Safety Assessment of CurQlife (solubilised curcuminoids)

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Novel Food Classification: 1.2 (f)/(e)

Introduction

An application for the authorisation of solubilised curcuminoids (CurQlife), was submitted to the Food Safety Authority of Ireland (FSAI) by Laila Pharmaceuticals Pvt. Ltd. of India in accordance with *Article 4* of the novel food Regulation (EC) No. 258/97. The application was accepted by the FSAI on October 19th, 2015.

CurQlife is a proprietary product of Laila Pharmaceuticals Pvt. Ltd. comprised of curcuminoids solubilised in polyethylene glycol (PEG) 200 and Tween 20 (polysorbate 20). Curcuminoids are a collective name for a group of compounds which include curcumin, demethoxycurcumin and bisdemethoxycurcumin which are characteristic components of the Asian perennial shrub *Curcuma longa* L (known generically as turmeric). Both turmeric and curcumin (isolated from the roots of *Curcuma longa* L) have a history of human use in foods, cosmetics and for therapeutic purposes in Asia, Europe and the USA. Products containing curcumin are also available on the market in India, the USA and in the EU. The open literature estimates the level of curcumin in turmeric powder at approximately 3.14%.

CurQlife is intended for the general EU population through its addition to food supplements and fortified foods. The applicant recommends a maximum daily intake of 180mg curcuminoids for a 60kg individual.

With no evidence of a history of consumption of CurQlife in the EU before 1997, it is considered novel and classified by the applicant in accordance with *Article 1.2(f)* of the novel food Regulation (EC) No 259/97; "Foods and food ingredients, to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances". The application dossier was prepared pursuant to Commission Recommendation 97/618/EC and in order to assess wholesomeness, the novel food was considered in Class 6; "Foods produced using a novel process". However, the novel ingredient could also be classified under *Article 1.2(e)* of the novel food Regulation: "food and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe use". In that case, the data required for safety assessment as set out in Commission Recommendation 97/618/EC would be the same as that already provided by the applicant.

I. Specification of the novel food

CurQlife is a dark red viscous liquid comprising 10 ± 2% curcuminoids (95% purity), 74% Tween 20 and 14% PEG 200. The 5% impurities in the curcuminoids are not defined. The curcuminoid component of the novel ingredient is a standardised extract from the plant *Curcuma longa*, with curcumin being a significant component. Curcumin is known to consist of three principal colouring components, namely the parent compound along with its desmethoxy- and bis-desmethoxy-derivatives in varying proportions. This conforms to the information available in a 2010 EFSA scientific opinion on the re-evaluation of curcumin (E 100) as a food additive, though the CAS registry numbers for the desmethoxy- and bis-desmethoxy-derivatives are at variance between the EFSA Opinion and this application.

Acetone and ethyl acetate are used in the extraction process of curcuminoids from turmeric and are controlled at ≤2,500 ppm each, and at ≤200 and ≤500ppm, respectively in the final CurQlife. However, no information is provided on the possible presence of ethylene oxide, a group 1 carcinogen that is used in the production of polysorbate and polyethylene glycol. Results from batch analyses demonstrate that the individual components and the final product meet the specifications outlined by the applicant with regard to physical and chemical characteristics, microbiological parameters and heavy metals. The applicant provides details of accelerated and real time stability studies carried out under ICH guideline conditions and proposes a shelf life of 24 months when the product is stored in high density polyethylene (HDPE) containers.

II. Effect of the production process applied to the novel food

Production of the novel food is carried out in a GMP certified plant, though the certificate provided covered a three year period from 18th March 2011 which expired in March 2014. Production involves heating the surfactants for a defined time at a specified temperature, followed by the addition of curcuminoids before further heating. The resulting clear solution is cooled to obtain a viscous, dark reddish brown solution which is then packaged into HDPE bottles or hard gelatine capsules. The applicant identifies the critical points in the manufacturing process as temperature control and holding time for solubilising curcuminoids.

