AGENCE FRANÇAISE
DE SÉCURITÉ SANITAIRE
DES ALIMENTS

Maisons-Alfort, 11 February 2010

OPINION

of the French Food Safety Agency on the assessment of the marketing authorisation application for a novel food ingredient, guar gum

THE DIRECTOR GENERAL

1. REVIEW OF THE REQUEST

On 31 July 2009 the French Food Safety Agency (AFSSA) received a request from the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) to assess the marketing authorisation application for a novel food ingredient, guar gum, under Regulation (EC) 258/1997 concerning novel foods and novel food ingredients.

2. BACKGROUND

Guar gum is a polysaccharide used in the food industry as a food additive (E412) for its properties as a thickener, stabiliser, emulsifier and bulking agent, according to the *quantum satis* principle.

It is obtained by traditional milling processes from seeds of *Cyamopsis tetragonolobus* (L.) Taub. (Fabaceae).

This application concerns the use of guar gum, meeting the specifications for the E412 additive, as an ingredient in common foods (excluding dietary supplements).
As there is no history of consumption within Europe of guar gum as an ingredient in the normal diet, this application falls under Regulation (EC) 258/97 concerning novel foods and novel food ingredients (NIs).
Guar gum exists in “native” or more or less hydrolysed or depolymerised forms.
It is currently licensed and used:

- in its native form as a processing aid;
- in its partially hydrolysed form as a processing aid;
- in its partially hydrolysed form as an additive for nutritional purposes.

The applicant intends to use the NI exclusively in its native form and:

- in powder form in dairy products and fruit and/or vegetable based products such as smoothies and compotes;
- in flake form in cereals, alongside a dairy product in a container divided into two compartments.

3. EXPERT ASSESSMENT METHOD

The collective expert assessment was conducted by the Scientific Panel (CES) on "Human Nutrition" which met on 29 November 2009 and 28 January 2010.

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The CES on “Human Nutrition” which met on 29 November 2009 highlighted concerns arising from the estimated consumption of the NI in young children, with regard to the range of vectors envisaged by the applicant. Therefore, AFSSA requested that the applicant review their proposed levels of incorporation and/or use categories, to ensure that the exposure of the highest consumers was consistent with the digestive tolerance level. A request for additional information was therefore sent to the applicant via the DGCCRF. In response, the applicant provided detailed calculations on exposure based on age range and proposed an advisory statement on the labelling indicating that "consumption of the products should be avoided in children aged under 5 years".

4. RATIONALE

AFSSA's reasoning is based on the opinion of the CES on "Human Nutrition", presented in detail below:

4.1. Specifications of the NI

Native guar gum is a polysaccharide from the galactomannan family consisting of a β-D-mannopyranose backbone linked to α-D-galactopyranose units. Its molecular weight ranges from 50,000 to 8,000,000 Da.
It is listed on the CAS register under the number 9000-30-0.

The applicant has presented the NI's main physico-chemical properties. These vary depending on the guar gum’s form and the processing treatments applied by the supplier.

Table 1. Physico-chemical properties of guar gum in powder and flake form

	POWDER	FLAKES
Duration of use	2 years	1 year
Colour	White	White / off-white with no or minimal presence of black specks
Odour	Slight	Slight
Mean diameter of particles	60 to 70 µm	1 to 10 mm
Humidity	Max 15%	Max 15%
Viscosity[1] at 1 h	/	Min 3000 mPa·s
Viscosity at 2 h	Min. 3600 mPa·s	/
Viscosity at 24 h	Min. 4000 mPa·s	/
Solubility	Soluble in cold and hot water	Soluble in cold and hot water
pH for 10 g/L, at 25°C	6 - 7.5	5 - 7.5

The applicant has indicated that the specifications of the NI are identical to those defined by the JECFA[2] (JECFA, 2008) and by the European regulations[3],[4] for the E412 additive.

