Minutes of the EFSA-ANSES-BfR Experts Meeting on the safety of caffeine

13 April 2015, Brussels (Belgium)

Participants

- **Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) Experts**
  Xavier Bigard (expert)

- **ANSES Staff**
  Dominique Gombert (Director of Risk Assessment Department)
  Irène Margaritis (Head of the Nutrition Unit)
  Isabelle Bordes (Nutrition Unit)

- **Bundesinstitut für Risikobewertung (BfR) Staff**
  Alfonso Lampen (Head of Department Food Safety)
  Anke Ehlers (Department of Food Safety)

- **EFSA Experts**
  Ambroise Martin (Chair of the EFSA NDA Panel)
  Ursula Gundert-Remy (Member of the Working Group on Caffeine)

- **EFSA Staff**
  Juliane Kleiner (Acting Head of Regulated Products Department)
  Valeriu Curtui (Head of the Nutrition Unit)
  Silvia Valtueña Martínez (Nutrition Unit)

- **European Commission** (Observer)
  Agnieszka Turek (Unit E.4 Nutrition, Food Composition and Information)

Background

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from the scientific community and all interested parties on the draft scientific opinion on the safety of caffeine, prepared by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) Panel and endorsed by the Panel for public consultation at its Plenary meeting on 10 December 2014. The written public consultation for this document was open from 15 January 2015 to 15 March 2015. As part of EFSA's public consultation, a stakeholder meeting was held in Brussels on 5 March 2015. Nearly 70 representatives from EU Member States, consumer organisations, industry bodies and the European Commission met to exchange views on the draft risk assessment of caffeine. The objectives of the meeting with EFSA/ANSES/BfR experts and staff of 13 April 2015 aimed to further clarify some of the remaining issues.

1. Opening and objectives of the meeting

The chair (Juliane Kleiner) welcomed the participants, who briefly introduced themselves. The chair presented the objectives of the meeting, which were to outline and discuss key aspects regarding the interpretation of the terms of reference (ToR) received from the European Commission, the sources of data used to derive dietary intakes of caffeine across the EU, and the rationale followed for the hazard assessment and risk characterisation. If potential divergent views are identified between EFSA and ANSES and/or BfR activities in relation to the safety assessment of caffeine EFSA, ANSES and BfR will discuss the source of divergence and try to resolve them, or alternatively explore how to effectively explain such divergences. Suggestions for changes in the EFSA opinion will be brought to the attention of the NDA Panel.

In addition, the participants agreed on the following procedural aspects: a draft joint report in the form of minutes of this meeting, prepared by EFSA, will be shared with all participants for comments and agreement within one week of the end of the meeting.

The agreed joint report will be published together with the EFSA NDA Panel's opinion on the safety of caffeine. EFSA's opinion on the safety of caffeine is scheduled for possible adoption at the 64th NDA Plenary meeting, which will take place from 22 to 24 April 2015. If adopted, the final opinion is likely to be published by the end of May 2015.

2. Interpretation of the Terms of Reference (ToR)

2.1 EFSA presentation

It was acknowledged that EFSA's task and the interpretation of the ToR made by the NDA Panel may have not been sufficiently communicated in the draft opinion, particularly in relation to the subgroups of the general population which were considered in the assessment.

EFSA was tasked to provide advice on:

i) a tolerable upper intake level (UL) for caffeine, from all sources, for the general population and as appropriate, for specific subgroups of the population, including but not limited to, individuals performing physical activity of various intensities, women of childbearing age, pregnant women, breastfeeding women, children and adolescents OR in the absence of a UL, to provide advice on a daily intake of caffeine, from all sources, that does not give rise to concerns about harmful effects to health for the general population and as appropriate, for specific subgroups of the population;

ii) a safe/recommended timing of caffeine consumption prior to the physical activity;

iii) the extent to which the consumption of caffeine together with other food constituents, such as alcohol or substances found in energy drinks, could present a risk to health and for which additional or different recommendations should be provided;

iv) possible interactions between caffeine and synephrine and the safety of food products containing these two substances.

