13 September 2011
EMA/HMPC/352591/2011
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on the draft Public Statement on *Chelidonium majus* L., herba (EMA/HMPC/743927/2010)

Table 1: Organisations and/or individuals that commented on the draft Public Statement on *Chelidonium majus* L., herba as released for public consultation on 15 January 2011 until 15 April 2011.

	Organisations and/or individuals
1	AESGP (The Association of the European Self-Medication Industry)
2	GA Gesellschaft für Arzneipflanzen- und Naturstoff-Forschung e.V. Society for Medicinal Plant and Natural Product Research
3	Gesellschaft für Phytotherapie e.V.
4	Kooperation Phytopharmaka GbR

PRELIMINARY REMARK

Table 2 deals with all comments sent by the interested parties.
The following order is respected:

1. General comments by AESGP and the Gesellschaft für Phytotherapie.
2. Comments on extracts taken from the expert reports sent by AESGP
3. Specific comments on the text of the public statement
4. Lists of references provided by Interested parties
5. Tables provided by AESGP

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Table 2: Discussion of comments

1. GENERAL COMMENTS BY AESGP AND THE GESELLSCHAFT FÜR PHYTOTHERAPIE ON DRAFT DOCUMENT

Interested party	Comment and Rationale	Outcome
AESGP	AESGP in principle welcomes the process of the development of Community Herbal Monographs, as this should facilitate mutual recognition in Europe. The publication of the draft assessment report in parallel to the drafts is especially welcomed, because it provides useful background information on the preparation of the HMPC drafts. In the case of Chelidonium majus, the assessment report did not lead to a Community monograph but to a public statement explaining why a Community monograph could not be developed. This is a bit surprising in light of the existing monographs on this plant (German Commission E (1985), ESCOP (2003) and WHO (2010)). The latter two are based on several of the references which have also been quoted for the HMPC draft public statement. A review of the cases of the potential adverse hepatic reactions which have been reported (based on the available publications and the case reports from the German regulatory agency) **shows that only few of the reports can be rated as possibly or more highly related to the use of *Chelidonium majus*,** and that the relevant case reports are correlated to preparations with a content of total alkaloids per daily dose mostly in the range of 12-30 mg, while no cases have been correlated to preparations of about 9 mg or below. For the preparations with a daily dose corresponding to a maximum of 2.5 mg total alkaloids, the lack of a hepatotoxic risk is also corroborated by an assessment of toxicological studies carried out according to current guidelines and by **the fact that mechanistic data do not support a risk of idiosyncratic reactions**. Thus these preparations, given their long history of use, are suggested to be suitable for traditional use in self-medication. A review of the clinical studies with *Chelidonium majus* includes more than 10 studies of	**Causality** is an important issue; however it should be balanced against the **risk-benefit ratio** of oral use of Chelidonium. The hypothesis about **an idiosyncratic mechanism of action is abandoned**. Despite considerations about a possible dose-relationship for hepatic toxicity, this **risk-benefit ratio remains negative** for an oral use.

Interested party	Comment and Rationale	Outcome
	different types with almost 9,000 patients, documenting both well-spread/common therapeutic use of *Chelidonium majus* and the low adverse event rates. Hence a reconsideration of the benefit-risk relation is suggested. Given the long-standing relevance of *Chelidonium majus* for phytotherapy in several European countries and the weight of evidence regarding pharmacology, toxicology and safety, we suggest the preparation of a Community Herbal Monograph.	
AESGP	**Please note that our suggestions/proposed wording are marked in bold.** Comments: we would appreciate the replacement of the Public Statement with a Community herbal monograph. For this purpose, the text of the draft public statement has also been commented in detail, providing additional evidence supporting the development of a Community monograph. For presenting this evidence, three expert reports are enclosed, on toxicology from Prof. Dr. Dr. D. Schrenk, Kaiserslautern, Germany, on clinical data from Dr. G. Lorkowski, Gauting, Germany, and on pharmacovigilance data from Dr. M. Schmidt, Mattsies, Germany. In the following, suggestions for changes of the text are also given.	Extracts of the expert reports are commented in part 2 (COMMENTS ON EXTRACTS TAKEN FROM THE EXPERT REPORTS SENT BY AESGP) of this overview of comments below.
AESGP **Problem statement**	The HMPC has discussed the Community Herbal Monograph on *Chelidonium majus* L., herba. The HMPC concurrently assessed the toxicological and safety aspects and its conclusions can be found in the assessment report on *Chelidonium majus* L., herba. Over 20 different Chelidonium alkaloids have been identified, among them alkaloids belonging to the benzylisoquinoline type (0.01-1%): more particularly benzophenanthridines (chelerythrine, chelidonine, sanguinarine, isochelidonine), protoberberines (berberine, coptisine, dihydrocoptisine, stylopine) and protopine. Among others chelidonine and	The suggested paragraph does not take into account the comparison **to other herbal medicinal products** with a **better benefit-risk balance.** After comparing the data in the assessment report and the analysis of the expert reports, HMPC **maintains its**

Interested party	Comment and Rationale	Outcome
	sanguinarine have been tested for their antitumoral activity in vitro. In some European countries all marketing authorisations for medicinal products were withdrawn, which lead to a daily intake of more than 2.5 mg alkaloids from *Chelidonium majus* according to the posology of the SPC. This restriction is based upon the repeatedly reported hepatotoxic reactions after oral intake of *Chelidonium majus* preparations. Most (65%) of the spontaneously reported adverse drug reactions in the World Health Organization database in Uppsala are related to liver and biliary conditions. **A thorough analysis of all available case reports revealed that a large number of them is not likely to be correlated to the intake of preparations from *Chelidonium majus*, and that no relevant cases have been reported for preparations with a daily intake of less than 9 mg total alkaloids.** The adverse events are addressed in a separate expert report of M. Schmidt (2011), which is enclosed to this comment, and which is to be included into the assessment of the public statement, as it is the basis for the following comments. According to Barnes et al., 2007, 147 spontaneous reports of adverse drug reactions are associated with *Chelidonium majus* preparations, as documented in the VigiSearch database of the WHO's Uppsala monitoring centre for the period up to 2005. Out of these 147 entries, 95 reports relate to hepatic events. It must however also be mentioned that the collection of adverse events of the WHO is made without causality assessment and that "quantity" does not translate into "causality". In addition to the qualitative caveat, the database necessarily suffers from many duplicate entries which increase the number of cases, but not their quality. Generally, the VigiSearch database may serve for the detection of signals of potential safety issues by data-mining, but the uncommented list as such cannot serve for the attribution of causality. It is therefore much more important to take a closer look at the known facts of the case reports.	**negative opinion**, also towards the preparations leading to an daily intake lower than 2.5 mg alkaloids: see comments on extracts of the expert report by Prof. Dr. D. Schrenk in part 2 of this Overview of Comments A paragraph on the CIOMS scale is included in the assessment report with reference to Garcia-Cortes *et al.* (2008) who adapted the Naranjo scale to causality with regard to drug-induced liver injury evaluation. Causality analysis is without doubt useful but should be combined with the possible **comparative benefit** of Chelidonium for the indication claimed. This safety analysis is based upon spontaneous reporting of side-effects following the use of several preparations in different conditions. It reads in the **DIRECTIVE 2001/83/EC** *… bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of*

Interested party	Comment and Rationale	Outcome
	For illustration, some published reports (partly already used in the German graduated plan procedure) are re-evaluated according to the CIOMS criteria in the table below (Table 1). A re-assessment of all case reports known from the literature and from the German graduated plan procedure (64 case reports) is contained in the expert report of Schmidt, 2011, which is enclosed to this comment as an attachment. It will be necessary to refer to this attachment to have a full overview of the relevant data. The data in table 1 (at the end of our comments) is taken from this expert report (Schmidt, M., 2011) and only include some of the case reports presented in this report. The CIOMS scale, used in this table, is a validated tool for the assessment of liver injury. Although still in need for further refinement, the CIOMS scale is judged as a reliable and reproducible tool, providing a maximum level of objectivity (Garcia-Cortes et al. 2008). Taking into account, in addition to the cases listed here, all 66 case reports available from publications and from the graduated plan procedures of the German BfArM, there are only two cases with highly likely causality by the herbal product. However these are not necessarily caused by *Chelidonium majus*, according to CIOMS (≥ 9 points): One of the products was a combination preparation where the effect cannot be attributed to any of the constituents. There are seven cases with probable causality according to CIOMS (6-8 points). Two of these cases referred to the intake of a tea infusion, one of which was composed of further herbs than *Chelidonium majus*. In all cases where information was available, the daily alkaloid dose exceeded 9 mg. All cases occurred within the usual and typical 90-day period for toxic hepatitis – not a single case allows the conclusion of an idiosyncratic reaction type. The conclusion, that there has been no idiosyncratic reaction, but, if any, a dose-dependent mechanism, is supported in detail by an	*the application, including at least 15 years within the Community …* Preparations fulfilling these conditions are not standardised on alkaloid content, and are not fitting into the safety analysis made. **The idiosyncratic mechanism is deleted from the public statement**.

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	expert report (Schrenk 2011). There are 29 cases with possible causality (3-5 points), among which five cases observed with combination products. The majority of these cases (n = 18) only has a weakly possible association (3 points), see also below. Among these cases there are four with an unusually long latency period, which is *de facto* strongly speaking against *Chelidonium majus* as the causative factor. The remainder of the cases is unlikely related to *Chelidonium majus*. With the poor documentation of the case reports with weak to moderate causality or less, it does not make sense to go too deeply into data-mining for these cases. Correspondingly, cases with more than 5-6 points according to CIOMS become suggestive, cases with less become all the more questionable the lower the total score is. Thus, the 29 cases with possible causality seem anecdotal. Taking into account the number of daily doses of preparations containing extracts of *Chelidonium majus* between 1995 and 2005 (1.1 billion daily doses) and calculating the incidence of case reports, irrespective of causality, with a view to the total alkaloid daily dose, the following incidence rates result: • Chelidonium-containing medicines providing total alkaloid daily doses of > 2.5 mg: Incidence of case reports is 1 per2.2 million daily doses or 1 per 73 thousand patient months. • Chelidonium-containing medicines with total alkaloid daily doses of ≤ 2.5 mg: incidence = 0, since there are no case reports in this dose range, i.e. no risk. A statement of occurrence of severe hepatotoxicity after chronic administration of high doses is based on the facts that all relevant case reports are correlated to the chronic intake of high doses (corresponding to daily doses of total alkaloids of 8 mg and above), while no such	

Interested party	Comment and Rationale	Outcome
	cases were reported with low dose preparations. In addition it is important to note that hepatotoxicity was reversible, as stated in the German graduated plan dated 2008 and the WHO monograph of 2010. Restrictions and warning texts with relationship to a relevant hepatotoxic or cytotoxic risk in the SPC (as given in the German graduated plan) therefore seem, due to the lack of such a risk, not justified in case of preparations containing not more than 2.5 mg total alkaloids per daily dose. It can be summarised that an analysis of 65 case reports, which result from the published literature and from the German graduated plan after duplicate elimination, revealed that the vast majority of the cases is only possibly or even weaker related, and that there are no relevant cases related to a dose of less than about 9 mg total alkaloids per daily dose. In addition in the studies, with about 8820 patients altogether, no hepatotoxic side effects have been observed. Taking into account the toxicological data (presented in the next section of these comments), which support a safe dose limit of not more than 2.5 mg, and the lack of case reports below this limit, preparations below this limit can be considered as being without a relevant risk and suitable for traditional use in self-medication, without the need for warnings related to hepatotoxicity in the SPC and without other restrictions. With regard to the text of the public statement, the inclusion of the following paragraph is suggested: **Data from toxicological studies in vivo, which show a low toxicity of the extract, support a safe dose limit of 2.5 mg total alkaloids per daily dose. All toxicological and clinical data suggest a dose-dependent mechanism for putative toxicity, possibly involving glutathione depletion, and contradict a dose-independent idiosyncratic mechanism.**	

<table>
<tr><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td>AESGP</td><td>Additional data supporting this conclusion are numerous and cover many relevant aspects from the fields of pharmacology, pharmacokinetics, toxicology and clinics.

