Data from literature search

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113. As mentioned in paragraph 5, a literature search was carried out using the search string "Garcinia cambogia" AND "toxicity" in PubMed, Science Direct and Google Scholar. No filters or restrictions were used. These were in addition to the data reviewed by ANSES.

Toxicokinetics

114. van Loon *et al*., (2000) investigated the acute effects of ingestion of HCA (“6-30 times the reported dosage applied in human weight-loss studies) on plasma HCA availability. They further investigated whether systemic HCA availability altered fat oxidation rates and plasma metabolite concentrations at rest and during moderate-intensity exercise in “endurance-trained” humans by assessing total fat and oxidation rate calculations. Ten cyclists presumed to be male (sex based on information from a pilot study (n=3 males; these males were not included in the main study); aged 25± 2 years; BMI 22.1 ± 0.5 kg/m^2) received a total of 0.5 g/kg bw of a liquid *G. cambogia* extract - Citrimax HCA-450-LS (48% HCA), which was divided over 4 boluses. This resulted in 18 ± 0.4 g HCA being ingested by every subject in the HCA trial. The placebo was water; the number of subjects in the control group were not detailed. It should be noted that beverages (HCA drink or water) were provided in a randomised order. A blood sample was taken at rest, and subjects were provided with either HCA or water to drink 45 mins before exercise. Blood samples were taken at 15 minutes intervals until t=0. Subjects received their second dose 15 minutes before exercise. Following a warm-up period (5 minutes), subjects started cycling at a moderate intensity of 50% Wmax for 2 h (t = 0–120). During exercise, subjects received another bolus of test drink at t = 30 and at t = 60. During exercise, blood samples were taken at 30-min intervals (t = 30 and 60).

115. In the pilot study, it was determined that plasma HCA concentrations increased over time after ingestion of a single dose of HCA solution 4.4g over a 3.5-hour period. Maximal values were attained after 60-90 minutes at 0.12 ± 0.03 mmol/L, after which the concentration decreased. No HCA was detected in the samples collected in the placebo trial.

116. In the main study, plasma HCA concentrations increased up to 0.08 ± 0.01 mmol/L (16.6 mg/L) after the ingestion of 4.4 ± 0.1 g HCA at t = -45 and t = -15 during resting conditions. Plasma HCA concentrations increased further up to 0.39 ± 0.02 mmol/L (82.0 ± 4.8 mg/L) after the ingestion of 4.4 ± 0.1 g HCA after 30 and 60 min of exercise. It was concluded by the authors that plasma HCA availability does not increase energy expenditure or stimulate skeletal fat muscle fat oxidation at rest or during exercise.

117. Loe *et al*., (2001) dosed fasting humans (n=4; 3 males and one female, subjects were anonymised; age range 21-42; weight range 52.3-86.2 kg) with 2 g of HCA (in the form of CitriMax HCA-600-SXP capsules, ~500 mg) to

assess the [bio]availability in humans using a novel gas chromatography/mass spectrometry (GC/MS) method. The subjects were all “healthy, non-smokers that had no history of cardiovascular disease or diabetes”. Blood samples were collected 30 minutes after ingestion of the supplement and every 30 minutes thereafter over a period of 3.5 to 4 hours. A 50 mL blood sample from a control subject (who did not take the supplement) was also collected to construct a standard curve. The peak plasma HCA concentration was observed 2 hours after administration, measuring 8.4 µg/mL, which demonstrated that HCA absorption is relatively fast.

118. Cruz *et al*., (2021) aimed to determine the main pharmacokinetic parameters of *G. cambogia* extract/HCA in “healthy” women (n=16 fasted period and n=13/16 for fed period; ages 21-41 years with BMI 20.29–25.82 kg/m^2), and to evaluate the food effects on HCA absorption. Subjects received 1,500 *G. cambogia*, of which 750 mg is HCA extract under 8 hours of fasting. In the fed period, a high-calorie breakfast (~600 calories) was given after dosing. Plasma HCA concentrations were significantly higher in the fasted state (1.21 µg/mL) compared to the fed state (0.40 µg/mL). Overall, plasma concentrations ranged from 0.05 – 2.74 µg/mL. Peak plasma concentration (Cmax) and area under the curve time concentration (AUC0-10hrs) were 3-fold and 2-fold lower (p0.001, 0.01), in the fed-condition, respectively. The maximum concentration for both groups were similar with 2 hours as the median. In the presence of food, it was observed that, HCA elimination was reduced (5 hours vs 3 hours under fasted conditions). The authors further noted substantial inter-individual variation for the different pharmacokinetic parameters in both periods. The authors suggested that “HCA might suffer an active absorption uptake and intense adsorption on food.”