Since the applicant has not chosen its supplier, it has only verified compliance with these specifications for batches of native guar gum used as an additive.

[1] Viscosity measurements are carried out under the following conditions: 1%, 25°C, 20 rpm
[2] Joint FAO/WHO Expert Committee on Food Additives
[3] Directive 2008/84/EC amended by Directive 2009/10/EC laying down specific purity criteria on food additives other than colours and sweeteners
[4] Commission Decision 2008/352/EC imposing special conditions governing guar gum originating in or consigned from India due to contamination risks of those products by pentachlorophenol and dioxins

AFSSA considers that the information provided by the applicant is sufficient to demonstrate that the NI complies with the specifications of the E412 additive and the criteria for safety and purity.

4.2. Effects of the production process applied to the NI

The NI is produced according to traditional milling processes.
The applicant has described the process for obtaining the native guar gum:

- seeds obtained from the dried pods are split by mechanical means to remove the germ;
- the endosperm is peeled to obtain the flakes;
- the flakes are ground and sieved to obtain the powder;
- the powder or flakes are washed with ethanol or isopropanol to control the microbiological content.

These elements require no comment from AFSSA.

4.3. Prior use of the organism used as the source of the NI

Native guar gum comes from the annual herb *Cyamopsis tetragonolobus*, cultivated in India, Pakistan and the United States. There is no history of the plant being consumed in Europe in an unprocessed form.

These elements require no comment from AFSSA.

4.4. Expected consumption/level of use of the NI

The applicant intends to use the NI in common food products:

- in powder form in dairy products and fruit and/or vegetable based products such as smoothies and compotes;
- in flake form in cereals, alongside a dairy product in a container divided into two compartments.

The applicant has indicated that with the exception of the cereals, the guar gum will be incorporated into products in which it is already used as an additive.
For comparison, according to the data provided by the applicant, in France the maximum levels of incorporation of the E412 additive vary between 0.3% in cheeses and 2% in confectionary products and cereal-based baby foods.
Incorporation of native guar gum into the cereals at a level of 10% corresponds, after the consumer has mixed together the cereal and dairy portions, to a level of 1% of guar gum in the product as consumed. This concentration in the ready-to-eat product is within the concentration range observed when the native guar gum is used as an additive.

The applicant estimated the exposure of the French population to guar gum, if authorised as an ingredient in the food uses proposed by the applicant, using data from the INCA 1 survey (Volatier, 2000).
Consumption data for the following food groups were selected on the basis of the food uses proposed by the applicant for the NI:

- dairy products;
- cereals;
- fruit drinks;
- mashed and cooked fruit.

Considering the maximum rate of incorporation of the NI into the proposed food uses and assuming that the reference foods are substituted at a rate of 100% by foods containing the NI, the levels of exposure to the NI were calculated for each proposed food use and for different age ranges:

- mean exposure varies from 0.2 g/d (cereals in adults aged over 65 years) to 2 g/d (fruit drinks in children aged 3-14 years);
- exposure of the 95th percentile varies from 2.9 g/d (dairy products in children aged 9-14 years) to 9 g/d (dairy products in children aged 3-8 years).

Considering the maximum hypothesis of cumulative consumption of foods containing the NI:

- mean exposure varies from 2.2 g/d (in adults aged over 65 years) to 5.5 g/d (in children aged 3-8 years), i.e. from 0.04 g/kg bw/d in adults (mean weight 60 kg) to 0.2 g/kg bw/d in children (mean weight 25 kg);
- exposure of the 95th percentile varies from 15.2 g/d (adults aged 25-64 years) to 23.2 g/d (children aged 3-8 years), i.e. from 0.3 g/kg bw/d to 0.9 g/kg bw/d.

