Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

VKM Report 2015:21

Risk assessment of "other substances" – D-Glucurono-γ-lactone

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) 2015:21
Risk assessment of "other substances" – D-Glucurono-γ-lactone

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
20.11.2015

ISBN: 978-82-8259-176-8
Norwegian Scientific Committee for Food Safety (VKM)
Po 4404 Nydalen
N – 0403 Oslo
Norway

Phone: +47 21 62 28 00
Email: vkm@vkm.no

www.vkm.no
www.english.vkm.no

Cover photo: iStock Photo

Suggested citation: VKM. (2015) Risk assessment of "other substances" – D-Glucurono-γ-lactone. 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: 978-82-8259-176-8, Oslo, Norway.

Risk assessment of "other substances" – D-Glucurono-γ-lactone

Author preparing the draft opinion

Trine Husøy

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. Trine Husøy 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

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. VKM has not in this series of risk assessments of "other substances" evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of D-glucurono-γ-lactone, and it is based on previous risk assessments. A literature search was performed, however, no articles fulfilled the inclusion criteria.

According to information from NFSA, D-glucurono-γ-lactone is an ingredient in energy drinks sold in Norway. NFSA has requested a risk assessment of 24 mg/100 ml of D-glucurono-γ-lactone in energy drinks. Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake were assessed.

D-glucurono-γ-lactone (CAS no. 32449-92-6; EINECS no. 251-053-3) and its hydrolysis product glucuronic acid are endogenous metabolites in humans and other mammals, they occur naturally in several dietary sources and are readily metabolized to innocuous products and excreted. The estimated exposure to D-glucurono-γ-lactone from naturally occurring sources in the diet is 1-2 mg/day.

No human toxicity data on D-glucurono-γ-lactone was available in the included literature. A no observed adverse effect level (NOAEL) of 1000 mg/kg bw per day, the highest dose tested, was set in 2009 by the European Food Safety Authority (EFSA) (EFSA, 2009) based on a 13 week rat study of daily oral administration of D-glucurono-γ-lactone performed under good laboratory practice. VKM has used the NOAEL of 1000 mg/kg bw per day for the risk characterisation in the present risk assessment.

The risk characterisation is based on the margin of exposure (MOE) approach; the ratio of the NOAEL to the exposure. An acceptable MOE value for a NOAEL-based assessment of D-glucurono-γ-lactone is ≥100, which includes a factor 10 for extrapolation from animals to humans, and a factor 10 for interindividual human variation

Due to lack of an acute reference dose or other data on acute toxicity for D-glucurono-γ-lactone, it is not possible to characterise the risk related to a high acute drinking pattern for any of the age groups.

For the mean chronic drinking pattern, the intake was estimated to be 58, 65, 64 and 71 ml/day for 3 to <10 year old children, 10 to <14 year old children, 14 to <18 year old adolescents and adults, respectively. With regard to the mean chronic drinking pattern, the MOE values are 1667 for the age group 3 to <10 years, 2500 for the age group 10 to <14 years, 3333 for the age group 14 to <18 and 5000 for adults ≥18 years. VKM concludes that it is unlikely that a daily mean chronic intake of D-glucurono-γ-lactone from energy drinks (containing 24 mg/100 ml) causes adverse health effects to children (3 years and above), adolescents or adults.

For the high chronic drinking pattern, the intake was estimated to be 163, 180, 211 and 320 ml/day for 3 to <10 year old children, 10 to <14 year old children, 14 to <18 year old adolescents and adults, respectively. With regard to the high chronic drinking pattern, the MOE values are 588 for the age group 3 to <10 years, 1000 for the age group 10 to <14 years, 1250 for the age group 14 to <18 and 909 for adults (≥18 years). VKM concludes that it is unlikely that a daily high chronic intake of D-glucurono-γ-lactone in energy drinks (containing 24 mg/100 ml) causes adverse health effects to children (3 years and above), adolescents or adults.

Short summary

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of D-glucurono-γ-lactone in energy drinks (containing 24 mg D-glucurono-γ-lactone/100 ml). VKM concludes that it is unlikely that a daily mean chronic or high chronic intake of D-glucurono-γ-lactone from energy drinks causes adverse health effects to children (3 years and above), adolescents (10 to <14 years) or adults (≥18 years). Due to lack of an acute reference dose or other data on acute toxicity for D-glucurono-γ-lactone, it is not possible to characterise the risk related a high acute drinking pattern for any of the age groups.

Key words: Adverse health effect, D-glucurono-γ-lactone, energy drink, 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 tilsetting av «andre stoffer» i kosttilskudd og energidrikk som selges i Norge. VKM har risikovurdert ulike bruksdoser oppgitt fra Mattilsynet Disse risikovurderingene vil gi Mattilsynet vitenskapelige 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 påståtte gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

Denne rapporten er en risikovurdering av D-glukurono-γ-lakton, og den er basert på tidligere risikovurderinger. Det ble gjort et litteratursøk, men ingen av artiklene oppfylte inklusjonskriteriene.

Ifølge informasjon fra Mattilsynet er D-glukurono-γ-lakton en ingrediens i energidrikker som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere 24 mg/100 ml av D-glukurono-γ-lakton i energidrikker. Drikkemønstre som reflekterer et høyt akutt inntak, et gjennomsnittelig kronisk inntak og et høyt kronisk inntak ble vurdert.

D-glucurono-γ-lakton (CAS nr. 32449-92-6; EINECS nr. 251-053-3), og glukuronsyre som dannes ved hydrolyse av D-glukurono-γ-lacton, er endogene metabolittere i mennesker og andre pattedyr. Begge forekommer naturlig i en rekke matvarer og de metaboliseres til uskadelige produkter og skilles ut. Estimert eksponering for D-glukurono-γ-lakton fra naturlig forekommende kilder i kosten er 1-2 mg/dag.

