

The Director General

Maisons-Alfort, 4 January 2019

## **OPINION**

### **of the French Agency for Food, Environmental and Occupational Health & Safety**

#### **on the risks associated with the consumption of food supplements for joint conditions containing glucosamine and/or chondroitin sulphate**

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*ANSES undertakes independent and pluralistic scientific expert assessments.*

*ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.*

*It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.*

*It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).*

*Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 4 January 2019 shall prevail.*

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On 20 March 2015, ANSES issued an internal request to conduct an expert appraisal on the following issue: risks associated with the consumption of food supplements for joint conditions containing glucosamine and/or chondroitin sulphate.

#### **1. BACKGROUND AND PURPOSE OF THE REQUEST**

Chondroitin sulphate is a glycosaminoglycan found in connective and cartilage tissues. It is synthesised by the body from glucosamine, which is itself synthesised from fructose-6-phosphate and glutamine. Among other things, these compounds maintain the structure and elasticity of cartilage, tendons and skin. Many food supplements containing glucosamine and/or chondroitin sulphate are available on the French market. They are presented as contributing to joint comfort and are very popular, with the number of packs sold in France each year being estimated at nearly one million<sup>1</sup>.

Between the establishment of its nutriviigilance scheme in 2009 and February 2018, ANSES received 74 reports of adverse effects likely to be associated with the consumption of food supplements for joint conditions containing glucosamine and/or chondroitin sulphate.

In this context, ANSES issued an internal request with a view to identifying the potential health risks, but not the possible effectiveness, of food supplements containing glucosamine and/or chondroitin sulphate. This opinion is based on the adverse effects reported to ANSES and likely to be associated with the consumption of food supplements containing these two substances.

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<sup>1</sup> Estimate provided by the French Food Supplements Association (SYNADIET) based on data collected in March 2016 by IMS Health for the "pharmacy and drug store" sector, and by IRI for the "supermarkets and hypermarkets" sector.

## **2. ORGANISATION OF THE EXPERT APPRAISAL**

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

The issues being appraised fall within the scope of the Expert Committee (CES) on "Human Nutrition". ANSES entrusted the expert appraisal to internal rapporteurs and to the Working Group (WG) on "Nutravigilance". The methodological and scientific aspects of the work were presented to the CES on 6 September 2018. It was adopted by the CES at its meeting on 4 October 2018.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the ANSES website ([www.anses.fr](http://www.anses.fr)).

In March 2015, ANSES published information on a case of very severe hepatitis where causality was found to be very likely (2014-SA-0192). It involved GCA 2700<sup>®</sup>, a food supplement for joint conditions. Since other cases of hepatitis had been identified in the nutravigilance database for this food supplement, a literature search was carried out by the experts of the "Nutravigilance" WG in order to identify the ingredients that might be responsible for these effects. Two ingredients for which liver damage has been reported in the literature are glucosamine and chondroitin sulphate. These two substances are therefore the subject of this formal request.

Two rapporteurs, members of the "Nutravigilance" WG, were then appointed to carry out an in-depth analysis of the literature data on these two ingredients.

Seventy-four reports of adverse effects likely to be associated with the consumption of food supplements containing glucosamine and/or chondroitin sulphate were collected in the framework of the nutravigilance scheme. These reports had been submitted by healthcare professionals, the French National Agency for Medicines and Health Products Safety (ANSM), the regional pharmacovigilance centres (CRPVs), and by manufacturers of food supplements containing these two substances.

ANSES's Health Alerts & Vigilance Department was asked to question the French poison control centres (CAPs) and the national toxicovigilance network about any adverse effects involving glucosamine and/or chondroitin sulphate that had been brought to their attention. The results of this enquiry were submitted in the form of a report, which has been summarised in Section 3.5.2.

ANSES contacted other health agencies in countries in the European Union, as well as in Canada and the United States, to obtain any insights they may have gained from surveillance and expert appraisals on the safety of food supplements containing glucosamine and/or chondroitin sulphate. Their responses have been summarised in Section 3.5.3.

The French Food Supplements Association (SYNADIET) was consulted with a view to asking its members to provide ANSES with any information they deemed relevant.

## **3. ANALYSIS AND CONCLUSIONS OF THE WG AND THE CES**

### **3.1. Regulatory status and compliance**

#### **3.1.1. In France**

Chondroitin sulphate and glucosamine are marketed in most European countries, as both medicinal products and food supplements. Glucosamine is also an ingredient in some cosmetics (e.g. in hair conditioners).

In France, five medicinal products contain glucosamine (in the form of sulphate or hydrochloride salt) as the only active ingredient:

- Dolenio<sup>®</sup> (glucosamine sulphate; 1178 mg/day);
- Flexea<sup>®</sup> (glucosamine hydrochloride; 625 mg/tablet; 1250 mg/day);

- Osaflexan<sup>®</sup> (mixture of glucosamine hydrochloride and anhydrous sodium sulphate; 1178 mg/single-dose sachet/day);
- Structoflex<sup>®</sup> (glucosamine hydrochloride; 625 mg/tablet; 1250 mg/day);
- Voltaflex<sup>®</sup> (glucosamine hydrochloride; 625 mg/tablet; 1250 mg/day).

The indication is "*relief of symptoms of mild to moderate osteoarthritis of the knee*".

Two medicinal products contain chondroitin sulphate, in the form of sodium salt, as the only active ingredient:

- Chondrosulf<sup>®</sup> (400 mg/capsule or sachet; 1200 mg/day);
- Structum<sup>®</sup> (500 mg/capsule; 1000 mg/day).

The indication is "*symptomatic treatment with a delayed effect of osteoarthritis of the hip and knee*".

There are no medicinal products that combine these two active ingredients.

In 2008, AFSSA decided on a maximum dose of 500 mg/day for glucosamine and chondroitin sulphate in food supplements (AFSSA 2008). The DGCCRF, considering that the pharmacological dose is 1178 mg for glucosamine and 1000 mg for chondroitin sulphate, recommends not exceeding a daily intake of 1000 mg/day for glucosamine and 900 mg/day for chondroitin sulphate in food supplements<sup>2</sup>.

To date, several claims for chondroitin sulphate and glucosamine in foodstuffs have been submitted and assessed by EFSA, which has not been able to establish a causal relationship between the consumption of these two substances and "maintenance of normal joints". None of the claims have therefore been authorised by the European Commission<sup>3</sup>.

In 2017, the DGCCRF conducted an investigation<sup>4</sup> into food supplements for joint conditions. One of the objectives was to verify the glucosamine and/or chondroitin sulphate content of the food supplements. The DGCCRF carried out 43 analyses. Of these, "*51% of the products tested were declared non-compliant because the actual levels were lower or higher than the indicated levels and/or because of levels above the pharmacological thresholds*". Most of the products had lower levels of glucosamine or chondroitin sulphate than indicated on the label. It should be noted that four products had levels that exceeded the limits set for food supplements.

### **3.1.2. In other countries**

According to the information collected in 2017 from EFSA's European focal points<sup>5</sup>, the regulatory status of glucosamine and chondroitin sulphate differs according to the states.

In Switzerland, the maximum daily doses of glucosamine (chloride or sulphate) and chondroitin sulphate in food supplements are 750 mg and 500 mg respectively. In addition, the following warning is required: "*contraindicated for pregnant and breastfeeding women, children, young adults and individuals taking anticoagulant drugs*"<sup>6</sup>.

<sup>2</sup> List of substances for nutritional or physiological purposes conditionally eligible for Article 15: [https://www.economie.gouv.fr/files/files/directions\\_services/dgccrf/secure/telecare/table-sbnp-sous-conditions.pdf](https://www.economie.gouv.fr/files/files/directions_services/dgccrf/secure/telecare/table-sbnp-sous-conditions.pdf) (accessed on 3 April 2018)

<sup>3</sup> The various claims and their status can be viewed on the European Commission's website: [http://ec.europa.eu/food/safety/labelling\\_nutrition/claims/register/public/?event=register.home](http://ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/?event=register.home)

<sup>4</sup> Verification of food supplements for joint health: <https://www.economie.gouv.fr/dgccrf/controle-des-complements-alimentaires-a-visee-articulaire> (accessed on 6 December 2017)

<sup>5</sup> List of EFSA focal points: <http://www.efsa.europa.eu/en/people/fpmembers> (accessed on 11 October 2017).

<sup>6</sup> DFI Ordinance on food supplements: <https://www.admin.ch/opc/fr/classified-compilation/20143410/201705010000/817.022.14.pdf> (accessed on 18 April 2018)

In Spain, the maximum daily dose of glucosamine (hydrochloride or sulphate) and chondroitin sulphate authorised in food supplements is 500 mg for both ingredients. For glucosamine, the following warning is required: "*should not be consumed by pregnant or breastfeeding women, or children and adolescents*". The restriction is the same for chondroitin sulphate, except for adolescents, who are not listed<sup>7</sup>.

In Italy, the maximum daily dose of glucosamine and chondroitin sulphate authorised in food supplements is also 500 mg for both ingredients<sup>8</sup>.

In Poland, the daily intake of glucosamine must not exceed 1200 mg. The maximum intake for chondroitin has not been specified.

In North American countries, glucosamine sulphate and hydrochloride and chondroitin sulphate are only available as food supplements, and no maximum dose has been established.

A study was conducted in Canada in which 14 commercially available samples of food supplements containing glucosamine sulphate or glucosamine hydrochloride were analysed blindly by HPLC. The results showed that the amount of glucosamine expressed as a free base ranged from 41% to 108% of the value stated on the package. Nearly 80% of the samples analysed contained far less glucosamine (base or salt) than labelled (Russell, Aghazadeh-Habashi, and Jamali 2002).

## 3.2. Characterisation of glucosamine and chondroitin sulphate

### 3.2.1. Structure

#### 3.2.1.1. Glucosamine

Glucosamine (2-amino-2-deoxy-D-glucose) (Figure 1) is an amino sugar, a natural constituent of mucosal secretions, skin, tendons, ligaments and cartilage. Endogenous glucosamine is synthesised in the body from glucose, fructose and glutamine. It is also a precursor in metabolic pathways leading to the synthesis of heparin, chondroitin sulphate and sialic acid. In acetylated form, it is a component of hyaluronic acid, found in particular in synovial fluid. The presence of a basic amine functional group explains why at physiological pH, glucosamine is preferably in salt form.

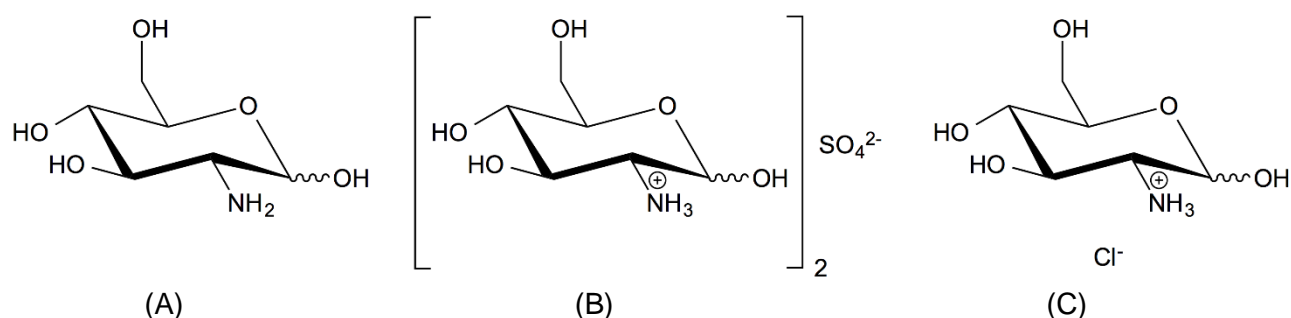


Figure 1: Structure of glucosamine (A), glucosamine sulphate (B) and glucosamine hydrochloride (C)

<sup>7</sup> Official State Bulletin of 27 March 2018:

<http://www.aecosan.msssi.gob.es/AECOSAN/docs/documentos/noticias/2018/BOE-A-2018-4245.pdf> (accessed on 18 April 2018)

<sup>8</sup> List of other substances with a nutritional or physiological effect:

[http://www.salute.gov.it/imgs/C\\_17\\_pagineAree\\_1268\\_listaFile\\_itemName\\_4\\_file.pdf](http://www.salute.gov.it/imgs/C_17_pagineAree_1268_listaFile_itemName_4_file.pdf) (accessed on 18 April 2018)

### 3.2.1.1. Chondroitin sulphate

Chondroitin sulphate is a glycosaminoglycan, formed by the repetition of a dimer consisting of glucuronic acid and *N*-acetylgalactosamine on the model GlcA( $\beta$ 1 $\rightarrow$ 3)GalNAc( $\beta$ 1 $\rightarrow$ 4) (Figure 2). It is synthesised by the body and plays a role in maintaining the structure and elasticity of cartilage, tendons, skin and artery walls. It is also a component of proteoglycans<sup>9</sup>.

