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General principles for the risk assessments of "other substances" in food supplements and energy drinks

Report of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety

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Assessed and approved

The report has been assessed and approved by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM).

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Members of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy are: Per Ole Iversen (chair), Livar Frøyland, Margaretha Haugen, Kristin Holvik, Martinus Løvik, Tor A. Strand, Grethe S. Tell and Arild Vaktskjold.

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

Acknowledgment

Per Ole Iversen (chair, Panel on Nutrition, Dietetic Products, Novel Food and Allergy) and Inger-Lise Steffensen (chair, Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics) are acknowledged for their valuable work on this report. Jan Alexander (the Scientific Steering Committee), Åshild Krogdahl (the Scientific Steering Committee) and Helle Margrete Meltzer (former member of Panel on Nutrition, Dietetic Products, Novel Food and Allergy) constituted a reference group and are acknowledged for their valuable comments and suggestions. Project leaders from the VKM secretariat have been Bente Mangschou and Gro Mathisen.

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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Glossary

"**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 (The European Parliament and the Council of the European Union, 2006). It is added mainly to food supplements, but also to energy drinks and other foods. In the present document, the general principles to be used for the safety assessments of "other substances" are presented.

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

An **adverse event** is considered serious if it results in death, is life-threatening, requires or prolongs hospitalisation, is a congenital anomaly or birth defect, is a persistent or significant disability/incapacity, or is another serious or important medical event.

The "**value for comparison**" is derived from the hazard identification and characterisation. The value for comparison is the level that is compared with the specific doses per day in food supplements and/or energy drinks in the risk characterisation.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food Safety (VKM) to prepare a guidance document outlining the methodology to be used for the safety assessments of "other substances".

General principles for the risk assessments of “other substances” in food supplements and energy drinks

From the terms of reference for the risk assessments of other substances:

- 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.
- For food supplements, NFSA requested risk assessment of specific doses of other substances for the general population from age 10 years and above.
- For energy drinks, NFSA requested risk assessments of drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake for energy drinks with a given concentration of other substances, for the general population from age 3 years and above.

Limitations applied to all risk assessments of other substances:

- The total exposure to a substance from other sources than food supplements and energy drinks, e.g. foods and cosmetic products, are not included in the risk assessment.
- Documentation of any potential beneficial effects from these substances is not evaluated.
- The risk assessments regard specific substances, not specific products.

General principles for the risk assessments

The risk assessments have been prepared in accordance with the template shown in Appendix 1.

Hazard identification and characterisation

The risk assessments are based on previous risk assessments of the substances and articles retrieved from literature searches. Literature searches were performed in MEDLINE and EMBASE, for some substances searches were also performed in Global Health and/or Web of Science.

A general literature search was set up (Appendix 2), and appropriate modifications were made for each search.

An inclusion criteria checklist was developed by members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the Panel on Nutrition, Dietetic Products, Novel Food and Allergy (Appendix 3). This checklist was modified when appropriate, e.g. when sufficient human studies were available, animal studies were not included. In the primary screening, titles and abstracts of all publications retrieved were independently screened against the inclusion criteria checklist. The articles that passed the primary screening were examined in full text against the same inclusion criteria. Articles were also retrieved by manual search.

Exposure

For food supplements, the exposure was estimated from the specified doses given by NFSA, and the age groups children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years) were included.

For energy drinks, the exposure was estimated for three drinking patterns (Appendix 4), for given concentrations of a substance in energy drinks, and the age groups children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years) were included.

The default body weights (bw) for these groups as determined by EFSA were used: 3 to <10 years; 23.1 kg, 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and ≥18 years; 70.0 kg (EFSA, 2012).

Risk characterisation

The estimated exposure is based on specified daily doses of food supplements and the intake of energy drinks calculated from the concentration of the substance in the energy drink and the intake of energy drink, for each age group. The risk characterisation is a comparison of these exposure estimates with the value for comparison determined in the hazard identification and hazard characterisation.

Children

When specific values for tolerance for a substance in children and/or adolescents were available, these values were used for the risk characterisation.

If no specific studies on children and/or adolescents were identified and no evidence indicated that age affects tolerance for a given substance, a tolerance as for adults, based on body weight, were assumed for these age groups.

If no studies on children and/or adolescents were available and there were reasons to assume that age affects tolerance, an additional literature search with focus on children and adolescent and no limitation back in time was conducted and examined, when the data in the main search were too scarce to conclude for subjects below 18 years.

Time limitations in the conclusions

Based on the available scientific data, conclusions may be given for limited time periods.

When there is a lack of human data of sufficient length to reach conclusions on long-term use, additional searches for subchronic or chronic animal studies were conducted.

Appendix

Appendix 1

The risk assessment template.

- Content
- Summary (in English)
- Summary (in Norwegian)
- Abbreviations and/or glossary
- Background as provided by the Norwegian Food Safety Authority
- Terms of reference as provided by the Norwegian Food Safety Authority
- Introduction
- Hazard identification and characterisation
- Exposure / Intake
- Risk characterisation
- Uncertainties
- Conclusions (with answers to the terms of reference)
- Data gaps
- References

Appendix 2

Literature search

1. Name of the substance and terms for adverse effects (risk* or adverse or side-effect*1 or hazard* or harm* or negative or toxicity or toxic)
2. Exclude conference abstracts, letters and editorals
3. The language must be English, Norwegian, Swedish or Danish

Appendix 3

The inclusion criteria checklist:

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

Appendix 4

The drinking patterns

High acute consumption

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

For adolescents (14-<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-<14 years), adolescents (14-<18 years) and adults (≥18 years). Children (3-<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 of the intake of energy drinks per day and kg bw were calculated for the age group children (10-<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 children (3-<10 years). In Table 1 the estimated intake of energy drinks for the various age groups in the three intake scenarios are presented.

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

Age groups	Intake (ml/day)		
	High acute	Mean chronic	High chronic
Children (3-<10 years)	1000	58	163
Children (10-<14 years)	1500	65	180
Children (14-<18 years)	2000	64	211
Adults (≥18 years)	2000	71	320

References

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