Ingen toksikologiske data for D-glukurono-γ-lakton fra humane studier var tilgjengelig i den inkluderte litteraturen. Et null-effektsnivå (NOAEL) på 1000 mg/kg kroppsvekt/dag ble satt i 2009 av den europeiske myndighet for næringsmiddeltrygghet (European Food Safety Authority - EFSA (EFSA, 2009) basert på en 13 ukers studie med rotter. Rottene inntok D-glukurono-γ-lakton daglig, og 1000 mg/kg kroppsvekt per dag var den høyeste dosen som ble testet. Studien ble gjennomført i henhold til god laboratoriepraksis. VKM har brukt denne NOAEL-verdien (1000 mg/kg kroppsvekt/dag) i risikokarakteriseringen i denne risikovurderingen.

Denne risikokarakteriseringen av D-glukurono-γ-lakton er basert på beregning av eksponeringsmargin ('margin of exposure' (MOE)), som er ratio mellom NOAEL-verdien og eksponeringen. En akseptabel MOE-verdi for en risikovurdering basert på NOAEL fra et dyreforsøk er ≥100, som inkluderer en faktor 10 for ekstrapolering fra dyr til mennesker og en faktor 10 for interindividuell variasjon mellom mennesker

På grunn av mangel på en akutt referansedose eller andre akutte data for D-glucurono-γ-lakton, er det ikke mulig å karakterisere risikoen knyttet til et høyt akutt inntak.

For det gjennomsnittlige kroniske drikkemønsteret ble intaket estimert til å være 58, 65, 64 og 71 ml/dag for henholdsvis barn (3 til <10 åringer og 10 til <14 åringer), ungdom (14 til <18 åringer) og voksne (≥18 år). For det gjennomsnittlige kroniske drikkemønsteret er MOE-verdiene 1667 for 3 til <10 åringer, 2500 for 10 til <14 åringer, 3333 for 14 til <18 åringer og 5000 for voksne (≥18 år). VKM konkluderer med at det er usannsynlig at et daglig gjennomsnittlig kronisk inntak av D-glukurono-γ-lakton fra energidrikker (som inneholder 24 mg/100 ml) fører til negative helseeffekter hos barn (3 år og oppover), ungdom eller voksne.

For det høye kroniske drikkemønsteret ble intaket estimert til å være 163, 180, 211 og 320 ml/dag for henholdsvis 3 til <10 åringer, 10 til <14 åringer, 14 til <18 åringer og voksne. For det høye kroniske drikkemønsteret er MOE-verdiene 588 for 3 til <10 åringer, 1000 for 10 til <14 åringer, 1250 for 14 til <18 åringer og 909 for voksne ≥18 år. VKM konkluderer med at det er usannsynlig at et daglig høyt kronisk inntak av D-glukurono-γ-lakton fra energidrikker (som inneholder 24 mg/100 ml) fører til negative helseeffekter hos barn (3 år og oppover), ungdom eller voksne.

Kort sammendrag

Vitenskapskomiteen for mattrygghet (VKM) har på oppdrag fra Mattilsynet vurdert risikoen ved D-glukurono-γ-lakton i energidrikker (som inneholder 24 mg/100 ml). VKM konkluderer med at det er usannsynlig at et daglig gjennomsnittlig kronisk eller høyt kronisk inntak av D-glukurono-γ-lakton fra energidrikker forårsaker negative helseeffekter hos barn (3 år og oppover), ungdom eller voksne. På grunn av mangel på en akutt referansedose eller andre akutte data for D-glucurono-γ-lakton, er det ikke mulig å karakterisere risikoen knyttet til et høyt akutt inntak.

Abbreviations and glossary

Abbreviations

ADI	- acceptable daily intake
ADME	- absorption, distribution, metabolism, exretion
AFSSA	- French Food Safety Agency
ANSES	- French Agency for Food, Environmental and Occupational Health & Safety
EFSA	- European Food Safety Authority
GLP	- Good Laboratory Practice
MOE	- Margin og Exposure
NFSA	- Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NOAEL	- no observed adverse effect level
SCF	- Scientific Committee on Food
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) requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of D-glucurono-γ-lactone in energy drinks at the following dose: 24 mg/100 ml. 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 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 D-glucurono-γ-lactone *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), D-glucurono-γ-lactone 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 24 mg D-glucurono-γ-lactone/100 ml. The total exposure to D-glucurono-γ-lactone from other sources than energy drinks, such as foods and cosmetic products, is not included in the risk assessment.

D-glucurono-γ-lactone (CAS no. 32449-92-6; EINECS no. 251-053-3) is a human metabolite formed from glucose. When D-glucurono-γ-lactone is given orally to humans, it is rapidly absorbed, metabolised and excreted as glucaric acid, xylitol and L-xylose. D-glucurono-γ-lactone occurs naturally in some foods (EFSA, 2009). At physiological pH, D-glucurono-γ-lactone is in equilibrium with glucuronic acid. Glucuronic acid occurs in plants, mainly in gums, but is in polymeric combination with other carbohydrates and is therefore not readily bioavailable. Glucuronic acid is also an important constituent of fibrous and connective tissues in all animals (SCF, 1999).

The estimated exposure to D-glucurono-γ-lactone from naturally occurring sources in the diet is 1-2 mg/day (SCF, 2003). D-glucurono-γ-lactone is used at much higher levels in energy drinks (EFSA, 2009). In this Norwegian risk assessment, the concentration of D-glucurono-γ-lactone used in energy drinks is 24 mg/100 ml.

2 Hazard identification and characterisation

2.1 Literature

The present risk assessment is based on previous risk assessments of D-glucurono-γ-lactone. A literature search was performed, however, no articles fulfilled the inclusion criteria.