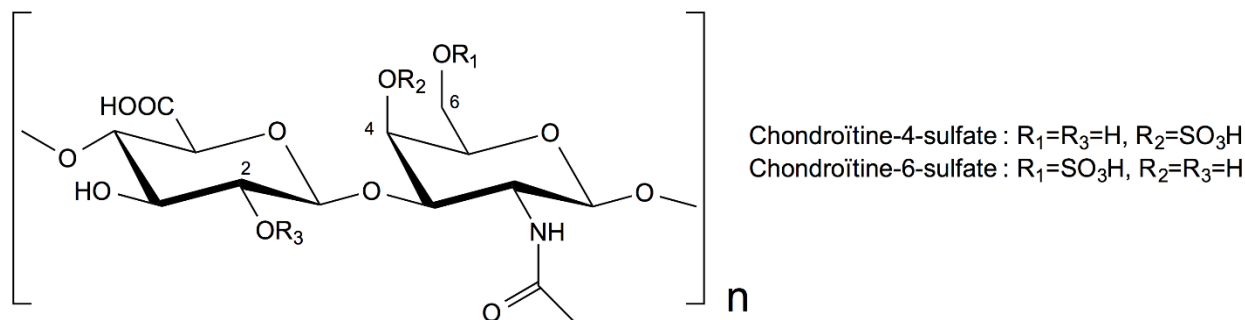


Figure 2: Structure of chondroitin sulphate

The proportions of the 4-sulphate and 6-sulphate groups and the molecular weight vary according to the source animal species. Bovine chondroitin sulphate has a molecular weight of 20 to 26 kDa. It consists of essentially monosulphated disaccharides on *N*-acetylgalactosamine (especially position 4, and 6). In shark chondroitin sulphate, which has a molecular weight of 50 to 60 kDa, 6-sulphated disaccharide predominates and a significant proportion of disulphated disaccharides can be observed (mainly from additional sulphation at position 2 of glucuronic acid). Chondroitin of fermentation origin does not appear to be sulphated in its natural state. It has an average molecular weight of 9 kDa.

## 3.2.2. Commercial source and form

### 3.2.2.1. Glucosamine

Commercial forms of glucosamine are prepared mainly from the hydrolysis of chitin, the main constituent of shells from crustaceans such as crabs and shrimps. The glucosamine thus produced is then transformed into sulphate or hydrochloride. Commercial forms of glucosamine can also be prepared from the hydrolysis of *Aspergillus niger* chitin (EFSA 2009).

The investigation conducted by the DGCCRF in 2017 on food supplements for joint conditions also sought to verify the origin of the glucosamine. Its analyses showed that *"the glucosamine comes mainly from shells of crustaceans (crab, shrimp, crayfish, etc.) supplied by companies located in France, Europe and China"*.

Glucosamine sulphate, which is intensely hygroscopic, is usually stabilised by co-crystallisation<sup>10</sup> or co-precipitation<sup>11</sup>. The most common forms are as follows:

- Glucosamine sulphate stabilised by co-crystallisation or co-precipitation with sodium chloride (Figure 1). This patented product is the most widely used in clinical trials in North America. It contains 1884 mg of glucosamine sulphate/NaCl co-precipitate corresponding to 1500 mg of glucosamine sulphate and 1178 mg of glucosamine base.

<sup>9</sup> Proteoglycans are compounds consisting of a core protein on which are grafted polysaccharide chains called glycosaminoglycans. They participate in assembly of the matrix while giving it many rheological properties.

<sup>10</sup> Crystallisation is a phenomenon by which the parts of a substance that was in a gaseous state or dissolved in a liquid gather together, by mutual attraction, to form a solid body of a regular and determined pattern.

<sup>11</sup> Precipitation is the formation in a solution of a solid compound (distinct from the liquid phase of the solvent) from one or more initially dissolved chemical species.

- Glucosamine sulphate stabilised by co-crystallisation or co-precipitation with potassium chloride.

Glucosamine hydrochloride (Figure 1) is marketed either in its pure state (> 99%) or in a mixture with sulphates or inorganic chlorides (e.g. of sodium).

A glucosamine derivative, *N*-acetylglucosamine (Figure 3), is also marketed as a food supplement, and is offered for similar uses and as an "adjuvant" in autoimmune diseases.

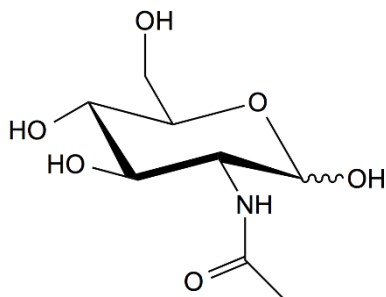


Figure 3: *N*-acetyl-D-glucosamine

#### 3.2.2.2. Chondroitin sulphate

Commercial chondroitin sulphate is mainly extracted and purified from the trachea of cattle, the nasal septum of pigs, shark fins and fish cartilage. Other production techniques using biotechnologies (enzymatic biotransformations or fermentation processes from an *Escherichia coli* strain) have been described in publications (Schiraldi, Cimini, and De Rosa 2010). There are many available extraction methods, which are subject to industrial secrecy. Most processes start with enzymatic digestion followed by a variable number of washing, incubation and elution steps (Coates *et al.* 2010).

The investigation conducted by the DGCCRF in 2017 showed that chondroitin sulphate primarily comes from fish (e.g. shark) cartilage shavings and extracts produced mainly in China.

### 3.3. Risk of contamination

Although chitin – mainly that of marine origin – has a strong metal chelating ability, the scientific literature has not so far reported any cases of products on the market containing glucosamine being contaminated by heavy metals.

Potential contaminants of chondroitin sulphate may include proteins or small organic molecules from the source tissue, or organic solvents or adjuvants used in the purification process (Schiraldi, Cimini, and De Rosa 2010).

Only medicinal products undergo thorough mandatory quality control.

### 3.4. Pharmacokinetic data

#### 3.4.1. Glucosamine

##### 3.4.1.1. Endogenous origin

Physiological plasma concentrations of glucosamine are around 0.04 mmol/L (Monauni *et al.* 2000, Pouwels *et al.* 2001). Endogenous production of glucosamine in humans is between 4 and 20 g/day (ANSES 2012).

#### **3.4.1.2. Exogenous origin**

A series of experimental trials using glucosamine sulphate showed that the pharmacokinetic parameters are relatively similar in humans, rats and dogs (Setnikar and Rovati 2001).

Glucosamine taken orally is absorbed by the small intestine. According to Setnikar *et al.* (1993), this intestinal absorption in humans accounts for about 85% of the glucosamine ingested, but only 20 to 30% is immediately bioavailable at the systemic level, with a significant fraction undergoing hepatic first-pass metabolism. Other authors believe that intestinal absorption is much lower and that the hepatic first-pass effect is limited (Aghazadeh-Habashi *et al.* 2002, Simon *et al.* 2011).

Exogenous glucosamine is then actively transported by glucose transporters to cells, where it is phosphorylated (Uldry *et al.* 2002, Anderson, Nicolosi, and Borzelleca 2005).

The bioavailability of the sulphate forms is not equivalent to the hydrochloride forms when taken orally. Pharmacokinetic studies show that oral administration of a 1500 mg dose of glucosamine sulphate once a day in healthy volunteers results in a steady-state plasma concentration of 9 mmol/L glucosamine, while oral administration of 500 mg of glucosamine hydrochloride three times a day results in a steady-state plasma concentration of only 1.2 mmol/L glucosamine (Persiani *et al.* 2005, Bruyère, Altman, and Reginster 2016). Despite differences in administration, these data indicate that bioavailability is lower for glucosamine hydrochloride than for the sulphate form.

Urinary excretion is low (2% of the dose ingested after 48 hours) (Setnikar and Rovati 2001).

#### **3.4.2. Chondroitin sulphate**

There are very few data available on the pharmacokinetics of chondroitin sulphate.

##### **3.4.2.1. Endogenous origin**

In the study by Volpi (2002), plasma concentrations of endogenous chondroitin sulphate were measured in six healthy volunteers every two hours from 8 a.m. to midnight. They ranged from 0.3 to 5.3 µg/mL. In the same study, the endogenous plasma concentration was also measured in 20 healthy volunteers prior to the administration of exogenous chondroitin sulphate. It was detectable in all of the subjects with an average concentration of  $3.80 \pm 1.77$  µg/mL (min 1.4 µg/mL and max 7.6 µg/mL).

##### **3.4.2.2. Exogenous origin**

In the previously mentioned study by Volpi (2002), an increase in plasma chondroitin sulphate concentrations was observed after administration of 4 g of Chondrosulf® to 20 healthy male subjects. The maximum plasma concentration ( $C_{max}$ ) of chondroitin sulphate measured was  $12.73 \pm 4.69$  µg/mL, 2.4 hours after administration. Previous studies had found the time to reach maximum plasma concentration ( $T_{max}$ ) was 3.2 hours, 4 or 5 hours.

Beef chondroitin sulphate is absorbed more rapidly than the same dose from shark cartilage, with the absorption percentage being roughly equivalent (Volpi 2002, 2003).

Vidal (2017) states that "*in animals, the concentration of labelled chondroitin sulphate enables absorption to be estimated at 66% with the labelled product being found in synovial fluid and cartilage. In humans, intestinal absorption is rapid. It has been assessed at 13% when in the form of a high molecular weight compound and 20% as a low molecular weight compound*".

The study by Jackson *et al.* (2010) (n=10) showed, however, that the endogenous plasma concentration of chondroitin sulphate was unchanged following administration of 1200 mg of exogenous chondroitin sulphate.

The extent of chondroitin sulphate's intestinal absorption and bioavailability is still under debate. The increased plasma concentration of chondroitin sulphate in humans was essentially detected at a high dose (4 grams) and appears to be lower at the usual dose (1.2 grams).

### **3.5. Adverse effects of chondroitin sulphate and glucosamine**

#### **3.5.1. Cases from nutrivigilance**

Between the establishment of the nutrivigilance scheme in 2009 and the month of February 2018, ANSES received 74 reports of adverse effects likely to be associated with the consumption of food supplements containing glucosamine and chondroitin sulphate.

The most commonly reported effects were haematological (such as thrombocytopaenic purpura and disrupted INR), gastroenterological (e.g. digestive disorders and abdominal pain), hepatic (mainly hepatitis) and dermatological disorders (e.g. skin rashes and pruritus).

Of these 74 reports, 23 were analysed for their causality by the "Nutrivigilance" WG, based on the method defined in the ANSES opinion of 11 May 2011 (ANSES 2011) (Table 1). The others were not sufficiently documented to be analysed (due, for example, to consumption dates being unknown or the consumed product not being identified).



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**Table 1: Analysable cases received by the nutrivigilance scheme between 2009 and February 2018**

Registration no.	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) <sup>12</sup> Onset time Dose ingested per day	Type(s) of adverse effect(s)	Level of severity of the clinical picture <sup>13</sup>	Chronological score <sup>14</sup>	Semiological score <sup>15</sup>	Intrinsic causality <sup>16</sup>	Comments
2012-015	GCA 2700 <sup>®17</sup> (Santé Verte)	M, 65 years	Cytolytic hepatitis 2 months unknown doses	Hepatic	2	C4 (timeframe consistent, progression suggestive, reintroduction positive)	S2 (a few aetiologies explored and excluded)	Very likely	Recurrence of hepatitis after reintroducing the same food supplement for 3 weeks
2013-213	GCA 2700 <sup>®</sup> (Santé Verte)	F, 60 years	Cytolytic hepatitis about 6 months 1052 mg of glucosamine 888 mg of chondroitin sulphate	Hepatic	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	Likely	Combined with levothyroxine and Speed Draineur <sup>®</sup> red fruit and summer fruit food supplements
2016-296	Govital Chondroflex <sup>®18</sup> (Urgo)	M, 64 years	Cytolytic hepatitis about 3 months 1000 mg of glucosamine 300 mg of chondroitin sulphate	Hepatic	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	Likely	Combined with Inspra <sup>®</sup> , Nebilox <sup>®</sup> , Plavix <sup>®</sup> , Amlor <sup>®</sup> , Burinex <sup>®</sup> and insulin

<sup>12</sup> Adverse effect selected by the Nutrivigilance WG after the case had been analysed.

<sup>13</sup> The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).

<sup>14</sup> The chronological score ranges from C0 to C4.

<sup>15</sup> The semiological score ranges from S0 to S3.

<sup>16</sup> The intrinsic score ranges from I0 (excluded) to I4 (very likely).

