



VKM Report 2016: 01

# Risk assessment of "other substances" – Inulin

**Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety**

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2016: 01  
Risk assessment of "other substances" - Inulin

Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact  
with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety  
01.03.2016

ISBN: 978-82-8259-190-4  
Norwegian Scientific Committee for Food Safety (VKM)  
Po 4404 Nydalen  
N – 0403 Oslo  
Norway

Phone: +47 21 62 28 00  
Email: [vkm@vkm.no](mailto:vkm@vkm.no)

[www.vkm.no](http://www.vkm.no)  
[www.english.vkm.no](http://www.english.vkm.no)

Cover photo: iStock Photo

Suggested citation: VKM. (2016) Risk assessment of "other substances" – Inulin. Opinion of  
the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food  
and Cosmetics of the Norwegian Scientific Committee for Food Safety, ISBN: 978-82-8259-  
190-4, Oslo, Norway.

# **Risk assessment of "other substances" – Inulin**

## **Author preparing the draft opinion**

Ragna Bogen Hetland

## **Assessed and approved**

The opinion has been assessed and approved by Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Members of the panel are: Inger-Lise Steffensen (Chair), Ellen Bruzell, Berit Granum, Ragna Bogen Hetland, Trine Husøy, Jens Rohloff, Trude Wicklund.

(Panel members in alphabetical order after chair of the panel)

## **Acknowledgment**

The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics has answered the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Gro Haarklou Mathisen. Ragna Bogen Hetland is acknowledged for her valuable work on this opinion. Jan Alexander (the Scientific Steering Committee), Åshild Krogdahl (the Scientific Steering Committee) and Helle Margrete Meltzer (former member of Panel on Nutrition, Dietetic Products, Novel Food and Allergy) constituted a reference group and are acknowledged for their valuable comments and suggestions on this opinion.

## **Competence of VKM experts**

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

# Table of Contents

<b>Summary</b> .....	<b>6</b>
<b>Sammendrag på norsk</b> .....	<b>8</b>
<b>Abbreviations and glossary</b> .....	<b>10</b>
<b>Background as provided by the Norwegian Food Safety Authority</b> .....	<b>11</b>
<b>Terms of reference as provided by the Norwegian Food Safety Authority</b> .....	<b>12</b>
<b>Assessment</b> .....	<b>13</b>
<b>1 Introduction</b> .....	<b>13</b>
<b>2 Hazard identification and characterisation</b> .....	<b>14</b>
2.1 Literature .....	14
2.1.1 Previous risk assessments .....	14
2.1.2 Literature search .....	15
2.1.2.1 Search strategy .....	15
2.1.2.2 Publication selection .....	15
2.2 General information .....	18
2.2.1 Chemistry .....	18
2.2.2 Occurrence .....	18
2.3 Absorption, distribution, metabolism and excretion (ADME) .....	19
2.3.1 In humans .....	19
2.3.2 Animal studies .....	19
2.4 Toxicological data/Adverse effects .....	19
2.4.1 Human studies .....	20
2.4.1.1 Interactions .....	27
2.4.1.2 Allergic sensitisation (including adjuvant effects) .....	27
2.4.2 Animal studies .....	27
2.4.2.1 Genotoxicity in vivo .....	29
2.4.2.2 Interactions .....	30
2.4.2.3 Allergic sensitisation (including adjuvant effects) .....	30
2.4.3 <i>In vitro</i> studies .....	30
2.4.4 Vulnerable groups .....	30
2.5 Summary of hazard identification and characterisation .....	30
<b>3 Exposure / Intake</b> .....	<b>33</b>
3.1 Food supplements .....	33

3.2	Other sources .....	33
<b>4</b>	<b>Risk characterisation.....</b>	<b>34</b>
<b>5</b>	<b>Uncertainties.....</b>	<b>36</b>
5.1	Uncertainty in hazard identification and characterisation .....	36
5.2	Uncertainty in exposure.....	36
5.3	Uncertainty in risk characterisation .....	36
<b>6</b>	<b>Conclusions with answers to the terms of reference .....</b>	<b>37</b>
<b>7</b>	<b>Data gaps .....</b>	<b>39</b>
<b>8</b>	<b>References .....</b>	<b>40</b>
<b>Appendix</b>	<b>.....</b>	<b>42</b>

# Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet, NFSA), assessed the risk of "other substances" in food supplements and energy drinks sold in Norway. VKM has assessed the risk of doses given by NFSA. These risk assessments will provide NFSA with the scientific basis while regulating the addition of "other substances" to food supplements and other foods.

"Other substances" are described in the food supplement directive 2002/46/EC as *substances other than vitamins or minerals that have a nutritional or physiological effect*. It is added mainly to food supplements, but also to energy drinks and other foods. In this series of risk assessments of "other substances", VKM has not evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of inulin, and it is based on previous risk assessments and articles retrieved from a literature search.

According to information from NFSA, inulin is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of the dose 3 g/day of inulin in food supplements.

The total exposure to inulin from other sources than food supplements and cosmetics, such as foods, is not included in the risk assessment.

Inulin is a naturally occurring carbohydrate found in a variety of vegetables and fruits such as onions, leeks, garlic, asparagus, artichokes, bananas and wheat. Chicory root is the most common source of industrially produced inulin. Inulin belongs to the nondigestible polysaccharides which are carbohydrates that resist digestion in the small intestine but are fermented by bacteria in the colon.

No serious adverse health effects were identified in the human studies included in this opinion. The reported negative health effects of inulin-type fibres are generally mild gastrointestinal symptoms and include diarrhea, abdominal rumbling, bloating, cramping and excessive flatulence. Such effects occur over a wide range of doses and may also depend on the source of inulin. Chain length influences the negative gastrointestinal effects, which will be less with long-chained inulin molecules. As a pragmatic approach, the intake of 5 g/day of inulin from agave and Jerusalem artichoke and 10 g/day of inulin from chicory root and globe artichoke were chosen as the values for comparison with the exposure to inulin from food supplements in the risk characterization. These doses were without serious adverse health effects, even though mild gastrointestinal effects may occur in some/sensitive individuals. These doses are in the same range as the estimated average consumption of inulin from food in Europe (3 – 11 g/day). Data indicates that also doses up to 20 g/day may

be well tolerated by most people. However, there is a wide interpersonal variability in the doses at which gastrointestinal effects associated with the colonic fermentation will appear.

No studies on children (10 to <14 years) and adolescents (14 to <18 years) were identified. Based on the included literature there was no evidence indicating that age affects tolerance for inulin. Therefore, in this risk assessment the same tolerance as for adults was assumed for these age groups (adjusted for body weight).

From a daily dose of 3 g inulin, the calculated intake levels are 69.1, 48.9 and 42.9 mg/kg bw per day for children (10 to <14 years), adolescents (14 to <18 years) and adults ( $\geq 18$  years), respectively. In the risk characterisation, the values used for comparisons with the exposure from food supplements is 5 g/day of inulin from agave and Jerusalem artichoke and 10 g/day of inulin from chicory root and globe artichoke (corresponding to 71 and 143 mg/kg bw per day, respectively, in a 70 kg adult).

Comparing the exposure of a daily dose of 3 g/day of inulin from food supplements with the inulin doses of 5 g/day and 10 g/day considered to be without appreciable risk for most healthy adults, it is unlikely that this dose in food supplements causes any adverse health effects in children above 10 years, adolescents and adults.

VKM concludes that it is unlikely that a daily dose of 3 g of inulin from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults ( $\geq 18$  years).

### **Short summary**

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of intake of 3 g/day of inulin in food supplements. In the risk characterization, the intake of 5 g/day of inulin from agave and Jerusalem artichoke and 10 g/day of inulin from chicory root and globe artichoke (corresponding to 71 and 143 mg/kg bw per day, respectively, in a 70 kg adult) were chosen as the values for comparison. No specific studies on children (10 to <14 years) and adolescents (14 to <18 years) were identified. Based on the included literature there was no evidence indicating that age affects tolerance for inulin. Therefore, a tolerance as for adults, based on body weight, was assumed for children and adolescents, in the comparison with human data.

VKM concludes that it is unlikely that a daily dose of 3 g of inulin from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults ( $\geq 18$  years).

**Key words:** Adverse health effect, food supplements, inulin, negative health effect, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, VKM

# Sammendrag på norsk

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved tilsetning av «andre stoffer» i kosttilskudd og energidrikk som selges i Norge. VKM har risikovurdert ulike bruksdoser oppgitt fra Mattilsynet. Risikovurderingene gir et vitenskapelig grunnlag for Mattilsynet i arbeidet med å regulere bruken av «andre stoffer».

«Andre stoffer» er stoffer som har en ernæringsmessig eller fysiologisk effekt, og som ikke er vitaminer og mineraler. De tilsettes i hovedsak til kosttilskudd, men også til energidrikker og andre næringsmidler. I disse risikovurderingene har VKM ikke sett på påståtte gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

I denne rapporten har VKM vurdert risiko ved inntak av inulin. Risikovurderingen er basert på tidligere risikovurderinger av inulin og artikler som er funnet ved et litteratursøk.

