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EMA/HMPC/44385/2012
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Symphytum officinale* L., radix

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on Symphytum officinale L. radix as released for public consultation on 15 August 2011 until 15 November 2011.

	Organisations and/or individuals
1	Association of the European Self-medication Industry (AESGP)
2	Kooperation Phytopharmaka

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Table 2: Comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	AESGP in principle welcomes the development of the above-mentioned European Union herbal monograph which, by providing harmonised assessment criteria for Symphiti radix-containing products, should facilitate mutual recognition in Europe. We have the following specific comments.	
KOOP PHYTO	Kooperation Phytopharmaka, a German scientific organisation, would like to comment on this HMPC draft monograph, because an important preparation is missing which is marketed in Germany. In the following, detailed remarks are given.	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition	AESGP	**A) Well-established medicinal use:** **We propose to add the liquid extract (1:2), extraction solvent: ethanol 60% (V/V) and to classify it as "well-established use".** Reasons: This extract is marketed in Germany as Kytta-Salbe® and further EU countries like Belgium, Hungary, Luxemburg, Portugal, UK, and Sweden. This product has a high importance in the market and is well-accepted by patients as well as by physicians. The following clinical data is available which justifies a well-established medicinal use: Five randomised, controlled studies support the therapeutic efficacy of comfrey extracts in the treatment of ankle sprains and complaints of the skeletal and locomotor system, such as osteoarthritis, epicondylitis, tendovaginitis and periarthritis [Petersen 1993; Koll 2004; Predel 2005; Grube 2007; Giannetti 2010]. The results of post-marketing surveillance studies [Koll 2002, Tschaikin 2004; Pabst 2004; Staiger 2008] accord with those of the controlled studies. **Placebo-controlled studies** The efficacy of an ointment containing 35% of a comfrey root extract (1:2, ethanol 60% V/V; less than 0.35 ppm of pyrrolizidine alkaloids in the finished product) was evaluated in a randomised, double-blind, placebo-controlled multicentre study involving 142 patients with a unilateral ankle sprain. Treatment started within the first 6 hours after injury and continued for 8 days with assessments on days 0, 4 and 7. The affected ankle joint was treated locally with about 2 g of the ointment four times a day. The primary parameter, tenderness of the ankle joint, was measured by tonometry (difference in tolerated pressure between injured and healthy ankles). During the course of treatment pain in the comfrey extract group regressed significantly more than in the placebo group (p = 0.0001) and at the final assessment	**Not endorsed.** This is a special extract and the exact manufacturing process is not available. The determination of the extracting solvent and the DER are not sufficient to characterise this extract, therefore it cannot be taken into consideration for evaluation.

		the reductions in tenderness compared to initial values were 2.44 kp/cm^2 in the verum group compared to only 0.95 kp/cm2 in the placebo group. Compared to placebo, superiority of the verum treatment was significant with regard to reduction in pressure pain (tonometric method, $p<0.0001$), ankle oedema (figure-of-eight method, $p = 0.0001$), ankle mobility (dorsiflexion, $p = 0.002$; plantar flexion, $p = 0.0116$) and global efficacy ($p<0.0001$) [Koll 2004]. A comment valued the trial as a well-executed and designed RCT with clearly shown beneficial effects [DeLange-de Klerk, 2005]. Another randomised, double-blind, placebo-controlled study investigated the effect of the same ointment containing 35% of a comfrey root extract (1:2, ethanol 60% V/V; less than 0.35 ppm of pyrrolizidine alkaloids in the finished product) over a 3-week period on 220 patients suffering from painful osteoarthritis of the knee. The primary target parameter was pain relief, assessed by the patient using a visual analogue scale (VAS) to record the reduction in total score from pain at rest and in movement. During the course of the study the total score decreased by 51.6 mm (54.7%) in the verum group and 10.1 mm (10.7%) in the placebo group, a significant difference of 41.5 mm (44.0%) between groups ($p<0.001$). The secondary target criterion was improvement in pain, stiffness and functional symptoms as determined by total scores in the WOMAC test (Western Ontario and McMaster Universities). At the end of the study reductions of 60.4 mm (58.0%) in the verum group and 14.7 mm (14.1%) in the placebo group were recorded, the difference of 45.7 mm (43.9%) being significant ($p<0.001$). Superiority of improvement in the verum group was also evident with respect to four explorative secondary parameters: SF-36 (quality of life), angle measurement (mobility of the knee), CGI (clinical global impression) and global assessment of efficacy by physicians and patients ($p<0.001$ for each parameter) [Grube 2007]. One comment on the trial mentioned the difficulties that are usually associated with the production of placebos for herbal drugs. It emphasised that due to the low inherent smell of the extract and the same perfume used in both placebo and verum, a very good blinding could be achieved for this preparation [Schulz, 2005b]. Another comment found the trial to be well-conducted and in accordance with the GCP-ICH	