<sup>17</sup> Composition of GCA 2700<sup>®</sup>: glucosamine, chondroitin sulphate, turmeric, methylsulfonylmethane, harpagophytum, hyaluronic acid

<sup>18</sup> Composition of Govital Chondroflex<sup>®</sup>: glucosamine, chondroitin sulphate, methylsulfonylmethane, collagen, vitamin C

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Registration no.	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) <sup>12</sup> Onset time Dose ingested per day	Type(s) of adverse effect(s)	Level of severity of the clinical picture <sup>13</sup>	Chronological score <sup>14</sup>	Semiological score <sup>15</sup>	Intrinsic causality <sup>16</sup>	Comments
2016-057	Kotor Articulations <sup>®19</sup> (Kotor Pharma)	F, 74 years	Cytolytic hepatitis about 5 months unknown doses	Hepatic	2	C2 (timeframe consistent, progression cannot be interpreted)	S0 (sarcoidosis and use of Crestor <sup>®</sup> are known aetiologies of hepatitis)	Unlikely	Consumer with a sarcoidosis of the salivary glands  Combined with Crestor <sup>®</sup> , citalopram, Cotareg <sup>®</sup> , sotalol, Orocal <sup>®</sup> , Piascledine <sup>®</sup> , Esberiven <sup>®</sup> and the food supplements Perfovitol <sup>®</sup> and Probiodiet <sup>®</sup>
2017-257	Cartilamine <sup>®20</sup> (Effi-science)	F, 73 years	Cytolytic hepatitis about 8 months unknown doses	Hepatic	2	C0 (timeframe inconsistent)	-	Responsibility excluded	History of icteric hepatitis  Combined with verapamil, spironolactone and Structum <sup>®</sup>

<sup>19</sup> Composition of Kotor Articulations<sup>®</sup>: skate cartilage, turmeric, black pepper, manganese, vitamins C and E

<sup>20</sup> Composition of Cartilamine<sup>®</sup>: glucosamine, vitamin C

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2018-023	Lipocyte <sup>®21</sup> (NHCO Nutrition)	F, 50 years	Cytolytic hepatitis about 6 months unknown doses	Hepatic	2	C1 (timeframe consistent, progression not suggestive)	S1 (no aetiology sought)	Unlikely	Combined with esomeprazole, fluoxetine, amitriptyline, Meteospasmyl <sup>®</sup> , Uvedose <sup>®</sup> , Oestrodose <sup>®</sup> , alprazolam, cromoglycate, paracetamol, Tiorfan <sup>®</sup> , ciclopirox, MycoSter <sup>®</sup> , Telfast <sup>®</sup> , Lumirelax <sup>®</sup> , ketoprofen and Lamaline <sup>®</sup> , and the food supplements CelluStepper <sup>®</sup> , Drain' Detox Drink <sup>®</sup> and Permaflore <sup>®</sup>
2013-012	Chondrosteo <sup>®22</sup> (EA Pharma)	M, 82 years	Cytolytic hepatitis, acute kidney failure about 3 months 750 mg of glucosamine 100 mg of chondroitin sulphate	Hepatic, uro-nephrological	2	C3 (timeframe consistent, progression suggestive)	S0 (sepsis probably led to kidney failure and then to heart and liver failure)	Possible	Consumer with chronic kidney failure Combined with Bactrim <sup>®</sup>

<sup>21</sup> Composition of Lipocyte<sup>®</sup>: L-arginine, L-aspartate, blackcurrant, green tea, grape marc, glycine, *N*-acetyl-D-glucosamine, nasturtium, L-histidine, fennel, horsetail, elderberry, sweet clover, pineapple stem, caffeine, papaya

<sup>22</sup> Composition of Chondrosteo<sup>®</sup>: glucosamine, chondroitin sulphate, methylsulfonylmethane, blackcurrant, bamboo, meadowsweet, harpagophytum, phosphate, calcium, copper, manganese

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2017-162	Cartilage de Raie <sup>®23</sup> (Diéti Natura)	F, 59 years	Acute pancreatitis, acute cholestatic and cytolytic hepatitis about 3 months 1600 mg of skate cartilage	Hepatic, gastroenterological	3	C2 (timeframe consistent, progression suggestive, reintroduction negative)	S0 (microlithiasis and alcohol consumption are two very likely aetiologies of pancreatitis)	Unlikely	Combined with the food supplement Harpagophytum <sup>®</sup> (Diéti Natura) Alcohol consumption
2016-136	Govital Chondroflex <sup>®</sup> (Urgo)	F, 77 years	Nausea 4-5 hours unknown doses	Gastroenterological	1	C2 (timeframe consistent, progression suggestive, reintroduction negative)	S1 (no aetiology sought)	Possible	Combined with Previscan <sup>®</sup> , bisoprolol, Hemigoxine <sup>®</sup> and perindopril
2016-213	Chondro Aid Fort <sup>®</sup> after 2013 <sup>24</sup> (Arkopharma)	F, 48 years	Digestive disorders (diarrhoea, bloating, spasms) 1 day 1125 mg of glucosamine 900 mg of chondroitin sulphate	Gastroenterological	1	C4 (timeframe consistent, progression suggestive, reintroduction positive)	S1 (no aetiology sought)	Likely	Combined with Temeritduo <sup>®</sup> , sertraline, Rabeprazole <sup>®</sup> and Ginkor Fort <sup>®</sup>

<sup>23</sup> Composition de Cartilage de Raie<sup>®</sup>: skate cartilage

<sup>24</sup> Composition of Chondro Aid Fort<sup>®</sup> (after 2013): glucosamine, chondroitin sulphate, harpagophytum, vitamin C

**ANSES Opinion**  
**Request No 2015-SA-0069**

Registration no.	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) <sup>12</sup> Onset time Dose ingested per day	Type(s) of adverse effect(s)	Level of severity of the clinical picture <sup>13</sup>	Chronological score <sup>14</sup>	Semiological score <sup>15</sup>	Intrinsic causality <sup>16</sup>	Comments
2016-233	Govital Chondroflex® (Urgo)	F, 48 years	Digestive disorders, fatigue 20 days unknown doses	Gastroenterological, general symptoms	1	C4 (timeframe consistent, progression suggestive, reintroduction positive)	S1 (no aetiology sought)	Likely	Combined with the food supplement Gestarelle A®, and a Phytostandard® product, marine magnesium and turmeric
2016-232	Govital Chondroflex® (Urgo)	F, 49 years	Headaches a few hours unknown doses	General symptoms	1	C4 (timeframe consistent, progression suggestive, reintroduction positive)	S1 (no aetiology sought)	Likely	-
2017-285	GCA 2700® (Santé Verte)	F, 67 years	Dizziness, loss of appetite, abdominal tightness a few hours 1052 mg of glucosamine 888 mg of chondroitin sulphate	General symptoms	2	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	Likely	Combined with Exforge® and omeprazole

**ANSES Opinion**  
**Request No 2015-SA-0069**

Registration no.	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) <sup>12</sup> Onset time Dose ingested per day	Type(s) of adverse effect(s)	Level of severity of the clinical picture <sup>13</sup>	Chronological score <sup>14</sup>	Semiological score <sup>15</sup>	Intrinsic causality <sup>16</sup>	Comments
2012-149	Cartilage de Requin <sup>®25</sup> (Ponroy)	F, 56 years	Blood hyperviscosity, central retinal vein occlusion unknown time 3 capsules morning and evening	Haematology	2	C2 (timeframe consistent, progression cannot be interpreted)	S2 (a few aetiologies explored and excluded)	Unlikely	Combined with harpagophytum bio <sup>®</sup> (Ponroy)
2014-342	Cuivramine <sup>®26</sup> (Labrha)	M, 35 years	Thrombocytopaenic purpura about 25 days 1500 mg of glucosamine	Haematology	3	C3 (timeframe consistent, progression suggestive)	S3 (no other aetiology)	Very likely	-
2017-258	Kinesamine <sup>®27</sup> (Monin Chanteaud)	M, 90 years	Increase in the INR about 15 days 750 mg of glucosamine	Haematology	1	C2 (timeframe consistent, progression cannot be interpreted)	S1 (no aetiology sought)	Unlikely	Combined with simvastatin, Lasilix <sup>®</sup> , Levothyrox <sup>®</sup> , lansoprazole and Previscan <sup>®</sup>
2017-280	Chondrosteo <sup>®</sup> (EA Pharma)	F, 67 years	Vascular purpura 1 month unknown doses	Haematology	2	C2 (timeframe consistent, progression cannot be interpreted)	S2 (a few aetiologies explored and excluded)	Unlikely	No other treatment

<sup>25</sup> Composition of Cartilage de Requin<sup>®</sup>: shark cartilage

<sup>26</sup> Composition of Cuivramine<sup>®</sup>: glucosamine, ginger, copper, vitamin C

<sup>27</sup> Composition of Kinesamine<sup>®</sup>: glucosamine, zinc, manganese, vitamin C

**ANSES Opinion**  
**Request No 2015-SA-0069**

Registration no.	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) <sup>12</sup> Onset time Dose ingested per day	Type(s) of adverse effect(s)	Level of severity of the clinical picture <sup>13</sup>	Chronological score <sup>14</sup>	Semiological score <sup>15</sup>	Intrinsic causality <sup>16</sup>	Comments
2015-291	Glucosamine Chondroïtine MSM <sup>®28</sup> (Solgar)	F, 71 years	Kidney failure about 5 months 750 mg of glucosamine 600 mg of chondroitin sulphate	Uro-nephrological	3	C0 (timeframe inconsistent)		Excluded	-
2017-270	Cartilamine <sup>®</sup> (Effi-science)	F, 73 years	Acute kidney failure, shock 13 days unknown doses	Uro-nephrological	3	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	Likely	Combined with Zocor <sup>®</sup> , Pariet <sup>®</sup> and another unidentified food supplement
2014-379	Glucosamine Chondroïtine Complex <sup>®29</sup> (Solgar)	F, 66 years	Increase in arthralgia and lower back pain 15 days 1500 mg of glucosamine 1500 mg of chondroitin sulphate	Rheumatology	3	C2 (timeframe consistent, progression cannot be interpreted)	S1 (no aetiology sought)	Possible	Consumer with back pain and generalised osteoarthritis Combined with Flécaïne <sup>®</sup> , Sectral <sup>®</sup> and Propofan <sup>®</sup>
2017-307	Artrobiol Plus <sup>®30</sup> (Ineldea)	M, 71 years	Pain in the lower back, left leg and ribs	Rheumatology	2	C1 (timeframe consistent, progression not suggestive)	S1 (no aetiology sought)	Unlikely	Taken with homeopathic medicine, Triatec <sup>®</sup> and Plavix <sup>®</sup>

<sup>28</sup> Composition of Glucosamine Chondroïtine MSM<sup>®</sup>: glucosamine, chondroitin sulphate, methylsulfonylmethane

<sup>29</sup> Composition of Glucosamine Chondroïtine Complex<sup>®</sup>: glucosamine, chondroitin sulphate

<sup>30</sup> Composition of Artrobiol Plus<sup>®</sup>: glucosamine, chondroitin sulphate, Osteol<sup>®</sup>, methylsulfonylmethane, harpagophytum, blackcurrant, manganese, copper

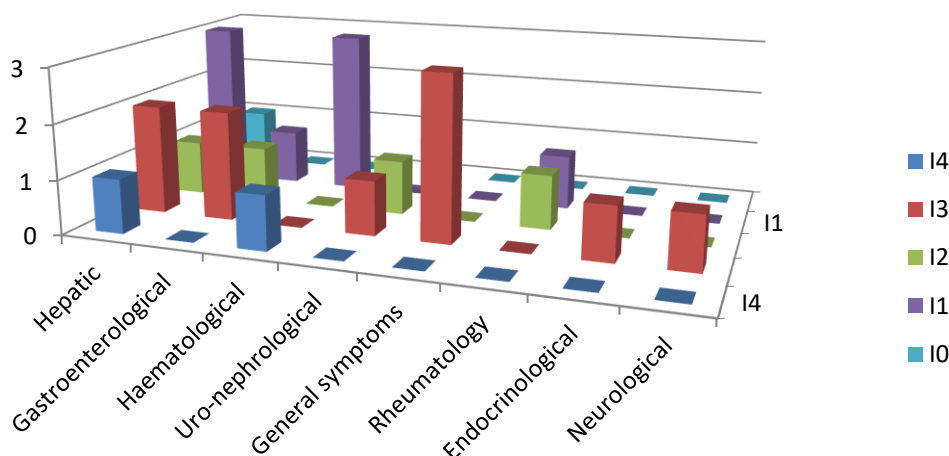
**ANSES Opinion**  
**Request No 2015-SA-0069**

Registration no.	Product name (manufacturer)	Consumer's sex and age	Adverse effect(s) <sup>12</sup> Onset time Dose ingested per day	Type(s) of adverse effect(s)	Level of severity of the clinical picture <sup>13</sup>	Chronological score <sup>14</sup>	Semiological score <sup>15</sup>	Intrinsic causality <sup>16</sup>	Comments
2011-061	GCA 2700® (Santé Verte)	M, 66 years	Hyperglycaemia during the GCA 2700® consumption period unknown doses	Endocrinological	1	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	Likely	Consumer with type-2 diabetes Combined with Glucophage®, Diamicon®, Lasilix®, Aprovel® and simvastatin
2016-131	Chondro Aid Fort® <sup>31</sup> before 2013 (Arkopharma)	M, 66 years	Sleep apnoea a few weeks 1125 mg of glucosamine 900 mg of chondroitin sulphate	Neurological	2	C3 (timeframe consistent, progression suggestive)	S1 (no aetiology sought)	Likely	No other treatment

<sup>31</sup> Composition of Chondro Aid Fort® (before 2013): glucosamine, chondroitin sulphate, vitamin E



The breakdown of the causality of the analysed cases by type of adverse effect is shown in Figure 4 (some products may have caused several different adverse effects).



