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ASSESSMENT REPORT ON *ALOE BARABADENSIS* MILLER AND *ALOE* (VARIOUS SPECIES, MAINLY *ALOE FEROX* MILLER AND ITS HYBRIDS)

Herbal substance	*Aloe barbadensis* Miller (barbados aloes) Aloe [various species, mainly *Aloe ferox* Miller and its hybrids] (cape aloes)
Herbal Preparation	the concentrated and dried juice of the leaves, standardised; standardised herbal preparations thereof
Pharmaceutical forms	Herbal substance for oral preparation
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I. INTRODUCTION

This assessment report reviews the scientific data available for the dried juice of the leaves of *Aloe vera* (L.) Burm. f., known also as *Aloe barbadensis* Miller, (barbados aloes), or of *Aloe ferox* Miller and its hybrids (cape aloes), primarily the clinical data.
The word "Aloe" in pharmacopoeias and formularies means a herbal substance derived from the dried leaf juice. This has always created confusion due to the fact that the leaves are the source of two products "aloe dried juice" and "aloe gel", which are quite different in their chemical composition and their therapeutic properties.
The plant material of interest here is aloe dried juice, which is prepared by cutting transversely the leaf near the base and taking it inclined so that the juice contained in the specialised pericyclic cells and sometimes in the adjacent parenchyma flow out in about 6 h. The juice is allowed to dry with or without the aid of heat.
Aloe gel is a colourless mucilaginous gel obtained from the parenchymatous cells of the leaves. The mucilaginous parenchymous tissue is excised from fresh leaves (6). Therefore the leaves are "filleted", that means that the external green parts of the leaves are peeled. Depending on whether the anthranoid-containing cells beneath are also removed, the gel is free of anthranoids or not. The fillets are immediately utilised for preparations or lyophilised and kept dry until use.
This report was prepared taking into consideration the monograph "Aloe" of the German Commission E (1), the German pharmacovigilance actions for anthranoid-containing laxatives of 21 June 1996 (2), the European Scientific Cooperative on Phytotherapy (ESCOP) monograph "Aloe capensis (Cape Aloes)" (3) (ESCOP Monographs, second edition 2003) and the World Health Organization (WHO) monograph "Aloe" (4).

Constipation is a common complaint in 1 – 6% of the middle-aged population and 20 – 80 % of the elderly people and may be treated by laxatives. Constipation also tends to be more prevalent among women. Functional constipation is the most common type without any specific aetiology (5). The most commonly used laxatives are either stimulant preparations (containing anthracenic derivates from senna, frangula or cascara), lubricant laxatives (e.g. mineral oils) or bulk forming agents.

Aloe preparations of the dried juice of the leaves belong to the stimulant laxatives containing hydroxyanthracene derivatives and are intended "for short-term use in cases of occasional constipation".
This indication is substantiated by empirical data (derived from research into the constituents and their pharmacology). There are only poor clinical data available.
Anthraquinone laxatives such as aloe and senna share a tricyclic anthracene nucleus modified with hydroxyl, methyl, or carboxyl groups to form monoanthrones (80). Therefore, reference is often made in this assessment of aloe to the assessment reports on "*Cassia senna* L. and *Cassia angustiolia* Vahl, folium" and on "*Cassia senna* L., fructus and *Cassia angustifolia* Vahl, fructus".
Aloe preparations have to be regarded as herbal medicinal products with a "well-established medicinal use" in this indication with respect to the application of Directive 2001/83/EC of the Parliament and of the Council on the Community code relating to medicinal products for human use as amended.

II. CLINICAL PHARMACOLOGY

II.1 Pharmacokinetics

II.1.1 Phytochemical characterisation

Barbados aloes consists of the concentrated and dried juice of the leaves of *Aloe barbadensis* Miller. It contains not less than 28% of hydroxyanthracene derivatives, expressed as barbaloin ($C_{21}H_{22}O_9$; M_r 418.4) and calculated with reference to the dried herbal substance. The material complies with the European Pharmacopoeia monograph "Aloes, Barbados" (ref. 0/2005:0257).

Cape aloes consists of the concentrated and dried juice of the leaves of various species of *Aloe*, mainly *Aloe ferox* Miller and its hybrids. It contains not less than 18% hydroxyanthracene derivatives, expressed as barbaloin ($C_{21}H_{22}O_9$; M_r 418.4) and calculated with reference to the dried herbal substance. The material complies with the European Pharmacopoeia monograph "Aloes, cape" (ref. 01/2005:0258).

The constituents with known therapeutic activity of barbados aloes are anthrone-10-C-glycosides *viz*. a mixture of aloin A (10S,1'S) and aloin B (10R,1'S), named barbaloin and their 6'-0-p-coumaroylesters, a mixture of 7-hydroxyaloins A (10S) and B (10R) and their 6'-0-p-coumaroylesters and a mixture of 8-0-methyl-7-hydroxyaloins A (10S) and B (10R) and their 6'-0-cinnamoylesters.

The constituents with known therapeutic activity of cape aloes are 10-C-glycosides *viz*. a mixture of aloins A (10S) and B (10R), named barbaloin, and 5-hydroxyaloin A (10S) besides 10-C-11-0-diglycosides *viz*. aloinosides A and B (11-0-α-L-rhamnosides of aloins A an B).

There are also small quantities in both aloes of the aglyka, aloe-emodin and chrysophanol, and 2-alkylchromones named aloeresins (4, 7).

II.1.2 Absorption, metabolism and excretion

Aloins A and B, hydroxyaloins and the aloinosides A and B are not absorbed in the upper gut. In humans, they pass into the colon unmodified after oral ingestion. Human intestinal flora are able to break down O-glycosides easily but only to some extent C-glycosides of most anthranoids. A strictly anaerobic, *Eubacterium* sp. BAR, was isolated from human faeces as one of the intestinal bacteria capable of metabolising barbaloin to aloe-emodin anthrone (8, 9). Barbaloin was transformed to aloe-emodin anthrone in the faeces from gnotobiotic rats mono-associated with the *Eubacterium* sp. BAR, but not in faeces from conventional rats or the gnotobiotic rats mono-associated with *Peptostreptococcus intermedius*, a human intestinal anaerobe capable of reducing sennidins to rhein anthrone. Only in gnotobiotic rats mono-associated with the *Eubacterium* sp. BAR administration of barbaloin causes severe diarrhea. The faecal water content was significantly increased (10). In contrast Ishii Y et al. showed that aloe-emodin-9-anthrone was produced in the rat large intestine (11, 12). Aloe-emodin-9-anthrone is the main active metabolite, which acts specifically on the colon (13).
It is not known to what extent aloe-emodin-9-anthrone is absorbed. In the case of senna, animal experiments with radio-labeled rhein anthrone administered directly into the caecum demonstrated absorption < 10% (14).

After oral administration of 4.5 mg/kg ^{14}C-aloe-emodin to rats 20 – 30% of the dose was excreted in urine and the rest in faeces. Aloe-emodin was quickly metabolised to rhein, to an unknown metabolite and to conjugates of all three. In the plasma about 10% of ^{14}C-activity was identified as free aloe-emodin. Maximum plasma values were reached 1.5 – 3 h p.a. with 248 (male) and 441 (female) ng equivalents aleo-emodin/ml. Maximum concentrations in plasma were about 3 times higher than those in ovaries and 10 times higher than those in testes. Because of the low activity concentrations in the reproductive organs TLC analysis was not possible. But if the metabolic profile of these organs is assumed to be the same as in plasma, concentrations of free aloe emodin can be calculated to be maximally about 2-4 ng/g in testes and 8-10 ng/g in ovaries after an oral dose of 4.5 mg/kg. Only liver, kidney and intestinal tract showed higher concentrations than plasma. Terminal half-life (for radioactivity) in blood was about 50 h (15).

The ESCOP monograph mentioned an unpublished research report of a human pharmacokinetic study in 6 healthy volunteers (ref. 39 in 3). After oral administration of aloes (equivalent to 16.4 mg of hydroxyanthracene derivates) for 7 days, aloe-emodin was detected as a metabolite in the plasma only sporadically and with maximum concentrations of less than 2 ng/ml. In the same study rhein was detected in the plasma in concentrations ranging from 6-28 ng/ml after single dose administration. In 7-day administration there was no evidence of accumulation of rhein.

The absorbed rhein anthrone is glucuronidised in the liver. One part of the glucuronides is excreted via the urine and cause the yellow or redbrown discolouration of the urine. The other part is excreted via the bile (61).

II.1.3 Progress of action

Aloes acts within 6 to 12 hours due to the time taken for transport to the colon and metabolisation into the active compounds.

II.2 Pharmacodynamics

II.2.1 Mode of action

- **Laxative effect**

Constipation is said to be present when passed stools are of hard consistency and when evacuation of faeces is too difficult, too infrequent and irregular. The physiological range for frequency of bowel movements is wide, extending from three times daily to once every 2 to 3 days. In the pathogenesis of constipation the colon plays a key role because this is where the contents of the gut remain for 24 – 48 hours. During this period the liquid contents from the small intestine are converted into faeces by absorption of water and electrolytes in response to the action of bacteria. These functions are dependent on the interplay of peristaltic processes which mix the contents and the normal coordination of the anorectal muscles during defaecation. A disturbance involving any of these individual areas may lead to constipation. In this context, functional disturbances are far more common than those of an organic origin. In addition, assessment is problematic because the symptoms are perceived differently by the individuals affected (16, 17), due to different concepts of what normal bowel habits are.