		guidelines [Chrubasik, 2007]. The efficacy of the same comfrey root extract ointment was investigated in a multicentre, randomised, double-blind, placebo-controlled clinical trial in patients with acute upper and lower back pain. Over a period of 5 days 120 patients were treated with 4 g verum or placebo ointment three times daily. The primary efficacy variable was the area under the curve (AUC) of the visual analog scale (VAS) on active standardised movement values assessed on 4 visits. During the treatment period the pain intensity on active standardised movement decreased on average (median) approximately by 95.2% in the comfrey extract group (104.8 to 12.7 mm (mean VAS sum)) and by 37.8% in the placebo group (100.0 to 56.5 mm (mean VAS sum)) ($p<0.001$). Compared to placebo, the verum treatment improved significantly with regard to secondary efficacy variables (each $p<0.001$): the AUC of the reported back pain at rest, the AUC of the pressure algometry in the trigger point, the global assessment of the efficacy by the patients and the investigators, and the functional impaiment measured with Ostwestry disability index [Giannetti 2010]. One comment on the trial asked for more data in patients with different sorts of other back pain but admits that the results are relevant and topical treatment is increasingly considered as a serious treatment option [Rannou, 2010]. In an earlier 4-week pilot study, 41 patients with different forms of musculoskeletal rheumatism (mainly epicondylitis, tendovaginitis and periarthritis) were treated topically with the same ointment as above (n = 20) or with placebo (n = 21). Efficacy was assessed using several pain parameters: tenderness when pressure applied, pain at rest and during exercise. With respect to “tenderness when pressure applied”, the ointment proved superior to placebo in patients with epicondylitis (n = 7/8) and tendovaginitis (n = 6/5), but not in patients with periarthritis [Petersen 1993]. **Comparison with reference drug** The same ointment was compared to a gel preparation containing 1% of diclofenac in a randomised, single-blind multicentre study. Patients suffering from acute unilateral	

		ankle sprain (distortion) applied 2 g of either the comfrey ointment (n = 82) or the diclofenac gel (n = 82) four times daily for 7 ± 1 days. The primary efficacy variable was pain arising from pressure on the injured area, measured with a calibrated caliper (tonometer) on days 0, 4 and 7 and evaluated by the AUC of the pain-time curve; the results indicated that the comfrey ointment was statistically non-inferior, and possibly superior, to the diclofenac gel for the treatment of acute ankle sprain. Results for secondary variables, including the circumference of the joint (swelling, figure-of-eight method), individual spontaneous sensations of pain at rest and during movement (assessed using a visual analogue scale), the use of rescue medication (paracetamol), and evaluations of global efficacy and tolerability by both physicians and patients, also showed equivalence of the comfrey and diclofenac treatments [Predel 2005, D'Anchise 2007]. **Post-marketing surveillance studies** In a surveillance study of the same comfrey root extract ointment the tolerability and efficacy were examined in 306 children aged 3 to 12 years. The children applied the preparation to varied conditions such as contusions (61.4%), strains (14.1%), distortions (30.4%) and other indications (6.9%). Most children applied the ointment three times daily (57.8%), others four times daily (26.1%) or twice a day (13.4%). The majority of children administered the treatment for 5 to 8 days (n= 281). During the observation period symptoms of pain at rest and during the night, pain during motion, tenderness when pressure applied, impaired mobility and general condition improved considerably. The physicians assessed the global efficacy as excellent in 52.3% of cases and good in 44.5% [Staiger 2008]. In one surveillance study 163 patients applied an ointment containing 35% of a comfrey root extract (1:2, ethanol 60% V/V; less than 0.35 ppm of pyrrolizidine alkaloids) for a variety of conditions, the most frequent being contusions (33% of patients), painful joint complaints (28%), sprains (26%) and painful muscle complaints (23%). Most patients applied the preparation two (38%) or three (48.5%) times daily and the median duration of treatment were 11.5 days. During the observation period symptoms of pain at rest and during the night, pain during motion,	

