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Risk assessment of "other substances" – Taurine

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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Risk assessment of "other substances" – Taurine

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Assessed and approved

The opinion has been assessed and approved by Panel on Food Additives, Flavourings, Processing Aids, Material 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 in food supplements and concentrations in energy drinks 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 taurine, and it is based on previous risk assessments and articles retrieved from a literature search.

According to information from NFSA, taurine is an ingredient in food supplements and energy drinks sold in Norway. NFSA has requested a risk assessment of 750, 800, 900, 1000 and 2000 mg/day of taurine in food supplements, and of 300, 350 and 400 mg/100 ml of taurine in energy drinks. Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake were assessed. For food supplements, the intake of taurine was estimated for the age groups children (10 to <14 years), adolescents (14 to <18 years) and adults (>18 years), whereas for energy drinks the age group children (3 to <10 years) was also included.

Other sources of taurine, such as foods and cosmetics, have not been included in the present risk assessment.

Taurine (CAS No. 107-35-7) is synthesised endogenously (average 50-125 mg per day), and participates in the formation of bile salts and is involved in a number of crucial physiological processes, including modulation of calcium flux and neuronal excitability, osmoregulation and membrane stabilisation. Taurine occurs naturally in food, especially in meat and seafood. The mean daily intake of taurine from the diet has been estimated to vary between 40 and 400 mg/day.

There are indications that taurine may have cardiovascular and neurological effects in humans. However, based on the human studies, an intake of approximately 21 mg/kg bw per day is considered unlikely to cause adverse health effects.

Based on a 13-week neurotoxicity study in rats, a no observed adverse effect level (NOAEL) of 1000 mg/kg bw per day for pathological changes was set in 2009 by the European Food

Safety Authority (EFSA). In the present risk assessment, VKM has used this NOAEL of 1000 mg/kg bw per day from rats.

The human studies available were not of sufficient quality (due to low number of participants, non-healthy populations, short duration) to be used as the sole basis for the risk characterisation. 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 taurine based on an animal study is ≥100, which includes a factor 10 for extrapolation from animals to humans and a factor 10 for interindividual human variation. However, since the NOAEL set by EFSA was based on the highest tested dose and there is a possibility that the actual NOAEL is higher than 1000 mg/kg bw per day, the intake that was considered unlikely to cause adverse health effects based on human studies (21 mg/kg bw per day) was also taken into consideration in the risk characterisation.

Food supplements

For children (10 to <14 years), the estimated daily intakes of taurine were 17.3, 18.4, 20.7, 23.0 and 46.1 mg/kg bw per day from daily doses of 750, 800, 900, 1000 and 2000 mg taurine, respectively, from food supplements. The margin of exposure (MOE) values was in the range of 22-58 for the various taurine doses, i.e. all below 100. However, from a daily intake of 750, 800 or 900 mg taurine from food supplements, the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore concludes that it is unlikely that a daily intake of 750, 800 or 900 mg taurine from food supplements causes adverse health effects in children (10 to <14 years). The estimated exposure from a daily intake of 1000 or 2000 mg taurine was above 21 mg/kg bw per day. Thus, VKM concludes that a daily intake of 1000 or 2000 mg taurine from food supplements may represent a health risk in children (10 to <14 years).

For adolescents (14 to <18 years), the estimated daily intakes were 12.2, 13.1, 14.7, 16.3 and 32.6 mg/kg bw per day from daily doses of 750, 800, 900, 1000 and 2000 mg taurine, respectively, from food supplements. For adults (≥18 years), the estimated intakes were 10.7, 11.4, 12.9, 14.3 and 28.6 mg/kg bw per day from a daily intake of 750, 800, 900, 1000 and 2000 mg taurine, respectively, from food supplements.

For adolescents (14 to <18 years) and adults (≥18 years), the MOE values were in the range of 31-82 and 35-93, respectively, i.e. all below 100. However, from a daily intake of 750, 800, 900 or 1000 mg taurine from food supplements the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for both age groups. Thus, VKM concludes that it is unlikely that a daily intake of 750, 800, 900 or 1000 mg of taurine causes adverse health effects in adolescents (14 to <18 years) and adults (≥18 years).

For adolescents (14 to <18 years) and adults (≥18 years) the estimated MOE values were 31 and 35, respectively, i.e. below 100, after a daily intake of 2000 mg taurine from food supplements. In addition, the estimated intakes were above the intake level of 21 mg/kg bw

per day (the intake considered unlikely to cause adverse health effects based on human studies) for both age groups. Thus, VKM concludes that a daily intake of 2000 mg of taurine may represent a risk of adverse health effects in adolescents (14 to <18 years) and adults (≥18 years).

Energy drinks

High acute drinking pattern, all age groups

For the high acute drinking pattern, the estimated consumption of energy drinks was 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 concentrations of 300, 350 and 400 mg taurine/100 ml energy drink, the intake levels of taurine after a high acute consumption of energy drinks (in mg/kg bw per day) were 130, 152 and 173; 104, 121 and 138; 97.9, 114 and 131; and 85.7, 100 and 114, for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

Due to lack of an acute reference dose or other data for acute toxicity of taurine, it was not possible to characterise the risk related to an acute intake of taurine for any of the age groups.

Mean chronic drinking pattern, all age groups

For the mean chronic drinking pattern, the estimated consumption of energy drinks was 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 concentrations of 300, 350 and 400 mg taurine/100 ml energy drink, the intake levels of taurine after a mean chronic drinking pattern (in mg/kg bw per day) were 7.5, 8.8 and 10.0; 4.5, 5.2 and 6.0; 3.1, 3.7 and 4.2; and 3.0, 3.6 and 4.1, for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

In all age groups, the estimated MOE values were 100-333, i.e. 100 or above, for all three taurine concentrations. In addition, the estimated intakes were all below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all age groups. Thus, VKM concludes that it is unlikely that the mean chronic intake of all three concentrations of taurine causes adverse health effects in children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

High chronic drinking pattern, all age groups

For the high chronic drinking pattern, the estimated consumption of energy drinks was 163, 180, 211 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. For the concentrations of 300, 350 and 400 mg taurine/100 ml energy drink, the intake levels of taurine after a high chronic drinking pattern (in mg/kg bw per day) were 21.2, 24.7 and 28.2; 12.4, 14.5 and 16.6; 10.3, 12.0 and 13.8; and 13.7, 16.0 and 18.3 mg/kg bw per day for children (3 to <10

years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

For children (3 to <10 years), the estimated MOE values were 47, 40 and 35, for the three taurine concentrations of 300, 350 and 400 mg/ml, respectively, i.e. all below 100. In addition, the estimated intakes were all above 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all three taurine concentrations. Thus, VKM concludes that a high chronic intake of all three concentrations of taurine from energy drinks may represent a health risk in children (3 to <10 years).

For children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), the estimated MOE values were in the range of 55-97, i.e. all below 100 for all three taurine concentrations. However, the estimated intakes were all below the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all three taurine concentrations in all age groups. Thus, VKM concludes that it is unlikely that a high chronic intake of any of the three concentrations of taurine from energy drinks causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Short 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 taurine in food supplements and energy drinks. Taurine is synthesised endogenously in the body and occurs naturally in foods. In this risk assessment, both data from human and animal studies were used.

Food supplements

For children (10 to <14 years), the margin of exposure (MOE) values were in the range of 22-58 for the various taurine doses, i.e. all below 100. However, from a daily intake of 750, 800 or 900 mg taurine from food supplements, the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore concludes that it is unlikely that a daily intake of 750, 800 or 900 mg taurine from food supplements causes adverse health effects in children (10 to <14 years). The estimated exposure from a daily intake of 1000 or 2000 mg taurine was above 21 mg/kg bw per day. Thus, VKM concludes that a daily intake of 1000 or 2000 mg taurine from food supplements may represent a health risk in children (10 to <14 years).

For adolescents (14 to <18 years) and adults (≥18 years), the MOE values were in the range of 31-82 and 35-93, respectively, i.e. all below 100. However, from a daily intake of 750, 800, 900 or 1000 mg taurine from food supplements the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for both age groups. Thus, VKM concludes that it is unlikely that a daily

intake of 750, 800, 900 or 1000 mg of taurine causes adverse health effects in adolescents (14 to <18 years) and adults (≥18 years).

For adolescents (14 to <18 years) and adults (≥18 years) the estimated MOE values were 31 and 35, respectively, i.e. below 100, after a daily intake of 2000 mg taurine from food supplements. In addition, the estimated intakes were above the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for both age groups. Thus, VKM concludes that a daily intake of 2000 mg of taurine may represent a risk of adverse health effects in adolescents (14 to <18 years) and adults (≥18 years).

Energy drinks

High acute drinking pattern, all age groups

Due to lack of an acute reference dose or other data for acute toxicity of taurine, it was not possible to characterise the risk related to an acute intake of taurine for any of the age groups.

Mean chronic drinking pattern, all age groups

In all age groups, the estimated MOE values were 100-333, i.e. 100 or above, for all three taurine concentrations. In addition, the estimated intakes were all below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all age groups. Thus, VKM concludes that it is unlikely that the mean chronic intake of all three concentrations of taurine causes adverse health effects in children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

High chronic drinking pattern, all age groups

For children (3 to <10 years), the estimated MOE values were 47, 40 and 35, for the three taurine concentrations of 300, 350 and 400 mg/ml, respectively, i.e. all below 100. In addition, the estimated intakes were all above 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all three taurine concentrations. Thus, VKM concludes that a high chronic intake of all three concentrations of taurine from energy drinks may represent a health risk drinks in children (3 to <10 years).