Ifølge informasjon fra Mattilsynet er inulin en ingrediens i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere 3 g/dag av inulin i kosttilskudd.

Andre kilder til inulin, som for eksempel mat og kosmetikk, er ikke inkludert i denne risikovurderingen.

Inulin er et karbohydrat som finnes naturlig i en rekke grønnsaker og frukter som løk, purre, hvitløk, asparges, artisjokker, bananer og hvete. Sikoriroot er den vanligste kilden til industrielt produsert inulin. Inulin hører til de ufordøyelige polysakkaridene, det vil si de som ikke blir fordøyd i tynntarmen, men blir brutt ned av bakterier i tykktarmen.

Ingen alvorlige helseeffekter hos mennesker ble identifisert i studiene som er inkludert i denne risikovurderingen. De negative effektene som ble rapportert hos noen personer var milde mage-tarm symptomer som diaré, rumlende mage, oppblåsthet, kramper, flatulens og magesmerter. Slike effekter forekommer over et bredt område av doser, og kan også være avhengig av typen inulin. Kjedelengden er av betydning for effektene, og negative effekter vil være redusert med langkjedete inulin-molekyler. Som en pragmatisk tilnærming ble inntaket av 5 g/dag av inulin fra agave og jordskokk og 10 g/dag av inulin fra sikorirøtter og artisjokk valgt som verdier for sammenligning med eksponeringen for inulin fra kosttilskudd. Disse dosene er uten alvorlige helseeffekter, selv om milde negative mage-tarm effekter kan forekomme selv ved disse dosene hos følsomme personer. Disse dosene er i samme størrelsesorden som beregnet gjennomsnittlig inntak av inulin fra mat i Europa (3 - 11 g/dag). Data indikerer at også doser opp til 20 g/dag tolereres godt av de fleste. Det er imidlertid stor variasjon blant personer når det gjelder hvilke doser som gir mage-tarm symptomer.

Det ble ikke funnet studier gjort spesifikt på barn (10 til <14 år) og ungdom (14 til <18 år). På grunnlag av den inkluderte litteraturen var det ikke grunn til å anta at alder påvirker toleranse for inulin, og derfor ble samme toleranse som for voksne, basert på kroppsvekt, antatt for barn og ungdom.



Ved inntak av en daglig dose på 3 g inulin fra kosttilskudd blir eksponeringen 69,1, 48,9 og 42,9 mg/kg kroppsvekt per dag for henholdsvis barn (10 til <14 år), ungdom (14 til <18 år) og voksne ( $\geq 18$  år). I risikokarakteriseringen sammenlignes denne eksponeringen med 5 g/dag av inulin fra agave og jordskock og 10 g/dag av inulin fra sikorirøtter og artisjokk (tilsvarende henholdsvis 71 og 143 mg/kg kroppsvekt per dag, for en person på 70 kg).

En direkte sammenligning av eksponeringen for inulin fra kosttilskudd med dosene på 5 g/dag og 10 g/dag som er rapportert å være uten nevneverdig risiko for de fleste friske voksne viser at det er usannsynlig at en daglig dose på 3 g av inulin forårsaker negative helseeffekter hos barn over 10 år, ungdom og voksne.

VKM konkluderer med at det er usannsynlig at en daglig dose på 3 g av inulin fra kosttilskudd forårsaker negative helseeffekter hos barn (10 til <14 år), ungdom (14 til <18 år) og voksne ( $\geq 18$  år).

### **Kort sammendrag**

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved inntak av 3 g per dag av inulin i kosttilskudd. I risikokarakteriseringen ble eksponeringen for inulin fra kosttilskudd sammenlignet med 5 g/dag av inulin fra agave og jordskock og 10 g/dag av inulin fra sikorirøtter og artisjokk (tilsvarende henholdsvis 71 og 143 mg/kg kroppsvekt per dag, for en person på 70 kg). Det ble ikke funnet studier gjort spesifikt på barn og ungdom. På grunnlag av inkluderte litteraturen var det ikke grunn til å anta at alder påvirker toleranse for inulin. Det ble derfor antatt samme toleranse som for voksne, basert på kroppsvekt, for barn (10 til <14 år) og ungdom (14 til <18 år).

VKM konkluderer at det er usannsynlig at en daglig dose på 3 g av inulin forårsaker negative helseeffekter hos barn (10 til <14 år), ungdom (14 til <18 år) og voksne ( $\geq 18$  år).

# Abbreviations and glossary

## Abbreviations

ACF	- aberrant crypt foci
ADI	- acceptable daily intake
ADME	- absorption, distribution, metabolism, excretion
AESAN	- Spanish Agency for Food Safety and Nutrition
DMH	- dimethylhydrazine
DP	- degree of polymerization
EFSA	- European Food Safety Authority
FOS	- fructooligosaccharides
GI	- gastrointestinal
GRAS	- Generally Recognized as Safe
IOM	- Institute of Medicine of the National Academy of Sciences, USA
LPD	- low protein diet
NFSA	- Norwegian Food Safety Authority [ <i>norw.</i> : Mattilsynet]
NPD	- normal protein diet
RCT	- randomised controlled trials
UL	- tolerable upper intake level
VLCI	- very long-chained inulin
VKM	- Norwegian Scientific Committee for Food Safety [ <i>norw.</i> : Vitenskapskomiteen for Mattrygghet]

## Glossary

"Other substances": a substance other than a vitamin or mineral that has a nutritional or physiological effect (The European Parliament and the Council of the European Union, 2006).

"Negative health effect" and "adverse health effect" are broad terms. VKM uses the definition recently established by EFSA for "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (WHO, 1994).

# Background as provided by the Norwegian Food Safety Authority

«Other substances» are substances other than vitamins and minerals, with a nutritional and/or physiological effect on the body. "Other substances" are mainly added to food supplements, but these may also be added to other foods and beverages, such as sports products and energy drinks. Ingestion of these substances in high amounts presents a potential risk for consumers.

In Norway, a former practice of classification of medicines had constituted an effective barrier against the sale of potentially harmful "other substances". Ever since this practice was changed in 2009, it has become challenging to regulate and supervise foods with added "other substances". Meanwhile, in the recent years, the Norwegian market has witnessed a marked growth in the sales of products containing "other substances". In 2011, food supplements containing "other substances" constituted more than 50% of the market share.

While within the European Economic Area, these substances fall under the scope of the European Regulation (EC) No. 1925/2006 on the addition of vitamins, minerals and certain other substances to foods and the European Regulation (EC) No 258/97 concerning novel foods and novel food ingredients, "other substances" remain largely unregulated. In order to ensure safe use of "other substances" many countries have regulated their use at a national level. For example, Denmark regulates these substances in a positive list, i.e. a list of substances with maximal daily doses, permitted for use in food supplements and other foods (FVM, 2014).

The Norwegian Food Safety Authority (NFSA) is working on the establishment of a regulation on the addition of "other substances" to foods at a national level. The regulation will include a list of substances with permitted maximal doses, based on the substances and doses found in products on the Norwegian market. In preparation for a regulation, NFSA has therefore requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of "other substances" found on the Norwegian market. NFSA, in consultation with the industry, has compiled a list of "other substances" found in products marketed in Norway. Only substances with a purity of minimum 50% or concentrated 40 times or more have been included in the list. Substances regulated by other legislations like those for novel foods, food additives, flavourings, foods for special medical purposes, etc. have been excluded from the list.

# Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of inulin in food supplements at the following dose: 3000 mg/day.

NFSA requested VKM to assess the safety of "other substances" (in accordance to the guidance document developed in Phase 2) at the doses specified (Phase 3). Safety assessments of "other substances" present in food supplements shall be carried out for a general population, ages 10 years and above.

# Assessment

## 1 Introduction

"Other substances" are described in the food supplement directive 2002/46/EC as substances other than vitamins or minerals that have a nutritional or physiological effect, and may be added to food supplements or e.g. energy drinks (The European Parliament and the Council of the European Union, 2006). VKM has in this series of risk assessments of "other substances" not evaluated any potential beneficial effects from these substances, but merely possible adverse effects and safe use. This risk assessment regards the substance inulin per se, and no specific products.

According to information from the Norwegian Food Safety Authority (NFSA), inulin is an ingredient in food supplements purchased in Norway. NFSA has requested a risk assessment of 3000 mg (3 g) of inulin per day in food supplements. The total exposure to inulin from other sources than food supplements, such as foods and cosmetics, is not included in the risk assessment.

Inulin is an energy storage polymer widely found in plants such as onions, leeks, garlic, asparagus, bananas, wheat, Jerusalem artichokes and chicory roots (Schaafsma and Slavin, 2015). Inulin belongs to the nondigestible polysaccharides which are carbohydrates that resist digestion in the upper gastrointestinal (GI) tract but are fermented by bacteria in the colon. In USA, a panel of experts (U.S. Food and Drug Administration, 2016), has confirmed the GRAS (Generally Recognized As Safe) status of chicory inulin (U.S. Food and Drug Administration). The average daily consumption of inulin and oligofructoses has been estimated to be in the range of 1 to 4 g in the United States and 3 to 11 g in Europe (van Loo et al., 1995).