		tenderness when pressure applied, impaired mobility, painful muscle complaints and swellings improved markedly. Morning stiffness of the joints decreased by 94% from 17 minutes initially to 1 minute. The use of non-steroidal anti-inflammatory drugs (NSAIDs) was reduced or discontinued by 13.5% of patients. The physicians assessed global efficacy as excellent in 38.7% of cases and good in 54.6% [Tschaikin 2004]. In a similar surveillance study 162 patients applied a preparation containing 30% of the same comfrey root extract to varied conditions such as painful joint complaints (34%), contusions (26.5%) or painful muscle complaints (21.6%). Most patients applied the preparation once (23.5%) or twice (52.5%) daily and the median duration of treatment was 11.8 days. Symptoms of pain at rest and pain during movement, impaired mobility, swelling and painful muscle complaints improved markedly during the observation period. Morning stiffness of investigated joints decreased by 90% from 20 minutes initially to 2 minutes. The use of NSAIDs was reduced or discontinued by 21% of patients. Global efficacy was assessed by the physicians as excellent in 65.4% of cases and good in 32.7% [Pabst 2004].	
2. Qualitative and quantitative composition	AESGP	**B) Traditional use:** *"Liquid extract (DER 2:1), extraction solvent ethanol 65% V/V»* This liquid extract was registered in United Kingdom as part of an ointment being on the market at least since 1968 (according to the assessment report). We suppose that thereby the DER is not correctly declared because it is not possible to produce a liquid extract with a ratio of herbal drug to liquid extract of 2:1. The result would not be a liquid extract. It could be possible that the DER is expressed in an old manner (1968) and really means a DER of 1:2 according to the Declaration Guideline of today. We therefore propose clarification with regard to the described product.	Clarification: The reason for the DER of 2:1 is that this DER is the final DER of the extract and not the native DER. The monograph was amended to give more unambiguous definition for the extract: "Liquid extract prepared by extraction with ethanol 65% (V/V) followed by partial evaporation and adjustment to a DER 2:1".
2. Qualitative and quantitative composition	AESGP	**Traditional use** **Comments:** A combination product containing an herbal preparation of *Symphytum officinale* L. used for external treatment in the specified indication area is on the market within the	**Not endorsed.** The European Union herbal monograph on *Symphytum*

		EU since 1968. The preparation is intended for cutaneous use in a semi-solid dosage form. The above-referred herbal preparation is a tincture manufactured from fresh roots of *Symphytum officinale* L. (ratio of herbal substance to extraction solvent 1: 4.2), ethanol. decoct, (extraction solvent: ethanol 30% m/m). This preparation should therefore be included in the monograph. **Proposed change:** Insertion of the herbal preparation: Liquid extract of *Symphytum officinale* L. radix rec. (1:4-5), ethanol. decoct, extraction solvent: ethanol 30 % m/m (equivalent to 2.5% herbal substance in ointment base). **References:** Justification for traditional use since 1968 is included in the following references: BfArM. Monographie der Kommission C zu Arnica/Symphytum comp.. Bundesanzeiger Nr. 99a vom 04.06.1986; incl. Korrektur: Bundesanzeiger 06.03.1991. Weleda 1968. Arzneimittelverzeichnis - Arnica/Symphytum comp. 12. Aufl. Schwäbisch Gmünd: Weleda AG; 1968. S. 33 Weleda 1973. Arzneimittelverzeichnis Weleda AG - Arnica/Symphytum comp. 13. Aufl. Schwäbisch Gmünd; 1971 bis 1976. S. 14 Weleda 2002. Weleda Arzneimittelverzeichnis mit Liste der Pflegepräparate. Arnica/Symphytum comp.. 20. Aufl. Schwäbisch Gmünd; 2002. S. 101. Weleda 2011. Weleda Arzneimittelverzeichnis mit Liste der Pflegeprodukte für Fachkreise. - Arnica/Symphytum comp. 25. Aufl. Schwäbisch Gmünd; 2011. S. 79	*officinale* L., radix refers to the traditional medicinal use of comfrey root as the only active ingredient in products. Combination products can be considered, if reasonable, for safety issues only, but not as sources of new herbal preparations in the monograph.
2. Qualitative and quantitative composition	AESGP	**Traditional use** **Comments:** Mono preparations containing Symphytum radix liquid extracts for external use in semi-solid dosage forms have been on the market for more than 50 years. The herbal preparation is a liquid extract prepared from fresh roots of *Symphytum officinale* L., ethanol. decoct, (extraction solvent: ethanol 45-55% V/V). The preparation is intended for cutaneous use in a semi-solid dosage form. This	**Not endorsed.** The traditional application of this preparation is not demonstrated in the literature provided. The Weleda documents do not contain information on the extract, only declare that ointments