**Figure 4: Breakdown of adverse effects in nutravigilance for glucosamine and chondroitin sulphate by type and causality<sup>32</sup> (analysable cases)**

For these analysable cases, the most frequently reported adverse effects were primarily hepatic, gastroenterological and haematological disorders. Causality in these cases was high, with two very likely cases and four likely cases.

Case 2012-015 was the subject of a publication in 2015 because of the seriousness of the reported adverse effect (hepatitis requiring hospital admission) and the very likely causality (ANSES 2015).

Glucosamine and chondroitin sulphate were rarely the only ingredients in the food supplements involved in these cases. However, the causality score applies to the food supplement as a whole and not to an ingredient. The role of another food supplement ingredient in the onset of the adverse effect cannot therefore be ruled out.

In addition, the occurrence of the adverse effects may have been facilitated by interactions between the different components of the food supplement, between several food supplements, or between the food supplement and any medicinal products consumed concomitantly.

### 3.5.1. Cases from pharmacovigilance

Between 1985 and February 2017, the ANSM collected nearly 100 cases of adverse effects likely to be associated with the use of drugs containing glucosamine and more than 300 cases for those containing chondroitin sulphate. The adverse effects most frequently reported for glucosamine were gastroenterological (nausea, abdominal pain, digestive disorders), neurological (headache, fatigue) and dermatological (rash, pruritus). For chondroitin sulphate, they were mainly dermatological (erythema, urticaria, eczema) and gastroenterological (nausea, vomiting). For these two ingredients, hepatobiliary adverse effects were also reported but with a lower frequency of occurrence.

### 3.5.2. Cases from toxicovigilance

Alongside the cases identified specifically by the nutravigilance scheme, two cases of adverse effects likely to be associated with the consumption of food supplements for joint conditions containing glucosamine and chondroitin sulphate were recorded by the French poison control centres between

<sup>32</sup> I0 = excluded, I1 = unlikely, I2 = possible, I3 = likely, I4 = very likely.

2010 and February 2017. These two cases occurred following the consumption of products containing only glucosamine. They are shown in Table 2 below.

**Table 2: Cases of adverse effects reported to the toxicovigilance scheme**

Product name	Sex and age of the consumer	Duration of treatment	Adverse effects	Comments
Cartilamine®	F, 73 years	1 day	Nausea	Single dose
Cartilan Plus® <sup>33</sup>	F, 88 years	1 month	Subicterus, death	Autopsy not performed

In addition, one suicide attempt involving glucosamine was reported to a poison control centre.

### 3.5.3. Cases identified abroad

#### 3.5.3.1. In Europe

In November 2016, ANSES approached its European counterparts with a view to obtaining more data on the adverse effects likely to be associated with the consumption of food supplements containing glucosamine and/or chondroitin sulphate. Several countries responded that no adverse effects had been brought to their attention with this type of product (Austria, Bulgaria, Cyprus, Croatia, Spain, Greece, Latvia, Lithuania, Luxembourg, Poland, Czech Republic, Slovakia, Slovenia and Switzerland). As most of them do not have a nutriviigilance scheme, adverse effects likely to be associated with the consumption of food supplements containing these substances are not collected in a systematic manner.

In Germany, 11 cases of adverse effects likely to be associated with the consumption of food supplements containing glucosamine and chondroitin sulphate were reported between 2003 and 2016. Three cases of liver damage and two cases of allergies were described. The consumers involved in the other cases presented with skin irritation, dizziness, nausea, pyrosis, tachycardia and an increase in INR.

In Italy, 17 cases, mainly of a dermatological and gastroenterological nature, were collected. They are shown in Table 3. The composition of the incriminated products was not specified.

**Table 3: Cases of adverse effects reported in Italy**

Sex and age of the consumer	Adverse effects	Comments
F, 54 years	Abdominal pain, nausea, dysentery syndrome	-
F, 40 years	Abdominal pain, vomiting, dysentery syndrome	-
F, 50 years	Lumps on the tongue	-
F, 74 years	Increased INR	Combined with warfarin
F, 77 years	Excessive sweating	Combined with metformin, doxazosin, atorvastatin and losartan
M, 36 years	Headache	-

<sup>33</sup> Composition of Cartilan Plus®: glucosamine, mangosteen extracts, apple pectin, sodium alginate, vitamin C, crab shell chitin oligosaccharides.

F, 60 years	Abdominal pain, diarrhoea	Combined with valsartan+hydrochlorothiazide
M, 52 years	Diffuse erythema, pruritus	Combined with lansoprazole, dexibuprofen, Vagostabil® and Grintuss®
F, 46 years	Diffuse erythema, pruritus	-
F, 72 years	Dry mouth, swollen lips	-
F, 66 years	Diffuse erythema	Combined with atorvastatin, irbesartan+hydrochlorothiazide
M, 74 years	Pain in the ribs and difficulty urinating	Combined with rosuvastatin, lansoprazole, acetylsalicylic acid, ketoprofen and zofenopril
F, 63 years	Headache	-
F	Abnormal hair growth	-
F, 74 years	Chest pain	-
F, 63 years	Dyspepsia, epigastralgia	-
M, 74 years	Urticaria	-

### 3.5.3.2. In the United States and Canada

ANSES also approached the FDA (Food and Drug Administration) in the United States and Health Canada.

In Canada, data were sought for the period from 1 January 1965 to 30 June 2016. Six cases involving glucosamine and chondroitin sulphate were collected and are shown in Table 4 below.

**Table 4: Cases of adverse effects reported in Canada**

Sex and age of the consumer	Duration of treatment	Adverse effects	Comments
F, 91 years	2 years	Bronchospasm	Asthmatic patient
F, 63 years	1 day	Generalised rash	-
M, 54 years	1 day	Paraesthesia Swollen pharynx Feeling of suffocation	-
F, 50 years	4 months	Eye irritation Eyesight disorder	-
F, 27 years	Unknown	Migraine	-
M, 87 years	Unknown	Increased INR	Combined with warfarin

The FDA did not send any data within the requested timeframe. However, a search of the FDA-Medwatch database was performed. The most commonly reported adverse effects after consuming glucosamine or chondroitin sulphate (or both in combination) were gastroenterological (diarrhoea, nausea), neurological (cognitive disorders, insomnia) and rheumatology disorders (arthralgia).

Causality could not be established for any of the cases transmitted by the toxicovigilance scheme or any of the foreign vigilance schemes, due to a lack of information.

The adverse effects collected in the pharmacovigilance and toxicovigilance schemes, and from the vigilance schemes of other European countries, Canada and the United States, are heterogeneous in nature. They mainly concern gastroenterological, neurological and dermatological effects. The effects collected by ANSES in the nutriviigilance scheme are characterised by a predominance of reports concerning liver effects and an absence of analysable reports concerning dermatological conditions.

### **3.5.4. Literature data**

#### **3.5.4.1. Effects of glucosamine *in vitro* and in animals**

##### **➤ Acute toxicity**

The median lethal dose (LD<sub>50</sub>) by the oral route is above 5 g/kg in mice, rats and rabbits (Anderson, Nicolosi, and Borzelleca 2005).

##### **➤ Chronic toxicity**

Chronic toxicity studies<sup>34</sup> show no side effects of glucosamine after 52 weeks at a dose of 2700 mg/kg/day in rats and after 26 weeks at a dose of 2149 mg/kg/day in dogs (Anderson, Nicolosi, and Borzelleca 2005).

##### **➤ Effects on glucose metabolism**

The US Institute of Medicine reviewed 14 reports on the potential effect of glucosamine on glucose metabolism in rats when administered intravenously or intraperitoneally at doses ranging from 240 to 9937 mg/kg of body weight. Twelve of these reports showed that glucosamine altered glucose metabolism (increased blood glucose levels, reduced glucose absorption and decreased glucose elimination). In two studies, infusion of 564 mg/kg glucosamine did not affect blood glucose concentration and 250 mg/kg did not induce hyperglycaemia, but it altered glucose metabolism (EFSA 2009).

On the other hand, no effect on blood glucose levels was observed in rats, rabbits<sup>35</sup> or dogs after oral administration of glucosamine (Echard *et al.* 2001, Stender and Astrup 1977, Setnikar, Pacini, and Revel 1991).

However, a study in mice fed a standard diet showed that oral administration of glucosamine hydrochloride (1450 mg/kg) led to an increase in weight and a decrease in insulin sensitivity, while paradoxically, insulin signalling was improved in mice made insulin dependent by a high-fat diet (Hwang *et al.* 2015).

##### **➤ Effects on reproduction**

Mice aged 8 weeks received daily intraperitoneal injections of glucosamine (20 or 400 mg/kg) for 3 to 6 days before and 1 day after mating. Results were assessed on the 18<sup>th</sup> day of gestation. The

<sup>34</sup> Chronic toxicity is toxicity by repeated exposure for more than 90 days.

<sup>35</sup> The rabbit study was funded by a food supplement manufacturer.

administration of glucosamine reduced litter size, regardless of the dose. In 16-week-old mice, 20 mg/kg glucosamine reduced foetal weight and increased birth defects, but did not alter litter size (Schelbach *et al.* 2013).

➤ **Effects on the development of atherosclerosis**

The metabolic and vascular effects of glucosamine supplementation (15 mg/kg/day and 50 mg/kg/day) were studied in LDL receptor-deficient mice of both sexes, fed a diet high in fat and sugar (Western diet). Supplementation accelerated the atherosclerosis process<sup>36</sup> in male mice in the medium term (5 weeks), but not in the long term for either sex (10 or 20 weeks), despite the hyperlipidaemia observed in animals after this supplementation period (Tannock *et al.* 2006).

➤ **Effects on platelet count**

Oral administration of glucosamine sulphate (20 mg/kg) for 30 days in rats induced a significant increase in platelet count. In contrast, simultaneous oral administration of glucosamine sulphate (20 mg/kg) and chondroitin sulphate (17 mg/kg) did not result in a significant increase in platelet count (Noushi and Al-Shawi 2013).

➤ **Effects on cultured chondrocytes**

In a study using a culture of bovine joint cartilage explants, the incorporation of increasing doses of glucosamine hydrochloride (2.5, 6.5 and 25 mg/mL) led to a sharp decrease in chondrocyte<sup>37</sup> activity and finally cell death from 6.5 mg/mL (De Mattei *et al.* 2002).

#### **3.5.4.1. Effects of chondroitin sulphate in animals**

➤ **Acute toxicity**

The median lethal dose (LD<sub>50</sub>) by the oral route is above 10,000 mg/kg in mice and rats (NTP 2002).

➤ **Chronic toxicity**

Only one chronic toxicity study was found in the literature, leading the WG and CES to present its results even though it did not report any adverse effects.

To investigate the toxicity of microbial-derived chondroitin sulphate sodium, Miraglia *et al.* (2016)<sup>38</sup> conducted a 90-day study in rats (10 per group) gavaged with chondroitin sulphate sodium at concentrations of 0, 250, 500 or 1000 mg/kg of body weight per day. The authors concluded that chondroitin sulphate administration does not cause any adverse effects. However, a significant decrease in leukocytes was observed in the females receiving 250 mg/kg/day, while higher doses of chondroitin sulphate in female or male rats showed no difference. In addition, a significant decrease (4%) in prothrombin time was observed in males treated with 1000 mg/kg/day. Fluctuations in some biological parameters were also recorded: increased aspartate aminotransferases (ASATs) in one animal (59% above the controls), increased triglycerides in another, significant increases in plasma concentrations of chloride and sodium in females receiving 1000 mg/kg/day, of phosphorus in females receiving 250 mg/kg/day and of potassium in female rats receiving 500 and 1000 mg/kg/day. The authors regarded these changes as accidental biological variations and not treatment-related

<sup>36</sup> Atherosclerosis is characterised by the build-up of plaque, mainly made up of lipids, on the walls of the arteries. This build-up can lead to the obstruction of vessels.

<sup>37</sup> Chondrocytes are the cells that make up cartilage.