Conclusions regarding pharmacokinetics and bioavailability of certain well-known alkaloids can be derived from the following data:

Psotova et. al., 2005: Sanguinarine (6,403 mg/kg b.w.) and chelerythrine (2.199 mg/kg b.w.) were applied via the food to rats for 109 days. The following concentrations were measured:

<table>
<tr><td>Sample</td><td>sanguinarine (µg/g)</td><td>Chelerythrine (µg/g)</td></tr>
<tr><td>Diet</td><td>42.4</td><td>34.9</td></tr>
<tr><td>Feces</td><td>138.5</td><td>86.0</td></tr>
<tr><td>Plasma</td><td>0.008</td><td>n.d.</td></tr>
<tr><td>Liver</td><td>0.083</td><td>0.024</td></tr>
<tr><td>Kidney</td><td>0.004</td><td>0.009</td></tr>
<tr><td>Muscle</td><td>0.004</td><td>n.d.</td></tr>
<tr><td>Myocardium</td><td>0.005</td><td>n.d.</td></tr>
</table>
The limit of detection/quantification was 0.003/0.004 µg/g

Liver concentrations were more than a factor of 3 below the concentration of 1 µM (0.330/0.348 µg/g) not being toxic in human liver cells in vitro. It was evidenced that 2% of QBA were absorbed through the GIT while 98% were excreted in the feces.</td><td>A consideration about absorption and toxic liver concentrations is now included in the assessment report.</td></tr>
<tr><td>AESGP</td><td>We would like to also mention relevant aspects in this context from the long-term-study of Kosina et al. (2004) by the following: in pigs:

Kosina et al. (2004) applied 5 mg/kg b.w. of an alkaloid fraction, corresponding to 3.2 mg/kg sanguinarine and 1.1 mg/kg chelerythrine, to pigs over 90 days. Concentrations of</td><td>A consideration about absorption and toxic liver concentrations is now included in the assessment report.</td></tr>
</table>

Interested party	Comment and Rationale	Outcome
	sanguinarine/chelerythrine were determined for muscle (below limit of detection), plasma (traces), liver (0.019/0.010 µg/g) and gingiva (0.079/0.048 µg/g) as well as feces (0.990/1.730 µg/g). The values in the liver are for a factor of more than 10 below concentrations of 1 µM (0.330/0.348 µg/g), shown to be non toxic in human hepatoma cells. It can be concluded, that these alkaloids are very poorly absorbed. *The dose of 3.2 mg/kg sanguinarine and 1.1 mg/kg chelerythrine, calculated for an adult human of 70 kg b.w., corresponds to a dose of 224 mg sanguinarine and 77 mg chelerythrine, which is the 30-60fold of the alkaloid dose applied with high-dose Chelidonium majus Chelidonium majus preparations according to the monograph of the German commission E. In addition, these both benzo[c]phenanthridine alkaloids have the highest toxic potential, but the lowest content of all alkaloids in Chelidonium majus Chelidonium majus extracts.* From the studies of Psotova et al. and Kosina et al., it can be concluded, that toxic concentrations of benzo[c]phenanthridine alkaloids are not to be expected in the liver even after long-term use of high doses.	
AESGP	Some aspects from the study from Li HL et al., 2006, may also be of relevance here. It seems important that the large calculatory volume of distribution of 30.07 l/kg, which was reported in that publication, was calculated from data obtained with i.v. application, and not with application via the oral route, which is the relevant route for the therapeutic use Chelidonium extracts. It highly likely mainly represents the rapid hepatic clearance. Also the extravascular system, where the substance is, according to the authors, widely distributed after i.v. injection, is likely to be mainly located in the liver. Given the high sensitivity of coptisine to nucleophilic attack, as is also the case in sanguinarine and berberine, the molecule is very likely to be poorly absorbed resp. quickly eliminated already in the intestine (Schrenk 2011).	Information is now included in the assessment report. However, it **relates to animal and not human data.**

Interested party	Comment and Rationale	Outcome
AESGP	In addition the study of Miyazaki et al., 1978 seems to be of relevance here: *Miyazaki et al. 1978: In this study a dose of 100 mg tritiated berberine was applied orally to human volunteers, with 0.043 % of the dose excreted in the urine within 24 h.* This result supports the assumption that animal data on alkaloid pharmacokinetics can be transferred to man.	It should be taken into account that the tritiated berberine was administered as such, and **not in the natural matrix**.
AESGP	As for the pharmacological properties of Chelidonium extracts, components other than the alkaloids are relevant. An existing in vitro study of the absorption of chelidonic acid, as characteristic component of the extracts, could be mentioned here: *Kelber et al. 2006: In this study, the uptake of chelidonic acid by rat small intestinal preparations in vitro has been shown, with a linear dependency of the uptake rate from the concentration on the luminal side.* Even if the role of chelidonic acid for the clinical efficacy of Chelidonium is not known, the study suggests the bioavailability of another component of Chelidonium, besides the alkaloids.	**The therapeutic role** of chelidonic acid should be further documented in order to complete the picture.
AESGP	Taken together, all studies documenting organ distribution as well as faecal excretion of Chelidonium alkaloids show very high faecal and very low hepatic concentrations, thus clearly showing that despite quick hepatic clearance there is no accumulation in the liver. Urinary excretion is consequently low, as has also been shown in humans. This strongly suggests that a very poor absorption, and not the high first pass effect, is mainly responsible for the low systemic bioavailability. This view is also supported by the high sensitivity of the alkaloids sanguinarine, chelerythrine and coptisine to nucleophilic attack, shown e.g. by Debiton et al. 2003 and Ulrichova et al.	Again bioavailability of isolated compounds should be compared with the one in **the natural matrix**, i.e. whole *Chelidonium* preparations.

Interested party	Comment and Rationale	Outcome
	2001, which hinder their intestinal absorption. As these publications suggest, metabolic inactivation by conjugation with glutathione also seems to play an important role for the low bioavailability (Schrenk 2011). Compared to other herbs, the availability of PK data on phytochemical components from Chelidonium seems to be rather good, so that a lack of further studies should not question the preparation of a community herbal monograph.	
AESGP	Additional information on toxicology seems to be of relevance too: With respect to acute toxicology it is of interest to also discuss older studies of low relevance, such as that of Sokoloff et al. (1964) who describes intraperitoneal application of 350 mg/kg b.w. of a methanolic extract in mice resulting in a 20 % mortality rate. Studies using the intraperitoneal route of application for herbal extracts are generally of low scientific value, as unspecific effects of non-absorbable components can severely confound the outcome, and are of no direct use for evaluations of toxicological exposure limits for medicinal products for oral use, as they do not reflect intestinal absorption and bioavailability. Irrespective of that, the study rather points to a low toxicity of the extract tested, given a LC_{50} above 350 mg/kg b.w. Other studies with i.p. application of sanguinarine are Dalvi et al. (1985), where increases of liver enzymes in blood of rats 24 hours after i.p. application of 10 mg/kg b.w. is described, and Ulrichova et al. (1996), where liver damage 24 hours after i.p. application of a dose of 10 mg/kg b.w. in rats is reported, while no histological changes occurred in the liver of rats after i.p. treatment with 0.2 mg /kg b.w. over 14, 28, 42, or 56 days.	The studies mentioned are now commented upon in the **assessment report.**
AESGP	It is also of interest to discuss some older data presented in the Hager monograph of 1992, with the warning that fatal poisoning of children has been associated with Chelidonium majus. That monograph has meanwhile been updated. It refers to only one single case of a 4-year-old boy reported in a textbook of toxic plants in 1937 and mentions that the association with	These data relate to **pure compounds** without a possible matrix effect. The data are included in the assessment report.

Interested party	Comment and Rationale	Outcome
	Chelidonium majus *Chelidonium majus* was never confirmed in this single report (Hoffmann-Bohm et al. 2006). With regard of the alkaloids contained in Chelidonium majus, data on the alkaloid chelidonine also are of interest, which has an acute oral LD_{50} of 1300 mg/kg in mice, and of 2000 mg/kg in rats (Jagiello-Wojtowicz et al. 1989). Two studies conducted with preparations from alkaloids and already mentioned above are relevant for the evaluation of toxicity, too: *Psotova et. al., 2005: Sanguinarine (6,403 mg/kg b.w.) and chelerythrine (2.199 mg/kg b.w.) were applied via the food to rats for 109 days. In plasma, bilirubin, urea, creatinine, glomerular filtration, AST, ALT, GMT, ALP and total antioxidant capacity were determined. In liver, GSH level, lipoperoxidation products, SOD and GPx activities and total amount of cytochrome P450 were evaluated. No adverse effects were observed. QBA had no influence on the gut mucosal epithelium, liver tissue and any biochemical parameters tested. Oxidative stress was not manifested during the experiment.* *Kosina et al., 2004: 5 mg/kg b.w. of an alkaloid fraction were applied to pigs over 90 days, corresponding to 3.2 mg/kg sanguinarine and 1.1 mg/kg chelerythrine. No haematological, histological or biochemical deviations of toxicological relevance compared to the control were seen, so that it can be concluded that these doses are non toxic.*	
AESGP	In contrast, the following studies have been conducted with homoeopathic preparations. *Manciaux, X. 2001/Weleda: Acute oral (gavage) toxicity study in rats* *The acute oral toxicity of Chelidonium majus extract (mother tincture according to HAB, extraction solvent ethanol 70 %, containing 0.147 % total alkaloids, calculated as chelidonine) was determined in 10 fasted rats per group (5 males and 5 females) under GLP*	The included data are referred to in the **assessment report**.

Interested party	Comment and Rationale	Outcome
	conditions and according to EU recommendations. A dose of 5 ml/kg b.w. of the test substance (70 % ethanol) was applied. The control group received 70 % ethanol under the same conditions. Clinical signs, mortality and body weight were checked for a period of 14 days following the single administration of the test substance and a necropsy was performed. No signs of toxicity (with the exception of hypoactivity in both groups on day one) were observed. The LD_{50} of the chelidonium fluid extract was higher than 5 ml/kg resp. 7.4 mg total alkaloids/kg b.w.	

Species	Sex	Route	LD_{50} (ml/kg)	No. of animals per sex/dose	Obs. period in days	Lethality	Reference
rat	m + f	oral	> 5.0	5	14	0	Manciaux 2001

Mheddhbi, S. 2001/Weleda: 4-week toxicity study by oral route (gavage) in rats
The oral toxicity of repeated doses of Chelidonium majus Chelidonium majus extract (mother tincture according to HAB, containing 0.147 % total alkaloids, calculated as chelidonine) over 4 weeks was determined in 20 rats per group (10 males and 10 females) under GLP conditions and according to EU recommendations. Daily doses of 0, 730, 1270 and 1820 mg/kg b.w. were applied as a solution in 70 % ethanol. 2 ml/kg of the solution (70 % ethanol) were applied. The control group received 70 % ethanol under the same conditions. Clinical signs, mortality, body weight and food consumption were recorded during the study. After necropsy, haematology, blood chemistry (including complete liver function parameters) and urine analysis were performed. In controls and the high dose group ophthalmological examinations were performed at the begin and the end of the study. The main organs were studied histologically. No test-related mortalities or changes of any other parameters studied, including liver, were observed.

The NOEL of Chelidonium fluid extract is the highest administered dose, 1820 mg/kg b.w./day, corresponding to 2.68 mg/kg b.w. total alkaloids.

<table>
<tr><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td colspan="2">Species: SD rats</td><td colspan="2">Route: oral gavage</td></tr>
<tr><td></td><td colspan="4">Period: 4 weeks; Schedule: 7 days/7</td></tr>
<tr><td></td><td>Control</td><td>Gr. 1</td><td>Gr. 2</td><td>Gr. 3</td></tr>
<tr><td>No of animals/sex</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>Daily dose of extract (mg/kg)</td><td>0</td><td>730</td><td>1270</td><td>1820</td></tr>
<tr><td>Daily dose of total alkaloids (mg/kg)</td><td>0</td><td>1.07</td><td>1.87</td><td>2.68</td></tr>
<tr><td>Deaths</td><td>7*</td><td>0</td><td>2*</td><td>0</td></tr>
<tr><td>Symptoms
Body weight
Food consumption
Clinical chemistry
Ophthalmoscopy
Anatomy/Pathology</td><td colspan="4">No treatment related symptoms
No dose-related effects
No dose-related effects
No abnormal values, no dose-related effects
No changes
No histopathological findings, including the liver</td></tr>
</table>
*Attributed to the regurgitation of the test item or the vehicle (ethanol 70%)
</td><td></td></tr>
<tr><td>AESGP</td><td>With the combination preparation Iberogast®, containing 10 ml/100 ml of an extract from Chelidonii herba (extraction solvent ethanol 30 %, 1:2.5-3.5), studies needed for marketing authorisation of an NCE according to recent international guidelines (EU, ICH, OECD, FDA, MHLW) have been performed in two animal species, including studies of acute, subchronic, chronic toxicity, reproduction toxicity and mutagenicity. By using a dry extract of identical composition, doses up to the about 1200fold of the recommended therapeutic dose could be studied. This corresponds to up to 5 ml/kg b.w. of the respective fluid extract of Chelidonii herba with a content of total alkaloids of 0.75 to 0.80 mg/ml, or 3.69 mg total alkaloids/kg b.w. Despite studies were not conducted with a mono preparation from Chelidonii herba, the studies of subchronic resp. chronic toxicity are of special relevance, as they included measurements of liver parameters and evaluations of liver histology:
Schoenmakers A.C.M. 2003 (Notox project 330211): 6 month oral gavage toxicity study in</td><td>Iberogast is a combination of Chelidonium with other herbal preparations. The data are specific for the product. It is difficult to extrapolate the findings to monopreparations.</td></tr>
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<table>
<tr><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td>male and female Wistar rats
In a GLP conform study the combination preparation Iberogast®, containing an extract of Chelidonii herba, was orally applied by daily gavage for a period of 6 month in groups of 20 male and 20 female rats.
<table>
<tr><td>Daily dose mg/kg KG dry extract</td><td>corresponding to Iberogast® ml/kg b.w.</td><td>corresponding to Chelidonii herba extract ml/kg b.w.</td><td>corresponding to total alkaloids mg/kg b.w.</td></tr>
<tr><td>0</td><td>0.0</td><td>0.00</td><td>0.00</td></tr>
<tr><td>500</td><td>12.5</td><td>1.25</td><td>0.92</td></tr>
<tr><td>1,000</td><td>25.0</td><td>2.50</td><td>1.85</td></tr>
<tr><td>2,000</td><td>50.0</td><td>5.00</td><td>3.69</td></tr>
</table>
Two further groups of 5 male and 5 female animals were treated with daily doses of 0 and 2,000 mg/kg b.w. over 6 month, followed by 1 further month without treatment. All parameters relevant according to the toxicological guidelines mentioned were documented, including especially liver enzymes in plasma and liver histology. Liver transaminases as well as liver pathohistology did not give any indications of any hepatotoxic effects, so that the highest dose corresponding to 3.69 mg/kg b.w. total alkaloids is the NOAL-level for potential hepatotoxic effects. With relation to other data the second highest dose, 1,000 mg/kg b.w. is the NOAEL.
It can be concluded, that there is no indication of an hepatotoxic effect. The dose of 3.69 mg/kg b.w. would correspond to a daily dose of 259 mg in a person of 70 kg b.w.</td><td></td></tr>
<tr><td>AESGP</td><td>van Rozendaal A.W.M. 2003 (Notox project 330222): 3 month oral gavage toxicity study in dogs
In a study conducted according to GLP in beagle dogs, 4 groups, of 4 male and female dogs each, were treated daily by gavage orally with the combination preparation Iberogast®, containing an extract of Chelidonii herba over a period of 3 months.</td><td>See previous remark.</td></tr>
</table>