		preparation should therefore be included in the monograph. **Proposed change:** Insertion of the herbal preparation: liquid extract of *Symphytum officinale* L. radix rec. (1:2.2-1.8), ethanol. decoct, extraction solvent 45-55% V/V **References:** Justification for traditional use since 1949 is included in the following references: BfArM. Monographie der Kommission C zu Symphytum. Bundesanzeiger Nr. 172a vom 12.09.1992 Weleda 1949*. Arzneimittelverzeichnis .- Symphytum off. Dec.. 6. Aufl. Arlesheim / Schwäbisch Gmünd / Stuttgart: Weleda AG; 1949. S. 116 Weleda 1968*. Répertoire des préparation Weleda Edition francaise du Weleda Arzneimittelverzeichnis- Symphytum Ung. 10 % - 12. Aufl. Schwäbisch Gmünd: Weleda AG; 1968. S. 159. Weleda 1989*. Nomenclature Weleda 4ème edition – 2ème Trimestre 1989 – Symphytum officinalis. Huningue: Weleda S.A.; 1989. S 123 Weleda 1993*. Präparateverzeichnis – Symphytum. 15. Aufl. CH-Arlesheim: Weleda AG; 1993. S 13. Weleda 1999*. Weleda Präparateverzeichnis – Symphytum. 16. Aufl. CH-Arlesheim; Oktober 1999. S. 434 *The 10% concentration mentioned in the references refers to herbal substance concentration in the final product.	containing 0.1-10% decoction of fresh *Symphytum officinale* roots are available. No further details or reference is published on the extraction method. The BfArM monograph from 1992 refers to an ointment containing 30% decoction of fresh *S. officinale* roots. As the method of preparation of this decoction a method of the German Homoeopathic Pharmacopoeia is referred to (method 19e). However, *Symphytum officinale* is not included in the most recent edition of GHP. Without the individual monograph of S. officinale the extraction method is meaningless, since it is not known how many ethanol has to be added to the extract at the end of the extraction and therefore DER cannot be calculated. Moreover, the preparation containing 30% of this extract was described only in the reference from 1992. Previously only the presence of products containing much lower amount (=> 10%) of an (unspecified) extract was confirmed and for these, no posology was described.

2. Qualitative and quantitative composition	KOOP PHYTO	**Comment:** We propose to add the liquid extract (1:2), extraction solvent: ethanol 60% (V/V) and to classify it as “well-established use”. **Rationale:** This extract is marketed in Germany as Kytta-Salbe® f. The well-established medicinal use is supported by the following studies which are available at the HMPC: Giannetti BM, Staiger C, Bulitta M, Predel H-G. Efficacy and safety of comfrey root extract ointment in the treatment of acute upper or lower back pain: results of a double-blind, randomised, placebo controlled, multicentre trial. Br J Sports Med 2010;44:637-41; DOI:10.1136/bjsm.2009.058677 Grube B, Grünwald J, Krug L, Staiger C. Efficacy of a comfrey root (Symphyti officinale. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: Results of a double-blind, randomised, bicenter, placebo-controlled trial. Phytomedicine 2007;14:2-10; DOI:10.1016/j.phymed.2006.11.006 Koll R, Buhr M, Dieter R, Pabst H, Predel H-G, Petrowicz O et al. Efficacy and tolerance of a comfrey root extract (Extr. Rad. Symphyti) in the treatment of ankle distorsions: results of a multicentre, randomised, placebo-controlled, double-blind study. Phytomedicine 2004;11:470-7; DOI:10.1016/j.phymed.2004.02.001 Predel H-G, Giannetti B, Koll R, Bulitta M, Staiger C. Efficacy of a comfrey root extract ointment in comparison to a diclofenac gel in the treatment of ankle distortions: results of an observer-blind, randomised, multicentre study. Phytomedicine 2005;12:707-14; DOI:10.1016/j.phymed.2005.06.001 Staiger C, Wegener T. Beinwell in der Therapie stumpfer Traumen: Anwendung bei Kindern. Z Phytotherapie 2008;29:58-64. Koll R, Klingenburg S. Therapeutische Eigenschaften und Verträglichkeit topischer Beinwellzubereitungen. Ergebnisse einer Beobachtungsstudie an Patienten. Fortschr Med 2002;120:1-9. Pabst H, Ottersbach P. Orthopädie: Beinwelltherapie. Topikum bei Muskel- und Gelenkbeschwerden. Geriatrie Journal 2004;6(6):45-7.	**Not endorsed.** This is a special extract and the exact manufacturing process is not available. Therefore, the determination of the extracting solvent and the DER are not sufficient to characterize this extract and this extract cannot be taken into consideration for evaluation.