The mandate was interpreted by EFSA as follows:

a) to provide advice on a daily intake of caffeine from all sources which, if consumed ad libitum and throughout the day for long periods of time, does not give rise to concerns about harmful effects to health for the healthy population, divided into various life-stage groups as appropriate, but excluding sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions;

b) for the specific group of individuals performing physical activity, to advise on caffeine consumption (dose and timing) prior to the physical activity which does not give rise to concerns about harmful effects to health for this population subgroup; and

c) to advise on whether, and the extent to which, the consumption of caffeine together with other food constituents, such as alcohol, or substances found in energy drinks, or p-synephrine could present a risk to health and for which additional or different recommendations should be provided. Advice should focus inter alia on:

    a. a daily intake of caffeine when combined with other food constituents, and

    b. a recommended interval between caffeine and other food constituents' consumption to prevent possible interactions.

EFSA clarified that it was out of the scope of this opinion to address possible adverse health effects of caffeine given as medicines, or administered via other routes than the oral route, in subgroups of the population selected on the basis of a disease condition, in combination with medicines and/or drugs of abuse, in combination with alcohol doses which, by themselves, pose a risk to health (e.g. during pregnancy, binge drinking), as well as to address possible adverse health effects of alcohol, p-synephrine or substances present in "energy drinks" other than caffeine (D-glucurono-γ-lactone and taurine), and/or the doses at which adverse effects may occur, when consumed on their own, rather than in combination with caffeine, or possible beneficial health effects of caffeine, or of particular dietary sources of caffeine.

Upon request of ANSES, the European Commission clarified that the outcome of EFSA's risk assessment on the safety of caffeine will be used by risk managers to decide on the authorisation of health claims on caffeine for which EFSA issued a positive scientific opinion and that are currently on hold (i.e. health claims related to caffeine and increased alertness, increased attention, increase in endurance capacity, increase in endurance performance, and reduction in the rating of perceived exertion/effort during exercise[1,2]).

3. Dietary intake of caffeine

3.1 ANSES presentation

ANSES summarised how dietary intake data and data used for risk characterisation reported in the EFSA opinion compared to ANSES data. ANSES noted the wide range of caffeine content in beverages and that the mean caffeine content in chocolate beverages seemed high. It was unclear where the figure for cappuccino attributed to ANSES in the EFSA opinion was coming from, and why maximum values, in addition to mean values,

[1] http://www.efsa.europa.eu/en/search/doc/2054.pdf

[2] http://www.efsa.europa.eu/en/search/doc/2053.pdf

were not used as a conservative approach to characterise the risk for acute caffeine consumption (worse-case scenario). It was also unclear the choice of figures from different publications to calculate mean concentrations of caffeine in food and beverages to be used for the intake assessment. It was proposed to use caffeine consumption from all sources on single days to characterise the risk of acute consumption in adolescents and adults, as has been done for children, and it was asked why data to calculate single doses of caffeine consumption in these population subgroups were not available. It was noted that results for caffeine intakes and risk characterisation were rather close in the EFSA and ANSES assessment, except for children and adolescents, for which the percentage of the population exceeding the threshold were lower in the ANSES assessment.