Aloe dried juice belongs to the stimulant laxatives. Aloe-emodin-9-anthrone is the main active metabolite, which acts specifically on the colon (13).
Ishii Y et al. 1990 (13) investigated the mechanism of action of aloe-emodin-9-anthrone in causing a significant increase in the water content of the rat large intestine. Aloe-emodin-9-anthrone inhibited rat colonic sodium/potassium-adenosine triphosphatase (Na^+/K^+-ATPase) *in vitro*, and increased the paracellular permeability across the rat colonic mucosa *in vivo*. Therefore, it seemed that the increase in water content of the rat large intestine produced by aloe-emodin-9-anthrone was due to both inhibition of absorption and stimulation of secretion without stimulation of peristalsis. Since, however, pretreatment with loperamide completely prevented the increase of paracellular permeability induced by aloe-emodin-9-anthrone, but did not completely reduce the concomitant increase in residual fluid volume, other multiple mechanisms of action might be involved in the increase of water content in the rat large intestine.

Hoenig J et al. 1992 (18, 19) studied the influence of 23 anthraquinones and anthrones on the regulatory volume decrease (RVD) which is effected in Ehrlichs ascites tumor cells by activation of Cl^- channels. They showed that the inhibition of the Cl-channels' activity was the strongest by aloe-emodin-anthrone and aloe-emodin. These anthraquinones reduce the Cl^- permeability of the cells, this influence being sometimes more pronounced than that of the Cl^- channel blocker 130B. In contrast to the investigations of Ishii Y et al. 1990 (13) both substances showed no pronounced inhibition activity of the Na^+/K^+-ATPase. Rhein, frangula-emodin and other anthraquinones with an additional phenolic hydroxyl group showed inhibition.

Ishii Y et al. 1994 (20) measured simultaneously in the same rat charcoal transport, as an indicator of the degree of peristalsis, and water content in the large intestine after intracaecal administration of barbaloin. Charcoal transport was significantly accelerated at both 3.5 and 6.5 h after the administration of barbaloin. At 6.5 h, diarrhoea instead of normal faeces was observed. Moreover, at 1 h before the acceleration of charcoal transport, a marked increase in water content of the large intestine was observed: It appeared that the increase in water content of the large intestine induced by barbaloin preceded the stimulation of peristalsis, attended by diarrhoea. The authors therefore

suggested that the increase in water content is a more important factor than the stimulation of peristalsis in the diarrhoea induced by barbaloin.

Results of investigations of **Capasso F et al. 1983** (27) in rat isolated colon suggest that the laxative properties of aloin and 1,8-dioxyanthraquinone may depend, at least in part, on increased prostaglandin synthesis by the intestinal tissue.

The exact mechanism of action is still unknown. Besides a direct influence of the motility leading to a reduced transit time, an influence on secretion processes by two concomitant mechanisms is assumed namely inhibition of absorption of water and electrolytes (Na^+,Cl^-) into the colonic epithelial cells (antiabsorptive effect) and increase of the leakiness of the tight junctions and stimulation of secretion of water and electrolytes into the lumen of the colon (secretagogue effect) resulting in enhanced concentrations of fluid and electrolytes in the lumen of the colon. The fluid absorption is reduced. This leads to an increase of the intestine content and the intraluminal pressure, which indirectly stimulates the peristalsis (7).
Recent studies continue to clarify the action of the stimulus on the colon.

Investigations of **Izzo AA et al.** suggest that nitric oxide (NO) is a possible mediator for the laxatives effect of anthranoid-containing products; in 1996 (81) and 1997 (82) they investigated the role of NO in senna- and cascara-induced diarrhoea in the rat, and in 1999 (83) the role of NO in aloe-induced diarrhoea in the rat.
Nine hours after oral administration to rats, aloe produced diarrhoea in 20% rats at doses of 5 g/kg bw and in 100% rats at doses of 20 g/kg bw. Lower doses of aloe (0.1 and 1 g/kg) did not produce a diarrhoeal response. Pre-treatment (i.p.) of rats with a NO synthase inhibitor (N^G-nitro-L-arginine methyl ester) reduced the diarrhoea induced by aloe (20 g/kg)) 9 h after its oral administration. The increase in faecal water excretion was also reduced. L-arginine administered to rats pre-treated with the NO synthase inhibitor, drastically reduced the effect of this inhibitor. Given alone, L-arginine did not modify aloe-induced diarrhoea. Basal Ca^{2+}-dependent NO synthase activity in the rat colon was dose-dependently inhibited by aloe (0.1 – 20 g/kg bw) and by aloin (0.1 - 1 g/kg bw), the active ingredient of aloe. The authors concluded that these results suggest that endogenous NO modulates the diarrhoeal effect of aloe (83).

Tavares IA et al. 1996 (84) compared the effects of rhein and aloe-emodin with that of ricinoleic acid and calcium ionophore A23187 on platelet-activating factor (PAF) release by human gastrointestinal mucosal pieces *in vitro*. Ricinoleic acid and calcium ionophore stimulated release of PAF from human stomach, ileum or colon mucosa. Aloe-emodin (100 µg/ml) stimulated a small release of PAF in ileum and colon mucosa. Rhein had no effect.
5-aminosalicylic acid (100 µg/ml) inhibited PAF release induced by the drugs. The authors concluded that rhein exerted its laxative effects by a mechanism that did not involve PAF release, and that aloe-emodin may act partly via PAF release.

Izzo AA et al. 1998 (85) reviewed the key features of the involvement of NO and PAF in the action of laxatives. PAF is a phospholipid mediator of inflammation and stimulates anion secretion in animals and in isolated preparations of human colon. NO, synthesised from the amino acid L-arginine, is an important enteric inhibitory neurotransmitter. In addition, NO-donating compounds stimulate anion secretion in rat and guinea-pig colon.

Longo R 2002 (86) referred in his monograph "Aloe today" (part four) to recent investigations that produced a better explanation of the mechanism of the action of stimulus on the colon. The inhibition of Na^+/K^+-ATPase and the release of NO are relevant to stimulate the secretion of electrolytes and the relaxation of smooth intestinal muscles. Furthermore, investigations outlined that NO plays a new physiopathological role regarding PAF, which causes the contraction of the smooth musculature.

Recapitulating, biological factors such as PAF and NO may play a role on the action of the stimulus on the colon, but it should be considered that the investigations mentioned above are only experimental ones.

Koch A 1995 (28) evaluated the laxative effect of aloin in experiments on herself. Neither a dose of 20 mg aloin nor an increase to 60 mg aloin caused a laxative effect. Aloin was found in the faeces.
The author also studied the use of aloe as a laxative in 3 patients given 50 mg aloin in a gelatine capsule in the evening at 8 p.m. Test person A (female) fed upon vegetable and animal products, test person E (female) predominantly fed upon fish and meat and test person H (male) was a vegetarian. Test person A experienced soft stools once at day 1 and 2 and normal stools at day 3. Test person E experienced soft stools at day 1 for four times. Test person H experienced soft stools once at day 1, 2 and 3. These different results corresponded to the cleavage of aloin and appearance of aloe-emodin in the faeces. Test person E consumed an oral ferric product additionally. This product seemed to support the cleavage of aloin. This was confirmed when test person A received a ferric product to. The author concluded that the laxative effect depends on the cleavage of aloin in aloe-emodin.

Kopp H 1979 (29) tested in an open study Chol-Kugeletten® for 10 days in a combined treatment of a total of 18 cholecystectomised patients or patients with gallstones, in comparison with a placebo (physiological saline solution) as to its choleretic properties and tolerability. Chol-Kugeletten® contains amongst others 25 mg aloe extract, 7 mg celandine extract, 5 mg curcuma root extract, 30 mg Fel Tauri depurat. sicc. (ox bile), 2.5 mg bisacodyl and 2.5 mg peppermint oil. Twelve patients received Chol-Kugeletten® and 6 patients placebo. Three patients of the verum group were excluded because of incomplete data. Before the therapy begun, and after 5 and 10 days of oral administration of one tablet three times a day, the secretion capacity of the individual patients was measured by means of an intraduodenal tube by Bartelheimer's method. At these dates the secretion capacity was measured before and hourly after intraduodenal application of 3.33 ml Chol-Kugeletten® suspension (corresponding to 1 Chol-Kugeletten® tablet) or placebo for five times. The choleresis could be raised significantly for hours. No further increase of the quantity of the secretion was obtained after 5 or 10 days of administration. The author concluded that there is a complete development of the action of the preparation that sets in immediately. Both the systemic and the local tolerability of Chol-Kugeletten® were good; the upper abdomen symptoms could be alleviated in both groups, but more with Chol-Kugeletten®. No details are given in the publication.
This investigation of a combination product of several agents cannot exactly show the contribution of aloe to the observed effects.

- **Other effects**

There are many experimental investigations, which study several effects of different ingredients of aloe. The part of the plant, from which the ingredients were isolated, has not always been defined exactly. Investigations of the gel or of substances isolated from the gel are not mentioned in the assessment report.

- Antitumour effect

Grimaudo S et al. 1997 (21) studied the antitumour effects of 5 purified compounds from the plant *Aloe vera* on human K562 leukaemia cells and on the multidrug resistant (MDR) variant cell line, K562/R. The glycosides aloin A and B, aloesin and aloeresin were devoid of antitumour activity up to 200 µM concentrations. Only the aglycon aloe-emodin produced reproducible antitumour effects. Aloe-emodin caused mainly cytostasis and accumulation of the cells in the S and G_2-M phases of the cell cycle during the first 48 h of treatment. Thereafter, massive cell death ensued.