III. History of the organism used for the novel food

Curcuma longa L (turmeric) is a member of the *Zingiberaceae* family; a perennial plant widely cultivated in Asia and with a long history of medicinal and culinary use. The rhizomes of the plant can be cooked, dried and ground to produce turmeric powder which is used as a spice and food colourant. Turmeric oil is also derived from the rhizomes and is used as a flavouring agent in food. In Europe and the USA, turmeric has a wide range of applications including use in foods (colouring agent), in pharmaceuticals and as a fabric dye. The major components of turmeric are collectively known as curcuminoids which include curcumin, demethoxycurcumin and bis-demethoxycurcumin. Curcumin is the most studied component and is

purported to possess anti-inflammatory, antioxidant and antimicrobial activity. The applicant provides details of several preparations containing curcumin that are currently available on the markets in India, the USA and the EU. Information is also provided relating to the status of *Curcuma longa* L across the USA, Europe, Australia, Canada and India, which indicate its use as a herbal medicine and an ingredient in foods and dietary supplements.

IX. Anticipated intake/extent of use of the novel food

Though the original application dossier indicated that the novel ingredient was intended for use in PARNUTS, the applicant subsequently clarified that CurQlife is intended for use only in food supplements and fortified foods. It was stated in the initial application that "the proposed dose of CurQlife" would be "400mg CurQlife when taken twice daily". This was subsequently clarified by applicant in table 1.

Table 1: Maximum daily intakes for CurQlife components in respect of acceptable daily intakes

Component	Quantity in CurQlife (mg)	ADI (mg/kg bodyweight)	Acceptable intake calculated on the base of ADI for 60 kg human (mg)	Intake of components calculated for maximum daily intake (mg)
Curcuminoids (95%)	46.00	0 – 3	180	180.0
PEG 200	57.53	0 – 10	600	236.9
Tween 20	296.48	0 – 25	1,500	1,221.2

A daily dose of 400mg CurQlife (46mg/day curcumin or 0.75 mg/kg bw/day for a 60kg adult), does not pose a significant level of risk and falls well within the ADI of 0-3mg/kg bw/day. However, the maximal recommended dose is nearly four times this level (approximately 1,600mg CurQlife or 180mg/day curcumin - 3mg/kg bw/day for a 60kg adult) which is at the level of the ADI of 3mg/kg bw/day that has been endorsed by JECFA and EFSA.

No information was provided in the application about the contribution of background intakes of curcumin. However, a 2010 EFSA re-evaluation of curcumin (E100) as a food additive concluded that intake from the normal diet amounts to less than 7% of the ADI of 3 mg/kg bw/day. In that re-evaluation, the only population groups with intake estimates above the ADI were children (1-10yr) at maximal levels of use. A more refined assessment by EFSA in 2014 revealed slightly lower exposure estimates. In 2014, the combined exposure to curcumin in foods (turmeric as a spice and in curry powder), and from its use as a food colour at the 95th percentile, was estimated to be in the range of 1.2 to 3.4mg/kg bw/day for children aged 3-9y, 0.7-2.3 mg/kg bw/day for adolescents aged 10-17y and at 0.4-1.5 mg/kg bw/day for adults. Although, mean intake values from this combined exposure were within the ADI, the possibility remains that ingestion of CurQlife at the proposed dose may exceed the ADI in high level younger consumers. The applicant intends to market the novel ingredient for the general population. However, further details on potential intakes through fortified foods and supplements as well as a proposed dosage regime are essential.

Co-Formulants (PEG 200 & Tween 20)

CurQlife also contains the non-ionic surfactants PEG-200 and Tween 20 as emulsifiers/solubilisers. Polyethylene glycol is approved as a food additive (E 1521) in the EU. It is used *quantum satis* as a carrier in sweeteners and also as a food supplement, supplied in a solid capsule or tablet form where the limit of addition is 10,000 mg/kg. An ADI of 10 mg/kg bw/day was assigned by JECFA in 1979 for 'Polyethylene glycols' and quoted in the 2006 EFSA opinion concerning Polyethylene glycols 400-8000. The proposed dosing regimen for CurQlife of 800 mg per day corresponds to an intake of PEG 200 of 115.06 mg/day or 1.92 mg/kg bw/day for a 60 kg adult which is <20% of the JECFA ADI. The EFSA opinion estimated a conservative combined intake of PEG from food supplements and pharmaceutical products to be approximately 4 mg/kg bw/day. Even at these high intake estimates, supplementation with CurQlife will not exceed the ADI for PEG. However, Poly Ethylene Glycols with molecular weights of between approximately 400 and 9,000 Da are approved as additives in the EU. Therefore, the PEG 200 used by the applicant in CurQlife is not currently authorised as a food additive in the EU and may require additional authorisation under food additives legislation.