For children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), the estimated MOE values were in the range of 55-97, i.e. all below 100 for all three taurine concentrations. However, the estimated intakes were all below the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all three taurine concentrations in all age groups. Thus, VKM concludes that it is unlikely that a high chronic intake of all three concentrations of taurine from energy drinks causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Key words: Adverse health effects, energy drink, food supplement, negative health effects, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, taurine, 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 doser brukt av kosttilskudd og konsentrasjoner i energidrikker 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 påståtte gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

Denne rapporten er en risikovurdering av taurin, og den er basert på tidligere risikovurderinger og artikler hentet fra et litteratursøk.

I følge informasjon fra Mattilsynet er taurin en ingrediens i kosttilskudd og energidrikker som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere inntak på 750, 800, 900, 1000 og 2000 mg/dag av taurin i kosttilskudd, og konsentrasjonene 300, 350 og 400 mg/100 ml i energidrikker. Drikkemønstre som reflekterer et høyt akutt inntak, et gjennomsnittlig kronisk inntak og et høyt kronisk inntak ble vurdert. For kosttilskudd ble inntak av taurin beregnet for aldersgruppene barn (10 til <14 år), ungdom (14 til <18 år) og voksne (>18 år), mens for energidrikker ble også aldersgruppen barn (3-10 år) inkludert.

Andre kilder til taurin, som mat og kosmetikk, er ikke inkludert i denne risikovurderingen.

Taurin (CAS nr. 107-35-7) syntetiseres endogent (gjennomsnittlig 50-125 mg per dag) og er med i dannelsen av gallesalter og en rekke andre nødvendige prosesser i kroppen, inkludert modulering av kalsiumstrømninger og nevronal eksitabilitet, osmoregulering og stabilisering av membraner. Taurin finnes naturlig i mat, spesielt i kjøtt og sjømat. Gjennomsnittlig daglig inntak av taurin fra kosten er estimert til å være mellom 40 og 400 mg/dag.

Det er indikasjoner på at taurin kan ha negative effekter på hjertet og nervesystemet hos mennesker. Basert på de humane studiene er det usannsynlig at et inntak på ca. 21 mg/kg kroppsvekt per dag for perioder opp til 5 måneder forårsaker negative helseeffekter.

Basert på en 13-ukers studie av nevrotoksisitet på rotter ble en NOAEL-verdi (null-effektsnivå) på 1000 mg/kg kroppsvekt per dag for patologiske forandringer satt i 2009 av den europeiske myndighet for næringsmiddeltrygghet (European Food Safety Authority - EFSA). I denne risikovurdering har VKM brukt denne NOAEL-verdien på 1000 mg/kg kroppsvekt per dag fra rotter.

De humane studiene som var tilgjengelige var imidlertid ikke av tilstrekkelig god kvalitet (få deltagere, ikke friske personer, kort varighet) til å brukes alene i risikovurderingen. Risikokarakteriseringen 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 av taurin 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. I og med at NOAEL satt av EFSA er basert på den høyeste testede dosen, er det mulig at den faktiske NOAEL-verdien er høyere enn 1000 kg/kg kroppsvekt per dag. Derfor er også den humane inntaksverdien på 21 mg/kg kroppsvekt per dag, som er et inntak som det er usannsynlig at forårsaker negative helseeffekter for perioder opp til 5 måneder, brukt i risikokarakteriseringen.

Kosttilskudd

For barn (10 til <14 år) var det estimerte daglige inntaket av taurin 17,3, 18,4, 20,7, 23,0 og 46,1 mg /kg kroppsvekt per dag etter daglige doser på henholdsvis 750, 800, 900, 1000 og 2000 mg taurin fra kosttilskudd.

For barn (10 til <14 år) var alle MOE-verdiene i området 22-58 for de ulike taurin-dosene, dvs. under 100. Men etter et daglig inntak av 750, 800 eller 900 mg taurin fra kosttilskudd var det estimerte inntaket av taurin under 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier). VKM konkluderer derfor med at det er usannsynlig at et daglig inntak av 750, 800 eller 900 mg taurin fra kosttilskudd vil representere en risiko for negative helseeffekter hos barn (10 til <14 år) for perioder opp til 5 måneder. Etter et daglig inntak av 1000 eller 2000 mg taurin fra kosttilskudd, var det estimerte inntaket av taurin over 21 mg/kg kroppsvekt per dag. VKM konkluderer derfor at et daglig inntak av 1000 eller 2000 mg taurin fra kosttilskudd vil kunne representere en risiko for negative helseeffekter for barn (10 til <14 år).

For ungdom (14 til <18 år) var det estimerte daglige inntaket av taurin 12,2, 13,1, 14,7, 16,3 og 32,6 mg/kg kroppsvekt per dag etter daglige doser på henholdsvis 750, 800, 900, 1000 og 2000 mg taurin fra kosttilskudd. For voksne (≥18 år) var det estimerte daglige inntaket av taurin 10,7, 11,4, 12,9, 14,3 og 28,6 mg/kg kroppsvekt per dag etter daglige doser på henholdsvis 750, 800, 900, 1000 og 2000 mg taurin fra kosttilskudd.

For ungdom (14 til <18 år) og voksne (≥18 år) var alle MOE-verdiene henholdsvis i området 31-82 and 35-93, dvs. alle er under 100. Men etter et daglig inntak av 750, 800, 900 eller 1000 mg taurin fra kosttilskudd, var det estimerte inntaket av taurin under 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier) for begge aldersgrupper. VKM konkluderer derfor med at det er usannsynlig at et daglig inntak av 750, 800, 900 eller 1000 mg taurin fra kosttilskudd vil representere en risiko for negative helseeffekter for ungdom (14 til <18 år) og voksne (>18 år).

For ungdom (14 til <18 år) og voksne (≥18 år) var MOE-verdiene henholdsvis 31 og 35, dvs. under 100, etter et daglig inntak av 2000 mg taurin fra kosttilskudd. I tillegg var eksponeringen over 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier) for begge aldersgrupper. VKM konkluderer derfor at et daglig inntak av 2000 mg taurin fra kosttilskudd vil kunne representere en risiko for negative helseeffekter for ungdom (14 til <18 år) og voksne (≥18 år).

Energidrikk

Høyt akutt drikkemønster, alle aldersgrupper

For det høye akutte drikkemønsteret var det estimerte forbruket av energidrikker 1000, 1500, 2000 og 2000 ml/day for henholdsvis barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år). For konsentrasjonene 300, 350 og 400 mg taurin/100 ml energidrikker var det estimerte inntaket av taurin (i mg/kg kroppsvekt per dag) etter det høye akutte drikkemønsteret 130, 152 og 173; 104, 121 og 138; 97,9, 114 og 131; og 85,7, 100 og 114, for henholdsvis barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

På grunn av mangel på en akutt referansedose eller andre data på akutt toksisitet for taurin, var det ikke mulig å karakterisere risikoen knyttet til et høyt akutt inntak for noen av aldersgruppene.

Gjennomsnittlig kronisk drikkemønster, alle aldersgrupper

For det gjennomsnittlige kroniske drikkemønsteret var det estimerte forbruket av energidrikker 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 konsentrasjonene 300, 350 og 400 mg taurin/100 ml energidrikker var det estimerte inntaket av taurin (i mg/kg kroppsvekt per dag) etter det gjennomsnittlige kroniske drikkemønsteret 7,5, 8,8 og 10,0; 4,5, 5,2 og 6,0; 3,1, 3,7 og 4,2; og 3,0, 3,6 og 4,1 0, 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 alle MOE-verdiene i størrelsesorden 100-333 for alle aldersgruppene. Siden MOE verdiene var 100 eller høyere for alle aldersgrupper, og alle estimerte inntak er under 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier), konkluderer VKM at det er usannsynlig at det gjennomsnittlige kroniske inntaket av taurin i alle tre konsentrasjoner i energidrikker fører til negative helseeffekter hos barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Høyt kronisk drikkemønster, alle aldersgrupper

For det høye kroniske drikkemønsteret var det estimerte forbruket av energidrikker 163, 180, 211 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). For konsentrasjonene 300, 350 og 400 mg taurin/100 ml energidrikker var det estimerte inntaket av taurin (i mg/kg kroppsvekt per dag) etter det høye kroniske drikkemønsteret 21,2, 24,7 og 28,2; 12,4, 14,5 og 16,6; 10,3, 12,0 og 13,8; og 13,7, 16,0 og 18,3, for henholdsvis barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

For barn (3 til <10 år) var de estimerte MOE-verdiene henholdsvis 47, 40 og 35 for de tre taurin-konsentrasjonene på 300, 350 og 400 mg/ml, dvs. alle var under 100. I tillegg var de

estimerte inntakene over 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier) for alle tre taurin-konsentrasjoner. VKM konkluderer derfor at det høye kroniske inntaket av taurin i alle tre konsentrasjoner i energidrikker vil kunne representere en risiko for negative helseeffekter for barn (3 til <10 år).

For barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år) var de estimerte MOE-verdiene i området 55-97, dvs. alle var under 100, for alle tre taurin-konsentrasjonene i energidrikker. Men de estimerte inntakene var alle under 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier) for alle taurin-konsentrasjonene i alle aldersgruppene. VKM konkluderer at det derfor er usannsynlig at det høye kroniske inntaket av taurin i alle tre konsentrasjoner i energidrikker fører til negative helseeffekter hos barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Kort sammendrag

På oppdrag fra Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert helserisiko ved inntak av taurin fra kosttilskudd og energidrikker. Taurin blir syntetisert endogent i kroppen og finnes naturlig i mat. I denne risikovurderingen er det brukt både data fra humane studier og fra dyrestudier.