2.1.1 Previous risk assessments

Opinion of the Scientific Committee on Food on Additional information on "energy" drinks. European Commission (SCF, 2003)

In 1999, the Scientific Committee on Food (SCF) adopted an opinion on so-called "energy drinks", which evaluated the safety of caffeine, taurine and D-glucurono-γ-lactone as constituents of "energy drinks" (SCF, 1999). The SCF commented that "there is insufficient information on which to set a safe upper level for daily intake of taurine and glucuronolactone". Since the 1999 opinion, further submissions of data were received from one manufacturer of energy drinks, including a new 13-week study of D-glucurono-γ-lactone in rats. The new data were evaluated by SCF in the 2003 opinion. SCF's description of the new data: "The new toxicokinetic data on glucuronolactone in rats, showing bioavailability and lack of accumulation, with peak plasma levels 1-2 hours after oral administration, were in accordance with findings from the limited published data on humans. In the new 13-week toxicity study, rats were given glucuronolactone at doses of 0, 300, 600 and 1000 mg/kg bw per day, dissolved in deionised water, orally by gavage once daily for 13 weeks from 6 weeks of age. There were no significant, treatment-related effects, apart from vacuolation and inflammatory changes localised to the papilla of the kidney in females at 600 and 1000 mg/kg bw per day, with a NOAEL of 300 mg/kg bw per day. The petitioner has commented that the occurrence of the lesions only in females may be related to the higher acidity and osmolality of urine in the female rat and went on to comment that the osmolality of human urine is considerably less than that of the Sprague-Dawley rat. However, in the Committee's view, the mechanistic cause of the kidney lesions remains unclear. The report (submitted by Red Bull GmbH, 2001) reviewed some additional studies on glucuronolactone, including a study on growing hamsters that had not previously been seen by the Committee. The purpose of the 28-day hamster study was to investigate whether glucuronolactone could prevent experimental cholelithiasis when given in the drinking water at doses up to 5.25%, equivalent to an intake of approximately 500 mg/kg bw per day. There were no clinical signs of toxicity in treated groups, which were comparable to controls." The SCF concluded that there is a lack of scientific evidence to support the safety of glucuronolactone present in beverages at concentrations that may result in intakes several-fold higher than that usually

obtained from the rest of the diet. Due to the lack of relevant data it is not possible to set a safe upper level for daily intake of glucuronolactone.

Opinion of the French Food Safety Agency 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 (AFFSA, 2006)

The safety of an energy drink containing other substances, including D-glucuronolactone, was assessed. Neither information on safety nor established maximum concentrations or recommended daily doses of D-glucuronolactone was available. In conclusion; "Based on available data and the experimental studies performed it is not possible to characterise the risk from this product and particularly from the high doses of taurine and D-glucuronolactone compared to dietary intake. In addition, as for any product the company must ensure its product is safe for the consumer. There is no question however that the data produced and evaluated by the committee do not provide a guarantee of safety under the recommended conditions of use. Further studies were required:
- To exclude or confirm the suspicions of nephrotoxic and neurotoxic risks.
- To answer the scientific uncertainties about the safety of use of the product in order to ensure the drink is safe for the consumer".

The use of taurine and D-glucurono-γ-lactone as constituents of the so-called "energy drinks". The European Food Safety Authority (EFSA, 2009)

The safety of D-glucurono-γ-lactone as individual ingredients of so-called "energy drinks" was evaluated based on a new 13-week oral (gavage or drinking water) toxicity study of D-glucurono-γ-lactone in the Crl:CD(SD) rat strain given 0, 300, 600 and 1000 mg D-glucurono-γ-lactone/kg bw per day, with specific focus on the kidneys. This study used the same rat strain as the study described in the SCF Opinion of 2003 and was performed according to FDA and OECD principles of Good Laboratory Practice. Complete necropsies were conducted on all animals, and selected organs were weighed at the scheduled necropsy. Selected tissues were examined microscopically from all animals. Results revealed no test article-related deaths. There were no effects on clinical observations, food or water consumption, body weights, clinical pathology parameters, organ weights or clinical chemistry parameters representing renal function. Extensive urinalysis demonstrated no treatment-related effects, and no differences between gavage and drinking water groups. There were no test article-related macroscopic or microscopic findings. Histopathological examinations revealed focal inflammation in the kidneys in a few male and female animals, scattered among the groups, including controls. The petitioner indicated that inflammation was observed in only a small number of animals at each dose level, that it was unilateral and not treatment-related and that these background lesions were typical for this strain of rats. There were no compound-related observations of vacuolisation of the cells lining the collecting tubules. The petitioner also indicated that a greater number of rats in this new study had healthy kidneys in comparison to the first study. There was no significant

incidence of cytoplasmic vacuolization in any groups. The petitioner also indicated that in light of the difference between the two studies the slides from the 2003 study had been carefully reassessed, and that cytoplasmic vacuolisation was confirmed not to be present in the first study. The petitioner also stated that the pathologist who undertook the histopathological examination had indicated that the effect in the previous study was most likely a preparation artifact which was exacerbated by the generally poor health status of the kidneys in the rats at that time. Vacuolisation of renal collecting tubules may arise as an artifact using normal fixation techniques.

Based on the results of this study, the NOAEL for daily oral administration of D-glucurono-γ-lactone of 1000 mg/kg bw per day was set, which was the highest dose tested. The NOAEL for D-glucurono-γ-lactone of 1000 mg/kg bw per day is 200-fold higher than the estimated mean and 71-fold higher than the estimated 95th percentile exposure to D-glucurono-γ-lactone from "energy drinks" only, when calculated for a 60 kg person. Given the fact that D-glucurono-γ-lactone is a natural body constituent, the Panel concluded that these margins of safety were sufficiently large to conclude that exposure to D glucurono-γ- lactone at the estimated exposure levels mentioned was not of safety concern.

