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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Curcuma longa* L. (*C. domestica* Valetton), rhizoma

Draft revision

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)		<i>Curcuma longa</i> L. ( <i>C. domestica</i> Valetton) <sup>1</sup> , rhizoma
Herbal preparation(s)		
Pharmaceutical form(s)		A) Powdered herbal substance B) Comminuted herbal substance C) Tincture (Ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 70% (v/v) D) Dry extract (DER 13-25:1), extraction solvent ethanol 96% (v/v) E) Dry extract (DER 5.5-6.5:1), extraction solvent ethanol 50% (v/v) F) Tincture (Ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% (v/v)
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Curcuma longa* L., rhizoma. It is a working document, not yet edited, and

<sup>1</sup> Conform European Pharmacopoeia 2016 8th edition 8.6-8.8

shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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# 1. Introduction

## 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

The European Pharmacopoeia defines *Curcuma longae* rhizoma or turmeric rhizome as the whole, cured (by boiling or steaming), dried rhizome of *Curcuma longa* L. (syn. *Curcuma domestica* Valetton) with roots and outer surface removed [88].

Other documented synonyms of *C. longa* are *C. aromatica* Salisbury and *Amomum curcuma* Jacq.) [17, 82]. Common names for *C. longa*: turmeric, curcuma.

Besides *C. longa* also *C. rotunda* is mentioned in some older references. Nowadays *C. rotunda* is considered to be a former trade name for the product containing the primary rhizomes (bulb or round turmeric) in distinction to the product consisting of the thinner and longer secondary rhizomes (longa-form), both originating from *C. domestica* L. [33, 43].

Other names: Curcuma, Indian saffron, Haridra (Sanskrit, Ayurvedic), Jianghuang (= yellow ginger in Chinese), Kyoo or Ukon (Japanese) [98].

The monographs of ESCOP and Commission E mention that the herbal substance contains not less than 2.5 resp. 3 percent dicinnamoylmethane derivatives, calculated as curcumin, and not less than 2.5 resp. 3 percent volatile oil, both calculated on a dry-weight basis of the drug [96, 83].

For *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich), another species of the genus *Curcuma*, and having similar properties as *C. longa*, a HMPC monograph was established in 2014. The European Pharmacopoeia describes in the monograph for *Curcuma xanthorrhizae* rhizoma a TLC-test for *C. domestica* and its modifications for identifying *C. xanthorrhiza* [88].

### Constituents (see also Fig. 1)

Carbohydrates: 69.4% of total mass [1].

Curcuminoids: this is a mixture of curcumin (diferuloylmethane), monodexmethoxycurcumin and bisdesmethoxycurcumin [2-6]. Curcumin makes up approximately 90% of the curcuminoid content in turmeric [7].

The phenolic groups in the structure of curcumin explain the ability of curcumin to eliminate oxygen-derived free radicals. [80] The free radicals which can be eliminated by curcumin are hydroxyl radical [9], singlet oxygen [10], superoxide radical [11], nitrogen dioxide and NO [108].

The curcumin content of the *C. longa* rhizome varies from 0.6 to 5% of the dry mass [14]. The dry turmeric rhizomes contain 3-5% curcumin, the curcumin content of turmeric oleoresin is 40% [15].

Essential oil: 5.8% of total mass, constituents are:  $\alpha$ -phellandrene 1%, sabinene 0.6%, cineol 1%, borneol 0.5%, zingiberene 25%, and sesquiterpenes 53% [1]. The mono- and sesquiterpenes include zingiberene, curcumene, aromatic turmerone ( $\alpha$ -turmerone) and  $\alpha$ - and  $\beta$ -turmerone [2-6].

Mineral matter: 3.5% of total mass [11].

Moisture: 13.1% of total mass [1].

Polypeptides: [5, 6].

Protein: 6.3% of total mass [1] and Fatty oil [16].

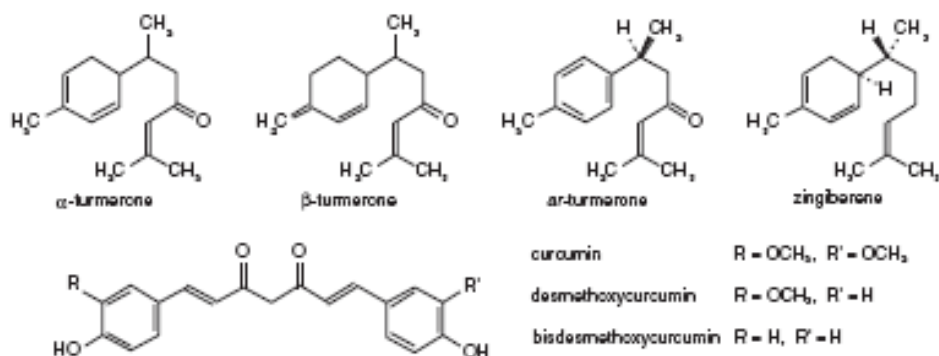


Fig. 1: Structures of main components of *Rhizoma Curcumae longae* [17].

### Treatment of the herbal substance immediately after harvesting

According to some handbooks the plant material is processed before drying [82, 83, 96]. Hager's Handbuch describes that after harvest, the rhizomes are cooked for a short time or heated with hot water [41-43]. The Indian and Japanese Pharmacopoeias also describe the 'curing', consisting of boiling and (sun) drying of the rhizomes as well as identification by different color reaction tests. The Chinese Pharmacopoeia mentions: collection of rhizomes, washing, boiling or steaming, cutting in thick slices, sun drying and separation from roots [101].

Max Wichtl's Herbal Drugs mentions that the yellowish brown color of the herbal substance is due to the steaming or scalding treatment after harvesting [33].

As pharmacological and (pre)clinical studies do not contain any data on the pretreatment of the plant material, and research data on the scalding effect are missing, the impact of the scalding treatment on the active compounds c.q. efficacy of *C. longa* preparations remains unclear. The scalding treatment is considered to be a traditional procedure mainly for food purposes.

- Herbal preparation(s)

The following herbal preparations are mentioned in literature: Powdered *C. longa* rhizome [17, 83, 87, 96]; Ethanolic (80%) extract [18], [19]-[27]; Aqueous extract: [28, 290]; Ointment: 0.5% [30]; Tincture (1:10) [17]; Paste: turmeric powder in petroleum jelly [31], or a mix of turmeric powder neem leaves (*Azadirachta indica*) [32]; Oil: 3-5.5% [33]; Oleoresin powder: 40% [34] and Essential oil: 70% (w/w) [34].

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable

## 1.2. Search and assessment methodology

The database that have been searched for relevant information on toxicological, pre-clinical and clinical data are EMBASE, PUBMED, TOXNET. Search terms were '*Curcuma longa*', 'curcuma' and 'curcumin' and date until 2016.

For information on traditional use herbal books in EMA library, containing herbal compendia and monographs were searched for '*Curcuma longa*'.

## 2. Data on medicinal use

### 2.1. Information about products on the market

#### 2.1.1. Information about products on the market in the EU/EEA Member States

##### Information on medicinal products marketed in the EU/EEA

**Table 1:** Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Dry extract (13-25:1) Extraction solvent: ethanol 96%	WEU: Dyspeptic complaints, particularly based on functional affections of the biliary tract  TU: Traditional used to promote the digestion	WEU: > 12 years, 90-162 mg daily: 1 tablet (30 mg/tablet), 3-5 times daily  or 1 capsule (81 mg/capsule), 2 times daily  TU: > 12 years, 40.5 mg daily: 1 capsule (13.5 mg/capsule), 3 times daily	WEU, Germany, at least from 1976 to 2011  WEU, Germany since 1976 TU, Germany, at least from 1976 to 2011
Dry extract (5.5-6.5:1) Extraction solvent: ethanol 50%	Symptomatic treatment of mild digestive disturbances due to biliary dysfunction	> 18 years 1-2 tablets (100 mg/tablet) 2 times daily	Spain Authorised in 2002, not specified
Tincture (1:5) Ethanol 70% v/v	treatment of mild digestive disturbances and minor biliary dysfunction	TU: > 18 years: 10 ml once daily or 5 ml in 60 ml water 3 times daily  TU: 12-18 years: 5 ml in 60 ml water once daily	TU, Poland Authorised in 1977

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

### **Information on relevant combination medicinal products marketed in the EU/EEA**

Member state: Belgium

Product: Boldic, coated tablet, containing *C. longa* 148.0 mg /Hyoscyamine Sulfate 0.02 mg /Boldine 1.0 mg/ Bovine Gall, depurated extract 50.0 mg.

