VKM
Vitenskapskomiteen for mat og miljø
Norwegian Scientific Committee for Food and Environment

Protocol for the risk assessment of energy drinks and caffeine

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

From the Norwegian Scientific Committee for Food and Environment (VKM)
Protocol for the risk assessment of energy drinks and caffeine

The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food and Environment
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Preparation of the protocol

Ellen Bruzell, Trine Husøy and Gro Haarklou Mathisen prepared this protocol for the risk assessment of energy drinks and caffeine. The VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics evaluated and approved the final protocol.

Assessed and approved

The protocol was drafted by (in alphabetical order):

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Gro Haarklou Mathisen – Member of the project group and project leader. Affiliation: VKM

Members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics that contributed to and approved the protocol:

In addition to Ellen Bruzell and Trine Husøy, these were (in alphabetical order):

Monica Hauger Carlsen - Member of the project group and member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) University of Oslo

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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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Abbreviations

Bw	Body weight
EFSA	European Food Safety Authority
KBS	Nutrition calculation software
NTP	National toxicology program
RCT	Randomized controlled trial
VKM	Norwegian Scientific Committee for Food and environment
WHO	World Health Organization
WoE	Weight of evidence

1 The request from the Norwegian Food Safety Authority

The Norwegian Food Safety Authority requests that the Norwegian Scientific Committee for Food and Environment (VKM) carries out a risk assessment of potential adverse health effects as a result of a) chronic mean consumption, b) chronic high consumption, and c) acute high consumption of energy drinks and caffeine among children and adolescents.

1.1 Background

The Royal Norwegian Ministry of Health and Care Services has asked the Norwegian Food Safety Authority to investigate and recommend alternative measures to protect children and adolescents from adverse health effects caused by high consumption of energy drinks.

Support material for the study shall constitute amassed knowledge of the potential health risks and data pertaining to consumption among children and adolescents in Norway.

The Norwegian Food Safety Authority is required to present the findings of the investigation along with recommendations by 15 February 2019.

1.2 Terms of reference

VKM conducted a risk assessment of the ingredients of so-called energy drinks in 2009, as well as four separate assessments of caffeine, taurine, inositol, and glucuronolactone in 2015. The Norwegian Food Safety Authority seeks a new assessment of the potential adverse health effects of a) chronic mean consumption, b) chronic high consumption, and c) acute high consumption of energy drinks and caffeine among children and adolescents.

We are predominantly interested in the age group between 9 and 18, but this will depend on the data available. A further breakdown of the material into different age ranges beyond this is likely also to be appropriate. This can be discussed in more detail.

Carrying out an assessment of this sort requires a new and expanded calculation of exposure in relation to those performed in conjunction with the risk assessments from 2009 and 2015. To accomplish this, calculations, among other things, must be performed in the KBS nutrition calculation software.

We request that you perform various scenario calculations pertaining to the caffeine content in energy drinks: 15 mg caffeine/100 ml, 32 mg caffeine/100 ml, 40 mg caffeine/100 ml and 55 mg caffeine/100 ml.

The Norwegian Food Safety Authority also requests an assessment of the synergistic effects of other substances included in energy drinks, such as taurine, glucuronolactone, inositol, and various B vitamins.

To expand the earlier assessments, the Norwegian Food Safety Authority requests:

- that you perform various scenario calculations pertaining to the caffeine content in energy drinks equivalent to 15 mg caffeine/100 ml, 32 mg caffeine/100 ml, 40 mg caffeine/100 ml and 55 mg caffeine/100 ml
- that other sources of caffeine (coffee drinks and tea drinks, chocolate milk, cocoa, etc.) are also included in the exposure calculations, and that you carry out a new literature search to ascertain any new knowledge of the health risks (post-2015) associated with the consumption of caffeine in addition to those indicated by the risk assessments conducted by VKM and EFSA
- that you assess the potential health risks associated with the (simultaneous) consumption of energy drinks and alcohol
- that you assess the potential health risks associated with the consumption of energy drinks in conjunction with physical activity and in relation to dehydration.

Definition

The following definition of an energy drink applies to this request:
Energy drinks are non-alcoholic beverages that contain at least 150 mg of caffeine (from all sources) per litre, or at least 150 mg of caffeine (from all sources) per litre together with one or more additional substance or plant extract such as glucuronolactone, inositol, guarana alkaloids, ginseng, ginkgo extract, and taurine. They may also include added vitamins, minerals and/or amino acids.