Risikovurdering av "energidrikker" med koffein, taurine, glukuronolakton, inositol og vitaminer. Norway (in Norwegian) (VKM, 2005)

New information on ingredients in so-called "energy drinks". Norway (VKM, 2009)

In 2005, VKM performed a risk assessment of the ingredients in the energy drink «Red Bull». VKM was asked to base the risk assessment on SCF's opinion from 2003 and newer studies published since 2003. VKM concluded that it was not possible based on the present knowledge to conclude that D-glucurono-γ-lactone does not pose a health concern at the estimated level of intake.

In 2009, VKM examined, on the basis of the EFSA 2009 opinion, whether the conclusion of the VKM opinion from 2005 needed to be revised. New studies had established a NOAEL for D-glucurono-γ-lactone of 1000 mg/kg bw per day. Based on this, EFSA concluded that exposure to D-glucurono-γ-lactone as an individual ingredient at the levels presently used in "energy drinks" and at intake levels presented in the EFSA opinion, is of no safety concern. The VKM Panel 4 endorsed this conclusion and considered it as valid also for Norway.

Opinion of the French Agency for Food, Environmental and Occupational Health and Safety on the assessment of risk concerning the consumption of so-called "energy drinks". (ANSES, 2013)

The purpose of ANSES's opinion was to assess the risk related to the consumption of so-called "energy drinks". The presence of one of the following substances of interest was used to define so-called "energy drinks": caffeine, taurine, glucuronolactone, guarana extract and ginseng extract. When the mean level of glucuronolactone in so-called "energy drinks" was

considered, the mean daily intake was 46 mg/day and the 90th percentile was 114 mg/day in all so-called "energy drink" consumers. In regular consumers with higher frequency of consumption, the intake was 115 mg/day, whereas intake at the 90th percentile was 411 mg/day. If maximum glucuronolactone levels in so-called "energy drinks" were considered, and for body weight of 60 kg, the safety margin between mean daily glucuronolactone intake and the NOAEL of 1000 mg/kg bw per day was 547, and the safety factor between daily intake at the 90th percentile and the NOAEL was 280. In regular consumers of so-called "energy drinks", these safety margins were 230 and 140 respectively.

The conclusions and recommendations by ANSES were given for so-called "energy drinks" and not specifically for D-glucurono-γ-lactone. It was concluded that consumption of so-called "energy drinks" should be avoided in children and adolescents, in pregnant and breast-feeding women, in individuals who were sensitive to the effects of caffeine, and in patients with specific disease states, in particular certain cardiovascular disorders, psychiatric and neurological disorders, kidney failure and severe liver conditions. It was further concluded that specific risks may also appear when consuming alcohol and during physical activity, in which the consumption of so-called "energy drinks" should be avoided. Finally, the need for clinical studies of long-term risks in chronic consumers of so-called "energy drinks" was stated.

2.1.2 Summary of previous risk assessments

In the present opinion, VKM uses the NOAEL of 1000 mg D-glucurono-γ-lactone/kg bw per day set by EFSA (2009) when evaluating the safety of D-glucurono-γ-lactone as an ingredient in energy drinks**.**

2.1.3 Literature search

2.1.3.1 Search strategy

Literature searches were performed in MEDLINE and EMBASE. The search strategy is included in Appendix 1.

2.1.3.2 Publication selection

The literature search identified eight articles. In the primary screening, titles and abstracts of all 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 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 by two persons. No articles fulfilled the inclusion criteria, thus, all articles were excluded.

A flowchart for publication selection is given in Figure 2.1.3.2-1.

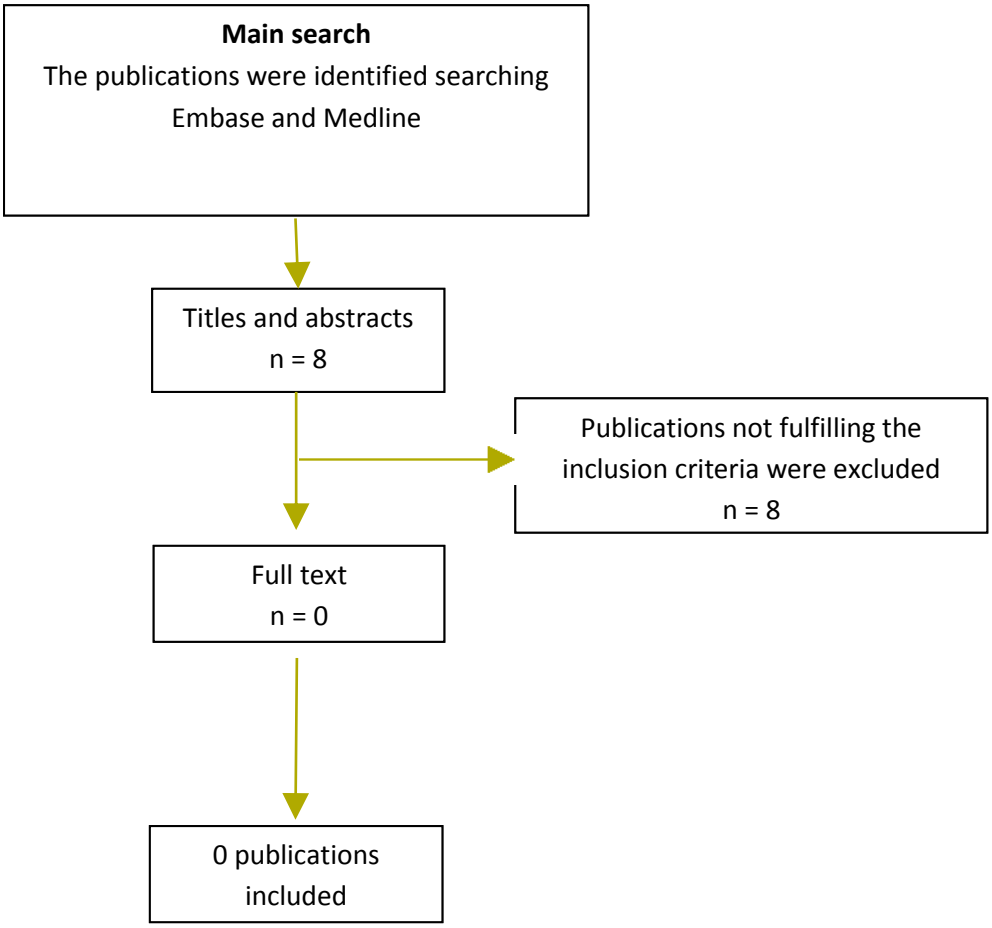

Figure 2.1.3.2-1 Flowchart for publication selection for D-glucurono-γ-lactone.