3.2 BfR presentation

BfR explained that, in its view, EFSA advice should consider realistic situations of high exposure to caffeine from "energy drinks", for example by taking into account the BfR report "Event-related survey of high consumers of energy drinks", in which adolescents attending e.g. discos, music and sports event or LAN parties were asked about consumption of energy drinks, also in combination with alcohol. From BfR's perspective, a higher risk for adverse effects from "energy drink" consumption may apply especially to these high consumers and in particular in combination with intensive physical activity and alcohol. BfR requested a clarification on why data in Table 4 reporting on "energy drink" consumption on a "single session" by adolescents were not used for the risk characterisation, but rather data on "energy drink" consumption in relation to physical activities (Table 5), noting that reference to Table 4 in the risk characterisation section may have been a mistake. Also the prevalence data of "high acute" adolescent consumers of "energy drinks" (> 1L) from the EFSA's "energy drinks" report could have been used for that purpose. It was pointed out that in Annex E of the draft EFSA opinion, the contribution of "energy drinks" to total caffeine consumption in the National Nutrition Survey II was reported as 0.0, but the fact is that this survey did not ask about the consumption of "energy drinks" specifically, and thus the zero value should be replaced by n.a or similar. This may have been the case in dietary surveys from other Member States, particularly those for which data was collected when "energy drinks" were not in the market, or had only been recently placed in the market. Questions were asked regarding which would be the "worse-case scenario" for adolescents and why national data from EFSA's "energy drinks" report was not included in the opinion.

3.3 EFSA presentation

EFSA presented a summary of the main comments received during the public consultation on the draft opinion, including the stakeholder's meeting, and how the WG on caffeine was considering to address this in preparation for the NDA Plenary meeting. Several comments were received questioning the use of EFSA's "energy drink" report to characterise the risk of acute caffeine consumption in adolescents, because intake data on a weight basis were not available in the published report and using the 200 mg value, as for adults, may have not been appropriate given the lower body weight of this population subgroup, and the fact that a "single session", defined as "a night out" or a "sports session", may have extended beyond two hours. It was considered, as an alternative, to characterise the risk for adolescents as for children i.e. using caffeine consumption from food and beverages on single days, as a conservative approximation, as suggested by ANSES. Data from dietary surveys in the EFSA's Comprehensive database currently lacks harmonisation to allow calculations of caffeine consumption from all sources on single sessions.

Clarifications have been introduced in the draft opinion regarding the assumptions made and the conversion factors used to calculate mean caffeine content in cocoa beverages.

Still, it was acknowledged that the value of 42 mg/L used for cocoa beverages consumed mostly by children may have been higher than in other assessments, and this may be one reason why the percentage of children and adolescents exceeding the threshold is higher in the EFSA opinion than in the ANSES opinion, since chocolate products are major contributors to total caffeine intakes in many countries for these population subgroups. Similarly, high variability regarding the caffeine content of coffee and coffee drinks was acknowledged. Since coffee was the major contributor to caffeine intakes in all countries for which estimates of the 95th percentile of daily caffeine intake exceeded 400 mg, the use of a mean value for caffeine in coffee for all countries may not accurately reflect caffeine intakes in all of them. More accurate estimates of caffeine intakes within a given country could be achieved by using national analytical data, whenever available. It was explained that data from the BfR report "Event-related survey of high consumers of energy drinks" was not used for the risk characterisation because the sample of adolescents interviewed could not be considered representative of the whole adolescent population in Germany, and that only national or regional surveys were usually used by EFSA for pan-European risk assessments. It was also explained that the use of maximum values to characterise the risk of caffeine consumption from food and beverages on single days would lead to caffeine intakes which are biologically implausible and that using the 95th percentile was already taking into consideration high caffeine consumers in the general population. It was finally acknowledged that, as further clarified in the draft opinion, the EFSA Comprehensive Database did not include data from food supplements.

3.4 Conclusions

- The caffeine value for cappuccino attributed to ANSES in Table 1 was a copy-and-paste mistake. This will be corrected in the opinion and mean values for this beverage recalculated, as well as the reference made to Table 4 throughout the opinion in relation to the percentage of subjects consuming "energy drinks" in combination with physical activities (which should read Table 5), as noted by BfR. The percentage of subjects exceeding single doses of caffeine of no concern at rest and in relation to physical exercise will be reported in sections 3 and 6 referencing the appropriate tables.

- The use of a mean value for caffeine in coffee for all countries may not accurately reflect caffeine intakes in each country. More accurate estimates of caffeine intakes within a given country could be achieved by using national occurrence data, whenever available.