Tween 20 is also approved as a food additive (E 432) in the EU. It is one of a group of Polysorbates permitted for use in a variety of food products at levels ranging from 500-10,000 mg/kg. It is used *quantum satis* as a carrier in 'food supplements supplied in a solid form including capsules and tablets and similar forms'. The EFSA opinion of 2015 allocated an ADI of 25 mg/kg bw/day. The proposed dosing regimen for CurQlife of 800 mg per day corresponds to an intake of Tween 20 of 592.96 mg/day or 9.88 mg/kg bw/day for a 60 kg adult which is approximately 40% of the EFSA ADI. The EFSA opinion expressed some concern regarding the potential exposure for toddlers close to the ADI. It is possible that further exposure to Tween 20 via supplementation with CurQlife could exceed the ADI for this vulnerable group (toddlers).

X. Information from previous human exposure to the novel food or its source

Curcumin is permitted for food use in the EU as a colour additive (E 100) in a range of general foodstuffs either at specified limits or *quantum satis* depending on the food. Maximum levels for beverages range from 100 - 200 mg/L and between 20 - 500 mg/kg for various food categories. In 2004, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an acceptable daily intake (ADI) for curcumin of 0-3 mg/kg bw/day based on a no observed adverse effect level (NOAEL) of 250-320 mg/kg bw/day in a multi-generation study in rats applying an uncertainty factor of 100.

Polyethylene glycol is currently permitted for use as a food additive in table top sweeteners and in food supplements under the designation E 1521. However, its permitted use in supplements (defined in Directive 2002/46/EC) does not include food

supplements for infants and young children (Commission Regulation (EU) No 1333/2008). In addition, E 1521 defined in Commission Regulation (EU) No 231/2012 relates to Poly Ethylene Glycols with molecular weights of between approximately 400 and 9,000 Da. Therefore, the PEG 200 used by the applicant in CurQlife is not currently authorised as a food additive in the EU and may require additional authorisation under food additives legislation.

Tween 20 (Polysorbate 20) is a non-ionic surfactant and is used as an emulsifier. JECFA evaluated this compound in 1973 and assigned an ADI of 0-25 mg/kg bw/day. Polysorbate 20 is currently permitted for use in the EU as a food additive (E 432) in several categories of general foodstuffs at levels between 500 - 10,000 mg/kg or mg/L. It is also permitted for use in dietary foods for special medical purposes at 1,000 mg/kg and *quantum satis* in chewable, capsule, tablet, syrup and liquid forms of supplements. It may also be added to other food additives as a carrier or to flavourings and nutrients.

XI. Nutritional information on the novel food

The nutritional value of CurQlife is relatively minor in terms of overall human nutrition. It is comprised of 82% carbohydrate, 2.6% fat, 0.37% protein and a negligible amount dietary fibre (<0.1%). The energy content of the novel food is given as 353 calories per 100g CurQlife (or 1.4kcal per 400mg quantity of CurQlife; 5.6 kcal if consumed at the maximal daily intake). Curcumin is relatively poorly absorbed when consumed, with a bioavailability of approximately 65%. Curcumin is reported to interact with the cytochrome P450 pathways and to influence glucuronide conjugation. Based on the data available, neither curcumin nor CurQlife appear to have adverse effects on digestion/absorption, micronutrient bioavailabity or basic clinical chemistry outcomes. Though there is evidence of a number of trials involving curcumin, turmeric, turmeric oleoresin and turmeric extract, it seems that there is no evidence of clinical trials where humans were supplemented with CurQlife.

XII. Microbiological information on the novel food

Microbiological specifications for the novel food indicate a total bacterial count of not more than 1,000 CFU/g, yeasts and moulds of not more than 100 CFU/g, absence of *Escherichia coli* in 10g, absence of *Salmonella* in 10g, and absence of *Staphylococcus aureus* in 1g. Batch analysis indicates the product meets these specifications.

XIII. Toxicological information on the novel food

Curcuminoids (≥95%), derived from the plant *Curcuma longa* are the predominant category of plant ingredients (approximately 10%) present in CurQlife. The applicant states that curcumin is a significant component of the curcuminoids in CurQlife without defining that proportion. The applicant has provided toxicological information on both curcumin and the novel ingredient CurQlife separately. However, curcumin (E 100) has been the subject of a number of EFSA scientific opinions in

2014 (Refined exposure assessment of curcumin) and in 2010 (Scientific opinion on the re-evaluation of curcumin as a food additive) and will not be further addressed in this assessment which only reviews the toxicological data related to the novel ingredient; CurQlife.