# 2 Hazard identification and characterisation

## 2.1 Literature

The present risk assessment is based on previous risk assessments of inulin and articles retrieved from a literature search.

### 2.1.1 Previous risk assessments

#### **Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements – 1. (AESAN, 2012)**

The report published by the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) includes the assessment of 49 substances with respect to their safety in doses proposed for use in manufacture of food supplements. The substances belong to different groups including polysaccharides and oligosaccharides, in which inulin was one of the assessed substances. AESAN based their assessment on the characteristics and sources, the nutrition, metabolism and safety of each substance.

In this report a proposal of a maximum daily amount of 9 g of fructooligosaccharides (FOS) or the sum of FOS plus inulin was assessed. This proposal was based on a favourable assessment of FOS in France, indicating that intake of 8 g of the oligofructose mixture enriched with inulin (4 g of oligofructose and 4 g of inulin) is free of risk. Furthermore, in Italy, FOS and inulin are authorized in food supplements without the establishment of a maximum daily amount. It is also stated in the assessment that the FOS, even at high doses, do not have consequences on mortality, morbidity, toxicity or carcinogenicity. AESAN considered, based on the information available and taking into account the general considerations reflected in the report, that the AESAN proposal of a daily dose of 9 g of FOS or the sum of FOS and inulin is acceptable from the safety point of view for use as food supplement. Nevertheless, AESAN recommended that the following warnings should be displayed on the packaging of FOS-based supplements:

- "Do not exceed a daily dose of 9 g of FOS/day, or the sum of FOS and inulin, as excessive consumption may cause stomach upsets.
- When taking this type of preparation, the intake of other dietary fibre-based food supplements should be avoided.
- Given that the fibre may interact with some medicines, altering their efficiency, please seek medical advice if taken at the same time as other medicines."

## **Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Institute of Medicine, USA (IOM, 2005)**

Institute of Medicine (IOM) of the National Academy of Sciences reviewed the role that the macronutrients carbohydrates, fibre, fat, fatty acids, cholesterol, protein and amino acids are known to play in traditional deficiencies as well as chronic diseases. This is included in a report that presents Dietary Reference Intakes for these macronutrients (IOM, 2005).

The evaluation of the intake of fibres included inulin, which belongs to the group dietary fibres. Most of the commercially available inulin and oligofructose is either synthesized from sucrose or extracted and purified from chicory roots. A tolerable Upper Intake Level (UL) was not set for any of the individual fibres evaluated. This decision was based on the lack of observations of serious chronic adverse effects, even if occasional adverse GI symptoms are observed when consuming some types of isolated or synthetic fibres. With respect to inulin, cramping, bloating, flatulence and diarrhea were observed at intakes ranging from 14 to 18 g/day. Due to the bulky nature of fibres, IOM also stated that excess consumption is likely to be self-limiting.

### **2.1.2 Literature search**

#### ***2.1.2.1 Search strategy***

Literature searches were performed in MEDLINE and EMBASE in order to retrieve publications on adverse effects caused by inulin. These databases were chosen to ensure comprehensive study retrieval. The literature searches were performed in June 2015. The strategy for the search is included in Appendix 1.

#### ***2.1.2.2 Publication selection***

The literature search identified 174 articles. In the primary screening, titles and abstracts of all unique publications retrieved were independently screened against the inclusion criteria checklist.

Inclusion criteria checklist:

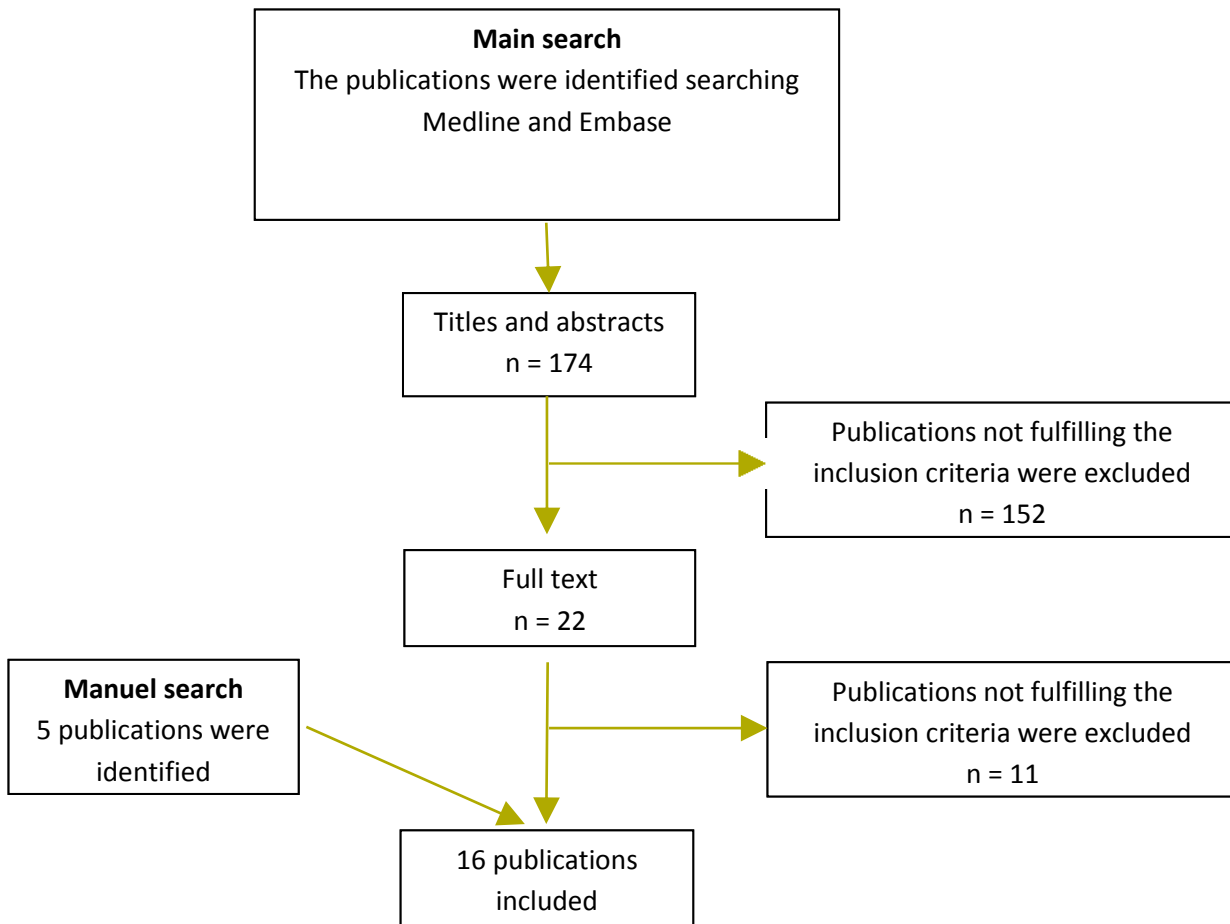
- Adverse effects in relation to the substance alone are addressed
- Route of exposure for humans is oral
- Route of exposure for animals is oral, in addition, subcutaneous exposure is included if the toxicokinetic is equal to oral exposure
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal absorption and metabolism of the assessed substance
- Animal model studies address adverse effects relevant to human health

The inclusion criteria checklist was developed by members of the VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the VKM Panel on Nutrition, Dietetic Products, Novel Food and Allergy. Articles that did not appear to meet the inclusion criteria were excluded from further analysis. In situations where it was unclear whether the publication was of relevance to the study, it was retained for further screening. The primary screening was performed independently by two persons.

The full text of the 22 articles that passed the primary screening was retrieved for secondary screening. In this screening, the full text articles were reviewed and compared against the inclusion criteria checklist. The secondary screening was performed by one person.

The secondary screening resulted in 11 articles. Additionally, 5 studies from manual search were identified. A final total of 16 publications were included in the results in this report (see Figure 2.1.2.2-1).



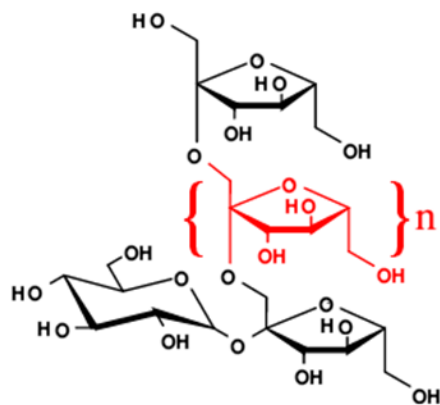


**Figure 2.1.2.2-1** Flow chart for the literature search for inulin and the subsequent publication selection.

## 2.2 General information

### 2.2.1 Chemistry

Inulin (CAS no. 9005-80-5; EINECS no. 232-684-3) is a generic term to cover polysaccharides (linear fructanes) with the similar basic structure of  $\beta(2 - 1)$  fructosyl – fructose linkage, including oligofructose and FOS. Inulin and the inulin-like fructanes oligofructose and FOS are composed of D-fructose units linked at the 1 and 2 positions and end-capped with a D-glucose, and they differ principally in their degree of polymerization (DP) (Carabin and Gary Flamm, 1999). The inulin molecules in chicory roots have a DP of 3 to over 60, and inulin molecules with a DP of 3 to 10 are often called oligofructose or FOS (Schafsma and Slavin, 2015). Differences in the DP are of importance for the physicochemical and physiological properties of inulin and oligofructose. The structural formula of inulin is  $C_{6n}H_{10n+2}O_{5n+1}$  (Figure 2.2.1-1). Total hydrolysis of inulin gives glucose and fructose.