Indication/posology: unknown

On the market: since 1962-1981

Product: Hepatoum, oral solution containing *C. longa* 1.5 mg/ml, Chloroform 1.25 mg/ml, Menthae Essential Oil 0.1 mg/ml, *Anemone Nemorosa* 1.5 mg/ml

Indication: traditional used to facilitate the elimination of bile

Posology: unknown

On the market: since 1961/1983

Product: *Tisane du Dr Ernst n 7*, herbal tea containing *C. longa* 78.67 mg/g/Greater Celandine 49.26 mg/g, *Marrubium Vulgare* L. 75.0 mg/g/Senna (Leaf) 122.05 mg/g, Peppermint Leaf 166.91 mg/g, Taraxacum Herbs 122.05 mg/g, Barberry 34.55 mg/g, Birch Tar 75.0 mg/g, Boldo 78.67 mg/g, Achilleae Millefolli Herba 83.08 mg/g, Agrimony 78.67 mg/g

Indication: normal working of the digestive system and support of the bile ducts

Posology: 5 – 10 drops three times daily

On the market: since 1969

Member state: Czech Republic

Product: *Cholagol*, WEU authorisation, oral drops containing Frangula emodinum 9 mg, Curcuma rhizomatis pigmenta 22.5 mg, Magnesii salicylas 100 mg, Eucalypti aetheroleum 1926 mg, Menthae piperitae aetheroleum 3600 mg, Levomentholum 9mg/10 ml.

Indication: cholelithiasis, chronic cholecystitis, dyspeptic disorders in chronic hepatitis and after surgery in biliary duct

Posology: 5 – 10 drops three times daily

On the market: since 1969

Member state: Denmark

Product name: *Kissinge* tablets and pills, combination products with 10 active substances

Indication: as laxative



On the market: at least between 1956 and 1993 (Agency has no further info on (these) food supplements)

Member state: Slovakia

Product: WEU authorisation, oral drops containing, Curcuma rhizomatis pigmenta 22.5 mg, Magnesii salicylas 100 mg, Menthae piperitae aetheroleum 3600 mg, Eucalypti aetheroleum 1926 mg, Frangula emodinum 9 mg.

Indication: cholelithiasis, chronic cholecystitis, and dyspeptic disorders.

### Information on other products marketed in the EU/EEA

Dried *C. longa* rhizome powder is a very common dietary spice and is marketed as health product and food supplement under Food Law, either as single component or in combination products. No information on non-medicinal use was collected.

### 2.1.2. Information on products on the market outside the EU/EEA

Not Applicable

### 2.2. Information on documented medicinal use and historical data from literature

**Table 2:** Overview bibliographic information on historical oral use in EU

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form	Reference
<b>Powdered herbal substance</b>	stomach and liver complaints (hepatitis)	1.5-3.0 g daily	Hagers handbuch by Hänsel <i>et al.</i> , 1992 [44]
	Cholagogum and cholericum; Stomach and liver disorders		Schneider, 1974 [38] Refers to presence in German pharmacies 17 <sup>th</sup> and 18 <sup>th</sup> century
<b>Comminuted herbal substance</b>	Dyspeptic complaints	0.5-1 g, 2-3 times daily as such or as infusion (in 150 ml boiling water)	Hagers handbuch by Hänsel <i>et al.</i> , 1992 [44] Refers to literature dating from 1970
	Liver and gall disorders	Daily 22-25 g fresh rhizome as infusion (in 500 ml boiling water) or 8-10 tablets (0,125 g dried rhizome)	Madaus, 1979 [40] Original publication in 1938

<b>Herbal preparation</b>	<b>Documented Use / Traditional Use</b>	<b>Pharmaceutical form</b>	<b>Reference</b>
	Liver, gall and stomach disorders		Hoppe, 1943 [39] Refers to DAB Erg.B 1941
	Stomach and liver complaints (hepatitis)		Hagers handbuch by Reichert, 1949 [42]
	Stomach and liver complaints (hepatitis)		Hagers handbuch by List, 1973 [43]
	Dyspeptic complaints; coloring agent for foods	0.5-1 g for tea	Hiller and Melzig [37] Publication year unknown
	Stimulates stomach and gall production	Rhiz. Curcuma conc. 200,0 D.S. boil 1 spoon with 1 glass water, 3 times daily	Weiss, 1974 [36]
	Cholagogum and cholericum; Stomache and liver disorders		Schneider, 1974 [38] Refers to German pharmacies 17 <sup>th</sup> - 19 <sup>th</sup> century, and DAB 1930
	Dyspeptic complaints	1.5-3 g of drug; equivalent preparations	German Com E 1985/1990 [82]
	Dyspeptic complaints	Oral, 1.5-3.0 g	Hagers handbuch by Hänsel <i>et al.</i> , 1992 [44] Refers to literature dating from 1970
<b>Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 70% v/v</b>			
	Dyspeptic complaints	10-15 drops in water, 3 times daily	Hagers handbuch by Hänsel <i>et al.</i> , 1992 [44] Refers to literature dating from 1970
<b>Tincture (ratio of herbal substance to</b>			

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form	Reference
extraction solvent 1:5), ethanol 70% v/v			
	Dyspeptic complaints and coloring agent	Refers to maceration of powder with alcohol	Hagers handbuch by Reichert, 1949 [42]
	Dyspeptic complaints	3 times daily 10-15 drops in some water	Hagers handbuch by Hänsel <i>et al.</i> , 1992 [44] Refers to literature dating from 1970

### Information on period of medicinal use outside the European Union

#### Experience with *C. longa* in traditional medicinal systems outside the EU

In many Asian countries the use of turmeric has a long tradition as a food spice, colorant and medicine.

#### China, Japan, Korea, Vietnam, Nepal

Turmeric is used extensively in traditional Chinese medicine. It is official in the Pharmacopoeia of the People's Republic of China as well as in the Japanese Herbal Medicines Codex (JSHM, 1993) and is used in these countries and Korea for a range of indications including abdominal fullness, kidney pain, and amenorrhea. In China an aqueous decoction dosage form is ingested orally and applied topically [102].

#### India

Turmeric is used extensively in the Indian systems of medicine (Ayurvedha, Unani, and Siddha) and is official (Haridra) in the Ayurvedic Pharmacopoeia of India (API, 1989). In Ayurvedic medicine turmeric has a long history of use as an anti-inflammatory drug for arthritis. In both the Ayurvedha and Siddha systems of medicine, turmeric paste is used topically to treat ulcers and scabies.

The Swami Prakashananda Ayurveda Research Centre lists as indications for turmeric: urticaria and skin allergy, viral hepatitis, inflammatory conditions of joints, sore throat and wounds [102].

### 2.3. Overall conclusions on medicinal use

Both historical data on medicinal use and actual marketing information confirm that *C. longa* has a longstanding use for the relief of several dyspeptic complaints.

**Table 3:** Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Powdered herbal substance	Stomache, dyspeptic complaints	1.5-3.0 g daily	Since 1970 (cited in Hagers handbuch by Hänsel <i>et al.</i> , 1992)

<b>Herbal preparation Pharmaceutical form</b>	<b>Indication</b>	<b>Posology, Strength</b>	<b>Period of medicinal use</b>
Comminuted herbal substance as infusion	Liver, gall and stomache disorders;	0.5-1 g in 150 ml boiling water, 2-3 times daily	Since 1970 (cited in Hagers handbuch by Hänsel <i>et al.</i> , 1992)
Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent: ethanol 70% v/v	Dyspeptic complaints	10-15 drops (0.5-1 ml), 3 times daily	Since 1970 (cited in Hagers handbuch by Hänsel <i>et al.</i> , 1992)
Dry extract (13-25:1) Extraction solvent: ethanol 96%	Dyspeptic complaints, particularly based on functional affections of the biliary tract	tablet 30 mg, 3 times daily	At least from 1976 to 2011 (Germany)
	Dyspeptic complaints, particularly based on functional affections of the biliary tract	capsule 81 mg, 2 times daily	Since 1976 (Germany)
	Traditional used to promote the digestion	capsule 13.5 mg, 3 times daily	At least from 1976 to 2011 (Germany)
Dry extract (5.5-6.5:1) Extraction solvent: ethanol 50%	Symptomatic treatment of mild digestive disturbances due to biliary dysfunction	100-200 mg, 2 times daily	Since 2002 (Spain)
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 70% v/v	treatment of mild digestive disturbances and minor biliary dysfunction	10 ml once daily or 5 ml in 60 ml water, 3 times daily	Since 1977 (Poland)

All herbal preparations mentioned above except, the dry extract (5.5-6.5:1) have been in medicinal use for 30 years or more according to literature and information provided by Member States. The dry extract was already included in the monograph which was published in 2009. It was decided to maintain this herbal preparation in the monograph because the extraction solvent and the posology is in the range of the other preparations listed in the monograph; e.g. daily intake of corresponding herbal substance is 1.1-2.3 g, posology of the comminuted herbal substance is 1.5-3 gr.