Fenig E et al. 2004 (67) conducted a study to determinate if members of the anthraquinone family could be used as adjuncts to increase the growth inhibiting effect of anticancer agents in Merkel cell carcinoma (MCC). An adherent variant of MCC was derived from a previously established MCC cell line suspension. Emodin and aloe-emodin inhibited proliferation of the adherent MCC cells, with a slight advantage of aloe-emodin over emodin. Aloin had no effect on cell proliferation. The chemotherapeutic agents, cis-platinol (abiplastin), doxorubicin (adriablastin), and 5-fluorouracil, and the tyrosine kinase inhibitor STI 571, all independently inhibited the proliferation of adherent MCC cells. The addition of aloe-emodin potentiated their inhibitory effect, especially when low concentrations of the anticancer compounds were used.

Chen HC et al. 2004 (68) evaluated the chemopreventive role of aloe-emodin in human promyelocytic leukemia HL-60 cells *in vitro* by studying the regulation of proliferation, cell cycle and apoptosis. The authors concluded that aloe-emodin appears to exert its anticarcinogenesis properties by inhibiting proliferation and inducing cell cycle arrest, and apoptosis underwent activation of caspase-3 in human leukemia HL-60 cells.

Lee HZ et al. 2001 (69), **2003** (70), and **2005** (71) demonstrated that aloe-emodin induced a significant change in the expression of lung cancer cell apoptosis-related proteins compared to those of control cells.

- Anti-inflammatory effect

In investigations using the contact hypersensitivity response **Yagi A et al. 2003** (22) showed a preventive effect of aloesin, isolated from *Aloe* species, on the UV-B-induced immune suppression. Furthermore, aloesin inhibited tyrosine hydroxylase and dihydroxyphenylalanine (DOPA) oxidase activities of tyrosinase from normal human melanocyte cell lysates. Therefore the authors regard this substance as a positive pigment-altering agent.
Furthermore the authors reported that aloesin stimulates the proliferation of cultured human hepatoma SK-Hep 1 cells.

- Antibacterial effect

Lorenzetti LJ et al. 1964 (23) showed a bacteriostatic effect of the "juice of the leaves" on *Staphylococcus aureus*, *Streptococcus pyogenes*, *Corynebacterium xerose* and *Salmonella paratyphi*. Aloe-emodin and chrysophanol were ineffective.

Another investigation by **Liu M et al. 1996** (24) showed potent antibacterial activity of aloe-emodin (source not mentioned) against methicillin-resistant *Staphylococcus aureus.*

- Antifungal effect

Shamim S et al. 2004 (25) evaluated the activity of *Aloe barbadensis* Miller and two other plants (*Allium sativum* L. and *Solanum nigrum* L.) against some common fungal species associated with superficial mycoses. The ethanol and aqueous extracts of these plants were tested to establish the antimycological effects against dermatophytes, saprophytes, and *Candida* species isolated from infected hospitalised patients. The *in vitro* antifungal activity was established by observing and measuring the zones of inhibition formed on selective nutrient media. Zones of inhibition were categorised as very high (41-50 mm), high (31-40 mm), medium (21-30 mm), and low (11-20 mm). High zones of inhibition were noted with the ethanol extracts of the three plants.

II.2.2 Interactions

Chronic use or abuse of aloe dried juice preparations may lead to hypokalaemia. This hypokalaemia and the increased loss of potassium may increase the activity of cardiac glycosides and interfere with the action of antiarrythmic agents (interaction with antiarrhythmic medicinal products, which induce reversion to sinus rhythm, e.g. quinidine) and medicinal products inducing QT-prolongation (87). Concomitant use with medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may aggravate electrolyte imbalance.

Chung JH et al. 1996 (26) investigated the influence of aloe on the ethanol metabolism in rats based on reports indicating that an extract of aloe enhances ethanol metabolism. Aloe contains aloin, a C-glycoside of anthraquinone. Quinones in general have a functional role in elevating the ethanol metabolism rate *in vivo*. Upon oral administration of aloin (300 mg/kg) 12 h before ethanol administration, the area under the curve of blood ethanol significantly decreased by 40%, while the slope of elimination and rate of disappearance from the body increased by 60% and 64%, respectively. Based on these results, the authors concluded that aloin could be the substance in aloe that promotes ethanol metabolism *in vivo*.

Lee A et al. 2004 (66) described a patient with massive intraoperative bleeding after oral consumption of *Aloe vera* tablets. A 35-year old woman lost 5l of blood during surgery as a result of a possible interaction between *Aloe vera* and sevoflurane. The authors stated that compounds contained in *Aloe vera* can cause a reduction in prostaglandin synthesis, which may inhibit secondary aggregation of platelets. Sevoflurane inhibits thromboxane A_2 formation by suppression of cyclooxygenase activity, impairs platelet aggregation, and prolongs bleeding. Although the vascularity and size of the haemangioma were the most important factors for the massive intraoperative blood loss, the authors concluded that concomitant use of sevoflurane and *Aloe vera* played a contributory role and that this adverse event was possible as a result of the sevoflurane and *Aloe vera* interaction.
The information given in the publication is insufficient. The *Aloe vera* preparation may not be comparable to the aloe preparations assessed in this report.

III. CLINICAL EFFICACY

III.1 Dosage

There are no dose-finding studies available.

The recommended dosage as a laxative for adults, elderly and adolescents over 12 years (10 – 30 mg hydroxyanthracene derivatives only once daily at night) is supported by experts' opinions and by clinical investigations with other anthranoid-containing laxatives like senna preparations. Please refer to the assessment report on "*Cassia senna* L. and *Cassia angustifolia* Vahl, folium".
The German Commission E monograph (1) indicates a daily dose of 20 – 30 mg hydroxyanthracene derivatives calculated as aloin but recommends that the pharmaceutical form must allow lower dosages than the usual daily dose.
The ESCOP monograph (3) and the WHO monograph (4) recommend 10 – 30 mg hydroxyanthracene derivates.
This dosage recommendation is also given in consideration of the toxicological data, which were evaluated and led to pharmacovigilance actions in Germany for anthranoid-containing laxatives in 1996 (2).
Through the individual product information (especially the package leaflet), patients should be informed that the correct individual dose is the smallest required to produce a comfortable soft-formed motion.
It is normally sufficient to take an anthranoid-containing laxative up to two to three times a week (100).

III.2 Clinical studies

There are no clinical studies, which evaluate the efficacy of barbados aloes or cape aloes in patients with occasional constipation.

Odes HS et al. 1991 (30) evaluated the effect of a laxative preparation, composed of celandine, *Aloe vera* and psyllium in patients with chronic constipation i.e. requiring laxative treatment for at least 2 years. The aloe preparation in this combination product derived from the leaves of Socotrine Aloes and also contained barbaloin and other anthraquinone derivatives. Capsules of 500 mg were made up to contain the active ingredients celandine, aloe vera and psyllium in the ratio 6:3:1. Thirty five men and women were randomised to receive capsules containing celandine-aloe vera-psyllium, or placebo, in a double-blind trial including a 14-day basal period and a 28-day treatment period. Twenty one of these had simple constipation, and the others suffered from irritable bowel syndrome with constipation. Organic causes for constipation were excluded. Nineteen patients on celandine-aloe vera-psyllium and 13 on placebo successfully completed the study. The initial dose was 1 capsules per day, taken with water at bedtime, and increasing to 3 capsules per day depending on the response. The patients kept a daily diary card during the basal and treatment periods and recorded: date, number of capsules taken, number of bowel actions, stool consistency, abdominal pain and distension, heartburn, other medications and fibre supplements taken to relieve constipation, medicinal products taken for

other conditions, and fluid intake. Symptoms of the last 2 weeks of the treatment period were compared to those in the 14-day basal period. Patients on celandine-aloe vera-psyllium took 10.1 +/- 4.1 capsules per week and patients on placebo 15.8 +/- 6.9 capsules (p=0.02). The mean number of bowel actions per week in patients on celandine-aloe vera-psyllium increased from 4.6 +/- 2.4 to 7.9 +/- 3.9 (p<0.002) and in the placebo group from 3.9 +/- 1.6 to 4.3 +/- 2.1 (p-value not mentioned). The stool consistency score decreased significantly in the verum group (p<0.002), while the placebo group demonstrated no changes. Subjects on celandine-aloe vera-psyllium group had a higher basal pain score than those receiving placebo (p<0.005), and there was no statistically significant improvement in either this or the placebo group during the trial. Overall, 16 of 19 patients on celandine-aloe vera-psyllium regarded themselves as improved as compared with only 4 of the 13 patients on placebo (p<0.05). No subjects developed any side-effects from the treatment.
This investigation of a combination product of three herbal substances cannot establish the contribution of aloe to the observed effects. Furthermore, the herbal substance is "Socotrine Aloes", which does not correspond to barbados aloes and cape aloes described in this assessment report and derives from a different species. This species however contains also barbaloin and other anthraquinone derivatives (31).

Conclusion

In the absence of clinical studies, the postulated laxative effect of barbados aloes and cape aloes is mainly based on pharmacological data, experts' opinions and clinical experiences. Clinical and pharmacological data obtained on other anthranoid-containing laxatives (please refer to the assessment report on "*Cassia senna* L. and *Cassia angustifolia* Vahl, folium") support the efficacy of these anthranoid-containing herbal substances for short-term use in cases of occasional constipation.

