anses
French agency for food, environmental and occupational health & safety

Investigate, evaluate, protect

ANSES opinion on the risks associated with the consumption of food supplements for joint conditions containing glucosamine and/or chondroitin sulfate

39th FP meeting, 22-23 May 2019, Sarajevo

Background and subject of the mandate

Background

- **74** reports of adverse effects including **23** analysed
- On French market: around **1 million** of packs sold each year

Objective

- identifying the potential health risks, **not the possible effectiveness**, of food supplements containing glucosamine and/or chondroitin sulphate.

Methodology of expertise

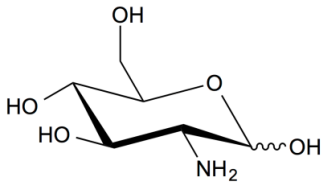
- Collection of reported adverse effects cases:
  - submitted by healthcare professionals, the French National Agency for Medicines and Health Products Safety (ANSM), the regional pharmacovigilance centres (CRPVs),
  - manufacturers of food supplements containing these two substances
  - French poison control centres (CAPs) and national toxicovigilance network
  - **Counterparts from European Union**, Canada and United States

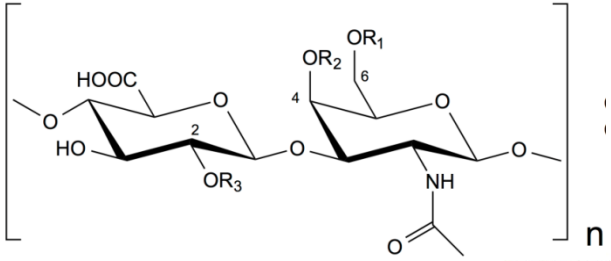
- Determination of imputablities
- Literature review
- Consultation of French Food Supple[illegible]ciation (SYNADIET)

Focal Point request (November 2016)

General information

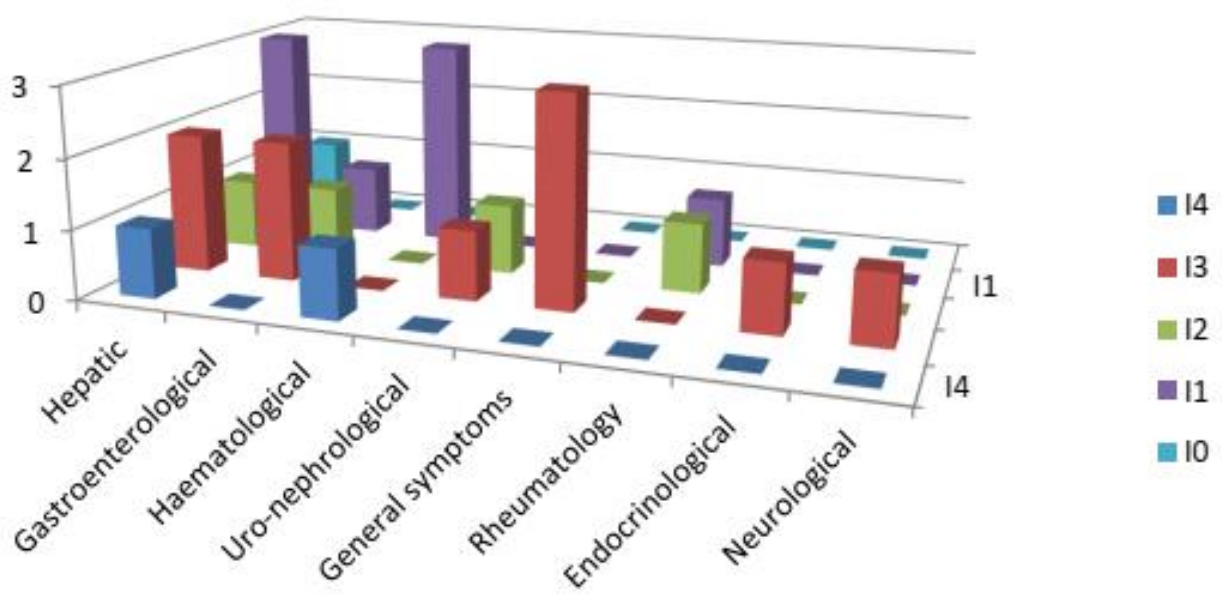
	Glucosamine	Chondroitin sulfate
Characterisation	aminosaccharide secreted from glucose, fructose and glutamine; Natural constituent of mucosal secretions, skin, ligaments, cartilage.	glycosaminoglycan ; Dimer of glucuronic acid and *N*-acetyl-galactosamine ; role in maintaining the structure and elasticity of cartilage, tendons, skin and artery walls.
Commercial forms	**Drug (Dolenio, Flexea, Osaflexan, Structoflex and Voltaflex) :** Sulfate or hydrochloride 1178 or 1250 mg/d **Food supplement :** Sulfate or hydrochloride max dose recommended by DGCCRF : 1000 mg/d	**Drug (Chondrosulf, Structum) :** 1000 or 1200 mg/d **Food supplement :** max dose recommended by DGCCRF : 900 mg/d
Sources	Hydrolysis of chitin (shells of crustaceans, *Aspergillus niger*)	extraction and tracheal purification of cattle, nasal septum of pigs, shark fin and fish cartilage