<sup>38</sup> Study financed by Gnosis S.p.A, a manufacturer of microbial-derived chondroitin sulphate.

adverse effects because they were not observed in both sexes, were small in magnitude and unrelated to histopathological changes.

#### **3.5.4.1. Effects of glucosamine and chondroitin sulphate on coagulation *in vitro* and in animals**

In studies of glucosamine's interaction with coagulation mechanisms, inhibited platelet aggregation induced by adenosine diphosphate (ADP) was observed *in vitro*. This inhibition was also reported *ex vivo* on platelets from individuals orally administered with 1500 mg of glucosamine per day over a seven-day period, or on guinea pig platelets for a daily dose of 400 mg of glucosamine (Bertram *et al.* 1981, Hua *et al.* 2004, Lu-Suguro *et al.* 2005). However, the BfR considered the clinical relevance of these studies to be uncertain (BfR 2009).

A study in rats showed that oral administration of 20 or 40 mg/kg/day of chondroitin sulphate for three days significantly decreased large platelet aggregates and increased blood flow (Ishikawa and al. 2010).

Yokotani *et al.* (2014) assessed whether glucosamine and chondroitin sulphate affected the anticoagulation activity of warfarin in mice, focusing on hepatic cytochrome P450 (CYP450) mediated mechanisms. The mice were divided into three groups. The first did not receive any glucosamine or chondroitin sulphate. The second received 443 mg of glucosamine and 464 mg of chondroitin sulphate for two weeks, and the third group received respectively 1523 mg and 1546 mg. Warfarin was then administered by gavage over the last two days. The authors showed that these two ingredients did not induce or inhibit CYP450s, suggesting that glucosamine and chondroitin sulphate do not affect the anticoagulation activity of warfarin through CYP450-mediated mechanisms.

#### **3.5.4.2. Adverse effects of glucosamine and chondroitin sulphate reported in the literature regarding humans**

A literature search was conducted for adverse effects reported in nutrivigilance in order to observe their frequency of occurrence and the doses of glucosamine or chondroitin sulphate at which they occurred. This search was only performed on the ingredients "glucosamine" and "chondroitin sulphate" and not on the other ingredients associated with them in the food supplements involved. In this section, the different types of effects are presented in decreasing order of frequency of occurrence in nutrivigilance.

##### **➤ Hepatic effects**

Seven reports of liver damage, where causality was not excluded, were analysed under the nutrivigilance scheme. Causality was found to be very likely in one case of hepatitis, likely in two cases, possible in one case and unlikely in three others. Four of these cases involved food supplements containing glucosamine combined with chondroitin sulphate. Two cases involved two food supplements containing skate cartilage. The last one concerned a food supplement containing *N*-acetyl-D-glucosamine in combination with other ingredients.

Other cases of liver damage involving glucosamine or chondroitin sulphate have been published in the literature and are described below. Only one article specified the doses of glucosamine or chondroitin sulphate contained in the consumed products.

- Glucosamine

Ossendza *et al.* (2007) reported the case of a 52-year-old man who developed cholestatic hepatitis after taking Glucosamine Forte® for 19 days for lower back pain. He did not consume any alcohol and was not taking any medication. Serological tests for viral hepatitis A, B, C and E, and for CMV, EBV, herpes, leptospirosis and HIV were negative. Anti-nuclear, anti-mitochondrial, anti-smooth muscle, anti-LKM1 and anti-cytosol antibodies were absent from the serum. Eight weeks after stopping the glucosamine, the hepatic enzyme abnormalities were corrected.

Fujii *et al.* (2008) reported the case of a 55-year-old woman diagnosed with cytolytic hepatitis. She had no personal or family history of liver disease, did not consume any alcohol and was not taking any medication. Six months before the adverse effect, she had started taking food supplements containing soy extract, glucosamine and lutein. Four weeks after stopping the food supplements, her liver function returned to normal without treatment.

Smith and Dillon (2009) described the case of three patients who developed acute liver injuries after consuming food supplements containing glucosamine. The first patient, 64 years old, developed acute hepatitis and kidney failure two weeks after discontinuing a food supplement combining glucosamine sulphate and chondroitin sulphate that he had been taking for four weeks. The patient died as a result of this hepatitis. The second patient was a 57-year-old woman who had consumed a food supplement combining glucosamine and cod liver oil for one month, before switching to a combination of glucosamine and methylsulfonylmethane taken for five days before her arrival at the hospital. She consulted for anorexia, general malaise, a 10-day history of jaundice and a 24-hour history of pruritus. Her health improved after she ceased taking the food supplement, although she later developed chronic hepatitis. The third patient, 55 years old and treated with bendroflumethiazide and diclofenac, had been taking five food supplements (glucosamine, black cohosh, valerian, cod liver oil, evening primrose oil) for several months. Hypertransaminasaemia was detected during biological testing. She recovered completely when the food supplements were discontinued. Since glucosamine was the only common ingredient in these three cases, the chronology was compatible and all other aetiologies had been ruled out, the authors concluded that the glucosamine was the cause of the hepatotoxicity.

Other authors reported the case of a 55-year-old woman who developed hepatic cytolysis (transaminases ten times higher than normal) after consuming a glucosamine food supplement for two weeks. Serological tests for hepatitis B and CMV were negative, as were autoimmune screening tests. Discontinuation of the glucosamine allowed the liver function to return to normal within four weeks. The authors indicate that the precise mechanism of hepatotoxicity is unknown but may be secondary to the production of toxic metabolites when the food supplement is metabolised by the liver (Ebrahim, Albeldawi, and Chiang 2012).

- Glucosamine combined with chondroitin sulphate

Linnebur, Rapacchietta, and Vejar (2010) reported evidence of hepatotoxicity in two people who consumed the Move Free Advanced® food supplement containing glucosamine, chondroitin sulphate, hyaluronic acid, methylsulfonylmethane, *Scutellaria baicalensis* and *Acacia catechu*. The first case concerned a 71-year-old woman treated with atenolol, mometasone, vitamins and calcium. Three weeks after first taking the food supplement, a disturbance in her liver function was detected, with values nine times higher than normal. Four to five weeks later, her liver function deteriorated. Serological tests for hepatitis A, B and C were negative. She then decided to stop the food supplement. Four weeks after discontinuation, her liver function improved and had returned to normal 12 weeks later. The second case involved an 85-year-old woman treated with levothyroxine, loratadine, guaifenesin, dextromethorphan, vitamin E, lutein and magnesium. Three weeks after starting Move Free Advanced®, her liver function was abnormal, with an increase in transaminases and alkaline phosphatase. It returned to normal seven weeks after discontinuation of the product. The authors reviewed the literature and indicated that the *Scutellaria baicalensis* was the most likely cause of the hepatotoxicity.

Cerda, Bruguera, and Parés (2013) used a questionnaire to follow up 151 patients with liver conditions of various aetiologies to assess the frequency of glucosamine and chondroitin sulphate use and to determine whether their use coincided with a worsening in liver function. Twenty-three patients (15.2%) reported taking food supplements containing glucosamine and/or chondroitin sulphate. An increase in transaminase values associated with the glucosamine intake was observed in two patients. In one of these patients, this disturbance was combined with a skin rash. This study did not include a control group.

Von Felden *et al.* (2013) reported the case of a man who developed severe autoimmune hepatitis eight weeks after starting Vita Mobility Complex<sup>®</sup>, a product containing a combination of glucosamine sulphate and chondroitin sulphate. This product provides 2460 mg of chondroitin sulphate per day<sup>39</sup>. The patient claimed to have taken two Chondrosulf<sup>®</sup> tablets per day – corresponding to 800 mg of chondroitin sulphate – for two years, apparently without any problems. Full remission was achieved following administration of treatment (prednisolone and then azathioprine).

- Chondroitin sulphate

No studies were found on the role of chondroitin sulphate alone in the development of liver damage.

Several cases of cytolytic hepatitis associated with glucosamine consumption combined or not with chondroitin sulphate were reported to the nutrivigilance scheme or are described in the literature. No mechanism has been described in the literature, and the doses at which these effects occur are unknown. Nevertheless, the WG and CES recommend that in the presence of hepatic cytolysis of undetermined origin, the consumption of food supplements containing glucosamine or chondroitin sulphate should be investigated.

#### ➤ **Gastroenterological effects**

Four cases of gastroenterological effects were analysed under the nutrivigilance scheme. These were two cases of digestive disorders where causality was considered likely, one case of nausea considered possible and one case of pancreatitis considered unlikely. The food supplements implicated in these cases contained glucosamine combined with chondroitin sulphate or skate cartilage.

Gastrointestinal disorders are side effects frequently reported in safety and efficacy trials following administration of glucosamine or chondroitin sulphate.

- Glucosamine

In a multicentre open-label study conducted in Portugal by 252 doctors with 1208 patients taking 500 mg of glucosamine sulphate three times a day over periods from 13 to 99 days, 12% of patients reported moderate adverse effects, mainly involving the gastrointestinal tract (epigastric pain, diarrhoea). All these effects were reversible upon discontinuation of treatment (Tapadinhas, Rivera, and Bignamini 1982).

Other studies report the same adverse effects following administration of 1500 mg/d of glucosamine for four weeks to three years. The frequency of occurrence was comparable to that of the placebo group (Müller-Faßbender *et al.* 1994, Rindone *et al.* 2000, Pavelká *et al.* 2002, Anderson, Nicolosi, and Borzelleca 2005, Sherman, Ojeda-Correal, and Mena 2012).

- Glucosamine combined with chondroitin sulphate

<sup>39</sup> The current composition of the product indicates that it provides 2460 mg of glucosamine and not chondroitin sulphate, suggesting an error in the article.



Zuluaga *et al.* (2011) published the case of a 66-year-old woman with osteoarthritis who developed ulcers in the small intestine after taking a product containing glucosamine, chondroitin sulphate and methylsulfonylmethane (at unspecified doses).

- Chondroitin sulphate

A case of severe gastritis was reported in the study by Verbruggen, Goemaere, and Veys (2002) following administration of 1200 mg of chondroitin sulphate, in a study conducted in 165 people for three years.

Although there have been reports of clinical cases of gastrointestinal disorders following consumption of glucosamine and, to a lesser extent, of chondroitin sulphate, controlled studies have not shown any difference compared to a placebo.

➤ **Haematological effects**

Four reports of haematological effects were analysed under the nutriviigilance scheme. One case of blood hyperviscosity associated with central retinal vein occlusion, one case of vascular thrombocytopaenic purpura and one case of increased INR were considered unlikely. One case of thrombocytopaenic purpura was considered very likely. The food supplements involved in the cases of increased INR and thrombocytopaenic purpura did not contain chondroitin sulphate.

No other cases of thrombosis, or vascular or thrombocytopaenic purpura have been found in the literature.

The only data available in the literature on haematological effects relate to INR disruption due to the interaction of glucosamine – with or without chondroitin sulphate – with coumarin anticoagulants. They will be presented in Section 3.6 on drug interactions.

➤ **General symptoms**

Three reports of general symptoms were analysed under the nutriviigilance scheme. These were one case of fatigue, another of headache, and one reporting dizziness and loss of appetite. Their causality was deemed to be likely. The food supplements involved contained glucosamine and chondroitin sulphate.

- Glucosamine

The development of headaches has been reported in several placebo-controlled studies. Two patients (8%) developed headaches after receiving 2000 mg/d of glucosamine for 12 weeks (Braham, Dawson, and Goodman 2003). Other cases (number not specified) appeared after consumption of 1500 mg/d of glucosamine for two months (Rindone *et al.* 2000). The frequency of occurrence was never significantly different from the placebo.

Reginster *et al.* (2001) conducted a randomised, double-blind, placebo-controlled trial involving 212 patients with osteoarthritis of the knee. They received 1500 mg of glucosamine sulphate orally or a placebo once a day for three years. Fatigue was felt in 9% of the subjects treated, headache in 6% and dizziness in 7%. The frequency of occurrence was comparable to that of the placebo group.

- Chondroitin sulphate

Headaches were also reported in 11 patients (7%) following consumption of 800 mg/d of chondroitin sulphate for two years (Michel *et al.* 2005). The frequency of occurrence was not significantly different to the placebo.

Although reports have been received of symptoms such as headache, dizziness or fatigue after consuming glucosamine and, to a lesser extent, chondroitin sulphate, controlled studies have not shown any difference in the frequency of occurrence of these adverse effects compared to a placebo.

### ➤ **Uro-nephrological effects**

Three reports of uro-nephrological adverse effects were analysed under the nutrivigilance scheme. They concerned three cases of kidney failure. Causality was respectively deemed to be excluded, possible and likely. For the report considered likely, the food supplement contained only glucosamine combined with vitamin C.

