assay with silver nitrate (*4*).
- That the major constituent is amygdalin (up to 4.9%), Other cyanogenic compounds present are prunasin and mandelonitrile. Also present are the amygdalin-hydrolysing enzyme, emulsin, and fatty acids and sitosterols (*8, 16*).

The source **NHI Corporate Information**[34] informs
(http://www.nhiondemand.com/viewcontent.aspx?mgid=1120)
that the seed contains the following constituents:

Amygdalin; Linoleic acid; Oleic acid; Palmitic acid; Hydrocyanic acid; Glutamic acid; Almondase; Chlorogenic acid; Inositol; Estrone; 17-b-estradiol; 3'-p-coumaroylquinic acid; 3'-feruloylguinic acid; Triolein; Benzaldehyde; Linalool; 4-terpinenol; a-terpineol (1), (2), (3)

1. Ding Dong Ning, et al. Chemical composition of Ku Xing Ren (Semen Armeniacae). Northwestern Journal of Pharmacy. 1990;(3):21-23.

[34] The source explains that **nhiondemand.com (NHI)** is based in Harleysville, Pennsylvania, suburban Philadelphia. NHI was founded in 2001 by a respected group of industry veterans and entrepreneurs, offering the trade, the industry's first online natural Medicine Library.

NHI develops and markets primary products and services that all leverage its industry knowledge, strategic alliances, technology platform, and information content. NHI currently offers both trade and consumer the most advanced technology-capability, leading natural medicine libraries, and healthy lifestyle content, supporting the $124.9 billion health and wellness industry.

2. Wang Ren Tang. How processing affects the content of protein in Xing Ren products. Journal of Chinese Patented Medicine. 1993;15(6):42.

3. Editorial Committee of Chinese Materia Medica, State Drug Administration of China. Chinese Materia Medica. Shanghai Science and Technology Press, 1998.

The source Herbal Medicine 3rd edition informs about the following content:

Acids Phenolic. Various quinic acid esters of caffeic, p-coumaric and ferulic acids. Neochlorogenic acid major in kernel, chlorogenic in fruit.

Glycosides Cyanogenetic. Amygdalin (mandelonitrile diglucoside). Cyanide content of kernel varies from 2 to 200mg/f00g. < "

Tannins Catechins, proanthocyanidins (condensed).

Other constituents Cholesterol, an oestrogenic fraction (0.09%) containing estrone (both free and conjugated) and ot-estradiol.

Annex 2

Examples of AKO products for which it is announced they contain B17 (amygdalin) and or are unrefined virgin oils:

- http://www.naturallythinking.com/products/Organic-Apricot-Kernel-Carrier-Oil.html
- http://www.bio-kosmetika.lt/en/kdikiams/29-abrikos-kauliuk.html
- http://www.baseformula.com/product.php/6707/apricot-kernel-carrier-oilhttp://www.kobashi.co.uk/essentialoils/Pure_as_can_be_Carrier_Oils.html
- http://www.amazon.co.uk/Organic-Expeller-Pressed-Apricot-Dispenser/dp/B00842648S

The following ones are said to be unrefined oils:

- http://www.organic-creations.com/servlet/the-2034/Detail
- http://naturaltransition.com/prestashop/product.php?id_product=1024
- http://www.ebay.com.au/itm/PRESSED-PURITY-Apricot-Kernel-Oil-2L-Cold-Pressed-Unrefined-Extra-Virgin-/230944578948
- http://www.apricotkerneloilaustralia.com.au/page/apricot-kernel-oil-info
- http://www.proteco.com.au/pressed-purity/
- http://aromatherapytoday.co.uk/component/jshopping/product/view/85/48
- http://blackgirllonghair.com/2013/04/spotlight-on-apricot-oil/

Annex 3

Other indications on use of high AKO concentrations

Knowledge about which concentrations are being applied we have gained also by looking up on the German online Codecheck database that currently contains data on 626 different cosmetics products

containing AKO. The list of ingredients is displayed for all these products. The positioning of AKO in the list gives a good clue as to the magnitude of the concentration. It appears that, generally, AKO is high up in the list. This shows that the concentrations applied are on average comparatively high. Among the 200 first product entries we identified the following numbers of product for which AKO is either on the top of the list (in the first place), in the second place or in the third place:

In the first place: 2 products; one body oil and a cleansing oil for the face[35]

In the 2nd place: 6 products

- Face oil (ant-age)
- Two oils for nails products
- Cream for dry skin (Vichy product)
- Day cream for very dry hair
- Soft peeling product

In the 3rd place: 6 products

- Hair oil (L'Oreal products)
- Body lotion
- Spray
- Face peeling
- Face milk
- Anti-wrinkling product

According to the source Bailey's Industrial oil& fat products, Vol 5, edited by YH Hui, AKO may be used up till 20 % in some products

In the source Poucher's Perfumes, Cosmetics and Soaps[36] page 439, is mentioned a replenishing night lotion wherein AKO figure on the top of the list of ingredients being present at a concentration of 8.00 %

One source say 15 % should be used in soaps: http://www.soapandthings.com/p-1006-apricot-kernel-oil.aspx

The source Happy present many products wherein the content vary from 4 % and upwards http://www.happi.com/contents/searchcontent/all/apricot+kernek+oil/

Annex 4: Concrete cosmetic products with AKO

EWG Skin Deep database
http://www.ewg.org/skindeep/ingredient/705357/PRUNUS_ARMENIACA_%28APRICOT%29_OIL/#jumptohere

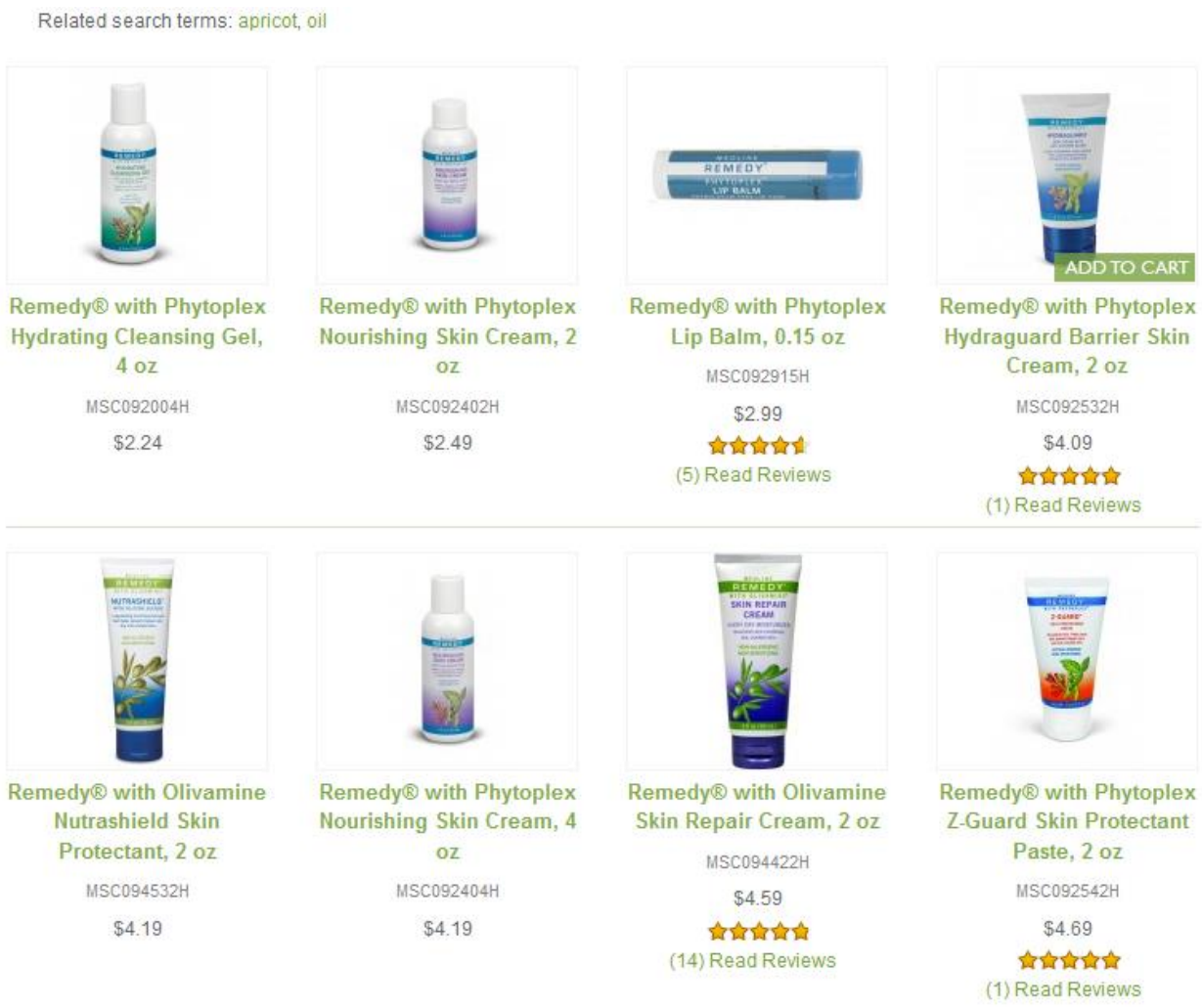
body oil: 11 products
moisturizer: 9 products
anti-aging: 4 products
exfoliant/ scrub: 4 products
facial moisturizer/ treatment: 3 products
body wash/ cleanser: 2 products
baby oil: 2 products
conditioner: 2 products
styling gel/ lotion: 1 products