### 3. Non-Clinical Data

#### 3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

##### 3.1.1. Primary pharmacodynamics

###### Extracts

###### In vivo:

In a study of Najafzadeh *et al.* (2011) choleric effect, the bile accumulation in gall bladder of mice, was compared between aqueous extract of *C. longa* and calcium channel blocker Verapamil. This animal model is approved and used for evaluation and screening pharmacological effect of agents on bile production or secretion. The mice were divided in 3 groups. Saline was administrated in group 1, an aqueous suspension of *C. longa* and Verapamil was orally administrated in groups 2 and 3 respectively. One hour after drug administration, the mice were euthanized and gall bladder was immediately removed. Verapamil as well as *C. longa* significantly increased the accumulation of bile in gall bladder in comparison to saline. Similar action on bile secretion (possibly via p-glycoprotein) was observed by Verapamil and *C. longa* [121].

###### Single substance curcumin:

###### In vivo:

Siegers *et al.* (1997) observed that intravenous application of curcumin or bis(desmethoxy)curcumin to rats at a level of 25mg/kg bw, the bile flow increased by 8- and 120%, respectively after a period of 2 hours; the authors concluded that the observed effect on bile secretion was due to the presence of curcumin [97].

**Table 4:** Overview of the main non-clinical data/conclusions

<b>Herbal preparation tested</b>	<b>Posology</b>	<b>Experimental model</b>	<b>Reference</b>	<b>Main non-clinical conclusions</b>
<i>C. longa</i> aqueous extract (600 mg powder of <i>C. longa</i> in 10 ml water)	0.5 ml extract oral administration	<i>In vivo</i> bile accumulation in gall bladder of mice	Najafzadeh <i>et al.</i> 2011	<i>C. longa</i> significantly increased the accumulation of bile in gall bladder in comparison to saline, similarly to Verapamil
Curcumin or bis(desmethoxy)curcumin	25mg/kg bw i.v.	<i>In vivo</i> In rats	Siegers <i>et al.</i> 1997	bile flow increase by 8- and 120%, respectively after a period of 2 hours

### 3.1.2. Secondary pharmacodynamics

#### Extracts

##### **Anti-depression**

A turmeric ethanolic extract (DER and concentration not specified) was found to prevent chronic mild stress induced increase of serum IL-6, TNF- $\alpha$ , CRF- and cortisol levels [19].

*C. longa* has antidepressant effects mediated through inhibition of monoamine oxidase A [57].

*C. longa* ethanolic extract reversed the decrease in serotonin, noradrenalin and dopamine concentrations as well as the increase in serotonin turnover, cortisol levels and the in serum corticotrophin-releasing factor [20].

##### **Diabetes**

A hexane extract (DER not specified), containing  $\alpha$ -turmerone, ethanolic extract (DER and concentration not specified), containing  $\alpha$ -turmerone, curcumin, demethoxycurcumin and bisdemethoxycurcumin and ethanolic extract from the residue of the hexane extraction (ethanol concentration not specified), containing curcumin, demethoxycurcumin and bisdemethoxycurcumin were found to dose-dependently stimulate adipocyte differentiation. The results indicate that turmeric ethanolic extract containing both curcuminoids and sesquiterpenoids is more strongly hypoglycemic than either curcuminoids or sesquiterpenoids [21].

The effect of an ethanolic extract of turmeric on blood glucose levels in type 2 diabetic KK-Ay mice and stimulated human adipocyte differentiation was investigated by Kuroda *et al.* The extract was prepared by a two time extraction of powdered turmeric, with five volumes of ethanol. The extract was concentrated under reduced pressure to give 12.2 g of ethanolic extract. In the experiment on the human adipocytes a stimulation of adipocyte differentiation was observed. The activity of 5.0  $\mu\text{g/ml}$  and 10.0  $\mu\text{g/ml}$  ethanolic extract was more potent than that of 0.22  $\mu\text{g/ml}$  and 0.44  $\mu\text{g/ml}$  of troglitazone, which was therapeutically used as anti-diabetic and anti-inflammatory drug in humans, until it was withdrawn in 2000 for causing drug-induced hepatitis [22].

Nishiyama *et al.* studied the influence of three turmeric extracts on blood glucose levels in type 2 diabetic KK-Ay mice. The extracts used were an ethanolic extract, a hexanic extract and an ethanolic extract from the residue of the hexane extraction. The ethanolic extract and hexanic extract were obtained from powdered *C. longa* by extracting twice with five volumes of ethanol or hexane and filtration and evaporation of the solvent. The ethanolic extract from the residue of the hexane extraction was obtained using the same method. To determine the mechanism of action the extracts were tested for adipocyte differentiation. No difference in bodyweight were observed between treated and control animals. The ethanolic extract stimulated adipocyte differentiation dose-dependently. The hexanic extract and the ethanolic extract from the residue of the hexane extraction showed similar effects but at higher concentration as the ethanolic extract [21].

##### **Antifungal, antibacterial, phytotoxic, cytotoxic and insecticidal activity**

Khattak *et al.* studied the antifungal, antibacterial, phytotoxic, cytotoxic and insecticidal activity of an ethanolic extract of *C. longa* (extract preparation not specified). The extract showed antifungal activity towards *Trichophyton longifusus* and *Microsporum canis* and weak antibacterial activity against *Staphylococcus aureus*. Toxic activity was observed against *Lemna minor*.

The LD<sub>50</sub> in a brine shrimp lethality bioassay *C. longa* was 33  $\mu\text{g/ml}$ . Curcuma showed no insecticidal activity [24].

##### **Antioxidant activity in atherosclerosis**

A high-cholesterol diet given to New Zealand White rabbits leads to development of atherosclerosis in the rabbits. Rabbits given a dietary supplement of a *C. longa* extract in combination with a high-cholesterol diet showed a positive effect on the animals' antioxidant status compared to controls. Curcumin has shown to mobilize  $\alpha$ -tocopherol from adipose tissue, thus protecting their body against oxidative damage produced during the development of atherosclerosis. Also more LDL cholesterol could be transported in plasma, increasing levels of  $\alpha$ -tocopherol. Overall the fatty acids in the animals were less susceptible to oxidation in the vessel wall [48].

### **Hepatoprotective activity**

Soni *et al.* investigated the preventive effect of aqueous and alcoholic extracts of turmeric on liver damage in ducklings induced by aflatoxin. The extract was prepared by boiling 1 g of turmeric powder in 100 ml water. After concentration it was made up to 10 ml. The aqueous turmeric extract (10 mg/ml) inhibited toxin production by 99%. An alcoholic extract of turmeric showed also inhibition though on a much lower level. Turmeric and curcumin treatment showed almost complete reversal of fatty changes and necrosis induced by aflatoxin [28].

### **Myocardial apoptosis**

The effect of *C. longa* on myocardial apoptosis in experimentally induced myocardial ischemic-reperfusion injury was investigated by Mohanty *et al.* Wistar rats were fed 100 mg/kg *C. longa* once a day, for one month. *C. longa* treated rats demonstrated significant anti-apoptotic property, which might contributed to the observed preservation in cardioprotective effects and cardiac function [59].

### **Metabolic transfer through lactation**

Singh *et al.* followed dams and their suckling neonates to determine the modulatory influence of turmeric and curcumin on hepatic biotransformation system enzymes. Turmeric and curcumin induced a significant increase in hepatic levels of glutathione S-transferase (GST) and sulfhydryl (SH) levels. Cytochrome b5 and cytochrome P450 levels were significantly elevated as well. This indicates that turmeric and/or curcumin metabolites can be transferred through lactation [60].

### **Anti-ulcer and cancer related activity**

Kim *et al.* investigated the protective effect of *C. longa* ethanolic extract against gastric ulcers by blocking H<sub>2</sub> histamine receptors (H<sub>2</sub>R) of male Sprague-Dawley (pylorus-ligated) rats. The extract was prepared by fluxing 100 g *C. longa* with 80% ethanol. This was shaken at room temperature for 24 hours, this was performed twice. After extraction, the fluid was concentrated with rotary vacuum evaporator (EYELA, Japan). The ethanolic extract was dissolved in 100 ml H<sub>2</sub>O and fractionated with organic solvents, n-butanol and ethyl acetate. For *in vitro* tests the dried material was resuspended in DMSO, for *in vivo* tests the dried material was resuspended in saline. The effect of *C. longa* extract was compared to the effects of ranitidine. Curcuma was found to protect the gastric mucosal layer as effective as ranitidine. Orally administered ethanolic extract (unknown amount) inhibited gastric acid, gastric juice secretion and ulcer formation comparable to the effects of ranitidine. Curcuma also suppressed histamine-induced cAMP production, caused by direct inhibition of H<sub>2</sub> histamine receptors, curcumin however had no effect on cAMP formation [23].

