Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

VKM Report 2015:23

Risk assessment of "other substances" – Inositol

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

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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)

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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.

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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 and/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 potential beneficial effects from these substances, only possible adverse effects.

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

According to information from NFSA, inositol is an ingredient in energy drinks sold in Norway. NFSA has requested a risk assessment of 10 mg/100 ml inositol in energy drinks. Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake were assessed.

Inositol (CAS no. 6917-35-7) is a sugar alcohol. Among the nine possible stereoisomers, *myo*-inositol (CAS no. 87-89-8) is the most abundant. The name inositol is frequently used as a synonym for *myo*-inositol. Inositol occurs naturally in all organisms including humans, and is an important component in all human cells. Inositol-containing lipids and phosphates are required for various structural and functional processes, including membrane formation, signalling, membrane trafficking and osmoregulation. Endogenous production of inositol in humans amounts to about 4 g/day (about 57 mg/kg bw per day in a 70 kg adult) (EFSA, 2014). The total dietary intake of inositol in adults is estimated to range between 500 to 1000 mg/day (about 7-14 mg/kg bw per day).

Inositol added to energy drinks in Norway denotes the compound *myo*-inositol, according to information from NFSA.

Myo-inositol is a water-soluble compound naturally occurring in the cells of all living organisms including humans, animals, plants and microorganisms.

Certain plant (fruits and vegetables) and foods from animals contain inositol, and seeds of cereals and legumes show high levels of the inositol storage form, phytic acid (inositol hexaphosphate).

With regard to hazard identification and characterisation of inositol, most of the adverse effects observed in several human studies were related to gastrointestinal symptoms such as nausea, flatulence, loose stools and diarrhoea.

Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake were assessed for energy drinks containing 10 mg inositol per 100 ml, for the age groups children (3 to <10 years and 10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

For the high acute drinking pattern, the intake was estimated to be 1000, 1500, 2000 and 2000 ml/day for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (>18 years), respectively. For the mean chronic drinking pattern, the intake was estimated to be 58, 65, 64 and 71 ml/day for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively. For the high chronic drinking pattern, the intake was estimated to be 163, 180, 210 and 320 ml/day for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

The data on toxicity of inositol was very limited. The human study with the longest exposure at highest doses (3 months treatment at maximum tolerated dose) that was available for risk assessment was a clinical study of 40-74 year old smokers with bronchial dysplasia, from which a NOAEL of 18 g/day of *myo*-inositol was established (Lam et al., 2006). VKM estimated the margins of exposure (MOE) based on the NOAEL established in this study.

The MOE is the ratio of the NOAEL value to the exposure. An acceptable MOE value for a NOAEL-based assessment of inositol based on a human study is ≥10, taking into account a factor 10 for the interindividual variation between humans in toxicokinetics and toxicodynamics. Due to the uncertainty regarding the relevance of the study by Lam et al. (2006) for the general healthy population, an additional safety factor of 3 was used. Therefore, an acceptable MOE value was 30.

For all age groups, the MOE values were in the range of 857 to 2570 for mean chronic intake and in the range of 367 to 857 for high chronic intake of energy drinks, respectively, i.e. far above the acceptable MOE value of 30.

Since neither the sub-optimal human study by Lam et al. (2006) or the animal studies in rodent models of chronic diseases available were on healthy subjects, as a supplement to the MOE values calculated from the human study, comparisons with endogenous production and amounts in food of inositol were also performed.

No studies specifically on children (3 to <10 years and 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 or endogenous production of inositol. Therefore, in this risk characterisation a tolerance and an endogenous production of inositol as for adults, based on body weight, was assumed for these age groups.

For the high acute drinking pattern, and for the mean chronic and the high chronic drinking patterns all estimated intakes of inositol from energy drinks containing 10 mg/100 ml were far below the endogenous production (57 mg/kg bw per day), and also below the dietary intake (7-14 mg/kg bw per day).

VKM concludes that it is unlikely that the exposure to inositol from the high acute, the mean chronic or the high chronic drinking patterns causes adverse health effects in children (3 to <10 years and 10 to <14 years), adolescents (14 to <18 years) and adults (≥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 10 mg inositol per 100 ml energy drink. Inositol occurs naturally in all organisms including humans and is present in food. Among the nine possible stereoisomers of inositol, *myo*-inositol is the most abundant. *Myo*-inositol is naturally occurring in the body and is present in various types of food.

The human study with the longest exposure at highest doses (3 months treatment at maximum tolerated dose) that was available for risk assessment was a clinical study of 40-74 year old smokers with bronchial dysplasia, from which a NOAEL of 18 g/day of *myo*-inositol was established (Lam et al., 2006). For all age groups, the MOE values estimated from this study were in the range of 857 to 2570 for mean chronic intake and in the range of 367 to 857 for high chronic intake of energy drinks, respectively, i.e. far above the acceptable MOE value of 30.

In addition, for the high acute drinking pattern and for the mean chronic and the high chronic drinking patterns all estimated intakes of inositol from energy drinks containing 10 mg/100 ml were far below the endogenous production (57 mg/kg bw per day), and also below the dietary intake (7-14 mg/kg bw per day).

VKM concludes that it is unlikely that the exposure to inositol from the high acute, the mean chronic and the high chronic drinking patterns causes adverse health effects in children (3 to <10 years and 10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Key words: Adverse health effect, energy drink, inositol, *myo*-inositol, negative health effects, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, phytic acid, risk assessment, VKM

Sammendrag på norsk

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved tilsetting av «andre stoffer» i kosttilskudd og energidrikker som selges i Norge. VKM har risikovurdert ulike bruksdoser oppgitt fra Mattilsynet. Disse risikovurderingene vil gi Mattilsynet vitenskapelig grunnlag for å regulere andre stoffer.

«Andre stoffer» er beskrevet i kosttilskuddsdirektivet 2002/46/EC som *stoffer som har en ernæringsmessig og/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 potensielle gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

Risikovurderingen er basert på tidligere risikovurderinger av inositol og artikler som er funnet ved et litteratursøk.

Ifølge informasjon fra Mattilsynet er inositol en ingrediens i energidrikker som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere 100 mg/100 ml inositol i energidrikker. Drikkemønstre som reflekterer et høyt akutt inntak, et gjennomsnittlig kronisk inntak og et høyt kronisk inntak ble vurdert.

