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EDE contribution to the hearing on the draft EFSA opinion on caffeine

EDE would like to thank EFSA for the invitation to present our views at the stakeholder meeting on the 5th of March and the opportunity to engage into discussions with members of EFSA's caffeine working group who have contributed to this opinion. In addition, EDE will also provide structured written comments through EFSA's website by the 15th of March as requested in the public consultation.

EDE and its members have reviewed EFSA's draft scientific opinion on the safety of caffeine in detail. We would like to thank the Working Group and Panel members for a well-structured opinion which reviews and summarises the very comprehensive scientific literature about caffeine. We also welcome the approach EFSA has taken regarding the inclusion and exclusion criteria for the available scientific literature and individual studies. As for every EFSA opinion, we are convinced that only papers and studies which meet certain scientific quality criteria should be considered, and data not meeting these criteria, as for example anecdotal evidence, should be excluded.

1. General comments and caffeine intake from all sources

We do support EFSA's finding that caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg bw) do not raise safety concerns for adults in the general population, except pregnant women. We also welcome the clear statement on lactating women which clarifies that this group can be treated in the same way as non-pregnant adults for which caffeine intakes from all sources up to 400 mg per day do not raise safety concerns.

EDE took note of the *Extensive literature search as preparatory work for the safety assessment for caffeine*[1] for which EFSA commissioned the consultancy Ricardo-AEA Ltd and others. We would be grateful if EFSA could elaborate on the approach the Working Group took for reviewing and analysing the literature in this literature search.

[1] Bull S. et al., 2015. Extensive literature search as preparatory work for the safety assessment for caffeine. EFSA supporting publication 2015:EN-561, 98 pp.

2. Caffeine consumption data

The Panel uses two main sources for assessing the intake of caffeine. The first one is the EFSA Comprehensive European Food Consumption Database. Here the Panel has taken a robust scientific approach, considering all sources of caffeine from unselected populations and population subgroups, and assessing the contribution of different food groups to total caffeine intakes. We agree that due to the differences between included surveys from different countries, direct between-country comparisons are impossible to make and thus, ranges of means and 95th percentiles of daily caffeine intake from all sources across surveys should be interpreted with caution. If included in the "Summary" section (page 2 ff.) of the scientific opinion at all, the 95th percentile data should be put into perspective, i.e. also the main contributors to daily caffeine consumption, namely coffee, tea, cola beverages and chocolate should be identified in the summary.

The second source for data on caffeine intake is the EFSA commissioned Zucconi-study from 2013[2]. On page 16, line 624 f of the draft scientific opinion, it is stated that a "single session" is defined as a period of time of about two hours. However, in the referenced report from Zucconi it is stated on page 32, footnote 22, that a "single session" is a period of time of a couple of hours (e.g. a night out, a study or sport session). Such activities can easily extend over a time period of 6 – 8 hours. Also considering an average caffeine plasma half-life of 4 hours for non-pregnant adults, we believe that a clarification of the term "single session" is needed.

We also refer to our letter to EFSA of 15th March 2013 with detailed comments regarding the methodological deficits of the Zucconi report. As there is not sufficient time to discuss those in detail at the hearing, we have attached our 2013 letter to our written contribution at hand.

In summary for the Zucconi report, we emphasize that in particular the findings for children are not representative and that due to the methodology the caffeine intake data overestimate consumption. Another important outcome of the report is that the contribution from energy drink consumption to total caffeine consumption is moderate, i.e. 8% for adults and 13% for adolescents, respectively, which clearly shows that other categories such as coffee, tea and soft drinks are key contributors to daily caffeine intake.

3. Caffeine and the cardiovascular system

In its draft opinion (lines 1067 ff.), the Panel states that early metabolic studies found that single caffeine doses of 200 – 250 mg are able to induce cardiac (mostly atrial) arrhythmias in healthy, caffeine naïve subjects and thereby references a study from Dobmeyer et al. (1983)[3]. The Dobmeyer study was a rather small study with twelve patients but only seven "normal" (i.e. healthy) volunteers. In line with the Panel's established inclusion and exclusion criteria[4] only data from the seven healthy

[2] Zucconi S, Volpato C, Adinolfi F, Gandini E, Gentile E, Loi A and Fioriti L, 2013. "Gathering consumption data on specific consumer groups of energy drinks". Supporting Publications. 190 pp.