- Data on "high consumers" only cannot be used by EFSA for the risk characterisation because they are selected groups and thus not representative of the general population or groups thereof.

- For dietary surveys included in the 2010 release of the EFSA Comprehensive Database (including the National Nutrition Survey II conducted in Germany), which was based on the FoodEx classification, products coded as "carbohydrate-rich energy food products for sports people" or "carbohydrate-electrolyte solutions for sports people" at the 3rd level of FoodEx, within the first level category of "Products for special nutritional use", were used to calculate caffeine consumption from "energy drinks" and their contribution to total caffeine intake. For dietary surveys included in the 2014 release (including the EsKiMo survey conducted in Germany), which was based on the FoodEx2 classification, a specific code for "energy drinks" was available. This will be further clarified in Appendices A and E. The years of data collection for each survey included in the EFSA Comprehensive Database are specified in Appendix A.

4. Hazard assessment and risk characterisation of caffeine

4.1 ANSES presentation

ANSES presented a summary of controlled intervention studies investigating the effects of caffeine consumed before/during/after exercise on blood pressure, body temperature, hydration status and myocardial blood flow. It was noted that in these types of studies conducted under controlled conditions, the exercise tests were stopped for safety reasons if a body temperature >39.5° Celsius was reached, which may not be the case in real life conditions. The major concern related to subjects with established hypertension or coronary heart disease who were advised to engage in physical activities as part of the management of the disease. It was noted that the conclusions in section 5 (i.e. single doses of caffeine up to 200 mg, corresponding to about 3 mg/kg bw for a 70 kg adult, or the same amount consumed within a short period of time, are unlikely to induce clinically relevant changes in blood pressure, myocardial blood flow, hydration status or body temperature) of the opinion were not in line with the interim conclusions in section 4.4.2.1. (conclusions on hydration status and body temperature), where it is stated that higher doses of caffeine (6 mg/kg bw equivalent to 420 mg for a 70 kg adult) ingested about one hour prior to prolonged endurance exercise in a hot environment do not affect body temperature or hydration status beyond what could be expected from the testing conditions, and that changes in body temperature and hydration status under these conditions are of no health concern if fluid losses can be timely replaced. It was found that these interim conclusions were not supported by the available evidence.

ANSES's concerns relative to the consumption of caffeine and its effects on the central nervous system, also in combination with alcohol were summarised. It was suggested that RCT on the effects of caffeine on subjective ratings of alcohol intoxication may not be the only evidence to consider as they don't represent real life conditions of consumption, but also the effects of caffeine on other outcomes which could influence risk taking behaviour in real life conditions, such us mood, sedation or stimulation. It was questioned why data used by the Nordic Working Group on Food Toxicology and Risk Evaluation to established a LOAEL for tolerance development with withdrawal symptoms in children (1.0–1.3 mg/kg bw) was not used by EFSA to establish a level of no concern for this population subgroup.

ANSES expressed its concerns regarding the adverse health effects of caffeine consumption in particularly sensitive subgroups of the population, e.g. polymorphisms of the CYP1A2 gene classified as "slow" caffeine metabolisers. It was pointed out that case-control studies reporting a higher risk of incident hypertension in this population subgroup should have considered by the NDA Panel in the risk assessment, and that this may be of particular concern in subjects with hypertension, as observed in a prospective cohort study. It was reiterated that specific subgroups of the population particularly at risk should be considered specifically in the risk assessment. More generally, ANSES questioned the sole use of RCT and prospective studies in EFSA's risk assessment: if there is no debate on their higher validity, other types of studies might still be of interest when RCT and prospective studies are not available, and consistency between different types of studies may add to the level of proof of a relationship. Clarification was asked regarding the EFSA conclusion that combining caffeine and synephrine did not give rise to concerns for the general population.

It was found that the EFSA opinion may not provide all the information needed by risk managers to take measures regarding the authorisation of health claims on caffeine, particularly regarding conditions and restrictions of use, as well as information to be provided to consumers on the label.