Inositol (CAS no. 6917-35-7) er en sukkeralkohol. Av de ni mulige stereoisomerene er det høyest forekomst av *myo*-inositol (CAS nr. 87-89-8). Navnet inositol brukes ofte synonymt med navnet *myo*-inositol. Inositol forekommer naturlig i alle organismer inkludert mennesker, og er en viktig bestanddel i menneskets celler. Inositol er en del av makromolekyler som for eksempel membranlipider, sekundære budbringere og fosforylerte forbindelser, som er involvert i viktige cellulære funksjoner. Endogen produksjon av inositol er på omtrent 4 g/dag (omtrent 57 mg/kg kroppsvekt per dag i en voksen person på 70 kg) (EFSA, 2014). Det totale inntaket av inositol fra mat er estimert til å ligge imellom 500 og 1000 mg/dag hos voksne (ca. 7-14 mg/kg kroppsvekt per dag).

Det er *myo*-inositol som tilsettes energidrikker som er på det norske markedet, i følge informasjon fra NFSA.

Myo-inositol er en vannløselig forbindelse som forekommer naturlig i cellene i alle levende organismer, inkludert mennesker, dyr, planter og mikroorganismer.

Utvalgte plante-baserte (frukt og grønnsaker) og animalske matvarer inneholder relativt store mengder av inositol. Frø av korn og belgfrukter viser høye nivåer av lagringsformen av inositol, fytinsyre (inositol heksafosfat).

Med hensyn til fareidentifisering og farekarakterisering av inositol var de fleste negative effektene observert i studier på mennesker relatert til gastrointestinale symptomer som kvalme, flatulens, løs avføring og diaré.

Drikkemønstre som reflekterer et høyt akutt inntak, et gjennomsnittlig kronisk inntak og et høyt kronisk inntak ble vurdert for energidrikker som inneholder 10 mg inositol per 100 ml energidrikk, for aldersgruppene barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Basert på et høyt akutt drikkemønster, ble inntaket estimert til å være 1000, 1500, 2000 og 2000 ml/dag for henholdsvis barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år). For det gjennomsnittlige kroniske drikkemønsteret var det estimerte inntaket 58, 65, 64 og 71 ml/dag for henholdsvis barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år). For det høye kroniske drikkemønsteret var det estimerte inntaket 163, 180, 210 og 320 ml/dag for henholdsvis barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Det var lite data tilgjengelig på toksikologiske effekter av inositol. Studien på mennesker med den lengste eksponeringen i høyeste doser (3 måneder med maksimal tolerert dose) som var tilgjengelig for risikovurderingen var en klinisk studie av 40-74 år gamle røykere med bronkopulmonal dysplasi, hvor det ble etablert en NOAEL-verdi på 18 g/dag for *myo*-inositol (Lam et al., 2006). Fra denne studien har VKM beregnet eksponeringsmargin ('margin of exposure' (MOE)), som er ratio mellom NOAEL-verdien og eksponeringen.

En akseptabel MOE-verdi for en risikovurdering som er basert på NOAEL fra en human studie er ≥10, som tar i betraktning en faktor 10 for interindividuell variasjon i toksikokinetikk og toksikodynamikk blant mennesker. På grunn av usikkerheten når det gjelder relevansen av denne studien (Lam et al., 2006) for den generelle friske befolkningen, ble det brukt en ekstra usikkerhetsfaktor på 3 i risikokarakteriseringen. En MOE-verdi på 30 anses derfor som akseptabel.

De beregnede MOE-verdiene for de ulike aldersgruppene var 857-2570 for gjennomsnittlig kronisk inntak og 367-857 for høyt kronisk inntak av energidrikker, dvs. langt over en MOE-verdi på 30.

Siden verken den sub-optimale studien til Lam et al. (2006) eller de tilgjengelige dyrestudiene i gnagermodeller av kroniske sykdommer var på friske individer, ble også eksponeringen sammenlignet med endogen produksjon og mengder i mat av inositol, som supplement til beregningene av MOE.

Det ble ikke funnet studier gjort spesifikt på barn (3 til <10 år og 10 til <14 år) og ungdom (14 til <18 år). Ut i fra den inkluderte litteraturen var det ikke grunn til å anta at alder påvirker toleranse eller endogen produksjon av inositol. Derfor ble samme toleranse og samme endogene produksjon som for voksne, basert på kroppsvekt, brukt for disse aldersgruppene i risikokarakteriseringen.

De estimerte inntakene av 10 mg/ml inositol ved et høyt akutt, et gjennomsnittlig kronisk eller et høyt kronisk drikkemønster var lavere enn den endogene produksjonen (57 mg/kg

kroppsvekt per dag i en 70 kg voksen), og lavere enn inntaket fra kosten (7-14 mg/kg kroppsvekt per dag i en 70 kg voksen).

VKM konkluderer med at det er usannsynlig at et høyt akutt, et gjennomsnittlig kronisk eller et høyt kronisk inntak av energidrikker fører til skadelige helseeffekter hos barn (3 til <10 år og 10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Ingen studier på barn (3 til <10 år eller 10 til <14 år) eller ungdom (14 til <18 år) ble funnet. Det var ingen informasjon i den inkluderte litteraturen som indikerte at alder er av betydning for toleransen for inositol. Derfor er det i denne risikovurderingen antatt at barn og ungdoms toleranse for inositol er lik voksnes toleranse, basert på kroppsvekt.

Kort sammendrag

På oppdrag fra Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved inntak av 10 mg inositol per 100 ml energidrikker. Inositol forekommer naturlig i alle organismer, inkludert mennesker, og er til stede i kosten. Av de ni mulige stereoisomerene er det høyest forekomst av *myo*-inositol. *Myo*-inositol finnes endogent i kroppen og forekommer i flere matvarer.

Studien på mennesker med den lengste eksponeringen i høyeste doser (3 måneder med maksimal tolerert dose) som var tilgjengelig for risikovurderingen var en klinisk studie av 40-74 år gamle røykere med bronkopulmonal dysplasi, hvor det ble etablert en NOAEL-verdi på 18 g/dag for *myo*-inositol (Lam et al., 2006). De beregnede MOE-verdiene fra denne studien for de ulike aldersgruppene var 857-2570 for gjennomsnittlig kronisk inntak og 367-857 for høyt kronisk inntak av energidrikker, dvs. langt over en MOE-verdi på 30 som anses som akseptabel.

I tillegg, ved et høyt akutt inntak, et gjennomsnittlig kronisk og et høyt kronisk drikkemønster var alle estimerte inntak av inositol fra energidrikker som inneholder 10 mg inositol/100 ml langt lavere enn den endogene produksjonen (57 mg/kg kroppsvekt per dag) og også lavere enn inntaket fra kosten (7-14 mg/kg kroppsvekt per dag).