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<tr><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td>
<table>
<tr><td>Daily dose mg/kg b.w. dry extract</td><td>corresponding to Iberogast® ml/kg b.w.</td><td>corresponding to Chelidonii herba extract ml/kg b.w.</td><td>corresponding to total alkaloids mg/kg b.w.</td></tr>
<tr><td>0</td><td>0.0</td><td>0.00</td><td>0.00</td></tr>
<tr><td>500</td><td>12.5</td><td>1.25</td><td>0.92</td></tr>
<tr><td>1000</td><td>25.0</td><td>2.50</td><td>1.85</td></tr>
<tr><td>1500</td><td>37.7</td><td>3.75</td><td>2.77</td></tr>
</table>
Two further groups of 3 male and female dogs each were treated with daily doses of 0 and 1500 mg/kg b.w. over 3 month, followed by 28 days without treatment. All parameters relevant according to the toxicological guidelines mentioned were documented, including especially liver enzymes in plasma and liver histology. Liver transaminases as well as liver pathohistology did not give any indications of any hepatotoxic effects, so that the highest dose corresponding to 2.77 mg/kg b.w. is the NOAL-level for potential hepatotoxic effects. It can be concluded, that there is no indication of an hepatotoxic effect. The dose of 2.77 mg/kg b.w. would correspond to a daily dose of 194 mg in a person of 70 kg b.w.
</td><td></td></tr>
<tr><td>AESGP</td><td>From these 3 studies, in the German graduated plan (decision coming into force on 9 April 2008) the following conclusions were drawn:

"From the chronic-toxicological study with a combination preparation containing Chelidonii herba extract over 6 months in the rat (Notox project 330211) results a limit of 2.6 mg total alkaloids/day, which already takes into account inter species variability and combination effect of the different components of the preparation with a safety factor of 100 vs. human exposition and, in addition, through the duration of the study of 6 months, covers also chronic use in man. The evaluation of this dose limit is based on a NOEL > 3.69 mg/kg /d in</td><td>This additional information about the limit set in German graduated plan is now included in the assessment report.</td></tr>
</table>

Interested party	Comment and Rationale	Outcome
	the rat (x 70 = 258.3 mg/d in man, divided by 10 x 10 = ca. 2.6 mg/d). *The limits of 2 and 0.2 mg/day, which are derived from the 4 week toxicity study in the rat (Weleda 2002) and the 3 month study in the dog (Notox project 330222), are also based on NOELs, which correspond to the maximum doses in the respective studies. They therefore do not contradict the higher limit of 2.6 mg/day. These studies can be seen as supportive, especially as in the study in dogs a second species (non-rodent) was tested without findings."* In the graduated plan a safe dose limit of up to 2.5 mg total alkaloids was derived from these studies.	
AESGP	Regarding higher doses, the following general remark has to be taken into account: as this limit is not derived from the observation of toxic effects in higher doses, but from the highest applicable doses for technical reasons, it does not allow the conclusion that the toxic risk in higher doses might be not acceptable. In case of preparations already on the market in well-established or traditional use, clinical data should be taken into account, too, when safe doses are determined.	This aspect is not taken into consideration as it relates **only to possible toxic effects**, without taking into account the therapeutic benefit.
AESGP	Genotoxicity data are of special relevance for establishing Community Herbal Monographs and List Entries, according to Directive 2001/83/EC and Guidelines EMEA/HMPC/32116/2005 and EMEA/HMPC/107079/2007. The following data support our comments on the draft Public Statement: In the study of Kosina et al (2004) in pigs, where 3.2 mg/kg sanguinarine and 1.1 mg/kg chelerythrine were applied over 90 days, no DNA adducts were observed. The same applies to the following study: *Psotova et. al. (2005) found, that sanguinarine (6,403 mg/kg b.w.) and chelerythrine (2.199 mg/kg b.w.), applied via the food to rats for 109 days, did not cause DNA damage.* In addition, an Ames test has been performed:	These observations open interesting perspectives, but should be combined with an added value as **therapeutic activity** is concerned. If possible data on mutagenicity of a preparation are proposed to be included in a monograph, they should be provided.

Interested party	Comment and Rationale	Outcome
	Haddouk, H., 2001: Bacterial reverse mutation test (Ames-Test) *Chelidonium majus Chelidonium majus extract (mother tincture according to HAB, extraction solvent ethanol 70 %, containing 0.147 % total alkaloids, calculated as chelidonine), was tested according to all current regulations in five strains of Salmonella typhimurium, in two independent experiments according to the preincubation method, using metabolic activation with S9-mix. Concentrations were between 312.5 and 5,000 µg/plate, with no precipitate being observed. Adequate positive controls were used. No relevant increases of numbers of revertants occurred with the test substance. The Chelidonium extract tested had no mutagenic properties in this test.*	
AESGP	Cytotoxicity data are also presented here to support mechanistic understanding of our comments on the public statement. The following two publications give valuable hints on putative mechanisms of toxicity of relevant alkaloids: *Gebhardt, R. (1999), cited according to ESCOP 2003: In rat hepatocytes, EC_{50} values of cytotoxicity were 5 µg/ml for sanguinarine, 8 µg/ml for chelerythrine, 13µg/ml for coptisine, 100 µg/ml for protopine, and > 100 µg/ml for Chelidonine. The EC50 for Chelidonium majus Chelidonium majus extract was about 5,000 µg/ml (mean of 34 different extracts), showing low cytotoxicity.* *Debiton et al. 2003: The quaternary benophenanthidine alkaloid sanguinarine was tested for cytotoxicity in a panel of human solid cancer cell lines and a human fibroblast primary culture. Sanguinarine markedly inhibited the growth of all test cells with IC_{50} of 0.9-3.3 µM (0.30-1.1 µg/ml) without differential cytotoxicity against normal versus cancer cells. In PC3 human prostatic adenocarcinoma cells cellular glutathione content and mechanisms of apoptosis were studied, showing a depletion of reduced glutathione within 10 min, insensitive to N-acetylcysteine treatment, and followed by an apoptotic response. Complementary assays*	These observations open interesting perspectives, but should be combined with an added value as **therapeutic activity** is concerned. If possible data on cytotoxicity of a preparation are proposed to be included in a monograph, they should be provided.

Interested party	Comment and Rationale	Outcome
	suggested that the glutathione depletion was caused by direct reactivity of sanguinarine with reduced glutathione, due to its sensitivity to a nucleophilic attack. This allows the conclusion that conjugation with glutathione could play an important role in the detoxification and the mechanisms of toxicity of alkaloids sensitive to a nucleophilic attack. *Ulrichova et al. 2001: Sanguinarine and chelerythrine were studied in primary cultures of human and porcine hepatocytes. Alkaloids were not toxic up to 10 µM (3.32 resp. 3.48 µg/ml), but in the range of 25-100 µM, causing LDH leakage into the medium and a decrease of mitochondrial dehydrogenase (MTT) activity and cellular levels of reduced glutathione (GSH) to 40 %, leading to the conclusion, that not the mitochondria, but a GSH depletion is the primary target of these alkaloids in the cell. There was no difference in the response of porcine and human hepatocytes.*	
	In addition to these studies with isolated benzophenanthridine alkaloids, studies with Chelidonii herba extract in different strains of human hepatocytes have been published: *Adler M. et al. 2006: Studies of cytotoxicity in human primary hepatocytes and human Chang liver cells* *An extract of Chelidonii herba (1.25-3.5, extraction medium 30 % ethanol, lyophilized under GMP conditions, total alkaloids 5.9 mg/g) was tested under GLP conditions in human primary hepatocytes in concentrations between 0,00074 ng and 148 mg extract/ml for 24 h. Vitality was determined by MTT- and neutral red test. Test substance was completely dissolved. EC50 was 0.83 mg/ml (MTT) and 0.82 (corresponding to 4.9 µg/ml total alkaloids), with clear dose dependency. EC50 of ascorbic acid in this test system was 1.3 mg/ml (details see study report, Gritzko and Wallner 2005).* *An extract of Chelidonii herba (1.25-3.5, extraction medium 30 % ethanol) was tested as native extract (total alkaloids 6.15 mg/g) and with reduced alkaloid content (0.67 mg/g) in human Chang liver cells. For comparison the respective alkaloid fraction, a Ginkgo biloba extract and paracetamol were tested. Test substances were dissolved completely. Vitality was*	These observations open interesting perspectives, but should be combined with an **added value as therapeutic activity** is concerned. If possible data on cytotoxicity of a preparation are proposed to be included in a monograph, they should be provided.

Interested party	Comment and Rationale	Outcome
	determined by the MTT test, cell integrity by microscope. EC50 over 24 h for the native extract was 0.96, for the extract with reduced alkaloid content 1.60 (corresponding to alkaloid contents of 5.9 mg/ml and 1.1 µg/ml). Cytotoxicity of the alkaloid fraction was, depending from the mode of dissolution, 86 to 189 µg/ml. EC50 of the Ginkgo biloba extract and paracetamol were 0,31 mg/g and 2,49 mg/ml. According to this, Chelidonii herba extract has no special hepatotoxicity, compared to other accepted medicinal products, and its hepatotoxic properties are depending from its alkaloid content only to a very limited extent (details see study report, Pascolo, L. and Ruzzier, F. 2005).	
AESGP	With regard to reproduction and developmental toxicity, the study of Basini et al. 2007 is of potential interest. In this in vitro study, cytotoxicity of sanguinarine was observed with a concentration of 500 nM (0.017 µg/ml) sanguinarine. Suppression of angiogenesis by inhibition of VEGF signalling was described in primary pig granulose cells and in porcine endothelial cells (AOC cells) after incubation with 300 nM (0.01 µg/ml) sanguinarine for up to 192 h. Cytotoxicity of sanguinarine in primary pig granulose cells was observed with a concentration of 500 nM (0.017 µg/ml) sanguinarine. Given the low difference between cytotoxic concentrations and concentrations inhibiting parameters of angiogenesis, the specifity of the results, and therefore their relevance for reproduction and developmental toxicology, is unclear.	These experimental data are **included i**n the assessment report.
AESGP	From the data presented above, the following concluding remarks can be drawn. With regard to *in vivo* toxicity studies, it is important to note that when evaluating toxicity for oral medicines only studies on oral toxicity, but not on parenteral application, allow direct conclusions. In more than six studies on oral toxicity of high doses of Chelidonii herba extracts as well as of isolated alkaloids, for up to 6 months, no toxicity has been observed. This leads to the conclusion of a low toxicity and a lack of hepatotoxicity. The studies with parenteral or in vitro application allow conclusions on potential mechanisms of action. There are sufficient studies on cytotoxicity of Chelidonii herba extract in different strains of human hepatocytes, which show a limited cytotoxicity within the normal range of	This information is included in the assessment report. However, it cannot be extrapolated to the eventual preparations on the market for at least **30 years**. Hence no monograph can be prepared.