Kosttilskudd

For barn (10 til <14 år) var alle MOE-verdiene i området 22-58 for de ulike taurin-dosene, dvs. under 100. Men etter et daglig inntak av 750, 800 eller 900 mg taurin fra kosttilskudd var eksponeringen under 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier). VKM konkluderer derfor at det er usannsynlig at et daglig inntak av 750, 800 eller 900 mg taurin fra kosttilskudd vil representere en risiko for negative helseeffekter for barn (10 til <14 år) for perioder opp til 5 måneder. Etter et daglig inntak av 1000 eller 2000 mg taurin fra kosttilskudd, var eksponeringen for taurin over 21 mg/kg kroppsvekt per dag. VKM konkluderer derfor at et daglig inntak av 1000 eller 2000 mg taurin fra kosttilskudd vil kunne representere en risiko for negative helseeffekter for barn (10 til <14 år).

For ungdom (14 til <18 år) og voksne (>18 år) var alle MOE-verdiene henholdsvis i området 31-82 and 35-93, dvs. alle under 100. Men etter et daglig inntak av 750, 800, 900 eller 1000 mg taurin fra kosttilskudd, var eksponeringen under 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier) for begge aldersgrupper. VKM konkluderer derfor at det er usannsynlig at et daglig inntak av 750, 800, 900 eller 1000 mg taurin fra kosttilskudd vil representere en risiko for negative helseeffekter for ungdom (14 til <18 år) og voksne (≥18 år).

For ungdom (14 til <18 år) og voksne (≥18 år) var MOE-verdiene henholdsvis 31 og 35, dvs. under 100, etter et daglig inntak av 2000 mg taurin fra kosttilskudd. I tillegg var eksponeringen over 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier) for begge aldersgrupper. VKM konkluderer derfor at

et daglig inntak av 2000 mg taurin fra kosttilskudd vil kunne representere en risiko for negative helseeffekter for ungdom (14 til <18 år) og voksne (≥18 år).

Energidrikk

Høyt akutt drikkemønster, alle aldersgrupper

På grunn av mangel på en akutt referansedose eller andre data på akutt toksisitet for taurin, var det ikke mulig å karakterisere risikoen knyttet til et høyt akutt inntak for noen av aldersgruppene.

Gjennomsnittlig kronisk drikkemønster, alle aldersgrupper

For det gjennomsnittlige kroniske drikkemønsteret er alle MOE-verdiene i størrelsesorden 100-333 for alle aldersgruppene. Siden MOE verdiene er 100 eller høyere for alle aldersgrupper, og alle estimerte inntak er under 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier), konkluderer VKM at det er usannsynlig at det gjennomsnittlige kroniske inntaket av taurin i alle tre konsentrasjoner i energidrikker fører til negative helseeffekter hos barn (3 til <10 år), barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Høyt kronisk drikkemønster, alle aldersgrupper

For barn (3 til <10 år) var de estimerte MOE-verdiene henholdsvis 47, 40 og 35 for de tre taurin-konsentrasjonene på 300, 350 og 400 mg/ml, dvs. alle var under 100. I tillegg var alle de estimerte inntakene over 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier). VKM konkluderer derfor at det høye kroniske inntaket av taurin i alle tre konsentrasjoner i energidrikker vil kunne representere en risiko for negative helseeffekter for barn (3 til <10 år).

For barn (10 til <14 år), ungdom (14 til <18 år) og voksne (>18 år) var de estimerte MOE-verdiene i området 55-97, dvs. alle var under 100, for alle tre taurin-konsentrasjonene i energidrikker. Men de estimerte inntakene var alle under 21 mg/kg kroppsvekt per dag (det inntaket som ikke antas å gi negative helseeffekter basert på humane studier) for alle taurin-konsentrasjonene i alle aldersgruppene. VKM konkluderer derfor at det er usannsynlig at det høye kroniske inntaket av taurin i alle tre konsentrasjoner i energidrikker fører til negative helseeffekter hos barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Abbreviations and/or glossary

Abbreviations

ADME	- absorption, distribution, metabolism, excretion
AESAN	- Spanish Agency for Food Safety and Nutrition
AFSSA	- French Food Safety Agency
ANSES	- French Agency for Food, Environmental and Occupational Health and Safety
EFSA	- European Food Safety Authority
FDA	- Food and Drug Administration
GLP	- Good Laboratory Practice
MOE	- Margin of exposure
NFSA	- Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NOAEL	- no observed adverse effect level
OECD	- Organisation for Economic Co-operation and Development
SCF	- Scientific Committee on Food
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. VKM uses the definition established by EFSA for "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (WHO, 1994).

Background as provided by the Norwegian Food Safety Authority/ Norwegian Environment Agency

«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 taurine in food supplements at the following doses: 750, 800, 900, 1000 and 2000 mg taurine/day, and in energy drinks at the following concentrations: 300, 350 and 400 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 food supplements shall be carried out for a general population, ages 10 years and above. 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 taurine *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), taurine is an ingredient in food supplements and energy drinks purchased in Norway. NFSA has requested a risk assessment of the intake of 750, 800, 900, 1000 and 2000 mg taurine/day from food supplements, and a risk assessment of high acute, mean chronic and high chronic intake of energy drinks containing 300, 350 and 400 mg taurine/100 ml. The total exposure to taurine from other sources than food supplements and energy drinks, such as foods and cosmetic products, is not included in the risk assessment.

Taurine (CAS No. 107-35-7) occurs naturally in food, especially in seafood and meat, and it is a normal metabolite in humans. In humans, taurine is synthesised in many tissues, but the main sites are the liver (SCF 1999). Cysteine and methionine are precursors of taurine (EFSA, 2012). Taurine participates in the formation of bile salts, and is involved in a number of crucial physiological processes including modulation of calcium flux and neuronal excitability, osmoregulation and membrane stabilisation (SCF, 1999).

In adults, the average daily synthesis is in the range of 0.4-1.0 mmol (50-125 mg). However, under stress the synthesis may be impaired (reviewed in Lourenco and Camilo (2002)). The mean daily intake of taurine from the diet has been estimated to vary between 40 and 400 mg/day ((Hayes and Trautwein, 1994) cited in SCF (1999)). In this risk assessment, the intake of 750, 800, 900, 1000 and 2000 mg/day taurine from food supplements, and the concentrations of 300, 350 and 400 mg/100 ml taurine in energy drinks, have been assessed.

2 Hazard identification and characterisation

2.1 Literature

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

2.1.1 Previous risk assessments/evaluations of taurine

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) concluded that the available data on taurine were insufficient to establish a safe upper level for daily intake of taurine. In 2003, data from a new 13-week study of taurine in rats were evaluated. In this study, 0, 300, 600 and 1000 mg/kg bw per day were administered by oral gavage once daily for 13 weeks. There were no persistent effects on body weight or food consumption. In addition, there were no histopathological changes in organs or tissues in any dose groups. There were, however, dose-related behavioural changes for all rats given taurine (persistent increased activity most noticeable one hour after dosing, occasional chewing of limbs, possible decrements in motor performance on a rotarod). The SCF concluded that these findings, together with the toxicokinetic data showing peak plasma levels after one hour, and the lack of increased locomotor activity when measured some hours after dosing, suggested that taurine may have exhibited an acute, central pharmacological effect. The results of the rat study showed that 1000 mg/kg bw per day was a clear effect level for behavioural changes while the lower doses of 300 and 600 mg/kg bw per day were marginal effect levels in males but clear effect levels in females. Thus, a NOAEL for behavioural effects in rats was not established.

The SCF concluded that the effects observed in the 13-week rat study should be taken into account in human risk assessment, noting that behavioural effects were observed at the lowest dose level tested. They further concluded that the absence of a NOAEL for these effects precluded the setting of a safe upper level for daily intake of taurine.

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 (AFFSA, 2006)

The risk assessment evaluates the safety of an energy drink containing other substances, including taurine. Neither information on safety nor established maximum concentrations or

recommended daily doses of taurine 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 European Food Safety Authority (EFSA) evaluated the safety-in-use of taurine as a constituent of the so-called "energy drinks". Since no NOAEL for neurological effects could be set based on the rat study described in the risk assessment by SCF in 2003, SCF was of the opinion that new focused neurological studies were needed. In addition, in 2009 EFSA stated the following: "The petitioner argued that there had been bias in the original study observations and the EFSA Working Group (2005) agreed that the observations reported in this study on certain behavioural patterns of the animals had not been well described in the original submission and could be discounted since there was no evidence of self-injury. However, the EFSA Working Group also concluded that, even combined with the expert analyses provided, this information was insufficient in itself to address all the concerns raised previously, notably the observation on increased activity and possible decrements in motor skills on the rotarod". A new 13-week rat neurotoxicity study was provided to EFSA and the risk assessment from 2009 was based on this new study.

Due to the absence of new acute and chronic exposure data, the exposure was based on data reported in a risk assessment by SCF in 2003. That is, a daily mean chronic consumption of 0.5 cans per person and a 95^{th} percentile exposure of 1.4 cans (one can is 250 ml). A reasonable high (acute) consumption was 3 cans/day. When it came to children, the panel assumed that children were to consume within the adult intake range, but only once per week. On a body weight basis, the average chronic exposure of children to "energy drinks" would be one third of that in adults.

In the risk assessment by SCF in 2003, no pathological changes were seen at the highest exposure dose of 1000 mg/kg bw per day. In 2009, the panel evaluated a new 13-week oral toxicity and neurotoxicity study in rats (both males and females) which included locomotor activity tests and the functional observational battery (FOB) (see section 2.4.3.2 for details). EFSA concluded that the new rat study confirmed a NOAEL of 1000 mg/kg bw per day for pathological changes. Furthermore, this study provided evidence for a NOAEL of 1500 mg/kg bw per day for behavioural effects. When calculated for a 60 kg person, the NOAEL of 1000 mg/kg bw per day for pathological changes was 120-fold higher than the estimated mean

and 43-fold higher than the estimated 95th percentile exposure from "energy drinks" only. Given that taurine is a natural body constituent, EFSA concluded that these margins of safety were sufficiently large to conclude that taurine was not of safety concern at the estimated level of intake.

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)

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. Since no new studies on taurine were published, VKM endorsed the conclusion of SCF in 2003.

