Terms of Reference and previous Safety Assessments

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BACKGROUND PROVIDED BY THE COMMISSION

Member States expressed concerns regarding conditions of use for health claims on physical performance proposed by the Commission ⇒ 300 mg per day ⇒ based on the conclusions of the Scientific Committee on Food in 1999 for pregnant women.

Since then, several bodies issued recommendations on maximum daily intakes of caffeine for the general population and specific population subgroups (e.g. adults, children, pregnant women) .

At EU level, caffeine has only been assessed in the context of “energy drinks”, but the safety of caffeine intake from all sources has not yet been assessed.

TERMS OF REFERENCE - 1

- Review the existing scientific data on the potential link between caffeine intakes, from all sources, and possible adverse health effects in the **general population and** as appropriate, in **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;
- **Provide advice on 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. Advice on a safe/recommended timing of caffeine consumption prior to the physical activity.
- **In the absence of tolerable upper intake level (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.

TERMS OF REFERENCES - 2

- Advise whether, and **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**. Advice should focus inter alia on: 1) a daily intake of caffeine when combined with other food constituents and 2) a recommended interval between caffeine and other food constituents' consumption to prevent possible interactions.

In a follow-up communication, the European Commission (EC) informed EFSA that a number of Member States have issued risk assessments or warnings in relation to food supplements **containing synephrine in combination with caffeine. In addition the European Commission** referred to a number of Rapid Alert System for Food and Feed notifications on food supplements containing synephrine which often contain also caffeine. The EC and EFSA agreed that this mandate will also cover **possible interactions between caffeine and synephrine** and the safety of food products containing these two substances.

PREVIOUS SAFETY ASSESSMENTS: CAFFEINE - 1

➢ **SCF (1999)**

- Pregnancy: intakes up to 300 mg/day appear to be safe during pregnancy.
- Children: 5.3 mg/kg bw/day could result in transient behavioural changes, such as increased arousal, irritability, nervousness or anxiety.

➢ **FSANZ (2000)**

- No causal relationship with hypertension or cardiovascular disease (CVD)
- 2.5 and 3 mg/kg/day increase axiety in children and adults, respectively
- 100 mg (1.4 mg/kg bw) reduce ability to sleep in adults.

➢ **Health Canada (2006)**

- Adults: 400 mg per day not associated with adverse health effects
- Pregnancy: should not exceed 300 mg per day
- Children: not more than 2.5 mg/kg bw (anxiety) in one RCT in children

PREVIOUS SAFETY ASSESSMENTS: CAFFEINE - 2

- **UK Committee of Toxicology (COT, 2008)**

Association with increased risk of fetal growth restriction (FGR) at caffeine intakes of about 200 mg/d and perhaps even lower.

- **NNT (2008)**

considered 2.5 mg/kg bw as a LOAEL for children (anxiety)

- **Belgium SHC (2012)**

Adults: 400 mg/d no association with adverse health effects
Pregnancy: adviced not to exceed 300 or even 200 mg/d
Children: maximum recommended intake: 2.5 mg/kg bw/d

COMBINATION WITH OTHER CONSTITUENTS - 1

➢ **SCF**

- **1999**: "Energy drinks" not of health concern for pregnant women based on the assumption that they would replace other caffeine sources.
- **2003**: Unlikely that D-glucuronolactone would have any interaction with caffeine, taurine, alcohol or the effects of exercise. Taurine: could not rule out interaction with stimulatory effects of caffeine on the CNS and with diuretic actions of caffeine and taurine; majority of studies suggest that caffeine would not exacerbate the adverse effects of alcohol.

➢ **EFSA ANS Panel (2009)**

- Unlikely that D-glucuronolactone would have any interaction with caffeine, taurine, alcohol or the effects of exercise
- Additive interactions between taurine and caffeine on diuretic effects are unlikely.
- No concerns regarding levels of taurine and D-glucuronolactone at the levels currently used in "energy drinks" and mentioned in that opinion.

COMBINATION WITH OTHER CONSTITUENTS - 2

➢ BfR (2008, 2009)

- Adverse health effects upon consumption of large amounts of “energy drinks” in combination with intense physical exercise or alcohol could not be ruled out
- Advised children, pregnant women, lactating women or individuals who are “sensitive” to caffeine not to consume “energy drinks”, particularly in large amounts.
- Consumption of “energy shots” pose no risk to health if consumed in accordance with the suggested daily intake levels of 50-200 mg caffeine.

➢ UK CoT (2012)

- Available evidence does not support a toxicological or behavioural interaction between caffeine and alcohol. The CoT noted the limitations of the data available and the uncertainty linked to this statement

COMBINATION WITH OTHER CONSTITUENTS - 3

➢ ANSES (2013)

- Among the 212 cases of adverse health effects reported through the French Nutritional Vigilance Scheme, 25 (12 %) were considered “very likely“ and 54 (24 %) were “likely“ to be causally related to the consumption of “energy drinks”.
- Although most adverse effects were attributed to the consumption of high doses of caffeine, it was suggested that taurine could have additional effects in raising blood pressure and inducing vasospasm of the coronary arteries
- ANSES warned about the chronic consumption of caffeinated beverages, including “energy drinks”, by certain subgroups of the population, including pregnant and lactating women, children and adolescents, “slow caffeine metabolisers”, and subjects with cardiac, psychiatric or neurological disorders, kidney failure or severe liver diseases.
- Concerns regarding different patterns of consumption of “energy drinks” (very high acute intakes), concomitant alcohol use, and/or concomitant intense physical exercise.

CAFFEINE AND P-SYNEPHRINE

- **BfR (2012)**

27 mg can be expected to significantly increase blood pressure in humans, and the effect may be observed at lower doses (of about 5 mg) in combination with caffeine. Daily intake of 6.7 mg *p*-synephrine from food supplements are safe, based on the assumption that total daily intakes of synephrine would remain < 25.7 mg (= 95th percentile of synephrine intake from conventional foods) among consumers.

- **Swedish National Food Agency (2012) and ANSES (2014)**

concluded that the effects of single ingredient preparations (p-synephrine) are seen from about 20 mg, that at 50 mg there is a clear effect on heart rate and systolic and diastolic blood pressure, and that caffeine could potentiate the cardiovascular effects of synephrine. ANSES (2014) recommended not combining synephrine with caffeine.

- **Health Canada (2011)**

established a limit of 50 mg of synephrine in supplements as a single active ingredient for healthy adults and daily doses up to 320 mg and 40 mg for the the combination of caffeine and synephrine, respectively.