		Petersen G, Lorkowski G, Kasper FR, Gottwald R, Lücker PW. Antiinflammatory activity of a pyrrolizidine alkaloid-free extract of roots of *Symphytum officinale* in humans. Planta Med 1993;59(Suppl):A 703-4. Tschaikin M. Wirksamkeit und Verträglichkeit bei topischer Anwendung: Extrakt aus *Symphytum officinale*. Naturheilpraxis 2004;57:576-8. The Pyrrolizidine alkaloids reduction process and the corresponding analytical methods of the above mentioned extract has been approved by the German health authority.	
4.1 Therapeutic indications	AESGP	**Well-established medicinal use:** For the **well-established used liquid extract (1:2, extraction solvent: ethanol 60% (V/V))** we propose the following wording: For the topical treatment of pain, inflammation and swelling of muscles and joints in the case of degenerative arthritis, acute myalgia in the back, sprains, contusions and strains after sports injuries and accidents. This indication is justified on the basis of the above-mentioned clinical studies, in particular for patients suffering from acute back pain or pain and swelling in blunt injuries and osteoarthritis [Koll 2004; Predel 2005; Grube 2007; Giannetti 2010].	**Not endorsed.** See above.
4.1. Therapeutic indications	KOOP PHYTO	**Comment:** For the well-established used liquid extract (1:2, extraction solvent: ethanol 60% (V/V)) we propose: "For the topical treatment of pain and swelling in the case of degenerative arthritis of the knee joint, acute myalgia in the back, sprains, contusions and strains after sports injuries and accidents." **Rationale:** This indication is justified on the basis of the above-mentioned clinical studies, in particular for patients suffering from acute back pain or pain and swelling in blunt injuries and osteoarthritis [Koll 2004; Predel 2005; Grube 2007; Giannetti 2010], see above under 2**.**	Not endorsed. See above.
4.2 Posology and method of	AESGP	**Posology** **Well-established medicinal use:**	**Not endorsed.**

administration		For the **well-established used liquid extract (1:2, extraction solvent: ethanol 60% (V/V))** we propose the following wording: Unless prescribed otherwise, adults and children aged 3 and over should use the cream as follows: A 4 to 12 cm long thread of cream two to four times a day, depending on the size of the area to be treated and the severity of complaints. This proposed posology is in line with the clinical studies of Petersen (1993), Koll (2004), Predel (2005), Grube (2007), Giannetti (2010). **The PA reduction process and the corresponding analytical methods of the above mentioned extract are approved in Germany, Hungary, UK, Belgium, Norway, Sweden, Portugal, and outside the EU in Brazil, Mexico and Australia.**	See above.
4.2 Posology and method of administration	AESGP	**Proposed change:** Adults and elderly Liquid extract in an ointment base (100 g ointment contains 10-30 g extract): apply the ointment 2 times daily. **References:** BfArM. Monographie der Kommission C zu Symphytum. Bundesanzeiger Nr. 172a vom 12.09.1992	**Not endorsed.** See above.
4.2 Posology and method of administration	KOOP PHYTO	**Comment:** For the well-established used liquid extract (1:2, extraction solvent: ethanol 60 % (V/V)) we propose "Unless prescribed otherwise, adults and children aged 3 and over should use the cream as follows: A 4 to 12 cm long thread of cream two to four times a day, depending on the size of the area to be treated and the severity of complaints." **Rationale:** This proposed posology is in line with the clinical studies of Petersen (1993), Koll (2004), Predel (2005), Grube (2007), Giannetti (2010), and the study Staiger (2008) as mentioned under 2.	**Not endorsed.** See above.
4.3 Contra-indications	AESGP	**Well-established medicinal use:** We propose: "None known" in line with the ESCOP monograph (2009).	**Not endorsed.**