Interested party	Comment and Rationale	Outcome
	other accepted medicines and a limited relevance of the alkaloids for cytotoxicity. An Ames test and in vivo studies confirm the lack of relevant genotoxicity. Studies with isolated benzophenanthridine alkaloids did show that, through the sensitivity of these compounds to nucleophilic attack, conjugation with glutathione might play a role in the detoxification of these substances. Taken together, pharmaceutical preparations of the dried parts of Chelidonium did not cause toxicity, including hepatotoxicity, when applied in toxicological studies via the oral route, even with high doses, pointing to a low bioavailability of Chelidonium alkaloids. Cytotoxicity studies with high doses in vitro allow conclusions regarding putative toxic mechanisms of Chelidonium alkaloids, pointing to a strongly dose-dependent mechanism involving glutathione depletion. Results allow establishing a safe exposure limit of Chelidonii herba extract corresponding to 2.5 mg total alkaloids per daily dose for therapeutic use in humans. As the NOELs supporting this limit are the highest applicable doses, it does not allow the conclusion that higher doses are not safe.	
AESGP	With regard to the public statement, further changes are suggested as follows: ~~Hepatotoxicity was not dose-dependent and an idiosyncratic mechanism has been put forward.~~	This sentence has been **deleted** from the Public Statement.
AESGP	Two possible therapeutic indications were suggested: Traditional herbal medicinal product for symptomatic relief of digestive disorders such as dyspepsia and flatulence (oral use). Herbal preparations for treatment of warts, callus and corns (cutaneous use). ~~For the first indication safer herbal and conventional medication is available.~~ **For the first indication, *Chelidonium majus* is in several European countries of long-standing relevance in traditional and well established use, with unique pharmacological mechanisms of action involving relaxation of tonic contraction in smooth muscle, while at the same time stimulating phasic contractions, so favourably influencing**	**Not endorsed**. See further comments.

Interested party	Comment and Rationale	Outcome
	symptoms related to spasms of the bile ducts and a lack of propulsive action in the stomach.	
AESGP	Additional data support this statement. These include pharmacological data regarding the mechanisms of action, giving additional information as to its effects in the gastrointestinal tract: Prokinetic effect (*in vitro*) • Schemann et al., 2006: Stomach smooth muscle preparations, incubated in 24 to 188 µg/ml of a dried Chelidonium majus *Chelidonium majus* fluid extract (1:2.5-3.5, extraction solvent 30 % ethanol), showed a dose-dependent increase of tonic (corpus, fundus) resp. phasic (antrum) contractions, pointing to a prokinetic effect in the stomach. • Sibaev et al., 2006: Chelidonium majus *Chelidonium majus* fluid extract (1:2.5-3.5), 2 ml/100 ml, significantly increased resting membrane potential and frequency and amplitude of myoelectrical slow waves of the smooth muscle of mouse colon. Receptor affinities (*in vitro*) • Simmen et al., 2006: IC50 values for the binding of a Chelidonium majus *Chelidonium majus* fluid extract (1:2.5-3.5) to rat intestinal 5-HT3, 5-HT4 and Muscarine M3-receptors were determined as extract dilutions of 1:1,000, > 1:10,000 and 1:3,500. In a human recombinant 5-HT4 receptor IC50 was 1:350. These receptors are involved in the aetiology of functional gastrointestinal diseases. Anti-inflammatory effect (*in vivo*) • Khayyal et al., 2001: In a model of indomethacine-induced gastric ulcer in rats in vivo, doses of 2.5-10 ml/kg of a Chelidonium majus Chelidonium majus fluid extract (1:2.5-3.5) showed dose-dependent antiulcerogenic effects. This allows the conclusion on gastroprotective properties.	The pharmacological effects described create plausibility for a therapeutic indication. However, mechanisms of action **must be translated into clinical evidence** for a specific therapeutic effect and an added clinical value as compared to similar herbals.

Interested party	Comment and Rationale	Outcome
AESGP	Even more than pharmacological data, clinical data are decisive whether a traditional use of a medicinal herb is plausible, and whether a well-established medicinal use is established. The classical indication, which also defines the most important area of the traditional use of this herb in Germany (Schilcher, H., 1997), has been defined by the German Commission E in 1985 as follows: "Cramp-like complaints in the area of the bile ducts and the gastro-intestinal tract". A detailed review of all studies which have been conducted in this indication is enclosed to this comment as an attachment (Lorkowski 2011). A tabulated summary of the studies is given below Table 2 at the end of our comments). Taking into account the additional studies presented in the expert report of Lorkowski (2011), there are 8,820 patients for whom treatment with preparations containing an extract of Chelidonii herba has documented within clinical studies. Hepatotoxic side effects have been found in none of these studies. Seen from a formal point of view, the lack of any case report of hepatotoxicity in studies with nearly 10,000 patients supports the rating of such side effect as very rare.	The clinical studies submitted **do not meet** the criteria for well-established use in a specific therapeutic indication. For a traditional use the benefit-risk balance remains negative (cf. supra).
AESGP	This impressing weight of clinical evidence suggests a well-established use of Chelidonii herba in this indication. Of all patients included in these studies, 4,977 have been treated with preparations according to the German commission E monograph, containing 12-30 mg total alkaloids per daily dose. These include 30 patients treated with Chelidonium in the placebo controlled study of Ritter et al., 1992. Another approx. 3,843 patients have been included in studies with lower doses of mono preparations and with combination preparations. Hence these studies also lend support to the suitability of low dosed preparations from extracts of Chelidonii herba for traditional use.	The number of patients treated in mostly observational studies is indeed high. However, the preparations used are diverse and partially contain combined formulae. Heterogeneity and lack of documented experience hamper consideration for well established or traditional use.

Interested party	Comment and Rationale	Outcome
AESGP	In this context, the German graduated plan concerning Chelidonium-containing medicinal products for internal use which came into force on 9 April 2008 shall be mentioned. This was the result of the revision of measures already announced in 2005. This announcement of measures only included some toxicological in vitro data and a very preliminary evaluation of case reports and mentioned 2.5 µg total alkaloids per daily dose as a safe upper dose limit. In the final decision of 9 April 2008, this preliminary upper dose limit changed by a factor of 1,000 due to the availability of new data. Unfortunately this revision did not take into account these new data to full extent, but retained several elements of the draft version. The above-mentioned final decision included toxicological data supporting a safe daily dose of total alkaloids of 2.5 mg and a review of case reports, as presented in these comments. The review resulted in the conclusion that no relevant case reports have been correlated to preparations with a daily dose corresponding to less than 8 mg, thus supporting a safe limit of 2.5 mg total alkaloids per daily dose. As preparations with a content of 2.5 mg total alkaloids and below have never been correlated to case reports of hepatotoxicity, and as this limit is also supported by toxicological data, a warning in the package leaflet, as given by the graduated plan, does not seem to be scientifically justified. Such low-dose preparations are traditionally used in Germany and also in some other European countries, and are not correlated to any toxic risk, so they should be suitable for traditional use within self-medication. As mentioned above, there is no signal of a hepatotoxic risk in preparations up to a dose limit of 2.5 mg total alkaloids per daily dose. In contrast, preparations corresponding to a daily dose of over 2.5 mg have been correlated to case reports of hepatotoxic reactions. Conclusions regarding the frequency of these reactions can be derived from the clinical data presented above (no report of any hepatotoxic reaction with about 8,820 patients included into these studies) and from a correlation of the number of daily doses sold over 10 years, to the number of relevant case reports (see Schmidt 2011). Even when taking into account considerable rates of underreporting and other confounders, it is clear that hepatotoxic reactions correlated to the use of these	An extensive analysis of toxicological data has been performed. However, there is a lack of preparations with a sufficiently long standing oral use and fixed content of alkaloids to be included in a monograph.

Interested party	Comment and Rationale	Outcome
	preparations have occurred only in very rare cases, or even in single cases, and have, in addition, been reversible. The clinical study data presented above support the assumption of a clinical benefit outweighing this potential risk, which could be even further reduced by a suitable labelling in the SPC, as it is part of the German graduated plan. All this points to suitability of these preparations for a well-established use. Regarding low dosed preparations from *Chelidonium majus* (with daily doses not above 2.5 mg total alkaloids) the following conclusion can be drawn from the data presented above: As pharmacovigilance data demonstrate the absence of hepatotoxic risks for preparations, which lead to a daily intake of not more than 2.5 mg alkaloids of *Chelidonium majus*, and as this safe dose limit is also supported by a toxicological risk assessment based on preclinical studies (Notox project 320211 and 330222; Weleda 2002), for these products no texts with relation to a hepatotoxic risk need to be included to the SPC. This allows the traditional use of preparations with a dosage of 2.5 µg-2.5 mg alkaloid/day in self-medication, based on the long-standing safe use of such preparations and the plausibility of a pharmacological and clinical effect.	
AESGP	It is suggested to reflect this in the text of the public statement in the following way: **Relevant for the benefit-risk assessment for the oral use of preparations from Chelidonii herba in the indications given above is the lack of any signals of a hepatotoxic risk in preparations with up to 2.5 mg total alkaloids per daily dose, qualifying these preparations for traditional use in self-medication.**	**Not endorsed** for the reasons given above.
AESGP Conclusions	For the part "Conclusions" of the Public Statement, the following changes are suggested: Conclusions Under the regulatory framework applicable to traditional herbal medicinal products laid down	**Not endorsed** for the reasons given above

Interested party	Comment and Rationale	Outcome
	in Chapter 2a of Directive 2001/83/EC as amended and in particular Article 16a(1)(a) on their use in minor indications that do not require supervision of a medical practitioner, the findings from the assessment imply that the benefit-risk analysis of *Chelidonium majus* L., herba is ~~negative~~ **suggesting the need of a differentiated rating**. The extent and the quality of the available scientific data ~~have not been sufficient~~ **allow the conclusion that for preparations containing not more than 2.5 mg total alkaloids per daily dose, there is no relevant risk of severe adverse events, thus permitting** to come to a positive benefit-risk assessment for oral treatment, taken into account the ~~expected~~ **plausibility of a** benefit from the **traditional use of respective** herbal medicinal products. As ~~no~~ **additional** data **from clinical studies** were retrieved ~~for more serious conditions that could~~ **documenting a well-established use, and** alter**ing** the benefit/risk assessment, the ~~HMPC has therefore concluded that the~~ benefits of *Chelidonium majus* L., herba**, even when doses above the limit of 2.5 mg total alkaloids per day are applied,** ~~do not~~ **may** outweigh its possible risks**, especially as far as these risks can be prevented by the proposed warnings and restrictions in the SPC**. **Within the frame of a herbal monograph, the traditional use of *Chelidonium majus* preparations, with a daily dose corresponding to no more than 2.5 mg total alkaloids, is possible in self-medication, without any warnings and restrictions regarding a hepatotoxic risk in the SPC.** The cutaneous use is not sufficiently supported by market information on monotherapy. If new information on clinical safety and efficacy of *Chelidonium majus* L., herba as a single ingredient were to be made available, such documentation may be re-assessed by the HMPC. ~~The currently available clinical and toxicological data on *Chelidonium majus* L., herba cannot be considered adequate to fulfill the criteria required for developing a Community herbal monograph.~~	

Interested party	Comment and Rationale	Outcome
Gesellschaft für Phytotherapie	*Chelidonium majus* L. is one of the best known herbs in the therapy of functional gastrointestinal diseases as summarized by the German commission E in the indication "Cramp-like complaints in the area of the bile ducts and the gastro-intestinal tract". There is a long tradition of use for preparations with low alkaloid content, while a well established use has been supported by data from observational, but also from controlled studies in almost 10,000 patients. The case reports of hepatotoxic reactions, which have been correlated with the use of preparations from C. majus, have led to a graduated plan step II in Germany. This plan reflects that the occurrence of these cases is restricted to high-dose preparations with daily doses corresponding to significantly more than 2.5 mg (up to 30 mg) alkaloids. Frequency of these cases can be rated as very low or even occurring in single cases only. As reactions have been restricted to high dose preparations after prolonged use only and have been reversible, their occurrence may be prevented by determination of liver enzyme values and by contraindication of the use in case of pre-existing liver diseases. All available data speak against an idiosyncratic mechanism of the putative toxicity and for a dose dependent etiology. In contrast, for low dose preparations with not more than 2.5 mg total alkaloids per daily dose, such side effects are not known. Given the traditional use of such low dose preparations in gastrointestinal complaints and the plausibility of their use, these preparations can be rated as safe for self medication. **Therefore GPT would welcome the preparation of a monograph for this important central European herb.**	**Not endorsed**. There is a lack of preparations with a sufficiently long standing oral use and fixed content of alkaloids to be included in a monograph.