The other effects mentioned in chapter II.2.1 have been predominantly investigated in experimental studies. Adequate clinical trials are not available.

III.3 Clinical studies in special populations

III.3.1 Use in children

First of all, change of nutrition is recommended in constipated children with an increase in daily fibre intake. According to the recommendations from a conference on dietary fibre in childhood, children older than 2 years of age should increase their intake of dietary fibre (increased consumption of a variety of fruits, vegetables, cereal and other grain product) to an amount equal or greater than their age plus 5 g (e.g. 8 g/day at age 3) (32). Change in nutrition should be accompanied with behaviour modification, e.g. increased physical exercise. There are no systematic clinical data available, which evaluate the use of aloe dried juice as a laxative in children.

According to the ESCOP and WHO monographs, the use in children under 10 years of age cannot be recommended.

According to the "Note for guidance on clinical investigation of medicinal products in the paediatric population" (CPMP/ICH/2711/99) of 27 July 2000, the age limit between "children" and "adolescents" is set to "12 years of age".

III.3.2 Use during pregnancy and lactation

There are no recent investigations available.

In theory, it is possible that reflex stimulation might occur, involving not only the colon but also uterine muscles and then might lead to the development of hyperaemia in the pelvic region and to miscarriage as a result of neuromuscular stimulation of uterine muscles. Especially high doses shall lead to metrorrhagia, and miscarriage (7).
Animal experiments demonstrated that placental passage of rhein is small. Aloe-emodin is quickly oxidised to rhein and an unknown metabolite, or conjugated.

Aloe extract

No teratogenic or foetotoxic effects were seen in rats after oral treatment with aloe extract (up to 1000 mg/kg) or aloin A (up to 200 mg/kg) (4). The pregnant rats were treated between the 10th and 13th day of the gestational period. A caesarean section was done on the 21st day post conception.

Morimoto I. et al. 1982 (76) reported the results of the Ames test and the rec-assay for 104 crude extracts including aloe. The investigators found neither water nor methanol extracts of aloe to have mutagenic activity in *Salmonella typhimurium* strains TA-98 or TA-100. A water extract of aloe was reported to produce a positive effect in the rec-assay using *Bacillus subtilis* (difference in diameter between the inhibition zones for H17 und M45 strains: 2-5 mm). Approximately 35% of the investigated extracts were found to have activity in this test.
Brown JP 1980 (77) reported that barbaloin, a C-glycoside of aloe-emodin anthrone, was not active in the rec-assay.

Marquardt et al. 1987 (cited in the unpublished report of Brusick DJ 1994 (78)) conducted a more thorough evaluation of aloe-extract in the Ames test. A wide range of mutant strains (TA-97, TA-98, TA-100, TA-102, TA-1535, TA-1537, and TA-1538) was included, and "fecalase" (gut flora enzymes) was employed in order to breakdown any potentially active glycosides. The results of this investigation were negative with the maximum test concentration set at 3,000 µg/plate. Barbaloin was also reported negative in this study.

In 1992 Cytotest Cell Research GmbH & Co. conducted a series of genetic tests using a batch of commercial aloe-extract (also cited in the unpublished report of Brusick DJ 1994 (78)). The Ames test (employing TA-1535, TA-1537, TA-1538, TA-98, and TA-100) only produced a mutagenic effect in strain TA-1537 at 5,000 µg/plate without and with S9 mix but not at the next lower concentration of 1,000 µg/plate.
A mammalian cell assay for gene mutation conducted in V79 cells showed no evidence of mutagenicity with aloe extract in concentrations up to 1,000 µg/ml without S9 mix and up to 5,000 µg/ml with S9 mix.
Aloe-extract was shown to be clastogenic in CHO cells. In the absence of S9 mix, aloe-extract induce significant increases in chromosome breakage at concentration of 3000 µg/ml (30-hour harvest) and 4000 µg/ml (24-hour harvest). No clastogenicity was observed with S9 mix at concentrations up to 4750 µg/ml. However, an *in vivo* test for clastogenicity with aloe-extract (**Bootman J et al. 1987a**, cited in the unpublished report of Brusick DJ 1994 (78)) produced no evidence of a response in the mouse micronucleus test at a maximum applicable dose of 1.5 gm/kg (orally).

Aloe-emodin

Brown JP and Dietrich PS 1979 (79) reported that aloe-emodin was mutagenic in *Salmonella typhimurium* strain TA-1537. The mutagenicity was observed in the absence of S9 mix (terms of revertants per nmol test agent: 0.22; terms of revertants per plate less background for a given quantity (µg) of test agent: 22 (50 µg) without S9 activation, 13 (50 µg) with S9 activation; 61 (100 µg) without S9 activation, 14 (100 µg) with S9 activation; 12 (250 µg) without S9 activation, 15 (250 µg) with S9 activation.

Westendorf J et al. 1990 (33) reported on the genotoxicity of aloe-emodin in a broad spectrum of *in vitro* assays. Positive results were obtained in the Ames test with *Salmonella typhimurium* strains TA1537, TA1538, TA98 and TA1978. In the HPRT test, no reproducible induction of mutations was obtained, while unscheduled DNA synthesis (UDS) and cell transformation was induced. These results led to the conclusion that aloe-emodin interacts with bacterial and mammalian DNA under certain *in vitro* conditions (see also assessment report on "*Cassia senna* L. and *Cassia angustifolia* Vahl, folium").

Heidemann A et al. 1996 (34) undertook *in vitro* and *in vivo* experiments to clarify the genotoxic potential of the hydroxyanthraquinone aloe-emodin. The results confirmed that aloe-emodin is able to induce mutagenic effects *in vitro*. In *in vivo* studies (micronucleus assay in bone marrow cells of NMRI mice; chromosome aberration assay in bone marrow cells of Wistar rats; mouse spot test [DBA/2J x NMRI]) no indication of a mutagenic activity of aloe emodin was found. Information about a possible reaction of aloe-emodin with DNA was derived from an *in vivo* UDS assay. Hepatocytes of aloe-emodin treated male Wistar rats did not show DNA damage via repair synthesis. These data suggest that aloe-emodin is able to interact with DNA under certain *in vitro* conditions. However, *in vivo* the results did not indicate a genotoxic potential. Therefore the authors assume that a genotoxic risk for man might be unlikely.

Lee KH et al. 2000 (36) isolated di(2-ethylhexyl)phthalate (DEHP) from *Aloe vera* L. For his studies he used freeze-dried powder of leaves. The substance was isolated using solvent extraction and chromatography. The identity of DEHP was confirmed using an authentic sample. As the investigators used the entire leaves, it is not possible to give evidence whether the juice contains this ingredient or not.

Shiota K 1985 (35) reported that di(2-ethylhexyl)phthalate (DEHP) and mono-(2-ethylhexyl)phthalate (MEHP) were administered by stomach intubation (per os, PO) or by intraperitoneal (IP) injection to pregnant ICR strain mice at varying doses on days 7, 8, and 9 of gestation. In groups given DEHP orally, resorptions and malformed foetuses increased significantly at 1,000 mg/kg. Fetal weights were also significantly suppressed. Anterior neural tube defects (anencephaly and exencephaly) were the malformations most commonly produced. No teratogenic effects were revealed by IPl doses of DEHP and PO or IP doses of MEHP, although high doses were abortifacient and lethal to pregnant females. The difference in metabolism, disposition, or excretion by the route of administration may be responsible for the difference in DEHP teratogenicity. Since IP injection of DEHP was not teratogenic, it is unlikely that metabolism outside the gastrointestinal tract converts DEHP to any teratogenic metabolites. DEHP was not mutagenic in the Ames' salmonella/microsome test using hepatic S-9 preparations. Although MEHP is a principal metabolite of DEHP and is several times more toxic than DEHP to adult mice, it seems that MEHP and its metabolites are not teratogenic in ICR mice.

The European Union classified DEHP as toxic to reproduction category 2 in the Directive 2003/36/EC of the European Parliament and the Council of 26 May 2003 (73). Category 2 includes substances, which should be regarded as if they impair fertility in humans or as if they cause developmental toxicity to humans based on sufficient evidence or other relevant information. DEHP has to be declared with the symbols R60 (may impair fertility) and R61 (may cause harm to the unborn child).

The 'Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with food (AFC)' assessed DEHP for use in the manufacture of food contact materials, on a request from the Commission and adopted an opinion on 23 June 2005 (74). Previously, a Tolerable Daily Intake (TDI) of 0.05 mg/kg bw was set by the Scientific Committee for Food (SCF), based on the endpoint of peroxisome proliferation in rodent liver. There was then a scientific consensus that liver peroxisome proliferation in rodents is not relevant for human risk assessment. The critical effects of DEHP relate to reproduction.

Testicular effects have been observed in several repeated dose toxicity studies in rats, mice, and ferrets. Minor effects were observed in hamsters, and in the available studies marmosets were not sensitive to DEHP. No studies on testicular effects in rabbits are available.

A 2-generation reproduction study of DEHP in rats (Schilling K et al.) has documented effects on reproductive performance and fertility in the F0 and F1 parental animals at 1,088 mg/kg bw/day. Substance-induced signs of adverse developmental toxicity were noted in the progeny of the F0 and F1 parents from 340 mg/kg bw/day onwards. The No Observed Adverse Effect Level (NOAEL) for reproductive performance and fertility was 340 mg/kg bw/day and for developmental toxicity 113 mg/kg bw/day, respectively.