2009: VKM examined, on the basis of the EFSA 2009 opinion, whether the conclusion of the VKM opinion from 2005 needed to be revised. The VKM endorsed the conclusion in EFSA's risk assessment on taurine from 2009 and considered the NOAEL of 1000 mg/kg bw per day to be valid also for Norway.

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. Spain (AESAN, 2012)

AESAN performed a risk assessment of 1000 mg taurine/day used in food supplements. No acute, subchronic or chronic toxicity studies of taurine after oral administration in animals were publicly available to AESAN. The risk assessment was based on published clinical tests in humans. They evaluated more than 30 clinical trials that were published, and 11 of these trials were placebo-controlled studies of safety in adults after oral intake for at least one week (not including studies on acute effects, bioavailability and parenteral administration). The study sample, dose and duration and measurements of the potential effects varied. Furthermore, the clinical studies involved healthy individuals and individuals with a wide range of diseases or health conditions. The highest dose applied was 10 g taurine per day for 6 months, whereas the longest test period was 12 months with a dose ranging from 500 to 1500 mg/day.

With the exception of gastrointestinal disorders described in one study, none of the studies reviewed in AESAN's opinion reported adverse effects of taurine. Therefore, there was no basis for identifying a NOAEL or LOAEL. Consequently, for each clinical test, the "observed safe level" method was applied. An "observed safe level" of 3 g taurine/day was identified from the data in humans who consume a large variety of diets. An upper limit for supplements based on toxicity data from clinical trials was found to be 3 g taurine/day. The AESAN, therefore, concluded that the proposal of a maximum daily intake of 1000 mg taurine was acceptable from the safety point of view for the use as a food supplement.

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". France (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 taurine in so-called "energy drinks" was considered, the mean daily intake in all so-called "energy drink" consumers was 181 mg/day. In regular consumers with higher frequency of consumption the intake was 429 mg/day, whereas intake at the 90th percentile was 714 mg/day. When maximum taurine levels were considered, and for a body weight of 60 kg, the margin of safety values between the NOAEL of 1000 mg/kg bw per day and the daily intake at the mean or 90th percentile were 328 and 168, respectively. In regular consumers of so-called "energy drinks", the safety margins were 138 and 84, respectively.

Adverse health effects of taurine alone or in combination with caffeine were assessed.

Cardiovascular effects: The effect of taurine alone on blood pressure was not well documented. However, several cross-sectional studies indicated an inverse relationship between taurine urine concentrations and blood pressure. Furthermore, an increase in blood pressure and coronary vasospasm has been observed after the intake of energy drinks containing both caffeine and taurine. This effect may not be related only to caffeine, but taurine may add to this effect. An effect of taurine on increased systolic ejection volume is possible in that this effect has been observed following consumption of taurine-containing energy drinks, but not after consumption of an analogue of this drink that was free from taurine.

Neurological effects: The possibility of taurine being involved in the onset of epileptic seizures was discussed in two case studies. Convulsion episodes could result from neuronal hyperexcitability caused by high chronic intake of taurine.

Haematological effects: Taurine is a component of platelets, and there were some human studies on reduced platelet aggregation following taurine exposure with contradicting results. Thus, no overall conclusion on platelet aggregation could be drawn from these studies.

Respiratory effects: Adverse effects on the respiratory system have not been described for taurine, neither in healthy subjects nor in patients.

The conclusions and recommendations by ANSES were only for so-called "energy drinks" and not specifically for taurine.

2.1.2 Summary of previous risk assessments

In the present opinion, VKM uses the NOAEL from rats of 1000 mg taurine/kg bw per day set by EFSA (2009) for the risk characterisation of taurine as an ingredient in food supplements and energy drinks.

2.1.3 Literature search

Literature searches were performed in MEDLINE, EMBASE, Global Health and Web of Science in order to retrieve human studies investigating adverse effects caused by taurine. These databases were chosen to ensure comprehensive study retrieval. The literature searches were performed by a librarian in June 2015. The search strategy is included in Appendix 1.

2.1.3.1 Publication selection

The literature search identified 158 articles. In the primary screening, duplications were removed, and then 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.

Reviews and original 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 one person.

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 five full text articles included in the results in this report (see Figure 2.1.2.2-1).

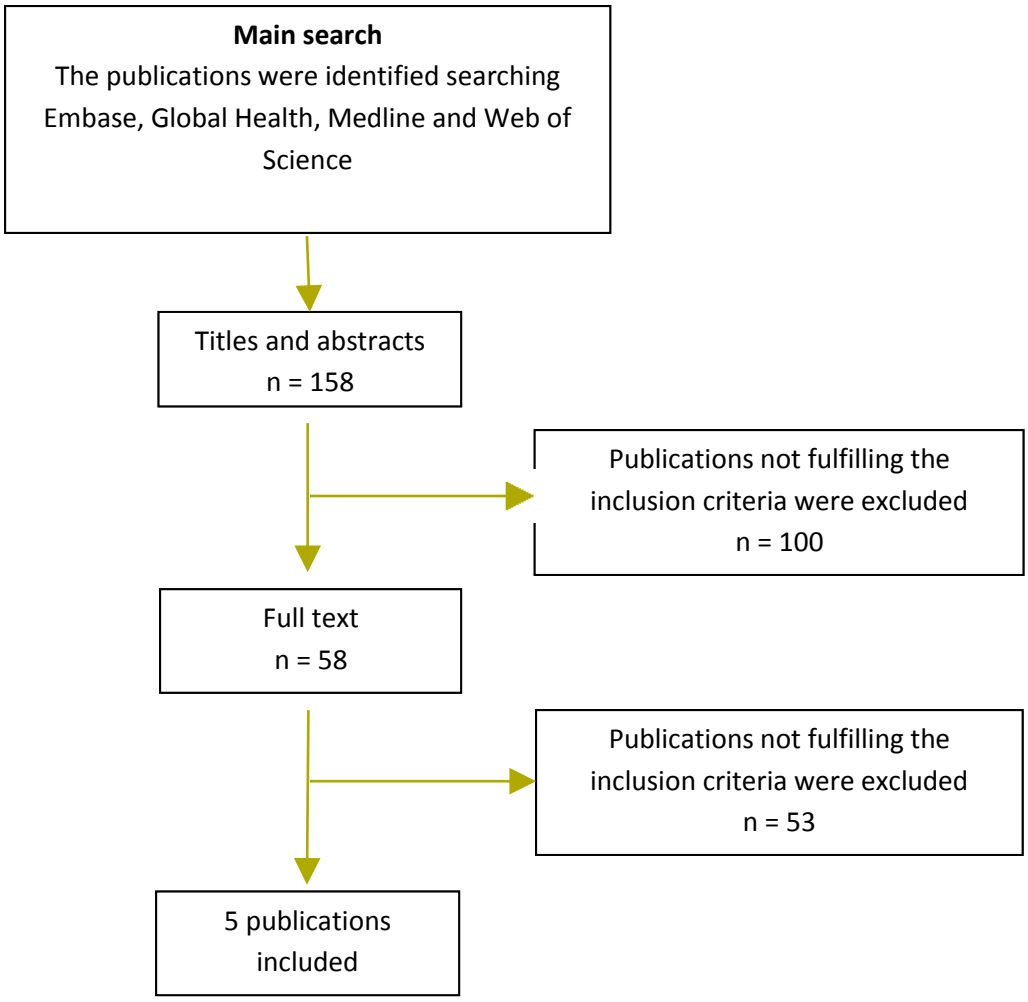

Figure 2.1.2.2-1: Flowchart for the literature search for taurine and the subsequent publication selection.

2.2 General information

2.2.1 Chemistry

The molecular formula of taurine (CAS No. 107-35-7) is $C_2H_7NO_3S$ and the molecular weight is 125.15 g/mol. The IUPAC name is 2-aminoethanesulfonic acid. Taurine can be manufactured from monoethanolamine and sulphuric acid or from ethylene oxide and sodium hydrogen sulphate as starting materials. The production can be followed by purification steps to reach a purity of at least 98.5% (EFSA, 2009). The structural formula is shown in figure 2.2-1.

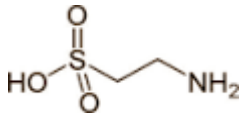

Figure 2.2-1. The structural formula of taurine.

2.2.2 Occurrence

Taurine is a metabolic product of sulphur-containing amino acids, and it is mainly biosynthesised from cysteine in the liver. In adults, the average daily synthesis ranges between 0.4-1.0 mmol (50-125 mg). However, under stress the synthesis may be impaired (reviewed in Lourenco and Camilo (2002)). Taurine occurs naturally in food, especially in meat and seafood. Taurine is also transferred to breast milk. In some cases the endogenous production is insufficient and taurine must be provided via the diet.

2.3 Absorption, distribution, metabolism and excretion (ADME)

2.3.1 In humans

After oral exposure, taurine was readily bioavailable in the systemic circulation, and significant increase in plasma was measured 90 minutes after consumption of a taurine-rich meal. The plasma level declined to the background level within 180-270 minutes. The absorption from oral intake was suggested to occur via an active transport mechanism in the gut wall (EFSA, 2009). Taurine is used for bile acid conjugation, and in the human adult, about one-fourth of the bile acids are conjugated with taurine. Taurine is excreted predominantly (95%) in urine, about 70% as taurine and 25% as sulphate. The sulphate was considered to be formed in the intestine by bacterial degradation of taurine and then absorbed (Sturman et al., 1975).

2.3.2 Animal studies

The SCF (2003) concluded that taurine in rats showed ready bioavailability and peak plasma levels one hour after oral exposure. These findings are in accordance with findings in humans. Furthermore, EFSA (2009) concluded that exogenous taurine rapidly equilibrates with endogenous body pools and that any excess is rapidly eliminated by the kidney. Exogenous exposure did not increase taurine levels in the brain of rats.