[35] This concerns a product named "Biodroga Reinigungsöl" (Biodroga Cleansing Oil) for which the list of ingredients reads: Apricot Kernel Oil, Tri-Laureth-4 Phosphate, Propylene Glycol, Fragrance, Benzyl Salicylate
[36] 10th edition 2000, Edited by Hilda Butler, ISBN: 0-412-27360-8

hand cream: 1 products
facial cleanser: 1 products
around-eye cream: 1 products

Total: 35 products

http://www.chooseremedy.com/catalogsearch/result/?q=Apricot+Kernel+Oil+PEG-6+Esters



Annex 5: Toxicity of cyanide derived from cyanogenic glycosides in apricot kernels

Acute toxic effects - related to cyanide - have occurred from e.g. consumption of stone fruit kernels (EFSA, 2004). The lethal dose in humans is about 0.5 – 3.5 mg/kg bw (EFSA, 2004; BfR, 2007). The estimated no-effect level in adults is 5 µg/kg bw, corresponding to the intake of a bitter apricot kernel (BfR, 2007). Thus, BfR advices a maximum daily limit of two kernels (but preferably no kernels at all).

Food:
Cyanogenic glycosides present in Apricot kernels (and/or Laetrile™), as sources of hydrocyanic acid (HCN), are relatively non-toxic until HCN is released. This can occur as a result of enzymatic hydrolysis of β-glucosidases following maceration of plant tissue or by the gut microflora; e.g. as part of the digestive process. Benzaldehyde is also produced by hydrolysis of amygdalin in addition to sugar moieties and HCN.

Fatal acute effects (e.g. deaths) have occurred from consumption of stone fruit kernels, whereas chronic uptake of HCN in sub-acutely toxic doses may be involved in disturbance of thyroid function and neuropathies.

EFSA concluded that data on chronic toxicity were not adequate to establish a no-observed adverse effect level (NOAEL) or Tolerable daily intake (TDI) in humans (EFSA, 2004). Apricot kernels (approximately 7-10) taken by mouth may be a lethal dose (www.naturalstandard.com[online]).

BfR has estimated that the safe amount of bitter apricot kernels in adults corresponds to about half a milligram hydrocyanic acid per day; i.e. no more than one or two apricot kernels per day. Misleading statements about therapeutic effects are not allowed. (BfR, 2007)

WHO 2007

In its monograph on Semen Armeniacae WHO in 2007 came out with the following assessment on the toxicology pertaining to exposure for ground **seeds** (WHO 2007)

Toxicology

Intragastric administration of 125.0 mg/kg bw of powdered defatted Semen Armeniacae per day for 7 days to mice or rabbits produced no behavioural, histological or microscopic toxic effects (*25*). Intragastric administration of 250.0 mg/kg bw of an aqueous suspension of the powdered defatted seeds to mice had no toxic effects within a 24-hour period (*25*). The median lethal dose (LD50) of amygdalin in rats was 880.0 mg/kg bw after intragastric administration. However, when a dose of 600.0 mg/kg bw was administered by the same route, together with β-glucosidase, all animals died. Total and magnesium adenosine triphosphatase activities in the heart decreased with increasing levels of administered amygdalin (*23, 24*).