In the additional information provided following AFSSA's request, the applicant detailed the results obtained in children aged between 3 and 8 years according to the maximum hypothesis. Consumption of 23.2 g/d of the NI would correspond to cumulative consumption of around 600 g of dairy products, 80 g of cereals and 350 g of smoothie products. The applicant considered this hypothesis unlikely and ptoposed an alternative hypothesis of daily consumption of a portion of each of the food uses. This hypothesis may, according to the applicant, be considered as maximal, given the portion sizes of foods likely to contain the NI and their satiating property. Considering the maximum rates of incorporation of the NI , daily consumption of the NI would be 9.8 g, i.e. 0.7 g/kg bw in children aged 3 years (mean weight 14 kg), 0.57 g/kg bw in children aged 5 years (mean weight 17 kg) and 0.39 g/kg bw in children aged 8 years (mean weight 25 kg).
In children aged under 5 years, this intake exceeds the digestive tolerance level of 0.66 g/kg bw/d, estimated by dividing the digestive tolerance level in adults (40 g) by the mean weight of an adult (60 kg) (AFSSA, 2002a). The applicant therefore proposes a labelling advisory statement indicating that consumption of the product should be avoided in children aged under 5 years.

AFSSA considers that these exposure estimates do not expose the population aged over 8 years to any risk of digestive discomfort.
Concerning the exposure of children aged from 3 to 8 years, AFSSA considers that the alternative consumption hypothesis proposed by the applicant (with the exposure of the 95th percentile to cumulative consumption of each of the vectors) leads to the maximum consumption of the NI being underestimated.
Because of the difficulty of estimating the maximum daily consumption of the NI and the risks of digestive discomfort from a high consumption of the NI in young children, AFSSA considers that labelling information is required, to indicate that a high consumption of products containing the NI may cause digestive disorders, particularly in children aged under 8 years.

4.5. Information provided from previous human exposure to the NI or its source

In Europe, previous exposure to guar gum relates to its use as an additive.
This section therefore contains information obtained from the use of guar gum in food as a food additive.

Native guar gum is a food additive (E412) whose conditions of use are laid down by Directive 95/2/EC[5]: it can be used according to the *quantum satis* principle in foodstuffs in which the use of additives is generally accepted, as well as in chestnuts preserved in liquid. It is also authorised without restriction as a carrier and carrier solvent.
Its use is restricted in certain foods. It is:

- prohibited in dehydrated foods which rehydrate on ingestion and in jelly mini-cups[6];
- limited in jams, jellies and marmalades, infant foods and foods for special medical purposes intended for infants and young children.

At the request of the applicant, a consulting company estimated the level of the French population's exposure to the E412 additive, using data from the ASPCC[7] survey conducted in

[5] European Parliament and Council Directive 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners
[6] Commission Decision 2004/374/EC of 13 April 2004 suspending the placing on the market and import of jelly mini-cups containing the food additives E 400, E 401, E 402, E 403, E 404, E 405, E 406, E 407, E 407a, E 410, E 412, E 413, E 414, E 415, E 417 and/or E 418

1994 (Nutri-Health, 2007). This study showed that the average exposure of adults is 0.5 g/d (i.e. 8 mg/kg bw/d), with a 95th percentile of 1.1 g/d (20 mg/kg bw/d). In children (aged 2-18 years) this exposure is estimated at 0.14 g/d on average with a 95th percentile of 1.0 g/d.

AFSSA reiterates that the acceptable daily intake (ADI) for the E412 additive had been described as "unspecified" by the JECFA (1975) and then by the Scientific Committee on Food (SCF, 1978). Moreover, AFSSA acknowledged the lack of toxicity of the E412 additive in an Opinion on its use in a dietary supplement (AFSSA, 2002a) and in an Opinion on its use in a dietetic food (AFSSA, 2002b). Finally, EFSA concluded that current average consumption levels of the E412 additive do not pose any particular risk (EFSA, 2007).