VKM konkluderer med at det er usannsynlig at et høyt akutt inntak, et gjennomsnittlig kronisk eller høyt kronisk inntak av energidrikker som inneholder 10 mg inositol/100 ml fører til skadelige helseeffekter hos barn (3 til <10 og 10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Abbreviations and glossary

Abbreviations

AESAN - Scientific Committee of the Spanish Agency for Food Safety and Nutrition
AFSSA - French Agency for Food Safety
ANSES - French Agency for Food, Environmental and Occupational Health & Safety
bw - body weight
CAS - Chemical Abstracts Service
CRF - chronic renal failure
EFSA - European Food Safety Authority
EINECS - European Inventory of Existing Commercial Chemical Substances
EWG - Environmental Working Group
FDA - Food and Drug Administration
GRAS - Generally Recognized as Safe [database]
IP - inositol phosphate
ML - maximum limit
MOE - margin of exposure
MRI - maximum recommended intake
NFSA - Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NOAEL - no observed adverse effect level
SCOGS - Select Committee on GRAS Substances
UL - tolerable upper intake level
VKM - Norwegian Scientific Committee for Food Safety [*Norw.*: 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 and WHO has established the following definition 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) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of inositol in energy drinks at the following dose: 10 mg/100 ml.

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 energy drinks shall be carried out for a general population, ages 3 years and above. Drinking patterns reflecting a high acute intake, an average chronic intake and a high chronic intake should be assessed.

Assessment

1 Introduction

"Other substances" are described in the food supplement directive 2002/46/EC (EC, 2002) as *substances other than vitamins or minerals that have a nutritional and/or physiological effect*, and may be added to food supplements or e.g. energy drinks.

This risk assessment regards the substance inositol per se, and no specific products.

VKM has in this series of risk assessments of "other substances" not evaluated documentation of any potential beneficial effects from these substances, but merely possible adverse effects at specified doses used in Norway. Thus, potential high intake consumer groups of the substance may not be identified and therefore not included in this assessment.

According to information from the Norwegian Food Safety Authority (NFSA), inositol is an ingredient in energy drinks purchased in Norway. NFSA has requested a risk assessment of high acute, mean chronic and high chronic intake of energy drinks containing 10 mg inositol/100 ml. The total exposure to inositol from other sources than energy drinks, such as foods and cosmetic products, is not included in the risk assessment.

Inositol (CAS no. 6917-35-7) is a sugar alcohol with the chemical formula $C_6H_{12}O_6$. Inositol occurs naturally in all organisms including humans, and is an important component in all human cells. Among the nine possible stereoisomers, *myo*-inositol (CAS no. 87-89-8) is the most abundant. The name inositol is frequently used as a synonym for myo-inositol. Based on the specifications for inositol provided by NFSA (Institute of Medicine, 2004), data on myo-inositol has been used in this risk assessment. Inositol-containing lipids and phosphates are required for various structural and functional processes, including membrane formation, signalling, membrane trafficking and osmoregulation. High inositol levels are also found in the nervous tissue, cerebrospinal fluid and breast milk.

Inositol is ingested via the daily diet, either as *myo*-inositol or in phosphorylated form such as e.g. phytic acid (inositol hexaphosphate, IP_6) or other phytates. The bioavailability of *myo*-inositol from ingested phytic acid is very limited due to low phytase activity in the digestive tract (Humer et al., 2015). In addition, inositol is also added to energy drinks and food supplements. The endogenous production in humans from glucose via glucose-6-phosphate and *myo*-inositol-3-phosphate amounts to about 4 g/day (about 57 mg/kg bw per day in a 70 kg adult) (EFSA, 2014). The production occurs mostly in the kidneys. The total dietary intake of inositol in adults is estimated to range from 500 to 1000 mg/day (equivalent to about 7-14 mg/kg bw per day for a 70 kg adult). In the present risk assessment, VKM has assessed inositol in energy drinks at a concentration of 10 mg/100 ml.

2 Hazard identification and characterisation

2.1 Literature

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

2.1.1 Previous risk assessments

Risk assessment of energy drinks containing caffeine, taurin, glucuronolactone, inositol and vitamins. Norway (in Norwegian) (VKM, 2005)

In VKM's risk assessment of energy drinks containing other substances, the potential negative health effects of inositol were evaluated. VKM concluded that, based on the available scientific information, no maximum concentrations or recommended daily doses could be established, and that it was unlikely that inositol in energy drinks will pose a safety risk in the population.

Opinion of the French Food Safety Agency (ANSES) on the assessment of risk from consumption of an "energy" drink containing substances other than technological additives: taurine, D-glucuronolactone, inositol, vitamins B2, B3, B5, B6 and B12. France (AFSSA, 2006)

The risk assessment evaluates the safety of an energy drink containing other substances, including inositol. Neither information on safety nor established maximum concentrations or recommended daily doses of inositol were available.

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) and (2). Spain (AESAN, 2012; AESAN, 2013)

In these two risk assessments by the Spanish Agency for Food Safety and Nutrition (AESAN), the use of inositol hexaphosphate (phytate) (AESAN, 2012) and *myo*-inositol (AESAN, 2013) in food supplement was assessed. No adverse effects of phytate were observed in any of the evaluated studies in animal models and humans. Regarding *myo*-inositol, only slight gastrointestinal upset was recorded in a 1-month human study establishing a NOAEL of 18 g/day (257 mg/kg bw per day for a 70 kg person). (Lam et al., 2006). Otherwise no adverse effects were observed in any of the evaluated human studies. AESAN concludes that the following maximum quantities are acceptable from the safety point of view for use as a food

supplement: inositol hexaphosphate 2000 mg/day; *myo*-inositol 2000 mg/day, i.e. 29 mg/kg bw per day for a 70 kg person.

Assessment of the Potential Health Risks in the Canadian Context. Canada (Rotstein et al., 2013)

In the risk assessment conducted by the Food Directorate, Health Products and Food Branch, Health Canada, Canada, energy drinks containing other substances were assessed with regard to potential negative health effects. The authors concluded that the content of inositol commonly present in energy drinks sold in Canada, does not pose any risk to consumers. Available data from the evaluated human studies suggested a very low toxicity of *myo*-inositol, and no adverse effects at the doses used in energy drinks were expected. Based on market studies, a typical serving of an energy drink (250-473 ml) contains 50-200 mg inositol. Though the risk assessment refers to the NOAEL of 18 g/day established by Lam et al. (2006), an upper tolerable limit (UL), maximum recommended intake (MRI) or maximum limit (ML) was not defined.

Scientific Opinion on the safety and efficacy of inositol as a feed additive for fish, dogs and cats - EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). The European Food Safety Authority (EFSA, 2014)

No conventional toxicological studies were available, but the results of studies in rodent models of chronic diseases (including diabetes and cancer) suggest that the toxicity of inositol is low over an oral dose range of 450–9000 mg/kg bw per day. Only one study showed adverse effects (at 1800 mg/kg bw per day), which was thickening of basement membranes of capillaries of the retina and glomeruli. EFSA concluded that the available and evaluated toxicological studies in animals (rodents) and humans indicated a low toxicity of *myo*-inositol. The data were too limited to allow an upper tolerable intake level (UL) to be defined.