119. Heymsfield *et al*., (1998) evaluated the efficacy of *G. cambogia* for body weight and fat mass loss in “overweight but otherwise healthy adults” (aged 18-65 years; BMI range 27 - 38 kg/m^2). The total daily dose of *G. cambogia* extract was 3,000 mg, of which 1,500 mg was HCA or a placebo was received. Both groups were prescribed a high-fibre, low energy diet. A total of 135 subjects were randomised to either active HCA (n=66) or placebo (n=69) groups; 42 (64%) in the active HCA group and 42 (61%) in the placebo group completed 12 weeks of treatment (*P*=.74). It was found that the co-administration of HCA with a high-fibre diet and low-energy may have inhibited the gastrointestinal absorption of HCA. There was no significant difference in group weight loss (mean [SD], 3.2 [3.3] kg vs 4.1 [3.9] kg; *P*=.14) between the exposed and placebo groups.

120. In the literature, (2S,3S)-HCA has been described to inhibit the ATP-citrate lyase enzyme (Jakopin, 2019). This is the primary enzyme responsible for the synthesis of cytosolic acetyl-CoA in many tissues. The product, acetyl-CoA, serves several important biosynthetic pathways, including lipogenesis and cholesterogenesis. In nervous tissue, ATP citrate-lyase may be involved in the biosynthesis of acetylcholine (NCBI, 2025). Thus, it is believed that HCA is widely distributed.

121. No other data were available for distribution, metabolism and excretion. It is also unclear if different *Garcinia* species influences the bioavailability of HCA.

Review articles

122. Andueza *et al*., (2021) performed a review to investigate the effectiveness and side-effects of nutritional supplements based on *G. cambogia* to promote weight loss. The efficacy of other *Garcinia* species was also provided. They utilised the Cochrane and PubMed databases; 13/51 and 29/53 articles were selected for detailed review, respectively. They concluded that toxicity cannot be reliably attributed to *Garcinia*, as it is typically present in MIDS. The authors were of the opinion that case reports describing adverse effects usually reflect the associations between the observed toxicity and the intake of the dietary supplement, rather than causality. Furthermore, the authors note that the use of these supplements should be discouraged for pregnant and lactating women, since HCA can affect the production of fatty acids and cholesterol, which can directly influence the production of sterols and steroid hormones.

123. Data from the LiverTox database noted that studies in rats and other animal models have suggested that *G. cambogia* and HCA do not have significant toxicities, although testicular toxicity was found with high doses (Saito *et al*., 2005). In humans, *Garcinia* has been linked to rare reports of serotonin syndrome, rhabdomyolysis and hepatic toxicity; however, the role of *Garcinia* as opposed to other components of MIDS typically used in humans is yet to be fully elucidated. The frequency of hepatic adverse reactions was estimated to be 1:10,000 and it was concluded that consumption of *G. cambogia* is likely a rare cause of clinically apparent liver injury (NCBI, 2019).

124. Márquez *et al*., (2012) noted that caution should be exercised when interpreting the results from human studies as other randomized, placebo-controlled clinical trials have not reported the same outcomes. Furthermore, most

studies in humans have been conducted on small samples and mainly in the short term. None of them have shown whether these effects persist beyond 12 weeks of intervention. Therefore, there is still little evidence to support the potential effectiveness and long-term benefits of *G. cambogia* extracts. Regarding toxicity and safety, it is important to note that except in rare cases, studies conducted in experimental animals have not reported increased mortality or significant toxicity. Furthermore, at the doses usually administered, no differences have been reported in terms of side effects or adverse events (those studied) in humans between individuals exposed to *G. cambogia* and controls.

125. Chuah *et al*., (2013) “critically assessed” the evidence from the *in vitro, in vivo,* and clinical trials on the safety of *Garcinia/*HCA as a dietary supplement for treating obesity. The methodology in which the authors collected and reviewed studies in the literature was not described. The following endpoints were considered: cytotoxicity, genotoxicity, acute toxicity (oral, dermal, dermal irritation and eye irritation), sub-chronic (90 days) toxicity and reproductive and teratogenic toxicity. The authors summarised that *G. cambogia*/HCA is generally safe and a NOAEL up to 1, 240 mg/kg per day based on a developmental toxicity study in rats by Deshmukh et al., (2008a) (see Subchronic section).

Genotoxicity

126. Lee & Lee (2007) evaluated the genotoxicity of HCA isolated from *G. cambogia* using three tests: the Ames test, the *in vitro* chromosomal aberration test, and an *in vivo* micronucleus test. The test item was described as “a natural, highly water-soluble, calcium-potassium salt of 60% HCA extract”; commercially known as Super CitriMax HCA-600-SXS (HCA-SX).

127. The Ames *Salmonella* mutation test was used according to the plate incorporation procedure described by Maron and Ames (1983). The five strains of *Salmonella typhimurium* (TA98, TA100, TA102, TA1535, and TA1537) were provided by Prof. B. N. Ames (University of California Berkeley). The assay was performed with and without metabolic activation using an S9 mixture. Negative and positive controls were used for each strain. The positive controls performed without metabolic activation were: 2-nitrofluorene (1 µg per plate) for TA98, sodium azide (1.5 µg per plate) for TA100 and TA1535, mitomycin (1 µg per plate) for TA102, and acridine mutagen (1 µg per plate) for TA1537. The positive controls performed with metabolic activation was 2-aminoanthracene (1 µg per plate) for all strains. Six concentrations of HCA-SX were examined with triplicate plates per dose: 0, 20, 200, 500, 2,500, and 12,500 µM/plate. HCA-SX did not

induce mutagenic activity in any of the five bacterial strains tested, under any of the activation conditions examined.