2.2 General information

2.2.1 Chemistry

The molecular formula of D-glucurono-γ-lactone (CAS No. 32449-92-6) is $C_6H_8O_6$ and the molecular weight is 176.12 g/mol. The IUPAC name is 2-aminoethanesulfonic acid. The structural formula is shown in Figure 2.2.1-1.

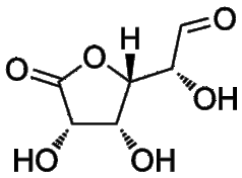

Figure 2.2.1-1 The structural formula of D-glucurono-γ-lactone.

2.2.2 Occurrence

D-glucurono-γ-lactone and its hydration product glucuronic acid are endogenous metabolites in humans and other mammals, they occur naturally in several foods and are readily metabolized to innocuous products and excreted (EFSA, 2009). Glucuronic acid is an important component in glucuronidation detoxification pathway of toxic substances in the liver. Glucuronic acid occurs in plants, mainly in gums, but is in polymeric combination with other carbohydrates and is therefore not readily bioavailable. The estimated exposure to D-glucurono-γ-lactone from naturally occurring sources in the diet was 1-2 mg/day (SCF, 2003).

2.3 Absorption, distribution, metabolism and excretion (ADME)

2.3.1 In humans

The SCF concluded that the available data indicated that D-glucurono-γ-lactone administered orally to humans was rapidly absorbed, metabolised and excreted as glucaric acid, xylitol and L-xylulose (SCF, 1999). D-glucurono-γ-lactone and glucuronic acid are endogenous metabolites in humans and other mammals, and in equilibrium at physiological pH (SCF, 1999).

2.3.2 Animal studies

The SCF Opinion of 2003 stated that the toxicokinetic data on D-glucurono-γ-lactone in rats, showing bioavailability and lack of accumulation, with peak plasma levels 1-2 hours after oral administration, were in accordance with findings from the limited published data on humans (SCF, 2003).

The use of rodents as a model for man in the study of the effects of D-glucurono-γ-lactone was discussed (SCF, 1999; SCF, 2003), since rodents have a metabolic pathway for D-glucurono-γ-lactone not present in primates (conversion of D-glucurono-γ-lactone into vitamin C). However, more recent data show that the synthesis of vitamin C from D-glucurono-γ-lactone was relatively small, and that D-glucurono-γ-lactone predominantly was metabolised via the pentose pathway in rats (EFSA, 2009).

2.4 Adverse effects

2.4.1 Human studies

There were no studies on toxicity in humans for D-glucurono-γ-lactone alone in the included literature.

D-glucurono-γ-lactone is a human metabolite formed from glucose and according to EFSA (2009) there were no structural alerts for mutagenicity or carcinogenicity.

2.4.1.1 Interactions

A potential for interactions between constituents of energy drinks was discussed in the included previous reports. In SCF (2003) the possibility of interactions between taurine, caffeine and D-glucurono-γ-lactone was discussed, and it was considered unlikely that D-glucurono-γ-lactone would have any interaction with caffeine and taurine.

In EFSA (2009), it was concluded that it was unlikely that D-glucurono-γ-lactone would have any interaction with caffeine, taurine, alcohol or the effects of exercise.

Other interactions were not described in the literature included 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 adjuvance 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

2.4.2.1 Genotoxicity

Animal studies on the genotoxic potential of D-glucurono-γ-lactone were not available.

2.4.2.2 Subchronic toxcitiy

For D-glucurono-γ-lactone, the SCF concluded that the 13-week study in Crl:CD(SD) rats showed that there were no significant, treatment-related effects, "apart from vacuolisation and inflammatory changes localised to the papilla of the kidney in females at 600 and 1000 mg/kg bw per day, with a NOAEL of 300 mg/kg bw per day" (SCF, 2003).

EFSA received a new 90 days study in Crl:CD(SD) rats given D-glucurono-γ-lactone orally by gavage and in drinking water (EFSA, 2009). In this new study, D-glucurono-γ-lactone was administered orally by gavage once daily for 13 consecutive weeks to 4 groups of Cr1:CD(SD) rats at dose levels of 0, 300, 600 and 1000 mg/kg bw per day. In addition, D-glucurono-γ-lactone was administered *ad libitum* in drinking water for 13 weeks to another 4 groups of Cr1:CD(SD) rats at target dose levels of 0, 300, 600 and 1000 mg/kg bw per day. Each group consisted of 20 males and 20 females. Actual mean D-glucurono-γ-lactone intake levels obtained in the drinking water groups were 311 and 322 mg/kg bw per day for the males and females, respectively, in the low dose group, and 598 and 635 mg/kg bw per day for the males and females, respectively, in the mid-dose group, and 980 and 1066 mg/kg bw per day for the males and females, respectively, in the high dose group. Clinical examinations were performed daily, and detailed physical examinations were performed weekly. Individual body weights and water consumption were recorded twice weekly. Serum chemistry evaluations were performed on all animals. Urine samples were collected from the drinking water groups at the same time of day. Complete necropsies were conducted on all animals, and selected organs were weighed at the scheduled necropsy. Selected tissues were examined microscopically from all animals. Results revealed no test article-related deaths. There were no effects on clinical observations, food or water consumption, body weights, clinical pathology parameters, organ weights or clinical chemistry parameters representing renal function. Extensive urinalysis demonstrated no treatment-related effects, and no differences between gavage and drinking water groups. There were no test article-related macroscopic or microscopic findings. Histopathological examinations revealed focal inflammation in the kidneys in a few male and female animals, scattered among the groups, including controls. There were no compound-related observations of vacuolization of the cells lining the collecting tubules. There were no differences between the gavage and drinking water groups. There was no significant incidence of cytoplasmic vacuolization in any groups. Vacuolisation of renal collecting tubules may arise as an artifact using normal fixation techniques. The NOAEL for daily oral administration of D-glucurono-γ-lactone to rats was 1000 mg/kg bw per day, the highest dose tested (EFSA, 2009).