[3] Dobmeyer DJ, Stine RA, Leier CV, Greenberg R and Schaal SF, 1983. The arrhythmogenic effects of caffeine in human beings. N Engl J Med, 308, 814-816.

[4] On page 27, in lines 1032-1039, it is stated: The Panel considers that […] studies conducted in subjects selected on the basis of a disease condition (e.g. established CVD, neurological or psychiatric diseases, behavioural or sleep disorders, diabetes mellitus and other metabolic disorders, renal or hepatic insufficiency, open angle glaucoma) do not allow conclusions to be drawn on the safety of caffeine for the

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volunteers allow conclusions to be drawn on the safety of caffeine for the general healthy population. Five out of seven healthy volunteers experienced provoked tachycardia after caffeine doses, however two of them also did so before caffeine treatment.

Furthermore, more recent publications have put the findings from this early study into perspective, such as a review about caffeine and cardiac arrhythmias by Pelchovitz and Goldberger from 2011[5]. In their review, the Dobmeyer study was discussed in detail and eventually found to have limitations that won't allow drawing firm conclusions. In their review, Pelchovitz and Goldberger also performed an assessment of eleven prospective studies to examine the effect of caffeine on arrhythmia. The Danish Diet, Cancer and Health study (47,949 subjects followed for an average of 5.7 years), the Women's Health Study (33,638 women followed for an average of 14.4 years), and some smaller-scale studies in healthy men or men with heart disease or known arrhythmias showed no effect of up to 450 mg caffeine/day on heart rhythm. The review concludes that in most patients (even those with known or suspected arrhythmia), moderate doses of caffeine are well tolerated. Further, the review concludes that human studies examining the effect of caffeine on cardiovascular endpoints are consistent in finding minimal to no effect of caffeine on coronary artery disease or stroke, and that large human studies generally reveal no association between caffeine and arrhythmias.

We suggest also to consider the study by Fernández-Elías VE et al. (2014)[6], investigating the metabolic, respiratory and cardiovascular post-exercise responses to pre-exercise graded caffeine ingestion. Twelve aerobically trained subjects cycled for 60-min at 75% VO_2max after ingesting placebo (0 mg of caffeine per kg of body weight) or 0.5, 1.5, 3.0 and 4.5 mg kg^{-1} on five occasions. During the 3 hours post-exercise, *inter alia*, heart rate and blood pressure were analyzed. None of these variables were statistically affected by pre-exercise caffeine ingestion between 0.5 and 4.5 mg kg^{-1}. In summary, pre-exercise ingestion of ergogenic caffeine doses did not alter post-exercise cardiovascular responses in this study.

4. Caffeine and hydration status

We suggest that the following publications should be considered for inclusion into the final scientific opinion:

- Recent scientific research (Silva et al., 2013)[7] showed that a caffeine dose of 5 mg/kg bw/day does not alter total body water and fluid distribution in healthy men, regardless of body composition, physical activity or daily water ingestion.
- A comprehensive meta-analysis by Zhang et al. from 2014[8] of sixteen studies looked into the diuretic effects of caffeine consumption (median 300 mg), comparing rest and exercise

general healthy population.

[5] Pelchovitz, D and Goldberger J, Caffeine And Cardiac Arrhythmias: A Review Of The Evidence, 124 Am. J. Med. 284, 285 (2011).

[6] Fernández-Elías VE, Del Coso J, Hamouti N, Ortega JF, Muñoz G, Muñoz-Guerra J, Mora-Rodríguez R. Ingestion of a Moderately-High Caffeine Dose Before Exercise Increases Post-Exercise Energy Expenditure. Int J Sport Nutr Exerc Metab, 2014 Jun 5

[7] Silva AM, Júdice PB, Matias CN, Santos DA, Magalhães JP, St-Onge MP, Gonçalves EM, Armada-da-Silva P, Sardinha LB. Total body water and its compartments are not affected by ingesting a moderate dose of caffeine in healthy young adult males. Appl Physiol Nutr Metab. 2013 Jun;38(6):626-32

[8] Zhang Y, Coca A, Casa DJ, Antonio J, Green JM, Bishop PA. Caffeine and diuresis during rest and exercise: A meta-analysis. J Sci Med Sport.