Rafatullah *et al.* investigated the ulceration induced by indomethacin or reserpine administration. Hypothermic-restraint stress reduction of gastric wall mucus, was inhibited by turmeric extract treatment. Treatment with turmeric extract reduced the severity of lesions induced by various necrotizing agents. Turmeric antiulcer activity of an ethanolic extract of turmeric in inbred Wistar albino rats. The extract tested was a dried 96% ethanol extract. Administration of turmeric extract led to a significant decrease in ulcer index and acidity of stomach contents. Turmeric extract not only

increased the gastric wall mucus significantly but also restored the non-protein sulfhydryl (NP-SH) content in the glandular stomachs of the rats. [18].

### **Wound healing**

The wound healing effects of *C. longa* paste were studied in rabbits. The *C. longa* treated group showed a significant higher mean value for contraction of the wound compared to controls. Furthermore the wounds showed less inflammation and an increasing trend in the formation of collagen [31].

Single substances: curcumin(oids), ar-turmerone

### **Anti-inflammation**

Curcuminoids inhibit LOX, COX, phospholipases, leukotrienes, prostaglandins, thromboxane, nitric oxide [45, 46], elastase, hyaluronidase, collagenase, monocyte chemoattractant protein-1, interferon inducible protein, TNF and interleukin-12 [46].

Curcuminoids decrease prostaglandin formation and inhibit leukotriene biosynthesis via the lipoxygenase pathway [47].

### **Anti-depression**

The effect of curcumin was investigated in a rat chronic mild stress (CMS) model. In comparison with normal rats, rats suffering the CMS procedure have a significant lower intake of sucrose, increased IL-6, TNF- $\alpha$  levels, CRF- and cortisol levels. Treatment with ethanolic extract increased the sucrose intake to normal control levels, reduced the CMS-induced increase in serum IL-6 and TNF- $\alpha$  levels and reduced the CRF levels in serum and medulla oblongata to lower than normal. It also lowered the cortisol levels in serum to normal levels [19].

Curcumin increased brain-derived neurotrophic factor in the frontal cortex and hippocampus [19].

### **Anti-oxidant activity**

Curcumin mobilizes  $\alpha$ -tocopherol from adipose tissue, this results in protection against oxidative damage produced during atherosclerosis development. Curcumin increases VLDL cholesterol transport in plasma, which results in increasing levels of  $\alpha$ -tocopherol [48].

Curcumin was found not to be an efficient hydroxyl radical scavenger or quencher of superoxide [67].

### **Hepatoprotective activity**

Curcumin protects cells against lipid peroxidation induced by paracetamol. This may be due to the antioxidative effects of the phenolic groups of curcumin [70].

Curcumin was found to decrease serum aspartate transaminase and alkaline phosphatase activity, and free fatty acid, cholesterol and phospholipid levels. The mechanism of action is still unclear [58].

Tacrine is known for its T-cell destructive activity and hepatotoxicity. In a study with cultures of human hepatocytes, which had been destroyed by tacrine, curcumin showed to be nearly ten times more effective than the regular treatment, ascorbic acid [56]. However, a study on carbon tetrachloride toxicity in mice, performed in 1996, showed no protective effects due to curcumin administration at dosages of 200 mg per kg [65].

Donatus *et al.* investigated the effect of curcumin on the cytotoxic effect of paracetamol in rat hepatocytes. Curcumin showed no protective effect against paracetamol induced GSH-depletion in hepatocytes of 3-methyl-cholanthrene pretreated rats. Curcumin in a concentration of  $5 \times 10^{-5}$ ,  $5 \times 10^{-4}$



and  $5 \times 10^{-3}$  M protected the cells against lipid peroxidation induced by paracetamol. This effect may be due to the two phenolic groups of curcumin, which give it strong anti-oxidant effects [70].

The effect of curcumin on alcohol induced hepatotoxicity in alcoholic rats were studied by Rajakrishnan *et al.* Compared to the control group curcumin administration resulted in a decrease of serum aspartate transaminase and alkaline phosphatase activity. The levels of serum free fatty acids, cholesterol and phospholipids decreased as well [58].

### **Antiplatelet property**

The antiplatelet property of ar-turmerone was investigated. Ar-turmerone showed strong inhibitory activity against platelet aggregation mediated by collagen and arachidonic acid.

At higher concentrations curcumin showed the same effect. However, only a weak or no inhibitory effect was observed against PAF or thrombin activated platelets. The other components in the ethanolic extract showed no inhibitory effects [26].

Comparison between ar-turmerone and aspirin showed that ar-turmerone inhibited platelet aggregation induced by collagen more effective than aspirin [26].

### **Cancer related activity**

Curcumin was found to inhibit *in vitro* tumor cell growth by inhibiting expression of basic fibroblast growth factor (FGF) in breast cancer-cell cultures and the angiogenesis factors vascular endothelial growth factor (VEGF) and basic fibroblast growth factors (b-FGF) [49]. Effects of curcumin on inhibition of angiogenesis and induction of apoptosis of cancer cells was also observed [51, 50].

Curcumin was effective in squamous-cell carcinoma model. The study of Li *et al.* showed a reduced occurrence of chemically induced tumors by 50 percent [61].

Curcumin blocks cyclosporine A-resistant phorbol myristate acetate + anti-CD28 pathway of T-cell proliferation and thus may be a potential adjuvant immunosuppressive agent for the treatment of cancer [52].

Farombi *et al.* carried out a study to determine the ameliorative effects of curcumin and kolaviron (a biflavonoid from the seeds of *Garcinia kola*) on the di-n-butylphthalate (DBP)-induced testicular damage in rats [62]. The level of glutathione (GSH), the glucose-6-phosphate dehydrogenase (G6PD) activity and the decreased testosterone levels were significantly increased [62].

The increased levels of malondialdehyde (MDA) were decreased, which is in agreement with Ishihara *et al.* [62, 63]. This may be due to the intrinsic antioxidative abilities to combat oxidative damage induced by DBP [62].

Mice exposed to human prostate cancer cells were treated with curcumin. The curcumin-treated animals showed a decrease in microvessel density and cell proliferation and an increase in apoptosis compared to controls [55, 64].

Incubation of endothelial cells from bovine aorta with curcumin (in a concentration range of 5-15  $\mu$ M) showed induction of heme oxygenase expression. Heme oxygenase is an enzyme that reacts to oxidative stress, by producing the antioxidant biliverdin, and it enhances resistance to oxidative damage to cells [69].

The efficacy of curcumin or turmeric extract in reducing chemically-induced tumours in male Swiss albino mice was studied by Soudamini and Kuttan. The extract was prepared by extraction of 5 g of powdered turmeric with 100 ml acetone/methanol (45:55). The extract was filtered using filter paper. 40 mg of curcumin was dissolved in 5 ml acetone/methanol (45:55). 7,12-dimethylbenz(a)anthracene (DMBA) was used to induce tumors. Single application of curcumin or turmeric extract failed to inhibit papilloma formation. A small, non significant, reduction in papilloma formation was seen in the

turmeric extract treated group, compared to the control group. Application of both curcumin and turmeric extract during carcinogenesis and promotion resulted in less papilloma production, compared to controls. This indicates that both curcumin and turmeric extract produce their best effects during tumour promotion [66].

The effect of dietary curcumin (0.2% and 1.0%) on DMBA and 12,0-tetradecanoylphorbol-13-acetate (TPA)-promoted skin tumor formation in Swiss albino mice was investigated by Limtrakul *et al.* They found a significant lower number of papillomas in the curcumin treated group compared to the control group. The enhanced expression of ras-p21 and fos-p62 oncogenes were decreased dose dependently in the curcumin treated group [53].

Curcumin reduces the testicular damage caused by exposure to di-n-butylphthalate (DBP), by increase in Glutathion (GSH), testosterone levels and glucose-6-phosphate dehydrogenase (G6PD) activity and decrease in malondialdehyde (MDA) levels. These effects may be due to intrinsic antioxidative abilities of curcumin [54-55]. Dietary curcumin was found to inhibit DMBA- and TPA-induced expression of ras-p21 and fos-p62 oncogenes [56].