The definition extends to energy drinks sweetened with sugar, or artificial sweetener, or both sugar and artificial sweetener.

Beverages based on coffee, tea, or coffee or tea extracts, where the name of the food includes the term "coffee" or "tea", are not covered by this definition of energy drinks. See Regulation on the Provision of Food Information to Consumers, Annex III.

1.3 Data

As the basis for this expanded exposure calculation, we recommend the utilisation of the following data:

- Ungkost 2015/2016 (Norwegian national dietary survey)
- Ungdata 2018 (Norwegian national survey) and other data provided by the Norwegian Directorate of Health (Hdir)
- The Consumer Council of Norway's new survey into the consumption of energy drinks among children and adolescents from 2018
- Unpublished data from the research carried out by Innlandet Hospital Trust

In addition, we request that data pertaining to the consumption of energy drinks produced by the Norwegian Mother and Child Cohort Study from autumn 2018 be included if possible.

The risk assessment can be based on VKM's risk assessment of ingredients in energy drinks from 2009, VKM's risk assessments of caffeine, glucuronolactone, inositol, and taurine from 2015 and EFSA's assessment of caffeine from 2015.

2 Problem formulation

2.1 Objectives of the risk assessment

The overall aim of the risk assessment will be to assess potential adverse health effects of energy drinks and caffeine to children and adolescents (≥9 - <18 years).

The sub-objectives will be to:

- Identify and characterise adverse health effects related to intake of energy drinks
- Identify and characterise adverse health effects related to intake of caffeine
- Evaluate whether studies published after 2015 require revision of the caffeine doses that were established by EFSA «not to give rise to safety concern» (EFSA, 2015)
- Identify and assess adverse health effects related to combined intake of energy drinks and alcohol
- Identify and assess adverse health effects related to intake of energy drinks during physical activity, especially with respect to dehydration
- Estimate the total exposure to caffeine from food and drinks
- Estimate the consumption of energy drinks and exposure to caffeine from food and drinks for three intake patterns: high acute consumption, mean chronic and high chronic consumption
- Characterise the risk
- Identify and describe factors contributing to uncertainty in the assessment

3 Hazard identification and characterisation

An effect is considered "adverse" when leading to "change in the morphology, physiology, growth, development, reproduction or lifespan 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, 2009).

3.1 Hazard identification and characterisation sub-questions

The sub-questions to be answered by the hazard identification and characterisation steps are presented in Table 3.1-1.

Table 3.1-1. Sub-questions to be answered in the hazard identification and characterisation steps.

No.	Sub-questions
1	Is intake of energy drinks related to adverse health effects in humans? Identify adverse effects and doses
2	Is intake of caffeine related to adverse health effects in humans? Identify adverse effects and doses
3	Evaluate whether studies published after May 2013 require revision of the caffeine doses that were established by EFSA «not to give rise to safety concern» (EFSA, 2015)
4	Is combined intake of energy drinks and alcohol related to adverse health effects in humans? Identify adverse effects and doses
5	Is intake of energy drinks during physical activity, especially with respect to dehydration, related to adverse health effects in humans? Identify adverse effects and doses

3.2 Literature

A full systematic procedure will be applied to the included articles.

3.2.1 Previous reports and risk assessments

Previous assessments and reports on safety/adverse effects of energy drinks and caffeine published 2013 or later will be included in the risk assessment.

3.2.2 Literature searches

An expert on literature searches at the Norwegian Institute of Public Health library will perform separate literature searches to identify relevant publications for answering the

hazard identification and characterisation sub-questions for energy drinks and caffeine. The Panel will develop the search strategies in cooperation with the search expert.

The publications will be imported and combined in the bibliographic reference management software EndNote.

Reviews will be used only to check them for citations of original studies not captured by the literature searches.

3.2.3 Study selection

A step-wise procedure is foreseen, as follows:

1. **Screening of titles and abstracts**: The screening of titles and abstracts will be performed by two reviewers working independently. When there is doubt as to whether a publication should be included, it is considered to meet the inclusion criteria.
2. **Screening of full-text publications**: For records passing the first screening based on titles and abstracts, the full-text will undergo a second screening against the inclusion and exclusion criteria by two reviewers working independently. In case of disagreement, the two reviewers will discuss the publication in order to reach consensus. If the disagreement persists, the Panel will reach a final decision.

