# Methodological considerations and main conclusions

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# STARTING POINT

- **Terms of Reference from the European Commission**

- **Health concerns expressed by risk assessment bodies:**

  - pregnancy outcomes
  - cardiovascular system
  - central nervous system
  - combination with taurine, D-glucuronolactone, alcohol, p-synephrine

Concerns were **based on human data** and refered to the **general population and specific subgroups** such as pregnant and lactating women, children and adolescents, subjects performing physical exercise.

# DATA SOURCES

- Literature search performed under a procurement project to retrieve articles from 1997 ff (RC/EFSA/NUTRI/2013/01; published)
- References from national and international risk assessment bodies
- Spontaneous submission from stakeholders

# TYPE OF EVIDENCE CONSIDERED

- **The Panel considered that human intervention studies and human observational studies** (prospective cohort, case control and cross-sectional studies) with adequate control for confounding variables, in (generally) healthy subjects were appropriate to evaluate potential adverse effects of caffeine consumption in humans.

- **Studies conducted in subjects selected on the basis of a disease condition** (e.g. established CVD, neurological diseases, behavioural or sleep disorders, metabolic disorders, renal or hepatic insufficiency...) do not allow conclusions to be drawn on the safety of caffeine for the general population.

# HIERARCHY OF THE EVIDENCE (1) …

## … for assessing causal relationship

- **Human intervention studies**
  - Randomised, controlled
  - Randomised, non-controlled
  - Non-randomised, controlled
  - Other intervention studies

- **Human observation studies**
  - Prospective cohort studies
  - Case control
  - Cross-sectional
  - Other observational studies (e.g. case reports)

# HIERARCHY OF THE EVIDENCE (2)

**Human intervention studies and prospective cohort studies** were preferred over case-control and cross-sectional studies due to the lower risk of reverse causality and recall bias.

Although case reports are useful to identify health concerns for further investigation, they generally provide insufficient information to conclude on a factor or combination of factors which trigger the adverse event and/or the doses of caffeine which could be considered as safe/unsafe for the general healthy population (not appropriate for deriving safe intake levels).

Whenever available, **systematic reviews** and **meta-analyses** were used to summarise the scientific evidence.

# TYPES OF STUDIES USED (1)

**Adverse effects of a single or repeated intakes within a day**

- **Cardiovascular system:**
  a) **intervention studies**: blood pressure, endothelial function, arterial compliance, myocardial blood flow
  b) **case-cross over studies**: sudden cardiac death, myocardial infarction, ischemic stroke

- **Hydration, body temperature:** **intervention studies**

- **Central nervous system (sleep, anxiety, behavior)** **intervention studies**

# TYPES OF STUDIES USED (2)

## Adverse effects of longer-term (>7d) and habitual consumption

- **Central nervous system:** intervention studies
- **Cardiovascular system:**
  a) **intervention studies:** blood pressure
  b) **prospective cohort studies:** hypertension, coronary heart disease, myocardial infarction, total cardiovascular risk. Case-control and cross-sectional studies were not considered for these endpoints.
- **Pregnancy outcomes:** one **RCT**, five **prospective cohort studies**. Case-control studies reviewed and included in the UK CoT assessment.

# MAIN CONCLUSIONS – ADULTS (1)

- **Single doses** of caffeine **up to 200 mg (≈3 mg/kg bw)** from all sources do not raise safety concerns for the general adult population, even if consumed < 2hrs prior to intense physical exercise under normal environmental conditions.

**About 4 % of the adult population may exceed 200 mg of caffeine on a single session of "energy drink" consumption in connection with physical exercise. This information is not available for other sources of caffeine.**

- **Single doses of 100 mg (≈1.5 mg/kg bw)** of caffeine close to bedtime may increase sleep latency and reduce sleep duration in some adult individuals.

# MAIN CONCLUSIONS – ADULTS (2)

- **Habitual** caffeine **intakes** (all sources) **up to 400 mg/day (≈5.7 mg/kg bw)** do not raise safety concerns for adults in the general population.

**In seven out of 13 countries, the 95th percentile of daily caffeine intake from all sources exceeded 400 mg. The estimated proportion of the adult population exceeding daily intakes of 400 mg ranged from 5.8 % to almost one third (32.9 %).**

- Other common constituents of "energy drinks" (taurine, D-glucurono-γ-lactone) or alcohol are **unlikely to adversely interact with caffeine**.

- The short- and long-term effects of **co-consumption of caffeine and synephrine** on the cardiovascular system have **not** been **adequately investigated** in humans.

# MAIN CONCLUSIONS – PREGNANCY AND LACTATION

## ➢ Pregnant women

**Habitual** caffeine **intake** from all sources **up to 200 mg/day** by pregnant women in the general population do not raise safety concerns for the fetus.

**Data on daily caffeine intake in this population subgroup are scarce.**

## ➢ Lactating women

**Single doses** of caffeine **up to 200 mg** and **habitual** caffeine **intake of 400 mg/day (≈5.7 mg/kg)** consumed by lactating women in the general population do not raise safety concerns for the breastfed infant.

**Data on daily caffeine intake in this population subgroup are scarce.**

# MAIN CONCLUSIONS – ADOLESCENTS

**Limited information** available ⇒ **caffeine intakes of no concern** derived from acute consumption in adults **(3 mg/kg bw/day)**

As in adults, caffeine **doses of about 1.5 mg/kg** bw **may increase sleep latency and reduce sleep duration**.

**About 8 % of adolescents (10 to < 18 years) may consume more than 200 mg of caffeine from "energy drinks" on a single session in connexion with physical exercise. This information is not available for other sources of caffeine. In five out of 13 countries, the 95$^{th}$ percentile of caffeine intake from all sources exceeded 3 mg/kg bw/d. The percentage of adolescents exceeding that amount ranged from 5.2 to 10.0 %.**

# MAIN CONCLUSIONS – CHILDREN

As for adolescents: same levels regarding **daily intakes (3 mg/kg bw/day)** and **sleep (1.5 mg/kg bw)**.

In **children** (3 to < 10 years), the 95$^{th}$ percentile of caffeine intake from all sources on a single day exceeded 3 mg/kg bw in nine out of 16 countries (6.2 % to 15.4 % of survey days). The proportion of children with daily caffeine intakes from all sources beyond 3 mg/kg bw ranged from 6.0 % to 12.6 % in the six out of 14 countries where the 95$^{th}$ percentile exceeded 3 mg/kg bw.

For **toddlers** (12 to < 36 months), the estimated 95$^{th}$ percentile of caffeine intake from all sources on a single day exceeded 3 mg/kg bw in three out of 10 countries (7.3 % to 36.7 % of survey days). Only in one out of nine countries the 95$^{th}$ percentile of daily caffeine intake from all sources exceeded 3 mg/kg bw (6 % of toddlers).

## METHODOLOGY AND CONCLUSIONS

# OPEN FOR DISCUSSION