- Glucosamine

Guillaume and Peretz (2001) described the case of a 79-year-old woman with knee osteoarthritis and myasthenia gravis, treated with corticosteroids and cyclosporine. Routine blood sampling revealed renal function abnormalities with elevated blood urea nitrogen and creatinine levels four months after starting daily glucosamine intake (at an unspecified dose). Discontinuing the use of glucosamine enabled the blood parameters to return to normal. The authors do not exclude the possibility that concomitant treatment with glucosamine and cyclosporine may be the cause of the nephrotoxicity.

Other authors reported the case of a 75-year-old man who had been taking glucosamine for 2-3 months (at an unspecified dose) without any other medication and who was hospitalised for acute urinary retention. Following a deterioration in renal function, a biopsy revealed acute tubulointerstitial nephritis. After dialysis started and the glucosamine was discontinued, the patient's health improved rapidly (Audimoolam and Bhandari 2006).

More recently, Gueye *et al.* (2016) published the case of a 67-year-old diabetic man treated with metformin and an antihypertensive agent who developed kidney failure three years after starting 1200 mg of glucosamine a day. The aetiological assessment was negative, there was no history of recurrent urinary tract infections, no consumption of nephrotoxic drugs and no exposure to lithium. The immunological examination was also negative. Three weeks after glucosamine was stopped, the GFR improved. The reintroduction of glucosamine resulted in renewed impairment of renal function after three weeks, with a reduction in GFR. The authors assume that the interstitial fibrosis observed in this case was associated with glucosamine-stimulated renal overexpression of Transforming Growth Factor  $\beta$ 1 (TGF- $\beta$ 1) and Connective Tissue Growth Factor (CTGF).

- Chondroitin sulphate

No studies have been found on the role of chondroitin sulphate in uro-nephrological disorders.

A few cases of kidney damage have been reported to the nutrivigilance scheme and described in the literature following glucosamine consumption. Although no nephrotoxicity mechanism has been identified, the consumption of food supplements containing glucosamine should be investigated in the presence of kidney failure of undetermined origin.

No cases following consumption of chondroitin sulphate have been published.

### ➤ **Rheumatology effects**

Two cases of rheumatology adverse effects were analysed under the nutrivigilance scheme. This included one report of increased arthralgia and lower back pain where causality was considered possible, and one of lower back and rib pain considered to be unlikely. The food supplements involved contained glucosamine and chondroitin sulphate.

- Glucosamine

Herrero-Beaumont *et al.* (2007) conducted a randomised, double-blind, six-month placebo-controlled study involving 318 participants. Of the 106 people who received 1500 mg of glucosamine per day, seven complained of lower back pain and four of neck pain. The prevalence of occurrence of these adverse effects was not significantly different from that of the placebo.

Pavelká *et al.* (2002) conducted a randomised, double-blind, three-year placebo-controlled study involving 202 participants. Musculoskeletal disorders were experienced by 30 patients in the 1500 mg of glucosamine sulphate/day group and 22 in the placebo group. The difference in occurrence is not significant. These were mainly symptoms associated with osteoarthritis and back pain. Two patients, one receiving glucosamine and the other a placebo, were removed from the study following the development of gouty arthritis. In addition, rheumatoid arthritis was diagnosed during the trial in two patients who received glucosamine. The authors assume that this disorder was pre-existing.

Several clinical trials have listed rheumatology effects as being adverse reactions experienced by participants. However, it is difficult to conclude as to any causal relationship because this type of symptom is the reason for the use of glucosamine or chondroitin sulphate.

#### ➤ **Effects on blood glucose levels**

One case reported to the nutrivigilance scheme of hyperglycaemia in a person with type-2 diabetes consuming a food supplement containing glucosamine and chondroitin sulphate was considered likely. Three other cases of blood glucose disturbance have been reported. They could not be analysed due to a lack of information. These were two cases of hyperglycaemia and one of hypoglycaemic coma in a woman with type-2 diabetes.

Several clinical studies have investigated the influence of glucosamine on glucose metabolism in humans, with respect to the effects observed in animals on hexosamine biosynthesis activation after parenteral administration. Table 5 lists studies that have not shown a link between glucosamine administration with or without chondroitin sulphate and blood glucose disturbance. Table 6 presents those that have shown blood glucose disturbances.

- Glucosamine

A systematic review of the literature conducted in 2011, including six randomised clinical trials and five prospective studies, the majority of which are presented in Tables 5 and 6, concluded that glucosamine administration has contradictory results on glucose metabolism. Four studies, including three clinical trials (one by the intravenous route and two oral), showed a decrease in insulin sensitivity and an increase in fasting serum glucose, particularly in subjects in the pre-diabetic stage who already showed abnormal glucose tolerance or insulin resistance (Dostrovsky *et al.* 2011).

In a similar review of glucosamine adverse effects observed in clinical trials (presented in Tables 5 and 6), the authors believe that the available data show that glucosamine has no effects on blood glucose levels, glucose metabolism and insulin sensitivity (Simon *et al.* 2011)<sup>40</sup>.

In a more recent review of clinical trials on the use of glucosamine in osteoarthritis, the authors consider that there are few data available on a possible diabetogenic effect of glucosamine and that it remains to be formally demonstrated using an appropriate methodology (Salazar *et al.* 2014).

Lastly, after reviewing the data available on Medline (from 1950 to November 2012) and Embase (from 1980 to November 2012), Bottegoni *et al.* (2014) stated that glucosamine intake by patients with type-2 diabetes should be undertaken with caution.

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<sup>40</sup> Some of the authors of this article indicate that they have a personal connection with Cargill Inc, a glucosamine manufacturer in the United States.

The SPCs of glucosamine-based medicinal products contain the following statement: "*In patients with impaired glucose tolerance, monitoring of the blood glucose levels and, where relevant, insulin requirements is recommended before start of treatment and periodically during treatment*" (Vidal 2017).

- Chondroitin sulphate

No studies were found on the role of chondroitin sulphate alone on glucose metabolism.

Results examining the influence of glucosamine on blood glucose control or insulin sensitivity are inconclusive. However, people in the pre-diabetic stage appear to be predisposed to decreased insulin sensitivity or fasting hyperglycaemia after consuming glucosamine.

In this context of uncertainty and in the absence of data for chondroitin sulphate alone, the WG and CES advise against the consumption of food supplements containing glucosamine with or without chondroitin sulphate by people with diabetes and pre-diabetic conditions.

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**Table 5: Studies not showing a link between glucosamine and chondroitin sulphate administration and blood glucose disturbance**

<b>Authors</b>	<b>Study plan</b>	<b>Participants and characteristics</b>	<b>Administered product, quantity</b> <b>Duration of administration</b>	<b>Authors' conclusions</b>	<b>Comments</b>
Tapadinhas, Rivera, and Bignamini (1982)	Uncontrolled intervention study	1088 people with osteoarthritis, including 92 diabetics, 74 taking hypoglycaemic agents	Glucosamine, 1500 mg/day 6 to 8 weeks	No variation in glucose tolerance observed in diabetics receiving glucosamine, with or without the use of hypoglycaemic drugs	
Yu, Boies, and Olefsky (2003)	Case-control study	7 obese subjects 7 non-obese subjects	Glucosamine, 1500 mg/day 28 days	No change in insulin sensitivity in any of the treated individuals	Two non-obese and three obese subjects had impaired glucose tolerance at baseline
Scroggie, Albright, and Harris (2003)	Randomised, double-blind, placebo-controlled study	22 type-2 diabetic subjects	Glucosamine hydrochloride, 1500 mg/day Chondroitin sulphate, 1200 mg/day 90 days	No change in glycated haemoglobin (HbA1c) levels after supplementation. The authors stated that there was no significant alteration in glucose metabolism in the treated patients.	
Tannis, Barban, and Conquer (2004)	Double-blind, placebo-controlled study	19 healthy subjects	Glucosamine sulphate, 1500 mg/day 12 weeks	No observed effects of glucosamine on fasting blood glucose, insulin levels or oral glucose tolerance	

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Authors	Study plan	Participants and characteristics	Administered product, quantity Duration of administration	Authors' conclusions	Comments
Muniyappa <i>et al.</i> (2006)	Randomised, double-blind, placebo-controlled study	20 obese subjects 20 non-obese subjects	Glucosamine hydrochloride, 1500 mg/day 6 weeks	No effect of glucosamine or the placebo on insulin resistance or other parameters associated with type-2 diabetes in thin or obese subjects. The authors concluded that glucosamine does not increase insulin resistance either in thin healthy subjects or in obese pre-diabetic subjects.	Prior to glucosamine administration, the obese group had significantly higher systolic blood pressure, fasting blood glucose and fasting plasma insulin levels.
Albert <i>et al.</i> (2007)	Double-blind controlled crossover study	12 type-1 or type-2 diabetic subjects	Glucosamine, 500 mg three times a day 2 weeks	No statistically significant or non-significant change in fasting blood glucose and HbA1c percentage after two weeks of treatment compared to the placebo. The authors concluded that glucosamine, at commonly consumed doses, has no significant effects on blood glucose control in diabetic subjects after two weeks of supplementation.	

**Table 6: Studies showing a link between glucosamine and chondroitin sulphate administration and blood glucose disturbance**

<b>Authors</b>	<b>Study plan</b>	<b>Participants and characteristics</b>	<b>Administered product, quantity Duration of administration</b>	<b>Authors' conclusions</b>
Reginster <i>et al.</i> (2001)	Randomised, double-blind, placebo-controlled study	212 subjects with osteoarthritis	Glucosamine, 1500 mg/day 3 years	All 108 subjects who received glucosamine had slightly decreased fasting blood glucose levels.
Biggee <i>et al.</i> (2007)	Crossover study	16 subjects with osteoarthritis	Glucosamine, 1500 mg Single dose	In patients with previously undiagnosed glucose intolerance, glucosamine sulphate is likely to increase blood glucose levels.
Pham <i>et al.</i> (2007)	Uncontrolled intervention study	38 healthy subjects	Glucosamine, 1500 mg/day 6 weeks	Glucosamine is likely to increase insulin resistance in people with poor insulin sensitivity, especially pre-diabetic patients.
Al-Razzuqi and Al-Jeboori (2011)	Intervention study	97 normoglycaemic subjects with osteoarthritis and a family history of diabetes	Glucosamine, 1500 mg/day Chondroitin sulphate, 1200 mg/day 8 weeks	Hyperglycaemia appeared in 84.7% of treated patients. Consecutive administration of a hypoglycaemic sulfonamide for eight weeks resulted in normalised blood glucose levels in 97.5% of these patients.

➤ **Neurological effects**

One report of sleep apnoea following the consumption of a food supplement containing glucosamine and chondroitin sulphate was analysed under the nutriviigilance scheme. Causality was deemed to be likely.

No other cases of sleep apnoea have been found in the literature.

➤ **Cardiovascular effects**

No cardiovascular reports were sufficiently documented to enable a causality score to be defined. Some data were found in the literature on this type of effect and are presented below.

- Glucosamine

In the randomised, double-blind, placebo-controlled trial of 212 patients with osteoarthritis of the knee receiving 1500 mg/d of glucosamine sulphate or a placebo for three years, conducted by Reginster *et al.* (2001), a rise in blood pressure was measured in 14%, a decrease in blood pressure in 2% and heart failure in 4% of the treated subjects. The frequency of occurrence was comparable to that of the placebo group.

Dos Reis *et al.* (2011) conducted a pharmaceutical industry-funded retrospective analysis of safety data on glucosamine from two randomised, double-blind, placebo-controlled trials that took place respectively over six months and three years. The analysis included 428 patients with osteoarthritis. No significant changes in blood pressure were observed after six months of consumption of 1500 mg of glucosamine compared to a placebo. No significant effects were observed in hypertensive individuals. Similarly, blood lipids (total cholesterol/LDL) and blood glucose levels were unchanged after three years and six months of treatment, respectively, even in subjects with hypercholesterolaemia or hyperglycaemia.

The SPCs of glucosamine-based medicinal products contain the following statement: "*In patients with a known risk factor for cardiovascular disease, monitoring of the blood lipid levels is recommended, since hypercholesterolaemia has been observed in a few cases in patients treated with glucosamine*" (Vidal 2017).

- Glucosamine combined with chondroitin sulphate

A follow-up study of the use of food supplements containing glucosamine and chondroitin sulphate by 200 patients with osteoarthritis was conducted between 1995 and 2000. Three previously undiagnosed cases of moderate systolic hypertension were observed (Danao-Camara 2000). No statistical tests were conducted and the doses involved were not specified.

- Chondroitin sulphate

No studies have been found on the role of chondroitin sulphate alone in cardiovascular disorders.

Cardiovascular events reported following the consumption of glucosamine or chondroitin sulphate are rare and difficult to interpret due to a lack of scientific data.

➤ **Effects on the respiratory system**

No pneumological reports were received under the nutriviigilance scheme. Some data were found in the literature on this type of effect and are presented below.