From a multigeneration reproductive study in which DEHP was administered to rats in the diet (Wolfe GW and Layton KA 2003), a NOAEL of 4.8 mg/kg bw/day for testicular toxicity and developmental toxicity can be derived.

Based on the current literature on DEHP testicular toxicity, the Panel allocated a TDI of 0.05 mg/kg bw, based on a NOAEL of 5 mg/kg bw/day, and making use of an uncertainty factor of 100.
The EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) had prescribed in 1998 the same value for the TDI (75).

III.3.3 Conclusion

Because the data are insufficient and the results of available investigations are not consistent, use during pregnancy cannot be recommended. Furthermore other actions like behavioural modification, dietary changes and use of bulk forming agents should be the first actions taken during pregnancy to treat constipation.

Use during lactation is not recommended as there are insufficient data on the excretion of metabolites in breast milk, too. Investigations with a "standardised senna laxative" (Agiolax®), which also contains *Plantago ovata* seeds/husks as bulk substances, showed that small amounts of active metabolites (rhein) are excreted in breast milk. No laxative effect in breast fed babies has been reported (37). Aloe-emodin is quickly oxidised to rhein and an unknown metabolite or conjugated.

The risk caused by DEHP following the administration of aloe dried juice preparations cannot be assessed. No clear evidence exists that these aloe preparations contain this substance at all, and, if any, in which amount. Children below the age of 12 years, pregnant and breast-feeding women are already excluded. Furthermore, the duration of use is limited. Up to now no further restrictions are justified.

III.4 Traditional use

In the available data on traditional use, it is not always possible to differentiate the various aloe preparations that are mentioned because of insufficient description/declaration of active ingredients. It is therefore not possible to attribute special traditional indications to defined aloe preparations, although it seems to be likely that aloe gel or similar preparations and not aloe dried juice were externally used.
Because of this lack of information, this report covers all traditional indications reported for "aloe" altogether.

Aloe has a long history as a medicine and skin care aid. For over 6,000 years aloe was used for a wide range of ailments. The ancient Egyptians used aloe to heal battle wounds and cure infections. The early Greeks used it for relieving blisters, burns and leg ulcers as well as bowel and stomach disorders. Legend it that Aristotle persuaded Alexander the Great to conquer the Isle of Socroto to secure enough aloe vera to heal his soldiers' wounds. In England aloe was already used in the 10th century. In the 12th century aloe was brought to Germany by Albertus Magnus (38).

Dioskurides (39) already mentioned aloe in his materia medica 50-70 A.D. Aloe is a purgative for the stomach and abdomen and in jaundice. It represses haemoptysis. Aloe administered externally heals wounds and ulcers as well as diseases of the eyes. It is good for headache administered with vinegar and rose ointment on the forehead and temples. Together with vine it slows up hair loss. For inflammation of the mouth and tonsils, it is mixed with honey and vine.

The **Britisch Pharmaceutical Codex 1911** (40) mentions aloe as a purgative. Because the action of aloe on the large intestine induces some pelvic congestion, it is therefore employed as an emmenagogue in amenorrhoea, generally with iron. The recommended dose is 1 to 3 decigrams (2 to 5 grains).

In the **Dispensatory of the United States of America 1918** (41) aloe is mentioned as a cathartic (purgative). It is also described that it was formerly almost universally believed that aloe possessed emmenagogue properties and it was accordingly largely used in the treatment of various forms of amenorrhea, but that it is extremely doubtful whether aloe exercises any action upon the pelvic organs which is not attributable to its cathartic effects.

In his "Manual of Materia Medica and Pharmacology", **Culbreth 1927** (42) mentions as indications constipation, atonic dyspepsia, jaundice, non-active haemorrhoids, amenorrhea, ascarides; for the two last may be given by enema.

Hager 1927 (43) mentions the use as an appetising agent in low doses (0.05 – 0.1 g) and as a cathartic in higher doses (0.2 – 1.0 g). The use in menstruation, pregnancy and bleeding haemorrhoids is not recommended because of congestion of the pelvis organs. The use as a clysma and as an eye ointment or powder is not very common.

Madaus 1938 (38) gives a review of the use of aloe like mentioned above. Paracelsus already indicated the use as a purgative and as vesicant for an abscess. Lonicerus 1564 described the purgative, emmenagogue and expectorant effects. Aloe was used for haemoptysis, jaundice, hydrops and as a vermifuge. Externally aloe was used for headache, wounds, abscess and bleeding haemorrhoids. Matthiolus 1626 added the use against hair loss. Hecker 1814 confirmed the indications mentioned above. Additionally he described the use in gout and external use in inflammations of the eyes. In Estonia aloe was sometimes used for tuberculosis.

Koenen 1977 (44) describes the use of "Aloe hereroensis Engler" in South Africa. An aqueous extract was used for complains of digestion and for pectoral complains.

Furthermore the South Africans used aloe for syphilis and for inflammations of the eyes (45).

The WHO monograph "Aloe" (4) mentions the following uses described in folk medicine, not supported by experimental or clinical data: treatment of seborrhoeic dermatitis, peptic ulcers, tuberculosis, fungal infections, and for reduction of blood sugar levels. The references given are not original sources and date from 1991 and 1995.

Conclusion

Besides the use as a laxative, the use as an emmenagogue and the external use for wounds and abscess are described in most references mentioned above, however the preparations used are not well defined. But, as already mentioned in the Dispensatory of the United States of America 1918, it is extremely doubtful whether aloe exercises any action upon the pelvic organs which is not attributable to its cathartic effects. There are no plausible pharmacological data for this indication, nor for haemoptysis, jaundice or gout etc.
Concerning the external use, the references do not describe exactly the preparations used.
Furthermore, the possible risks as described in chapter IV Safety have to be taken into account.
None of the above-mentioned uses can therefore be accepted for inclusion in the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products'.

IV. Safety

IV.1 Genotoxic and carcinogenic risk

IV.1.1 Preclinical Data

As mentioned in chapter III.3 Clinical studies in special populations, toxicological data from *in vitro* investigations (33) indicate that the hydroxyanthraquinones, emodin and aloe-emodin, might represent a genotoxic risk. However, results from *in vivo* investigations (34) did not indicate a genotoxic potential. *In vitro* assays overestimate the potential hazard from exposure and must be reevaluated by *in vivo* experiments.

The genotoxic actions reported for certain constituents of aloe species indicate a carcinogenic potential for certain hydroxyanthraquinones. There are a very few investigations in animals which do not, however, so far permit adequate assessment.

The occurrence of intestinal tumours in rats has been reported by **Mori H et al. 1985** (46) following the dietary administration of chrysazin (1,8-dihydroxy-9, 10-anthracenedione = danthrone) for 16 months at the concentration of 1%. Twelve out of 18 rats survived more than one year. Of these, 7 rats developed intestinal tumours of the colon or caecum, adenomas or adenocarcinomas. Besides these neoplasms, focal hyperplastic lesions of the glandular epithelium of the colon and caecum were frequently encountered in treated animals both with and without intestinal tumours. In the liver of several rats, some histological changes such as focal necrosis, fibrosis, cystic lesions and bile duct proliferation were seen.

Another carcinogenicity testing of chrysazin was performed in 1986 (47) in C_3H/HeN mice by dietary administration for 540 days at a concentration of 0.2% since mice did not tolerate larger doses (1% and 0.5%). All the mice that were given the chemical and survived more than 500 days, developed adenomatous hyperplasia with cystic glands of the caecum and colon. These lesions were not seen in animals of the control group. Some of the hyperplastic lesions were difficult to distinguish from true neoplasms. Similar hyperplastic lesions were also recognised together with the carcinomas in rats (see above 46). Carcinogen-induced hyperplastic lesions have been regarded as an important precursor change for malignancies in various experimental models.The authors therefore stated that the lesions obtained here appear to indicate a certain carcinogenic potency of chrysazin in mice, and mouse intestine may be less sensitive than rat intestine to the carcinogenic action of the chemical. The incidence of hepatocellular carcinoma of mice given chrysazin (4/17) was significantly higher than that of the controls (0/19). However, benign hepatocellular neoplasms were also seen in the animals of the control group. The authors therefore concluded that chrysazin enhanced the progression of spontaneously occuring hepatocarcinogenesis.

Danthron and 8 other hydroxyanthraquinones were comparatively investigated by **Wölfle D et al. 1990** (48) for activities associated with tumour promotion, such as stimulation of cell proliferation and enhancement of malignant transformation. The *in vivo* treatment of primary rat hepatocytes with danthron, aloe-emodin, chrysophanol, and rhein resulted in a 2-3-fold increase of DNA synthesis; lucidin and purpurin were less active, and emodin, purpuroxanthin, and alizarin were essentially inactive. In addition, danthron, rhein, and chrysophanol, but not alizarin, enhanced transformation of C3H/M2 mouse fibroblasts initiated by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine or 3-methylcholanthrene. The results of these *in vitro* studies suggest that hydroxyanthraquinones, possessing 2 hydroxy groups in 1,8-positions, e.g. danthron, rhein, and chrysophanol, may have tumour-promoting activities .

In a model of dimethylhydrazine(DMH)-induced colorectal tumours in male mice neither aloin- nor sennoside-enriched diets (0.03% corresponding to 100 mg/kg/day) promoted incidence and growth of adenomas and carcinomas after 20 weeks as evidenced by different endpoint parameters, based on a macroscopic evaluation and microscopic examination. In the DMH-induced tumour model a tumour incidence appeared which allowed an increasing or decreasing effect to be detected after additional treatment, i.e. a 50% incidence of tumour-bearing animals. With regard to hepatotoxic and nephrotoxic effects, DMH itself enhanced plasma levels of GPT and SDH which were further significantly increased by coadministration of aloin. The anthranoids alone had no effect. No effects on serum electrolyte concentrations were observed after any of the treatments (49).