### **Anti-mutagenic activity**

Nagabhushan *et al.* tested curcumin against tobacco products and several environmental mutagens in a Salmonella/microsome test with or without Aroclor 1254-induced rat liver homogenate (S-9 mix), in order to determine the difference between mutagens which require metabolic activation and those who do not. Curcumin inhibited the mutagenicity of bidi smoke condensate, cigarette smoke condensate and masher (a tobacco product) and tobacco extracts in a dose-dependant manner. Curcumin is only antimutagenic against mutagens which require metabolic activation [68].

### **Diabetes**

Arbiser and Okamoto *et al.* reported that curcumin reduces the destructive angiogenesis associated with diabetic retinopathy [54, 55].

### **Stress**

Xu *et al.* investigated the effect of orally administered curcumin on behavior in a chronic stress model of depression in rats. The molecular targets of curcumin were studied as well. The antidepressant imipramine was used as a positive control. Chronic curcumin administration (at 10 mg/kg) showed similar effects as imipramine. These findings suggest that the effects of chronic administration of curcumin on the behavior of chronic stressed rats may be related to the modulating effects of the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, through selective increase in brain-derived neurotropic factor in the frontal cortex and the hippocampus of the rats [20].

### **3.1.3. Safety pharmacology**

No data available.

### **3.1.4. Pharmacodynamic interactions**

The poor bioavailability of curcumin if applied as single component is well known and described in literature. However regarding the complex composition of herbal preparations and the interplay of the many constituents (actions of synergy and inhibition), adequate general conclusions on pharmacodynamic interactions after intake of curcuma (extracts) cannot be drawn.

### 3.1.5. Conclusions

For curcumin the studied amounts after oral application are many times higher than the human daily posology used in traditional herbal medicinal products. Based on this finding it is not likely that a significant effect of curcumin on human bile secretion is obtained at doses traditionally used.

### 3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

#### Curcumin

##### **Absorption and bioavailability**

In rodents, curcumin demonstrates poor systemic bioavailability, because of poor absorption by the gastrointestinal tract and rapid metabolism. Oral administration of a single dose of 2 g of curcumin to rats resulted in very low concentrations in plasma (less than 5 µg/ml) indicating a poor absorption from the gut [119]. After oral administration of curcumin to rats at 1 g/kg bw about 75% was excreted in the faeces and only traces in the urine; concentrations in plasma and bile were negligible. Blood levels of less than 5 µg/ml indicate poor absorption from the gut [130, 120].

Oral administration of radio-labelled curcumin to rats resulted in radioactivity being found only in the liver and kidneys [124, 125]. Curcumin administered intravenously was excreted in the bile [72]. 3H-labelled curcumin administered orally to rats at 0.6 mg/kg led to faecal excretion of about 89% of the radioactivity in 72 hours; about 6% was excreted in the bile. After intraperitoneal administration about 73% of the radioactivity was excreted in the faeces and about 11% in the bile [111]. When a single 400 mg dose of curcumin was administered orally to rats about 60% was absorbed and 40% excreted unchanged in the faeces over an period of 5 days. No curcumin could be detected in urine and only traces were found in the portal blood, liver and kidney [124].

Recently research has focussed on the preparation of nanocurcumin because it has a better solubility than curcumin and therefore a better bioavailability [128]. Also fytosome-curcumin in which curcumin is linked to phosphatidylcholine has been observed to result in a better bioavailability and activity after oral application in rats [118, 127].

##### **Metabolism**

After p.o. dosing, curcumin undergoes metabolic O-conjugation to curcumin glucuronide and curcumin sulfate and bioreduction to tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol in rats and mice *in vivo* and in suspensions of human and rat hepatocytes [112].

Studies with isolated perfused rat liver and isolated rat intestine suggested initial metabolism of curcumin in the intestine, producing easily absorbable metabolites, and intensive second metabolism in the liver. Major metabolites were glucuronides of tetrahydrocurcumin and hexahydrocurcumin, with dihydroferulic acid and traces of ferulic acid as further metabolites, all of which were excreted in the bile [72, 124].

LC-MS analysis of plasma after oral administration of curcumin to rats showed that the predominant metabolites were glucuronide and glucuronide-sulphate conjugates, which reached maximum plasma concentrations about 1 hour after administration [104].

There is increasing evidence that in rodents and humans the intestinal tract substantially contributes to the overall metabolite yield. Metabolism of curcumin to curcumin glucuronide, curcumin sulfate, tetrahydrocurcumin, and hexahydrocurcumin was demonstrated in intestinal fractions from humans and rats, and its conversion to curcumin sulfate was demonstrated *in situ* in intact rat intestine [112].

Certain curcumin metabolites, such as tetrahydrocurcumin, possess anti-inflammatory [103] and antioxidant activities [105, 126]. similar to those of their metabolic progenitor.

Metabolism also appeared to be rapid *in vivo*. After intravenous dosing more than 50% of the dose was excreted in the bile within 5 h. This finding was interpreted as evidence in support of the hypothesis that curcumin undergoes biotransformation during absorption in the intestinal tract and enterohepatic recirculation [125]. Major metabolites included the glucuronides of tetrahydrocurcumin and hexahydrocurcumin, with dihydroferulic acid and ferulic acid present as minor metabolites [111].

### **Drug Interactions**

Interactions between curcumin and other phytochemicals have been observed. When healthy human subjects took a 2 g dose of curcumin in combination with 20 mg of piperine, extracted from black pepper, the bioavailability of curcumin increased twenty-fold compared to subjects who took only 2 g of curcumin [94].

Curcumin is a potent inhibitor of cytochrome P450 (CYP 2C9 and CYP3A4) and a moderate inhibitor of CYP2B6, CYP1A2 and CYP2D6, with IC<sub>50</sub> values ranging from 4.3 to 50.3 µM (Appiah-Opong *et al.* 2007). These CYPs are responsible for the hepatic metabolism of about 80% of drugs currently on the market and notably CYP3A4 is also abundant in the intestine. The inhibitory activity of curcumin towards CYP3A4 may well have implications for drug-drug interactions in the intestine, rather than in the liver when the intestines are exposed to high concentrations upon oral ingestion together with drugs metabolised by this enzyme. Curcumin is also a potent inhibitor of the three major human glutathione S-transferases (GSTs), i.e. GSTA1-1, GSTM1-1 and GSTP1-1. Curcumin is also an inhibitor of the bile acid transporter P-glycoprotein 1 (P-gp). The IC<sub>50</sub> value is in the range of 50 -100 µM (Aurade *et al.*, 2010). After the combined oral application of 4 g curcuminoids and 24 mg piperine to healthy volunteers in a randomised placebo-controlled crossover study no effect on the metabolism of midazolam, flurbiprofen or paracetamol was observed, indicating that a clinically significant interaction is not likely [130].

### **Assessor's comment:**

Curcumin demonstrates poor systemic bioavailability, because of low solubility and poor absorption by the gastrointestinal tract and rapid metabolism, which already starts in the intestinal mucosa. Secondary metabolism occurs in the liver.

The observed interactions of curcumin with other herbs is not considered relevant for the traditional use of *C. longa*, while the maximum daily dose of curcumin is much lower than the dose for which interactions have been observed. Therefore it is not likely that interactions will occur during the use of the traditional herbal products as described in the monograph.

## **3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof**

### **3.3.1. Single dose toxicity**

#### Extracts:

The study of Majeed *et al.* revealed that a single feeding of 30% turmeric diet to rats had no toxic effects [71].

#### Single substance Curcumin:

The oral median lethal dose (LD<sub>50</sub>) of curcumin in mice is higher than 2.0 g/kg bw [113]. Single oral doses of curcumin at 1-5 g/kg bw induced no toxic effects in rats [72].

Donatus *et al.* observed curcumin to be moderately cytotoxic *in vitro*, inducing slightly increased LDH-leakage from rat hepatocytes, accompanied by an increase in GSH-depletion [70].

### 3.3.2. Repeat dose toxicity

#### Extracts:

In a subchronic toxicity study liver toxicity had been reported, but most of these incidents involved large dietary doses (turmeric 0.2%, 1.0%, 5.0%) or turmeric ethanolic extract 0.05%, 0.25%) given to mice or rats. In mice fed for 14 days with a diet containing 1% and 5% turmeric hepatotoxicity was observed. Rats fed with turmeric 1% for the same period showed no adverse effect. The rats fed turmeric at a dose of 5% of their diet for a period of 90 days showed a reduction in body weight gain and hepatotoxicity [25, 76].

#### Single substance Curcumin:

Gastric ulceration was observed after oral administration of curcumin to rats at 100 mg/kg bw for 6 days; but not at 50 mg/kg bw [1094]. For the national toxicity programme (NTP) long-term (103-weeks) dietary exposure studies were performed in rats and mice. Based on the findings in rats the NOEL for gastrointestinal irritation (ulcers, hyperplasia and inflammation) was established at 440 mg curcumin/kg/day. In mice, there were absolute and relative increases in liver weights after 15 months of treatment, with a NOEL of 220 mg/kg/day [122]. Based on these results and reckoned with a safety factor of 200, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established at its 44<sup>th</sup> meeting the temporary ADI to 0–1 mg/kg for human, pending submission of the results of a study on reproductive toxicity [115, 116].

