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Locust bean gum safety in neonates and young infants: An integrated review of the toxicological database and clinical evidence

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ABSTRACT

Locust bean gum (LBG) is a galactomannan polysaccharide used as thickener in infant formulas with the therapeutic aim to treat uncomplicated gastroesophageal reflux (GER). Since its use in young infants below 12 weeks of age is not explicitly covered by the current scientific concept of the derivation of health based guidance values, the present integrated safety review aimed to compile all the relevant preclinical toxicological studies and to combine them with substantial evidence gathered from the clinical paediatric use as part of the weight of evidence supporting the safety in young infants below 12 weeks of age. LBG was demonstrated to have very low toxicity in preclinical studies mainly resulting from its indigestible nature leading to negligible systemic bioavailability and only possibly influencing tolerance. A standard therapeutic level of 0.5 g/100 mL in thickened infant formula is shown to confer a sufficiently protective Margin of Safety. LBG was not associated with any adverse toxic or nutritional effects in healthy term infants, while there are limited case-reports of possible adverse effects in preterms receiving the thickener inappropriately. Altogether, it can be concluded that LBG is safe for its intended therapeutic use in term-born infants to treat uncomplicated regurgitation from birth onwards.

1. Introduction

Regurgitation is a characteristic symptom of uncomplicated gastro-oesophageal reflux (GER) occurring as a common physiological process in healthy infants, it usually starts at 2–3 weeks of age (Vandenplas, 2009). It is reported that 50% of normal healthy infants regurgitate at least once per day with associated discomfort, and 20% of the caregivers are looking for a medical assistance to that phenomenon, primarily to lower parents anxiety and strengthen their reassurance (Lightdale et al., 2013; Vandenplas, 2009). In more severe cases, excessive regurgitation can possibly lead to insufficient nutrient intake, failure to thrive and an increased risk of health problems such as respiratory illness (Vandenplas et al., 1997). In the context of *uncomplicated* but persistent GER, one of the recommended approaches is the use of dietary interventions employing thickening agents or thickened infant formulas to decrease the number of troublesome regurgitation (Vandenplas et al., 1997, 2009). Such kind of dietary interventions are most often based on slowly or non-digestible polysaccharide food components (cereals, starch, guar gum, soy fibre, locust bean gum, which is also designated as carob bean gum). Among those thickening agents, the food additive locust bean gum (LBG) is

Abbreviations: ADI, Acceptable Daily Intake; AR, anti-reflux/anti-regurgitation; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; EU, European Union; FAO, Food Agricultural Organization; FDA, Food and Drug Administration; FOS, fructo-oligo saccharides; FSMP, Foods for Special Medical Purposes; GER, gastro-oesophageal reflux; GERD, gastro-oesophageal reflux disease; GD, gestational day; JECFA, Joint FAO/WHO Expert Committee on Food Additives; LBG, locust bean gum; IF, infant formula; MoS, Margin of Safety; NASPGHAN, North American Society for Pediatric Gastroenterology Hepatology and Nutrition; NOAEL, No Observed Adverse Effect Level; NTP, National Toxicology Program; OECD, Organization for Economic Co-operation and Development; SCF, Scientific Committee on Food; TDI, Tolerable Daily Intake; WHO, World Health Organization.

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extensively used in a large range of commercially thickened infant formulas prescribed to treat GER (or thickener to be added to food). To exert a beneficial effect on reflux, LBG-thickened formulas in general contain an average level situated at 0.5 g/100 mL of LBG. A clear distinction is made between GER and GERD (gastro-oesophageal reflux disease), since GERD is present when the reflux of gastric contents causes troublesome symptoms and/or complications and can also have different underlying pathophysiological causes (a.o. neurologic impairment, obesity, congenital oesophageal disease, cystic fibrosis) requiring a more specific medical treatment (Vandenplas et al., 2009). In order to avoid the masking of more severe pathophysiological causes, LBG-thickened formulas are therefore only prescribed by Health Care professionals to healthy term infants with uncomplicated GER.

To date LBG has been evaluated by different expert groups of competent food safety authorities for its use as thickener or stabilizer in a range of various foodstuffs aimed for the general population (Joint FAO/WHO Expert Committee on Food Additives, EU Scientific Committee on Food, US Food and Drug Administration). The main detailed evaluations have been conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in the seventies and, the latest one in 1981, mainly referred to *in vitro* and *in vivo* animal data (JECFA, 1981). On that occasion, the JECFA allocated a non-numerical Acceptable Daily Intake (ADI) 'not specified' that applies to substances with very low toxicity.

According to the scientific concept when deriving health-based guidance values (Acceptable or Tolerable Daily Intake), such ADI (or TDI) covers the overall population only from 12 weeks onwards (Larsen et al., 1997; Ostergaard and Knudsen, 1998; SCF, 1998a; World Health Organization, 2009). Likewise, since the general guidance is not to use additives in foods for infants and young children, and given that the use of LBG as a therapeutic dietary thickener in healthy term infants was not considered for safety evaluation at that time, the innocuousness of this food additive has up to now never been put into perspective of that population (0–12 weeks old) for which also data generated in paediatric trials conducted with LBG should be taken into consideration. In absence of an extended safety evaluation, the European Union (EU) Scientific Committee on Food (SCF) considered the use of LBG as therapeutic agent acceptable in view of the demonstrated benefits in the treatment of GER (SCF, 2003).