The aim of the study of **Schörkhuber M et al. 1998** (50) was to demonstrate the effect of the 1,8-dihydroxyanthraquinone (DHA)-laxatives, danthrone, rhein, aloe-emodin and sennidine, on colorectal tumour cells, because available information on their implication in colon carcinogenesis was still inconclusive. In SW480 carcinoma cultures, dose-dependent induction of urokinase secretion into the medium was the predominant effect. Simultaneously, cell numbers were decreased by DHA-aglyka, but not by sennoside nor the biphenylic laxative bisacodyl. DNA synthesis was not similarly reduced: 0.4-4 µM danthrone and sennidine even stimulated 5-bromo-2'-desoxyuridine (BrdU) uptake into DNA. When uptake was normalised to cell number, danthrone and sennidine doubled BrdU uptake/10^6 cells, 18 µM rhein and 0.7 µM aloe-emodin induced increases of 37 and 50%, respectively. This may at least partially be due to selective resistance of S-phase cells to DHA-caused cell loss. In VACO235 adenoma cells, sennidine and aloe-emodin did not affect urokinase secretion, but stimulated growth.

Both cell numbers and DNA synthesis were increased. In contrast to SW480 carcinoma cells, VACO235 cells were also sensitive to sennoside and bisacodyl. No effects of DHA were observed in normal colorectal epithelial cells. The biological effects were preceeded by specific phosphorylation of cellular proteins with molecular weights of 110, 78, 63, 57 kDa, indicating the specific induction of a cellular signalling cascade by the laxatives.

In 2001 the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services published a technical report on toxicology and carcinogenesis studies of emodin (107).

- 16-day study in F344/N rats

Groups of 5 male and 5 female rats were fed diets containing 0, 600, 2,000, 5,500, 17,000, or 50,000 ppm emodin. This corresponds in males to average daily doses of approximately 50, 170, 480, 1,400, or 3,700 mg emodin/kg bw and in females to 50, 160, 460, 1,250, or 2,000 mg/kg bw. Three female rats died before the end of the study. Mean body weights of males and females exposed to 5,500 ppm or greater were significantly less than those of the controls. Feed consumption by males and females receiving 17,000 or 50,000 ppm was decreased throughout the study. Macroscopic lesions were present in the kidney of rats exposed to 17,000 or 50,000 ppm.

- 16-day study in B6C3F1 mice

The size of the groups and the administered concentrations were the same as described above. The concentrations correspond in males to average daily doses of approximately 120, 400, 1,200 or 3,800 mg/kg bw and in females to 140, 530, 1,600 or 5,000 mg/kg bw. 50,000 ppm equivalents were not calculated due to high mortality. All mice exposed to 50,000 ppm died before the end of the study. Mice in the 17,000 ppm groups lost weight during the study. Feed consumption by 5,500 ppm females was greater than that by the controls. Macroscopic lesions were present in the gallbladder and kidney of mice exposed to 17,000 ppm.

- 14-week study in rats

Groups of 10 male and 10 female rats were fed diets with 0, 312.5, 625, 1,250, 2,500 or 5,000 ppm emodin. This corresponds to average daily doses of approximately 20, 40, 80, 170, or 300 mg/kg bw in males and females. Among others relative kidney weights of rats exposed to 1,250 ppm or greater and relative lung weights of rats exposed to 625 ppm or greater were significantly increased compared to the control groups. Relative liver weights were increased in females exposed to 625 ppm or greater. The estrous cycle length was significantly increased in females exposed to 1,250 or 5,000 ppm. All male rats exposed to 1,250 ppm or greater and all exposed female rats had pigment in the renal tubules; and the severity of pigmentation generally increased with increasing exposure concentration. The incidences of hyaline droplets in the cortical epithelial cytoplasm were increased in all groups of exposed males and in females exposed to 312.5, 625, or 1,250 ppm.

- 14-week study in mice

The size of the groups and the administered concentrations were the same as described above. This corresponds to average daily doses of approximately 50, 100, 190, 400, or 800 mg/kg in males and 60, 130, 240, 500, or 1,100 mg/kg in females. Relative kidney weights of male mice exposed to 1,250 ppm or greater, relative lung weights of males exposed to 625 ppm or greater, and relative liver weights of female mice exposed to 625 ppm or greater were increased. The incidences and severities of nephropathy were increased in males and females exposed to 1,250 ppm or greater. The incidences of renal tubule pigmentation were significantly increased in males exposed to 1,250 ppm or greater.

- 2-year (105 weeks) study in rats

Groups of 65 male and 65 female rats were fed diets containing 0, 280, 830, or 2,500 ppm emodin (equivalent to average daily doses of approximately 110, 320, or 1,000 mg/kg in males and 120, 370, or 1,100 mg/kg in females).

Three Zymbal's gland carcinomas were observed in female rats exposed to 2,500 ppm. This incidence exceeded the range observed for current historical controls and was considered an equivocal finding. At the 6- and 12-month interim evaluations and at 2 years, emodin-related increases in the incidences of renal tubule hyaline droplets occurred in all exposed groups. The incidences of renal tubule pigmentation were significantly increased of all exposed groups of males at 2 years. There were negative trends in the incidences of mononuclear cell leukaemia in male and female rats, and the incidences in the 2,500 ppm groups were significantly decreased. In females exposed to 2,500 ppm, the incidence was below the historical control range; the incidence in males exposed to 2,500 ppm was at the lower end of the historical control range.

- 2-year (105 weeks) study in mice

Groups of 60 male mice were fed diets containing 0, 160, 312, or 625 ppm emodin (equivalent to average daily doses of approximately 15, 35, or 70 mg/kg). Groups of 60 female mice were fed diets containing 0, 312, 625, or 1,250 ppm emodin (equivalent to average daily doses of approximately 30, 60, or 120 mg/kg). Low incidences of renal tubule adenoma and carcinoma occurred in exposed male mice; these incidences included one carcinoma each in the 312 and 625 ppm groups. Renal tubule neoplasms are rare in male mice, and their presence in these groups suggested a possible association with emodin exposure. At the 12-month interim evaluation, the severity of nephropathy was slightly increased in males exposed to 625 ppm. Also at 12 months, the severity of nephropathy increased from minimal in the lower exposure groups to mild in females exposed to 1,250 ppm; the incidence in this group was significantly increased compared to the control group. At 2 years, the severities of nephropathy were slightly increased in males exposed to 625 ppm and females exposed to 1,250 ppm. The incidences of nephropathy were significantly increased in all exposed groups of females. At the 12-month interim evaluation, the incidences of renal tubule pigmentation were significantly increased in all exposed groups of males and in females exposed to 625 or 1,250 ppm. The severities increased with increasing exposure concentration. At 2-years, the incidences of renal tubule pigmentation were significantly increased in all exposed groups; severities also raised with increasing exposure concentration.

- Genetic toxicology

Emodin was mutagenic in *Salmonella typhimurium* strain TA100 in the presence of S9 activation; no mutagenicity was detected in strain TA98, with or without S9. Chromosomal aberrations were induced in cultured Chinese hamster ovary cells treated with emodin, with and without S9. Three separate *in vivo* micronucleus tests were performed with emodin. A male rate bone marrow micronucleus test, with emodin administered by 3 intraperitoneal injections, gave negative results. Results of acute-exposure (intraperitoneal injection) micronucleus tests in bone marrow and peripheral blood erythrocytes of male and female mice were negative. In a peripheral blood micronucleus test on mice from the 14-week study, negative results were seen in male mice, but a weakly positive response was observed in similarly exposed females.

Conclusion by the "National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee":

- The studies give no evidence of carcinogenic activity of emodin in male rats and female mice, and equivocal evidence in female rats and male mice.
- In view of conflicting results on genotoxicity, it was noted the first pass effect and need for metabolic activation suggesting a metabolite as the genotoxic form. The metabolite 2-hydroxyemodin acts as the genotoxin (88).

IV.1.2 Clinical Data

Siegers CP et al. 1993 (51) reported about a retrospective study of 3,049 patients, who underwent diagnostic colorectal endoscopy. The incidence of pseudomelanosis coli was 3.13% in patients without pathological changes. In those with colorectal adenomas, the incidence increased to 8.64% ($p<0.01$), and in those with colorectal carcinomas it was 3.29%. This lower rate was probably caused by incomplete documentation of pseudomelanosis coli in those with carcinoma. In a prospective study of 1,095 patients, the incidence of pseudomelanosis coli was 6.9% for patients with no abnormality seen on endoscopy, 9.8% ($p=0.068$) for patients with adenomas and 18.6% for patients with colorectal carcinomas. From these data a relative risk of 3.04 (1.18, 4.9; 95% confidence interval) can be calculated for colorectal cancer as a result of chronic anthranoid laxative abuse.