2. COMMENTS ON EXTRACTS TAKEN FROM THE EXPERT REPORTS SENT BY AESGP

Interested party	Comment and Rationale	Outcome
AESGP	Expert reports on toxicology from **Prof. Dr. Dr. D. Schrenk, Kaiserslautern, Germany ...**. *… There is no scientific indication to believe that **idiosyncratic effects** towards preparations containing Chelidonium majus extracts are more likely, than for other drugs … In contrast, the current data support 'direct' **dose-related toxic effects** with respect to the benzo[c]phenanthridine alkaloids … (p.1) ...* *… A relative lack or shortage of **glutathione or a glutathione-consuming co-medication** could thus lead to increased liver cell toxicity of sanguinarine … (p.2)* *… With respect to C. majus extracts, **Schmidt (2011)** has compiled and evaluated the reports on adverse liver effects and their possible relationship to C. majus. He concludes that up to 2010, 66 case reports from the German regulatory agency and from publications were available. Altogether >92 accompanying medications make the evaluation difficult. Taking into account those medications, the presence of or likelihood for other liver diseases, and other factors (alcohol consumption etc.), Schmidt classified the 66 reports. With respect to the hypothesis of a causal relationship between liver symptoms and the intake of C. majus according to CIOMS they classified 6 reports as 'very unlikely or rejected', 21 reports as 'unlikely', 29 reports as 'possible', 7 reports as 'probable', and 2 reports (for an unknown and a combination product) as 'highly likely'… An analysis of the average daily alkaloid doses revealed that the 'possible/probable' and/or 'likely' cases where related to relatively high daily doses. **In particular, applied daily doses were mostly between 12.5 and 25 mg, but there were no relevant cases in patients with daily doses below 8 mg alkaloids**.* (p.3) Conclusion by Prof. Schrenk *- C. majus extracts have been proven safe in animals with oral application and have shown not to be hepatotoxic.* *- C. majus extracts can be toxic, when applied parenterally. Given orally, with low intestinal*	**Prof. Dr. D. Schrenk, Kaiserslautern: Statement on the toxicology of Chelidonium majus extracts** This report mainly deals with the discussion about hepatotoxicity and repeatedly refers to the expert report made by Dr. Schmidt. Idiosyncratic mechanisms are **abandoned**. Toxicity is now approached from a pure **benefit-risk viewpoint**. In some European countries, marketing authorizations for medicinal products containing *Chelidonium majus* have been withdrawn because of concerns with reported adverse effects, particularly liver toxicity. **The products withdrawn to date have been those which would lead to a daily intake of more then 2.5 mg alkaloids from *Chelidonium majus***, according to the posology of the SPC. However the HMPC **maintains its negative opinion**, also towards the

Interested party	Comment and Rationale	Outcome
	absorption of alkaloids, it has not shown toxicity in animal experiments to date. *- the low oral bioavailabilty of benzo[c]phenanthridine alkaloids is likely to be due to their cationic nature, and to their high reactivity (e.g., with sulfhydryl groups) and not to 'idiosyncratic reactions'.* *- in patients, C. majus extracts have not not led to adverse hepatic effects when the daily dose of total alkaloids was below 8 mg - certain benzo[c]phenanthridine alkaloids from C. majus are hepatotoxic in a dose-related manner when given by parenteral routes. After oral exposure their hepatotoxicity is much lower.* *A 'lack of an identified causative factor' can not be stated since* ***all findings point to the benzo[c]phenanthridine alkaloids being the causative factor****. Taken together, preparations with daily doses corresponding to up to 2.5 mg total alkaloids* ***do not bear a relevant risk*** *of hepatic side effects and can be rated as safe even in self medication.*	preparations leading to an daily intake lower than 2.5 mg alkaloids

Interested party	Comment and Rationale	Outcome
	… on clinical data from Dr. G. Lorkowski, Gauting, Germany, … **Dr. G. Lorkowski, Gauting: Clinical efficacy and tolerability of celadine containing medicines** *… In addition to the* ***German commission E monograph*** *statement, that "celandine containg medicines belong to the medicines, ... whose actions and side effects are already known", from 2010 (8) and the* ***ESCOP monograph from 2003*** *(3) did also describe a well established use of celandine extracts. They refer also to an efficacy at dosages "lower than the recommended doses prescribed by other authorities". Both monographs have been prepared on a complete data set regarding* ***the existing clinical data, which has not been considered in the EMA HMPC draft public statement****, and so came to a clearly positive conclusion regarding the therapeutic usefulness …* (p.4) Dr. Lorkowski comes with a conclusion on the historical overview: *… The documentation of the published literature presented below involves more than 1,000 systematically investigated patients, about 600 of these in post-marketing surveillances. The number adds up to almost 10,000 patients together with the data from unpublished investigations. About half of the patients were treated with celandine containing medicines conforming to the monograph. The evaluation confirms the efficacy of celandine containing medicines conforming to the monograph. The effect size is pronounced even with small numbers of cases and clear dose and time effects are found. This is consistent with the positive statement on efficacy in the monograph of the German commission E: "****Celandine containing medicines belong to medicines, …whose actions and side effects are already known …*** (p.5) *… Under verum treatment, adverse drug reactions (restlessness or sleeplessness 4x; dryness of the mouth 3x) were reported for 3 patients and, in the placebo group, for 5 patients (sleeplessness 1x; urticaria or eczema 3x; somnolence 3x) …*(p.6).	This report describes the measures taken by BfArM (Germany), limiting the daily dose of alkaloids to 2.5 mg, as mentioned in the actual assessment report under section 5.2 (Patient exposure). It also refers to other monographs with a positive outcome. Dr. Lorkowski cites the clinical study by Ritter *et al*. (1993), also reflected upon in the assessment report. Side effects mentioned are now included in the assessment report. Dr. Lorkowski makes a statement about the clinical value of the results. However no statistical **power calculation** was performed in the original publication. This power calculation is necessary to define the required number of patients in order to evaluate the therapeutic results for the primary endpoint, which was well defined. **No further changes with regard to the benefit-risk assessment were made in the assessment report.** The Clinical Trial by Niederau and Göpfert (1999) was added to the assessment report. However, this trial is performed

Interested party	Comment and Rationale	Outcome
	… It is not the case that the number of cases is too small to demonstrate efficacy. A significant result is only attainable with a sufficient number of cases. Due to ethical consideration and regulatory requirements, the required number of cases just sufficient to show efficacy is to be kept as small as possible in order to minimise the number of ill clinical trial participants treated with placebo or with an ineffective substance. The therapy effect in this clinical trial is apparently so strong that a significant and clinically relevant result can be demonstrated with 30 patients for the symptoms of the disease … (p.7)	with a **combined product** and yielded a daily dose of 12 mg chelidonine. Some considerations were made about the power calculation. However, the calculations are **indirect and based upon extrapolations** (pp. 7-9). Therefore no further considerations were made in the assessment report. Dr. Lorkowski describes the open Clinical Trial Neumann-Mangoldt (1977). Also this study is now included in the assessment report. The comparative therapies are not specified. However, no details are given on the extraction solvent used. There is some information on the transaminase levels during treatment. The study by Ardja (1991) describes the safety of medicines containing celandine for patients **with already damaged liver function** (alcoholics) and in comparison to other medicines. However, no specification of the comparator is given. The dose of chelidonine is low. The study by Knöpfel (1991) is included in the assessment report. This is an open study without comparator.

Interested party	Comment and Rationale	Outcome
	Dr. Lorkowski concludes: ***… the benefit-risk relation for the self medication within the frame of the traditional use of celandine containing medicines, corresponding to not more than 2.5 mg total alkaloids, is positive …***	Post marketing surveillance studies are included under heading **5.2 (Patient exposure).** There is the surveillance study by Kniebel & Urlacher (1993) with only 6 suspected cases of an adverse drug reaction (3 cases of diarrhoea or soft stools, 2 cases of nausea and one case of mild tiredness) reported. A connection with the medication was not claimed in any case. This post-marketing surveillance is sufficient to provide a statistically significant assurance for adverse events which occurred with an incidence of 1:200. Another benefit-risk investigation by Gutsche (1977) is now included in the assessment report under the same heading. It has been carried out with respect to the criteria in the pharmacovigilance procedure. It is positive for long-term use of the chelidonium (lower dose). Despite the conclusions by Dr. Lorkowski, the HMPC maintains its opinion in the Public Statement, as safer herbal

Interested party	Comment and Rationale	Outcome
		medicinal products are available for oral use in the same indication.
	… and on pharmacovigilance data from Dr. M. Schmidt, Mattsies, Germany. **Dr. M. Schmidt, Mattsies: Comments on the Public Statement on Chelidonium majus L. herba** *… The hypothesis of a dose-independent toxicity or **an idiosyncratic mechanism**, as proposed by some publications, is not in accordance with the analysis of case data according to the CIOMS scale and to the toxicological data and needs reconsideration …* His conclusion reads: *… A closer look at the known facts shows that there is no scientific foundation for a conclusion on unforeseeable idiosyncratic reactions. In fact, the number of case reports which can be attributed to greater celandine with a minimum degree of certainty is very low and potentially insignificant when compared with market and exposure figures. In regulatory terms the Comments on Public HMPC-Statement on Chelidonium majus L. would be classified in the package leaflets as "in single cases", not even as "very rare".* *However, in addition, the analysis clearly shows that the reaction may in fact be related to elevated exposure to alkaloids – all relevant cases occurred with daily doses well above 9 mg. The German graduated plan procedure had already in 1998 defined a limit of 2.5 mg of alkaloids in the daily dose, below which no warning would have to be given. There is no reason to further decrease this dose threshold, e.g. below 2.5 µg. Upon commenting on toxicity including hepatotoxicity in the context of the preclinical data it is important to notice that in fact hepatotoxicity after oral application of greater celandine extracts has not been observed in animal experiments. Furthermore, there is new and relevant data supporting the safety of greater celandine extract preparations.*	The idiosyncratic mechanism is **abandoned**. Dr. Schmidt mainly refers to the same clinical studies as in the report by Dr. Lorkowski. Dr. Schmidt included a table on causality of toxicity (cf. pp.58-68). It contains interesting information as to possible dose-relationship. However, the clinical benefit should be combined with possible hepatological risks, and therefore the HMPC considers the final benefit-risk ratio as negative.

Interested party	Comment and Rationale	Outcome
	Efficacy is proven and commonly accepted as well-established for the monographed dose, while the tradition of medicinal use is given for lower doses. Consequently, the overall picture drawn for Chelidonii herba should be decisively more positive …	

3. SPECIFIC COMMENTS ON TEXT OF THE PUBLIC STATEMENT

Section number and heading	Interested party	Comment and Rationale	Outcome
Page 2, Lines 1-38	**GA** Gesellschaft für Arzneipflanzen - und Naturstoff-Forschung e.V.	The draft public statement and the assessment report on greater celandine come to a negative benefit-risk ratio based on an emphasis on toxicological aspects and the presentation of case reports of hepatotoxicity, as opposed to the lack of data on clinical efficacy for preparations with a dose range of 2.5 mg of alkaloids in the daily dose and less. This conclusion must be questioned after a thorough analysis of the available data.	Not endorsed. Vide supra.
	GA Gesellschaft für Arzneipflanzen - und Naturstoff-Forschung e.V.	Comment: The following facts need to be considered: • The pre-clinical database is not as sinister as it might be concluded from the assessment report: Although hepatotoxicity is suggested and discussed in the sections related to toxicology, there is in fact no evidence pointing to hepatotoxicity of greater celandine herb preparations from experimental studies. Signals of toxicity might be derived from examinations based on the effects of isolated	Causality is important when considering side effects, However, considerations about possible hepatotoxicity should be combined with eventual therapeutic benefits. The benefit-risk ratio for *Chelidonium* remains negative as there is a lack of preparations with a sufficiently long standing oral use and fixed content of alkaloids to be included in a monograph.

Section number and heading	Interested party	Comment and Rationale	Outcome
		sanguinarine, but sanguinarine is not a major constituent of Herba Chelidonii, as it is a typical secondary metabolite of the roots. Consequently, liver toxicity should require rather high doses of greater celandine extract preparations (see below). • The clinical experience undoubtedly makes Herba Chelidonii one of the major medicinal plants with rational use in the treatment of disorders of the hepatobiliary system. • An evaluation of the publications on case reports of hepatotoxicity confirms that a signal of potential liver toxicity is only observed with daily doses of alkaloids exceeding 8 mg. In contrast to the conclusions drawn in reviews and case publications, there is no evidence for idiosyncratic reactions, and there are no case reports with a plausible causality by greater celandine in a dose range up to 8 mg of alkaloids. The dose limit of 2.5 mg, currently valid in Germany as a threshold for the mandatory statement of contraindications and precautionary measures for the protection against liver disease, could still be used unchanged as a limit for the differentiation between traditional preparations and preparations classified as well-established. Doses above 2.5 mg could be justified by the existing clinical trials, whereas there is no recognizable risk associated with doses below 2.5 mg, which would justify their application in traditional herbal medicinal products.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		The logical consequence of the draft public statement would be a *de facto* ban of existing preparations for which serious adverse effects have never been observed and, in view of their dose scheme, are unlikely to occur (a negative public statement would have an immediate devastating effect on existing and well-controlled medicinal products). Prior to taking the decision to adopt the public statement we urgently propose to carefully re-consider the various sections of the assessment report: • The entire section on toxicology should be re-considered, as much of the information given herein either **refers to the clinical section**, or refers to the toxicological assessment of secondary plant metabolites such as the **typical root alkaloid sanguinarine**, which is of doubtful relevance in preparations prepared from the aerial parts. • The case reports and the conclusions drawn from these reports cannot simply be taken over from the publications without checking the details: a closer analysis shows that many of the conclusions drawn by the reporters must be considered premature. This especially refers to the question of dose-dependence: Whereas a dose-independent mechanism is reported in several articles, all refer to the case collection of Benninger et al. (1999) [1], without distinguishing between cases with different grades of causality scores. Conclusions on dose-effect relationships can only be drawn from cases with at least possible,	Clinical and experimental toxicology are separated in the adapted version of the assessment report. A remark has been included with regard to the toxicological data on sanguinarine. Side effect reporting should indeed be interpreted with caution. However, one should take into account that apart from reports of bad quality also underreporting occurs.