**Figure 2.2.1-1** The structural formula of inulin.

### 2.2.2 Occurrence

Inulin is a naturally occurring carbohydrate found in a variety of vegetables and fruits such as onions, leeks, garlic, asparagus, artichokes, bananas and wheat (Carabin and Gary Flamm, 1999). Chicory root is the most common source of industrially produced inulin. Standard inulin is slightly sweet (10% sweetness in comparison with sugar), whereas high performance inulin (from which the fraction with a DP lower than ten has been removed) is not.

## **2.3 Absorption, distribution, metabolism and excretion (ADME)**

### **2.3.1 In humans**

Inulin resists both enzymatic digestion in the upper GI tract and absorption in the small intestine. Thus, inulin reaches the colon almost intact and is fermented completely by the colonic microflora producing gases and short chain organic acids (lactic, acetic, propionic and butyric acids). The fermentation of the long-chain inulin molecules takes place in the distal colon, whereas FOS is fermented in the proximal colon (AESAN, 2012).

### **2.3.2 Animal studies**

No animal studies on ADME are referred to since only human data are referred to by AESAN (2012) and EFSA (2015). However, inulin is preferentially metabolized by the same type of bacteria, the bifidobacteria, in both humans and rodents (Cantero et al., 2015).

## **2.4 Toxicological data/Adverse effects**

General information, from review studies and a risk assessment, show that the reported negative effects of inulin-type fibres are mild GI symptoms and include diarrhea, abdominal rumbling, bloating, cramping and excessive flatulence caused by gas formation and osmotic effects of certain fermentation products (Kelly, 2009; Schaafsma and Slavin, 2015). Chain length influences the negative GI effects, which will be less with long-chained inulin molecules since they are fermented at a rate of about 50% lower than that of short-length inulin molecules. There is also a wide interpersonal variability in the doses at which such effects associated with the colonic fermentation will appear. Other dietary fibres can have other unwanted side-effects such as negative influence on vitamin or mineral absorption, allergic reactions and an undesirable influence on the gut flora and their metabolism. No such negative effects have been found for inulin and oligo-fructose (Coussement, 1999). Intestinal acceptability of nondigestible fermentable carbohydrates differs from person to person, and it also depends on the food in which the fibre is contained. In general, the intake of up to 20 g/day of inulin and/or oligofructose is not considered to produce significant negative effects, even though some people may experience intestinal upset after intake of small quantities (AESAN, 2012; Carabin and Gary Flamm, 1999; Schaafsma and Slavin, 2015). Studies have demonstrated that inulin-type fructans, when administered in the diet at high levels, do not influence mortality, morbidity, target organ toxicity, reproductive or developmental toxicity or carcinogenicity (Coussement, 1999). Little information is available concerning the acceptability of indigestible carbohydrates for children and adolescents, but no significant undesirable negative effects were shown in children of 10 to 13 years at daily doses of 3, 6 and 9 g of oligofructose in drinks and confectionery products (Coussement, 1999) (original data not available).

### **2.4.1 Human studies**

An overview of the included human studies investigating adverse health effects of inulin is given in Table 2.4.1-1.

**Table 2.4.1-1** An overview of human studies investigating inulin and adverse health effects (F: female; M: male).

Reference	Study design/ Participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Study duration	Negative health effects
			Inulin	Control/ placebo				
Holscher et al. (2014)	Randomized, double-blind, placebo-controlled, cross-over (healthy adults)	USA	29 (F + M)	29 (F + M)	5 and 7.5 g agave inulin/day. Control: 0 g inulin/day	GI tolerance and utilization	A 7 days baseline period, then 3 x 21 days treatment periods with a 7 day washout period among treatment periods	No serious symptoms were reported. However, mild but statistically significant increases in frequencies and intensities of GI intolerance symptoms (nausea, GI rumblings, abdominal pain, bloating, flatulence and diarrhea) were reported for both doses.
Slavin and Feirtag (2011)	Randomized, double-blind, cross-over (no wash-out period); healthy non-smoking males	USA	12 (M)	12 (M)	20 g chicory inulin/Day. Placebo: Corn syrup	Examined several GI parameters. Subjective measures of tolerance were given	21 + 21 days of each diet (treatment and placebo)	No adverse effects were observed. The test meal was well tolerated by all, although flatulence measures by self-report were significantly higher when subjects were on the inulin diet.
Ramnani et al. (2010)	Three-arm parallel, randomized, double-blind, placebo controlled (healthy volunteers)	The Netherlands	22 (11 F + 11 M) + 22 (11 F + 11 M)	22 (11 F + 11 M)	5 g Jerusalem artichoke inulin/day. Placebo: Water-based, flavoured preparation with added sugar	Assess the prebiotic capability of fruit and vegetable shots containing inulin from Jerusalem artichoke	2 weeks run-in period, then 3 weeks intervention + 3 weeks wash-out	No serious adverse events were recorded, whereas a statistically significant but slight increase in flatulence was observed in the inulin group compared to placebo.

Reference	Study design/ Participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Study duration	Negative health effects
			Inulin	Control/ placebo				
Bonnema et al. (2010)	Randomized, double-blind, controlled, cross-over (healthy subjects)	USA	26 (13 F + 13 M)	26 (13 F + 13 M)	5 or 10 g chicory inulin or FOS per day, one day per week. Ten randomised groups with determined sequence of fibre type and dosage. Placebo: Maltodextrin	Evaluate GI tolerance of native inulin and a shorter-chain oligofructose	Challenge one day/week with a 1-week wash-out. GI tolerance scored at 0, 2, 4, 24 and 48 h after challenge.	No adverse effects reported. All treatments showed greater overall GI score (measure for reduced GI tolerance) compared to control, but only treatment with 10 g oligofructose reached significance (P < 0.05).
Costabile et al. (2010)	Randomized, double-blind, controlled, cross-over (healthy subjects)	UK	18 + 13 (F + M in both groups, distribution between genders unknown)	13 + 18 (F + M in both groups, distribution between genders unknown)	10 g inulin (very long-chained inulin (VLCI) from globe artichoke). Placebo: Maltodextrin	Assess the capacity of VLCI to selectively increase numbers of bifidobacteria and lactobacilli in faeces	3 weeks (inulin or placebo) + 3 weeks wash-out + 3 weeks (placebo or inulin)	No adverse GI symptoms were reported apart from a statistically significant increase in mild and moderate bloating after VLCI ingestion (P < 0.05).
Bruhwyler et al. (2009)	Randomized, double-blind, controlled, cross-over (healthy subjects)	Belgium	28 in each group (A, B and C) (F + M in all groups)	28 in each group (A, B and C) (F + M in all groups)	Group A: 5 g inulin/day Group B: 10 g inulin/day. Group C: 20 g inulin/day, all three inulin types from chicory.	Compare the GI tolerance of three inulin-type fructans given daily at different doses (Fibulose F97, Fibruline Instant and	2 weeks run-in + 2 weeks treatment + 2 weeks wash-out + 2 weeks treatment + 2 weeks	No serious adverse events were reported, but statistically significant increase in GI symptoms was observed at 20 g/day for Fibruline Instant. Regarding unsolicited adverse events, 8 of 86 (7 in the placebo period and 1 in the 5 g/day period) were considered causally related to the treatment (3

Reference	Study design/ Participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Study duration	Negative health effects
			Inulin	Control/ placebo				
					Placebo: Saccharose	Fibrulose XL)	run-out	gastroenteritis, 1 intestinal flu, 1 colopathy, 2 headaches and 1 moderate pyrosis). All three inulin-type fructans were well tolerated.
Davidson et al. (1998)	Randomized, double-blind, controlled, cross-over (adults with mild-to-moderate hypercholesterolemia)	USA	13 (6 F + 7 M) + 12 (7 F + 5 M)	12 (7 F + 5 M) + 13 (6 F + 7 M)	18 g chicory inulin (DP = 10)/day. Placebo: Control food, ingredients not reported	Compare the serum lipid profile after consumption of inulin-supplemented food vs. consumption of similar food without inulin	6 weeks treatment + 6 weeks wash-out + 6 weeks treatment	Side effects were recorded as the sum of increased flatulence, abdominal cramping, bloating and changes in frequency and consistency of bowel movement. Severe side effects were reported by 1 out of 21 persons during control period, whereas moderate side effects were reported by 3/21 during inulin period. Mild side effects were reported by 13/21 during inulin period vs. 7/21 during control period.