### 3.3.3. Genotoxicity

#### Extracts:

No effects on chromosomal damage, pregnancy rate, number of dead embryos, total implants and mutagenic effects were observed in mice fed with turmeric (0.5%) or curcumin (0.015%) [75].

#### Single substance Curcumin:

#### ***In vitro***

Curcumin showed no mutagenic potential in the Ames test, in *Salmonella typhimurium* strains TA1535, TA100 and TA98, with or without metabolic activation [117].

No mutagenic effects were found in the Ames tests for curcumin and turmeric extracts (information on preparation could not be found) [74].

No mutagenic activity was demonstrated in bacteria treated with curcumin preparations of purity up to 85%, or of unknown purity. A 79-85% purity preparation induced chromosomal aberrations and sister chromatid exchanges *in vitro* [114].

Donatus *et al.* found curcumin to be moderate cytotoxic. At a concentration of  $5 \times 10^{-3}$  curcumin slightly increased LDH-leakage from rat hepatocytes. This increase was accompanied by an increase in GSH-depletion, which can result in increased susceptibility to cytotoxicity [70].

#### ***In vivo***

Curcumin given to mice at 0.015% of their diet for 12 weeks induced no genotoxic effects as measured by the incidence of micronucleated polychromatic erythrocytes and chromosomal aberrations in bone marrow cells [75]. *In vivo*, a curcumin preparation of unknown purity administered to mice by

intraperitoneal injection did not induce micronuclei in bone marrow cells, whereas a low level of chromosomal aberrations was reported in the same cell population [114]. In another *in vivo* study in mice injected i.p. with curcumin of unknown purity, there was some evidence of sister chromatid exchanges induction at low frequency above 25 mg/kg, while in rats fed curcumin of unknown purity there was equivocal evidence for the induction of chromosomal aberrations [108].

Based on these data, the JECFA concluded that there was no adequate evidence for the genotoxicity of curcumin. In reaching this conclusion, the sister chromatid exchange data in particular was considered to be of little relevance in the evaluation, while other studies could not be reliably interpreted because of the impurities in the curcumin preparations used [115, 116].

### **3.3.4. Carcinogenicity**

#### Extracts:

No data available.

#### Single substance Curcumin:

Curcumin is considered to be not carcinogenic (JECFA) [115, 116]. Long-term (103-weeks) carcinogenicity studies have been performed in mice and rats, fed ad libitum diets containing 0, 2000, 10.000 or 50.000 mg/kg turmeric oleoresin (79%-85% curcumin). These doses were equal in males/females to daily doses of 0, 220/320, 1520/1620 or 6000/8400 mg turmeric oleoresin/kg in mice and to 0, 80/90, 460/440 or 2000/2400 mg turmeric oleoresin /kg/day in rats. These results showed marginal increases in hepatocellular adenomas and carcinomas in mice and in clitoral gland adenomas in rats. These effects were not considered to be treatment related and it was concluded that curcumin is not carcinogenic [122].

### **3.3.5. Reproductive and developmental toxicity**

#### Extracts:

No data available.

#### Single substance Curcumin:

The reproductive toxicity of curcumin, was studied in Wistar rats [107]. It was concluded that the no observed adverse effect level (NOAEL) for reproductive toxicity of curcumin, fed in the diet for two successive generations to rats in this study was 847 and 959 mg/kg bodyweight (bw) per day for male rats and 1043 and 1076 mg/kg bw for females for F0 and F1 generations, respectively. This study was the final toxicology study on curcumin reviewed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at the 61st Meeting, 2003. The JECFA group considered that the small body weight reduction in the F2 pups of the highest dose group prevented this from being regarded as a no adverse effect level, and so allocated an ADI for curcumin of 0–3 mg/kg bw based on the intake of 250–320 mg/kg bw in the mid-dose group as the NOEL [115, 116].

There is one report indicating that rats fed high doses of turmeric (4 g/kg/d) or curcumin (0.4 g/kg/d) for 14-21 days can pass sufficient quantities of these compounds (or their metabolites) into milk to cause the induction of hepatic enzymes in exposed offspring [60].

### **3.3.6. Local tolerance**

No data available

### **3.3.7. Other special studies**

The finding that curcumin can cause gastrointestinal irritation (ulcers, hyperplasia and inflammation) has been shown at doses of 100 mg/kg bw [109] and therefore is not relevant for the daily doses of curcumin that are contained in the products that are described in the monograph (maximum daily dose is 200 mg curcumin and 3.33 mg/kg bw), therefore no warning is taken up for individuals with gastrointestinal diseases (peptic ulcer disease, ulcerative colitis, Crohn's).

### **3.3.8. Conclusions**

In absence of toxicological data on the herbal substance and only one report on single dose toxicity on rats fed with 30% turmeric diet, which showed no toxic effects, data on the constituents can give an indication about the safety of the herbal product. The constituents do not appear to be toxic or mutagenic in traditional use doses. No reproductive toxicity has been observed. However because it is known that curcumin and/or metabolites are transferred to sucklings via lactation it is not recommended to use *Curcuma longa* or preparations thereof during breastfeeding. For curcumin an ADI of 0-3 mg/kg bw has been established. The maximum daily dose in the monograph is 200 mg curcumin. For an adult of 60 kg this means 3.33 mg/kg bw, and therefore the proposed human traditional use dose can be used safely.

The finding that curcumin can cause gastrointestinal irritation (ulcers, hyperplasia and inflammation) has been shown in rats at doses of 100 mg/kg bw [109] and therefore is not relevant for the daily doses of curcumin that are contained in the products that are described in the monograph (maximum daily dose is 200 mg curcumin and 3.33 mg/kg bw), therefore no warning is taken up for individuals with gastrointestinal diseases (peptic ulcer disease, ulcerative colitis, Crohn's).

### **3.4. Overall conclusions on non-clinical data**

The primary pharmacodynamic data presented supports the proposed traditional use indication: "Traditional herbal medicinal product used for the relief of symptoms of digestive disturbances such as feelings of fullness, slow digestion and flatulence".

A warning is taken up that the use of the product is not recommended in case of biliary obstruction and other liver function disorders. For curcumin an ADI of 0-3 mg/kg bw has been established. The maximum daily dose in the monograph is 200 mg curcumin. For an adult of 60 kg this means 3.33 mg/kg bw, and therefore the proposed human traditional use dose can be used safely.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have mainly been performed with curcumin, and not with the herbal substance. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Union suggest that there is a high risk associated with the use of *C. longa* preparations. In absence of reproductive toxicity, genotoxicity and carcinogenicity data, a list entry cannot be recommended from a non-clinical point of view.

## **4. Clinical Data**

### **4.1. Clinical pharmacology**

#### **4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

No data available

#### **4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

Curcumin

In a small study observing the influence of curcumin on blood lipids with 10 healthy volunteers was found that oral intake of 500 mg/day curcumin for 7 days resulted in a significant decrease in the level of serum lipid peroxides (33%) and increase in HDL cholesterol (29%) and a decrease in level of total serum cholesterol (12%) [101].

After oral administration the bioavailability of curcumin was estimated to be 65% [27].

In a Phase I clinical study, low systemic bioavailability following oral dosing has been demonstrated. Efficient first-pass metabolism and some degree of intestinal metabolism, particularly glucuronidation and sulfation of curcumin, might explain its poor systemic availability when administered via the oral route. A daily oral dose of 3.6 g of curcumin is compatible with detectable levels of the parent compound in colorectal tissue (7-20 nmol/g). There appears to be negligible distribution of the parent drug to hepatic tissue or other tissues beyond the gastrointestinal tract [129, 110].

In another Phase I clinical trial, patients with high risk or pre-malignant lesions were treated with curcumin for 3 months. The serum concentration of curcumin usually peaked at 1 to 2 hours after oral intake of curcumin and gradually declined within 12 hours. The average peak serum concentrations after taking 4-8 g of curcumin were 0.51-1.77 µM, respectively. Urinary excretion of curcumin was undetectable [80]. The levels demonstrated might be sufficient to exert pharmacological activity.

##### **Assessor's comment:**

The amounts of curcumin that were tested in these studies (4-8 g of curcumin) exceed by far the theoretical maximal amounts of curcumin on the basis of literature values in the products containing *C. longa* L. that are mentioned in the monograph (estimated maximum daily dose of curcumin is 200 mg).