The Select Committee on GRAS Substances (SCOGS) Database, U.S. Food and Drug Administration. USA (FDA, 1975; FDA, 2014)

SCOGS concluded that there is no evidence in the available information on inositol that demonstrates, or suggests, reasonable evidence to suspect a hazard to the public when it is used at levels that are now current or that might be expected in the future. No maximum concentrations or recommended daily doses were established.

2.1.2 Literature search

2.1.2.1 Search strategy

Literature searches were performed in MEDLINE, EMBASE, Global Health and Web of Science in order to retrieve publications on adverse effects caused by inositol. These databases were

chosen to ensure comprehensive study retrieval. The literature searches were performed by a librarian in February 2015. The search strategy is included in Appendix 1.

2.1.2.2 Publication selection

The literature search identified 296 articles. In the primary screening, titles and abstracts of all publications retrieved, after duplicates were removed, 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
- Animal model studies address adverse effects related to human health

The inclusion criteria checklist was developed by members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the 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 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 four full text articles, of which one was a risk assessment (EFSA, 2014) and one was a review (Carlomagno and Unfer, 2011), respectively. Additionally, 3 studies from manual search/retrieval of relevant literature cited in the full-text papers (Carlomagno and Unfer, 2011) have been identified and included. A final total of seven publications was identified and included in the results in this report (see Figure 2.1.2.2-1).

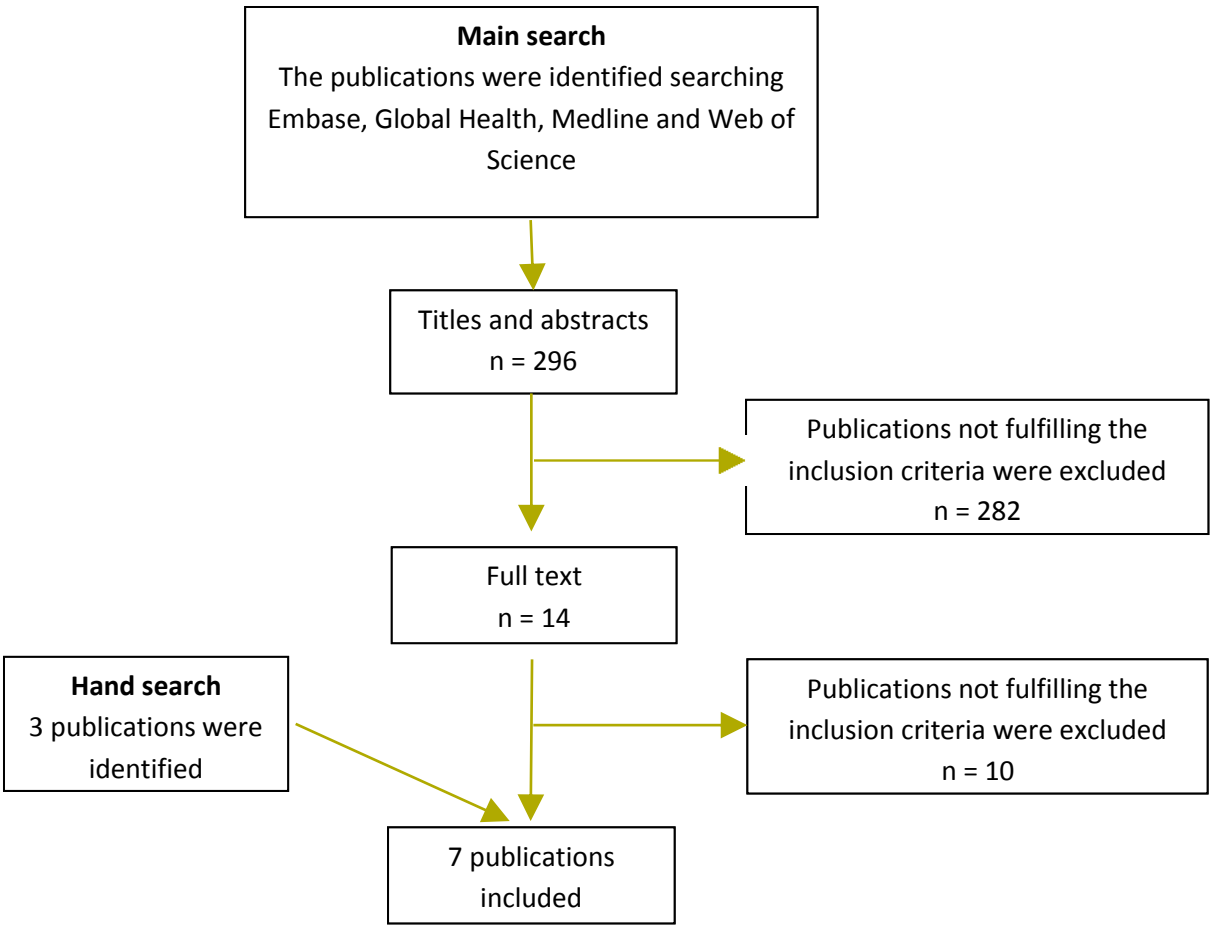

Figure 2.1.2.2-1: Flowchart for the literature search for inositol and the subsequent publication selection.

2.2 General information

2.2.1 Chemistry

Inositol is a white or almost white crystalline odourless powder with a very slight sweet taste. The molecular formula of inositol (CAS no. 6917-35-7; EINECS no. 230-024-9), which is a sugar alcohol, is $C_6H_{12}O_6$ and the molecular weight is 180.16 g/mol. The IUPAC name is (1R,2R,3S,4S,5R,6S)-cyclohexane-1,2,3,4,5,6-hexol. Inositol occurs naturally in nine stereoisomeric structures with *myo*-inositol (CAS no. 87-89-8; EINECS no. 201-781-2; $C_6H_{12}O_6$) being the most abundant form beside *scyllo*-, *muco*-, D-*chiro*-, and *neo*-inositol. Other possible stereoisomers comprise L-*chiro*-, *allo*-, *epi*-, and *cis*-inositol. The name inositol is frequently used as a synonym for *myo*-inositol.

Based on the specifications for inositol provided by NFSA, data on myo-inositol has been used in this risk assessment. By specification, inositol as feed additive (EFSA, 2014) contains ≥97% *myo*-inositol (anhydrous substance) in compliance with European Pharmacopoeia.

Myo-inositol is highly soluble in water (140 g/l), and the pH is approximately neutral. Inositol is extracted as bi-product from sugar cane processing. Main production methods are based on hydrolysis of natural phytic acid. More recent methods comprise the enzymatically breakdown of phytate with phytase derived from microorganisms, and the production of *myo*-inositol based on fermentation technology. The molecular structures of *myo*-inositol and phytic acid are shown in Figure 2.2.1-1.