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situations. Based on a corresponding sub-group analysis, the authors found clear indication that caffeine induced diuresis disappears under physical exercise. The authors suggest that sports, exercise, and work occurring in hot climates could reduce the renal plasma flow and glomerular filtration rate and accordingly, even less diuretic effect of caffeine could be expected. Therefore, this recent meta-analysis provides further scientific evidence that caffeine consumption in combination with physical exercise and heat conditions does not lead to dehydration.

5. Caffeine in combination with alcohol consumption

Please note that with regard to page 41, lines 1703 f., of the draft scientific opinion, Marczinski and Fillmore (2006)[9] did not report a so-called "masking effect" of caffeine at the highest caffeine dose tested (4 mg/kg bw). In the corresponding review and meta-analysis by Benson et al. (2014)[10] the following explanation is provided: Intoxication rates were significantly reduced after combining alcohol with the lower dose of caffeine (2 mg/kg bw) but not after combining alcohol with the higher dose of caffeine (4 mg/kg bw). Closer inspection of the data reveals that the authors appear to have conducted a one-tailed t-test (although this is not specified in the paper) between the alcohol-alone and alcohol–caffeine group and erroneously reported a t statistic of 1.77 as producing a p value of 0.05. In fact the correct p value for a t of 1.77 with 11 degrees of freedom is 0.052; the critical value of t for a one-tailed test at 0.05 with 11 degrees of freedom is 1.796, thus the reported difference between the alcohol only and alcohol–energy drink conditions is questionable. In summary, this leads to the conclusion that all alcohol - caffeine conditions investigated by Marczinski and Fillmore (2006) did not show any significant "masking effect" of caffeine at the doses tested (2 mg/kg bw and 4 mg/kg bw).

EFSA's clear statements regarding the absence of interactions between, caffeine, alcohol, physical activity and energy drink constituents – which confirm their opinion on energy drink ingredients from 2009 – support the adequacy and proportionality of currently existing risk management measures such as additional labelling.

6. Caffeine intake levels of no concern in children

In order to derive a safe daily intake level for caffeine in children and adolescents, the Panel has considered the full body of currently available scientific evidence. It should be noted in the final scientific opinion that the proposed daily caffeine intake level of no concern in children (3 mg/kg bw) adequately considers the fact that the children's body is still developing, and also that caffeine clearance in children and adolescents is at least that of adults, if not faster. This level therefore represents the cautious approach which is warranted in this age group.

2014 Aug 9. pii: S1440-2440(14)00143-1

[9] Marczinski, C.A., Fillmore, M.T., 2006. Clubgoers and their trendy cocktails: implications of mixing caffeine into alcohol on information processing and subjective reports of intoxication. Exp. Clin. Psychopharmacol. 14, 450–458

[10] Benson S, Verster JC, Alford C, Scholey A, Effects of mixing alcohol with caffeinated beverages on subjective intoxication: A systematic review and meta-analysis, Neurosci Biobehav Rev, 2014 Jul 15;47C:16-21. doi: 10.1016

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However, children and adolescents encompass an age range of 3 to 18 years. Considering the available knowledge and evidence about caffeine metabolism, we raise the question if a staged approach for setting a daily caffeine intake which is of no concern would be possible for older adolescents. For example, a daily caffeine intake which is of no concern of 3 mg/kg bw for the age group 3 – 12 years, 4 mg/kg bw for 13 – 14 years and 5 mg/kg bw for 15 – 17 years. For adults (18 years and older) the level of 5.7 mg/kg bw – as already recommended in the draft opinion – would apply.

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ABOUT EDE

Energy Drinks Europe is the leading trade association in the area of energy drinks. Our objective is to take leadership on all issues related to energy drinks, engage in open dialogue with public stakeholders and promote the responsible marketing of energy drinks.

Attachment:
EDE letter to EFSA of 15 March 2013 with comments on the Zucconi report

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