## **4.2. Clinical efficacy**

### **4.2.1. Dose response studies**

Curcuma longa (preparations)

No data available

Curcumin

In a randomised, single-blind, three phase, cross-over study on 12 healthy volunteers the effect of different dosages of curcumin on the gall bladder contraction was measured against placebo (amylum) over an observation time of 2 hours. Dosages of 20-80 mg curcumin were taken orally. A dosage of 40 mg produced 50% decrease in the volume of the gall bladder, indicating an increase in the contraction of the gall bladder, 2 hours after intake. No side effects were reported by the participants in this study [123].

### **4.2.2. Clinical studies**



**Table 5:** Clinical studies on humans, in dyspeptic disorders, and other applications with *C. longa* preparations (herbal substance or extract)

Type (aim)	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
<b>Dyspeptic disorders</b>							
Thamlikitkul <i>et al.</i> 1989 <i>Effect of turmeric on dyspepsy compared to traditional treatment</i> [100]	MC R P DB <sup>1</sup> 3-arm, 7 days	2 g powder of dried turmeric rhizome (2 x 250 mg capsules 4 times) or traditional treatment 'Flatulence'	116	patients with dyspepsia (acid / flatulent /atonic)	Response: Placebo: 53%, Flatulence: 83%, <i>C. longa</i> : 87% improvement of symptoms, compliance & acceptance		only placebo controlled trial with <i>C. longa</i> ; very little information on the medical protocol used; no information on blinding of the clinical assessors; no difference was observed with regard in the patient's satisfaction. Comparator is not a standard treatment
Prucksunand <i>et al.</i> , 2001 <i>Effect of C. longa on peptic ulcer</i> [78]	Phase II, uncontrolled 4 weeks	2 capsules of 300 mg turmeric, 5 times daily oral intake 4 weeks	45 (24 males, 21 females) Age: 16-60 y	Patients with peptic ulcers / symptoms indicating peptic ulcers	Abdominal pain and discomfort subsided in 1 <sup>st</sup> and 2 <sup>nd</sup> week, no significant changes in blood chemistry		Methodological shortcomings (e.g. baseline, not all patients endoscoped)
Häringer, 2004 <i>Effect of turmeric on functional dyspepsy</i> [98]	MC <sup>1</sup> observational study	2.8 g (2 tablets of 81 mg dry extract (DER13-25:1), extraction solvent	221	patients with functional dyspepsy (Rome II criteria)	154 patients finished trial; after 6 weeks 33%, after 12 weeks 54% less		No Placebo, subjective assessments; Methodological shortcomings

Type (aim)	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		ethanol 96 % (v/v)			symptoms		
Kammerer & Fintelmann, 2001 <i>Effect of turmeric in dyspeptic disorders</i> [99]		2 tablets of 81 mg dry extract (DER13-25:1), extraction solvent ethanol 96 % (v/v)  Oral use  28 days	440	patients with dyspepsy, functional disorders of bile ducts	64% reduction of symptoms; 36% of patients symptom free; 56% continued treatment; 7% ended prematurely, for no relief		No Placebo, subjective assessments; Methodological shortcomings
Bundy <i>et al.</i> , 2004 <i>Role of turmeric extract in IBS</i> [45]	Pilot study, partially blinded  R <sup>1</sup> two-doses,  8 weeks	1 or 2 tablets of 72 mg standardised turmeric extract (no details)  Oral use  8 weeks	207	volunteers selected with Rome II criteria	IBS prevalence reduced in both groups, significant reduction in abdominal pain / discomfort score by 22% and 25% in 1- tablet and 2- tablets groups resp., symptoms improved, no significant differences between groups		No data on preparation, no placebo
<b>Skin disorders</b>							

Type (aim)	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Kuttan <i>et al.</i> , 1987 <i>Turmeric paste in wound healing</i> [30]		Ethanol extract of <i>C. longa</i> (not specified) / ointment of curcumin  Topical use	62	Patients with external cancerous lesions	Reduction in smell (90% of cases),  Reduction of itching (all cases), dry lesions (70% of cases), reduction in lesion size and pain (10% of cases)		No details on study, formulation, application
<b>Urinary excretion of mutagens</b>							
Polasa <i>et al.</i> , 1992 <i>Effect of turmeric on urinary mutagens in smokers</i> [77]	Uncontrolled  30 days	2 tablets of 750 mg turmeric  oral use  30 days	22	normal men (16 chronic smokers, 6 non-smokers)	Urine testing after 0,15, 30 days, biochemical parameters, and mutagenicity assay revealed reduction of urinary excretion of mutagens in smokers		Turmeric administration may reduce the genotoxicity of tobacco mutagens. Clinical relevance is not clear.

<sup>1</sup> R = randomised P = placebo-controlled DB = double blind MC = multi centre CO = cross-over

**Table 6:** Clinical studies on humans, with curcumin.

Type (aim)	Study Design	Test Product(s):	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Comments
Soni and Kuttan, 1992 <i>Effect of oral curcumin on serum peroxides and cholesterol levels</i> [101]	Uncontrolled; 7 days	500 mg curcumin Oral use 7 days	10	Healthy volunteers	Decrease serum lipid peroxides (33%), increase in HDL cholesterol (29%), decrease in total serum cholesterol (12%)		Follow-up study needed of curcumin as preventive substance against arterial diseases
Rasyid and Lelo, 1999 <i>Effect of different curcumin dosages on human gall bladder</i> [81]	R DB P CO <sup>1</sup>	20 mg curcumin / placebo (amylum) Oral use Wash-out period: 1 week	12 Age: 24-48 y Weight: 45-65 kg Length: 150-168 cm	Healthy volunteers	Significant reduction of gall bladder volume after 0.5 h-2.0 h: 12-29%, respectively	Student's <i>t</i> -test analysis	Further dose-responding studies needed to find optimal dose of curcumin to induce 50% contraction
James, 1996 <i>Antiviral effect of curcumin</i> [89]		Curcumin Oral intake 8 weeks	40	Aids patients	No evidence that curcumin reduced viral load		

<sup>1</sup> R = randomised P = placebo-controlled DB = double blind MC = multi centre CO = cross-over

**Table 7:** Clinical studies on humans, in other indications with *C. longa* containing combination preparations

Type (aim)	Study Design	Test Product(s):	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Comments
Kulkarni <i>et al.</i> , 1991 <i>Treatment of osteoarthritis with a herbomineral formulation</i> [35]	R DB P CO <sup>1</sup> 8 months	3x2 capsules of 650 mg of <i>C. longa</i> containing Ayurvedic formulation (corresponding to 50 mg turmeric each) / placebo, oral use  Duration of both treatments: 3 months	42	patients with osteoarthritis	Significant drop in severity of pain (p<0.001) and disability score (p<0.05)	CI 95%	Efficacy was not assessed because efficacy of a combination can not be extrapolated to mono-preparations and no detail on formulation is given
Charles and Charles, 1992 <i>Use and efficacy of Azadirachta indica (neem) and C. longa (turmeric) in scabies</i> [32]	Pilot study	Paste of 'neem' and 'turmeric' (Ayurvedic formulation)  Topical use	814	Patients with scabies	Number, size and type of lesions: cure within 3-15 days in 97% of cases		Efficacy was not assessed because efficacy of a combination can not be extrapolated to mono-preparations and no detail on formulation is given

<sup>1</sup> R = randomised P = placebo-controlled DB = double blind MC = multi centre CO = cross-over

### **4.3. Clinical studies in special populations (e.g. elderly and children)**

No data available.

### **4.4. Overall conclusions on clinical pharmacology and efficacy**

The clinical data suggest some possible effect of curcumin on the depletion of the gallbladder, and reduction of symptoms in dyspeptic disorders, supporting the traditional use of *C. longa* for digestive complaints.

## **5. Clinical Safety/Pharmacovigilance**

### **5.1. Overview of toxicological/safety data from clinical trials in humans**

No side effects were reported during a study in which 12 healthy volunteers took 20 mg curcumin [81].

In a study with 8 healthy volunteers no adverse effects have been reported after oral doses of 2 g curcumin and also not after combining curcumin with piperine and thereby raising the serum level of curcumin [94].

In a phase I trial with 25 subjects, who had various high-risk cancerous conditions, no toxic reactions were observed. The subjects received up to 8 g of curcumin a day for 3 months [80].

In a clinical study, two of 19 patients treated with 2500 mg of curcumin per day, complained of gastric irritation. No other adverse effects were reported [89].

Mild side effects (nausea, dermatitis, pain in abdomen) were also reported by participants in the study of Kulkarni after oral intake of a turmeric containing combination product, corresponding to 300 mg turmeric daily, however the side effects did not necessitate discontinuation of the treatment [35].