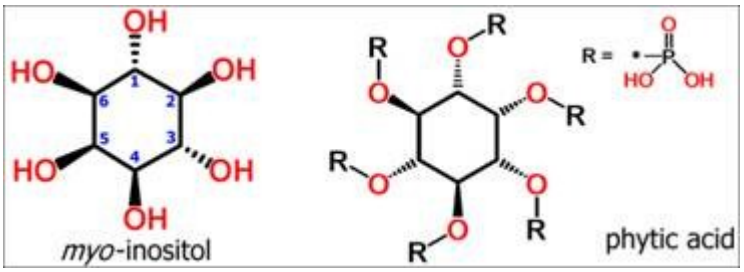

Figure 2.2.1-1. The molecular structures of *myo*-inositol and phytic acid.

2.2.2 Occurrence

Myo-inositol and structurally related stereoisomers occur naturally in all living organisms including humans, animals, plants and microorganisms. It is an important precursor of macromolecules such as membrane lipids (phosphatidylinositol, phosphatidylinositol phosphate and glycosylphosphatidylinositol), secondary messengers in eukaryotes (inositol-3-phosphate, IP_3), and other phosphorylated compounds (IP, IP_2 and IP_5) being involved in essential cellular functions. Fruits (citrus fruits, cantaloupe, kiwi and mango) and vegetables (e.g. green beans) contain *myo*-inositol. In addition, the storage form of inositol, phytic acid (inositol hexaphosphate IP_6) and also IP_5, are highly abundant in seeds of cereals and legumes. Animal-derived food products contain inositol in the form of free and phosphorylated inositol and as inositol phospholipids.

The endogenous production in humans amounts to about 4 g/day (about 57 mg/kg bw per day in a 70 kg adult) (EFSA, 2014). The total dietary intake of inositol in adults is estimated to range from 500 to 1000 mg/day (equivalent to about 7-14 mg/kg bw per day for a 70 kg adult).

2.3 Absorption, distribution, metabolism and excretion (ADME)

2.3.1 In humans

Free inositol dissolves readily in water and is easily absorbed in the small intestine. The bioavailability of *myo*-inositol from ingested phytic acid (inositol hexaphosphate) is very limited due to low phytase activity in the digestive tract, and depends on a variety of factors, such as phytate solubility and the presence of minerals, plant phytases, intestinal microbial phytases, supplemented phytases and food processing (EFSA, 2014).

Endogenous inositol is synthesised mainly in the kidney, and concentrations of free inositol in the renal medullary cells are 1000-fold higher than in blood. In humans, about 4 g/day (about 57 mg/kg bw per day in a 70 kg adult) is estimated to be produced (EFSA, 2014), while adults ingest about 500 to 1000 mg of inositol daily (Rotstein et al., 2013). Plasma levels are regulated by the kidneys with a high capacity to catabolise inositol compared to excretion. In tissues of mammals, including humans, *myo*-inositol can be converted to either L- or D-chiro-inositol by epimerases. Inositol is catabolised to D-glucuronic acid, and through subsequent metabolic steps, *O*-xylulose 5-phosphate is produced and enters the pentose phosphate cycle (EFSA, 2014).

2.3.2 Animal studies

Free inositol is extensively absorbed (>90%) by active transport in the small intestine in rodent. Inositol from dietary phosphoinositol, a minor component of phospholipids, is similarly absorbed extensively as lysophosphatidylinositol after removal of the fatty acid at the syn-2 position of glycerol by pancreatic phospholipases in rats (EFSA, 2014). Inositol is incorporated in the phospholipid pool, in particular as phosphatidylinositol, and concentrated mainly in the liver, whereas small amounts also accumulate in muscle tissue, but not at all in adipose tissue. In young rats, dietary concentrations of 1500 mg/kg had no significant influence on liver deposition compared with counterparts fed a purified *myo*-inositol-free diet, whereas 5000 mg *myo*-inositol/kg diet increased the levels of *myo*-inositol in the liver and kidney (EFSA, 2014). However, daily dose levels could not be calculated from data of this study due to *ad libitum* feeding and variable animal body weight.

2.4 Toxicological data/Adverse effects

2.4.1 Human studies

An overview of the included studies on inositol and adverse health effects in humans is given in Table 2.4.1-1.

Table 2.4.1-1 Overview of human studies investigating effects of inositol and observed adverse health effects.

Reference	Study design / Participant characteristics	Country	Number in treatment group		Dose	Main endpoints	Study duration	Adverse effect
			Inositol	Control/ placebo				
Agostini et al. (2006)	Double-blind, randomized, placebo-controlled; type 2 diabetes men	Italy	88 men (treatment group)	88 men (placebo)	4 g/day, plus 400 µg folic acid	Effectiveness against erectile dysfunction	2 weeks single-blind placebo run-in phase, 12 weeks of treatment	Two patients complained of mild insomnia and one of flatulence
Lam et al. (2006)	Open-label, multiple dose, dose escalation clinical study (2-stage); 40-74 years old smokers with bronchial dysplasia	Canada	16 (both sexes) in Stage I; 10 (both sexes) in Stage II	Data of external reference group (placebo) used for regression analysis	12-30 g/day (Stage I) 18 g/day (Stage II)	Potential for lung cancer chemoprevention	Stage I: 1 month dose escalation study; Stage II: 3 months treatment at maximum tolerated dose (NOAEL level) established in Stage I: 18 g/day	Flatulence, loose stool or diarrhea and mild gastrointestinal symptoms (Stage I and II); a significant decrease in blood pressure and slight increase in hemoglobin levels after more than one month with 18 g/day (Stage II), not regarded as adverse effects by the authors
Palatnik et al. (2001)	Double-blind, controlled, crossover trial; patients with panic disorder	Israel	10 (both sexes) in treatment group,	10 (alternative medication or placebo)	12 g/day (1. week) 18 g/day (2.-4. week)	Potential for treatment of panic disorder	1 week single-blind placebo run-in phase, 4 weeks of treatment	Several subjects with nausea (8) and tiredness (1)

Reference	Study design / Participant characteristics	Country	Number in treatment group		Dose	Main endpoints	Study duration	Adverse effect
			Inositol	Control/ placebo				
Levine (1997)	Double-blind, placebo-controlled, four week, random-assignment crossover treatment; patients with depressive or bipolar disorder	Israel	13 (gender distribution not known) in treatment group (total 26)	15 (gender distribution not known); cross-over study	12 g/day	Effectiveness against depression	1 month	Mild increases in glycemia after 4 weeks (2); 1 nausea and 1 flatulence
Benjamin et al. (1995)	Double-blind, placebo-controlled, crossover trial; patients with panic disorder	Israel	21 (gender distribution not known) in treatment group	21 (gender distribution not known); cross-over study	12 g/day	Effectiveness against panic disorder	1 week run-in phase (open placebo/no inositol), 4 weeks exposure study	Sleepiness (2 patients)

In a large-scale Italian study (88 subjects) assessing effects of combined inositol/folic acid treatments for erectile dysfunction in type 2 diabetes men (Agostini et al., 2006), doses of 4 g/day of *myo*-inositol were administered over a 12-week period. Adverse effects recorded included mild insomnia (2 patients) and flatulence (1 patient).