Pharmacokinetics

The pharmacokinetics of different curcuminoid formulations (unknown content; either an orange-yellow powder or a dark red viscous solution) was investigated in Sprague Dawley rats following single oral doses equivalent. However, this is of relevance to curcuminoids only rather than the novel ingredient *per se*.

Acute Toxicity

The acute oral toxicity of CurQlife was determined in a single dose oral (gavage) study in female Sprague Dawley rats in accordance with OECD guidelines (No. 425). Distilled water was used as the vehicle and the limit test was conducted at 2,000 mg/kg bw, using five animals with no treatment related mortalities or clinical signs of toxicity recorded. The LD_{50} of CurQlife in female Sprague Dawley Rats was >2,000 mg/kg bw.

Two week dose range finding study

A dose range finding toxicity study on CurQlife in Sprague Dawley Rats was performed in accordance with OECD Guideline No. 407. CurQlife was administered at doses of 250, 500, 1000 and 2000 mg/kg bw/day for 14 days in 10 ml of distilled water. No treatment-related effects were recorded in relation to mortality, clinical signs of toxicity, body weight, body weight gain, food consumption, ophtalmology, haematology and clinical pathology or urinalysis parameters. Gross pathology and histopathology were unremarkable. CurQlife was well tolerated up to 2,000 mg/kg bw/day when administered once daily for 2 weeks.

Acute eye irritation

This study was performed in accordance with OECD Guideline No. 405 using New Zealand white rabbits. Corrosive or irritant effects were not recorded in the initial study or in the confirmatory test. There were no clinical signs of toxicity or gross pathological changes, or effects on mortality, body weight and body weight gain.

Acute dermal irritation

This study was performed in accordance with OECD Guideline No. 404 using New Zealand white rabbits. In the initial test, 0.5 ml CurQlife was applied to a skin area of approximately 6 cm^2 for up to 4 hours. Irritation or corrosion of the skin was not recorded during 24 hours. In the confirmatory test, CurQlife did not cause irritation or corrosion at any stage up to 14 days after the study and, as a result, CurQlife was classified as non-irritant to skin.

Bacterial reverse mutation test

This study was performed in accordance with OECD Guideline No. 471. CurQlife was found to be non-cytotoxic to Salmonella typhimurium TA 100 strain. The

mutagenic effects on *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 was assessed using the plate incorporation and pre-incubation methods, with distilled water as the solvent. CurQlife was tested at concentrations of 0.05, 0.25, 0.5, 2.5 and 5 µL/plate with and without the S9 fraction. There was no significant increase in number of revertant colonies and CurQlife was deemed to be non-mutagenic.

Conclusions

This application seeks to place CurQlife as an ingredient in fortified foods and food supplements on the EU market. In general, curcumin seems to be well tolerated by humans when administered orally at doses up to 12 g/day, with no convincing evidence of allergic or intolerance reactions.

However, a number of issues have been noted with respect to the novel ingredient:

1. CurQlife consists of 10 ± 2% curcuminoids with a purity of 95%. The 5% of non-curcuminoid content is not defined and therefore CurQlife is not fully characterised
2. Production of the novel food is carried out in a GMP certified plant, but the certificate provided expired in March 2014
3. Details of the specific amounts of the novel ingredient to be used in fortifying food or food supplements are not provided
4. Details of the foods to be fortified are not provided
5. The maximum recommended dose of CurQlife is approximately 1,600mg (180mg/day curcumin - 3mg/kg bw/day for a 60kg adult) which is at the level of the ADI of 3mg/kg bw/day that has been endorsed by JECFA and EFSA. At this level of intake, the consumption of curcumin from the other sources would mean that the ADI is exceeded
6. PEG 200 is not currently authorised as a food additive in the EU and may require additional authorisation before it can be used in food in the EU
7. EFSA previously expressed concerns regarding the potential over-exposure of younger consumers to Tween 20, which becomes more pertinent upon the availability of a new source (CurQlife)
8. No analytical data is provided to demonstrate the absence of ethylene oxide, a group 1 carcinogen that is used in the production of polysorbate and polyethylene glycol

Recommendation

In light of the issues highlighted in the "Conclusions" section, and in accordance with *Article 6.3* of the novel food Regulation (EC) No 258/97, the FSAI recommends that this application requires additional assessment.