Nutrivigilance cases

- **23 cases that could be analysed**

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anses Nutrivigilance

Télédéclaration d'effet indésirable susceptible d'être lié à la consommation de complément(s) alimentaire(s) ou de certains produits alimentaires

FICHE DE NOTIFICATION D'EFFET(S) INDESIRABLE(S) SUITE A LA CONSOMMATION D'UN PRODUIT ALIMENTAIRE

A - Déclarant

Profession ○ Médecin ○ Pharmacien ● Autre

Autre, précisez

Nom *

Adresse *

Code postal *

Ville

Téléphone

Telecopie

Courriel

B - Données relatives au consommateur

Nom* (2 premières lettres)

https://pro.anses.fr/nutrivigilance/ 19/01/2017

- Diversity of adverse effects
- 2 very likely cases & 9 likely cases
- Severity level 1 for 6 cases, level 2 for 3 cases, level 3 for 2 cases.

Other vigilance

- **Pharmacovigilance (drugs)**
  - 315 reports
  - Gastroenterological effects (nausea, abdominal pain)
  - Dermatological effects (rash, pruritus, eczema)
  - Neurological effects (headache, fatigue)
- **Pharmacovigilance (food supplements)**
  - 22 reports including 4 that could be analysed
- **Toxicovigilance**
  - 2 cases suite following glucosamine consumption (nausea, subicterus and death)
- **Vigilance in other countries**
  - Germany : 3 cases of hepatitis, 2 cases of allergy
  - Italy : gastroenterological disorders, dermatological disorders, increased INR
  - Canada : allergy, increased INR

Adverse effects: bibliography (1)

- **Pre-clinical data**

  - **Acute toxicity glucosamine** :
    - LD50 in mice, rats, rabbits: 5000 mg/kg
  - **Acute toxicity chondroitin sulfate**:
    - LD50 in mice, rats, rabbits : > 10 000 mg/kg
  - **Glucosamine and glucose metabolism**
    - Increased blood glucose levels, reduced glucose uptake and decreased glucose elimination after IV or IP administration in rats (doses 240 to 9937 mg/kg/bw) ;
    - Ano effects observed after oral administration in rats, rabbits and dogs
  - **Glucosamine, chondroitin sulfate and coagulation**
    - Inhibition pf platelet aggregation induced by ADP (*in vitro* and *ex vivo* for 1500 mg glucosamine for 7 days)
    - Decrease in platelet aggregates and increase in blood flow after administration of 20 or 40 mg/kg/day of chondroitin sulfate for 3 days in rats

Adverse effects: bibliography (2)

Clinical data

Hepatic effects

Cytolytic or cholestatic hepatitis

GI, GI+Ch

When faced with hepatic cytolysis of undetermined origin, the consumption of glucosamine or chondroitin sulfate should be sought

Effects on blood sugar levels

Blood glucose disturbance

GI, GI+Ch

Conflicting data

Consumption of glucosamine associated or not with chondroitin sulfate is not recommended for people with diabetes and pre-diabetic patients

Allergological effects

Hives, anaphylactic shock

GI

The allegic risks associated with glucosamine consumption seem to concern only people allergic to chitin. The consumption of glucosamine is not recommended for people allergic to crustaceans or insects

Uro-nephrological effects

Renal insufficiency

GI

3 published cases.
In the case of renal failure of undetermined origin, glucosamine intake should be sought.