2.4 Adverse effects

2.4.1 Human studies

The published studies on taurine retrieved from the literature search are primarily studies on possible beneficial effects from oral exposure to taurine. Only five of these studies also

report adverse health effect and were thus included. An overview of the included studies on taurine and adverse health effects in humans is given in Table 2.4.1-1.

Table 2.4.1-1 Overview of human studies on taurine where information on adverse effects has been reported.

Reference	Study design /Participant characteristics	Country	Number in treatment group		Dose	Main endpoints	Exposure duration	Adverse effect
			Taurine	Control/placebo				
Sirdah et al. (2002)	RCT. Anemic adult women (18-22 years)	Palestine	26	25	1 g (corresponding to 14.3 mg/kg bw per day for a 70 kg adult)	Ameliorative effects of taurine in the treatment of iron-deficiency anaemia	20 weeks	No adverse effects related to taurine were observed
Brons et al. (2004) Spohr et al. (2005)	RCT crossover study. Nondiabetic obese adults (40±8 years) with genetic predisposition for type II diabetes mellitus	Denmark	20 (successive taurine or placebo treatment)		1.5 g (corresponding to 21.4 mg/kg bw per day for a 70 kg adult)	Insulin secretion and action, plasma lipid levels Platelet aggregation	8 weeks	Participants reported no indications of side effects or symptoms of toxicity
Galloway et al. (2008)	RCT. Crossover study. Healthy men (22 years)	UK	8 (successive placebo then taurine treatment)		4.98 g (corresponding to 71.1 mg/kg bw per day for a 70 kg adult)	Muscle taurine content, altered substrate metabolism during prolonged exercise	7 days	One experienced side effects (slight muscle cramping), which occurred during the taurine ingestion period
Pearl et al. (2014)	Open-label study. Patients with succinic semialdehyde dehydrogenase (SSADH) deficiency (0.5-28 years; mean 12 years)	US	18		Subjects were titrated weekly from a starting dose of 50 mg/kg bw per day to a target dose of 200 mg/kg bw per day A maximum dosage of 10 g/day (corresponding to 142.9 mg/kg bw per day for a 70 kg adult) was established after a serious adverse event that prompted the lowering of the doses	Efficacy measured by change in adaptive behaviour	3-50 months (median 8.5 months)	One severe adverse event, hospitalisation for hypersomnia, occurred while a subject (adult) was on a dosage of 16 g/day (200 mg/kg bw per day) 10 g/day was well tolerated, with no further serious incidents reported Other adverse events reported with the highest frequency included moderate fatigue, somnolence and cognitive change Mild insomnia, ataxia, somnolence, fatigue and mildly diminished cognitive function were also noted for some individuals

2.4.1.1 Randomised controlled studies

In a double-blinded randomised study, 51 subjects (females; 18-22 years) with iron-deficiency anemia were included (Sirdah et al., 2002). The aim of the study was to investigate whether the addition of oral taurine enhanced the effectiveness of oral ferrous sulphate in the treatment of iron deficiency. All subjects were treated for 20 weeks with a daily dose of oral tablets containing ferrous sulphate only. In addition, one group (n=26) received daily a capsule containing 1000 mg taurine, whereas another group received a placebo (n=25). Every fourth week, the participants underwent interviews and clinical examinations. The authors reported that no adverse effects related to taurine were noted.

Brons et al. (2004) and Spohr et al. (2005) studied the effect of taurine on insulin secretion and action (Brons et al., 2004) and on platelet aggregation (Spohr et al., 2005) in overweight men with a predisposition to type 2 diabetes mellitus. Twenty non-diabetic subjects (40±8 years) were included in the double-blinded randomised, crossover study. The subjects were assigned to either 8 weeks of taurine or placebo (cellulose) intervention during the first period, followed by a 2-week wash-out period. The subjects thereafter began a second 8-week period with the opposite intervention of the first period. Taurine was administered at a daily dose of 1500 mg divided into two capsules of 750 mg each (morning and evening). Eighteen subjects completed the study. The participants reported no indications of adverse effects or symptoms of toxicity.

In a single-blinded study, eight healthy recreationally active men (22±0 years) underwent two 7-day periods of oral supplementation of their diet with placebo and taurine (Galloway et al., 2008). The aim of the study was to investigate whether taurine supplementation can increase muscle taurine content or alter substrate metabolism during prolonged exercise. The subjects attended the laboratory in the morning and cycled for two hours to establish the correct power output for the main trials and to ensure that they could exercise for the required durations. Immediately after the visit, subjects were provided with a 7-day supply of placebo capsules (glucose). On day 7, the first main two hours exercise trial occurred. After one week recovery period, subjects received a 7-day supply with a daily dose of 4980 mg taurine (2 capsules 3 times daily, each containing 830 mg taurine). A final exercise trial was conducted at the end of the 7-day period. All subjects complied with the supplementation protocol. One person experienced an adverse effect (slight muscle cramping) during the taurine ingestion period.

2.4.1.2 Open-label study

The objective of the open-label study Pearl et al. (2014) was primarily to assess the effect of taurine on adaptive behaviour and secondly to collect safety and tolerability data in patients with succinic semialdehyde dehydrogenase deficiency. Eighteen subjects (0.5-28 years, mean 12 years) were titrated weekly from a starting dose of 50 mg/kg bw per day to a target 200 mg/kg bw per day. Three subjects withdrew because of perceived lack of

efficiency but 16 subjects had follow-up data for a range of 3-50 months of continuous treatment (median treatment: 8.5 months). One severe adverse event (hospitalisation for hypersomnia) occurred while a subject was dosed with 200 mg/kg bw per day (16 000 mg/day). This event prompted lowering of the doses establishing a maximum of 10 000 mg/day for all patients. Other adverse events reported most frequently were moderate fatigue, somnolence and cognitive changes (diminished focus and attention). Mild insomnia, ataxia, somnolence, fatigue and mildly diminished cognitive functions were also noted for some individuals. However, there was no information on age, dose or exposure period for the patients experiencing adverse effects.

2.4.1.3 Interactions

Renal effects
In humans, taurine has a diuretic effect by inhibiting the release of antidiuretic hormone (ADH) and vasopressin in the central nervous system, resulting in salt and water losses. However, the diuretic effect of energy drinks appears to be primarily related to caffeine with no taurine-caffeine synergistic effect (ANSES, 2013). Similarly, in EFSA (2009) it was concluded that the diuretic potential and natriuretic effects of energy drinks are largely mediated by caffeine and that additive interactions between taurine and caffeine on diuretic effects are unlikely.

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.

2.4.1.4 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 Summary on human studies

In the study by Pearl et al. (2014), one severe event occurred in an adult at a daily dose of 16 g taurine (200 mg/kg bw per day). The doses for the participants were therefore reduced to a maximum of 10 g taurine per day. According to the authors, at doses ranging from 88-222 mg/kg bw per day, other adverse effects were observed (ataxia, cognitive changes (decrease in attention, focus), fatigue, insomnia, somnolence). There is no available information with regard to the age of the participants experiencing adverse effects, at which doses these adverse effects occurred or the length of the exposure period for each participant. This study gives indications that daily doses of 10 and 16 g taurine (88-222 mg/kg bw per day) may represent a health risk. However, these doses are much higher than the doses to be evaluated in this risk assessment.

In the study by Galloway et al. (2008), no adverse effects were observed after a daily intake of 4980 mg taurine (corresponding to 71.1 mg/kg bw per day in a 70 kg adult) for a period of 7 days. Due to the short exposure period, this study will not be used in the risk characterisation in the present risk assessment.

Based on the studies by Sirdah et al. (2002), Brons et al. (2004) and Spohr et al. (2005) (20 to 50 participants, from 8 weeks to 5 months treatment), there are indications that an intake of 1000-1500 mg taurine per day (corresponding to 14.3-21.4 mg/kg bw per day in a 70 kg adult) do not cause adverse health effects. VKM considers, based on these studies, that it is unlikely that an intake of taurine up to approximately 21 mg/kg bw per day causes adverse health effects.

2.4.3 Animal studies

2.4.3.1 Genotoxicity

In 1999, SCF concluded that toxicological studies did not reveal any indications of a genotoxic potential of taurine (SCF, 1999).

No new studies were available for EFSA's risk assessment in 2009.

2.4.3.2 Subchronic toxicity

A new 13-week study with focus on neurotoxicity performed in male and female rats according to the Food and Drug Administration (FDA) and OECD GLP guidelines was provided by the petitioner (cited in EFSA (2009)). In this study, taurine in deionized water was administered orally by gavage once daily for 13 weeks to two groups of 20 male and 20 female Cr1:CD(SD) rats at dose levels of 600 and 1000 mg/kg bw per day. In two other groups of 20 male and 20 female rats, taurine was administered *ad libitum* in drinking water for 13 weeks at target dose levels of 1000 and 1500 mg/kg bw per day. The actual mean taurine intake levels were 1095 and 1117 mg/kg bw per day for the males and females, respectively, in the low dose group, and 1647 and 1656 mg/kg bw per day for males and females, respectively, in the high dose group. Concurrent control groups received the vehicle only, using comparable regimes. Clinical examinations were performed daily, whereas detailed physical examinations were performed weekly. Individual body weights and water consumption were recorded twice weekly and food consumption weekly. Functional observational battery (home cage, handling, open field, sensory, neuromuscular and physiological observations) and locomotor activity data (activity counts (total and ambulatory) and patterns) were recorded for all animals prior to the initiation of dose administration and during study weeks 0, 6 and 12. Furthermore, complete necropsies were conducted, and selected tissues and organs were collected at the scheduled necropsy. There were no treatment-related deaths, clinical findings or macroscopic findings. Furthermore, no test-article-related effects were observed on body weights or food consumption. There were no test-article-related effects on functional observational battery parameters, and locomotor

activity was unaffected. Some differences were observed in water consumption when the animals were supplied taurine *ad libitum* in the drinking water. However, these differences were not considered as adverse effects but occurred temporarily and reflected adaption to the osmotic property of the test article (EFSA, 2009).