			See above.
4.4 Special warnings and precautions for use	AESGP	**Well-established medicinal use:** We suggest: “Comfrey root preparations should be applied only to unbroken skin” in accordance with Schilcher (2010).	**Not endorsed.** See above.
4.5 Interactions with other medicinal products and other forms of interaction	AESGP	**Well-established medicinal use:** We propose: “None reported” in line with the ESCOP monograph (2009).	**Not endorsed.** See above.
4.6 Pregnancy and lactation	AESGP	**Well-established medicinal use:** As a general statement we propose: “As no human data is available, the potential risk is unknown. In accordance with general medical practice the product should not be used during pregnancy and lactation without medical advice.”	**Not endorsed.** See above.
4.7 Effects on ability to drive and use machines	AESGP	**Well-established medicinal use:** We propose: “None known” in line with the ESCOP monograph (2009).	**Not endorsed.** See above.
4.8 Undesirable effects	AESGP	**Well-established medicinal use:** We suggest: “None reported” in line with the ESCOP monograph (2009).	**Not endorsed.** See above.
4.9 Overdose	AESGP	**Well-established medicinal use:** “No toxic effects reported” in line with the ESCOP monograph (2009).	**Not endorsed.** See above.
5.1 Pharmacodynamic properties	AESGP	**Well-established medicinal use:** Pharmacotherapeutic group: Other topical products for joint and muscular pain, ATC code: M02AX The *Symphytum officinale* root extract content of the cream has an anti-inflammatory and analgesic effect, decreases swellings and promotes granulation and regeneration	**Not endorsed.** See above.

		of tissues. The analgesic, swelling-reducing and anti-inflammatory effects of a cream containing comfrey root extract have been proven in several ICH-GCP compliant clinical trials (randomised clinical trials RCT). The trials included patients with blunt injuries, painful gonarthrosis and acute back pain or pain in the upper back region (pectoral girdle). In these cases, the comfrey root extract significantly reduced pain on motion as well as pain on palpation (tenderness to pressure) and rest pain. Mobility was also improved significantly. The key activity-determining constituents of comfrey root extracts and its molecular mechanisms of action have not been completely elucidated. However, the constituents allantoin, mucopolysaccharides and tannins are likely to be of critical importance for efficacy.	
5.2 Pharmacokinetic properties	AESGP	**Well-established medicinal use:** "No data available."	**Not endorsed.** See above.
5.3 Preclinical safety data	AESGP	**Well-established medicinal use:** We propose the following wording: "No data available for the external use of comfrey root. The pyrrolizidine alkaloids (PAs) in comfrey root are considered to be toxic, especially after oral ingestion, however, processes are available to remove over 99% of PAs during the production of extracts from comfrey root, enabling preparations for topical application to contain less than 0.35 ppm of pyrrolizidine alkaloids [Grube 2007]. The same extract and preparation was used in other clinical trials [Koll 2004; Predel 2005; Giannetti 2010]. The use of such preparations, as exemplified by new clinical studies summarized above, has already been considered earlier to have an acceptable level of safety [Schilcher 1982]. This is in line with the ESCOP monograph (2009) and the result of the risk assessment performed by the German health authority between 1988 and 1992, the results being officially published in Bundesanzeiger of 17 June 1992. The HMPC draft Assessment Report does not take this decision into account but focuses on literature on individual pyrrolizidine alkaloids (PA). This very detailed chapter of the draft Assessment Report provides a good compilation on PA and their occurrence in numerous plants but has unfortunately nothing to do with comfrey root. We therefore	**Not endorsed.** See above.

		suggest to add a paragraph at the end of the respective chapter: “For *Symphytum officinale*, radix, however, only the official assessment published by the German health authority in Bundesanzeiger of 17 June 1992 is still relevant: For external use the daily exposition must not exceed 100 µg of the sum of all PA with a 1,2-unsaturated necine structure and their N-oxides with a restriction of use in pregnancy and lactation. No restriction has been found necessary for external preparations not exceeding 10 µg of these substances.” For “Mutagenic activity” we propose: A comfrey root extract (1:2, ethanol 60% V/V) was investigated to induce gene mutations in *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 with and without metabolic activation using the mammalian microsomal fraction S9 mix. The extract showed no biologically relevant increases in revertant colony numbers and was not mutagenic in the bacterial reverse mutation assay [Benedek 2010].	