- Glucosamine combined with chondroitin sulphate

Tallia and Cardone (2002) described the case of a 52-year-old woman with chronic asthma who experienced an exacerbation of her symptoms, including severe shortness of breath and wheezing



causing difficulty moving and singing, while consuming a preparation containing 500 mg of glucosamine and 400 mg of chondroitin sulphate three times a day. Twenty-four hours after stopping this product, the asthma adverse effects had completely disappeared. Three months later, she recalled having an allergic episode during a shark dissection as part of her studies. In their article, the authors note that no other similar cases have been reported, but that several cases of asthma have been observed in a professional setting when shark powder is inhaled (Ortega *et al.* 2002, San-Juan *et al.* 2004).

No other cases of asthma associated with the consumption of food supplements containing chondroitin sulphate or glucosamine have been reported since the publication of this clinical case.

- Chondroitin sulphate

In their article, Tallia and Cardone (2002) made a link with experimental work showing the involvement of chondroitin sulphate in the pathophysiology of bronchial wall fibrosis observed in asthma (Johnson *et al.* 2000, Huang *et al.* 1999). However, this work studied endogenous chondroitin sulphate as a component of the extracellular matrix, and therefore as a marker of asthma pathophysiology, which in no way presupposes increased bronchial deposition when exogenous chondroitin sulphate is consumed as a food supplement.

- Glucosamine

The SPCs of glucosamine-based medicinal products contain the following statement: "*A report on exacerbated asthma symptoms triggered after initiation of glucosamine therapy has been described (symptoms resolved after withdrawal of glucosamine). Asthmatic patients starting on glucosamine should therefore be aware of potential worsening of symptoms*" (Vidal 2017).

Only one case of asthma aggravated by glucosamine and chondroitin sulphate consumption in a patient suspected of being allergic to a component of shark cartilage has been reported in the literature. Nevertheless, the SPCs describe the existence of asthma symptoms exacerbated by glucosamine therapy.

### ➤ **Dermatological effects**

Ten reports of dermatological adverse effects (pruritus, rash, drug eruption) were received under the nutriviigilance scheme. However, none of them were sufficiently documented to be able to determine causality relating to the use of a food supplement. Some data were found in the literature on this type of effect and are presented below.

Dermatological disorders are among the undesirable effects listed in the SPC for drugs containing glucosamine or chondroitin sulphate (Vidal 2017).

- Glucosamine

Several studies report the appearance of skin reactions or pruritus following the consumption of 1500 mg of glucosamine (Tapadinhas, Rivera, and Bignamini 1982, Müller-Faßbender *et al.* 1994, Pavelká *et al.* 2002).

Several cases of adverse dermatological effects occurring after consumption of glucosamine and/or chondroitin sulphate have been reported in the literature. Dermatological adverse effects are listed in the SPCs for drugs containing glucosamine or chondroitin sulphate. Their allergic or toxic nature has not been determined.

### ➤ **Allergic effects**

Five reports of allergic adverse effects, including three cases of urticaria, were received under the nutriviigilance scheme. However, none of them were sufficiently documented to enable a causality

score to be defined. Some data were found in the literature on this type of effect and are presented below.

- Glucosamine

The case of a 76-year-old woman with hypertension and osteoarthritis in whom erythematous lesions and facial oedema appeared a few hours after taking glucosamine sulphate (unspecified dose) was reported (Matheu *et al.* 1999). The next day, a facial erythema, with swelling of the face, tongue and throat, appeared five minutes after taking glucosamine again. Although the skin-prick test was negative and specific IgE antibodies were not detected *in vitro*, the intradermal reaction with the product at a concentration of 1.5 mg/mL was positive in the patient but negative in 10 controls. The authors concluded that there was a non-allergic hypersensitivity to glucosamine. In addition, recent experimental studies suggest that glucosamine has anti-allergic effects (Jung, Heo, and Kim 2017, Kim, Nakayama, and Nayak 2018).

Since food supplements containing glucosamine can be prepared from the shell of crustaceans, a possible risk of glucosamine allergy in patients who are allergic to shrimp was investigated. However, oral administration of 500 mg or 1500 mg of glucosamine was tolerated by the 21 patients tested (Gray, Hutcheson, and Slavin 2004, Villacis *et al.* 2006)<sup>41</sup>.

Food allergies to crustaceans mainly, but not exclusively, involve tropomyosin and arginine kinase, allergens found in the flesh of crustaceans. However, the French Allergo-Vigilance Network (RAV) reported one case of anaphylactic shock in a 28-year-old woman following consumption of a soup made from shrimp head shells, despite her tolerating shrimp meat. In this case, chitin, the main non-protein component of shrimp shell, was suspected of being the allergen responsible. This suspicion seems to be supported by the observation of Rolland *et al.* (2013), who described a case of anaphylaxis where the involvement of chitin, found in a food supplement, was demonstrated. The immunogenicity<sup>42</sup> of chitin has also been demonstrated (Elieh Ali Komi, Sharma, and Dela Cruz 2018).

In addition, chitin is also found in the shells of insects (Burton and Zaccone 2007, Van der Brempt, Beaudouin, and Lavaud 2016). Patients who have had an allergic reaction to insect consumption are likely to have one when consuming glucosamine.

The SPCs of glucosamine-based medicinal products contain the following statement: "*The product must not be given to patients who are allergic to shellfish as the active substance is obtained from shellfish.*" (Vidal 2017).

Allergy to crustaceans is mainly associated with ingestion of the flesh. In two studies, administration of glucosamine to people who are allergic to shellfish meat was not followed by an allergic reaction. However, allergy to chitin, a component of the shell, was demonstrated in one case. According to these data, the allergic risks associated with glucosamine consumption seem to concern only people allergic to chitin. The WG and the CES therefore advise against the consumption of food supplements containing glucosamine by people with a food allergy to crustaceans or insects.

### **3.6. Drug interactions**

#### **➤ Coumarin anticoagulants (vitamin K antagonists)**

Several cases of increased INR following the consumption of glucosamine and chondroitin sulphate in combination with an anticoagulant have been reported in different countries. This was the case in

<sup>41</sup> The study by Villacis *et al.* 2006 was financed by Weider Nutrition Group, a manufacturer of food supplements

<sup>42</sup> The ability of a substance to provoke an immune response, manifested by a visible cellular inflammatory response or antibody production.

France with the nutrivigilance scheme, as well as in Italy and Canada. Other cases are described in the literature.

- Glucosamine combined with chondroitin sulphate

In 2004, Rozenfeld, Crain, and Callahan (2004) described a case of elevated INR in a patient taking warfarin (47.5 mg/week) for four months who consumed a food supplement containing glucosamine hydrochloride (500 mg) and chondroitin sulphate (400 mg) at a dose of six capsules per day. The INR before taking the food supplement was 2.58. Four weeks later, it was 4.52. The food supplement was maintained and the dosage of warfarin decreased to 40 mg/week to reach an INR of 2.15 again. The case was discussed by Scott (2004), who highlighted the high daily intakes of glucosamine (3 g) and chondroitin (2.4 g).

In 2008, Knudsen and Sokol (2008) reported an increase in INR associated with an increase in the intake of a food supplement containing glucosamine and chondroitin sulphate. This concerned a 71-year-old man, treated for five years with warfarin (stabilised dose) and also taking a food supplement containing 500 mg of glucosamine hydrochloride and 400 mg of chondroitin sulphate twice a day for five years. He decided to increase the doses of the food supplement to 1500 mg of glucosamine hydrochloride and 1200 mg of chondroitin sulphate twice a day. Three weeks later, the patient's INR had increased from 2.3 to 3.9. Despite a decrease in the amount of food supplement consumed, the INR measured 16 days later was 4.7. Finally, 16 days after complete discontinuation of the food supplement, the INR decreased to 2.6. This isolated case seems questionable insofar as a decrease in dosage was then associated with a greater increase in INR. However, the authors supplemented their observation with a search of FDA and WHO databases, and found 42 other cases of potential interactions between warfarin and glucosamine, chondroitin sulphate or a combination of the two:

- of the 20 cases registered by the FDA, only one mentioned chondroitin sulphate alone, four mentioned glucosamine alone and 15 both.
- none of the 21 cases registered by the WHO mentioned chondroitin sulphate. Glucosamine appeared alone in all cases.

- Glucosamine

Garrote García *et al.* (2004) reported the case of a 71-year-old hypertensive male with a history of perforated duodenal ulcer, taking anticoagulants (acenocoumarol) and suffering from bilateral gonarthrosis. A fall in his INR value was observed while taking 1500 mg of glucosamine per day. This effect seems unusual, because when it exists, the interaction between glucosamine and anticoagulants is most often manifested by an increase in INR.

In 2006, the British health authorities recommended that patients treated with warfarin refrain from consuming glucosamine<sup>43</sup>.

The German Federal Institute for Risk Assessment (BfR) believes that food supplements containing glucosamine, at doses of 390 to 790 mg/day or more, constitute a health risk to patients taking coumarin anticoagulants, as they can amplify the anticoagulant effect of these drugs and thus lead to haemorrhage (BfR 2009).

An EFSA opinion on the safety of glucosamine for patients receiving coumarin anticoagulants, based on more than 40 cases reported to drug-monitoring agencies, showed an increase in INR after glucosamine intake. These cases were mostly asymptomatic, but in some, haemorrhage occurred in various organs and in one case this resulted in a persistent vegetative state following intraventricular bleed and a subdural haematoma. Evidence of an interaction between glucosamine and coumarin anticoagulants is reinforced by the fact that in the majority of cases, the INR values

<sup>43</sup>

<http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023859> (accessed on 1 February 2017).

returned to normal when the glucosamine intake was discontinued. EFSA points out that even if the level of risk cannot be ascertained because of insufficient data, there is a risk of haemorrhage through the interaction between glucosamine and coumarin anticoagulants in some individuals (EFSA 2011).

The SPCs of glucosamine-based medicinal products contain the following statement: *"Increased effect of coumarin anticoagulants (e.g. warfarin) during concomitant treatment with glucosamine has been reported. Patients treated with coumarin anticoagulants should therefore be monitored closely when initiating or ending glucosamine therapy"* (Vidal 2017).

The mechanism of interaction between glucosamine, chondroitin sulphate and warfarin has not been elucidated, as presented in Section 3.5.4.1 concerning the effects of these two ingredients *in vitro* or in animals.

The consumption of food supplements containing glucosamine alone or in combination with chondroitin sulphate can cause an imbalance in the coumarin anticoagulant treatment. The WG and the CES advise against the consumption of food supplements containing glucosamine alone or in combination with chondroitin sulphate by people treated with vitamin K antagonists.

### **3.7. Vulnerable populations and at-risk situations**

#### **3.7.1. Children and pregnant or breastfeeding women**

Given the reasons for consuming glucosamine and chondroitin sulphate, there are no safety data for their consumption by children.

For pregnant women, only one study was found, which sought to determine whether glucosamine intake may be associated with an increased risk of malformations or other adverse effects in children. Fifty-four women who used glucosamine during pregnancy were recruited. They were matched for age, alcohol consumption and smoking with women who did not consume glucosamine. Sixty-three per cent of the women only consumed glucosamine in the first trimester, 30% throughout the entire pregnancy, 4% during the second and third trimesters, and 1% during the third trimester only. The authors found no significant differences in pregnancy outcomes between the two groups. Only one malformation (scrotal hernia) was observed in the exposed group. The main limitation of this study was the small sample size. About 800 women would be needed in each group to detect a doubling in the risk of relatively common malformations, and thousands would be needed to detect rare abnormalities (Sivojelezova, Koren, and Einarson 2007).

No data are available on the effect of chondroitin sulphate administration to pregnant women.

No data are available on the effect of glucosamine or chondroitin sulphate administration to breastfeeding women.

In the absence of clinical data, the consumption of food supplements containing glucosamine or chondroitin sulphate by children is not recommended.

In light of the animal reprotoxicity data for glucosamine and in the absence of sufficient clinical data, the consumption of food supplements containing glucosamine or chondroitin sulphate by pregnant or breastfeeding women is not recommended.

### **3.7.2. People following a special diet**

#### **3.7.2.1. Potassium**

Some glucosamine sulphate preparations are stabilised with potassium chloride, and potassium intake can reach 6.6 mmol/day (corresponding to 495 mg) (Huskisson 2008). Asahina, Hori, and Sawada (2010) showed that the potassium content of food supplements containing glucosamine sulphate could correspond to 20% of the maximum daily potassium intake for haemodialysis patients.

In its report on the revision of food consumption guidelines, ANSES did not set a population reference intake (PRI) for potassium but proposed adopting an equimolar ratio of sodium and potassium. The choice of a PRI for potassium is therefore determined by sodium intake. In addition, there are insufficient data for proposing a tolerable upper intake level (UL) (ANSES 2017). EFSA has established an adequate daily potassium intake of 3500 mg for adults (EFSA 2016).