In the rat study used by SCF in their risk assessment in 2003, no pathological changes were seen at the highest exposure dose of 1000 mg/kg bw per day (SCF, 2003). EFSA concluded that the new rat study used in the risk assessment in 2009 confirmed a NOAEL of 1000 mg/kg bw per day for pathological changes. In addition, the study provided evidence of a NOAEL of 1500 mg/kg bw per day for behavioural effects.

2.4.3.3 Chronic toxicity and carcinogenicity

In 1999, SCF concluded that toxicological studies did not reveal any indications for a carcinogenic potential of taurine (SCF, 1999). However, the SCF also indicated that there was no adequate chronic toxicity/carcinogenicity study for taurine.

2.4.3.4 Reproductive and developmental toxicity

In 1999, the Scientific Committee of Food (SCF) concluded that toxicological studies did not reveal any indications of a teratogenic potential of taurine (SCF, 1999).

No new studies were available for EFSA's risk assessment in 2009.

2.4.3.5 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.

2.4.3.6 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.

2.4.4 Summary of animal studies

There are no indications of genotoxicity, neurotoxicity, chronic toxicity, carcinogenicity, and reproductive and developmental toxicity described in the included previous reports.

EFSA (2009) defined a NOAEL of 1000 mg/kg bw per day for pathological changes in a 13-week rat study. In addition, they concluded that there is evidence of a NOAEL of 1500 mg/kg bw per day for behavioural effects.

2.4.5 Mode of action for adverse effects

In the previous risk assessments by EFSA (2009) and ANSES (2013), no mode of action for adverse effects of taurine was reported.

2.4.6 Vulnerable groups

There was no information concerning specific groups vulnerable for taurine in the literature reviewed in the present risk assessment.

2.5 Summary of hazard identification and characterisation

Taurine is readily bioavailable in humans. There is a significant increase in plasma taurine 90 minutes after intake and levels decline to background levels within 180-270 minutes. In rats, exogenous taurine is rapidly equilibrated with endogenous body pools (except in the brain) and any excess is rapidly excreted unchanged in the urine (EFSA, 2009).

Based on the studies by Sirdah et al. (2002), Brons et al. (2004) and Spohr et al. (2005) (20 to 50 participants, from 8 weeks to 5 months treatment), there are indications that an intake of 1000-1500 mg taurine per day (corresponding to 14.3-21.4 mg/kg bw per day in a 70 kg adult) do not cause adverse health effects. Therefore, VKM considers that it is unlikely that an intake of taurine up to approximately 21 mg/kg bw per day causes adverse health effects.

The human studies available were not of sufficient quality (due to low number of participants, non-healthy populations and short duration) to be used alone in the risk characterisation.

A NOAEL of 1000 mg/kg bw per day for pathological changes was set by EFSA (2009), based on a 13-week neurotoxicity study in rats. Since the NOAEL set by EFSA was based on the highest dose tested, there is a possibility that the actual NOAEL is higher than 1000 mg/kg bw per day. Therefore, VKM has applied the margin of exposure (MOE) approach (the ratio of the NOAEL to the exposure) combined with comparisons with the intake of approximately 21 mg/kg bw per day, which is considered unlikely to cause adverse health effects based on human studies, in the risk characterisation.

The values used for comparison with the estimated exposure in the risk characterization are 21 mg/kg bw per day (from human studies) and the NOAEL of 1000 mg/kg bw per day (rat study).

3 Exposure / Intake

Exposure of taurine was estimated from the intake of food supplements and energy drinks. For food supplements, the intake of taurine was estimated for the age groups children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), whereas for energy drinks the age group children (3 to <10 years) was included in addition to the above-mentioned age groups.

3.1 Food supplements

NFSA requested VKM to perform a risk assessment of 750, 800, 900, 1000 and 2000 mg/day of taurine in food supplement for children (10 to <14 years), adolescents (14 to <18 years) and adults. The default body weights (bw) for these groups as determined by EFSA were used: 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and adults; 70.0 kg (EFSA, 2012).

The estimated exposure to taurine from food supplements for the various age groups is presented in Table 3.1-1.

From a daily dose of 750 mg taurine, the calculated intake levels are 17.3, 12.2 and 10.7 mg/kg bw per day for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively. From a daily dose of 800 mg taurine, the calculated intake levels are 18.4, 13.1 and 11.4 mg/kg bw per day for children, adolescents and adults, respectively. From a daily dose of 900 mg taurine, the calculated intake levels are 20.7, 14.7 and 12.9 mg/kg bw per day for children, adolescents and adults, respectively. From a daily dose of 1000 mg taurine, the calculated intake levels are 23.0, 16.3 and 14.3 mg/kg bw per day for children, adolescents and adults, respectively. From a daily dose of 2000 mg taurine, the calculated intake levels are 46.1, 32.6 and 28.6 mg/kg bw per day for children, adolescents and adults, respectively.

Table 3.1-1 Estimated daily intake of taurine (mg/kg bw per day) from food supplements for the various age groups.

Intake (mg/kg bw per day)	**Daily doses (mg)**				
	750	800	900	1000	2000
Children (10 to <14 years)	17.3	18.4	20.7	23.0	46.1
Adolescents (14 to <18 years)	12.2	13.1	14.7	16.3	32.6
Adults (≥18 years)	10.7	11.4	12.9	14.3	28.6

3.2 Energy drinks

NFSA requested VKM to perform a risk assessment of 300, 350 and 400 mg/100 ml of taurine for the age groups children (3 til <10 and 10 to <14 years), adolescents (14 to <18

years) and adults (≥18 years). The default body weights 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.

High acute consumption

For children (3 til <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 Norkost 3 (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 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. In Table 3.2-1 the estimated intake of energy drinks for the various age groups in the three intake scenarios is presented.

Table 3.2-1 The estimated consumption 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 estimated exposure to taurine from energy drinks for the various age groups in the three scenarios is presented in Table 3.2-2.

For 3 to <10 year old children, the intake level of taurine has been estimated to be in the range of 130-173 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels range from 7.5-10.0 and 21.2-28.2 mg/kg bw per day, respectively.

For 10 to <14 year old children, the intake level of taurine has been estimated to be in the range of 104-138 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels range from 4.5-6.0 and 12.4-16.6 mg/kg bw per day, respectively.

For 14 to <18 year old adolescents, the intake level of taurine has been estimated to be in the range of 97.9-131 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels range from 3.1-4.2 and 10.3-13.8 mg/kg bw per day, respectively.

For adults (≥18 years), the intake level of taurine has been estimated to be in the range of 85.7-114 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels range from 3.0-4.1 and 13.7-18.3 mg/kg bw per day, respectively.

Table 3.2-2 The estimated exposure to taurine from energy drinks for the various age groups in the three intake scenarios.

Age groups	Intake scenarios	Estimated exposure (mg/kg bw per day)		
		300 mg/100 ml	350 mg/100 ml	400 mg/100 ml
Children (3 to <10 years)	High acute	130	152	173
	Mean chronic	7.5	8.8	10.0
	High chronic	21.2	24.7	28.2
Children (10 to <14 years)	High acute	104	121	138
	Mean chronic	4.5	5.2	6.0
	High chronic	12.4	14.5	16.6
Adolescents (14 to <18 years)	High acute	97.9	114	131
	Mean chronic	3.1	3.7	4.2
	High chronic	10.3	12.0	13.8
Adults (≥18 years)	High acute	85.7	100	114
	Mean chronic	3.0	3.6	4.1
	High chronic	13.7	16.0	18.3

3.3 Other sources

Taurine occurs naturally in food (EFSA, 2009). The mean daily intake of taurine from the diet has been estimated to vary between 40 and 400 mg/day (Hayes and Trautwein, 1994).

In the EU, taurine can be used in cosmetic products, and there are no restrictions with regard to either product type or use concentrations. Taurine is a buffering agent with the purpose to assure the stability of cosmetic products (CosIng, 2015).

4 Risk characterisation

The human studies available were not of sufficient quality (due to low number of participants, non-healthy populations and short duration) to be used as the sole basis in the risk characterisation.

A NOAEL of 1000 mg/kg bw per day was set by EFSA based on a 13-week rat study. Since the NOAEL was based on the highest tested dose, there is a possibility that the actual NOAEL is higher than 1000 mg/kg bw per day.

The risk characterisation is therefore based on both the Margin of Exposure (MOE), the ratio of the NOAEL to the exposure, using the NOAEL value from the rat study, combined with comparisons with the intake of approximately 21 mg/kg bw per day, which was considered unlikely to cause adverse health effects based on human studies (for details, see chapter 2.5).

An acceptable MOE value for a NOAEL-based assessment of taurine based on an animal study 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 assessments must be based on supporting scientific literature and expert judgement. In the present risk characterization, results from human studies were used in addition to the MOE values.

Since taurine is synthesised endogenously (the average daily synthesis is 50-125 mg), occurs naturally in foods (estimated intake is 40-400 mg/day) and any excess of taurine is rapidly eliminated by the kidneys, no safety factor was applied for the intake value of 21 mg/kg bw per day.

4.1 Food supplements

NFSA requested VKM to perform a risk assessment of 750, 800, 900, 1000 and 2000 mg/day of taurine in food supplement for a general population, ages 10 years and above. The calculated margins between the NOAEL of 1000 mg/kg bw per day and the exposure of taurine from food supplements (MOE values) are presented in Table 4.1-1. The estimated exposures are presented in Table 3.1-1.

Children (10 to <14 years)

For a daily intake of 750 mg taurine from food supplements, the estimated exposure was 17.3 mg/kg bw per day. The corresponding MOE was 58.

For a daily intake of 800 mg taurine from food supplements, the estimated exposure was 18.4 mg/kg bw per day. The corresponding MOE was 54.