2.4.2.3 Chronic toxicity and carcinogenicity

Long term studies on D-glucurono-γ-lactone were not available. However, there was no evidence of any putative preneoplastic or hyperplastic lesions in the 13-week rat studies (EFSA, 2009; SCF, 2003).

2.4.2.4 Reproductive and developmental toxicity

Studies on reproductive and developmental toxicity for D-glucurono-γ-lactone were not available.

2.4.2.5 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.

2.4.2.6 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

2.4.3.1 Genotoxicity

In a study on the antimutagenic activity of lactones in *Escherichia coli*, D-glucurono-γ-lactone was reported not to be mutagenic to *E. coli* strains WP2 and WPs (EFSA, 2009).

2.4.5 Mode of action for adverse effects

In the included previous risk assessments, no mode of action for adverse effects of D-glucurono-γ-lactone was reported.

2..4.6 Vulnerable groups

There was no information concerning specific groups vulnerable for D-glucurono-γ-lactone in the literature reviewed in the present risk assessment.

2.5 Summary of hazard identification and characterisation

D-glucurono-γ-lactone administered orally to humans is rapidly absorbed, metabolised and excreted as glucaric acid, xylitol and L-xylulose (SCF 1999).

D-glucurono-γ-lactone is a human metabolite formed from glucose, and there were no structural alerts for mutagenicity or carcinogenicity (EFSA, 2009). In a study on the antimutagenic activity of lactones in *E. coli*, D-glucurono-γ-lactone was reported not to be mutagenic. Animal studies on the genotoxic or carcinogenic potential of D-glucurono-γ-lactone were not available in the included literature.

There were no studies on toxicity in humans for D-glucurono-γ-lactone alone in the included literature.

There were no indications of genotoxicity, neurotoxicity, chronic toxicity, carcinogenicity, reproductive or developmental toxicity of D-glucurono-γ-lactone from animal studies.

EFSA (2009) defined a NOAEL of 1000 mg/kg bw per day for daily oral administration of D-glucurono-γ-lactone to rats, which was the highest dose tested. The NOAEL was based on a 13-week rat study of daily oral administration of D-glucurono-γ-lactone performed under good laboratory practice (GLP).

In the present opinion, the value used for comparison with the estimated exposure in the risk characterization is the NOAEL of 1000 mg D-glucurono-γ-lactone/kg bw per day (EFSA, 2009).

3 Exposure/Intake

Exposure to D-glucurono-γ-lactone from the intake of energy drinks was estimated for children (3 years and above), adolescents and adults.

3.1 Energy drinks

NFSA requested VKM to perform a risk assessment of 24 mg/100 ml of D-glucurono-γ-lactone for the age groups children (3 to <10 and 10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years). The default body weights (bw) for these groups as 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 intakes of energy drinks for the various age groups in the three intake scenarios are shown.

High acute consumption

For children (3 to <10 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 (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 concentrated product 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 aged 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 age group, the ratio for the intake of energy drinks per day and kg bw was calculated for the age group 10 to <14 years using the intake reported by DTU and the default bw set by EFSA (EFSA, 2012). 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 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	211
Adults (≥18 years)	2000	71	320

The intake estimates of D-glucurono-γ-lactone for the different age groups are shown in Table 3.1-2.

For 3 to <10 year old children, the intake of D-glucurono-γ-lactone has been estimated to be 10.4 mg/kg bw per day for high acute consumption of energy drinks, 0.6 mg/kg bw per day for mean chronic consumption, and 1.7 mg/kg bw per day for high chronic consumption.

For 10 to <14 year old children, the intake of D-glucurono-γ-lactone has been estimated to be 8.3 mg/kg bw per day for high acute consumption of energy drinks, 0.4 mg/kg bw per day for mean chronic consumption, and 1.0 mg/kg bw per day for high chronic consumption.

For 14 to <18 year old adolescents, the intake of D-glucurono-γ-lactone has been estimated to be 7.8 mg/kg bw per day for high acute consumption of energy drinks, 0.3 mg/kg bw per day for mean chronic consumption, and 0.8 mg/kg bw per day for high chronic consumption.

For adults (≥18 years), the intake of D-glucurono-γ-lactone has been estimated to be 6.9 mg/kg bw per day for high acute consumption of energy drinks, 0.2 mg/kg bw per day for mean chronic consumption, and 1.1 mg/kg bw per day for high chronic consumption.

Table 3.1-2 Estimated exposure to D-glucurono-γ-lactone from energy drinks for the various age groups in the three scenarios.

Age groups	Intake scenarios	Estimated exposure (mg/kg bw per day)
Children (3 to <10 years)	High acute	10.4
	Mean chronic	0.6
	High chronic	1.7
Children (10 to <14 years)	High acute	8.3
	Mean chronic	0.4
	High chronic	1.0
Adolescents (14 to <18 years)	High acute	7.8
	Mean chronic	0.3
	High chronic	0.8
Adults (≥18 years)	High acute	6.9
	Mean chronic	0.2
	High chronic	1.1

3.2 Other sources

D-glucurono-γ-lactone and its hydrolysis product glucuronic acid occur naturally in several dietary sources. The estimated exposure to D-glucurono-γ-lactone from naturally occurring sources in the diet was 1-2 mg/day (SCF, 2003).