Evaluation of the GI tolerance and utilization of 5 and 7.5 g agave inulin per day was performed in 29 healthy American adults (age  $27.1 \pm 4.1$  years) (Holscher et al., 2014). The randomized, double-blind, placebo-controlled crossover study consisted of three 21 day treatment periods with a 7 day washout between periods. The number of males and females (specific number not reported) per treatment group and the six treatment sequences were balanced by number and sex to minimize potential carry-over effects. All participants completed a 7-day baseline period prior to the first treatment period. Each 21 day treatment period consisted of a 15 day adaptation phase, a 5 day fecal collection phase and 1 day of breath gas testing. Participants were also required to keep accurate dietary diary during the 7 day baseline period and each 21 day treatment period. The amount and type of all foods and liquids consumed in each 24 hour period was recorded. Of the daily symptoms ratings, flatulence was the most intense GI symptom reported, however, the intensity scores were mild. On the weekly symptoms ratings, composite GI symptoms scores revealed that both 5 g and 7.5 g agave inulin per day increased the frequency of GI intolerance symptoms ( $P < 0.05$  for nausea, bloating, GI rumbling, gas/flatulence, abdominal pain and diarrhea). However, the mean frequencies for all symptoms were low. Study records indicated that the subjects consumed nearly 100% of treatment (3 chews per day) and maintained a moderate-fibre diet (average fibre intake 17.9 g/day). The overall conclusion of the study was that daily consumption of a supplement containing 5 g and 7.5 g agave inulin was generally well tolerated by healthy adult humans with only mild frequencies and intensities of GI intolerance symptoms.

In a randomized, double-blind crossover study conducted in USA, 12 healthy male non-smokers (age 27 – 49 years) were randomly assigned to either basal, low fibre control diet or to a basal diet with the addition of chicory inulin incorporated into low fat vanilla ice cream (Slavin and Feirtag, 2011). The objective of the study was to examine the effects of a 20 g/day supplementation of chicory inulin (average DP = 9) on several GI parameters, including stool weight, defecation frequency and intestinal transit time, fecal microbes, fecal microbial enzyme activity, fecal short-chain fatty acids and fecal ammonia. Each treatment period lasted 21 days, after which the subjects were crossed over to the other diet for 21 days. All 12 subjects completed the study without complications and test meals were well tolerated by all subjects. Consumption of 20 g/day of inulin by healthy adults resulted in increased fecal microbes and a decrease in ammonia levels and  $\beta$ -glucuronidase activity. However, this dose had minimal effects on bowel function measures, although flatulence measures by self-report were significantly higher when on the inulin treatment.

In a Dutch three-arm parallel, placebo-controlled, double-blind study, 66 healthy volunteers (33 males and 33 females, aged 18 – 50 years) were randomized into three groups ( $n = 22$ ) (Ramnani et al., 2010). The study was designed to assess the prebiotic capability of two different fruit and vegetable shots where juice containing inulin was from Jerusalem artichoke present at similar levels in both. The placebo shot was a water-based fruit and vegetable preparation without the Jerusalem artichoke inulin juice. Subjects consumed two 100 ml shots containing 2.5 g inulin/100 ml per day, resulting in a total dose of 5 g inulin/day. The volunteers were randomly assigned to consume either one of the two test



formulations containing Jerusalem artichoke inulin or placebo. After a 2-week run-in and a three weeks intervention period, the treatment period was followed by a 3-week washout period. The results demonstrated an increase in levels of bifidobacteria and the *Lactobacillus/Enterococcus* group. No serious adverse events were observed, although a slight but statistically significant increase in flatulence was reported in the subjects consuming the inulin-containing shots when compared to placebo.

GI tolerance of native inulin and shorter-chain oligofructose from chicory was studied in a total of 26 healthy Americans of 18 to 60 years (Bonnema et al., 2010). The study group consisted of 13 women ( $32 \pm 15$  years) and 13 men ( $29 \pm 9$  years). The randomized, double-blind, controlled, cross-over designed study included a phone screening and five visits for fibre challenges. Subjects were randomized for assignment across one of ten groups with a determined sequence of fibre type and dosage. Fibre challenges were conducted once a week with a 1-week wash-out period. The treatments were placebo, 5 g oligofructose, 10 g oligofructose, 5 g inulin or 10 g inulin. Tolerance was measured by assessing frequency and severity of GI cramping, diarrhea, constipation and GI rumbling. Questionnaires were used to record the occurrence and the severity of individual symptoms at 0, 2, 4, 24 and 48 hours with a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Baseline scores were established for each subject from the sum of the time = 0 record at the start of every visit. All subjects completed the study. All fibre-treatments showed greater overall GI symptom score compared to control (geometric mean = 2.0), the most frequently reported symptoms were flatulence and bloating. Geometric means of total scores in the treatment groups were 2.5, 2.7, 2.8 and 3.6 for 5 g inulin, 10 g inulin, 5 g oligofructose and 10 g oligofructose, respectively. Only the 10 g oligofructose reached statistical significance ( $P < 0.05$ ). Most of the subjects who experienced GI symptoms reported only mild occurrences. Also, many of the subjects rarely or never reported symptoms for any of the variables whereas some reported multiple symptoms continuously. According to the authors, this suggests a wide range in individual tolerance to inulin. It was concluded that doses up to 10 g/day of native inulin and up to 5 g/day of oligofructose were well tolerated in healthy, young adults.

The impact of a very-long-chained-inulin (VLCI), derived from globe artichoke (*Cynara scolymus*) on the human intestinal microbiota compared with maltodextrin (placebo) was determined in a double-blind, placebo-controlled cross-over study carried out with 31 healthy American adults (18 females and 13 males) aged 20 – 42 years (Costabile et al., 2010). Before intervention, the subjects followed a restricted diet for 2 weeks. Then they were randomly allocated into one of two groups. The first group (n=18, gender not reported) consumed VLCI (10 g/day) for 3 weeks, then after a 3 weeks wash-out they consumed placebo (10 g/day) for 3 weeks. The second group (n=13, gender not reported) received first placebo (10 g/day) for 3 weeks, then a 3 weeks wash-out before they consumed VLCI (10 g/day) for 3 weeks. The volunteers were asked to keep diaries to record stool frequency, consistency, abdominal pain (none, mild, moderate or severe), intestinal bloating (none, mild, moderate or severe) and flatulence (none, mild, moderate or severe) on a daily basis. Any concomitant medication and adverse events were also recorded. Daily consumption of VLCI extracted from globe artichoke exerted a probiotic effect on the faecal microbiota

composition. The tested dose of 10 g/day was well tolerated by all volunteers and no adverse GI symptoms apart from statistically significant increase in mild and moderate bloating were recorded ( $P < 0.05$ ).

A total of 84 healthy Belgian volunteers (males and females), aged between 18 and 45 years, were included in a double-blind, placebo-controlled, randomized, cross-over and dose-ranging study (Bruhwylers et al., 2009). The aim of the study was to compare the GI tolerance for three inulin-type fructans from chicory administered at different doses (5 – 20 g/day) for two weeks. The three inulin-type fructans differed in their chain length (degree of polymerization, DP), with Fibrulose F97 (DP 2 – 20), Fibruline Instant (DP 2 – 60, average of 10) and Fibrulose XL (DP 2 – 60, average of 20). The subjects were randomized into three different dose-groups ( $n = 28$ ): 5 g/day (group A), 10 g/day (group B) and 20 g/day (group C). After a placebo run-in period of two weeks, subjects in each group received two of the three test treatments according to a cross-over design. Each treatment period lasted 2 weeks and was separated from the next treatment period by a placebo wash-out period of 2 weeks. The total study period for each subject was 10 weeks, and all participants completed. Tolerance was assessed as the severity of eight predetermined symptoms of GI effects by using a visual, analogue scale (nominal scale) from 0 to 100 mm, and was recorded daily. The primary variable was the mean difference between treatment and placebo. Symptoms were mild and a statistically significant difference was only demonstrated at 20 g/day (Fibruline Instant). All three products tended to increase digestive symptoms, and the mean tolerance score tended to increase with increasing dose (5, 10 and 20 g/day) for Fibrulose F97 and Fibruline Instant. Statistical differences were reported between placebo and 20 g/day and between 5 g/day and 20 g/day of Fibruline Instant. Tolerance was also assessed as the frequency of unsolicited adverse events (ordinal scale), and 8 out of 86 such events were considered treatment related (7 under placebo period ( $n = 4, 2$  and  $1$ ) in the 5, 10 and 20 g inulin/day groups, respectively) and 1 under the Fibruline Instant period (5 g/day). The recorded unsolicited adverse events were three gastroenteritis, one intestinal flu, one colopathy and two headaches under placebo, and one moderate pyrosis under Fibruline Instant. No serious adverse events were reported and it was concluded that all three inulin-type fructans were very well tolerated.