The results of the different steps of the study selection process will be presented in the final assessment in a flowchart.

3.2.4 Inclusion/exclusion criteria

3.2.4.1 Energy drinks

For energy drinks, the aim of the literature search is to identify studies on adverse effects related to consumption. The search period will be from May 2013 to present, and the search result will be limited to human studies.

An overview of the inclusion and exclusion criteria for energy drinks is given in Table 3.2.4.1-1.

Table 3.2.4.1-1. Inclusion/exclusion criteria for studies on energy drinks.

Literature screening for data related to the following sub-questions (all sub-questions are given in Table 3.1-1) to be answered in the hazard identification and characterisation steps. 1: Is intake of energy drinks related to adverse health effects in humans? Identify adverse effects and doses 4: Is combined intake of energy drinks and alcohol related to adverse health effects in humans? Identify adverse effects and doses 5: Is intake of energy drinks during physical activity, especially with respect to dehydration, related to adverse health effects in humans? Identify adverse effects and doses		
Study design	In	Human studies
	Out	Animal studies and *in vitro/in silico* studies
Population	In	All age groups
Exposure	In	Oral
	Out	All other exposure routes
Outcome of interest	In	Adverse health effects related to oral intake of energy drinks
	Out	Studies not reporting on adverse effects of energy drinks Studies reporting on energy drink ingredients alone
Publication type	In	Scientific articles, systematic reviews, reports
	Out	Editorials Letters to the editor Commentaries Book chapters Meeting abstracts and posters

3.2.4.2 Caffeine

For caffeine, the aim of the literature search is to identify original studies on adverse health effects related to exposure. The search period will be from May 2013 to present, and the search result will be limited to human studies.

An overview of the inclusion and exclusion criteria is given in Table 3.2.4.2-1.

Table 3.2.4.2-1. Caffeine; inclusion/exclusion criteria

Literature screening for data related to the following sub-questions (all sub-questions are given in Table 3.1-1) to be answered in the hazard identification and characterisation steps 2. Is intake of caffeine related to adverse health effects in humans? Identify adverse effects and doses 3. Evaluate the need for revision of safe doses as established by EFSA 2015		
Study design	In	Human studies
	Out	Animal studies and *in vitro/in silico* studies
Population	In	All age groups
Exposure	In	Oral
	Out	All other exposure pathways
Outcome of interest	In	Adverse effects related to oral intake of caffeine
	Out	Studies not reporting on adverse effects of caffeine
Publication type	In	Scientific articles, systematic reviews, reports
	Out	Editorials Letters to the editor Commentaries Book chapters Meeting abstracts and posters

3.2.5 **Data extraction and evaluation of risk of bias**

Data from the included studies will be extracted using Table 3.2.5-1.

Table 3.2.5-1. Data extraction form (modified from EFSA et al. (2017)).

Study ID • Reference • Study name and acronym (if applicable) • Health outcome(s)	
Funding • Funding source(s) • Public/private	

Study design • Study type (e.g. RCT, cohort, etc.) • Type of blinding • Method for randomization • Year the study was conducted (start) • Duration/length of follow-up	
Subjects • Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) • Completion rate • Number of exposed/non-exposed subjects or number of cases/controls • Follow-up rates by group (%) • Sex (male/female) • Geography (country) • Age • Ethnicity • Socioeconomic status • Confounders and other variables as reported • Inclusion/exclusion criteria • Other	
Intervention/exposure • Measured levels in human biological samples (e.g. breast milk, blood, and urine) and method used (validation of the method, measures to avoid contamination of samples, etc.) • Estimated dietary exposure/intake and method used (validation of the method, measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) • Co-exposure description if applicable	
Methods for endpoint assessment • Parameters measured (units of measure, measures of central tendency and dispersion, confidence interval) • Diagnostics or method to measure health outcome (including self-reporting)	

Statistical analysis • Were sub-groups analyses predefined (yes/no, including justification)? • Statistical test • How the variables were treated (continuous, transformed, or categorical)	
• Measures of effect and all relevant statistics at each exposure level as reported in the paper, and for each sub-group and end-point when applicable • Outcome assessment (e.g. mean, median, measures of variance as presented in paper such as standard deviation, standard error of the mean, 75th/90th/95th percentile, minimum/maximum)	

The Panel will include consideration of two aspects in the evaluation of risk of bias:

- Aspects that introduce a systematic difference between the control and the exposed group only (e.g. non-randomised allocation of animals to study groups)
- Aspects potentially affecting, to the same extent, control and exposed study groups (e.g. the reliability of the method used to test the outcome).