Adverse effects: bibliography (3)

Effects on the respiratory system
Asthma

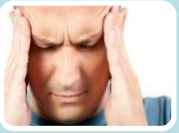
→ **GI, Ch, GI+Ch**
Caution in the CPR

Dermatological effects
Pruritus, skin rash

→ **GI**
Effects listed in the CPR
Allergic or toxic nature not determined

Gastroenterological effects
Digestive disorders, diarrhea

→ **GI, Ch, GI+Ch**
Similar occurrence frequency/placebo



General symptoms
Headaches, fatigue, diziness

→ **GI, Ch**
Similar occurrence frequency/placebo

Neurological effects
Sleep apnea

→ **GI, Ch, GI+Ch**
No other cases found

Cardiovascular effects
Hypertension, hypotension

→ **GI, GI+Ch**
Rare cases

Rheumatological effects
arthralgia, musculoskeletal disorders

→ **GI**
Listed as an adverse event in several clinical trials

Drug interactions

- **Coumarinic anticoagulants**

- Several cases of increased INR
- Recommendation issued by some countries (United Kingdom, Germany)
- Unresolved interaction mechanism

→ **The consumption of glucosamine of glucosamine alone or in combination with chondroitin sulfate exposes an imbalance in coumarin anticoagulant treatment**

→ **The consumption of these 2 ingredients is not recommended for people treated with anti-vitamin K**

Sensitive populations

- **Children**
  - No existing safety data

- **Pregnant or breastfeeding women**
  - Insufficient safety data

→ The consumption of food supplements containing glucosamine ou chondroitin sulfate is not recommended for children, pregnant or breastfeeding women

- **People on a special diet**
  - Potassium
  - Calcium
  - Sodium

→ Persons whose diet must be controlled for any of these minerals should consume these products with caution

Recommendations

Few toxicological or clinical data are available for chondroitin sulfate alone -> difficult analysis of its responsibility for the occurrence of adverse effects

- **For healthcare professionals**

- Healthcare professionals should look for possible consumption of Food supplements containing glucosamine alone or in combination with chondroitin sulfate:
  - In response to an unexplained increase in INR in people treated with anti-vitamins K
  - In the presence of hepatic cytolysis or renal failure of undetermined origin

Recommendations

For consumers

- The consumption of glucosamine or chondroitin sulfate is **not recommended** for
  - The children
  - pregnant or breastfeeding women
  - People allergic to crustaceans or insects
  - People with diabete or pre-diabet conditions
  - People treated with anti-vitamin K

- Food supplements containing glucosamine or chondroitin sulfate can be an important source of minerals such as calcium, potassium or sodium -> **consumption with caution** for people following a controlled diet for one of these minerals

- **Do not multiply the sources** of glucosamine or chondroitin sulfate (drugs or food supplements)

Recommendations

- ## For manufacturers

- Measures to be taken to **better inform consumers** about the risks associated with the consumption of these food supplements by these specific populations

- ## For public authorities

- **Harmonise at European level** the maximum authorised daily doses of glucosamine and chondroitin sulfate in food supplements, based on safety data from robust safety studies (currently lacking)

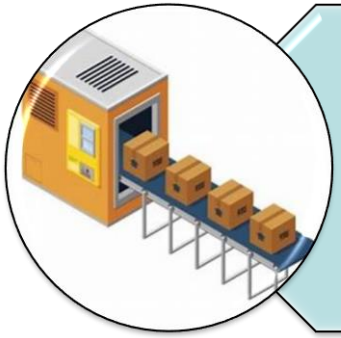
Reminder of general recommendations on the consumption of food supplements and reporting of adverse effects

For consumers:

- Seek the advice of a doctor when consuming food supplements;
- Avoid multiple intakes of an ingredient from several sources (food supplements, medications, etc.);
- Avoid the concomitant consumption of several different food supplements;
- Favour the consumption of food supplements with simple formulations;
- Favour supply channels monitored by public authorities;
- Report your consumption of food supplements to your doctor or pharmacist.

For health professionals:

- Ask patients about their consumption of food supplements, particularly if biological abnormalities or clinical manifestations of undetermined origin are detected.
- Report to the nutrivigilance scheme any adverse reactions likely to be related to the consumption of food supplements of which they are aware.



For food supplement manufacturers:

- Report to the nutrivigilance scheme any adverse reactions likely to be related to the consumption of food supplements of which they are aware.

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Thanks for your answer to our multilateral request in the context of this ANSES self task

For more information:

Press news and ANSES Opinion in English:
https://www.anses.fr/en/content/certain-food-supplements-joint-pain-should-be-avoided-risk-populations

French Nutrivigilance scheme:
https://www.anses.fr/fr/node/103072

Article on food supplements:
https://www.anses.fr/en/content/food-supplements-0

Thank You!