128. For the chromosomal aberration test, the Chinese hamster ovary (CHO) cell line was provided by the Cancer Research Institute, Seoul National University, Korea. CHO cells were maintained under monolayer conditions in Eagle's minimum essential medium supplemented with 10% foetal bovine serum, with L-glutamine and ampicillin at 37°C in a 5% CO2 atmosphere. For each treatment, 3×10^5 cells were cultured in duplicate in 5 mL of culture medium in a 2.5-L flask. After the cells were incubated for 24 h, they were treated with an HCA-SX 10 µL reaction volume. A 5-hr pulse treatment was then carried out with and without the S9 mixture (used at a final concentration of 10% in the treatment medium). Benzo[a]pyrene (BaP) was used as a positive control in the presence of S9. Mitomycin C (MMC) was used as a positive control in the absence of S9 mixture. Chromosomal aberration percentages included by HCA-SC in the treated groups were >3% and 4%, respectively. In the positive control groups, the percentage of structural chromosome aberrations in the BaP and MMC-treated groups were >21% with S9 and >25% without S9, respectively. HCA-SX was not observed to induce any cytotoxic effect.

129. For the micronucleus test, 7- to 8-week-old ICR male mice (n=5/group) were acclimatised for at least 7 days prior to the start of the test. HCA-SX were dissolved in dimethyl sulfoxide (DMSO). The groups were as follows: DMSO (negative control), 20, 100, 500, 2,500 or 12,500 HCA-SX µmol/kg dissolved/suspended in DMSO, mitomycin C at 2 mg/kg (positive control). Animals were administered the treatments by intraperitoneal injection and were sacrificed by cervical dislocation 24 hours after the test substance administration. Numbers of micronucleated cells were determined by counting the number of polychromatic erythrocytes (PCEs) from at least 1,000 PCEs per animal. The micronucleated polychromatic erythrocytes (MNPCEs) that contained micronuclei were counted from at least 1,000 PCEs. No mortality was observed. MNPCE/1,000 PCEs were induced at the highest HCA-SX dose (12,500 µmol/kg) and PCE/(PCE + NCE) ratios decreased with increasing dose.

130. The authors concluded that HCA-SX was not found to be genotoxic by bacterial or by chromosome aberration testing. It demonstrated "a weak mutagenic effect by micronucleus testing but did not induce structural chromosomal aberrations or significantly induce MNPCEs at the doses used.

131. The article by Lee & Lee (2007) (as summarised in paragraphs 126-130) was refuted by Lau *et a*l., (2008), stating that for the *in vivo* micronucleus

test, the authors: i) selected an inappropriate route of administration intraperitoneal rather than the oral route; ii) the use of vehicle for the test item (DMSO) was not justified and varied to that of the positive control (water), as DMSO may react with the test compound to induce an adverse effect; iii) a dose-range finding test was not performed and the range of selected doses (separated by a factor of 5) differed from conventional dose levels used in toxicological studies; iv) discrepancy with reporting of results; v) “very weak” statistical analysis, where a *t*-test was utilised without performing a one-way analysis of variance previously; a regression or correlation analyses was also not performed.

132. Ghosh & Mukherjee (2017) evaluated the *in vitro* genotoxicity of HCA (50.9% HCA in calcium salt of HCA) in human lymphocytes. The following methods were used: trypan blue dye exclusion test, MTT assay, Comet assay and a DNA diffusion assay. The trypan blue and MTT assay were performed according to the test methods of Tennant (1964) and Mosmann (1983), respectively, with modifications by Sinha *et al*., (2014). The Comet assay was performed following the method of Tice *et al.,* (2000), with modifications based on Sinha *et al*., (2014). Cells were exposed to HCA (0, 10, 20, 40 or 100 µg/mL) for 3 hours or 24 hours and processed for cytotoxicity and genotoxicity analyses. The effects of HCA on erythrocytes were determined by a haemolysis test using the same doses and exposure duration. Results from the trypan blue and MTT assay in human lymphocytes demonstrated the absence of significant induction of cytotoxicity when compared to the positive control groups. However, as observed in the Comet assay, HCA induced DNA damage that was statistically significant at concentrations of 40 and 100 µg/mL. The authors noted that these concentrations were “almost identical to and approximately double the maximum permitted dose [author does not detail if this the human equivalent dose] (i.e. 900 – 2,800 mg/day or 15 – 47 mg/kg/day, respectively).” Oxidative stress, as a potential mechanism of DNA damage was evaluated using DCFH-DA dye. A significant increase in reactive oxygen species (ROS) production was found at concentrations of 40 and 100 µg/mL at both time points compared to the respective controls. As for the effects on the erythrocytes, no haemolytic potential was observed. The authors concluded that HCA-induced genotoxicity may not lead to apoptotic/necrotic cell death. The observed DNA damage can be attributed to oxidative stress, which was independent of mitochondrial ROS generation.