The questions addressed to assess the risk of bias in the studies are presented in Table 3.2.5-2 (NTP, 2015). For each question, the response options are "Definitely low risk of bias (++)", "Probably low risk of bias (+)", "Probably high risk of bias (-)", "Definitely high risk of bias (--)" (Table 3.2.5-3). Whenever an element to be evaluated is not reported, this will by default be judged as "Probably high risk of bias".

Table 3.2.5-2. Evaluation of risk of bias (modified from EFSA et al. (2017)).

Number	Question	Domain	Rating (++, +, -, --)
1	Did selection of study participants result in appropriate comparison groups?	Selection	
2	Can we be confident in the exposure characterisation?	Detection	
3	Can we be confident in the outcome assessment?	Detection	
4	Did the study design or analysis account for important confounding and modifying variables?	Confounding	
5	Do the statistical methods seem appropriate?	Other sources of bias	

Table 3.2.5-3. Response options for evaluation of risk of bias (modified from EFSA et al. (2017)).

Rating	Response to the question	Description
++	**Definitely low** risk of bias	There is direct evidence of low risk of bias practices
+	**Probably low** risk of bias	There is indirect evidence of low risk of bias practices, or it is deemed that deviations from low risk of bias practices for these criteria during the study would not appreciably bias results. This includes consideration of direction and magnitude of bias
-/not reported	**Probably high** risk of bias	There is indirect evidence of high risk of bias practices, or there is insufficient information provided about the relevant risk of bias practices
--	**Definitely high** risk of bias	There is direct evidence of high risk of bias practices

The ratings of the questions (++, +, -, --) will be integrated to classify the studies in tiers from 1 to 4 corresponding to decreasing levels of risk of bias. Two reviewers will perform each evaluation independently. In case of disagreement, the reviewers will discuss until consensus is reached or the VKM Panel will reach a final decision.

3.2.6 **Weighting the body of evidence (WoE)**

All studies reporting on a given endpoint will be grouped, and the evidence will be weighted using a modified version from EFSA et al. (2017), downgrading or upgrading the confidence in the evidence. Several elements will be considered for downgrading or upgrading the confidence in the evidence:

Elements that may cause downgrading of the confidence in the evidence are:

- Risk of bias
- Unexplained inconsistency
- Imprecision

Elements that may cause upgrading of the confidence in the evidence are:

- Large effect (e.g. incidence, degrees of severity)
- Dose-response relationship
- Consistency, across study design type, dissimilar populations, or gender
- Consistency in direction of effect
- Confounding, if all relevant confounders are described and taken into account

Table 3.2.6-1 will be used for the downgrading/upgrading of the evidence. One table will be used per endpoint for energy drinks, energy drinks in combination with alcohol, energy drinks in combination with physical exercise/dehydration, and caffeine. After the downgrading/upgrading of the evidence, the overall confidence interval will be determined. The terms used to describe the levels are:

- **High confidence (++++)** in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected in the apparent relationship.
- **Moderate confidence (+++)** in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.
- **Low confidence (++)** in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship.
- **Very low confidence (+)** in the association between exposure to the substance and the outcome. The true effect is highly likely to be different from the apparent relationship.

The final decision on whether energy drinks and/or caffeine induces an adverse health effect to a given endpoint will be based on the overall confidence in the body of evidence.

Table 3.2.6-1. Form to grade confidence in the body of evidence per endpoint (modified from EFSA et al. (2017)).

Endpoint [describe]:								
	Elements triggering downgrading			**Elements triggering upgrading**				**Confidence level**
Reference number	**Risk of bias**	**Unexplained inconsistency**	**Imprecision**	**Large effect**	**Dose-response relationship**	**Consistency**	**Confounding**	
1	Describe identified risks	Describe results in terms of consistency Explain apparent inconsistency (if it can be explained)	Discuss ability to distinguish treatment from control Describe confidence intervals	Describe magnitude of response	Outline evidence for or against dose response	Describe cross-species, model, or population consistency	Address whether there is evidence that confounding would bias toward null	Confidence level of each endpoint
2 *[Repeat procedure for all relevant references]*								
3 *[Repeat procedure for all relevant references]*								
Overall conclusion on confidence								Overall confidence interval (e.g. ++)

3.3 Method for performing hazard characterisation

For the hazard characterisation, the overall confidence in the evidence for each endpoint will be transformed to likelihood (Table 3.3-1). It must be emphasized that the likelihood assessed by the WoE approach addresses only the likelihood of an association between the effect under consideration and exposure to energy drinks or caffeine. It does not address the likelihood or frequency of the effect actually occurring in humans, which depends on additional factors including the dose-response relationship of the effect (considered in hazard characterisation) and the levels of human exposure (considered in exposure assessment).