4.6. Nutritional information on the NI

The applicant provided the mean nutritional composition of the NI:

Table 2. Indicative nutritional composition per 100 g of guar gum

Energy	182 kcal / 774 kJ
Protein	5 g
Carbohydrates	0
of which sugars	0
Fat	1 g
of which saturated	0
Fibre	81 g
Sodium	0

Guar gum is not hydrolysed by human digestive enzymes, it is degraded and fermented by the colonic flora, producing short-chain fatty acids (mainly acetate and propionate). AFSSA has acknowledged the fibre properties of guar gum and has found good intestinal tolerance of guar gum with consumption below 40 g/d (AFSSA, 2002a; Pasman *et al.*, 1997).
Guar gum is water-soluble and has a high viscosity. Its physiological and nutritional properties are related to its rheological properties (swelling, viscosity).
However, these properties can also cause oesophageal obstructions, as described in the literature and highlighted previously by AFSSA (AFSSA, 2006).

The applicant conducted a study to assess the risk of gastrointestinal obstruction following consumption of cereal flakes containing 10% guar gum in flake form. This study, which combined *in vivo* and *in vitro* tests, analysed the rheological changes in cereal flakes containing 10% guar gum in flake form, during the oral, gastric and intestinal (small intestine) phases of digestion, compared with commercially available cereal flakes.

AFSSA considers that the risk of oesophageal and/or intestinal obstruction associated with the consumption of cereal flakes containing up to 10% of guar gum can be regarded as negligible. However, the labelling should specify that it is not recommended to ingest cereals alone, but accompanied by water (AFSSA, 2006).

4.7. Microbiological information on the NI

The applicant states that it will seek to ensure the quality of the guar gum with which it is supplied, through compliance with specifications based on those defined for the E412 additive, supplemented by microbiological specifications relating to Enterobacteria and aerobic mesophilic spore-forming bacteria.
The applicant's products containing guar gum will be manufactured in accordance with the quality assurance procedures in place in its factories.

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[7] *Association Sucre-Produits sucrés Communication Consommation* [Association for Sugar, Sweet Products, Communication, Consumption]

These elements require no comment from AFSSA.

4.8. Toxicological information on the NI

The toxicological information provided by the applicant is based on an analysis of 107 publications from the synthesis compiled by an external organisation at the request of the applicant (Bibliographic synthesis, 2007a).

- Kinetic data

Guar gum is neither digested nor absorbed in the digestive tract. It is fermented by the intestinal flora in the colon. This fermentation produces volatile short-chain fatty acids such as acetic and propionic acids which can be absorbed in the colon.

AFSSA considers that the data provided by the applicant on the fermentation of guar gum in animals are imprecise, particularly the nature of the guar gum used (native or hydrolysed), the nature of the volatile fatty acids formed, and the transposition of these results to humans. Studies not cited by the applicant (Khan 200; Weaver 1996) have indicated that guar gum, following* in vitro *fermentation by intestinal microflora, predominantly produces acetic acid (55%) and propionic acid (35%).

- Data on single dose toxicity

Guar gum has lethal effects from doses of around 6 to 8 g/kg bw depending on the animal species.

- Data on repeated dose toxicity

Several 13-week studies were performed in rodents:

- in the only available study in mice (NTP, 1982; n=10/sex/dose), administration of 1.9 to 15 g/kg bw/d of guar gum caused a significant decrease in body weight of about 15% at the two highest doses. With the exception of one unexplained death at the dose of 15 g/kg bw/d, no adverse effects were reported;
- in rats (n=65) receiving doses of 0.6 to 10.3 g/kg bw/d (males) or 0.7 to 13.4 g/kg bw/d (females), a decrease in feed intake was observed from 4.6 and 5.4 g/kg bw/d. A decrease in liver and kidney weight was also observed as well as hypocellularity affecting all lines at the highest dose of 10 g/kg/d (male) (Graham, 1981);
- in rats (n=10/sex/group), a decrease in food consumption of up to 80% at the highest dose (10 g/kg bw/d) caused a decrease in body weight of about 16% in males. Two cases of unexplained deaths were recorded among females respectively at 5 and 10 g/kg bw/d. No histological damage was reported (NTP, 1982).
- in rats (n=20/sex/group) receiving from 300 to 600 mg/kg bw/d of guar gum, no adverse effects were reported (Freeman, 1992).