In the EU, D-glucurono-γ-lactone can be used in cosmetic products (CosIng, 2015).

Summary of exposure / intake

NFSA requested VKM to perform a risk assessment of the following concentration: 24 mg/100 ml of D-glucurono-γ-lactone for the age groups children (3 to <10 and 10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years). The intake levels of D-glucurono-γ-lactone have been estimated for three intake scenarios: high acute consumption, mean chronic and high chronic consumption.

The highest intake of D-glucurono-γ-lactone was found for the age group 3 to <10 year old children with high acute, mean chronic and high chronic exposure of 10.4, 0.6 and 1.7 mg/kg bw per day, respectively. For the other age groups, the exposure to D-glucurono-γ-lactone ranged from 6.9 to 8.3 mg/kg bw per day for high acute exposure, from 0.2 to 0.4 mg/kg bw per day for mean chronic exposure and from 0.8 to 1.1 mg/kg bw per day for high chronic exposure.

4 Risk characterisation

4.1 Energy drinks

NFSA requested VKM to perform a risk assessment of 24 mg/100 ml of D-glucurono-γ-lactone in energy drinks for the general population, ages 3 years and above, and for drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake.

Due to lack of an acute reference dose or other data on acute toxicity for D-glucurono-γ-lactone, it is not possible to characterise the risk related a high acute drinking pattern for any of the age groups.

No human toxicity data on D-glucurono-γ-lactone was available in the included literature The risk characterization is based on the Margin of Exposure (MOE) approach; the ratio of the NOAEL to the exposure. An acceptable MOE value for a NOAEL-based assessment of D-glucurono-γ-lactone is ≥100, which includes a factor 10 for extrapolation from animals to humans, and a factor 10 for interindividual human variation (EPA, 2012). A MOE below 100 may also be acceptable, however, such assessment must be based on supporting scientific literature and expert judgement.

MOE is calculated from the NOAEL of 1000 mg/kg bw per day from the subchronic rat study (EFSA, 2009).

The estimated margin of exposure values after intake of D-glucurono-γ-lactone from energy drinks for the various age groups are presented in Table 4.1-1.

With regard to the mean chronic drinking pattern, the MOE values are 1667 for the age group 3 to <10 years, 2500 for the age group 10 to <14 years, 3333 for the age group 14 to <18, and 5000 for adults ≥18 years. VKM, therefore, considers a daily mean chronic intake of 24 mg/100 ml of D-glucurono-γ-lactone for all age groups to be without appreciable health risk.

With regard to the high chronic drinking pattern, the MOE values are 588 for the age group 3 to <10 years, 1000 for the age group 10 to <14 years, 1250 for the age group 14 to <18, and 909 for adults ≥18 years. VKM, therefore, considers a daily high chronic intake of 24 mg/100 ml of D-glucurono-γ-lactone for all age groups to be without appreciable health risk.

Table 4.1-1 The calculated margins between the NOAEL and the exposure to D-glucurono-γ-lactone from energy drinks containing 24 mg D-glucurono-γ-lactone per 100 ml for children, adolescents and adults for two drinking patterns.

Age groups	Exposure scenarios	Margin of exposure (MOE)
Children (3	Mean chronic	1667

Age groups	Exposure scenarios	Margin of exposure (MOE)
to <10 years)	High chronic	588
Children (10 to <14 years)	Mean chronic	2500
	High chronic	1000
Adolescents (14 to <18 years)	Mean chronic	3333
	High chronic	1250
Adults (≥18 years)	Mean chronic	5000
	High chronic	909

4.1.1 Summary of the risk characterisation - energy drinks

Mean chronic drinking pattern, all age groups

In all age groups, the estimated MOE values are above 100. Thus, it is unlikely that the mean chronic intake of D-glucurono-γ-lactone causes adverse health effects to children (3 years and above), adolescents and adults.

High chronic drinking pattern, all age groups

In all age groups, the estimated MOE values are above 100. Thus, it is unlikely that the high chronic intake of D-glucurono-γ-lactone causes adverse health effects to children (3 years and above), adolescents and adults.

5 Uncertainties

5.1 Hazard identification and characterization

The NOAEL value was derived from a subchronic rat study.

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, an average 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 characterization

The NOAEL of 1000 mg/kg bw per day set by EFSA is based on the highest dose tested in the 13-week rat study. Therefore, there is a possibility that the actual NOAEL is higher than 1000 mg/kg bw per day, and a risk evaluation based on MOE estimated from the NOAEL set by EFSA may be too conservative. On the other hand, since the duration of the rat study was 13 weeks (subchronic exposure) and not life-long (chronic exposure), there is som uncertainty related to safety of longer duration of exposure to D-glucurono-γ-lactone.

6 Conclusions with answers to the terms of reference

The present risk assessment includes 24 mg D-glucurono-γ-lactone/100 ml energy drink for the general population, ages 3 years and above for drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake. It is based on previous risk assessments of D-glucurono-γ-lactone (see 2.1). A no observed adverse effect level (NOAEL) derived from a 13-week rat study was used for the risk characterisation. Only animal data was available for use in the risk characterisation.

Due to lack of an acute reference dose or other data on acute toxicity for D-glucurono-γ-lactone, it is not possible to characterise the risk related a high acute drinking pattern for any of the age groups. With regard to the mean chronic drinking pattern, the margin of exposure (MOE) values are 1667 for the age group 3 to <10 years, 2500 for the age group 10 to <14 years, 3333 for the age group 14 to <18 and 5000 for adults above 18 years.