The effects of inulin on serum lipids were studied in a randomized, double-blind, cross-over trial in men and women (age 30-75 years) with mild-to-moderate hypercholesterolemia (Davidson et al., 1998). The primary objectives of the study were to compare the serum lipid profile after 6 weeks with inulin-supplemented food (total of 18 g chicory inulin/day divided in 3 servings) vs. 6 weeks consuming similar food without inulin, and to evaluate the practicality of including 18 g/day of inulin in the diets of this group. The inulin had an average DP of 10, varying between 2 and 65. Twenty-six subjects were randomized and started the first treatment phase (7 males/6 females and 5 males/7 females, in the two groups respectively), whereas a total of 21 completed. The first 6 weeks treatment period was followed by a 6 weeks wash-out, after which the subjects crossed over and received the other treatment for 6 weeks. Dietary adherence was confirmed by computerized analysis of three day food records collected at the start and end of each of the two treatment periods.

At each clinical visit, vital signs and body weight were measured, dietary counseling was completed, fasting blood sample was collected and adverse events and medication changes were documented. With respect to negative health effects (side effects), the recorded GI symptoms were significantly higher during the inulin phase than during control phase (77 and 44, respectively). The most frequent effects reported were increased flatulence, abdominal cramping, bloating and changes in the frequency and consistency of bowel movements. While most of the events were mild, moderate or severe complaints were reported by one person during the control period vs. three persons during the inulin period. The authors concluded that the GI effects were generally mild and similar to that of other soluble fibers.

#### ***2.4.1.1 Interactions***

No information concerning interactions was identified in the human studies reviewed in this risk assessment. However, the Scientific Committee of the AESAN recommended to include a warning to be displayed on the packaging of FOS-based supplements regarding possible interaction between fibre and some medicines and encourage to seek medical advice if such supplements and medicines are taken at the same time (AESAN, 2012).

#### ***2.4.1.2 Allergic sensitisation (including adjuvant effects)***

There was no information concerning allergic sensitisation or allergy adjuvant effects in the human studies reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

### **2.4.2 Animal studies**

An overview of the included studies on inulin and adverse effects in animals is given in Table 2.4.2-1.

**Table 2.4.2-1** An overview of animal studies on inulin and adverse health effects.

Reference	Study	Dose and number in treatment group		Conclusion with regard to adverse effects
		Inulin	Control	
Volek et al. (2007)	Effect of inulin on health status, caecal metabolism, digestibility of nutrients and growth of early weaned rabbits  Study duration: 74 days	4% inulin in diet (at the expense of wheat bran) or 0.3% mannan-oligosaccharide  (n = 110 per group at start)	Control diet (some more starch and less fructans than the inulin diet)  (n = 110)	No significant study-related adverse effects were revealed.
Propst et al. (2003)	Dose-response experiment evaluating effects of oligofructose and inulin on nutrient digestibility, stool quality and fecal protein catabolites in dogs  Study duration: 7x7 Latin square design with 14 days treatment periods, total 98 days	0.3, 0.6 and 0.9% (1.9, 3.8 and 7.5 g/day) of inulin (or oligofructose, 1.5, 3 and 4.5 g/day) administered by gelatin capsule twice daily  (n total = 7)	Control diet with no supplemental fructan  (n total = 7)	No adverse effects were reported.

The effect of a dietary supplementation with mannan-oligosaccharide and inulin on growth, health and caecal traits was studied in 348 rabbits, weaned at 25 days of age (Volek et al., 2007). Animals were given one of three diets; control (C), mannan-oligosaccharide (M) (0.3%) or inulin (I) (4%) from weaning until 46 days of age, then all rabbits got control diet until slaughter at 74 days of age. Due to how the study was performed, feed intake (g per rabbit per day) was calculated based on weekly measured consumption of feed per group, number of animals and days. Mean feed intake in the period 25 – 46 days was 57.8 g/day, 58.1 g/day and 60.0 g/day in the C, M and I group, respectively. The corresponding body weights at day 46 were 1361 g, 1301 g and 1318 g. For the period from weaning, this represents a mean intake of 2022, 2127 and 2168 mg/kg bw per day for the C, M and I groups, respectively. No adverse effects on health due to mannan-oligosaccharide or inulin supplementation were reported. No differences in mortality rate were observed among the groups. A lower morbidity ( $P = 0.05$ ) and health risk index (sum of morbid and dead rabbits,  $P = 0.03$ ) was observed in the inulin group for the intervention period, but this difference was not statistically significant when recorded for the whole period.

In a dose-response experiment, three doses of oligofructose and inulin were tested against control in a meat-based diet (0.3, 0.6 and 0.9% of diet) (Propst et al., 2003). The aim of the study was to investigate the effects of selected oligofructose and inulin concentrations on nutrient intake, nutrient digestibility, stool quality and fecal protein catabolites. Seven ileal-cannulated healthy, adult female dogs were assigned to treatments in a 7 x 7 Latin square design with 14 days treatment periods. Dogs were administered oligofructose and inulin by gelatin capsules twice a day with the following doses: 0 g/day (control), 1.5 g/day, 3 g/day and 4.5 g/day oligofructose, and 1.9 g/day, 3.8 g/day and 7.5 g/day inulin. Body weights of the dogs were not reported, thus the intake per kg body weight per day could not be calculated. Total duration of the experiment was 98 days, where day 1 through 10 constituted the diet adaption phase and day 11 through 14 constituted the collection phase, during each period. The results demonstrated that low-level dietary inclusion of oligosaccharide and inulin positively affected indices known to be associated with gut health without seriously compromising nutrient digestibility or stool quality.

#### **2.4.2.1 Genotoxicity in vivo**

The effects of restricting protein and calories and supplementation of inulin on the deficiency status were examined in male Swiss mice in which genomic lesions were measured by Comet assay and colorectal carcinogenesis was induced by dimethylhydrazine (DMH) (Cantero et al., 2015). Only the data on mice on a commercial normal protein diet (NPD) throughout the experimental period was considered relevant for this risk assessment. The four groups ( $n = 11$  mice/group) on NPD diet included negative control (EDTA 0.1 ml/10 g bw), positive control (DMH, 20 mg/kg bw), inulin (50 mg/kg bw daily, also given EDTA) and an associate group (DMH 20 mg/kg bw and inulin 50 mg/kg bw). Genomic lesions were assessed by the Comet assay on cells from peripheral blood and the development of DMH-induced aberrant crypt foci (ACF) was used as biomarkers of carcinogenicity. The results indicated that inulin increased the frequency of damaged cells, since the genotoxicity was higher in the EDTA +

inulin group ( $53.33 \pm 8.07\%$ ) than in the EDTA negative control group ( $1.00 \pm 1.80\%$ ). However, in these mice, inulin also exhibited an anti-genotoxic activity demonstrated as a lower frequency of damaged cells after exposure to both inulin and DMH (associate NDP group,  $71.22 \pm 5.95\%$ ) compared to exposure to DMH alone (positive control NDP group,  $95.44 \pm 4.79\%$ ). The authors concluded that inulin both possessed genotoxic activity, which they said needed further research, and exhibited low anti-genotoxic potential. Since the reported genotoxicity in this publication is difficult to interpret and there are no other data available indicating that inulin is genotoxic, VKM has considered inulin as a non-genotoxic substance in this risk assessment.

#### **2.4.2.2 Interactions**

There was no information concerning interactions in the animal studies reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of interactions.

#### **2.4.2.3 Allergic sensitisation (including adjuvant effects)**

There was no information concerning allergic sensitisation or allergy adjuvant effects in the on animal studies reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

#### **2.4.3 In vitro studies**

No data on *in vitro* genotoxicity was available.

#### **2.4.4 Vulnerable groups**

No specific vulnerable groups were identified with respect to adverse health effects due to intake of inulin or inulin-type fibres.

No information was found regarding effects of daily intake of inulin-like fibres in pregnant and lactating women.

## **2.5 Summary of hazard identification and characterisation**

Inulin is a naturally occurring carbohydrate found in a variety of fruits and vegetables such as onions, leeks, garlic, asparagus, artichokes, bananas and wheat (Carabin and Gary Flamm, 1999). Inulin resists both enzymatic digestion in the upper GI tract and absorption in the small intestine. However, inulin is fermented completely by the colonic microflora producing gases and short chain organic acids (lactic, acetic, propionic and butyric acid) which may cause intestinal upsets and effects such as flatulence, increase of osmotic pressure, abdominal distention, diarrhea etc.

The AESAN has stated that a daily dose of 9 g of FOS or the sum of FOS and inulin is acceptable from the safety point of view for use as food supplement (AESAN, 2012). It is also stated that the FOS, even at high doses, do not have consequences for mortality, morbidity, toxicity or carcinogenicity. IOM has evaluated the intake of inulin, as one of several dietary fibres (IOM, 2005). Based on the lack of observations of serious chronic adverse effects an UL was not set for any of the individual fibres evaluated. With respect to inulin, cramping, bloating, flatulence and diarrhea was observed at intakes ranging from 14 to 18 g/day.

No serious adverse health effects were identified at the doses (5 - 20 g/day) reported in the human studies included in this opinion. However, intake of inulin may cause intestinal upsets and negative GI effects such as flatulence, increase of osmotic pressure, abdominal distention and diarrhea. An overview of the doses where statistically significant negative GI effects were reported, as well as the dose tested and type of inulin in the respective studies, is presented in Table 2.4.1.2. None of the referred studies included children or adolescents. However, it is referred that no statistically significant negative effects were shown in children of 10 to 13 years at daily doses of 3, 6 and 9 g of oligofructose in drinks and confectionery products (original data not available) (Coussement, 1999).