4.2 BfR presentation

BfR shared with ANSES concerns regarding subgroups of the population particularly at risk, and that case reports of adverse reactions to caffeine when consumed in "energy drinks" in high amounts, also in combination with alcohol, should be considered in the risk assessment. It was proposed to clearly explain in the opinion the health outcomes and the doses of other components of "energy drinks" and alcohol which were considered to conclude that no interaction between caffeine and these substances was to be expected. It was found that conclusions on the lack of interaction between caffeine and alcohol regarding cardiovascular disease risk for acute consumption on the basis of the three case cross-over studies described were inappropriate, because not enough information was contained in these studies about co-consumption.

4.3 EFSA presentation

EFSA explained that sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions are excluded from the safety assessment. In addition, the genetic polymorphisms for genes involved in caffeine metabolism, like CYP1A2, explain only a small proportion of the inter-individual variability in caffeine intake, and there is no evidence that such polymorphisms influence the risk of CVD-related outcomes in the general population, although prospective cohort or human intervention studies investigating this hypothesis are currently not available for any subgroup of the general population. Taking into account that the distribution of "fast" and "slow" caffeine metabolisers in the general population is roughly 50:50, both phenotypes may have been equally represented in the human studies considered for the risk assessment. EFSA noted that there is currently no evidence to conclude that "slow metabolisers" are at higher risk for adverse health effects of caffeine consumption *ad libitum*, or to establish caffeine levels of no concern for this population subgroup. Data from cross-sectional studies on the relationship between genetic polymorphisms for genes involved in caffeine metabolism, like CYP1A2, and health outcomes, also available for pregnancy outcomes, were contradictory (studies were reviewed by EFSA but not included in the draft opinion due to the high risk of bias and reverse causality, as specified in the methodological considerations). EFSA clarified that data available from studies in children regarding the adverse effects of caffeine on the CNS are generally poor. Studies are small and heterogeneous, and do not provide a basis to derive a level of intake of no concern. Data in infants receiving very high doses of caffeine for the treatment of medical conditions do not show long-term adverse effects on the CNS. In this context, the Panel extrapolated from data for adults on a weight basis, as is done in most risk assessments for which robust data in children and adolescents are lacking, and used the available studies in this population subgroup as supporting evidence only.

EFSA clarified that the conclusions of the Panel refer to the lack of available data to conclude on whether the addition of synephrine would modify the effects of caffeine on BP, and not to a lack of interaction. EFSA also explained that the adverse health effects of alcohol when consumed either alone or in combination with caffeine at amounts beyond 0.65 g alcohol/kg bw, leading to a BAC of about 0.08 % were not assessed because of being outside the scope of the opinion. The effects of caffeine consumption in combination with alcohol on outcomes other than the subjective perception of alcohol intoxication has not been systematically assessed prospectively using validated measures.

4.4 Conclusions

- The scientific advice will address all aspects which may be needed by risk managers to take decisions about the authorisation of health claims on caffeine and physical performance. However, EFSA is obliged to respect the boundaries between risk assessment and risk management, and the advice provided cannot go beyond the scientific assessment, carried out under the ToR provided by the EC, as interpreted by EFSA. Interim conclusions regarding hydration status and body temperature, and how they relate to the final conclusion in section 5, will be revisited by the NDA Panel, as well as the conclusions on the interaction between caffeine intakes and alcohol for acute cardiovascular events.The text and conclusions of the draft opinion will be expanded to clarify the health outcomes and the doses of caffeine and other components of "energy drinks" and alcohol which were considered by the Panel to reach such conclusions.

- Efforts will be made to introduce more clarifications on the ToR, on the results of the risk assessment, and on the results of the risk characterisation in the conclusions and summary, in particular regarding the fact that the derived safe intake levels refer only to the general healthy population and subgroups thereof.

Concluding remarks

The chair thanked all participants for their availability and contributions.