Section number and heading	Interested party	Comment and Rationale	Outcome
		preferably probable causality by greater celandine. By analysing the case reports it quickly becomes evident that many of the published case reports (as reviewed in [2]) do not convincingly support the conclusion of causality by greater celandine. A careful evaluation of the case reports using the most recent standard, the liver-specific CIOMS scale, must be performed. As of now, the public statement is based on quantity instead of quality of case reports, which is not acceptable. • The section on clinical efficacy should also be updated: Even though the efficacy itself is derived from randomized double-blind trials, the available open studies still give valuable insight into the risk situation. The number of adverse events must – after an appropriate causality assessment – be placed against patient exposure in clinical trials. Patient exposure from market sales figures should also be taken into account.	There is indeed an impressive number of patients treated. However, controlled clinical trials have been done with a restricted number of patients. Open studies are characterised by heterogeneity and are done partly with combined preparations.
Conclusions	***GA*** Gesellschaft für Arzneipflanzen - und Naturstoff-Forschung e.V.	It is not justified to adopt the current draft public statement without going back into the details. The risk emphasized in the draft public statement is not confirmed by the available data and especially by the analysis of the known case reports. This analysis shows first signals of a hepatic risk only above a daily dose of 8 mg of alkaloids, a dose for which the small risk stands against a proven efficacy. Doses above 2.5 mg could therefore be considered well-established, whereas there is no reason to deny products with up to 2.5 mg the status as traditional preparations; consequently there is no known risk	**Not endorsed.** The benefit-risk ratio for *Chelidonium* remains negative as there is a lack of preparations with a sufficiently long standing oral use and fixed content of alkaloids to be included in a monograph.

Section number and heading	Interested party	Comment and Rationale	Outcome
		justifying a negative statement by the HMPC.	
Page 2, Lines 11-17	Gesellschaft für Phytotherapie	Comment: The use of preparations from Greater Celandine is not restricted in several European countries. In Germany, the withdrawal of marketing authorizations is restricted to preparations which lead to the intake of more than 2.5 mg alkaloids from *Chelidonium majus* according to the posology of the SPC. This dose limit has been based on the fact that reported hepatotoxic reactions have been correlated to preparations with high doses, above 8-9 mg alkaloids per daily dose, while for preparations with doses of 2.5 mg and below, despite being much more widely used, such reports are lacking. While some case reports have been published, others have been cited by the German BfArM (Analysis of the BfArM ADR Reports of 6 May 2005 concerning the Hepatotoxicity of Chelidonium and employed in the Rationale for Step II of the Stufenplanverfahren [Graduated Plan]). Assessments of these reports have revealed that most of them have significant drawbacks which exclude an objective evaluation. Several plant species have been associated with hepatotoxic reactions, even though it is hard to establish their direct involvement (Pittler MH and Ernst E: Aliment. Pharmacol. Therapeutics 2003; 18: 451-71). The same is the case with *Chelidonium majus*. The case reports often do not allow an understanding of the relationship between the ingestion of the	The content on alkaloids of the preparations withdrawn is specified in the Public Statement. Analysis of side effect reporting should be matched with possible therapeutic benefits. The position of he HMPC is maintained because there are safer plant preparations to cover the therapeutic indication related to oral use.

Section number and heading	Interested party	Comment and Rationale	Outcome
		herbal drug and the onset of a liver disorder or disease, and the reports are inadequately documented, due to the following major drawbacks: a) the lack of information on pre- and concomitant diseases, pre- and co-medication, allergies, other agents (e.g. alcohol, nutritional supplements, occupational exposure) as well as trips abroad, b) lack of information on other medicines possibly responsible for the observed hepatotoxicity, c) lack of information on histology (chronic liver process?, pre-existing liver damage?), d) inadequate or insufficient exclusion diagnosis (e.g. of autoimmune hepatitis, primary biliary cirrhosis, tumours, malaria, pancreatitis, diverticulosis, etc.), e) lack of information on the quality of the herbal product administered (ingredients, standardization, purity, shelf life), f) inadequate data about pre-existing symptoms, duration of treatment, unclear anamnesis g) lack of information about indication and dosage of the used herbal drug, h) no de-challenge, no re-challenge. These drawbacks do not allow an exhaustive and concluding assessment of the adverse reactions. Following the WHO classification, none of the known cases could be assessed as probably related to Greater Celandine.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Until today, none of the submitted reports or of the publications sufficiently sums up all the characteristics needed to clearly evaluate the toxicity of *Herba Chelidonii*. The publication from J. Benninger et al. from Gastroenterology 117: 5: 1234-7 demonstrates very poorly described and incomplete case reports.	
Page 2, Lines 11-17	Gesellschaft für Phytotherapie	If there is a potential hepatotoxic effect of Greater Celandine, the underlying mechanism remains to be elucidated. J. Benninger and coworkers (1999) assumed that the herbal extract may show idiosyncratic drug reaction as underlying mechanism. This assumption is not correct. The term idiosyncratic drug reactions denotes a non-immunological hypersensitivity reaction to a substance, without connection to a pharmacologically derived toxicity reaction. Idiosyncratic drug reactions frequently occur with exposure to new drugs, as they have not been fully tested, and the full range of possible side effects has not been discovered yet. However, Greater Celandine is no new drug, and a considerable body of data exists, which needs to be considered for understanding underlying mechanisms of potential hepatotoxicity. S.Strahl et al. (Dtsch. Med. Wochenschr. 1998; 123: 1410-4) suppose an 'immunological reaction with sensitization' which is not in line with the contemporary definition of idiosyncrasy. Additionally, idiosyncrasy is not dose-dependent. In contrast, pharmacological data with greater celandine are in line with a dose-dependency in case of	Idiosyncrasy is no longer mentioned in the public statement. Dose-dependent toxicity is considered in the assessment report and Mazzanti (2009) is now included.

Section number and heading	Interested party	Comment and Rationale	Outcome
		hepatobiliary disturbance. The following reports and publications are indicative for such dose dependency: a) Runge D et al: Hepatotoxic assessment of *Chelidonium majus* L. and its alkaloids in primary hepatocyte cultures of different species. Zeitschrift für Phytotherapie 2009; 30 (Suppl. 1):14: The liquid extract showed a concentration-dependent toxicity in human hepatocytes and at concentrations of 7.5 mg/kg for rat, canine and monkey hepatocytes b) Mazzanti G et al. *Chelidonium majus* is not hepatotoxic in Wistar rats, in a 4 weeks feeding experiment. J. Ethnopharmacol. 2009; 126: 518-24.: The authors tested the same batch used by one of the two patients for whom a hepatotoxic reaction was reported by the Italian Surveillance System. As a result from the investigations, the study suggested that Greater Celandine, at doses about 50 and 100 times higher than those generally used in human, does not alter hepatic function. The results excluded the possibility of cellular hepatic toxicity, cholestasis, inflammation, or other hepato-biliary disease that could affect liver function: High doses of Greater Celandine led to a reduction of GSH levels and SOD activity which is indicative of a dose-dependency. In adverse drug reactions involving overdoses, such an effect is simply an extension of the pharmacological effect, and not an effect of idiosyncratic drug reaction. c) Adler M et al. Effects of *Chelidonium majus* extracts in human hepatocytes in vitro. Planta Medica 2006; 72(11):P	

Section number and heading	Interested party	Comment and Rationale	Outcome
		322: Primary human hepatocytes, Chang hepatocytes and HepG2 cells were incubated with *Chelidonium majus* dry extract. Data showed a clear dose dependency of all observed effects. Cytotoxicity was in the same range as that of substances with accepted safety, as ascorbic acid or *Ginkgo biloba* extract. d) BfArM: Bekanntmachung zur Abwehr von Gefahren durch Arzneimittel, Stufe II, Bescheid (hier: Schöllkraut-haltige Arzneimittel zur innerlichen Anwendung) [Notification on prevention of hazards of medicines, Stage II, notification (here: celandine containing medicines for internal use)]. 9. April 2008: A toxicological evaluation, based on unpublished studies, comes to the conclusion of a safe dose of 2.5 mg C. majus alkaloids/d: "From the chronic-toxicological study with a combination preparation containing Chelidonii herba extract over 6 months in the rat (Notox project 330211) results a limit of 2.6 mg total alkaloids/day, which already takes into account inter species variability and combination effect of the different components of the preparation with a safety factor of 100 vs. human exposition and, in addition, through the duration of the study of 6 months, covers also chronic use in man. The evaluation of this dose limit is based on a NOEL > 3.69 mg/kg /d in the rat (x 70 = 258.3 mg/d in man, divided by 10 x 10 = ca. 2.6 mg/d). The limits of 2 and 0.2 mg/day, which are derived from the 4 week toxicity study in the rat (Weleda 2002) and the 3 month study in the dog (Notox project 330222), are also	

Section number and heading	Interested party	Comment and Rationale	Outcome
		based on NOELs, which correspond to the maximum doses in the respective studies. They therefore do not contradict the higher limit of 2.6 mg/day. These studies can be seen as supportive, especially as in the study in dogs a second species (non-rodent) was tested without findings." The work of Mazzanti et al. might be a clue to a toxicological mechanism of extracts containing benzylisoquinoline alkaloids, as these compounds are sensitive to the nucleophilic attack by GSH, so that excessive doses might lead to a GSH depletion and subsequently could cause dose-dependent hepatotoxic reactions. Toxicological data pointing to a dose-dependency are confirmed by the clinical evidence that no hepatobiliary disorders are seen at daily doses of 2.5 mg alkaloids from Greater Celandine and below. Correspondingly, the actual working document of the HMPC on *Chelidonium majus* describes the use of therapeutic doses as safe due to the low quantity of alkaloids in the plant preparations, and that only its excessive use for long periods should be avoided because of risk of hepatotoxic effects. Additionally, the assessor's overall conclusion on toxicology is that when the dried parts of *Chelidonium* are used in normal dose, the toxicity is limited. As a consequence, we deem it proper to speak of a dose-dependent potential hepatotoxicity instead of an idiosyncrasy.	

Section number and heading	Interested party	Comment and Rationale	Outcome
Page 2, Line 19-21	Gesellschaft für Phytotherapie	Comment: For the indication "Cramp-like complaints in the area of the bile ducts and the gastro-intestinal tract" there exist a considerable number of clinical studies and post-marketing surveillances, which cover also the dosage of 2.5 µg - 2.5 mg total alkaloids/day. The public statement does also not agree upon with the available monographs of the German Commission E, the ESCOP (2003) and also not with the WHO monograph on Herba Chelidonii as latest published monograph (WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS), 2010, pp.73-89; ISBN: 978 92 4 159772 2). There exists a number of systematic investigations supporting clinical efficacy and tolerability of celandine containing medicines, which should be regarded as sufficient supportive evidence for the efficacy of Greater Celandine in the accepted indications and in the permitted dose range: a) Ritter R et al.: Standardisierter Schöllkrautextrakt bei Oberbauchbeschwerden - Ergebnisse einer placebokontrollierten Doppelblindstudie [Standardised celandine extract for upper abdominal complaints – Results of a placebo-controlled, double-blind, study]. Natur und Ganzheitsmedizin, 1992; 5: 198-202. Ritter R et al.: Clinical trial on standardised celandine extract in patients with functional epigastric complaints: results of a placebo-controlled double-blind trial. Complementary Therapies in Medicines, 1993; 1: 189-193: C. majus extract (12-24 mg alkaloids/d) had a significant efficacy in cramp-like complaints in the area of the bile ducts and the gastrointestinal tract vs. placebo in30 patients per	**Not endorsed.** A part of the studies were made with comninations. The suggested studies do not take into account the comparison **to other herbal medicinal products** with a **better benefit-risk balance.** For a traditional use the benefit-risk balance remains negative (cf. supra).