With regard to the high chronic drinking pattern, the MOE values are 588 for the age group 3 to <10 years, 1000 for the age group 10 to <14 years, 1250 for the age group 14 to <18 and 909 for adults ≥18 years.

With regard to mean and high chronic intake of 24 mg D-glucurono-γ-lactone per 100 ml, VKM concludes that:

- it is unlikely that the mean chronic intake of D-glucurono-γ-lactone causes adverse health effects in children (3 years and above), adolescents and adults.
- it is unlikely that the high chronic intake of D-glucurono-γ-lactone causes adverse health effects in children (3 years and above), adolescents and adults.

An overview of the conclusions on the energy drinks is given 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 energy drinks containing 24 mg/100 ml D-glucurono-γ-lactone. Green: estimated exposure is unlikely to cause adverse health effects.

D-Glucurono-γ-lactone			
Energy drinks 24 mg/ 100 ml / **Age groups**	**High acute drinking pattern**	**Mean chronic drinking pattern**	**High chronic drinking pattern**
Children (3 to <10 years)	Not possible to conclude due to lack of data		
Children (10 to <14 years)	Not possible to conclude due to lack of data		
Adolescents (14 to <18 years)	Not possible to conclude due to lack of data		
Adults (≥18 years)	Not possible to conclude due to lack of data		

7 Data gaps

- There is lack of an acute reference dose or other data on acute toxicity for D-glucurono-γ-lactone.
- Human studies on D-glucurono-γ-lactone are lacking for all age groups.
- Adequate studies on chronic toxicity, carcinogenicity, reproduction, development or genotoxicity are lacking.

8 References

AFFSA. (2006) Opinion La Directrice Generale of the French Food Safety Agency 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, The French Food Safety Agency, https://www.anses.fr/en/system/files/NUT2006sa0236EN.pdf.

ANSES. (2013) Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of risks concerning the consumption of so-called "energy drinks", ANSES, French Agency for Food, Environmental and Occupational Health & Safety, France, https://www.anses.fr/en/system/files/NUT2012sa0212EN.pdf.

Christensen LM, Iversen JD, Biltoft-Jensen A, Petersen MA, Søndergaard AB, J M. (2014) Consumption of energy drinks among 10-35-y-old Danes (in Danish with an English summary), National Food Institute, Technical University of Denmark, http://www.food.dtu.dk/english/News/2014/12/Many-children-and-adolescents-get-too-much-caffeine-from-energy-drinks.

CosIng. (2015) Cosmetic ingredient database – CosIng, European Commission http://ec.europa.eu/growth/tools-databases/cosing/.

EFSA. (2009) The use of taurine and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food, EFSA Journal, European Food Safety Authority, http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/ans_ej935_Taurine%20and%20D-glucuronolactone_op_en%2C3.pdf. pp. 1-31.

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.

EPA. (2012) Quantitative Risk Assessment Calculations, Sustainable Futures / P2 Framework Manual 2012 EPA-748-B12-001, Environmental Protection Agency, http://www.epa.gov/oppt/sf/pubs/iad_discretes_doc_june2012.pdf.

FVM. (2014) Bekentgørelse 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. pp. 15.

Johansen A.M.W., Andersen L.F. (2013) Rapport for Ungkost-3. Pilotstudien 2013. Gjennomførbarhet og deltakelse ved bruk av en nyutviklet og internettbasert matdagbok blant 9- og 13-åringer, Universitetet i Oslo, Helsedirektoratet, Mattilsynet.

SCF. (1999) Opinion on Caffeine, Taurine and D-Glucurono -gamma-Lactone as constituents of so-called "energy" drinks SCF, Scientific Committee on Food, Health & Consumer Protection Directorate-General, European Commission, http://ec.europa.eu/food/fs/sc/scf/out22_en.html.

SCF. (2003) Opinion of the Scientific Committee on Food on Additional information on "energy" drinks, SCF, Scientific Committee on Food, Health & Consumer Protection Directorate-General, European Commission, http://ec.europa.eu/food/fs/sc/scf/out169_en.pdf.

Storvik A.G. (2014) Mener energidrikk ga nyresvikt hos barn, Dagens Medisin, http://www.dagensmedisin.no/artikler/2014/03/19/mener-energidrikk-ga-nyresvikt-hos-barn/?x=MjAxNS0xMC0zMSAxNjoxMDoxOQ==.

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.

Totland T.H., Melnæs B.K., Lundberg-Hallén N., Helland-Kigen K.M., Lund-Blix N.A., Myhre J.B., Johansen A.M.W., Løken E.B., Andersen L.F. (2012) Norkost 3 En landsomfattende kostholdsundersøkelse blant menn og kvinner i Norge i alderen 18-70 år, 2010-11, Universitetet i Oslo, Mattilsynet og Helsedirektoratet, https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/301/Norkost-3-en-landsomfattende-kostholdsundersokelse-blant-menn-og-kvinner-i-norge-i-alderen-18-70-ar-2010-11-IS-2000.pdf.

VKM. (2005) Risikovurdering av "energidrikker" med koffein, taurin, glukuronolakton, inositol og vitaminer (in Norwegian), VKM, the Norwegian Scientific Committee for Food Safety, Norway, http://www.vkm.no/dav/59955595ba.pdf.

VKM. (2009) New information on ingredients in so-called "energy drinks", 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, VKM, the Norwegian Scientific Committee for Food Safety, Norway, http://www.vkm.no/dav/a8859a2195.pdf.

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.

9 Appendix

Search Strategy

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

Search Strategy:

---

1. glucuronolactone*.ti. (150)
2. (conference abstract* or letter* or editorial*).pt. (4457566)
3. 1 not 2 (148)
4. limit 3 to (danish or english or norwegian or swedish) (106)
5. remove duplicates from 4 (62)
6. limit 5 to yr="2009 -Current" (8)