A Canadian study established a maximum tolerated dose (NOAEL level) for inositol exposure based on a 1-month dose escalation study (Stage I) ranging from 12 to 30 g/day of *myo*-inositol in smokers (age: 40 to 74 years) with ≥30 pack-years of smoking history and one or more sites of bronchial dysplasia (Lam et al., 2006). In Stage II (3 months), 10 patients were given *myo*-inositol at the following level: NOAEL 18 g/day (established in Stage I). Reported adverse effects were flatulence, loose stool or diarrhea, and mild gastrointestinal symptoms in Stage I. In addition, a significant decrease in the blood pressure after taking 18 g/day *myo*-inositol for 1 month or more was reported. There was also a statistically significant, although probably clinically insignificant, increase in the hemoglobin after taking 18 g/day of *myo*-inositol for more than 4 weeks (Lam et al., 2006).

A review of 12 controlled clinical trials with a total of 250 adults given oral doses of 4 to 30 g inositol/person per day (equal to 57 and 429 mg/kg bw per day for a 70 kg person) over 1 to 12 months, found that the most frequently reported and dose-related adverse effects were nausea, flatulence, loose stools and diarrhoea (Carlomagno and Unfer, 2011). Notably, the dosage of 4 g/day of inositol, commonly used in clinics, was reported to be completely free of side effects (Carlomagno and Unfer, 2011). Five relevant studies found in Carlomagno and Unfer (2011), reporting adverse effects upon inositol exposure are included in Table 2.4.1-1.

In a clinical trial performed in Israel comparing inositol vs. fluvoxamine for the treatment of panic disorder in otherwise healthy persons (Palatnik et al., 2001), the following adverse effects were observed when administrating 12 g/day (1. week) to 18 g/day (2.-4. week) of inositol: nausea (8 persons) and tiredness (1 person).

In an Israelian study focusing on effects of inositol against depression including 13 subjects in the inositol-treatment group (Levine, 1997), a dose of 12 g/day of inositol was used. The following side-effects were recorded during the 4-week study: mild increases in glycemia in 2 persons, nausea (1 person) and flatulence (1 person).

A study carried out by Benjamin et al. (1995) in Israel assessed the effects of inositol against panic disorders in 21 subjects, using a dose of 12 g/day of inositol. Two subjects complained of sleepiness during inositol treatment (4-week study), and no other side-effects were observed.

2.4.1.1 Interactions

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

2.4.1.2 Allergic sensitisation (including adjuvant effects)

There was no information concerning allergic sensitisation or allergy adjuvant effects in the literature 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

No conventional toxicological studies were available, but the results of studies in rodent models of chronic diseases (including diabetes and cancer) suggest that the toxicity of inositol is low, as concluded by EFSA (2014). The only adverse effects observed were thickening of basement membranes of capillaries of the retina and glomeruli of non-diabetic rats treated for nine months with 2% *myo*-inositol in the diet. The value was equivalent to 1800 mg/kg bw per day, using the EFSA default conversion factor of 0.09 for converting chemical substance concentrations in feed into daily doses in animal studies with rats (EFSA, 2012a). Worsening of the capillary thickening in glomeruli was observed, along with an increase in the amount of pericyte-containing capillaries in the retina of diabetic and non-diabetic rats treated for five or nine months with 2% *myo*-inositol in the diet. A NOAEL could not be determined, as only one dose level was used.

The effect of inositol on cancers induced by other chemicals has been investigated in mice, using long-term exposure in drinking water to cyclic dextran sulphate sodium (DSS) in combination with an iron-enriched diet to induce ulcerative colitis (which is associated with colon cancer) in female C57BL/6 mice. *Myo*-inositol or hexaphosphate inositol was given at 1% (equivalent to 9000 mg/kg bw per day) in the drinking water of groups of colitis-induced or non-induced mice for 255 days. None of the treatments affected mortality, body weight gain or feed consumption.

2.4.2.1 Interactions

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

2.4.2.2 Allergic sensitisation (including adjuvant effects)

There was no information concerning allergic sensitisation or allergy adjuvant effects in the literature 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 was available from the previous risk assessments.

2.4.4 Mode of action for adverse effects

No data was available from the previous risk assessments.

2.4.5 Vulnerable groups

The metabolism of inositol in the human body is altered by various clinical conditions, including diabetes and kidney disorders such as chronic renal failure (CRF). High levels of circulating inositol might have toxic effects on nerve tissue and may aggravate polyneuropathy in people with CRF. However, people with kidney failure are not considered to be relevant consumers of energy drinks in view of strict regulation of their dietary habits (VKM, 2005).

No data were found in the included literature specifically addressing effects of inositol on infants, children, pregnant or lactating women.

2.5 Summary of hazard identification and characterisation

With regard to genotoxicity and mutagenicity, the properties of inositol have not been thoroughly investigated.

A review of 12 controlled clinical trials in a total of 250 adults given oral doses of 4 to 30 g inositol/person per day (equal to 57 and 429 mg/kg bw per day for a 70 kg person) over 1 to 12 months found that the most frequently reported and dose-related adverse effects were related to gastrointestinal symptoms such as flatulence, loose stools and diarrhoea (Carlomagno and Unfer, 2011).

A NOAEL of 18 g/day (257 mg/kg bw per day for a 70 kg person) of *myo*-inositol was established in a clinical study of smokers (40-74 years) with bronchial dysplasia (Lam et al., 2006).

No conventional toxicological studies were available, but the results of studies in rodent models of chronic diseases (including diabetes and cancer) suggest that the toxicity of inositol is low over an oral dose range of 450–9000 mg/kg bw per day, as concluded by EFSA (2014). Only one study showed adverse effects (at 1800 mg/kg bw per day), including thickening of basement membranes of capillaries of the retina and glomeruli. However, a NOAEL could not be identified in these studies (EFSA, 2014).

For the present risk assessment, the human studies available were not of sufficient quality to be used alone in the risk characterisation. With regard to the animal model studies, no conventional toxicological studies were available. Results of studies in rodent models of

chronic diseases (including diabetes and cancer) suggested that the toxicity of inositol is low over an oral dose range of 450–9000 mg/kg bw per day.