Kune GA et al. 1988 (52) and **Kune GA 1993** (53) reported about the "Melbourne Colorectal Cancer Study". Commercial laxative use as a risk factor in colorectal cancer was investigated as one part of this large population based epidemiological study of colorectal incidence, aetiology and survival. Commercial laxative use was similar in 685 colorectal cancer patients and 723 age/sex matched community based controls. Also, when laxatives were subdivided into various groups containing anthraquinones, phenolphthalein, mineral salts and others, previous laxative intake was similar between cases and controls. Previous use of anthraquinone laxatives and of phenolphthalein containing laxatives was not associated with the risk of colorectal cancer. Furthermore the results of this study suggest that chronic constipation, diarrhoea, and the frequency and consistency of bowel motions are unlikely to be etiologic factors in the development of colorectal cancer. They indicate that it is the diet and not the constipation that is associated with the risk of large-bowel cancer. Additionally, a highly statistically significant association ($p=0.02$) with the risk of colorectal cancer was found in those who reported constipation and also had a high fat intake.

In a retrospective study a cohort of 2,277 patients was defined by colonoscopy. Among other factors **Nusko G et al. 1993** (54) tested whether in these patients laxative use or the endoscopically diagnosed presence of melanosis coli were risk factors related to colorectal neoplasm. In comparison to patients taking no laxatives there was no significant increase in colorectal cancer rate either in laxatives users or in patients with melanosis coli. However, there was a statistically significant association between the occurrence of colorectal adenomas and laxative use (relative risk of all patients exposed to laxatives = 1.72; of patients exposed to laxatives without melanosis coli = 1.47). The relative risk of adenoma development in patients with melanosis coli was 2.19. Taking into account that polyps can be diagnosed in the dark mucosa of melanosis coli patients more easily, the authors concluded that even this relative risk of 2.19 seems to be related to a generally enhanced risk of laxative intake rather than to a special group of (anthranoid-containing) laxatives.

Sonnenberg A et al 1993 (55) performed a meta-analysis, since individual case control studies failed to resolve the question whether constipation and use of cathartics (purgatives) represent significant risk factors of colorectal cancer. The analysis of 14 previously published (from 1954 to 1988) case control studies revealed statistically significant risks for colorectal cancer associated with both constipation and use of cathartics, the pooled odds ratios (OR) and their 95 percent confidence intervals being 1.48 (1.32-1.66) and 1.46 (1.33-1.61), respectively. The increased risk applied similarly to both sexes, it was higher in cancer of the colon than rectum. Since constipation and cathartics are associated with much lower odds ratios than various dietary components, such as fat, meat, alcohol, and low-vegetable or low-residue diets, the authors concluded that their risk reflects the confounding influence of underlying dietary habits.

Loew D et al. 1994 (56) conducted a comparative study involving 423 patients with colorectal neoplasms and 522 patients with benign proctologic disorders who were regular users of laxatives for bowel regulation. A pseudomelanosis coli (PMC) test was used as an indicator of exposure to anthranoid-containing laxatives to determine if these preparations were potential colorectal carcinogenics. Results indicated no significant difference of the PMC rates between carcinoma (6.1%) and the control groups (4.2%) ($p\leq0.197$).

Jacobs EJ et White E 1998 (90) examined the associations of colon cancer with constipation and use of commercial laxatives in a case-control study among men and women aged 30 – 62 years (424 incident cases and 414 random-digital-dial controls). Constipation was defined by "feeling constipated to the point of having to take something". The adjusted relative risk (RR) was 2.0 [95% confidence interval (CI) = 1.2-3.6] for constipation 12-51 times per year, and 4.4 (95%CI = 2.1-8.9) for constipation 52 or more times a year. Cumulative lifetime use of commercial laxatives was also associated with increased risk of colon cancer. When adjusted for constipation, commercial laxative use was no longer associated with increased risk (RR = 0.3, 95%CI = 0.1-0.9 for less than 350 uses; RR = 0.9, 95% CI = 0.4-2.3 for 350 or more uses). The association with constipation remained. In this study, no subject reported use of anthranoid-containing laxatives.

Nusko G et al. 2000 (57) performed a prospective case control study at the University of Erlangen to investigate the risk of anthranoid-containing laxative use for the development of colorectal adenomas or carcinomas. A total of 202 patients with newly diagnosed colorectal carcinomas, 114 patients with adenomatous polyp, and 238 patients (controls) with no colorectal neoplasm who had been referred for total colonoscopy were studied. The use of anthranoid preparations was assessed by standardised interview, and endoscopically visible or microscopic melanosis coli was studied by histopathological examination. There was no statistically significant risk of anthranoid use for the development of colorectal adenomas (unadjusted odds ratio 1.0; 95% CI 0.5-1.9) or carcinomas (unadjusted odds ratio 1.0; 95% CI 0.6-1.8). Even after adjustment for the risk factors age, sex, and blood in the stools by logistic regression analysis the odds ratio for adenomas was 0.84 (95% CI 0.4-1.7) and for carcinomas 0.93 (95% CI 0.5-1.7). Also, there were no differences between the patient and control groups for duration of intake. Macroscopic and high grade microscopic melanosis coli were not significant risk factors for the development of adenomas or carcinomas.

Willems M et al. 2003 (58) described a case of melanosis coli, which occurred in a 39-year old liver transplant patient, who took an over-the-counter product containing aloe, rheum and frangula. The typical brownish pigmentation of the colonic mucosa developed in a period of ten months. The anthranoid medication was stopped and follow-up colonoscopy one year later showed normal looking mucosa once more. However, in contrast to previous examinations, a sessile polypoid lesion was found in the transverse colon. Histology showed tubulovillous adenoma with extensive low-grade dysplasia. Since there had been preliminary reports suggesting a possible role of anthranoid-containing laxatives in the development of colorectal adenomas and cancer, the authors discouraged their use.

Roberts MC et al. 2003 (91) conducted a population-based, case-control study with equal representation by white and black men and women aged 40 – 80 years. Constipation, defined as fewer than three reported bowel movements per week, was associated with a greater than two-fold risk of colon cancer (OR 2.36; 95% CI = 1.41-3.93) adjusted for age, race, sex, and relevant confounders. The OR for constipation was slightly higher for distal than for proximal colon cancers. There was no association with laxative use (OR 0.88; 95% CI = 0.69-1.11). The authors did not explicitly mention anthraquinone-containing laxatives. They mentioned the group "stimulants, fibers, natural remedies, stool softeners, oils, osmotic agents, enemas, suppositories, and unknown". They mention in particular phenolphthalein and magnesium.

Nilsson SE et al. 2004 (59) examined the impact of constipation and laxative treatment on the blood levels of homocysteine, folate and cobalamine in a population-based sample of aged people. Elevated plasma homocysteine secondary to reduced supply of folate and cobalamine, might indicate an increased risk of cancer, and cardiovascular and neurological diseases. The homocysteine level depends on the supply of folate and cobalamine, which constipation and/or laxative treatment might compromise. The study was based on biochemical tests in 341 females and 183 males aged 82 years and older. The concentrations of homocysteine (plasma), folate, cobalamine and urea (serum) were measured in subjects with and without ongoing treatment with laxative products. Values were adjusted for age, gender and frailty, as well as for clinical diagnoses and medicinal product therapies known to affect homocysteine levels. Homocysteine levels were increased and those of folate reduced in aged subjects on laxatives. Homocysteine remained elevated after adjusting for frailty and various neurological disorders. There was no significant effect on homocysteine and folate in constipated subjects without laxatives.

Jae Sik Joo et al. 1998 (62) investigated changes occurring on barium enema in patients ingesting stimulant laxatives. The study consisted of two parts. In part 1, a retrospective review of consecutive barium enemas performed on two groups of patients with chronic constipation (group 1, stimulant laxative use (n=29); group 2, no stimulant laxative use (n=26)) was presented to a radiologist who was blinded to the patient group. A data sheet containing classic descriptions of cathartic colon (historic term for the anatomic alteration of the colon secondary to chronic stimulant laxative use) was completed for each study. Chronic stimulant laxative use was defined as stimulant laxative ingestion more than three times per week for 1 year or longer. To confirm the findings of the retrospective study, 18 consecutive patients, who were chronic stimulant laxative users underwent barium enema examination, and data sheets for cathartic colon were completed by another radiologist (part 2). Colonic redundancy (group 1, 34.5%; group 2, 19.2%) and dilatation (group 1, 44.8%; group 2, 23.1%) were frequent radiographic findings in both patient groups and were not significantly different in the two groups. Loss of haustral folds, however, was a common finding in group 1 (27.6%) but was not seen in group 2 ($p<0.005$). Loss of haustral markings occurred in 15 (40.5%) of the total stimulant laxative users in the two parts of the study and was seen in the left colon of 6 (40%) patients, in the right colon of 2 (13.3%) patients, in the transverse colon of 5 (33.3%) patients, and in the entire colon of 2 (13.3%) patients. Loss of haustra was seen in patients chronically ingesting bisacodyl, phenolphthalein, senna, and casanthranol. The authors concluded that long-term stimulant laxative use results in anatomic changes in the colon characterised by loss of haustral folds, a finding that suggest neuronal injury or damage to colonic longitudinal musculature caused by these agents.

IV.1.3 Conclusion

Because of the possible genotoxic or tumourigenic risk in experimental investigations and the results of Siegers 1993, pharmacovigilance actions for anthranoid-containing laxatives (2) were initiated in Germany in 1996: the daily dose and the duration of administration were limited and children, pregnant women and nursing mothers were excluded from the application of aloe containing laxatives.

The results of the most recent studies are inconsistent and the question of a possible carcinogenic risk of long-term use of anthranoid-containing laxatives is still open. Some studies revealed a risk for colorectal cancer associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to determine the carcinogenic risk definitely. Therefore the conditions determined in the above-mentioned pharmacovigilance actions for anthranoid-containing laxatives (2) have to be maintained for the moment.