Table 3.3-1. Set of terms used to transform the overall confidence "interval" in the evidence per endpoint to overall likelihood.

Overall confidence level range	Likelihood of an association between energy drinks/caffeine and the adverse effect under consideration
++++	Very likely
From ++++ to +++	Likely
From +++ to ++	As likely as not
From ++ to +	Unlikely
+	Very unlikely

Dose-response analysis will be performed for "Very likely" and "Likely" adverse effects.

3.4 Uncertainty in hazard identification and characterisation

Factors that may contribute to uncertainty in the results of the hazard identification and characterisation steps will be identified, and possible influence on the outcome of the assessment will be described qualitatively (Table 3.4-1).

Table 3.4-1. Qualitative evaluation of influences of uncertainties in the hazard identification and characterisation steps.

Endpoint	Source of uncertainty	Direction
E.g. cardiovascular	Old patient cohorts consisting of patients with higher risk than today	+
E.g. psycho-behavioural	Analysis/self-reporting	-
E.g. various	Bias in questionnaires/peer-influence	+/-

+: uncertainty likely to cause overestimation of the hazard
-: uncertainty likely to cause underestimation of the hazard

4 Exposure

The consumption of energy drinks will be calculated for three intake patterns for three age groups.

- Intake patterns: high acute consumption, mean chronic and high chronic consumption
- Age groups: children (9 to 12 years), children/adolescents (13 to 15 years) and adolescents (16 to 17 years).

The intake scenarios will be based on national data when possible.

An overview of the sub-questions to be answered by the exposure assessment is given in Table 4-1.

Table 4-1. Exposure assessment sub-questions for the age groups children (9 to 12 years), children/adolescents (13 to 15 years) and adolescents (16 to 17 years).

No.	Sub-questions
1	What is the consumption of energy drinks in a high acute drinking pattern?
2	What is the consumption of energy drinks in a mean chronic drinking pattern?
3	What is the consumption of energy drinks in a high chronic drinking pattern?
5	What is the exposure to caffeine from energy drinks in the three drinking scenarios?
6	What is the exposure to caffeine from food and drinks?

The default body weights (bw) determined by EFSA will be used for the exposure calculations (EFSA, 2012): 3 to <10 years; 23.1 kg, 10 to <14 years; 43.4 kg, 14 to ≤18 years; 61.3. In parts of the exposure assessments Norwegian age specific body weights will be used, if applicable.

Scenarios based on actual caffeine content of energy drinks will be used to calculate exposure to caffeine from energy drinks.

Scenarios based on actual consumption and caffeine contents of caffeine-containing foods and drinks will be used to calculate the exposure to caffeine from food and drinks (not including energy drinks).

4.1 Uncertainty in the exposure assessment

Factors that may contribute to uncertainty in the results of the exposure assessment will be identified, and possible influence on the outcome of the assessment will be described qualitatively (Table 4.1-1).

Table 4.1-1. Qualitative evaluation of influences of uncertainties in the exposure estimations.

Endpoint	Source of uncertainty	Direction
E.g. intake estimates of energy drinks	Participants inclusion method	+/-
	Dietary assessment method	+/-
	Social desirability bias	-
E.g. intake estimates of caffeine	Variability in caffeine content estimates of different food items	+/-

+: uncertainty likely to cause overestimation of the exposure
-: uncertainty likely to cause underestimation of the exposure

5 Risk characterisation

The following aspects will be included in the risk characterisation:

- The consumption of energy drinks in the different drinking patterns will be compared to the consumption reported to induce adverse health effects.
- The caffeine exposure, from energy drinks alone and from other foods and drinks, will be compared to the doses reported to induce adverse health effects.
- The doses reported to induce adverse health effects will be compared to the doses concluded not to give rise to safety concerns for the included age groups (EFSA, 2015).
- Food and drinks that contribute the most to caffeine intake will be identified.

6 References

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