The consumption of food supplements containing glucosamine sulphate can represent a significant potassium intake. This should be taken into account by patients on a controlled potassium or sodium diet, in order to maintain the equimolar ratio of sodium and potassium.

#### **3.7.2.2. Calcium**

The article by Lagman and Walsh (2003) indicates that shark cartilage can be an important source of calcium. Hypercalcaemia was caused or aggravated by the consumption of shark cartilage by two cancer patients. The authors estimated the calcium intake through cartilage to be 900 mg/day. However, the first patient was also taking calcium and vitamin D. For the second, hypercalcaemia episodes had occurred before they started taking the shark cartilage.

For calcium, ANSES has adopted a PRI of 950 mg/d for men and women over 24 years of age, and a UL of 2500 mg/d (ANSES 2017).

The consumption of food supplements containing shark cartilage can contribute significantly to calcium intake.

#### **3.7.2.3. Sodium**

Some products containing chondroitin sulphate may be high in sodium, while products containing glucosamine may be stabilised with sodium chloride. However, the sodium levels in finished products are not specified.

The consumption of food supplements containing glucosamine or chondroitin sulphate may contribute to sodium intake, which has not been assessed.

### **3.8. Safety data examined**

#### **3.8.1. Glucosamine**

One review examined the safety of glucosamine supplementation. Hathcock and Shao (2007) reported that 2000 mg/day of glucosamine supplementation in efficacy studies did not result in any adverse effects being reported.

In 2009, EFSA published an opinion on the safety of glucosamine hydrochloride from *Aspergillus niger* and concluded that up to 750 mg of glucosamine per day was safe for adults (EFSA 2009).

#### **3.8.2. Chondroitin sulphate**

For chondroitin sulphate, Hathcock and Shao (2007) reported that 1200 mg/day of chondroitin sulphate supplementation in efficacy studies did not result in any adverse effects being reported.

### **3.9. Conclusions and recommendations of the CES and the WG**

Glucosamine and chondroitin sulphate are naturally present in connective and cartilage tissues where, among other things, they maintain the structure and elasticity of cartilage, tendons and skin. In France, these compounds are marketed as medicinal products or food supplements.

Seventy-four cases of adverse effects occurring following consumption of food supplements containing glucosamine or chondroitin sulphate were brought to the attention of the nutriviigilance scheme. In 11 of the 23 cases for which a causality score could be established, this was either very likely or likely. Other reports have been received by the toxicovigilance schemes and vigilance systems of a few Member States of the European Union, and of Canada and the United States. The adverse effects reported vary widely, with in particular gastroenterological, neurological, dermatological, allergic, hepatic and haematological effects.

The WG and the CES stress that few toxicological or clinical data for chondroitin sulphate alone are available in the scientific literature, making it difficult to analyse its role in the occurrence of adverse effects.

With regard to the allergy cases, the literature data show that the allergic risks attributed to glucosamine consumption in patients who are allergic to crustaceans only seem to concern people allergic to chitin. The WG and the CES therefore advise people with a known food allergy to crustaceans or insects not to consume food supplements containing glucosamine.

In view of the toxicological and clinical data, the WG and the CES advise against the consumption of glucosamine in the form of food supplements, whether or not combined with chondroitin sulphate, by diabetics, pre-diabetics or people treated with vitamin K antagonists.

In the absence of sufficient safety data, the WG and the CES advise against the consumption of food supplements containing glucosamine or chondroitin sulphate by pregnant and breastfeeding women and children.

The WG and the CES recommend that health professionals look for possible consumption of food supplements containing glucosamine alone or in combination with chondroitin sulphate:

- when faced with an unexplained increase in INR in people treated with vitamin K antagonists;
- in the presence of hepatic cytolysis or kidney failure of undetermined origin.

Food supplements containing glucosamine or chondroitin sulphate can be an important source of minerals such as calcium, potassium or sodium. People whose intake of any of these minerals needs to be controlled should consume these products with caution. The WG and the CES recommend that consumers be informed of the levels of calcium, potassium or sodium provided by these food supplements.

In the absence of sufficient safety data, the WG and the CES also recommend never combining multiple sources of glucosamine or chondroitin sulphate (drugs or food supplements).

## **4. AGENCY CONCLUSIONS AND RECOMMENDATIONS**

The French Agency for Food, Environmental and Occupational Health & Safety adopts the recommendations of the Working Group on "Nutriviigilance" and the Expert Committee on "Human Nutrition".

ANSES conducted an analysis of the 23 reports of adverse effects identified as likely to be associated with the consumption of food supplements containing glucosamine or chondroitin sulphate, received between the creation of the nutriviigilance scheme in 2009 and February 2018. This analysis was supplemented by the study of bibliographic data, enabling ANSES to identify the risks associated with their use.

The expert appraisal revealed the existence of specific populations for whom the consumption of food supplements containing glucosamine or chondroitin sulphate presents a risk. The consumption of these food supplements by people with diabetes or pre-diabetic conditions, asthmatics, people treated with vitamin K antagonists, with a food allergy to crustaceans or insects, or whose diets are controlled for sodium, potassium or calcium is therefore not recommended.

In addition, in the absence of sufficient safety data, the consumption of food supplements containing glucosamine or chondroitin sulphate by pregnant or breastfeeding women and children is not recommended.

ANSES considers that manufacturers must take the necessary measures with regard to consumers in this respect.

The information gathered from the consultation with the European Focal Points of the European Food Safety Authority (EFSA) shows high variability in the maximum daily doses of glucosamine and chondroitin sulphate authorised in food supplements in Europe. Depending on the country, doses range from 500 mg to 1000 mg for glucosamine and from 500 mg to 900 mg for chondroitin sulphate, and are based on a limited amount of available safety data and not on a full risk assessment. ANSES believes that the maximum daily doses of glucosamine and chondroitin sulphate authorised in food supplements should be harmonised at European level on the basis of safety data from robust safety studies – currently lacking – for glucosamine and chondroitin sulphate.

When faced with biological abnormalities or clinical manifestations of undetermined origin, ANSES recommends that healthcare professionals ask their patients about their consumption of food supplements.

In general, ANSES recommends that consumers:

- seek the advice of a doctor when consuming food supplements;
- avoid intakes of the same ingredient from different sources (food supplements, medicines, etc.);
- give preference to the consumption of food supplements with simple formulations;
- avoid the concomitant consumption of several food supplements;
- inform their doctor or pharmacist that they are taking food supplements.

ANSES reminds healthcare professionals and manufacturers of the need to report to its nutrivigilance scheme any adverse effects likely to be associated with the consumption of food supplements about which they become aware.

Lastly, ANSES emphasises the value of setting up a joint international project on the monitoring of adverse effects associated with the consumption of food supplements.

Dr Roger GENET

## KEYWORDS

Nutrivigilance, effets indésirables, compléments alimentaires, glucosamine, chondroïtine sulfate  
Nutrivigilance, adverse effects, food supplements, glucosamine, chondroitin sulphate

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## **ANNEX 1**

### **Presentation of the participants**

**PREAMBLE:** The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

### **WORKING GROUP 2015-2018**

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#### **Chair**

Mr Alexandre MACIUK – University Lecturer (Paris-Sud University) – Speciality: pharmacognosy

#### **Members**

Ms Catherine ATLAN – University Lecturer – Hospital Practitioner (Luxembourg Hospital Centre) – Specialities: metabolic diseases, nutrition and endocrinology

Mr Alain BOISSONNAS – Retired, University Professor – Hospital Practitioner (University Hospital Paris-Sud) – Speciality: general medicine

Ms Sabrina BOUTEFNOUCHET – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Mr Pierre CHAMPY – University Lecturer (Paris-Sud University) – Speciality: pharmacognosy

Mr Pascal CRENN – University Professor – Hospital Practitioner (Raymond Poincaré Hospital) – Speciality: hepato-gastroenterology

Mr Thierry HENNEBELLE – University Lecturer (Lille II University) – Speciality: pharmacognosy

Ms Raphaële LE GARREC – University Lecturer (University of Western Brittany) – Speciality: toxicology

Mr Jean-Marie RENAUDIN – Hospital Practitioner (Emilie Durkheim Hospital Centre) – Speciality: allergology

Ms Dominique Angèle VUITTON – Retired, University Professor – Hospital Practitioner (University of Franche Comté) – Specialities: allergology, hepato-gastroenterology

Mr Bernard WENIGER – Retired, University Lecturer (Strasbourg University) – Speciality: pharmacognosy

Mr Jean-Fabien ZAZZO – Retired, Hospital Practitioner (Antoine Bécère Hospital) – Specialities: general medicine, anaesthesia and resuscitation, nutrition

### **RAPPORTEURS**

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Mr Thierry HENNEBELLE – University Lecturer (Lille II University) – Speciality: pharmacognosy

Mr Bernard WENIGER – Retired, University Lecturer (Strasbourg University) – Speciality: pharmacognosy

## **EXPERT COMMITTEE**

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The work that is the subject of this report was monitored and adopted by the following Expert Committee:

- CES on "Human Nutrition" – 2018-2021

### **Chair**

Mr François MARIOTTI – Professor (AgroParisTech) – Specialities: protein metabolism, amino acids, nutritional requirements and recommendations, postprandial metabolism, cardiometabolic risk

### **Members**

Mr Frédérick BARREAU – Research Manager (Inserm / UMR 1220 / Digestive Health Research Institute, Toulouse Purpan Hospital) – Specialities: chronic inflammatory diseases of the intestine, intestinal mucosa

Ms Charlotte BEAUDART – Post-doctoral researcher (University of Liège) – Specialities: sarcopaenia, epidemiology

Ms Catherine BENNETAU-PELISSERO – Professor (Bordeaux Sciences Agro) – Specialities: phyto-oestrogens, isoflavones, endocrine disruptors, bone health

Ms Clara BENZI-SCHMID – Researcher (Federal Food Safety and Veterinary Office, Switzerland) – Specialities: legal bases of foodstuffs, health claims, food supplements

Ms Marie-Christine BOUTRON-RUAULT – Research Director (CESP Inserm) – Specialities: nutritional epidemiology and cancer, digestive system

Ms Blandine DE LAUZON-GUILLAIN – Research Director (INRA, CRESS, Sorbonne Paris Cité) – Specialities: epidemiology, infant nutrition, nutrition of pregnant and breastfeeding women, public health

Ms Amandine DIVARET-CHAUVEAU – University Hospital Practitioner (Nancy Regional University Hospital) – Specialities: infant nutrition, breastfeeding, food diversification, allergy, epidemiology

Ms Christine FEILLET-COUDRAY – Research Manager (INRA Montpellier) – Specialities: mineral metabolism, metabolic disorders and obesity, polyphenols

Ms Amandine GAUTIER-STEIN – Research Manager (INRA / Inserm U1213, Lyon Est) – Specialities: carbohydrate metabolism, food intake, energy expenditure, nutrition and cognition, metabolic disorders of the liver

Mr Jacques GROBER – University Lecturer (Inserm U1231 / University of Burgundy / Agrosup Dijon) – Specialities: nutrition, lipids, lipid transfer proteins, lipoprotein metabolism

Mr Jean-François HUNEAU – Professor (INRA/AgroParisTech) – Speciality: human nutrition

Ms Emmanuelle KESSE-GUYOT – Research Director (INRA, UMR Inserm U1153 / INRA U1125 / CNAM / University of Paris 13) – Specialities: epidemiology, nutrition and pathologies, nutrition and public health

Ms Corinne MALPUECH-BRUGERE – Professor (University of Clermont Auvergne) – Specialities: nutrition of pathologies, metabolism of macro- and micronutrients

Ms Christine MORAND – Research Director (INRA Clermont-Ferrand) – Specialities: plant bioactive compounds, vascular dysfunctions

Ms Béatrice MORIO-LIONDORE – Research Director (INRA Lyon) – Specialities: human nutrition, energy metabolism, obesity, physical activity

Ms Anne-Sophie ROUSSEAU – University Lecturer (University of Nice Sophia Antipolis) – Specialities: nutrition and physical activity, bioavailability, oxidative stress

Mr Stéphane WALRAND – Research Director (INRA Clermont-Ferrand/Theix) – Specialities: pathophysiology, protein metabolism and amino acids

## **ANSES PARTICIPATION**

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### **Scientific coordination**

Ms Fanny HURET – Scientific Project Leader for Nutrivigilance – Risk Assessment Department

### **Scientific contribution**

Ms Gwenn VO VAN-REGNAULT – Nutrivigilance Project Officer – Risk Assessment Department

Ms Irène MARGARITIS – Head of the Nutritional Risk Assessment Unit – Seconded University Professor (University of Nice Sophia Antipolis) – Risk Assessment Department

### **Administrative secretariat**

Ms Virginie SADE – Risk Assessment Department