Long-term administration of anthranoid-containing medicinal products leads to the development over a period of 4 – 13 months of pseudomelanosis coli – pigmentation of the gut wall in the caecum and colon. This condition is produced by the accumulation of macrophages that have stored a brown pigment from the breakdown products of anthranoid (probably lipofuscin) and consequently cause the mucosa to appear brown to blackish-brown in colour. Prevalence among patients with chronic constipation is reported to be 12 – 31%, and 62% following chronic ingestion of anthranoid-containing laxatives. This finding disappears 6 – 12 months after stopping chronic laxative administration.
Long-term stimulant laxative use may result in anatomic changes in the colon characterised by loss of haustral folds.

Regardless of whether a definitive causal relationship can be demonstrated between the use of anthraquinone laxatives and colonic pathology, these agents should not be recommended for chronic or long-term use (80).

IV.2 Toxicity

No specific toxicity was observed in mice when aloes extract was orally administered up to 50 mg/kg daily for 12 weeks and aloin was orally administered up to 60 mg/kg daily for 20 weeks (3).

IV.3 Contraindications

Aloe preparations should not be used by patients with known hypersensitivity to aloe.
The German Health Authority has received one report of an adverse event concerning a combination preparation of aloe, senna, curcuma, and mandrake root. Half an hour after ingestion the patient developed an urticaria and an angiooedema. An allergy test showed a positive result for aloe.
There are several publications available dealing with allergic reactions. Most of all these reactions were caused by local application and the aloe preparations used are not exactly specified.

Ernst E 2000 (63) reported that remedies which can cause dermatological side-effects include "aloe vera" besides others.
Anliker MD et al. 20002 (64) describe a case of an anaphylactic shock due to local application of "aloe vera leaves".
Schempp CM et al. 2002 (65) categorise "aloe" as sensitising plant in cosmetics.

Furthermore, like all anthranoid-containing laxatives, aloe-containing medicinal products should not be used in cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration states with water and electrolyte depletion.

IV.4 Special warnings and precautions for use

The following warnings and precautions for use are recommended:

Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking aloe preparations concomitantly (see chapter II.2.2 Interactions).

Like all laxatives, aloe should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting unless advised by a doctor because these symptoms can be signs of potential or existing intestinal blockage (ileus).

If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives should be avoided.

Use for more than 1 - 2 weeks requires medical supervision as outlined in the posology section of the Community herbal monograph.

Aloe preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.

It cannot be assessed definitely if a longer than a brief period of treatment with stimulant laxatives leads to dependence requiring increasing quantities of the medicinal product, to an atonic colon with impaired function and to aggravation of the constipation.

Müller-Lissner 2005 (92) concluded in his review that the arguments in favour of laxative-induced damage to the autonomous nervous system of the colon are based on poorly documented experiments and that, in contrast, the investigations that do not support such damage are well done. The studies in the cited references (**Smith B 1968** (93); **Riemann JF et al. 1980** (94) and **1982** (95); **Berkelhammer C et al. 2002** (96); **Meisel JL et al. 1977** (97); **Pockros PJ et al. 1985** (98)) showed abnormalities observed in humans (damage to enteric nerves, smooth muscle atrophy; distension or ballooning of axons, reduction of nerve-specific cell structures and increase in lysosomes, and sometimes a total degeneration of whole nerve fibers; short-lived superficial damage to the mucosa). They were uncontrolled observations and the author therefore concluded that the cause of these damages can also be the constipation itself or pre-existing changes of unknown aetiology.

The only study comparing the morphology of the autonomous nervous system of constipated patients taking anthraquinones (aloe) to that of an appropriate control group of constipated patients without laxative intake (**Riecken EO et al. 1990** (99)) did not support the hypothesis that anthraquinone-containing laxatives are able to provoke relevant degenerative changes in the colonic nerve tissue. But this investigation was conducted in 11 matched pairs only.

In the light of existing safety concerns, further warnings and precautions for use are recommended:

If stimulant laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives.

Patients with kidney disorders should be aware of possible electrolyte imbalance.

When aloe preparations are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces (60).

IV.5 Undesirable effects

Like all anthranoid-containing laxatives, aloe preparations may produce abdominal pain and colickly gastrointestinal symptoms and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary. The correct individual dose is the smallest required to produce a comfortable soft-formed motion (2).

As mentioned above hypersensitive reactions may occur.

Chronic use may lead to disorders in water equilibrium and electrolyte metabolism, and may result in albuminuria and haematuria.

Furthermore, use over a long period may lead to pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation (see chapter IV.1.3 Conclusion).

Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment (see chapter II.1.2 Absorption, metabolism and excretion).

Luyckx VA et al. 2002 (72) reported a case of a 47-year old man from Soweto, South Africa, who developed acute oliguric renal failure and liver dysfunction after ingestion of an herbal remedy. The patient's renal function recovered slowly, and dialysis was discontinued after several weeks, although serum creatinine did not return to the normal range. Mass spectrometric and chromatographic analysis of the herbal remedy used by the patient revealed the presence of "Cape aloes".
The causality cannot be assessed definitely.

The German Health Authority has received one report of an adverse event concerning a mono-preparation (a Mexican aloe extract). A 45-year old patient, who regularly takes levothyroxine, developed glucosuria, albuminuria, haematuria, and leucocyturia after taking the aloe extract. This patient was suspected to have a toxic-interstitial nephritis and nutritive-toxic tubular injury. One week after dechallenge the urinary findings improved. The aloe extract was suspected to cause these adverse events. The extract was not specified. Therefore an assessment whether the extract is comparable with the preparations described in this assessment report or not is not possible. Nevertheless albuminuria and haematuria are known adverse reactions of chronic misuse of aloe preparations.

IV.6 Interactions

See II.2.2

IV.7 Overdose

Like for all anthranoid-containing laxatives, the major symptoms of overdose/abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolyte, which should be replaced. Diarrhoea may cause potassium depletion, in particular. Potassium depletion may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics or adrenocorticosteroids are being taken at the same time.
Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly.
Furthermore chronic ingestion of overdoses of anthranoid-containing medicinal products may lead to toxic hepatitis (see below).

Hepatitis

Beuers U et al. 1991 (101) reported a case of toxic hepatitis related to abuse of senna glycosides in a 26-year old female, who had taken an extract of senna fruits corresponding to 100 mg of sennoside B daily in addition to the usual dose of 10 g senna leaves twice a week in a laxative tea. When the patient stopped taking senna, aminotransferases fell by 70% within a week and ranged from 20 – 40 U/l subsequently. When the patient took senna alkaloids again, 2 months later, liver function rapidly deteriorated and improved once more when the product was stopped.
Vanderperren B et al. 2005 (102) reported a case of a 52-year old woman, who had ingested, for more than 3 years, one litre of an herbal tea each day made from a bag containing 70 g of dry senna fruits. She developed renal impairment and acute hepatic failure with increase in prothrombin time (international normalised ratio > 7) and development of encephalopathy. The patient recovered with supportive therapy. Surprisingly, large amounts of cadmium were transiently recovered in the urine.

According to the Rucam score (Roussel UCLAF causality assessment method - for detailed information, please see the assessment report on "*Cassia senna* L. and *Cassia angustifolia* Vahl, folium"), these hepatoxic cases are related to the chronic ingestion of overdoses. Concentrated and dried juice of the leaves of *Aloe barbadensis* Miller and *Aloe* (various species, mainly *Aloe ferox* Miller and its hybrids) being anthranoid-containing herbal substances, the possibility of toxic hepatic reactions is referred to in the section 'Overdose' of the Community herbal monograph on aloe.

V. Overall conclusion

Well-established use: short term use of occasional constipation

There are no clinical studies available, which evaluate the clinical efficacy of barbados aloes and cape aloes in patients with occasional constipation.

The postulated laxative effect is mainly based on pharmacological data, experts' opinions and clinical experiences. Clinical and pharmacological data obtained on other anthranoid-containing laxatives (primarily senna leaf preparations) support the efficacy of these anthranoid-containing herbal substances for short-term use in cases of occasional constipation.
The current level of evidence[1] of the available scientific data for "the short term use of occasional constipation" can be identified as level IV because well-designed studies with mono-preparations of aloe are missing.

The conditions determined in the pharmacovigilance actions for anthranoid-containing laxatives have to be maintained for the moment because further investigations are needed to clarify the carcinogenic risk. The results of the most recent studies are inconsistent. However, a risk was also revealed for constipation itself and underlying dietary habits.

[1] As referred to in the HMPC 'Guideline on the assessment of clinical safety and efficacy in the preparation of Community herbal monographs for well-established and of Community herbal monographs/entries to the Community list for traditional herbal products/substances/preparations' (EMEA/HMPC/104613/2005)

The use in children under 12 years of age is contraindicated and use during pregnancy and lactation is not recommended.

Traditional use

Besides the use as a laxative, the use as an emmenagogue and the external use for wounds and abscess are described in most references mentioned above. But as already mentioned in the Dispensatory of the United States of America 1918, it is extremely doubtful whether aloe exercises any action upon the pelvic organs which is not attributable to its cathartic effects. There are no plausible pharmacological data for this indication, nor for haemoptysis, jaundice or gout etc. Furthermore, the preparations used are not described exactly, even for the external use

In view of existing possible risks, such traditional uses cannot be recommended and referred to in the 'Community list of herbal substances, preparations and combinations thereof for use traditional herbal medicinal products'. This is in accordance with the German pharmacovigilance actions for anthranoid-containing laxatives.