**Table 2.4.1-2** An overview of the doses with statistically significant negative GI effects, the doses tested in the included human studies and the sources of inulin (F; female; M; male).

Reference	Age (years) (gender)	Dose(s) with significant negative GI effects (g/day)	Doses tested* (g/day)	Sources of inulin
Holscher et al. (2014)	27 ± 4 (F and M)	5 and 7.5	5 and 7.5	agave
Slavin and Feirtag (2011)	27 – 49 (M)	20	20	chicory
Ramnani et al. (2010)	18 – 50 (F and M)	5	5	Jerusalem artichoke
Bonnema et al. (2010)	18 - 60 (F and M)	10 (FOS)	<b>5</b> and 10 (FOS) <b>5</b> and <b>10</b> (inulin)	chicory (both FOS and inulin)
Costabile et al. (2010)	20 – 42 (F and M)	10 (VLCI)	10 (VLCI)	globe artichoke
Bruhwyler et al. (2009)	18 – 45 (F and M)	20	<b>5</b> , <b>10</b> and 20	chicory (all three products)
Davidson et al. (1998)	30 - 75 (F and M)	18	18	chicory

\*Doses in bold are without statistically significant negative GI effects.

Only two of the animal studies contained information that was relevant in order to draw any conclusions on possible adverse health effects of inulin. In one study, rabbits were given inulin supplemented feed (2168 mg/kg bw per day) from weaning to 46 days of age (Volek et al., 2007). No study-related adverse effects were reported. In another study, dogs were given three different daily doses of inulin in the feed (1.9 g/day, 3.8 g/day or 7.5 g/day) (Propst et al., 2003). No serious adverse events were reported. However, since total intake per day was reported, but not the body weight of the dogs, daily intake per kilo body weight could not be calculated. Information from the animal studies will not be used in the risk characterization.

In this risk assessment, the values for comparison with the exposure to inulin from food supplements were based on results from the available human studies. All doses tested in the available studies were without serious adverse health effects. However, mild negative GI effects were demonstrated at various doses (5 – 20 g/day) in the different studies. Slight, but statistically significant effects were reported after intake of 5 g/day of Jerusalem artichoke inulin for 3 weeks (Ramnani et al., 2010) and of 5 and 7.5 g/day of inulin from agave for 3 weeks (Holscher et al., 2014). Mild but statistically significant negative GI effects were demonstrated at 10 g/day of inulin from globe artichoke for 3 weeks (Costabile et al., 2010). In one study, a single intake of 5 g or 10 g of inulin from chicory was well tolerated (Bonnema et al., 2010), whereas mild but statistically significant negative GI effects were reported in two other studies after intake of 20 g/day and 18 g/day of inulin from chicory (Slavin and Feirtag, 2011 and Davidson et al., 1998, respectively). In another study, the reported negative effects (mean tolerance score) tended to increase with increasing dose (5, 10 and 20 g/day) for two of the three tested types of inulin from chicory (Fibrulose F97 (DP 2 – 20) and Fibruline Instant (average DP = 10)) (Bruhwylter et al., 2009). Statistical differences were reported between placebo and 20 g/day and between 5 g/day and 20 g/day of Fibruline Instant. No negative effects were reported after intake of 5 or 10 g/day for any of these tested types of inulin in this study.

The included studies illustrate that similar type and level of reported negative GI effects occur over a wide range of doses, and may also depend on the source of inulin. Chain length influences the negative GI effects, which will be less with long-chained inulin molecules. Intestinal acceptability of nondigestible fermentable carbohydrates differ from person to person, and it also depends on the food in which the fibre is contained (Coussement, 1999).

Thus, as a pragmatic approach based on the results demonstrated in the available studies, and taking into account the wide interpersonal variability in doses at which doses GI effects may appear, the intake of 5 g/day of inulin from agave and Jerusalem artichoke and 10 g/day of inulin from chicory and globe artichoke were chosen as the values for comparison with the exposure to inulin from food supplements, even though mild effects may occur at these doses in sensible persons. These doses are in the same range as the estimated average consumption in Europe (3 – 11 g/day) (van Loo et al., 1995).



# 3 Exposure / Intake

Exposure of inulin was estimated from the intake of food supplements for the age groups children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

## 3.1 Food supplements

NFSA requested VKM to perform a risk assessment of 3 g/day of inulin in food supplements for children above 10 years, adolescents and adults. The default body weights (bw) for these age groups as determined by EFSA were used: 10-14 years; 43.4 kg, 14-18 years; 61.3 kg and adults 70.0 kg (EFSA, 2012). From a daily dose of 3 g inulin, the calculated intake levels were 69.1, 48.9 and 42.9 mg/kg bw per day for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively (Table 3.1-1).

**Table 3.1-1** Estimated exposure to inulin in children, adolescents and adults from food supplements.

Age groups	Daily doses (mg)	Body weight (kg)	Exposures (mg/kg bw per day)
<b>Children (10 to &lt;14 years)</b>	3000	43.4	69.1
<b>Adolescents (14 to &lt;18 years)</b>	3000	61.3	48.9
<b>Adults (≥18 years)</b>	3000	70.0	42.9

## 3.2 Other sources

Inulin is present in the daily diet of many populations, and several grams per day may be ingested through a normal diet. The average inulin consumption is reported to be 1 to 4 g in the United States and 3 to 11 g in Europe (van Loo et al., 1995). Inulin is also used as supplements to food or as macronutrient substitutes to replace fat. As fat replacement, typically 1 g of fat is replaced by 0.25 g of inulin. This is possible in water-based foods such as dairy products, and can consequently lead to inulin concentrations of approximately 2 – 6 g/portion (Coussement, 1999). In the EU, inulin can be used in cosmetics in skin conditioning (CosIng, 2015).

## 4 Risk characterisation

In this opinion, VKM has used the intake of 5 g/day of inulin from agave and Jerusalem artichoke and 10 g/day of inulin from chicory and globe artichoke for the risk characterization of inulin in food supplements.

No studies on children (10 to <14 years) and adolescents (14 to <18 years) were identified. Based on the included literature there was no evidence indicating that age affects tolerance for inulin. Therefore, in this risk characterisation a tolerance as for adults, based on body weight, were assumed for these age groups.

The dose received from NFSA for risk assessment is 3 g/day of inulin in food supplements. This dose corresponds to intakes of 69.1, 48.9 and 42.9 mg/kg bw per day in children (10 to <14 years), adolescents (14 to <18 years) and adults ( $\geq$ 18 years), respectively (Table 3.1-1).

No serious adverse health effects were identified at the doses (5 - 20 g/day) reported in the human studies included in this opinion. However, in adult humans, it is well documented that mild GI effects occur over a wide range of doses and may also depend on the source of inulin. The chosen doses of 5 g/day of inulin from agave and Jerusalem artichoke and 10 g/day of inulin from chicory and globe artichoke are considered to be without appreciable health risk even though mild effects may occur at these doses in sensible persons. The daily doses for all age groups, based on body weight, are presented in Table 4.1. As shown, the dose received from NFSA for evaluation of risk is below these levels for GI effects for all age groups, when based on kg body weight.

**Table 4.1** Daily exposure levels per kg bw for each age group from 5 g/day of inulin from agave and Jerusalem artichoke and 10 g/day of inulin from chicory and globe artichoke.

<b>Calculated exposure from the values for comparison</b>	<b>Exposures from 5 g/day (in mg/kg bw per day)</b>	<b>Exposures from 10 g/day (in mg/kg bw per day)</b>
<b>Age groups</b>		
<b>Children (10 to &lt;14 years)</b>	115	230
<b>Adolescents (14 to &lt;18 years)</b>	82	163
<b>Adults (<math>\geq</math>18 years)</b>	71	143

The available data indicated that also doses up to 20 g/day may be well tolerated by most people. However, it is well known that there is great variability among persons at which doses GI effects may appear, and some people may experience intestinal upset after intake

of small quantities (AESAN, 2012; Schaafsma and Slavin, 2014; Carabin and Gary Flamm, 1999).

The dose of 3 g/day of inulin from food supplements is below the levels of 5 g/day (agave and Jerusalem artichoke inulin) and 10 g/day (chicory inulin and globe artichoke) in all age groups. VKM concludes that it is unlikely that 3 g inulin per day in food supplements causes adverse effects in any of the age groups.

# 5 Uncertainties

## 5.1 Uncertainty in hazard identification and characterisation

Several of the studies referred to are RCTs, specifically designed to investigate the positive effects of inulin, and not negative effects. The mild and moderate GI effects reported were mostly based on self-reporting questionnaires.

There is a lack of human studies that have investigated the effect of high doses for longer periods than 6 weeks.

There is a lack of chronic toxicity studies in animals.

No studies on children and adolescents were identified. A tolerance as for adults, based on body weight, was assumed for these groups.