The values used for comparison with the estimated exposure in the risk characterization are 57 mg/kg bw per day (the endogenous production in a 70 kg adult), 7-14 mg/kg bw per day (the total dietary intake of inositol in a 70 kg adult), and the NOAEL of 18 g/day (257 mg/kg bw per day for a 70 kg person).

3 Exposure / Intake

3.1 Energy drinks

NFSA requested VKM to perform a risk assessment of 10 mg/100 ml of inositol in energy drinks for the age groups children (3 to <10 years and 10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years). The default body weights (bw) for these groups determined by EFSA were used: 3 to <10 years; 23.1 kg, 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and adults; 70.0 kg (EFSA, 2012).

The consumption of energy drinks has been estimated for three drinking patterns: high acute consumption, mean chronic and high chronic consumption. In Table 3.1-1, the estimated intake of energy drinks for the various age groups in the three intake scenarios is shown.

High acute consumption

For children (3 to <10 years and 10 to <14 years), the high acute consumption was based on a small Norwegian food consumption survey (Johansen and Andersen, 2013) and actual cases of high acute intake of energy drinks (BfR, 2008; Storvik, 2014). Based on expert judgment, the values used are about 0.5 l higher than the maximum reported intake of soft drinks and "saft" in this survey ("saft" is a concentrate that shall be mixed with water before drinking).

For adolescents (14 to <18 years) and adults (≥18 years), the high acute consumption was based on the food consumption survey Norkost3 (Totland et al., 2012). The 97.5 percentile for total intake of soft drinks and "saft" in this survey (18-70 years) was 1.5 l and the maximum reported intake of soft drinks and "saft" in Norkost 3 was about 2 l. Based on expert judgement, the value used is the maximum reported intake of soft drinks and "saft".

Mean chronic and high chronic consumption

The daily mean and high chronic intakes were based on a report from the Technical University of Denmark (DTU) (Christensen LM et al., 2014) for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years). Children (3 to <10 years) were not included in the report from DTU (Christensen LM et al., 2014). To estimate mean chronic and high chronic intake for this group, the ratio for the intake of energy drinks per day and kg bw was calculated for the age group children (10 to <14 years) using the intake reported by DTU and the default bw set by EFSA (EFSA, 2012b). Based on the default values for intake of drinks per day and bw, this ratio was used to estimate the intake for the age group children (3 to <10 years).

Table 3.1-1 The estimated intake of energy drinks (ml/day) for the various age groups in the three intake scenarios.

Age groups	Consumption (ml/day)		
	High acute	Mean chronic	High chronic
Children (3 to <10 years)	1000	58	163
Children (10 to <14 years)	1500	65	180
Adolescents (14 to <18 years)	2000	64	210
Adults (≥18 years)	2000	71	320

For 3 to <10 year old children, the intake level of inositol has been estimated to be 4.3 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels are 0.3 and 0.7 mg/kg bw per day, respectively.

For 10 to <14 year old children, the intake level of inositol has been estimated to be 3.5 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels are 0.1 and 0.4 mg/kg bw per day, respectively.

For 14 to <18 year old adolescents, the intake level of inositol has been estimated to be 3.3 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels are 0.1 and 0.3 mg/kg bw per day, respectively.

For adults (≥18 years), the intake level of inositol has been estimated to be 2.9 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels are 0.1 and 0.5 mg/kg bw per day, respectively.

The estimated exposure to inositol from energy drinks for the various age groups in the three scenarios is presented in Table 3.1-2.

Table 3.1-2 Estimated exposure to inositol from energy drinks containing 10 mg inositol per 100 ml energy drink for children, adolescents and adults for the three drinking patterns.

Age groups	Exposure scenarios	Estimated exposure (mg/kg bw per day)
Children (3 to <10 years)	High acute	4.3
	Mean chronic	0.3
	High chronic	0.7
Children (10 to <14 years)	High acute	3.5
	Mean chronic	0.1
	High chronic	0.4
Adolescents (14 to <18 years)	High acute	3.3
	Mean chronic	0.1
	High chronic	0.3
Adults (≥18 years)	High acute	2.9
	Mean chronic	0.1
	High chronic	0.5

3.2 Other sources

Inositol is ingested via the daily diet, either as *myo*-inositol or in a phosphorylated form (e.g. phytic acid or other phytates) (EFSA, 2014). It is also used as a humectant ingredient in cosmetic products for skin and hair care including hair conditioners, creams and body lotions (CosIng, 2015; EWG, 2015). The total dietary intake of inositol in adults is estimated to range from 500 to 1000 mg/day (7 to 14 mg/kg bw per day for a 70 kg person) (Rotstein et al., 2013).

4 Risk characterisation

NFSA requested VKM to perform a risk assessment of 10 mg/100 ml of inositol in energy drinks for the general population, ages 3 years and above. Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake should be assessed.

Calculations of margins of exposure (MOE)

The data on toxicity of inositol was very limited. The human study with the longest exposure at highest doses (3 months treatment at maximum tolerated dose) that was available for risk assessment was a clinical study of 40-74 year old smokers with bronchial dysplasia, from which a NOAEL of 18 g/day of *myo*-inositol was established (Lam et al., 2006). VKM has estimated MOE values based on the NOAEL established in this study.

The MOE is the ratio of the NOAEL value to the exposure. An acceptable MOE value for a NOAEL-based assessment of inositol based on a human study is ≥10, taking into account a factor 10 for the interindividual variation between humans in toxicokinetics and toxicodynamics. Due to the uncertainty regarding the relevance of the study by Lam et al. (2006) for the general healthy population, an additional safety factor of 3 was used. Therefore, an acceptable MOE value was 30.

For all age groups, the margins of exposure were in the range of 857 to 2570 for mean chronic intake and in the range of 367 to 857 for high chronic intake of energy drinks, respectively (Table 4.1-1), i.e. above 30.

Table 4.1 Estimated margins of exposure (MOE) values for inositol from energy drinks in mean and high chronic consumers from the different age groups.

Age groups	Exposure scenarios	Margin of exposure
Children (3 to <10 years)	Mean chronic	857
	High chronic	367
Children (10 to <14 years)	Mean chronic	2570
	High chronic	643
Adolescents (14 to <18 years)	Mean chronic	2570
	High chronic	857
Adults (≥18 years)	Mean chronic	2570
	High chronic	514

With regard to animal studies, no conventional toxicological studies were available. Results of studies in rodent models of chronic diseases (including diabetes and cancer) suggest that the toxicity of inositol is low in an oral dose range of 450–9000 mg/kg bw per day.