- Genotoxicity data

An Ames assay on 5 bacterial strains with and without metabolic activation showed no mutagenic effect up to 10000 µg/plate (Batt, 1992). The mouse lymphoma assay using the TK locus, when conducted at concentrations of up to 150 µg/mL, did not reveal the occurrence of any mutations (Cifone, 1992), although the poor solubility of the samples has raised doubts as to the accuracy of concentrations used.
An *in vitro/in vivo* DNA repair assay (UDS test) performed on hepatocytes from rats receiving 150 µg of guar gum was negative (McKeon, 1992).
An *in vivo* micronucleus assay in mice receiving a cellulosic feed enriched to 15% with guar gum, corresponding to a very approximate dose of 750 mg of guar gum, showed no induction of micronuclei in bone marrow 48h and 72h after treatment (Murli 1992).
Another micronucleus assay performed in rats (n=5/sex/dose) with estimated doses of 0, 30, 2500 and 5000 mg/kg bw, showed no induction of micronuclei 6h after treatment (Maxwell, 1975).
Other very old tests cited by the applicant were negative. However because of the absence of details on the methodology adopted,, these results cannot be taken into account.

These data elicit the following comments from AFSSA:

- ***in vitro, the negative results on bacteria are acceptable;***
- ***in the mouse lymphoma assay (Cifone, 1992) and in the UDS test (MCKeon, 1992) the choice of the highest concentration of 150 µg/mL is not justified on the basis of preliminary cytotoxicity tests;***
- ***the results of the micronucleus assay in mice (Murli, 1992) were obtained at doses too low compared to the sub-lethal dose and through feed and not gavage, so they have no toxicological significance;***
- ***the micronucleus assay in rats (Maxwell, 1975) did not show evidence of exposure of the bone marrow of the animals.***

- Carcinogenic potential

Two studies by the National Toxicology Program (NTP, 1982) performed in F344 rats and B6C3F1 mice, consuming feed enriched to 25000 and 50000 ppm with guar gum for two years, showed a decrease in body weight gain in the growth of both species in connection with a lesser feed intake. Pituitary adenomas were reported to be significant in male rats (37 and 40% compared with 18% in controls), although after cumulating the adenomas and carcinomas the difference in incidence was no longer significant. The incidence of other adrenal tumours (female rats) and hepatocellular carcinomas (male mice) was no different in control animals and those receiving guar gum. The NTP concluded that guar gum had no carcinogenic potential.

AFSSA considers that the carcinogenic potential in mice and rats can be regarded as negligible.

- Data on toxicity for reproductive functions

A study in rats showed no effect on reproductive capacity, however at 11.8 g/kg bw, a reduction in the number of *corpora lutea*, implantation sites and viable foetuses was observed.
The absence of teratogenic effects has been shown in mice, rats and hamsters after administration by gavage of doses close to 1 g/kg bw depending on the species considered (JECFA, 1975).
In rats, doses of up to 0.7 g/kg bw/d had no impact on implantation sites, resorptions, mortality or foetal abnormalities (McCarty, 2006).
A study in rabbits exposed dermally to doses of up to 50 mg/kg bw/d of guar gum indicated high maternal toxicity with lethal effects, a significant rise in early resorptions and a decrease in the number of viable foetuses at the high dose, without any foetal malformations being observed. The author indicated a no effect dose of 2 mg/kg bw/d (IRDC, 1988).
A study in pregnant rats (6 animals/group) receiving doses of 2.5, 5 and 7 g/kg bw/d of guar gum or cellulose or wheat bran showed maternal toxicity at 5 g/kg bw/d. High mortality at the first two doses was also reported (respectively 41 and 29%) with impaired foetal growth at the dose of 7 g/kg bw/d (Olejeme, 1992).