For a daily intake of 900 mg taurine from food supplements, the estimated exposure was 20.7 mg/kg bw per day. The corresponding MOE was 48.

For a daily intake of 1000 mg taurine from food supplements, the estimated exposure was 23.0 mg/kg bw per day. The corresponding MOE was 43.

For a daily intake of 2000 mg taurine from food supplements, the estimated exposure was 46.1 mg/kg bw per day. The corresponding MOE was 22.

For children (10 to <14 years), the MOE values were in the range of 22-58 for the various taurine doses, i.e. all below 100. However, from a daily intake of 750, 800 or 900 mg taurine from food supplements, the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore considers it unlikely that a daily intake of 750, 800 or 900 mg taurine from food supplements causes adverse health effects in children (10 to <14 years). The estimated exposure from a daily intake of 1000 or 2000 mg taurine was above 21 mg/kg bw per day. Thus, VKM considers that a daily intake of 1000 or 2000 mg taurine from food supplements may represent a health risk in children (10 to <14 years).

Adolescents (14 to <18 years)

For a daily intake of 750 mg taurine from food supplements, the estimated exposure was 12.2 mg/kg bw per day. The corresponding MOE was 82.

For a daily intake of 800 mg taurine from food supplements, the estimated exposure was 13.1 mg/kg bw per day. The corresponding MOE was 76.

For a daily intake of 900 mg taurine from food supplements, the estimated exposure was 14.7 mg/kg bw per day. The corresponding MOE was 68.

For a daily intake of 1000 mg taurine from food supplements, the estimated exposure was 16.3 mg/kg bw per day. The corresponding MOE was 61.

For a daily intake of 2000 mg taurine from food supplements, the estimated exposure was 32.6 mg/kg bw per day. The corresponding MOE was 31.

The MOE values were all below 100. However, for a daily intake of 750, 800, 900 or 1000 mg taurine from food supplements, the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore considers it unlikely that a daily intake of 750, 800, 900 or 1000 mg taurine from food supplements causes adverse health effects in adolescents (14 to <18 years)).

For a daily intake of 2000 mg taurine from food supplements, the MOE value was below 100 and the estimated intake was above 21 mg/kg bw per day. Thus, VKM considers that a daily intake of 2000 mg taurine from food supplements in adolescents may represent a health risk in adolescents (14 to <18 years).

Adults (≥18 years)

For a daily intake of 750 mg taurine from food supplements, the estimated exposure was 10.7 mg/kg bw per day. The corresponding MOE was 93.

For a daily intake of 800 mg taurine from food supplements, the estimated exposure was 11.4 mg/kg bw per day. The corresponding MOE was 88.

For a daily intake of 900 mg taurine from food supplements, the estimated exposure was 12.9 mg/kg bw per day. The corresponding MOE was 78.

For a daily intake of 1000 mg taurine from food supplements, the estimated exposure was 14.3 mg/kg bw per day. The corresponding MOE was 70.

For a daily intake of 2000 mg taurine from food supplements, the estimated exposure was 28.6 mg/kg bw per day. The corresponding MOE was 35.

The MOE values were all below 100. However, for a daily intake of 750, 800, 900 or 1000 mg taurine from food supplements, the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore considers it unlikely that a daily intake of 750, 800, 900 or 1000 mg taurine from food supplements causes adverse health effects in adults (≥18 years).

For a daily intake of 2000 mg taurine from food supplements, the MOE value was below 100 and the estimated intake was above 21 mg/kg bw per day. Therefore, VKM considers that a daily intake of 2000 mg taurine from food supplements may represent a health risk in adults (≥18 years).

Table 4.1-1 The calculated margins between the NOAEL and the exposure to taurine from food supplements (MOE values) for the various age groups.

Age groups	Margin of exposure				
	750 mg/day	800 mg/day	900 mg/day	1000 mg/day	2000 mg/day
Children (10 to <14 years)	58	54	48	43	22
Adolescents (14 to <18 years)	82	76	68	61	31
Adults (≥18 years)	93	88	78	70	35

4.1.1 Summary of the risk characterisation - food supplements

An overview of the conclusions on food supplements is given in table 4.1.1-1.

For children (10 to <14 years), the MOE values were all below 100. However, for a daily intake of 750, 800 or 900 mg taurine from food supplements, the estimated intakes were

below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore considers it unlikely that a daily intake of 750, 800 or 900 mg taurine from food supplements causes adverse health effects in children (10 to <14 years). The estimated exposure from a daily intake of 1000 or 2000 mg was above 21 mg/kg bw per day. Thus, VKM considers that a daily intake of 1000 or 2000 mg taurine from food supplements may represent a health risk in children (10 to <14 years).

For adolescents (14 to <18 years) and adults (≥18 years), the MOE values were all below 100. However, for a daily intake of 750, 800, 900 or 1000 mg taurine from food supplements the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). Thus, VKM considers it unlikely that a daily intake of 750, 800, 900 or 1000 mg of taurine causes adverse health effects in adolescents (14 to <18 years) and adults (≥18 years).

For adolescents (14 to <18 years) and adults (≥18 years) the estimated MOE values were below 100 after a daily intake of 2000 mg taurine from food supplements. In addition, the estimated intakes were above the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). Thus, VKM considers that a daily intake of 2000 mg of taurine may represent a risk of adverse health effects in adolescents (14 to <18 years) and adults (≥18 years).

4.2 Energy drinks

NFSA further requested VKM to perform a risk assessment of 300, 350 and 400 mg/100 ml of taurine in energy drinks for the general population, ages 3 years and above. The estimated intake of energy drinks (ml/day) is given in Table 3.2-1. The estimated exposure to taurine from energy drinks (mg/kg bw per day) is given in Table 3.2-2. Due to lack of an acute reference dose or other data for acute toxicity of taurine, it was not possible to characterise the risk related to an acute intake. Therefore, only drinking patterns reflecting a mean chronic intake and a high chronic intake were assessed. The calculated margins between the NOAEL and the exposure of taurine from energy drinks (MOE values) are presented in Table 4.2-1.

Mean chronic drinking pattern

For mean chronic consumption of 300, 350 and 400 mg/100 ml of taurine from energy drinks, the intake levels were 7.5, 8.8 and 10.0 mg/kg bw per day in 3 to <10 year old children, 4.5, 5.2 and 6.0 mg/kg bw per day in 10 to <14 year old children, 3.1, 3.7 and 4.2 mg/kg bw per day for 14 to <18 year old adolescents and 3.0, 3.6 and 4.1 0 mg/kg bw per day for adults (≥18 years), respectively. For the mean chronic drinking pattern, the MOE values were in the range of 100-333 for all age groups. In addition, the estimated intakes are below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all age groups. VKM therefore considers it unlikely that a daily mean chronic intake of 300, 350 and 400 mg/100 ml of taurine for the age groups

children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years) causes adverse health effects).

High chronic drinking pattern

For children (3 to <10 years) with a high chronic intake of 300, 350 and 400 mg/100 ml of taurine from energy drinks, the estimated intakes were 21.2, 24.7 and 28.2 mg/kg bw per day, respectively. The corresponding MOE values were 47, 40 and 35. All the MOE values were below 100, and the estimated intakes were all above 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). Thus, VKM considers that a high chronic intake of taurine from energy drinks in children (3 til <10 and 10 to <14 years) may represent a health risk.

For children (10 to <14 years) with a high chronic intake of 300, 350 and 400 mg/100 ml of taurine from energy drinks, the estimated intakes were 12.4, 14.5 and 16.6 mg/kg bw per day, respectively. The corresponding MOE values were 81, 69 and 60. All the MOE values were below 100. However, the estimated intakes were all below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). Thus, VKM considers it unlikely that a high chronic intake of taurine from energy drinks in children (10 to <14 years) may represent a health risk.

For adolescents (14 to <18 years) with a high chronic intake of 300, 350 and 400 mg/100 ml of taurine from energy drinks, the estimated intakes were 10.3, 12.0 and 13.8 mg/kg bw per day, respectively. The corresponding MOE values were 97, 83 and 72. The MOE values were all below 100. However, the estimated intakes were all below the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore considers it unlikely that a high chronic intake of taurine from energy drinks in adolescents causes adverse health effects.

For adults (≥18 years) with a high chronic intake of 300, 350 and 400 mg/100 ml of taurine from energy drinks, the estimated intakes were 13.7, 16.0 and 18.3 mg/kg bw per day, respectively. The corresponding MOE values were 73, 63 and 55. The MOE values were all below 100. However, the estimated intakes were all below the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore considers it unlikely that a high chronic intake of taurine from energy drinks in adults (≥18 years) causes adverse health effects.

Table 4.2-1 The calculated margins between the NOAEL and the exposure to taurine from energy drinks (MOE values) for the various age groups for the two drinking patterns.

	Exposure scenarios	**Margin of exposure**		
Age groups		300 mg/100 ml	350 mg/100 ml	400 mg/100 ml
Children (3 to <10 years)	Mean chronic	133	114	100
	High chronic	47	40	35
Children (10 to <14 years)	Mean chronic	222	192	167
	High chronic	81	69	60

	Exposure scenarios	Margin of exposure		
Adolescents (14 to <18 years)	Mean chronic	323	270	238
	High chronic	97	83	72
Adults (≥18 years)	Mean chronic	333	278	244
	High chronic	73	63	55

4.2.1 Summary of the risk characterisation - energy drinks

An overview of the conclusions on mean and high chronic intake of energy drinks is given in Table 4.2.1-1 and Table 4.2.1-2, respectively.

High acute drinking pattern, all age groups

Due to lack of an acute reference dose or other data for acute toxicity of taurine, it was not possible to characterise the risk related to an acute intake for any of the age groups.