The present integrated safety review aims to discuss and update the current evidence obtained from the toxicological tests and, to evaluate to what extent their outcome is relevant to address the safety of LBG for healthy term infants below 12 weeks of age. The additional safety and tolerance evidences from paediatric data have now been integrated as part of the total weight of evidence to confirm the safety and tolerability of LBG in healthy term infants treated by dietary interventions for uncomplicated gastro-oesophageal reflux.

2. Chemical aspects

Locust bean gum (LBG, C.A.S 9000-40-2, Einecs 232-541-5) is obtained from the endosperm seed of the locust/carob tree (*Ceratonia siliqua* (*L.*) *Taub*) of the plant family of *Leguminosae*. The seeds are generally prepared either by thermal, mechanical or by chemical treatment and then the germ is eliminated. The next steps are milling and screening of the endosperm. The gum may be washed with ethanol or isopropanol to control microbiological load. Commercialized LBG is standardized with sugars for reactivity and viscosity, and complies with the JECFA and EU specifications as summarized in Table 1 (European Commission, 2012; JECFA, 2008). The prepared gum is a white to yellowish, nearly odourless powder. The substance consists of high molecular weight polysaccharides (50,000–3,000,000 daltons) consisting of at least 75% galactomannans. The general chemical structure is presented in Fig. 1. The high molecular weight polysaccharides are composed of the galactomannan units consisting of a linear chain of (1 → 4)-linked β-D-mannopyranosyl units (mannopyranose) with (1 → 6)-linked α-D galactopyranosyl residues (galactopyranose) as side chains. The mannose and galactose contents have been reported as 73–86% and 27–14%, respectively (mannose:galactose ratio of approximately 4:1). Galactomannans are commonly found in other gums such as guar, tara or cassia gum but with differences in mannose to galactose ratios. LBG is coded as INS/E 410 according to food additives numbering.

LBG is commonly used in various foodstuffs as a food additive with thickening, stabilizing, emulsifying or gelling properties. As indicated above, its important thickening properties have been extensively employed in infant formulas in the context of the dietary management of infant regurgitation for more than 20 years.

3. Scientific evaluations, regulatory context and uses in baby foods

At international level, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the safety of LBG in 1981 (JECFA, 1981). Considering the very low toxicity profile of LBG observed mainly *in vitro* and in animal studies, the committee allocated a non-numerical ADI 'not specified'. However, as for now the JECFA committee did not consider the use of LBG as therapeutic ingredient in Foods for Special Medical Purposes especially in infants below 12 weeks of age, having the consequence that LBG is only authorized in the Codex Alimentarius as basic technological thickener in infant formula up to 0.1 g/100 mL, but not approved for use at sufficiently high levels to be effective as a therapeutic thickener (therapeutic dosage of approximately 0.5 g/100 mL).

In the European Union, LBG up to 0.1 g/100 mL was assessed by the Scientific Committee on Food (SCF) and, as a result, it was authorized for technological purposes in follow-on formulas for older infants in good health (SCF, 2003). Its use is also approved up to 1 g/100 g in weaning foods (SCF, 2003). The SCF specifically evaluated the use of LBG up to 1 g/100 mL as thickener in the context of infant formulas and follow-on formulas aimed for term infants in good health and in Foods for Special Medical Purposes (FSMP) (SCF, 1998b, 2003). The committee considered the available clinical evidences of benefits and safety, and concluded that LBG was acceptable for use up to 1 g/100 mL (10 g/L) for its use in FSMP when prescribed under medical supervision to treat gastro-oesophageal reflux (GER) (SCF, 1998b, 2003). As a result, LBG at this level was authorised for this purpose by EU legislation. In Russia, LBG is allowed as in the EU (CU Regulation 029/2012).

In other jurisdictions, LBG is approved for use in standard infant formula, follow-on formula or infant foods. In Australia and New Zealand, LBG is authorized up to 0.1 g/100 mL in infant formula and up to 1 g/100 g in food for infants (FSANZ, 2013). In Korea, the use of LBG in infant formula and follow-on formula is authorized according to the Quantum Satis principle meaning the lowest level to achieve the technological function.

In the US, the use of LBG is addressed in 21 CFR 184.1343, 21 CFR 582.7343 and in the reviews of the Centre for Food Safety & Applied Nutrition of the Food and Drug Administration (FDA). Based on these references, LBG could be used in infant formula as a stabiliser and thickener at a level not exceeding 5 g/L. However, infant formula with LBG is not on the market in the US. Therefore, a pre-market infant formula notification is required (US Food and Drug Administration (FDA, 1972).

In China, the food safety standard on additives (GB 2760-2011) allows an LBG level for infant and young children formula up to 0.7 g/100 ml. The standard is under revision and, if adopted