Diets containing 10% ground seeds were fed to young and breeding male and female rats. The seeds were obtained from 35 specific apricot cultivars and divided into groups containing low amygdalin (cyanide < 50.0 mg/100 g), moderate amygdalin (cyanide 100–200.0 mg/100 g), or high amygdalin (cyanide > 200.0 mg/100 g). Growth of young male rats was greatest in the low and moderate amygdalin groups, indicating that the animals were more sensitive to the bitter taste of the kernels with high amygdalin content. In female rats, but not males, liver rhodanase activity and blood thiocyanate levels were increased with the high-amygdalin diet, but both males and females efficiently excreted thiocyanate, indicating efficient detoxification and clearance of cyanide hydrolysed from the dietary amygdalin. No other changes in blood chemistry were observed (*26*).

Toxic amounts of cyanide were released into the blood of rats following intragastric administration of amygdalin (proprietary laetrile) (dose not specified); cyanide blood concentrations and toxicity were lower when amygdalin was given intravenously (dose not specified). Analysis of the time course of cyanogenesis suggests that cyanide could accumulate in blood after repeated oral doses of amygdalin (*27*). Following intraperitoneal administration of 250.0 mg/kg bw, 500.0 mg/kg bw or 750.0 mg/kg bw of amygdalin per day to rats for 5 days, mortalities were 30.8%, 44.1% and 56.8%, respectively. The mode of death and the elevated serum cyanide levels in the dying animals strongly suggested cyanide poisoning as the cause of death (*28*).

The systemic effects of an oil prepared from the seeds containing 94% unsaturated fatty acids, and oleic and linoleic acids were assessed in a 13- week feeding study in rats. The animals were fed a diet containing 10% oil. No toxic effects were observed and no macroscopic or microscopic lesions in any of the organs were found (*29*).

External applications of 0.5 ml of the seed oil to rabbits did not produce any observable toxic effects (*25*).

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Annex 6

FDA risk assessment as concerns hormonal cosmetic products

The FDA does not regulate cosmetics containing less than 10 000 IU of estrogen per ounce, only stating that the label should direct consumers to limit the amount of product used to less than 2 mg/month (Zimmerman PA et al 1995 and "Estrogens in cosmetics. *Med Lett Drugs Ther.* 1985;27:54-55. MEDLINE»

FDA Cosmetics Handbook:

http://www.mlmlaw.com/library/guides/fda/Coshdbok.htm

Products Containing Estrogenic Hormones, Placental Extract or Vitamins

Products containing estrogen, estrone, estradiol, progesterone, placental extract or vitamins may be considered drugs, misbranded drugs, or misbranded cosmetics, particularly if the label declaration is supplemented with standards implying prevention or treatment of disease or effect on the structure or any function of the human body. See Federal Register notice of the proposed rule of October 28, 1977 (42 FR 56757) and 21 CFR 201.300.

The estrogen content of an OTC product, be it a drug or a drug as well as cosmetic, may not exceed 10,000 IU per ounce. Users must be directed to limit the amount of product applied daily so that no more than 20,000 IU of estrogen or equivalent be used per month. Some estrogen-containing products have been claiming to prevent or reduce wrinkles, treat seborrhea, or stimulate hair growth. The Advisory Review Panel on OTC Miscellaneous External Drug Products has concluded that there are inadequate data to establish the safety of these products and that they are ineffective and may therefore be misbranded, even if marketed as cosmetics without making medicinal claims. See Advance notice of proposed rulemaking, Federal Register of January 5, 1982 (47 FR 430). It should be noted, however, that this panel's recommendation has not yet been accepted by the FDA as a basis for regulatory decisions.

http://vm.cfsan.fda.gov/~dms/cos-hdbk.html