Section number and heading	Interested party	Comment and Rationale	Outcome
		group. b) Niederau C and Göpfert E: Die Wirkung von Schöllkraut- und Curcumawurzelstock-Extrakt auf Oberbauchbeschwerden infolge funktioneller Störungen des ableitenden Gallensystems - Ergebnisse einer placebokontrollierten Doppelblindstudie [The action of celandine and curcuma rootstock extract on upper abdominal complaints as a result of functional disorders of the conducting biliary system – Results of a placebo-controlled, double-blind study]. Medizinische Klinik, 1999; 94: 425-430.: A combination preparation containing 12 mg C. majus alkaloids/d had a significant effect in upper abdominal complaints vs. placebo, in 39/37 patients per group. c) Neumann-Mangoldt P: Erfahrungen bei der Behandlung von Gallenwegserkrankangen mit Panchelidon [Experience in the treatment of bile duct diseases with Panchelidon]. Medizinische Welt, 1977; 28: 181-185: Chelidonium extract, 20 mg alkaloids/d, was effective in pain symptoms in patienst with inflammatory bile duct diseases in an open setup vs. comparator, in altogether 77 patients. d) Ardjah H: Therapeutische Aspekte der funktionellen Oberbauchbeschwerden bei Gallenwegserkrankungen [Therapeutic aspects of functional upper abdominal complaints in bile duct diseases]. Fortschritte der Medizin, 1991; 109, Suppl. 115: 2-8: The medication as used by Neumann-Mangoldt was tested in an open setup vs. comparator, in upper abdominal symptoms, in altogether 236 patients e) Knöpfel SA: Auch gegen Gallenleiden ist ein Kraut gewachsen - Behandlung von Erkrankungen der Gallenwege und der Gallenblase mit dem natürlichen Choledynamikum Chelidonin [A herbal remedy	

Section number and heading	Interested party	Comment and Rationale	Outcome
		for biliary ailments – Treatment of diseases of the bile ducts and gall bladder with the natural choledynamic chelidonine]. Therapeutikon, 1991; 4: 205-208: A low dose of C. majus extract (50 – 250 µg) was tested in a non-comparative observational study with 92 patients. f) Kniebel R and Urlacher W: Therapie krampfartiger Abdominalschmerzen - Hochdosierter Schöllkrautextrakt bei krampfartigen Abdominalbeschwerden [Therapy of cramp-like abdominal pain - High dosed celandine extract for cramp-like abdominal complaints]. Zeitschrift für Allgemeinmedizin, 1993; 69: 680-684: Post-marketing surveillance study with C. majus extract, 12-24 mg/d, over up to 2.5 month in 608 patients. g) Gutsche H: Langzeitbehandlung mit einem Phytocholagogum [Long-term treatment with a phytocholagogue]. Ärztliche Praxis, 1977; 98: 3999-4000: C. majus extract, 150 -600 µg alkaloids/d, was used in 162 patients h) BfArM: Bekanntmachung zur Abwehr von Gefahren durch Arzneimittel, Stufe II, Anhörung (hier:Schöllkraut-haltige Arzneimittel zur innerlichen Anwendung) [Notification on prevention of hazards of medicines, Stage II, Hearing (here: celandine containing medicines for internal use)]. Bundesanzeiger of 6th May 2005: Unpublished post-marketing surveillances with different preparations in about 7000 patients are reported. The available evidence of clinical efficacy from these controlled and non-controlled clinical studies and post-marketing surveillances was the basis for the positive monographs of the Commission E, the ESCOP and the WHO. Including non-	

Section number and heading	Interested party	Comment and Rationale	Outcome
		published data, almost 10,000 patients were treated, about 50% being treated with drugs of monograph conformity. Drug evaluation was done with standardized and validated scales, and the effects were positively superior compared to placebo and similar to comparable preparations. Clear dose- and time-related effects were seen, as well as good clinical efficacy by possible dose reductions into the lower range of the monograph. Additionally in these controlled clinical investigations, the use of Greater Celandine showed no risk, which is even supported by the statement of the WHO monograph on Herba Chelidonii under precautions that "the Drug and Medicinal Institute of Germany recommends a maximum daily dose of 2.5 mg total alkaloids, which is lower than the recommended doses prescribed by other authorities" Given the rarity and reversibility of hepatic side effects even in the high dose C. majus preparations conforming to the commission E monograph (with up to 30 mg total alkaloids/d), and the available evidence of clinical efficacy, a benefit/risk analysis is likely to be positive, given that texts related to a potential hepatotoxicity (according to the German notification from 2008) are included into the SPC. In preparations with a dose corresponding to not more than 2.5 mg total alkaloids/d, no cases of hepatotoxicity have been observed. Toxicity is also not to be expected from preclinical data, as it has to be considered dose-dependent and restricted to parenteral application. So, a traditional use in self medication is possible.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		In accordance with most of the evaluations and scientific papers, the benefit/risk relation for the use of Greater Celandine containing medicines remains definitely positive.	
Page 2, Line 25-38:	Gesellschaft für Phytotherapie	Comment: Based on the data supporting safety and efficacy of preparations from C. majus presented and discussed above, a new benefit-risk analysis is suggested. Especially in the preparations which lead to a daily intake of not more than 2.5 mg alkaloids from C. majus and for which reasons for safety concerns are lacking, a positive outcome of this analysis would be appreciated, as this would allow the continuation of the long-standing traditional use of this prominent traditional herb in Europe. , and would be in accordance with the lack of reasons for safety concerns in preparations. Especially for preparations with doses above the limit of 2.5 mg, the extent and quality of the available scientific data is even indicative of a well established use, while remaining safety concerns would need to be addressed by the inclusion of texts in the SPC related to hepatotoxic side effects. Whereas the statement, that the cutaneous use is not sufficiently supported by market information on monotherapy is rated to be appropriate, a re-evaluation of the data on oral use in functional gastro-intestinal diseases and the creation of a HMPC herbal monograph is suggested.	**Not endorsed.** Cf. risk-benefit analysis compared with safer alternatives.

Section number and heading	Interested party	Comment and Rationale	Outcome
Non-clinical Data	Kooperation Phytophar-maka	• According to the European Pharmacopoeia, herbal medicinal products of Chelidonii herba consist of the dried aerial parts of *Chelidonium majus* L. collected during flowering. It contains not less than 0.6 per cent of total alkaloids, expressed as chelidonine and calculated with reference to the dried drug. • Preparations of *Chelidonium majus* L., herba, made from standardized hydroalcoholic extracts have an accepted place in the symptomatic treatment of mild to moderate spasms of the upper gastrointestinal tract; minor gall bladder disorders; dyspeptic complaints such as bloating and flatulence (ESCOP, 2003). • According to the ESCOP monograph (2003), a daily dose of 125-700 mg of standardized hydroalcoholic extracts corresponding to 9-24 mg of total alkaloids, calculated as chelidonine, was recommended. • The maximum daily dose of 24 mg total alkaloids corresponds to a dose of 0.4 mg/kg b.w. daily. • <u>As an example:</u> Based on the benzylisoquinoline type alkaloid coptisine, where the distribution volume (Vd = 30.07 l/kg)(Li et al, 2006) is known, the following context can be constructed: Assuming that the possible total alkaloid dose would refer to a dose of daily 0.4 mg coptisine per kg b.w., a maximum plasma concentration of 0.0133 mg (= 13.3 µg) coptisine per litre (= 13.3 ng/ml) can be expected after a single dose according to the equation M = C * Vd (M: total amount of drug; C: drug blood plasma concentration).	A daily dose of 9-24 mg of total alkaloids, calculated as chelidonine cannot be accepted, according to the analysis by Schmidt (2011). Conclusions on acceptable intake should be made from pharmacovigilance data, rather than laboratory results.

Section number and heading	Interested party	Comment and Rationale	Outcome
		• For the benzylisoquinoline type alkaloid berberine, a distribution volume of 38.30 l./kg was determined (Chen CM et al, 1995; Moffat et al, 2004). Assuming that the possible total alkaloid dose would refer to a dose of daily 0.4 mg berberine per kg b.w., a maximum plasma concentration of 0.01044 mg (= 10.44 µg) berberine per litre (= 10.44 ng/ml) can be expected after a single dose. An *in vitro* study investigated the hepatotoxic potential of different alkaloids from aqueous herbal extracts of *Chelidonium majus* L. using primary hepatocyte cultures of different species including human. Toxic alkaloid effects were investigated by using various concentrations of coptisine, chelerythrine and protopine in rat hepatocyte cultures. Analytics included microscopic documentation, urea and albumin release, LDH and ASAT leakage and MTT-assay. Light microscopy revealed a high decrease of vitality at extract concentrations above 5´000 µg/ml for all species except rat. Identification of EC50 (LDH) revealed an order of decreasing sensitivity, with human being the most sensitive species at 1´000 – 2´500 µg/ml, followed by cynomolgus and beagle at 5´000 – 7´500 µg/ml, and rat at > 10´000 µg/ml. This order correlated well with data obtained for ASAT, urea and MTT assays. Liquid extract contained a total alkaloid amount of 75 µg/ml, consisting of 36 µg/ml protopine and 12 µg/ml coptisine among others. Of all alkaloids investigated, coptisine was found to be most toxic, revealing an EC50 (LDH) of 12.5 - 25 µg/ml, followed by chelerythrine 50 - 100 µg/ml and protopine > 200 µg/ml (Runge et al. 2009). Data in primary human hepatocytes and human liver cells show	

Section number and heading	Interested party	Comment and Rationale	Outcome
		an EC50 in the range of 0.8-1.0 mg/ml, with a distinct, but limited influence of the alkaloid fraction (Adler et al. 2006). • From the results of this *in vitro* study, the available concentrations of alkaloids after single dose but also after repeated dosing (due to the short half lifes) in human are below that of these hepatotoxic concentrations by a factor of about 1´000 (!). Moreover, it should be noted that the results have been determined using aqueous herbal extracts of *Chelidonium majus* L. in contrast to hydroalcoholic extracts used in pharmaceutic preparations. • A hepatotoxic risk of commercial hydroalcoholic herbal extracts of *Chelidonium majus* L. can therefore not be regarded to be confirmed on the basis of these findings. In the years 2001 and 2002, the pharmaceutical company Weleda has performed, studies on acute and sub-chronic toxicity (4 weeks) using Chelidonium mother tincture ((Extrait de Hydroalcoolique Chélidoine) in rats. The mother tincture was prepared according to the monograph of HAB and contained 0.147 percent alkaloids, calculated as chelidonine. 80 Sprague-Dawley rats were randomly allocated into four groups (each 10 males and 10 female animals). Each of the groups received the following daily concentrations of the test substance:	

Section number and heading	Interested party	Comment and Rationale	Outcome
		<table><tr><th>Extract dose</th><th>Total alkaloid dose</th></tr><tr><td>0 mg/kg/d</td><td>0,00 mg/kg/d</td></tr><tr><td>730 mg/kg/d</td><td>1,07 mg/kg/d</td></tr><tr><td>1270 mg/kg/d</td><td>1,87 mg/kg/d</td></tr><tr><td>1820 mg/kg/d</td><td>2,68 mg/kg/d</td></tr></table> The result of this study revealed that daily, oral administration of Chelidonium mother tincture over four weeks and at doses of 0, 730, 1´270 and 1´820 mg/ kg/day (0; 1.07; 1.87 and 2.68 mg/ kg/d total alkaloids) did not have any effects of toxicological relevance, especially no signs of liver toxicity in rats. Similarly, the histological examinations showed no pathological findings, which pointed to toxicologically relevant effects of the test substance. Similarly, the blood tests showed no pathological changes in the routine laboratory. From results of this sub-chronic toxicity study, the NOAEL (No Observed Adverse Effect Level) for oral administration of a hydroalcoholic herbal extracts of Chelidonium (mother tinctures) was derived to be above 1´820 mg/kg/day (2.68 mg/kg/d total alkaloids). A 90-day sub-chronic toxicity study investigated the safety of Chelidonii herba in pigs. The diet for treated animals (Group 2) was supplemented with 50 ppm of Chelidonium powder. One gram of the powder contained 4.71 ± 0.37 mg chelidonine, 1.52 ± 0.15 mg sanguinarine, 1.19 ± 0.12 mg chelerythrine, 0.52 ± 0.05 mg berberine, and 2.78 ± 0.30 mg coptisine. During the 90-day experiment no impairment of the animals' health status was observed. No statistically significant	

Section number and heading	Interested party	Comment and Rationale	Outcome
		differences between the control group and the test group of animals were found for the weight gain and feed consumption. No signifieant differences between experimental and contral animals were found by histological examinations in specimens of selected tissues. In plasma. globuline, creatinine, AST (Aspartate aminotransferase), GMT (γ-glutamyltransferase) and cholesterol were significantly decreased in test group vs control group ($P < 0.05$) (Kosina et al. 2007). Both subchronic toxicity studies show no evidence of a hepatotoxic risk of commercially available hydroalcoholic herbal extracts of *Chelidonium majus* L. for the range of recommended dosages.	
Clinical Data	Kooperation Phytofar-maka	In a controlled, randomised, double-blind, placebo-controlled clinical study, the efficacy of a herbal medicinal product containing *Chelidonium majus* extract (containing 66.0 to 167.2 mg native dry extract, equivalent to 4 mg total alkaloids, calculated as chelidonine; DER and extraction solvent not stated)) was compared to placebo in 60 patients with functional epigastric complaints. The patients received a daily dose of 24 mg total alkaloids (2 tablets t.i.d.) for six weeks. The reduction in symptom score, assessed using the von Zerssen list, was significantly greater in the *Chelidonium majus* group, compared with the placebo group (p=0.003). Physician's assessment of efficacy was that 18/30 patients in the treatment group were improved or symptom free, compared with 8/30 in the placebo group. No adverse events were reported (Ritter et al, 1993).	See critical analysis of the study by Ritter (1993) (answer to AESGP comments). The Public Statement is revised. **However a negative benefit-risk ratio is maintained**, due to the low level of therapeutic evidence, the discussion about possible toxic levels and the non-availability of safe monopreparations with a sufficient longstanding use on the EU market.