Mean chronic drinking pattern, all age groups

In all age groups, the estimated MOE values were above 100. In addition, the estimated intakes were all below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all age groups. Thus, VKM considers that it is unlikely that the mean chronic intake of taurine causes adverse health effects in any age groups).

High chronic drinking pattern, all age groups

For children (3 til <10 and), the estimated MOE values were all below 100. In addition, the estimated intakes were all above 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). Thus, VKM considers that a high chronic intake of taurine from energy may represent a health risk drinks in children (3 to <10 years).

For children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), the estimated MOE values were all below 100. However, the estimated intakes were all below the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). Thus, VKM considers it unlikely that a high chronic intake of taurine from energy drinks causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

5 Uncertainties

5.1 Uncertainties related to the hazard identification and characterisation

The NOAEL value used was derived from a subchronic, not a chronic, rat study, and it was the highest dose tested.

5.2 Uncertainties related to the exposure estimation

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 risk 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 Uncertainties related to the risk characterisation

The human studies available were not of sufficient quality (due to low number of participants, non-healthy populations and short duration) to be used as the sole basis for the risk characterisation. The rat NOAEL value was based on the highest dose tested, thus, there is a possibility that the actual NOAEL is higher than 1000 mg/kg bw per day.

The risk characterisation is therefore based on both a value derived from human studies (approximately 21 mg/kg bw per day, the intake considered unlikely to cause adverse health effectss) and the NOAEL from a rat study (calculating the Margin of Exposure (MOE) using the NOAEL value of 1000 mg/kg bw per day set by EFSA from a 13-week rat study) (for details, see chapter 2.5)).

Since both the human studies and the rat study were of limited duration (approximately 3-5 months), there is some uncertainty related to safety of longer duration of exposure to taurine.

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 (NFSA), assessed the risk of taurine in food supplements (750, 800, 900, 1000 and 2000 mg per day) and energy drinks (containing 300, 350 or 400 mg taurine per 100 ml). Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake were assessed. The present risk assessment is based on previous risk assessments of taurine and a literature search (see 2.1, 2.4 and 2.5). Both data from animal studies and human studies were used for the risk characterisation.

There are indications that taurine may have cardiovascular and neurological effects in humans. However, based on the human studies, 21 mg/kg bw per day was considered unlikely to cause adverse health effects. Based on a 13-week neurotoxicity study in rats, a no observed adverse effect level (NOAEL) of 1000 mg/kg bw per day for pathological changes was set in 2009 by the European Food Safety Authority (EFSA, 2009).

Food supplements

For children (10 to <14 years), the estimated daily intakes of taurine were 17.3, 18.4, 20.7, 23.0 and 46.1 mg/kg bw per day from daily doses of 750, 800, 900, 1000 and 2000 mg taurine, respectively, from food supplements. The margin of exposure (MOE) values was in the range of 22-58 for the various taurine doses, i.e. all below 100. However, from a daily intake of 750, 800 or 900 mg taurine from food supplements, the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies). VKM therefore concludes that it is unlikely that a daily intake of 750, 800 or 900 mg taurine from food supplements causes adverse health effects in children (10 to <14 years). The estimated exposure from a daily intake of 1000 or 2000 mg taurine was above 21 mg/kg bw per day. Thus, VKM concludes that a daily intake of 1000 or 2000 mg taurine from food supplements may represent a health risk in children (10 to <14 years).

For adolescents (14 to <18 years), the estimated daily intakes were 12.2, 13.1, 14.7, 16.3 and 32.6 mg/kg bw per day from daily doses of 750, 800, 900, 1000 and 2000 mg taurine, respectively, from food supplements. For adults (≥18 years), the estimated intakes were 10.7, 11.4, 12.9, 14.3 and 28.6 mg/kg bw per day from a daily intake of 750, 800, 900, 1000 and 2000 mg taurine, respectively, from food supplements.

For adolescents (14 to <18 years) and adults (≥18 years), the MOE values were in the range of 31-82 and 35-93, respectively, i.e. all below 100. However, from a daily intake of 750, 800, 900 or 1000 mg taurine from food supplements the estimated intakes were below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for both age groups. Thus, VKM concludes that it is unlikely that a daily

intake of 750, 800, 900 or 1000 mg of taurine causes adverse health effects in adolescents (14 to <18 years) and adults (≥18 years).

For adolescents (14 to <18 years) and adults (≥18 years) the estimated MOE values were 31 and 35, respectively, i.e. below 100, after a daily intake of 2000 mg taurine from food supplements. In addition, the estimated intakes were above the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for both age groups. Thus, VKM concludes that a daily intake of 2000 mg of taurine may represent a risk of adverse health effects in adolescents (14 to <18 years) and adults (≥18 years).

An overview of the conclusions on food supplements is given in Table 6-1. Estimated exposures unlikely to cause adverse health effects is shown in green, whereas estimated exposures that may represent a risk of adverse health effects is shown in red.

Table 6-1 An overview of the conclusions on food supplements. Green: the estimated exposure to taurine is unlikely to cause adverse health effects. Red: the estimated exposure to taurine may represent a risk of adverse health effects.

	Taurine				
Food supplement / **Age groups**	**750 mg/day**	**800 mg/day**	**900 mg/day**	**1000 mg/day**	**2000 mg/day**
Children (10 to <14 years)					
Adolescents (14 to <18 years)					
Adults (≥18 years)					

Energy drinks

High acute drinking pattern, all age groups

For the high acute drinking pattern, the estimated consumption of energy drinks was 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 concentrations of 300, 350 and 400 mg taurine/100 ml energy drink, the intake levels of taurine after a high acute consumption of energy drinks (in mg/kg bw per day) were 130, 152 and 173; 104, 121 and 138; 97.9, 114 and 131; and 85.7, 100 and 114, for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

Due to lack of an acute reference dose or other data for acute toxicity of taurine, it was not possible to characterise the risk related to an acute intake of taurine for any of the age groups.

Mean chronic drinking pattern, all age groups

For the mean chronic drinking pattern, the estimated consumption of energy drinks was 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 concentrations of 300, 350 and 400 mg taurine/100 ml energy drink, the intake levels of taurine after a mean chronic drinking pattern (in mg/kg bw per day) were 7.5, 8.8 and 10.0; 4.5, 5.2 and 6.0; 3.1, 3.7 and 4.2; and 3.0, 3.6 and 4.1, for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

In all age groups, the estimated MOE values were 100-333, i.e. 100 or above, for all three taurine concentrations. In addition, the estimated intakes were all below 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all age groups. Thus, VKM concludes that it is unlikely that the mean chronic intake of all three concentrations of taurine causes adverse health effects in children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

An overview of the conclusions on the mean chronic drinking pattern is given in Table 6-2. Estimated exposures unlikely to cause adverse health effects are shown in green.

Table 6,-2 An overview of the conclusions on mean chronic intake of energy drinks. Green: estimated exposure to taurine is unlikely to cause adverse health effects.

	Taurine **Mean chronic drinking pattern**		
Energy drinks **Age groups**	**300 mg/100 ml**	**350 mg/100 ml**	**400 mg/100 ml**
Children (3 to <10 years)			
Children (10 to <14 years)			
Adolescents (14 to <18 years)			
Adults (≥18 years)			

High chronic drinking pattern, all age groups

For the high chronic drinking pattern, the estimated consumption of energy drinks was 163, 180, 211 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. For the concentrations of 300, 350 and 400 mg taurine/100 ml energy drink, the intake levels of taurine after a high chronic drinking pattern (in mg/kg bw per day) were 21.2, 24.7 and 28.2; 12.4, 14.5 and 16.6; 10.3, 12.0 and 13.8; and 13.7, 16.0 and 18.3, for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively.

For children (3 to <10 years), the estimated MOE values were 47, 40 and 35, for the three taurine concentrations of 300, 350 and 400 mg/ml, respectively, i.e. all below 100. In addition, the estimated intakes were all above 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all three taurine concentrations. Thus, VKM concludes that a high chronic intake of all three concentrations of taurine from energy drinks may represent a health risk in children (3 to <10 years).

For children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), the estimated MOE values were in the range of 55-97, i.e. all below 100 for all three taurine concentrations. However, the estimated intakes were all below the intake level of 21 mg/kg bw per day (the intake considered unlikely to cause adverse health effects based on human studies) for all three taurine concentrations in all age groups. Thus, VKM concludes that it is unlikely that a high chronic intake of any of the three concentrations of taurine from energy drinks causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

An overview of the conclusions on the high chronic drinking pattern is given in Table 6-3. Estimated exposures unlikely to cause adverse health effects is shown in green, whereas estimated exposures that may represent a risk of adverse health effects is shown in red.

Table 6-3 An overview of the conclusions on high chronic intake of energy drinks. Green: estimated exposure to taurine is unlikely to cause adverse health effects. Red: estimated exposure to taurine may represent a risk of adverse health effects.

	Taurine **High chronic drinking pattern**		
Energy drinks **Age groups**	**300 mg/100 ml**	**350 mg/100 ml**	**400 mg/100 ml**
Children (3 to <10 years)			
Children (10 to <14 years)			
Adolescents (14 to <18 years)			
Adults (≥18 years)			

7 Data gaps

- There is lack of an acute reference dose or other data on acute toxicity of taurine.
- Human studies on adverse effects after long-term oral exposure to taurine are lacking.
- Animal studies on chronic toxicity and carcinogenicity of taurine are lacking.

8 References

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Appendix I

Search Strategy in Ovid Medline and Embase

1. taurine*.ti. (10786)
2. (risk* or safety or adverse or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or toxicity or toxic).tw. (8776533)
3. 1 and 2 (1467)
4. (conference abstract* or letter* or editorial*).pt. (4457566)
5. 3 not 4 (1390)
6. limit 5 to (danish or english or norwegian or swedish) (1338)
7. limit 6 to human (384)
8. remove duplicates from 7 (223)
9. limit 8 to yr="2000 -Current" (158)