Regarding potentially vulnerable groups, no studies were found that addressed pregnant and lactating women.

## 5.2 Uncertainty in exposure

With use of the default (mean) body weight of an age (population) group, the variance in all individuals in the group will not be covered.

## 5.3 Uncertainty in risk characterisation

No ADI or human tolerance level is set for inulin. Although inulin is regarded as without serious adverse effects at high levels (up to 20 g/day), there is a wide interpersonal variability in the doses at which GI effects associated with the colonic fermentation will appear. Little information is available concerning the acceptability of indigestible carbohydrates specifically for children and adolescents.

## 6 Conclusions with answers to the terms of reference

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of inulin (3 g/day) in food supplements. The present risk assessment is based on previous risk assessments and a literature search.

No serious adverse health effects were identified at the doses (5 - 20 g/day) reported in the human studies included in this opinion. The reported negative effects of inulin-type fibres are generally mild GI symptoms, including diarrhea, abdominal rumbling, bloating, cramping and excessive flatulence. The dose of 5 g/day of inulin from agave or Jerusalem artichoke and 10 g/day of inulin from chicory and globe artichoke were considered to be without appreciable health risk, even though mild effects may occur at these doses in sensible persons.

No studies on children (10 to <14 years) and adolescents (14 to <18 years) were identified. Based on the included literature there was no evidence indicating that age affects tolerance for inulin. Therefore, in this risk characterisation a tolerance as for adults, based on body weight, were assumed for these age groups.

For the risk characterisation, as a pragmatic approach the values used for comparison with the estimated exposure are 5 g/day of inulin from agave or Jerusalem artichoke and 10 g/day of inulin from chicory and globe artichoke (corresponding to 71 and 143 mg/kg bw per day, respectively, in a 70 kg adult).

When comparing the doses of 5 g/day and 10 g/day considered to be without appreciable health risk in adults with the estimated exposure from food supplements, it is unlikely that a daily dose of 3 g of inulin causes adverse health effects in children above 10 years, adolescents and adults.

VKM concludes that it is unlikely that a daily dose of 3 g of inulin from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults ( $\geq 18$  years).

An overview of the conclusions on food supplements containing 3 g/day of inulin is presented in Table 6.1.

**Table 6.1** An overview of the conclusions on daily intake of inulin from food supplements.  
Green: estimated exposure to inulin is unlikely to cause adverse health effects.

<b>Food supplement</b>	<b>Inulin</b> <b>3 g/day</b>
<b>Children</b> <b>(10 to &lt;14 years)</b>	
<b>Adolescents</b> <b>(14 to &lt;18 years)</b>	
<b>Adults</b> <b>(≥18 years)</b>	

# 7 Data gaps

No studies on adverse health effects of inulin in children, adolescents, pregnant women or lactating women were identified.

There is lack of chronic toxicity studies in animals.

## 8 References

- AESAN. (2012) Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements - 1, The Spanish Agency for Food Safety and Nutrition (AESAN), [http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion\\_riesgos/comite\\_cientifico/ingl es/FOOD\\_SUPPLEMENTS\\_1.pdf](http://aesan.msssi.gob.es/AESAN/docs/docs/evaluacion_riesgos/comite_cientifico/ingl es/FOOD_SUPPLEMENTS_1.pdf).
- Bonnema A.L., Kolberg L.W., Thomas W., Slavin J.L. (2010) Gastrointestinal Tolerance of Chicory Inulin Products. *J Am Diet Assoc* 110:865-868. DOI: 10.1016/j.jada.2010.03.025.
- Bruhwyler J., Carreer F., Demanet E., Jacobs H. (2009) Digestive tolerance of inulin-type fructans: a double-blind, placebo-controlled, cross-over, dose-ranging, randomized study in healthy volunteers. *Int J Food Sci Nutr* 60:165-175. DOI: Pii 79140597110.1080/09637480701625697.
- Cantero W.B., Takahachi N.A., Mauro M.O., Pesarini J.R., Rabacow A., Antonioli A., Oliveira R.J. (2015) Genomic lesions and colorectal carcinogenesis: The effects of protein-calorie restriction and inulin supplementation on deficiency statuses. *Genetics and Molecular Research* 14:2422-2435.
- Carabin I.G., Gary Flamm W. (1999) Evaluation of safety of inulin and oligofructose as dietary fiber. *Regul Toxicol Pharmacol* 30:268-282.
- CosIng. (2015) Cosmetic ingredient database – CosIng, European Commission <http://ec.europa.eu/growth/tools-databases/cosing/>.
- Costabile A., Kolida S., Klinder A., Gietl E., Buerlein M., Froberg C., Landschütze V., Gibson G.R. (2010) A double-blind, placebo-controlled, cross-over study to establish the bifidogenic effect of a very-long-chain inulin extracted from globe artichoke (*Cynara scolymus*) in healthy human subjects. *Br J Nutr* 104:1007-1017.
- Coussement P.A.A. (1999) Inulin and oligofructose: Safe intakes and legal status. *J Nutr* 129:1412S-1417S.
- Davidson M.H., Maki K.C., Synecki C., Torri S.A., Drennan K.B. (1998) Effects of dietary inulin on serum lipids in men and women with hypercholesterolemia. *Nutrition Research* 18:503-517.
- EFSA. (2012) SCIENTIFIC OPINION. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data, European Food Safety Authority, EFSA Journal, [http://www.efsa.europa.eu/sites/default/files/scientific\\_output/files/main\\_documents/2579.pdf](http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2579.pdf).
- FVM. (2014) Bekendtgørelse om tilsætning af visse andre stoffer end vitaminer og mineraler til fødevarer. Ref.no. 2014-27-31-00005, Fødevareministeriet (FVM),



- Fødevarestyrelsen, Denmark, [www.retsinformation.dk/pdfPrint.aspx?id=163394](http://www.retsinformation.dk/pdfPrint.aspx?id=163394). pp. 15.
- Holscher H.D., Doligale J.L., Bauer L.L., Gourineni V., Pelkman C.L., Fahey G.C., Swanson K.S. (2014) Gastrointestinal tolerance and utilization of agave inulin by healthy adults. *Food & Function* 5:1142-1149. DOI: 10.1039/c3fo60666j.
- IOM. (2005) Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids, Institute of Medicine, [https://www.nal.usda.gov/fnic/DRI/DRI\\_Energy/energy\\_full\\_report.pdf](https://www.nal.usda.gov/fnic/DRI/DRI_Energy/energy_full_report.pdf).
- Kelly G. (2009) Inulin-type prebiotics: A review (Part 2). *Altern Med Rev* 14:36-55.
- Propst E.L., Flickinger E.A., Bauer L.L., Merchen N.R., Fahey Jr G.C. (2003) A dose-response experiment evaluating the effects of oligofructose and inulin on nutrient digestibility, stool quality, and fecal protein catabolites in healthy adult dogs. *J Anim Sci* 81:3057-3066.
- Ramnani P., Gaudier E., Bingham M., Van Bruggen P., Tuohy K.M., Gibson G.R. (2010) Prebiotic effect of fruit and vegetable shots containing Jerusalem artichoke inulin: A human intervention study. *Br J Nutr* 104:233-240.
- Schaafsma G., Slavin J.L. (2015) Significance of Inulin Fructans in the Human Diet. *Comprehensive Reviews in Food Science and Food Safety* 14:37-47. DOI: 10.1111/1541-4337.12119.
- Slavin J., Feirtag J. (2011) Chicory inulin does not increase stool weight or speed up intestinal transit time in healthy male subjects. *Food & function* 2:72-77.
- The European Parliament and the Council of the European Union. (2006) Regulation (EC) No 1925/2006 of The European Parliament And of The Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods, <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1925&from=en>.
- U.S. Food and Drug Administration. (2016), <http://www.fda.gov/default.htm>.
- van Loo J., Coussement P., de Leenheer L., Hoebregs H., Smits G. (1995) On the presence of inulin and oligofructose as natural ingredients in the western diet. *Crit Rev Food Sci Nutr* 35:525-52. DOI: 10.1080/10408399509527714.
- Volek Z., Marounek M., Skrivanova V. (2007) Effect of a starter diet supplementation with mannan-oligosaccharide or inulin on health status, caecal metabolism, digestibility of nutrients and growth of early weaned rabbits. *Animal* 1:523-530.
- WHO. (1994) Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits, Environmental Health Criteria, WHO (World Health Organisation), <http://www.inchem.org/documents/ehc/ehc/ehc170.htm>.

# Appendix

## Search Strategy

Database: Ovid MEDLINE(R) <1946 to May Week 5 2015>, Embase <1974 to 2015 June 09>

1. inulin\*.ti. (3414)
2. (risk\* or safety or adverse or side-effect\*1 or hazard\* or harm\* or negative or 2. contraindicat\* or contra-indicat\* or interact\* or toxicity or toxic).tw. (8776533)
3. 1 and 2 (353)
4. (conference abstract\* or letter\* or editorial\*).pt. (4457566)
5. 3 not 4 (336)
6. limit 5 to (danish or english or norwegian or swedish) (320)
7. remove duplicates from 6 (174)