Section number and heading	Interested party	Comment and Rationale	Outcome
		• Assessment report shows 47 reports of adverse event associated with the intake of *Chelidonium majus* preparations held in the Vigisearch database of the World Health Organization´s Uppsala Monitoring Centre for the period up to the end of June 2005. These reports include 147 adverse events; among these 95 events of the hepato-biliary system. – However, no information is given on the used herbal preparations. • The Assessment report refers to some case reports of hepatitis and jaundice. – Again, the information about the used herbal preparations was sparse. In one case only, information was given: The patient took daily a cup of a *Chelidonium majus* decoction (boiling 4-5 spoons of dried leaves in 150 ml of water, straining and leaving it overnight) (Moro et al, 2009). – It should be highlighted also that several herbal combinations have been associated with adverse events of the hepato-biliary system. – Usually, hepatitis is diagnosed by laboratory parameters, imaging methods and liver biopsy. However, in most cases, liver biopsies were not performed. – On the background of reported adverse events and the pharmacovigilance experience of manufacturers and physicians, aqueous herbal extracts of *Chelidonium*	

Section number and heading	Interested party	Comment and Rationale	Outcome
		majus L. seem to be more often associated with hepato-biliary events than hydroethanolic extracts. – Additionally, rare hepato-biliary events were associated with daily doses of total alkaloids of 30 mg and above. In conclusion, we can not support the general assessment of the Public Statement: "Under the regulatory framework applicable to traditional herbal medicinal products laid down in Chapter 2a of Directive 2001/83/EC as amended and in particular Article 16a(1)(a) on their use in minor indications that do not require supervision of a medical practitioner, the findings from the assessment imply that the benefit-risk analysis of *Chelidonium majus* L., herba is negative." 1. The Assessment report does not assess the real Patient exposure (paragraph 3.3.1.) but cited the German graduated plan which came into force on 09 April 2008. 2. *In vitro* investigations using rodent and human hepatocytes do not confirm a hepatotoxic risk of plasma concentrations achievable with maximum daily doses of 24 mg total alkaloids corresponding to a dose of 0.4 mg/kg b.w. daily. 3. In vivo studies of subchronic toxicity do not justify the conclusions of the Public Statement of the HMPC. 4. Further, no valid assessment can be made from unknown preparations containing *Chelidonium majus* L. To our knowledge, no case of hepato-biliary disturbances is known from herbal medicinal products containing hydroalcoholic extracts of *Chelidonium majus* L., herba. It is our	

Section number and heading	Interested party	Comment and Rationale	Outcome
		impression that apples were compared with oranges when the adverse events resulting from very different and mostly unknown preparations of *Chelidonium majus* L. were thrown together. This procedure does not meet the usual scientific practice. We would appreciate if the public statement being subject to revision or lead to the preparation of a positive monograph	

4. LISTS OF REFERENCES PROVIDED BY INTERESTED PARTIES

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5. TABLES PROVIDED BY AESGP

Table 5.1.: Examples of case reports associated with *Chelidonium majus* preparations (from Schmidt 2011). Causality assessments given relate to the product (including combination partners) but not specifically to *Chelidonium majus*.

Identifier	Age (years)	Sex	Preparation	Daily dose alkalo-ids (mg)	Duration of intake	Co-medica-tion	ADE	Outcome	Additional data	CI-OMS
Cases with probable causality association with *Chelidonium majus* (6-8 points)										
Moro et al. (2008)	65	m	*Chelidonium majus* tea	un-known	4 weeks	Lansoprazole	Cholestatic hepatitis	recovered	History of hepatitis C infection	6
Benninger et al. (1999) #6	65	f	Unknown	9-27	3 months	None	Toxic hepatitis	recovered		6
Cases with probable causality association with products containing, among other constituents, *Chelidonium majus* (6-8 points)										
Bichler (2009)	82	m	*Chelidonium majus* tea	un-known	unknown (several months?)	Not specified, but other herbs present	Hepatitis, elevated LFTs	recovered		6
Cases with possible causality association with *Chelidonium majus* (3-5 points)										
Benninger et al. (1999) # 10 / BfArM #4 98007984	51	f	Panchelidon cps.	12.6 or 21.6	2-3 months	Hypericum extract, contracep-tives	Toxic hepatitis with fatigue, decreased appetite and upper abdominal pain. Elevated LFTs	recovered		3
Benninger et al. (1999) #7	40	f	Unknown	9-27	3 months	Amitryptiline, silymarin, thyroxin, ASA, Zinc,	Cholestatic hepatitis	recovered	Evidence of pre-existing liver disease	3

Identifier	Age (years)	Sex	Preparation	Daily dose alkalo-ids (mg)	Duration of intake	Co-medica-tion	ADE	Outcome	Additional data	CI-OMS
						hymecromone and others				
Benninger et al. (1999) #8 BfArM 97008586?	66	f	Unknown	9-27	4-7 months	Atenolol, nifedipine, triamterene, hydrochlorothiazide	Toxic hepatitis	recovered	Evidence of hepatitis C	3
Benninger et al. (1999) #9	40	f	Unknown	9-27	2 months	Magnesium, estradiol	Toxic hepatitis	recovered	Potential autoimmune hepatitis	3
Cases with possible causality association with combinations containing, among other constituents, *Chelidonium majus* (3-5 points)										
Stickel et al. (2003) #2, BfArM 00002873	69	m	Cholagogum Nattermann cps. or Cholarist tbl.	9, 12 or 21.6	6 weeks	Curcumae rhizoma in the combination ASA	Elevated LFTs, jaundice	unknown		5
Hardeman et al. (2008)	58	f	Curcumaran tbl. with 50 mg C. majus/tablet	unknown	6 weeks	Curcuma root and gentian root in the combination	Hepatitis with jaundice and ascites	recovered	Dilated gall bladder with obstruction of choledochus	4
Stickel et al. (2003) #1	39	f	Gallemolan forte cps.	12.6	2x 4 weeks (re-exposure)	Taraxacum root and herb extract, Artemisiae herba extract in the combination Sulphomethoxazol and trimethoprim with the first episode, penicillin with the second	Cholestatic hepatitis	recovered	Rechallenge?	3
Benninger et al. (1999) #5	37	f	Neurochol C (form unknown)	13.8	3 months	Extracts from *Taraxacum* and *Artemisia absithium*, other herbal preparations and homeopathic remedies	Cholestatic hepatitis	recovered		4

Identifier	Age (years)	Sex	Preparation	Daily dose alkalo-ids (mg)	Duration of intake	Co-medica-tion	ADE	Outcome	Additional data	CI-OMS
Cases with unlikely causality association with *Chelidonium majus* (1-2 points)										
Benninger et al. (1999) #1, BfArM 01000141	67	f	Panchelidon N cps.	12.6-25.3	min. 9 months	None	Hepatitis, jaundice	recovered		2
Benninger et al. (1999) # 4 BfArM 97008589	46	f	Panchelidon N cps. and drops (?)	13.2	>7 months	Loperamide, valerian extract, pancreas enzymes	Cholestatic hepatitis with jaundice	recovered		2
Cases where causality of *Chelidonium majus* is very unlikely or rejected (≤ 0 points)										
Benninger et al. (1999) #2; BfArM 97008587	46	f	Cholarist	9	4 months	Estradiol, levonorgestrel, iodine	Hepatitis	recovered		0
Benninger # 3, BfArM 97009054	54	f	Panchelidon N	4.4-25.3	6 months	Diclofenac, tramadol, heparin-sodium s.c., piroxicam	Hepatitis and jaundice	not recovered	Possibly autoimmune hepatitis	-5
Cases where causality of combinations containing, among other constituents, *Chelidonium majus* is very unlikely or rejected (≤ 0 points)										
Crijns et al. (2002); BfArM #16 02007637	42	f	Steigal coated tabl. or Ardeycholan N coated tbl.	15-18	5 weeks (14-18 days to onset)	Curcuma extract (combination with *Chelidonium majus*) Paracetamol	Hepatitis with icterus	recovered	Evidence of pre-existing liver disease	-1

Table 5.2. Overview of clinical investigations with *Chelidonium majus* preparations (from Lorkowski 2011)

Author [Lit.]	Preparation Extract	Patients [n]	Design	Dose/ Duration	Indication	Outcome parameter	Result	Comment
Ritter 1992	Gallopas® 100 4 mg Total alkaloids / Tablets (= 12-24 mg)	60 (30/30)	Monocentre, double-blind vs. placebo	1-2 tablets 3 x daily/ 6 weeks	Functional upper abdominal complaints, cramp-like complaints in area of bile ducts and gastrointestinal tract	Ailment list (B-L) acc. to von Zerssen; symptoms list, physician verdict on efficacy and tolerability	Significant p=0.003 vs. placebo in B-L; significant advantages for symptoms: stomach and gall complaints, flatulence, nausea, feeling of fullness	Laboratory values in normal range
Niederau 1999	Cholagogum F Nattermann® dry extract combi with curcuma rootstock, 12 mg chelidonium total alkaloids/ daily dose	76 (39/37)	Multicentre, double-blind vs. placebo	1 Capsule 3 x daily/ 3 weeks	Upper abdominal complaints resulting from functional disorders	Frequency of cramp-like and dull upper abdominal complaints	Partly statistical significant exploratory significance of the intensity and frequency of the complaints	Pilot clinical trial that led with cases numbers of 94 patients/group to significant demonstration of efficacy
Knöpfel 1991	Panchelidon® capsules/drops Kanoldt/ 0.25 mg or 50 µg * standardised total alkaloids/ capsule or 1 ml of drops	92 (54*)	Multicentre, non-comparative clinical trial	20 Drops 3 x daily before meals (approx. 1 ml)	Chronic gall bladder inflammation and/or gall stones	Subjective pain (nature and frequency), feeling of fullness, meal intolerance, objective findings	20% completely free of pain and complaints, statistically significant reduction of pain intensity (p=0.001)	Improvement of laboratory values, * clinical trial on 54 patients with capsules likewise successful
Kniebel 1993	Cholarist®	608	Post-marketing surveillance	1-2 Tablets 3 x daily corresponding to 9-18 mg total alkaloids/ 22 days to 2.5 months	Functional dyspeptic of colic-like complaints in gastrointestinal tract and/or in area of bile ducts	Adverse events 1:200 with 95% certainty, therapy success, time to onset of effect, influence of concomitant therapy	Efficacy in almost 90% good to very good, in patients with monotherapy 50% very good, concomitant medication only about 38%, onset of effect within 30 min. and lasting 3 hours	No influence on blood pressure, no side effects.
Neumann-Mangoldt 1977	**Panchelidon®, Kanoldt, 20 mg% total alkaloids**	**77**	**Open, comparative with reference medication**	**20-30 drops 3 x/day, on average 43-52 days**	**Cholangitis, cholelithiasis, dyskinesia (inflammatory bile duct diseases)**	**Subjective pain (nature and frequency), feeling of fullness, obstipation or diarrhoea, meal intolerance, objective findings**	**2/3 good to very good success, better results than reference preparations**	**No side effects, mainly improvement of transaminases**
Ardjah 1991	**Panchelidon® drops, capsules, cholinergic, spasmolytic**	**236**	**Open, comparative depending on the diagnosis**	**1 Capsule 3x daily, 20-30 drops 3 x daily**	**Upper abdominal symptoms (49), cholecystitis cholangitis (37), postcholecystectomy syndrome (44), gall bladder dyskinesia (64), double gall bladder (6), porcelain gall bladder (7),**	**Reduction of the subjective complaints (nature, intensity, frequency), rendering symptoms objective based on sonographic investigations,**	**Mainly good healing success and no differences to therapy with spasmolytics and cholinergics.**	**Premature termination by 5 patients due to stomach intolerance and ulcers. After healing, successful therapy due to existing**

Author [Lit.]	Preparation Extract	Patients [n]	Design	Dose/ Duration	Indication	Outcome parameter	Result	Comment
					septum formation (7), weight gain (21), choledocholithiasis (1)	laboratory parameters		dyskinesia. .
Gutsche 1977]	Aristochol granulate (combination) alkaloid content: 0.15 to 0.6 mg chelidonium alkaloids/ daily dose	162	Retrospective, long-term surveillance	½ to 2 bags per day	Chron. gall bladder and bile duct ailment, chron. inactive, liver diseases, excretory pancreas function disorders and chronic obstipation	Reduction of complaints (descriptive), descriptive and statistical evaluation of laboratory parameters	Good ailment reduction up to 10 years, no changes in laboratory values, stabilisation of liver function, no interactions with concomitant therapy, no toxic liver changes.	Carefully performed clinical trial and safety evaluation
Witzel, unpub-lished data**	Daily Doses of total alkaloids below 12 mg	approx. 133						
Boots Pharma, unpublished data**	Daily Doses of total alkaloids partly below 12 mg (759 patients) and 12 mg an higher (759 patients)	1518						
Jung and Jung, unpublished data**	Daily Doses of total alkaloids between 12 and 30 mg	5924						
Beyer 1997, unpublished data**	Daily Dose of total alkaloids below 12 mg	1						
Overall Sum		8820						no hepatic side effects

****Cited according to the draft notice (graduated plan) from the German BfArM from 06 May 2005**