Rare cases of allergic contact dermatitis have been reported [90, 91]. In an 18-month study on the topical use of curcumin to treat skin and mucous membrane cancers, scalp itching was observed in 1 patient of 62 patients [30]. Patch testing led to allergic reactions (not further classified) in persons who were regularly exposed to the substance or who already had dermatitis of the finger tips. Few allergic reactions (skin rash) occurred in people not previously exposed to curcumin [92].

In a phase II study, a gastro protective action was observed in patients with peptic ulcer disease after oral intake of 600 mg curcumin 5 times daily [78]. Therefore no contraindication for duodenal/gastric ulcers was included in the monograph.

A dietary supplement containing curcumin has received a GRAS notification from the FDA up to 1500 mg per day for a 60 kg person.

According to the EFSA panel, the daily intake of curcumin from the normal diet amounts to less than 7% of the ADI of 3 mg/kg/day, with a theoretical maximum daily exposure of 6.9 mg/kg bw/day for adults and of 11.9 mg/kg/day for a typical 3 year-old child [106].

The Reprotox database reports that although there is no evidence that dietary consumption of curcuma extract as a spice adversely affects pregnancy or lactation, the safety of curcumin supplements in pregnancy and lactation has not been established [132]

## **5.2. Patient exposure**

No data available.

## **5.3. Adverse events, serious adverse events and deaths**

In the database of the Dutch Pharmacovigilance Centre LAREB no adverse events were reported for *C. longa*.

The Food and Drug Administration classifies turmeric as a substance Generally Recognized as Safe.

No major side effects have been reported in the cited clinical studies after oral intake of curcuma extracts and curcumin in doses up to 8 g/day for 3 months [45, 79, 80, 81].

In a clinical study in patients with irritable bowel syndrome dry mouth and flatulence was reported by approximately 25% of the patients [45]. In another study two of 19 patients treated with 2500 mg of curcumin per day, complained of gastric irritation [89]. In the study of Thamlikitkul mild side-effects as nausea, diarrhoea, headache, tiredness and sleepiness have been reported in the turmeric group (2 g/day) as well as in the other groups (placebo and comparative herbal combination) [100].

With respect to topical use rare cases of allergic contact dermatitis have been reported [90, 91]. In an 18-month study on the topical use of curcumin to treat skin and mucous membrane cancers, scalp itching was observed in 1 patient out of 62 patients [31]. Patch testing led to allergic reactions (not further classified) in persons who were regularly exposed to the substance or who already had dermatitis of the finger tips. Few allergic reactions (skin rash) occurred to people not previously exposed to curcumin [92].

Pharmacovigilance problems have been reported for a product containing curcuma and a amino acid. Further study revealed that the observed liver toxicity was not due to curcuma.

## **5.4. Laboratory findings**

No data available.

## **5.5. Safety in special populations and situations**

### **5.5.1. Use in children and adolescents**

No data available

### **5.5.2. Contraindications**

The available data do not justify to include a contraindication. The warning concerning the potential effect on bile secretion was moved to "Special warning and precautions of use" to align with the *Curcuma xanthorrhiza* monograph.

### **5.5.3. Special Warnings and precautions for use**

Because of a potential effect on bile secretion, *C. longa* is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases [17,81,82, 96] Therefore as a precautionary measure a warning is taken up into the monograph.

#### **5.5.4. Drug interactions and other forms of interaction**

Turmeric may interact with NSAIDs, antiplatelet agents or antihyperlipidemics, and a case report mentions interaction with warfarin. These findings are mainly based on *in vitro* data, animal studies or individual case reports. More studies are needed to confirm and assess the clinical significance of these potential interactions [84, 86, 93].

As clinical data is lacking, these effects are not included in the monograph.

Several studies reported interactions between curcumin and other phytochemicals.

Fetrow suggested that curcumin could decrease the effect of immunosuppressants, but also here no supporting clinical data was provided [86].

Shoba et al. demonstrated that the bioavailability of curcumin increased twenty-fold when healthy human subjects took a 2 g dose of curcumin in combination with 20 mg of piperine, extracted from black pepper, compared to subjects who took only 2 g of curcumin [94].

Animal studies revealed that green tea enhances the effect of curcumin. In mice and hamster tumor models the combination of catechin and turmeric was more effective than the individual components [95]. Li *et al.* suggested that curcumin and green tea extract have synergistic effect in reducing oral squamous-cell carcinomas in hamsters [61].

The interpretation of the clinical relevance of the findings retrieved from animal studies and/or effects of isolated substances (as curcumin) is difficult and may lead to doubtful conclusions; therefore no interactions are included in the monograph.

#### **5.5.5. Fertility, pregnancy and lactation**

Singh *et al.* observed pharmacological effects in dams as well as their suckling neonates when turmeric and/or curcumin was administered to the dams. The results indicate that turmeric and/or curcumin metabolites (not specifically mentioned) can be transferred through lactation [60].

The constituents do not appear to be toxic or mutagenic in traditional use doses. No reproductive toxicity has been observed. However because it is known that curcumin and/or metabolites are transferred to sucklings via lactation [60] it is not recommended to use *C. longa* or preparations thereof during breastfeeding.

#### **5.5.6. Overdose**

No toxic effects were observed in patients after three months oral daily intake of 8,000 mg or 2.2 g of turmeric (equivalent to max. 110 mg of curcumin) for four months [80, 85].

#### **5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability**

No data available

#### **5.5.8. Safety in other special situations**

Not applicable



## 5.6. Overall conclusions on clinical safety

No serious side effects have been reported up to now. Furthermore the chemical composition of *C. longa* does not give any reason for concerns regarding safety.

Potential interactions between *C. longa* and NSAIDs, antiplatelet agents, antihyper-lipidemics and immunosuppressants have been described/reported, but clinical evidence for these effects is lacking [84, 86].

The use of *C. longa* in pregnant women and during lactation is not recommended while there are indications that curcumin and/or metabolites can be transferred through lactation.

Because of possible effect on bile secretion, as a precautionary measure, *C. longa* preparations are not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases.

## 6. Overall conclusions

*C. longa* is in use in Europe for a long time, mainly for dyspeptic complaints, skin problems and liver diseases and infections. The available data is not sufficient to support a "well established use" indication for curcuma. As the medicinal use of curcuma has been documented continuously in European handbooks, *C. longa* fulfils the requirements of Directive 2004/24 EC for classification of traditional herbal medicinal products. The use of *C. longa* is considered plausible in the treatment of dyspeptic complaints on the basis of bibliography and pharmacological data.

The initial indication: 'Traditional herbal medicinal product used to increase bile flow for the relief of symptoms of indigestion (such as sensation of fullness, flatulence and slow digestion' was slightly amended for the 5-year's revision to align with with the *Curcuma xanthorrhiza* monograph. Reference to a lack of bile secretion was not considered to fulfill the criteria as laid down in Article 16a of Directive 2004/24 EC, because this is a potential effect and can only be diagnosed with the help of a medicinal practitioner.

Therefore the proposed indication for traditional monograph reads as follows: 'Traditional herbal medicinal product used for the relief of symptoms of digestive disturbances, such as feelings of fullness, slow digestion and flatulence'.

Although the (topical) use for skin diseases is also described in authoritative texts, it is not included in the monograph because no information is available that *C. longa* containing products are currently on the market of EU Member States for such indications and data on the preparations and posology is lacking.

The pharmacological activity is attributed to the whole extract; however the majority of activities were observed with curcumin.

*C. longa* is used in the following pharmaceutical forms and posology:

- powdered herbal substance: 1.5-3.0 g daily
- Comminuted herbal substance as herbal tea (infusion): 0.5-1 g in 150 ml boiling water, 2-3 times daily
- tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 70% v/v: 0.5-1 ml 3 times daily
- dry extract (13-25:1) extraction solvent: ethanol 96%: 90-162 mg daily, divided in 2-5 partial doses

- dry extract (5.5-6.5:1) extraction solvent: ethanol 50%: 100-200 mg 2 times daily
- tincture (ratio of herbal substance to extraction solvent 1:5) extraction solvent ethanol 70%, v/v: 10 ml once daily or 5 ml in 60 ml water 3 times daily

Only mild side effects have been reported for *C. longa*: dry mouth, flatulence, and gastric irritation. No serious side effects have been reported.

Due to lack of data, the use of *C. longa* in children under the age of 18 years cannot be recommended.

As relevant data on the use during pregnancy and lactation is lacking, *C. longa* cannot be recommended in these conditions.

Due to the nature of the potential effect on bile secretion it is not recommended to use *C. longa* preparations in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases.

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

## **Annex**

### ***List of references***