Comparisons with endogenous levels and levels in food

Since neither the sub-optimal human study by Lam et al. (2006) or the animal studies available were on healthy subjects, as a supplement to the MOE values calculated from the human study, comparisons with endogenous production and amounts in food of inositol were also performed. The endogenous production of inositol in humans amounts to about 4 g/day (about 57 mg/kg bw per day in a 70 kg adult) (EFSA, 2014). The total dietary intake of inositol in adults is estimated to range from 500 to 1000 mg/day (equivalent to about 7-14 mg/kg bw per day for a 70 kg adult).

No studies specifically on children (3 to <10 years and 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 or endogenous production of inositol. Therefore, in this risk characterisation a tolerance and an endogenous production of inositol as for adults, based on body weight, was assumed for these age groups.

For a high acute consumption of energy drinks with concentration 10 mg inositol per 100 ml, the intake level was 4.3 mg/kg bw per day in children (3 to <10 years), 3.5 mg/kg bw per day in children (10 to <14 years), 3.3 mg/kg bw per day for adolescents (14 to <18 years) and 2.9 mg/kg bw per day for adults (≥18 years), respectively.

For a mean chronic consumption of energy drinks with concentration 10 mg inositol per 100 ml, the intake level was 0.3 mg/kg bw per day in children (3 to <10 years), 0.1 mg/kg bw per day in children (10 to <14 years), 0.1 mg/kg bw per day for adolescents (14 to <18 years) and 0.1 mg/kg bw per day for adults (≥18 years), respectively.

For a high chronic consumption of energy drinks with concentration 10 mg inositol per 100 ml, the intake level was 0.7 mg/kg bw per day in children (3 to <10 years), 0.4 mg/kg bw per day in children (10 to <14 years), 0.3 mg/kg bw per day for adolescents (14 to <18 years) and 0.5 mg/kg bw per day for adults (≥18 years), respectively.

For the high acute, the mean chronic and the high chronic drinking patterns, all estimated intakes of inositol from energy drinks containing 10 mg/100 ml were far below the endogenous production (57 mg/kg bw per day) and the dietary intake (7-14 mg/kg bw per day).

Based on both the calculated MOE values as well as comparisons with endogenous levels and levels in food, VKM considers that it is unlikely that the exposure to inositol from the high acute, the mean chronic and the high chronic drinking patterns causes adverse health effects in children (3 to <10 years and 10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

5 Uncertainties

5.1 Hazard identification and characterization

The NOAEL value was derived from a clinical study of 40-74 year old smokers with bronchial dysplasia treated for 3 months only (Lam et al., 2006). The relevance of this population exposed for a rather short duration to the general healthy population potentially exposed much longer is uncertain.

5.2 Exposure

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

Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake are included in the present assessment. The intakes of energy drinks for the various age groups for the three drinking patterns are estimates based on dietary surveys and expert judgement.

5.3 Risk characterisation

Assumptions about the safety for children (3 years and above) and adolescents (14 to <18 years) were based on studies in adults.

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 inositol in energy drinks. The present risk assessment is based on previous risk assessments of inositol and articles retrieved from a literature search. The adverse effects of oral intake of inositol reported in the included literature were generally limited to nausea, flatulence, loose stools and diarrhoea.

Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake were assessed for energy drinks containing 10 mg inositol per 100 ml, for the age groups children (3 to <10 years and 10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

The data on toxicity of inositol was very limited. The human study with the longest exposure at highest doses (3 months treatment at maximum tolerated dose) that was available for risk assessment was a clinical study of 40-74 year old smokers with bronchial dysplasia, from which a NOAEL of 18 g/day of *myo*-inositol was established (Lam et al., 2006). VKM estimated the margins of exposure (MOE) based on the NOAEL established in this study.

For all age groups, the MOE values were in the range of 857 to 2570 for mean chronic intake and in the range of 367 to 857 for high chronic intake of energy drinks, respectively.

Since neither the sub-optimal human study by Lam et al. (2006) or the animal studies in rodent models of chronic diseases available were on healthy subjects, as a supplement to the MOE values calculated from the human study, comparisons with endogenous production and amounts in food of inositol were also performed. The endogenous production of inositol in humans amounts to about 4 g/day (about 57 mg/kg bw per day in a 70 kg adult) (EFSA, 2014). The total dietary intake of inositol in adults is estimated to range from 500 to 1000 mg/day (equivalent to about 7-14 mg/kg bw per day for a 70 kg adult).

No studies specifically on children (3 to <10 years and 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 or endogenous production of inositol. Therefore, in this risk characterisation a tolerance and an endogenous production of inositol as for adults, based on body weight, was assumed for these age groups.

For the high acute drinking pattern, and for the mean chronic and the high chronic drinking patterns all estimated intakes of inositol from energy drinks containing 10 mg/100 ml were far below the endogenous production (57 mg/kg bw per day), and also below the dietary intake (7-14 mg/kg bw per day).

VKM concludes that it is unlikely that the exposure to inositol from the high acute, the mean chronic or the high chronic drinking patterns causes adverse health effects in children (3 to <10 years and 10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

An overview of the conclusions on energy drinks containing 10 mg/ 100 ml inositol is presented in Table 6.1. Estimated exposures unlikely to cause adverse health effects (below the value for comparison) are shown in green.

Table 6.1 An overview of the conclusions on high acute, mean chronic and high chronic intake of energy drinks containing inositol (10 mg/100 ml). Green: the estimated exposure to *myo*-inositol is unlikely to cause adverse health effects.

Energy drink 10 mg/100 ml / **Age groups**	**High acute drinking pattern**	**Mean chronic drinking pattern**	**High chronic drinking pattern**
Children (3 to <10 years)			
Children (10 to <14 years)			
Adolescents (14 to <18 years)			
Adults (≥18 years)			

7 Data gaps

- There was very little data available on toxicity of *myo*-inositol from human or animal studies.
- No studies on negative health effects related to inositol in children and adolescents were identified in the literature search, and no studies were found that include effects of inositol in lactating or pregnant women.
- There was lack of an acute reference dose or other data on acute toxicity for inositol.

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9 Appendix

Search Strategy Medline, Embase and Global Health

1. inositol*.ti. (20517)
2. (inositol* adj3 (risk* or safety or adverse or reaction* or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or consequence* or toxicity or toxic)).tw. (607)
3. 1 and 2 (358)
4. (conference abstract* or letter* or editoral*).pt. (3483123)
5. 3 not 4 (350)
6. remove duplicates from 5 (189)

Search strategy Web of Science

# 3	**235**	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years*
# 2	**480**	TS=(inositol* NEAR/3 (risk* or safety or adverse or reaction* or "side-effect*" or hazard* or harm* or negative or contraindicat* or "contra-indicat*" or interact* or consequence* or toxicity or toxic)) *Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years*
# 1	**8,052**	(TI=inositol*) *AND* **DOCUMENT TYPES:** (Article OR Book OR Book Chapter OR Proceedings Paper OR Review) *Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years*

The total number of articles, after removal of duplicates, was 196.