AFSSA notes that the data on reproductive functions are heterogeneous. The study by McCarty (2006) made clear the lack of teratogenic effects in rats at the dose of 700 mg/kg bw/d by oral route. However, the available data in rabbits are inadmissible: the authors did not justify the choice of dermal exposure and stated a no effect dose of 2 mg/kg bw/d, without specifying the level of systemic passage of the guar gum. Due to the lack of experimental details and the insufficient number of animals in the study by Olejeme (1992) relating to the period of gestation and lactation, it is impossible to take into account the results briefly summarised in the bibliographic synthesis (2007a) without having access to the detailed publication (not available).
AFSSA therefore considers that the lack of teratogenic effects is shown in rats, but that the available data in rabbits are unusable.

- Allergenic potential

This aspect is not addressed in the applicant's dossier.

AFSSA notes that the bibliographic synthesis (2007a) reports several studies describing allergic reactions following ingestion or inhalation of guar gum in a few isolated subjects. In addition, reference is made to a publication (Yamada, 2003) showing that in

rats, consumption of partially-hydrolysed guar gum (5% in the feed, the actual absorbed dose was not specified) for 3 weeks led to a decrease in serum concentration of IgG and an increase in levels of IgA, IgG and IgM in lymphocytes of mesenteric lymph nodes. This observation, however, has limited scope since the animal model is not generally very predictive of the allergy risk in humans.

AFSSA regrets the inaccuracies and shortcomings of certain toxicological studies presented in the synthesis provided by the applicant. AFSSA notes that two points are inadequately documented, namely genotoxic potential and toxicity for reproductive functions. However, on account of the nature of guar gum and its history of use in France as an additive, and given the lack of toxicity of other dietary plant fibres such as cassia gum (AFSSA, 2007; EFSA, 2007), AFSSA considers that the NI, at the doses proposed by the applicant, do not present any risk of toxicity to consumers.

5. CONCLUSION

AFSSA considers that the NI complies with the specifications of the E412 additive authorised in Europe in common foods. It meets the requirements of safety and chemical purity established by the regulations on additives.
The use of native guar gum as an ingredient would imply an estimated increase in the current level of average exposure as an additive of a factor of 4 to 5.
According to simulations provided by the applicant, the average exposure would range from 0.04 g/kg bw/d in adults to 0.2 g/kg bw/d in children aged from 3 to 8 years. The exposure of the 95th percentile would be between 0.3 g/kg bw/d in adults and 0.9 g/kg bw/d in children aged from 3 to 8 years.
Intestinal tolerance is regarded as acceptable for a dose lower than 0.66 g/kg bw/d, estimated by dividing the digestive tolerance level in adults (40 grams) by the average weight of an adult (60 kg).

The study conducted by the applicant shows that the risk of gastrointestinal obstruction following ingestion of cereal flakes containing 10% guar gum is negligible. However it is preferable to specify on the product labelling that it is not recommended to ingest these cereals alone, and that they should be accompanied by water.

AFSSA considers that the use of the NI in the products considered by the applicant does not present a safety concern for consumers over the age of 8 years.
Given the possible exposure of children under the age of 8 years to the NI and the risks of digestive discomfort associated with this exposure, AFSSA requests a labelling advisory statement indicating that high consumption of products containing the NI can cause digestive disorders, especially in children aged under 8 years.

Finally, AFSSA emphasises the need to monitor consumption of the NI with regard to cumulative intakes of guar gum in its various forms (additive and ingredient, in native and partially hydrolysed form).

The Director General

Marc MORTUREUX

KEYWORDS

Novel food, additive, initial assessment, fibre, oesophageal obstruction, dairy product, cereal, digestive discomfort

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